第 1 回長期大型研究助成
京都大学高等研究院
医学物理・医工計測グローバル拠点

最終報告書

公益財団法人 中谷財団

中谷財団
第１回長期大型研究助成　京都大学高等研究院
最終報告書

目　　次

部門長ごあいさつ

「医学物理・医工計測グローバル拠点（英語名：Center for Integrative Medicine and Physics, CiMPhy）」は、中谷医工計測技術振興財団（現・中谷財団）の支援の下、特設寄附部門として京都大学高等研究院に 2018 年 4 月に設立されました。

当寄附部門は、(1) 既存の枠を超えた**非平衡物理学と医学の連携**による『**ヒト臨床材料の医工計測・解析**』というこれまでになかった新たな学問分野を開拓すること、また (2) ハイデルベルク大学（1386 年設立）を主な拠点として、25 年以上にわたって欧州トップ大学で研究・教育に携わってきた私の国際経験を最大限に活かした、世界トップ研究者との分野横断型の共同研究を通じたグローバル人材を育成することで、

我が国発の Biomedical Engineering を広く世界に発信する国際ハブ拠点

を確立することを設立時からの目標として高く掲げ、日々の研究に精進してまいりました。

新型コロナウイルス感染拡大というこれまで経験したことのない状況のため国際事業が 2 年以上ストップするといったピンチもありましたが、１年間の事業延長を承諾いただいたおかげで、当初の計画を大きく上回るさらにダイナミックな活動ができたと自負しております。

この 6 年間、アカデミアだけでなく産業界からも多くの方から既存の枠を超えて我々のビジョンにご賛同をいただき、我々の研究成果を広く社会に実装することもできました。皆様のご指導・ご支援、また京都拠点・欧州ハブ拠点（ハイデルベルク大学）のメンバーの奮闘に深く感謝申し上げます。

この度寄附事業の終了にあたって、これまでの活動を最終報告書としてまとめました。

この節目を迎えるにあたり、本拠点の設立から日々の運営に至るまで我々の活動を支え応援していただいております、中谷医工計測技術振興財団・家次恒代表理事、故 輕部征夫 理事長、松森信宏 事務局長、寶田馨 前事務局長、また京都大学・湊 長博 総長、山極 壽一 前総長、北川 進 理事・副学長（前 iCeMS 拠点長）、森 重文 高等研究院長、上杉 志成 iCeMS 拠点長はじめ、中谷財団や京都大学のスタッフの皆様、また日々の共同研究でお世話になっております国内外の共同研究パートナーの皆様に、拠点メンバーを代表して心よりお礼を申し上げます。

本寄附事業は終了いたしましたが、京都大学で生まれた新たな学問的流れを今後ともより大きく発展展開させ、その成果を広く世界へ発信し社会へと還元してまいります。

これからも皆様のご指導とご支援をお願い申し上げます。

令和７年１月吉日

京都大学 高等研究院 医学物理・医工計測グローバル拠点 前部門長

ハイデルベルク大学 物理化学研究所 教授

田中　求

拠点スタッフ紹介

【部門長】

田中　求
Habilitation 上級学位・工学博士
部門長・京都大学高等研究院特任教授
ハイデルベルク大学物理化学研究所教授

【教員・研究員】

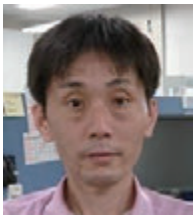
山本 暁久
助教
理学博士（物理学）

鈴木　量
助教
理学博士（物理学）

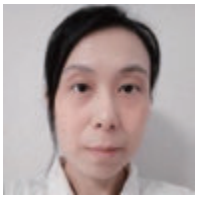
林　健太郎
助教
理学博士（生物学）

【研究支援・技術補佐】

日夏 聡子
教務補佐員
修士（食品科学）



竹内 一郎
技術補佐員
修士（化学）



藤田 由香里
技術補佐員
修士（生物学）

本川 順子
技術補佐員
修士（生物学）

【秘書業務・事務補佐】

浅岡 香緒里
事務補佐員

林　ちよ
事務補佐員

【学生・支援スタッフ】

永井 翔吾
卒業研究・修士課程
理学部物理学専攻

【客員教授】

Anthony D. Ho

Dr. med.
ハイデルベルク大学名誉教授（医学）
前　血液内科・腫瘍内科部長
カリフォルニア大学サンディエゴ校教授
（1992-1998）

吉川 研一

工学博士
京都大学名誉教授（理学）
同志社大学名誉教授（生命医科学）
ハイデルベルク大学客員教授
国際純粋応用物理学連合・生命物理チェア
（2011-2014）

Thomas W. Holstein

Dr. rer. nat.
ハイデルベルク大学
Center for Organismal Studies 教授
ハイデルベルク科学アカデミー総裁
（2015-2020）

太田 隆夫
理学博士
京都大学名誉教授（理学）
豊田理化学研究所フェロー（2014-2017）

Martin Bastmeyer
Dr. rer. nat.
カールスルーエ工科大学
動物学研究所教授

【客員研究員】

鶴山 竜昭　教授

京都大学医学研究科創薬医学講座
現・放射線影響研究所
病理画像の機械学習と病理試料の力学の相関
2018 年度、2019 年度

杉村 佳織　博士

島津製作所　基盤技術研究所
人工授精における非侵襲卵子評価技術
2019 年度、2020 年度

上野 盛夫　准教授

京都府立医科大学　眼科学教室
角膜再生医療の物理的バイオマーカー開発
定期ミーティング
2019 年度―

田中 寛　助教

京都府立医科大学　眼科学教室
角膜再生医療の物理的バイオマーカー開発
2018 年度

【過去に在籍した学生・スタッフ】

酒巻 裕介
研究生
2018

古仲 裕貴
オフィスアシスタント
生命科学研究科（M2）
2019-2020

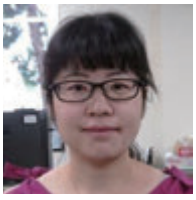
吉田 美枝子
教務補佐員
2013-2021

山中 智子
技術補佐員
2016-2018

小川 裕之
技術補佐員
2020-2022

大谷 暢宏
医学部マイコース
プログラム
医学部医学科（B4）
2020-2023

山本 大智
医学部マイコース
プログラム
医学部医学科（B4）
2021



川阪 純花
オフィスアシスタント
医学研究科（M2）
2021

江成　涼
オフィスアシスタント
工学部電気電子
工学科（B3）
2021

餘多分 萌瑛
オフィスアシスタント
医学部医学科（B3）
2021

【オフィス・実験室所在地】

高等研究院本館（地図７７）
オフィス（１階）
実験室（２階）
京都市バス「京大正門前」バス停前
総合図書館（１８）
本部棟（１４）

北部総合教育研究棟（地図１３）
実験室（３階）
北部構内・基礎物理学研究所横
農学部グラウンド
基礎物理学研究所（１２）
湯川記念館（１１）

拠点の活動ハイライト

2018 年

記者発表（1月27日）

於　京都大学
東京オフィス


京大の医学物理拠点に助成
シスメックス関連財団、最大3億円

医療用検査機器大手シスメックス（神戸市中央区）にゆかりの深い中谷医工計測技術振興財団（東京）は、5年で最大3億円の長期大型研究助成制度を創設し、初めての助成先に京都大学高等研究院の「医学物理・医工計測グローバル拠点」設置事業を選んだ。

同財団は、シスメックスを創業した故中谷太郎氏らが1984年に設立し、先進的な研究などに助成してきた。

同事業は、物理学と臨床医学を融合させた研究拠点を設け、細胞や組織を高速で精密に計測し、感染症やがんの高度な診断などに取り組む。世界の研究者の交流も進める方針で、今年4月の設置を目指す。

東京都内で26日に開かれた贈呈式に臨んだ同研究院の田中求特任教授は「研究成果を社会に発信する。グローバル人材の育成につなげたい」と述べた。同財団は創設した助成制度を今後も年1件程度続けたい考え。（佐伯竜一）

記者発表での記念写真


京大、物理学と臨床医学融合　独ハイデルベルク大などと４月めど始動

(2018/1/29 05:00)

京都大学は物理学と臨床医学の融合研究プロジェクトを４月にも始める。新設する同大高等研究院医学物理・医工計測部門に、１０人程度のスタッフを配置。物理学と医学の連携により、疾患の進行度の数値化技術確立や、再生医療での移植後の組織を早期に予後診断できるソフトウエアの開発などをする。基盤研究を担う京大の同部門を中核とし、臨床研究のパートナーである独ハイデルベルク大学、国内外の大学、産業界と共同で進める。

京大と中谷医工計測技術振興財団（東京都品川区）が会見して発表した。

プロジェクトの概要を説明する田中ハイデルベルク大教授

新聞各紙や雑誌などで報道

贈呈式（2月23日）

財団・輕部理事長と

於　マンダリンオリエンタル


長期大型研究助成　5年間で最大3億円

国際的・分野横断的な研究であると同時に，人材育成に資する研究を対象として，今年度から新設された助成。

田中 求
Motomu Tanaka
ハイデルベルク大学
物理化学研究所
教授

医学物理の基礎学理を中核とする医工計測の新たな研究・教育グローバル拠点の確立

第1回の助成対象は，京都大学高等研究院に「医学物理・医工計測グローバル拠点」を設置するプロジェクトだ。この研究部門では「物理学と臨床医学の融合」という観点から新たな計測・解析技術の基盤研究に取り組む。国内外の医学・工学・理学の研究者と連携することで，田中教授がハイデルベルク大学で進めてきた分野横断型の研究を発展させることが目標だ。同時にトップレベルの国際共同研究を通じた人材育成システムの確立も目指す。田中教授は「5年間で様々な成果も出るし，将来のための種が播かれることもあるでしょう」と期待をにじませている。

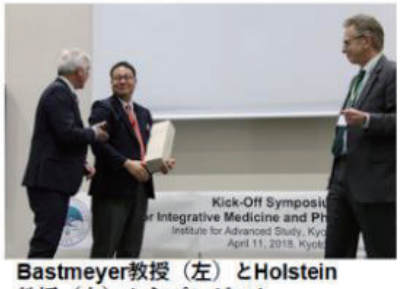
キックオフシンポジウム（4月11日）

於　京都大学高等研究院

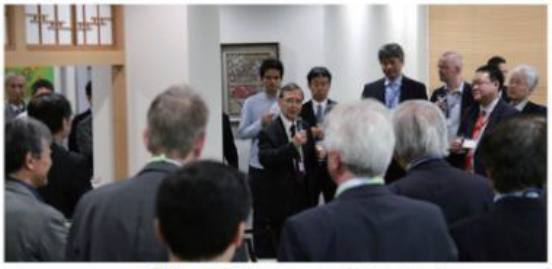
出席者との記念写真

スタート時のメンバーと客員教授

湊理事、森高等研究院長、評価委員の先生方はじめ、国内外からおよそ150人の研究者のご出席をいただき、その激励のもと寄付部門が本格的にスタート



Bastmeyer教授（左）とHolstein教授（右）からプレゼント

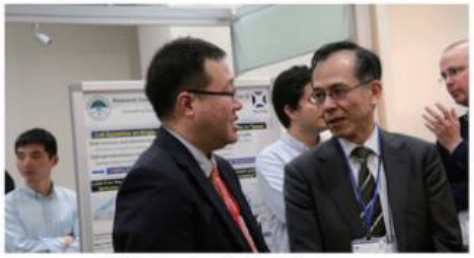


Ho教授（中央）による乾杯の発声

拠点スタッフによるピアノ連弾

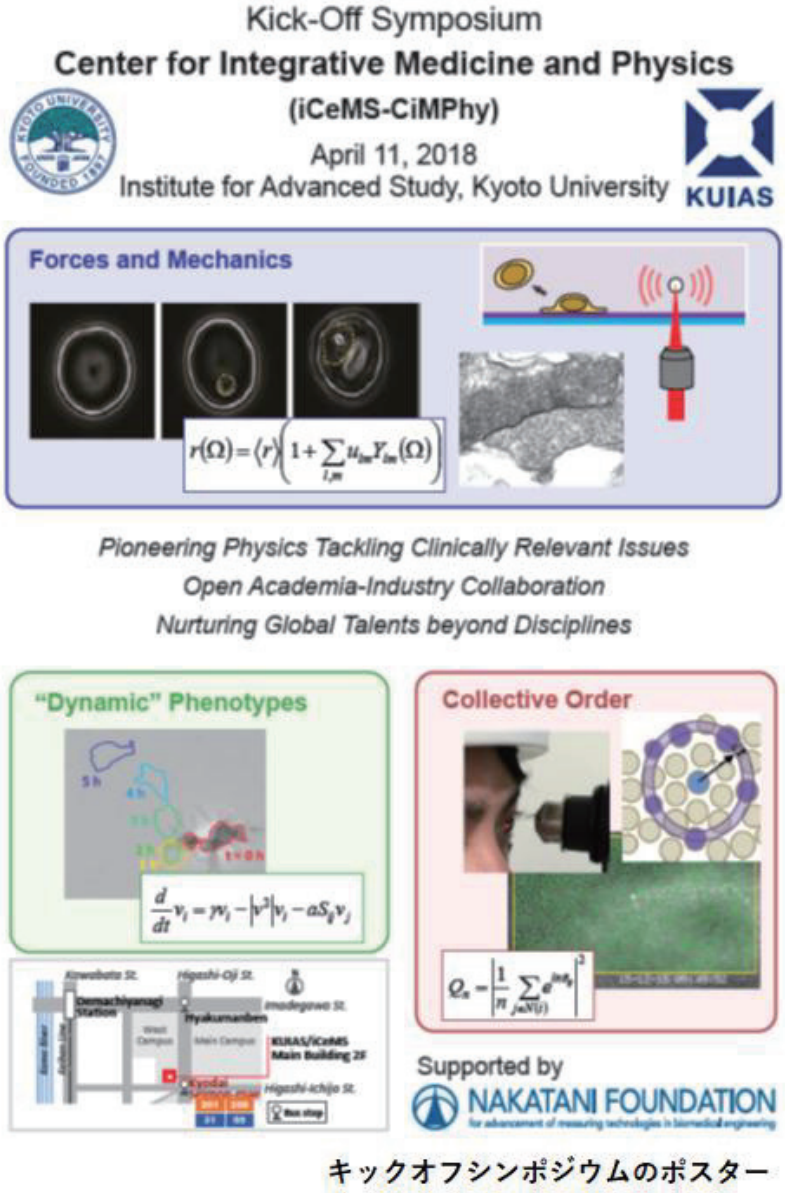
拠点客員教授の歓談

湊理事・富樫教授と



森院長とポスターの前で

キックオフ終了後スタッフ一同で



キックオフシンポジウムのポスター

開所にあたっていただいた激励のメッセージ

肩書は 2018 年 4 月当時のものを使用

京都大学・湊 長博 プロボスト・副学長（現・京大総長）

湊　長博 (Prof. Dr. Nagahiro Minato)

プロボスト、理事・副学長
（Provost, Executive Vice President, Kyoto University）

iCeMS は発足以来 12 年目を迎え、化学と基礎生物学の融合研究の文字通り世界拠点(World Premier Institute)として確立し、新たに高等研究院の主力研究組織として大きく展開しています。今回さらに高等研究院に、中谷財団の寄付部門として統合医学・物理学研究センター（CiMPhy）が設置される運びとなったことは、まことに喜ばしい限りです。本部門は特に医学領域に物理学の Discipline を導入して新しい定量科学領域を開拓することをめざす極めて独創的な研究部門であり、iCeMS との連携によって世界に先駆けた新領域の研究が大きく展開されることが期待されています。研究代表者の田中求教授はこの領域の世界の第一人者であり、充分にこの期待にこたえていただけるものと信じています。さらに田中教授は新進の世界の学生や若手研究者の交流活動にも大きな実績をもっておられ、高等研究院における世界の若手研究者の交流ハブとしての機能にも貢献していただけるものと強く期待しております。

京都大学・森 重文 高等研究院長

Prof. Dr. Shigefumi Mori

Director-General
Kyoto University Institute for Advanced Study

Our Kyoto University Institute for Advanced Study (KUIAS) was established in April 2016 with the aims to pursue advanced research by capitalizing on the strengths of Kyoto University, nurture next-generation researchers, and to serve as an international research hub where preeminent researchers gather from Japan and overseas. KUIAS is now implementing innovative research activities with Center for Advanced Study, iCeMS, the Institute for Integrated Cell-Material Sciences, which is a research center and with collaborative research centers through collaboration with institutions outside the university.

The Center for Integrative Medicine and Physics was established in KUIAS by the munificence of Nakatani Foundation. We sincerely hope that this center will advance cutting-edge measuring technologies in biomedical engineering and will further intensify the research activities of KUIAS by stimulating mutually with related research centers such as iCeMS, which is a WPI institute.	

京都大学・北川 進 iCeMS 拠点長

Prof. Dr. Susumu Kitagawa Director iCeMS, Kyoto University	
I would like to congratulate Professor Motomu Tanaka for this kick-off symposium of Center for Integrative Medicine and Physics (iCeMS-CiMPhy), which has just been inaugurated by patronage of Nakatani Foundation. iCeMS seeks to develop materials to comprehend cellular functions and produce materials to control processes in cells, and eventually to create functional materials inspired by cellular processes. I, as Director of iCeMS, am happy to provide laboratory space and facilities to support the Center whose mission is closely related to ours. I really hope that researchers of iCeMS-CiMPhy and iCeMS will be mutually inspired and pursue close collaborative research, and that researches of both will be greatly promoted by synergy.	

中谷財団・輕部征夫 理事長

Prof. Dr. Isao Karube President, Nakatani Foundation President, Tokyo University of Technology Professor Emeritus, The University of Tokyo	
Firstly, let me express my congratulations on starting the Center for Integrative Medicine and Physics (iCeMS-CiMPhy) with this kick-off symposium. Since its foundation more thatn 30 years ago, the Nakatani Foundation has been striving for development of the biomedical measurement technologies by subsidizing technology developments and commending researchers with outstanding works. We added a new large grant program last year, after getting approval from the Cabinet Office, and Prof. Tanaka was chosen as the first grantee. It is our pleasure and honor as well to celebrate the official start of the new program.	

Lastly, I sincerely hope that iCeMS-CiMPhy will lead to a successful results thus contributing to development of biomedical engineering technologies and fostering young researchers.	

中谷財団・家次 恒 専務理事

Mr. Hisashi Ietsugu Executive Director, Nakatani Foundation Chairman and CEO, Sysmex Cororation	
I would like to congratulate the kick-off of the Center for Integrative Medicine and Physics (iCeMS-CiMPhy) at this symposium. The Nakatani Foundation, founded in 1984, has been subsidizing the biomedical engineering measuring technologies as its core activity. To further contribute to the development of this field, we started a new program last year with larger grant for a longer period. Prof. Tanaka's proposal was chosen as the first which led to the establishment of iCeMS-CiMPhy at Kyoto University. We are very glad to start this Center since it matches quite well with our purpose of the program which is to encourage interdiciplinary, advanced research and to foster young researchers. I sincerely hope this Center will bear fruitful results in five years and would like to ask all of you related for your cooperation.	

ハイデルベルク大学・Bernhard Eitel 総長

Prof. Dr. Dr. h.c. Bernhard Eitel President of Heidelberg University	
The Universities of Heidelberg and Kyoto have enjoyed close contacts since 1990. The bilateral university partnership was the starting point for the foundation of the German-Japanese University Consortium HeKKSaGOn in 2010. Member institutions include the Universities of Heidelberg and Göttingen, the Karlsruhe Institute of Technology and the Universities of Kyoto, Osaka, and Tohoku Sendai in Japan. The goal of the consortium, which is unique in German-Japanese cooperation, is to intensify scientific cooperation in particular with focus on research, innovation and student exchange. I am confident that the new "Center for Integrative Medicine and Physics" will further strengthen the scientific cooperation between Heidelberg and Kyoto.	

JSPS Bonn オフィス・小平 桂一 所長（元国立天文台長）

小平 桂一 (Prof. Dr. Keiichi Kodaira)

日本学術振興会ボン研究連絡センター長
Director, JSPS Bonn Office

田中求先生、この度は中谷医工計測技術振興財団から京都大学高等研究院への長期大型研究助成によって「物理学と医学を繋ぐ」寄付研究部門を立ち上げる大役を果たされることになったと伺い、心よりお喜び申し上げます。私がボンに赴任して以来、田中先生のハイデルベルク大学でのご活躍や、日独学術交流のための継続的なご尽力、そして京都大学 WPI における精力的な研究教育活動を折につけ身近に伺って参りました一人として、いよいよ先生の兼ねてからの目標に向かって大きな一歩を踏み出される契機が訪れたものと、当該研究部門の今後の発展に期待いたして居ります。先端的学問分野が従来の個々の専門や国境を超えて広がる中で、ご自分の専門を軸としながらも分野を超えて人類の幸せに結びつく研究を志される強い精神をお持ちの田中求先生こそ、この大型助成寄付部門のリーダーとして最適と感じて居ります。残念ながら出席できませんが、今回のキックオフ・シンポジュウムが新部門の将来に豊かな示唆を与えるようなものとなりますよう祈念いたして居ります。

特別なメッセージ

ミュンヘン工科大学・Erich Sackmann 名誉教授

ポスドク時代から田中を鍛え、励まし、導いたサイエンスの師

Prof. Dr. Erich Sackmann

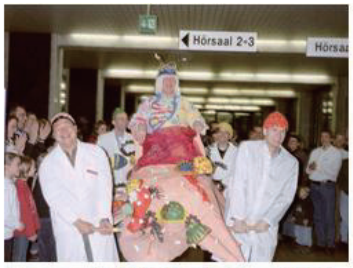
Professor Emeritus of Physics
Technical University of Munich (Germany)

After 45 years of biomimetic physics it is time for Biological Physicists to penetrate the secrets of the physicochemical basis of the survival of living systems and the adaption of their material properties to changing environmental conditions.

Only a small group of courageous physicists is prepared to make this big step. One of these scientists is my scientific child Motomu Tanaka.

Please beware:
Nature can teach us how to generate new self-healing materials by making use of natures' strategy to generate order in multicomponent systems based on the concept of logistically controlled self-organization and highly sophisticated control systems. The future progress in medicine depends on our deeper insights into the control systems by the adaption of the mechanical impedances of cells tissues, i.e. tensional homeostasis.

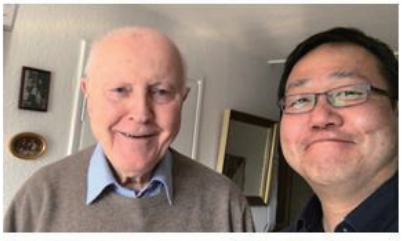
Prof. Sackmann is my teacher, who taught me how to become a scientist.



Munich (2003) Retirement Party


Utö, Finland (2011) Summer School


Zürich (2014) 2D Polymer Conference


Munich (2018) Visit to Erich's Home

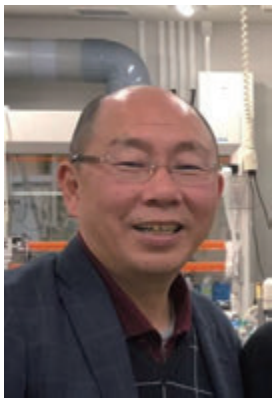
I joined his lab as a postdoc (JSPS/ Humboldt Fellow, 1998 - 2001) and a junior group leader (Emmy Noether Fellow, 2001 - 2005) at the Department of Physics, Technical University Munich (Germany). I am the only non-German, and the last "Habilitand (junior group leader)" in the Sackmann Lab, which produced > 30 chair holders and directors of Max-Planck and Helmholtz Institutes. Our review article on cell surface models (Tanaka and Sackmann, *Nature* (2005)) now counts almost 1000 citations.

彌田 智一 同志社大学教授（東京工業大学名誉教授）

京大院生時代、小学生の田中に科学の楽しさを教えてくれた「家庭教師のお兄さん」

彌田 智一（Prof. Dr. Tomokazu Iyoda）

同志社大学ハリス理化学研究所，教授
Professor, Doshisha University (Japan)



生まれ故郷の京都で新しい研究拠点のスタートおめでとうございます．まっさらの白いキャンバスにどんな絵を描くのか、どんな若い人が登場するのか、ゆっくり楽しみにしています． まだ若いけど、そろそろいいお歳、健康に留意され、やりたいことを素直にシンプルに表現されますよう期待しています

Prof. Iyoda is my first teacher in science. He (at that time, a PhD student in Kyoto University) was my tutor. Tomokazu told a 12-year-old boy (me) how fascinating is science. When I entered the junior high school, he gave me two books: "The Chemical History of a Candle" by Michael Faraday, and "The Origin of Life" by Alexander Oparin. These books and Tomokazu strongly motivated me to become a scientist. It was a great honor for me to introduce this story to my students, when he gave a lecture in Heidelberg.

2019 年

国際ウィンタースクール
（3月11日－20日）

於　京都大学高等研究院

- **参加者　計36名　→　海外13名、国内23名（うち外国人6名）**
- **聴講生　11名（うち外国人5名）**
  国内他大学（阪大、東北大、東工大）から16名が参加

  寄附金に加え、ハイデルベルク大・カールスルーエ工科大の中央経費、DAAD奨学金、研究費（EU Project）などで海外からの参加者の旅費支援
- **講師　28名　→　海外9名、国内19名**
  UC Davis、ミュンヘン大、ハイデルベルク大、カールスルーエ工科大
  京大・東大・東北大・阪大・東工大・埼玉大・京都府立医大・大分大
  九大・同志社・立命館・JAMSTEC・天文台
  寄附金、中谷財団招聘助成（アメリカ１・ドイツ２）、JSPS招聘助成（ドイツ１）、ドイツ科学イノベーションフォーラム（ドイツ１）などで海外からの講師の旅費をカバー

Kyoto Winter School

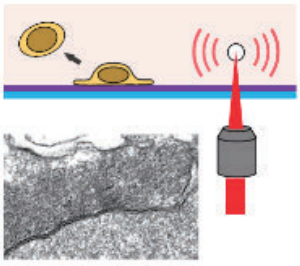
"*Quantifying Dynamics of Life*"

March 11 – 20, 2019

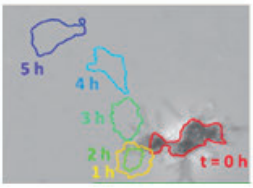
Center for Integrative Medicine and Physics

Institute for Advanced Study, Kyoto University

KUIAS



$$\frac{d}{dt}v_i = \gamma v_i - |v^2|v_i - aS_{ij}v_j$$



Aim:

Cross-disciplinary, international winter school for graduate students and junior researchers from medicine, physics, mathematics, chemistry, biology, and engineering sciences, etc.

Confirmed lecturers:

T. Holstein (Heidelberg), A. Parikh (Davis), M. Bastmeyer (Karlsruhe), J. Rädler (Munich), J. Korvink (Karlsruhe), A. D. Ho (Heidelberg), K. Yoshikawa (Doshisha), S. Kinoshita (KPUM), A. Harada (Osaka), S. Takeuchi (Tokyo), H. Suito (Tohoku), S. Deguchi (JAMSTEC), R. Nagatomi (Tohoku), S. Kidoaki (Kyushu), O. Tabata (Kyoto), K. Svadlenka (Kyoto), T. Tsuruyama (Kyoto), H. Wada (Ritsumeikan), T. Hayashi (Tokyo Tech), H. Y. Yoshikawa (Saitama), M. Sano (Tokyo) F. Tamanoi (Kyoto / UCLA), K. Kodaira (NAOJ)

Organizer:

M. Tanaka (Kyoto / Heidelberg)

Local committee:

A. Yamamoto, R. Suzuki

M. Yoshida

Supported by

NAKATANI FOUNDATION
for advancement of measuring technologies in biomedical engineering

HeKKSaGOn
NETWORK OF UNIVERSITIES

DWIH Tokyo
Land der Ideen

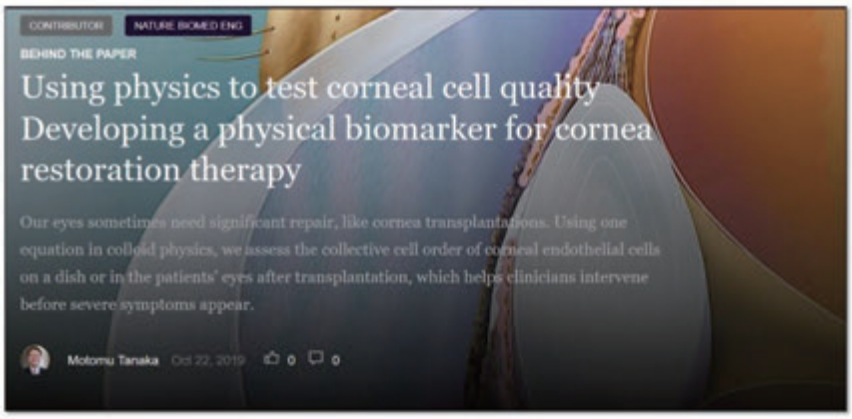
プレスリリース「コロイド物理を活用した革新的角膜内皮細胞評価技術」

2019年5月29日　於・京都大学高等研究院

上段左から　中谷財団・資田事務局長、筆頭著者・山本助教、京都府立医大眼科・外園教授、下段左から　共責任著者・上野講師（京都府立医大、拠点客員研究員）、部門長・田中

日経サイエンス（2019年10月号・12－13頁）

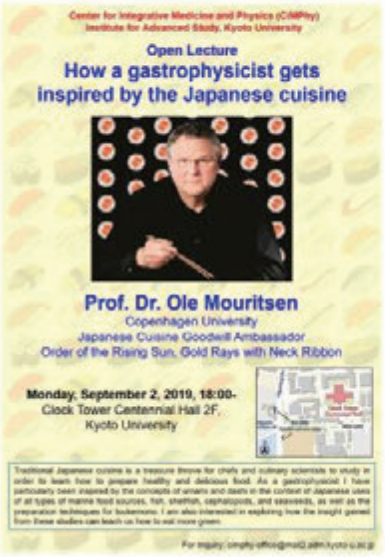
オンラインニュース記事（Nature Blog）



日刊工業新聞（7月23日29面）、日本経済新聞（7月29日29面）、電子情報通信学会学会誌（2020年1月号）など

市民講座『和食の科学』物理学と和食の幸せな出会い

2019年9月2日　於・京都大学百周年時計台記念館



講師
コペンハーゲン大学
Ole G. Mouritsen 教授

旭日中授章
農水省・日本食親善大使

南デンマーク大学・膜物理学センター・
設立拠点長
部門長 田中を学生時代に受入・指導

多くの留学生も参加

市民・中高生など百人以上が聴講

食を通じた教育の実践例

ノートルダム女子中高の生徒と

KUIAS-ハイデルベルク-理研ワークショップ「数理と医学」第一回（10月10日）

世話人

於　京都大学SUURI COOL

田中 求

ハイデルベルク大学教授
京都大学高等研究院
CMPhy部門長

初田 哲男

理化学研究所
数理創造プログラム
プログラムディレクター

坂上 貴之

京都大学教授
京都大学SACRA
学際融合部門長

主に数物系の中堅・若手が最新の成果を紹介・議論

森高等研究院長（中央）を囲んで

2020 年

German-Japanese Worksop 「Aquatic Materials Made to Order」 （3月4・5日）

於　ハイデルベルク大学

文部科学省科学研究費補助金新学術領域研究（研究領域提案型）
「水圏機能材料：環境に調和・応答するマテリアル構築学の創成」

MEXT Grant-in-Aid for Scientific Research on Innovative Areas
Area Number: 6104, FY2019-FY2023

Aquatic Functional Materials

領域代表
加藤隆史教授
（東京大学）

田中 求 は計画研究A03（機能開拓班）班長

ドイツ科学財団（Deutsche Forschungsgemainschaft）
German Excellence Cluster「3D Matter Made to Order」

3D MATTER
MADE TO ORDER

Germany's Excellence Strategy
- 2082/1 – 390761711

領域代表

Martin Wegener 教授
（カールスルーエ工科大学）

Uwe Bunz 教授
（ハイデルベルク大学）

田中 求とM. Bastmeyer 教授（拠点客員教授）は共に
設立メンバー・運営委委員

田中が実行委員長として二つの異分野融合型の大型拠点をつなぎ日独間のネットワークづくりを目指したが、コロナ禍のため開催5日前にオンサイトでの開催を断念（紙面開催）

KUIAS-ハイデルベルク-理研ワークショップ「数理と医学」第二回（9月18・19日）

当初2020年3月22・23日を予定していたが
延期しオンラインで開催

京大－ハイデルベルク大－理研ワークショップ

医学と数理

第１回のノーベル物理学賞がレントゲンに授与されるなど、医学の進歩は物理はじめ基礎科学の応用展開なしに語れません。京都大学では、2017年に京大高等研究院（KUIAS）と理化学研究所・数理創造プログラム（iTHEMS）が共同で理研-京大数理科学研究拠点（SUURI-COOL Kyoto）をスタートさせ、2018年にはKUIASに医学物理・医工計測グローバル拠点（CiMPhy）が、さらには2019年に京大理学研究科附属サイエンス連携探索センター（SACRA）が発足しました。

このような背景のもとで、ハイデルベルク大学（独）とCiMPhyにおいて臨床医学との連携を推進している田中求教授、理研iTHEMSの初田哲男プログラムディレクター、そして京大SACRA学際融合部門長の坂上貴之教授が協力し、「第１回京大－ハイデルベルク大－理研ワークショップ「医学と数理」」を2019年の10月にSUURI-COOL Kyotoにて開催し、ここでは主に数物系の研究者が意見の交換を行いました。

第２回目となる今回の会議では、融合分野研究に取り組んでいる臨床医学と数物系の第一線の研究者がそれぞれ最新の成果報告・意見交換を行い、「臨床医学の作業仮説」→「精密計測・定量解析」→「数理モデル構築」→「臨床医学へのフィードバック」を目指したネットワークを形成することによって、第１回目の会議の成果をさらに大きく展開・発展させることを目指します。

2020年9月18日[金]・19日[土]

9時30分～（18日）・10時～（19日）

世話人

田中 求
ハイデルベルク大学教授
京都大学高等研究院
CiMPhy部門長

初田 哲男
理化学研究所
数理創造プログラム
プログラムディレクター

坂上 貴之
京都大学教授
京都大学SACRA
学際融合部門長

祝辞

森　重文
高等研究院長

湊　長博
京大総長
（当時副学長）

200人以上が登録、新たな学問の流れを生み出すハブとなる

臨床医学・数物系から多彩な講師を招聘、（臨床）医学と数物の融合研究をチームで紹介
当拠点の山本助教・鈴木助教も運営に携わるだけでなく、自身の融合研究の成果を報告

アウトリーチ・公開シンポジウム

日本化学会 CSJ化学フェスタ 特別企画「感染症と向き合う社会における化学」
花王と新学術領域で共催

招待講演

高原　淳
（九大）他

花王&新学術領域研究「水圏機能材料」
特別企画：感染症と向き合う社会における化学

企画担当：井上 雄登（花王株式会社）、田中 求（ハイデルベルク大学）、山田 泰司（花王株式会社）
担当委員：○村田 英明（株式会社島津製作所）

新型コロナウイルスがもたらした難局において、細菌やウイルスなどによる感染の脅威や不安を払拭する方法や感染の予防方法などは、今後の生活行動を考える科学基盤となります。本セッションでは、化学・生化学的な観点でこのような衛生課題に資する技術基盤や応用研究について紹介します。

日　時　10月21日（水）13:00～16:30
会　場　B会場

13:00-13:05		開会挨拶 清見 基晃（花王株式会社 衛生科学研究センター・執行役員/センター長）
13:05-13:55	B2-07	【招待講演】細菌・抗菌の物理化学：界面から読み解くケミカルの機能 田中 求（ハイデルベルク大学/京都大学・教授）
13:55-14:15	B2-08	放射光を用いたバクテリアへの抗菌剤の作用機序の解明 脇角 一平（花王株式会社 解析科学研究所・主任研究員）
14:25-14:45	B2-09	カテキン－ムチン相互作用に着目した上気道感染症の予防

化学を学ぶ大学生・化学を志す高校生向けに
「ウィルス・細菌が身体と出会う場所＝界面の物理化学」を解説

2021 年

コロナ禍のため、ほぼすべての研究会等がオンライン開催

日独6大学コンソーシアム（HeKKSaGOn Alliance）

国際交流事業

2021年9月9日・10日（オンライン開催）

新たにスタートした作業部会の世話役としてプレナリーセッションで講演

2021年HeKKSaGOn会議・講演資料から

WG1: Next-Generation Biomedical Sciences

- Fusion of Molecular Engineering, Imaging, and Modeling -

Lead Coordinator
Motomu Tanaka (Biophysics)
Institute of Physical Chemistry, Heidelberg University
Institute for Advanced Study, Kyoto University


Coordinators
Martin Bastmeyer (Neurobiology)
Zoological Institute, Karlsruhe Institute of Technology
Hiroshi Suito (Mathematics)
Advanced Institute for Materials Research, Tohoku University

若手教員のプロモーション

研究人材育成

山本暁久助教が「世界視力を備えた次世代トップ研究者育成プログラム」（L-INSIGHT）第二期フェロー（全学より7人選抜）に選出

2021年10月

http://www.l-insight.rp.kyoto-u.ac.jp/ja/fellows

社会への成果発信（1）広告記事

『現代化学』2021年9月号

水圏機能材料

シリーズ 第5回

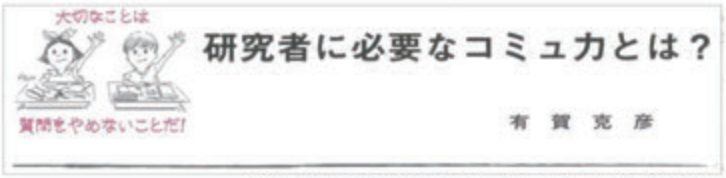
生物にならい生物を超える水圏機能材料を働かせる

新学術領域『水圏機能材料』計画研究の内容を「生物にならい生物を超える水圏機能材料を働かせる」のタイトルで紹介

研究代表者　田中　求
研究分担者　中畑雅樹（阪大基礎工）

社会への成果発信（2）インタビュー記事

『現代化学』2021年9月号



大切なことは

研究者に必要なコミュ力とは？

質問をやめないことだ！

有賀克彦

「米国の研究者はどうやってコミュニケーションをとっているですか？」

講義の結果ですね。日常的に自分の言葉で発表、討論することが講義になっています。日本語では曖昧にぼやかしてものを言うことが日常化しているので、それが科学の論文や口頭発表にも出てきます。普音相の記者会見や国会答弁を聞いていると、総合的に判断するとか、前向きに検討するとか、中身のない言葉の羅列です。僕が記者だったり議員だったりしたら具体的にはどうするの？と聞きたいですね。日本ではそんな失礼なことは聞くものではないと顰蹙を買うかも。これは日本語の「奥ゆかしい人」という観念に関係しているようです。英語ではいときは率先して質問すること、でもいつもこれを実行すると、日本では嫌がられそうです。日本の会合ではなかなか質問が出ないのはほかの人はわかって黙っているのだと思ってしまうこと、実はわからないと認めないで済むように誰かが質問してくれるのを待っている人が多いんですがね。

ドイツ・ハイデルベルグ大学の
田中 求先生

ドイツで20年以上にわたって研究生活を送ってきましたが、研究上のコミュニケーションで深刻なギャップは感じたことがありません。ただ、国民性でしょうか、いくつか違いを感じることはあります。

僕正しい・奥ゆかしいというのは日本人の優れた美徳であるので、大切にすべき部分だと思います。一方で日本の研究者、特に若手の方の講演を国際学会などで見ていて、議論が弱いという印象を受けることが多いのも事実です。「ガイジンは口（英語）が達者で得している」とかいうレベルの話ではありません。

どちらが優れているというのではなく、相手の長所を認めてうまく取入れられるといいのですが、なかなか難しいですね。

これらの意見を見ると、「受けの名手」として相手の話を聞くということだけではなく、積極的かつ具体性をもって意見を言う「攻めの姿勢」の重要性が同

国立材料科学研究機構（NIMS）有賀克彦主任研究者の連載に田中のインタビューが掲載

2022 年

日本化学会コロイド界面討論会　総合講演

2022年9月21日コロイド界面討論会
総合講演

界面から解き明かす生命現象のダイナミクス

Life as a Matter of Interface Dynamics

田中　求

ハイデルベルク大学・物理化学研究所

京都大学・高等研究院

広島大学・サタケメモリアルホール（ハイブリッド開催）
参加登録600人超（会場300名）

研究会の企画・運営

第3回
京大–ハイデルベルク大－理研
ワークショップ『医学と数理』

京大・益川ホール（ハイブリッド開催）
参加登録250人超

研究会の企画・運営

湊長博・京大総長、森重文・京大高等研究院長、小安重夫・理研理事から開会にあたって祝辞と激励をいただいた

臨床の医師はオンラインながら活発な議論が展開された

テーマ3：Medicine and Numerical Analysis - Activities in Heidelberg -

ハイデルベルク大で臨床グループと共同研究を行っている
シニア・若手研究者にオンラインで講演を依頼

Thomas Höfer

Professor
DKFZ

Infectious Disease (HBV)

Anna Marciniak Czochra

Professor
Inst. Appl. Math.

Cancer (Leukemia)

Anil Dasanna

Senior Scientist
Inst. Theor. Phys.
(now in Saarbrücken)

Infectious Disease (Malaria)

Judith Thoma

PhD student
Inst. Phys. Chem.

Cancer (Leukemia)

国際研究会の企画・運営

研究会の企画・運営

YITP Workshop
25th Anniversary Symposium of German-Japanese Joint Research Project on Nonequilibrium Statistical Physics
Perspectives for Future Collaboration

October 12 - 14, 2022
Yukawa Institute for Theoretical Physics, Kyoto University

日独「非平衡統計物理学」共同研究
25周年記念シンポジウム

Organizers
Motomu TANAKA (Heidelberg / Kyoto)
Ryoichi YAMAMOTO (Kyoto)
Masaki SANO (Shanghai / Tokyo)
Hartmut LÖWEN (Düsseldorf)
Helmut BRAND (Bayreuth)
Hisao HAYAKAWA (Kyoto)

For registration, please visit: https://www2.yukawa.kyoto-u.ac.jp/~german.japan2022/index.php

YITP　NAKATANI FOUNDATION

京大基研・パナソニックホール（ハイブリッド開催）
参加登録者７０人（うち対面での参加者50人）

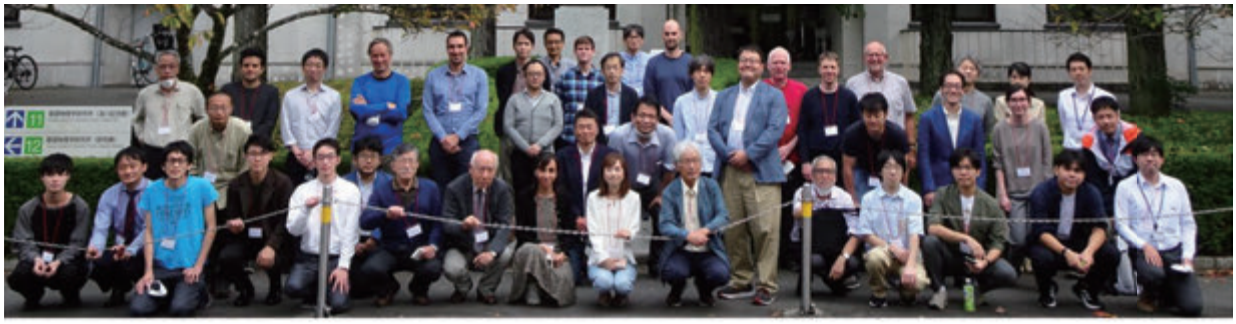

田中　求
(HD・京都)


佐野雅己
(東京・上海)


山本量一
(京都)


H. Löwen
(Düsseldorf)


H. Brand
(Bayreuth)




Brand教授の永年にわたる貢献に感謝して
記念のプレートをプレゼント


Roundtable Discussionで今後の展開計画について議論

2023 年

日独6大学コンソーシアム（HeKKSaGOn Alliance）

国際交流事業

2023年9月21日・22日（Göttingen）

HeKKSaGOn – Network of Universities

9th Japanese - German University Presidents' Conference - 21/22 September 2023

Working Group 1 の世話役としてワークショップを主催
プレナリーセッションで講演

2021年HeKKSaGOn会議・講演資料から

HeKKSaGOn NETWORK OF UNIVERSITIES

WG1: Next-Generation Biomedical Sciences

- Fusion of Molecular Engineering, Imaging, and Modeling -

Lead Coordinator
Motomu Tanaka (Biophysics)
Institute of Physical Chemistry, Heidelberg University
Institute for Advanced Study, Kyoto University

Coordinators
Martin Bastmeyer (Neurobiology)
Zoological Institute, Karlsruhe Institute of Technology
Hiroshi Suito (Mathematics)
Advanced Institute for Materials Research, Tohoku University

Pre-Workshop (Sept. 19)

Universität Heidelberg
Physikalisch-Chemisches Institut
Physikalische Chemie von Biosystemen

Prof. Dr. Motomu Tanaka

HeKKSaGOn Workshop

"New-Generation Biomedical Science"

Dr. Masaki Nakahata (Graduate School of Science, Osaka University)
Development of polymeric materials based on bio-inspired design, bio-synthetic interaction, and bio-synthetic fusion

Dr. Yuuki Fujiwara (United Graduate School of Child Development, Osaka University)
A newly identified intracellular degradation system in lysosomes and its physiological significances

Dr. Gabriel Salg (Department of Surgery, Heidelberg University Hospital)
Towards bioartificial insulin-secreting tissue: Addressing vascularization limitations by tissue and vascular network profiling

Prof. Dr. Hiroshi Suito (Advanced Institute for Materials Research, Tohoku University)
Blood Flow Problems in the Human Body

19.09.2023

13:00 – 16:30, PCI Seminarraum (2OG)

Nakahata (Bio-inspired *materials*)

Fujiwara (*Biochemistry* autophagy)

Salg (Bioprinting and multiscale *cancer imaging*)

Suito (*Mathematical model* of blood flow)

研究会の企画・運営

第４回『医学と数理』研究会

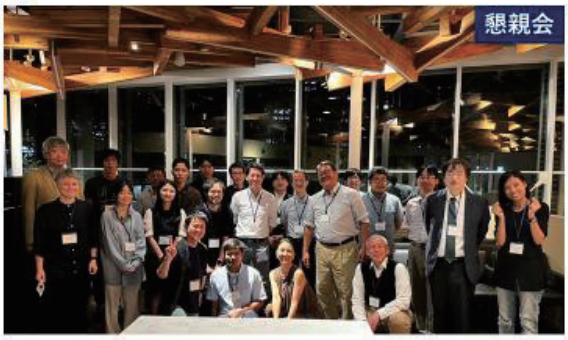
9月29日・30日

東北大・知の館（ハイブリッド開催）

参加登録約150人

研究会の企画・運営

祝辞：京大・湊総長、理研・宮園理事、東北大・小谷理事



International Session ：Medicine and Numerical Analysis

Thomas Stiehl

Professor
Mathematician, Physician

Inst. Comp. Medicine, RWTH Aachen
Leukemia

Stefan Kallenberger

Junior Group Leader
Physicist, Physician

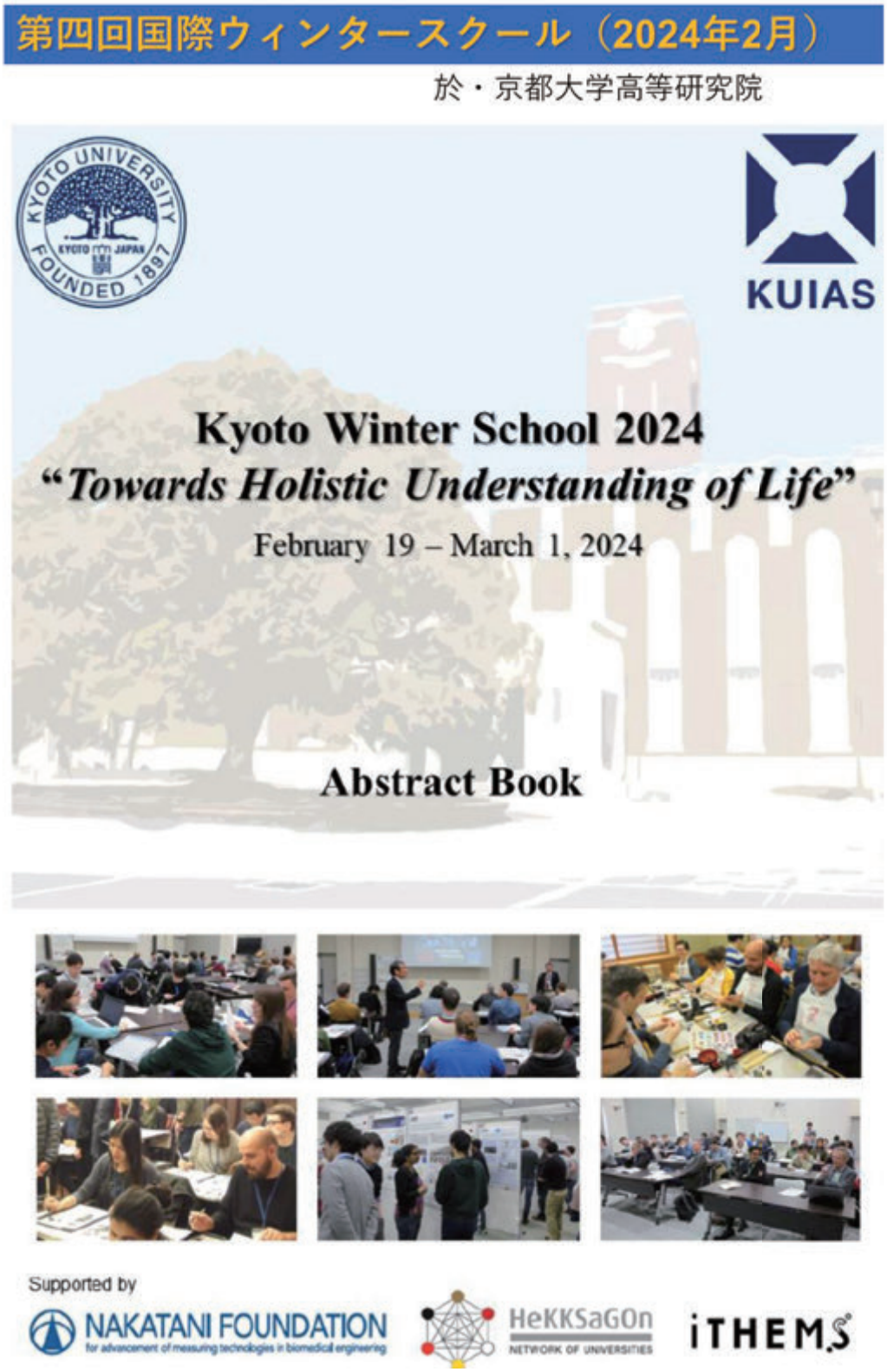
Natl. Center Tumor Research
Hepatitis B Virus

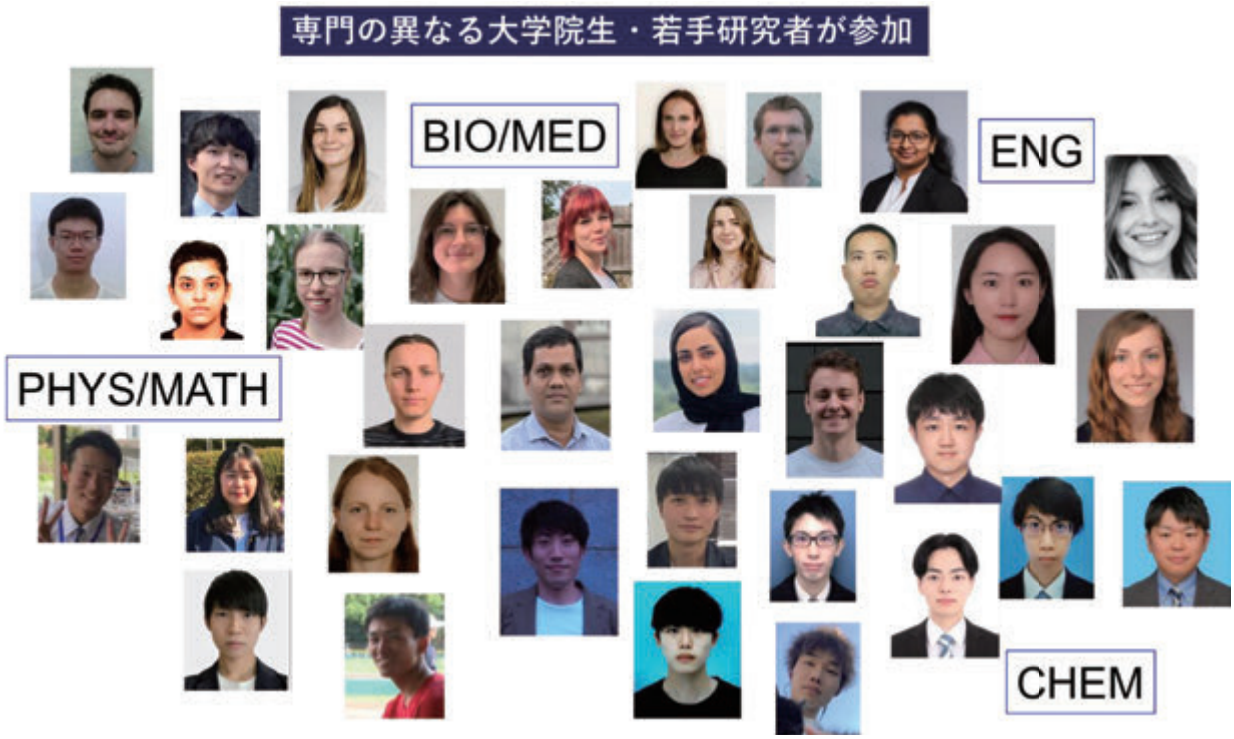
Catherine Beauchemin

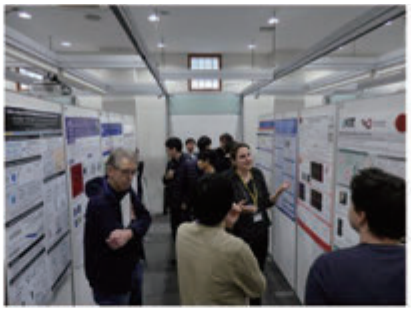
Deputy Director
Physicist

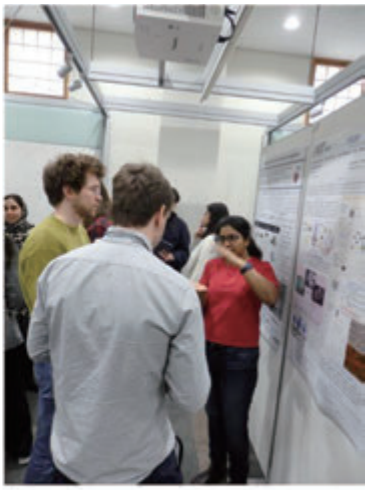
iTHEMS (on leave)
Virology modeling

2024 年


第四回国際ウィンタースクール（2024年2月）
於・京都大学高等研究院
KYOTO UNIVERSITY
KYOTO JAPAN
FOUNDED 1897
KUIAS
Kyoto Winter School 2024
"Towards Holistic Understanding of Life"
February 19 – March 1, 2024
Abstract Book
Supported by
NAKATANI FOUNDATION
for advancement of measuring technologies in biomedical engineering
HeKKSaGOn
NETWORK OF UNIVERSITIES
iTHEMS


専門の異なる大学院生・若手研究者が参加
BIO/MED
ENG
PHYS/MATH
CHEM






春

研究業績ハイライト

A. 数理解析を駆使した新たな診断技術の開拓

A1. 角膜再生医療に用いる移植用細胞（*in vitro*）の品質評価と再建角膜（*in vivo*）の予後評価を一つの数式で可能にする物理的バイオマーカーを開発

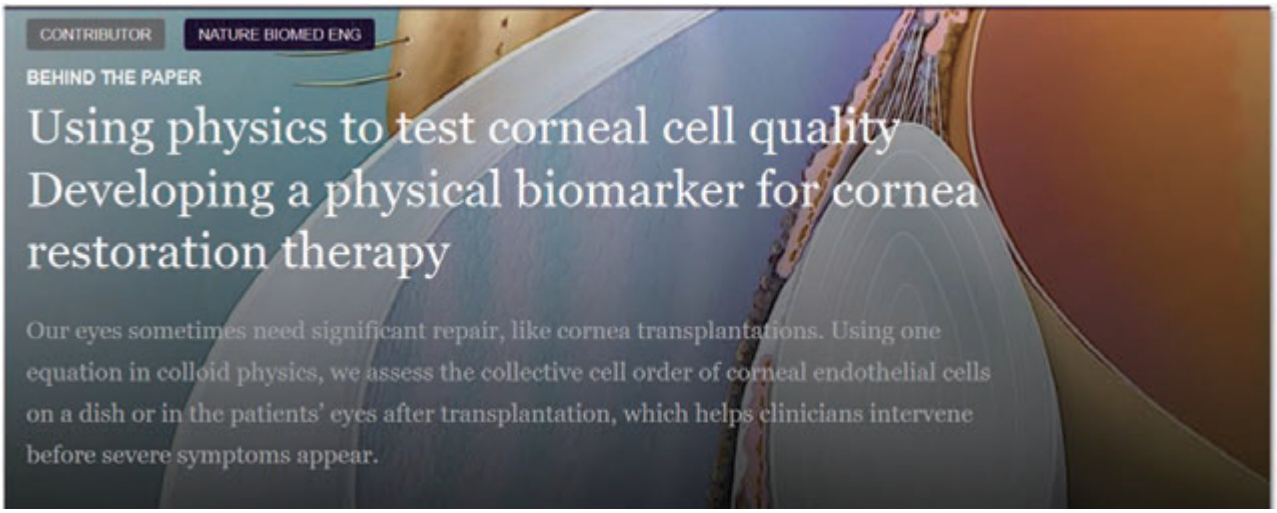
A. Yamamoto, H. Tanaka, M. Toda, C. Sotozono, J. Hamuro, S. Kinoshita, M. Ueno* and M. Tanaka*

Nature Biomedical Engineering, 3, 953–960 (2019)

京都府立医科大学眼科学教室・上野盛夫講師（拠点客員研究員）らとの共同研究

京都大学・京都府立医科大学が共同記者発表

日本経済新聞、日経サイエンス、Nature Blog などで紹介



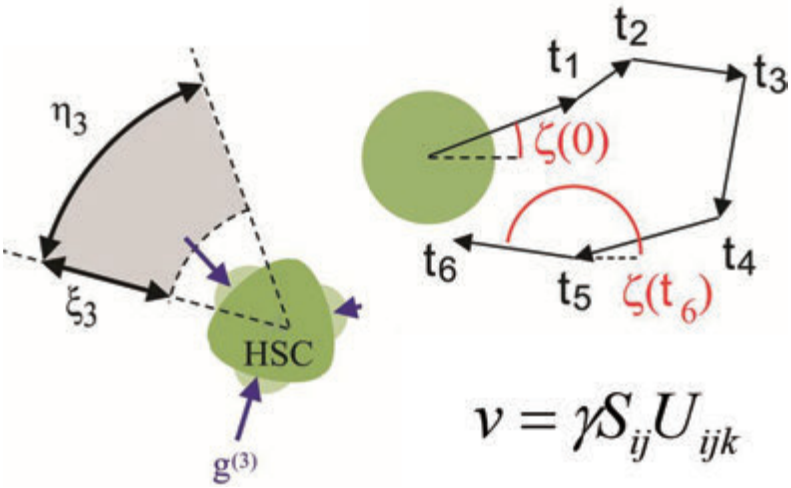
トーメーコーポレーションによりライセンス化、角膜検査装置・臨床医療として実装

A2. 患者・ドナー細胞の動態を表す指標を用いて臨床薬やケモカインの効果を数値で表す理論モデルを開発

T. Ohta, C. Monzel, A.S. Becker, A.D. Ho and M. Tanaka*

Scientific Reports, 8, 10630 (2018)

京都大学理学研究科 太田隆夫名誉教授（拠点客員教授・左）、ハイデルベルク大学病院血液内科 A.D. Ho 教授（拠点客員教授・右）との共同研究

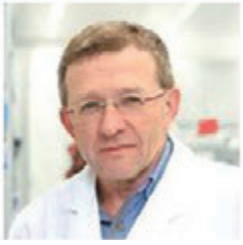


A3. 血液スメアの定量解析により、加齢による造血幹細胞の代謝を変調させることを数値的に解明

Laura Poisa-Beiro, Judith Thoma, Jonathan Landry, Sven Sauer, Akihisa Yamamoto, Volker E ckstein, Natalie Romanov, Simon Raffel, Georg F. Hoffmann, Peer Bork, Vladimir Benes, Anne-Claude Gavin, Motomu Tanaka* and Anthony D. Ho

Scientific Reports, 10, 11597 (2020)

ハイデルベルク大学病院血液内科 A.D. Ho 教授（拠点客員教授・左）、欧州分子生物学研究所 V. Benes 主任研究員（中）, A.C. Gavin 教授（右）との共同研究

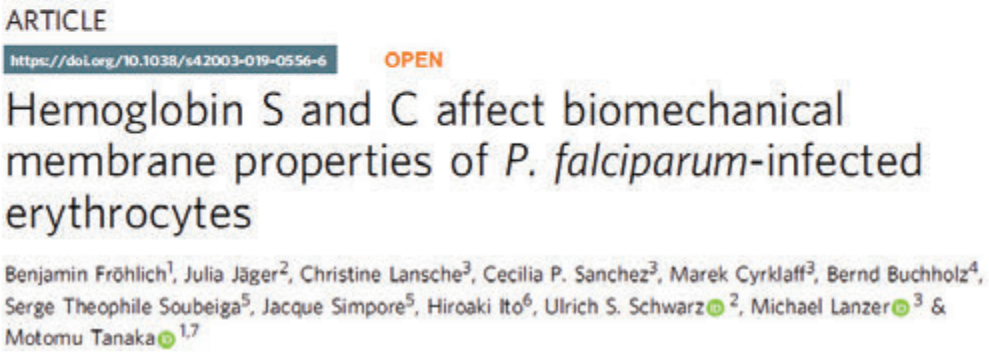




B. 新たな計測・解析技術の開拓

B1. 異常ヘモグロビン症が細胞の力学特性に与える影響を形状の熱揺らぎのフーリエ解析から解明

B. Fröhlich, J. Jäger, C. Lansche, C.P. Sanchez, M. Cyklaff, B. Buchholz, S.T. Soubeiga, J. Simpore, H. Ito, U.S. Schwarz, M. Lanzer* and M. Tanaka*

Communications Biology, 2, 311 (2019)



ハイデルベルク大学 感染症研究所 M. Lanzer 教授、
ハイデルベルク大学 理論物理学研究所 U.S. Schwarz 教授との共同研究

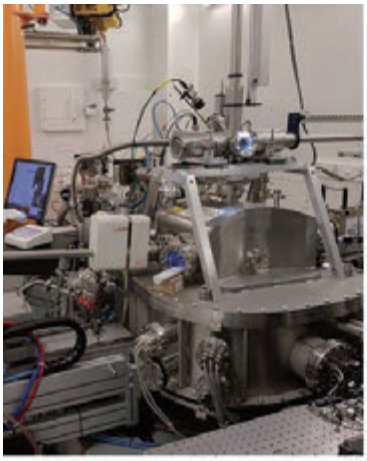
UNIVERSITÄTS KLINIKUM HEIDELBERG

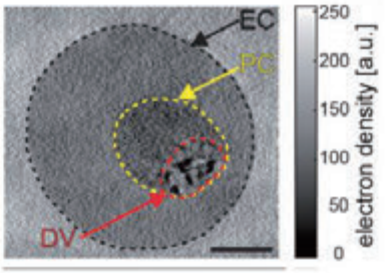
B2. 異常ヘモグロビンの持ち主がマラリアに感染しても重症化しないことと、寄生虫の生理活性の遅延の相関を放射光 X 線を用いた元素選択ナノイメージングで精密定量

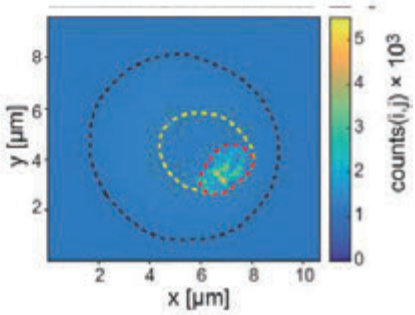
B. Fröhlich, Y. Yang, J. Thoma, J. Czajor, C. Lansche, C. Sanchez, M. Lanzer, P. Cloetens and M. Tanaka*

Analytical Chemistry, 92, 5765 – 5771 (2020)

欧州放射光機構 P. Cloetens 主任研究員、ハイデルベルク大学 感染症研究所 M. Lanzer 教授との共同研究







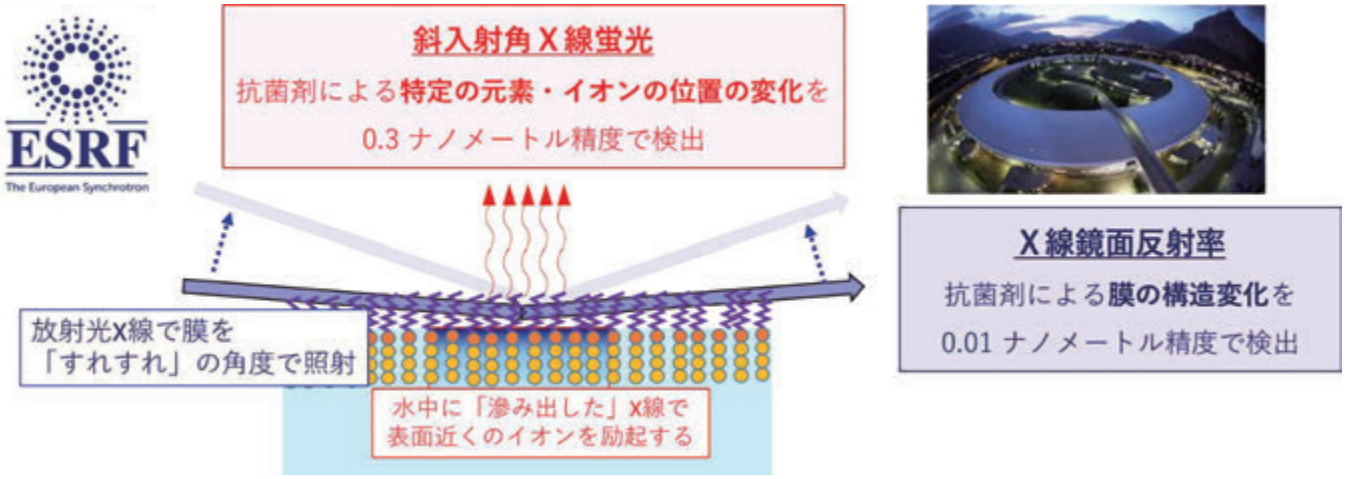
B3. カチオン性界面活性剤と芳香族アルコールの組み合わせが相乗的に抗菌作用を向上させるメカニズムを放射光 X 線を用いた超精密元素選択プロファイリングで証明

J. Thoma, W. Abuillan, I. Furikado, T. Habe, A. Yamamoto, S. Gierlich, S. Inoue and M. Tanaka*

Scientific Reports, 10, 12302 (2020)

花王解析科学研究所 井上滋登 主任研究員、欧州放射光機構 O. Konovalov 主任研究員らとの共同研究

花王ニュースリリースで発表、日刊工業新聞、週間粧業などで紹介

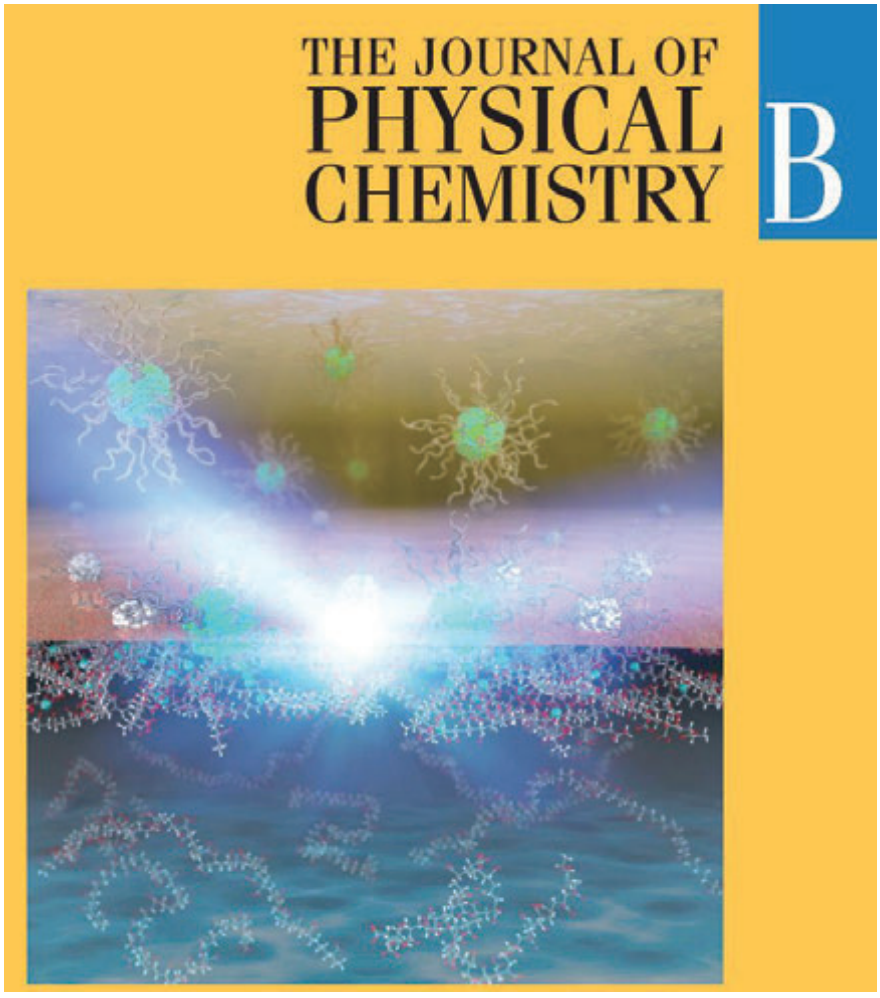


B4. 油・水界面におけるバイオマテリアルのゲル化反応をリアルタイムで計測できる高エネルギーX 線光子相関分光法の開発

Federico Amadei, Judith Thoma, Julian Czajor, Esther Kimmle, Akihisa Yamamoto, Wasim Abuillan, Oleg V. Konovalov, Yuriy Chushkin,* and Motomu Tanaka*

J. Phys. Chem. B, 124, 8937 (2020) **Cover**

欧州放射光機構 Y. Chushkin 主任研究員らとの共同研究



B5. 高解像度顕微鏡画像の解析と、ナノフォーカス X 線表面散乱、弾性率マップの組み合わせで、再生するヒドラの細胞外基質の硬さが Wnt シグナルによって制御されていることを解明

Mariam Veschgini, Ryo Suzuki, Svenja Kling, Hendrik O. Petersen, Bruno Gideon Bergheim, Wasim Abuillan, Philipp Linke, Stefan Kaufmann, Manfred Burghammer, Ulrike Engel, Frank Stein, Suat Oezbek, Thomas W. Holstein,* and Motomu Tanaka*

iScience, 26, 106416 (2023) **Supplementary Cover**

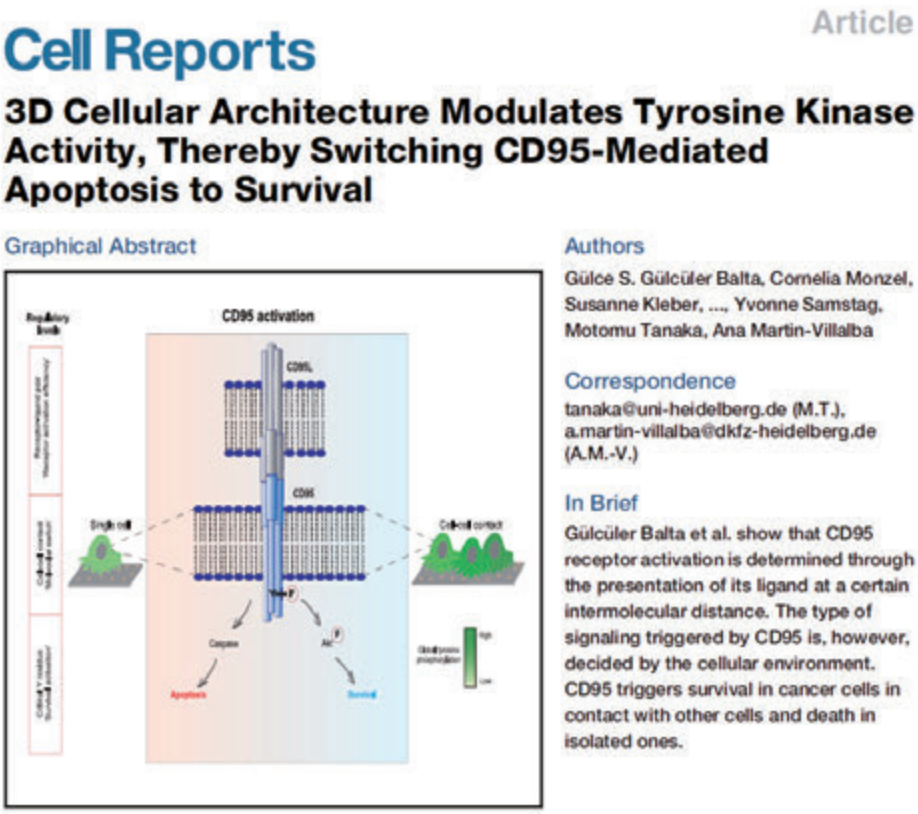
ハイデルベルク大学生命科学 T.W. Holstein 教授（拠点客員教授・左）、ハイデルベルク大学ニコンイメージングセンター U. Engel センター長（中左）、欧州放射光機構 M. Burghammer 主任研究員（右）との共同研究

C. 細胞微小環境の超精密モデルの開発

C1. CD95 によるがん細胞のアポトーシスが、隣接細胞があると逆にがんの増殖へと切り替わることを CD95 リガンドで超精密機能化した細胞表面モデルを用いて解明

G.S.G. Balta, C. Monzel, S. Kleber, J. Beadouin, E. Balta, T. Kaindl, S. Chen, M. Thiemann, C.R. Wirtz, Y. Samstag, M. Tanaka* and A. Martin-Villalba*

Cell Reports, 29, 2295 – 2306 (2019)



ドイツがん研究センター(DKFZ) A. Martin Villalba 教授らとの共同研究

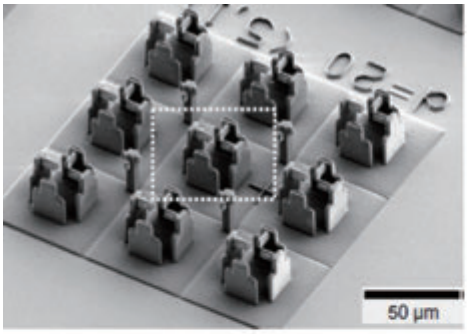
C2. 超精密 2 光子 3D レーザープリンティングと刺激応答性超分子ゲルを用いて、一細胞制御プラットフォームを創製

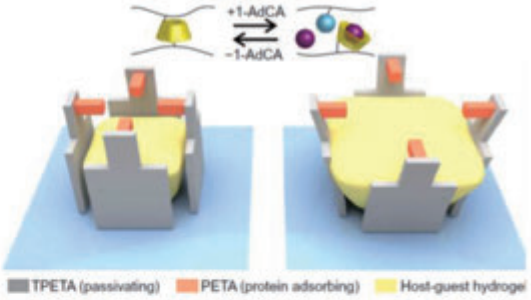
M. Hippler, W. Weißenbruch, K. Richler, E.D. Lemma, M. Nakahata, B. Richter, C. Barner-Kowolik, Y. Takashima, A. Harada, E. Blasco, M. Wegener*, M. Tanaka* and M. Bastmeyer*

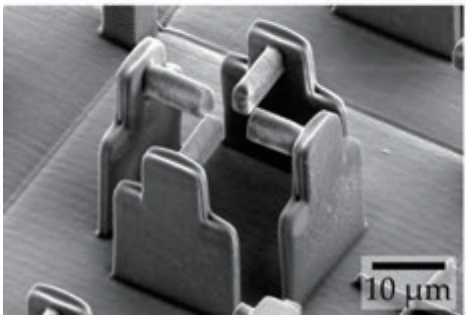
Science Advances, 6, eabc2648 (2020)

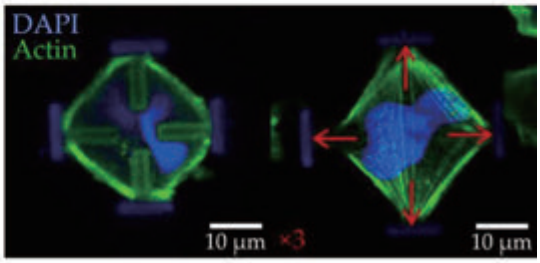
カールスルーエ工科大学 物理学 M. Wegener 教授、同生物学 M. Bastmeyer 教授（拠点客員教授）、大阪大学理学研究科 高島 義徳 教授らとの共同研究

カールスルーエ工科大学、ハイデルベルク大学、京都大学がプレスリリース









C3. 硬さをオンデマンドで制御可能な『超分子ヒドロゲル』を用いて、ヒト間葉系幹細胞が周囲の『硬さを感じる閾値』や『分化・増殖を止める力学的刺激の周波数』を解明

Philipp Linke, Natalie Munding, Esther Kimmle, Stefan Kaufmann, Kentaro Hayashi, Masaki Nakahata, Yoshinori Takashima, Masaki Sano, Martin Bastmeyer, Thomas Holstein, Sascha Dietrich, Carsten Müller-Tidow, Akira Harada, Anthony D. Ho, and Motomu Tanaka*

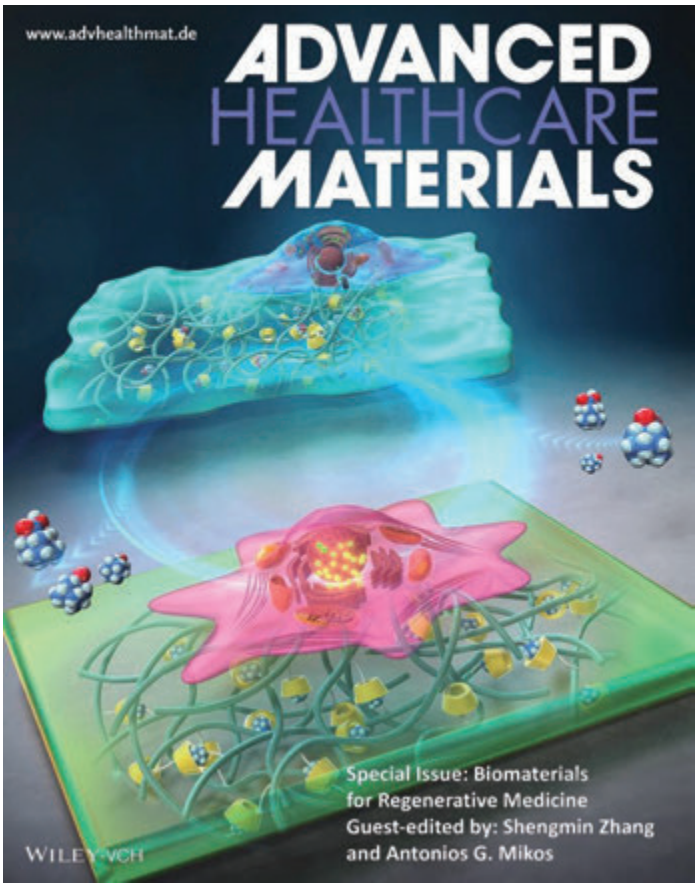
Advanced Healthcare Materials, DOI: 10.1002/adhm.202302607 **Inside Cover**

大阪大学理学研究科 高島 義徳 教授（左）、ハイデルベルク大学病院血液内科 A.D. Ho 教授（拠点客員教授・右）らとの共同研究

大阪大学 OSAKA UNIVERSITY

UNIVERSITÄTS KLINIKUM HEIDELBERG

Ibidi GmbH 社（独）が独占ライセンス化

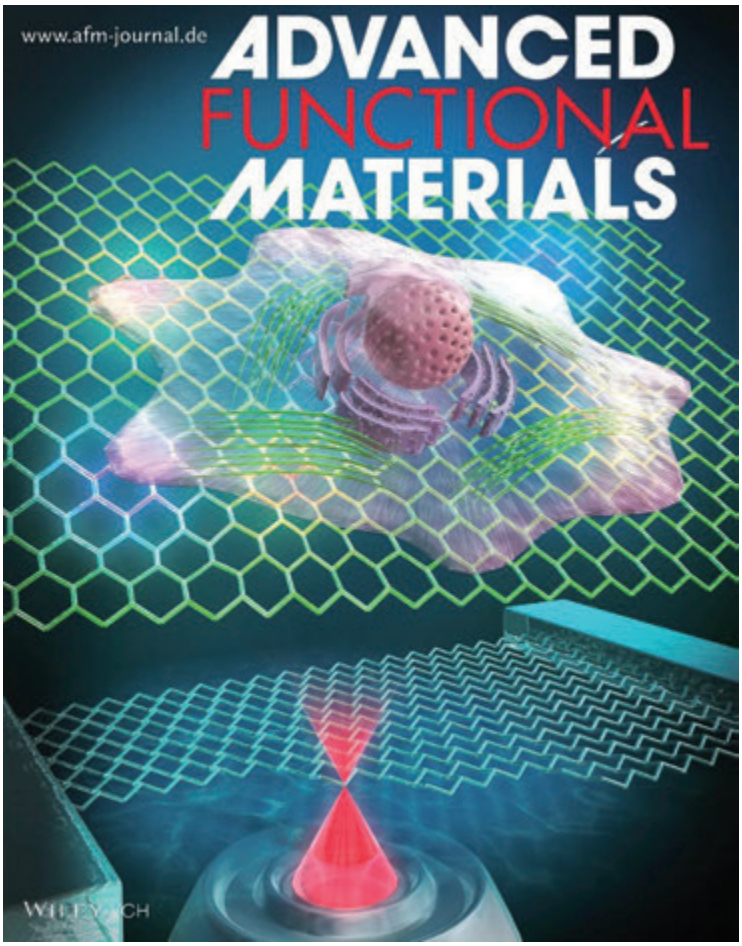


C4. 超高速 2 光子 3D レーザープリンティングを駆使した『力学的メタマテリアル』を用いて、ヒト間葉系幹細胞を力学的に制御することに成功

N. Munding, M. Fladung, Yi Chen, Marc Hippler, Anthony D. Ho, Martin Wegener,* Martin Bastmeyer,* and Motomu Tanaka*

Advanced Functional Materials, DOI: 10.1002/adfm.202301133 **Back Cover**

カールスルーエ工科大学 物理学 M. Wegener 教授、同生物学 M. Bastmeyer 教授（拠点客員教授）らとの共同研究



D. その他の新技術・新材料の開拓

D1. 厚さ数 nm の電子材料となるフラーレン単分子の水面での微細構造を X 線鏡面反射率と表面散乱技術を駆使して解明

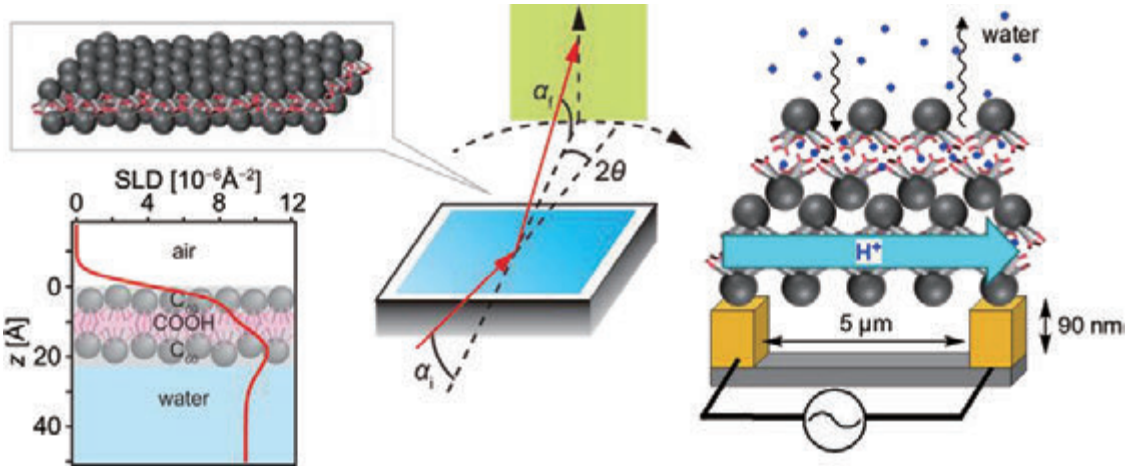
Prince Ravat, Hikaru Uchida, Ryosuke Sekine, Ko Kamei, Akihisa Yamamoto,

Oleg Konovalov, Motomu Tanaka,* Teppei Yamada,* Koji Harano,* and Eiichi Nakamura

Advanced Materials, 34, 2106465 (2022)

東京大学 中村栄一教授、原野幸治 准教授、欧州放射光機構 O. Konovalov 主任研究員らとの共同研究



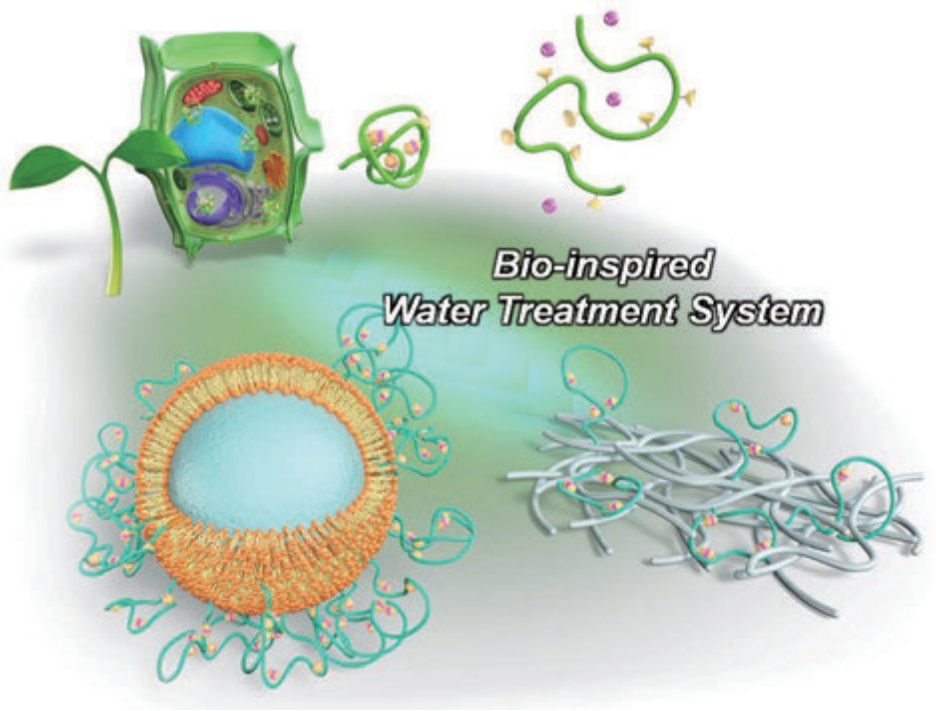


D2. 植物に着想を得た材料を超集積化することで世界記録レベルの効率で水中の重金属イオンを飲料水レベルまで浄化するシステムを開発

Masaki Nakahata*, Ai Sumiya, Yuka Ikemoto, Takashi Nakamura, Anastasia Dudin, Julius Schwieger, Akihisa Yamamoto, Shinji Sakai, Stefan Kaufmann and Motomu Tanaka*

Nature Communications, DOI: 10.1038/s41467-024-49869-8

大阪大学理学研究科・中畑雅樹助教、ハイデルベルク大学 S. Kaufmann 講師らとの共同研究



大阪大学・京都大学・ハイデルベルク大学からプレスリリース、日本経済新聞等で紹介

注：投稿は 2023 年 10 月、採択は拠点終了後の 2024 年 6 月

発表論文リスト

2018 年

1. W. Abuillan, A. S. Becker, B. Demé, T. Homma, H. Isobe, K. Harano*, E. Nakamura* and **M. Tanaka***
"Neutron Scattering Reveals Water Confined in a Watertight Bilayer Vesicle"

J. Am. Chem. Soc. 140, 11261–11266 (2018).

2. **T. Ohta***, C. Monzel, A. S. Becker, **A. D. Ho** and **M. Tanaka***
"Simple physical model unravels influences of chemokine on shape deformation and migration of human hematopoietic stem cells"

Sci. Rep. 8, 10630 (2018).

3. C. Monzel, A. S. Becker, R. Saffrich, P. Wuchter, V. Eckstein, **A. D. Ho*** and **M. Tanaka***
"Dynamic cellular phenotyping defines specific mobilization mechanisms of human hematopoietic stem and progenitor cells induced by SDF1α versus synthetic agents"

Sci. Rep. 8, 1841 (2018).

4. F. Amadei, B. Fröhlich, W. Stremmel and **M. Tanaka***
"Nonclassical Interactions of Phosphatidylcholine with Mucin Protect Intestinal Surfaces: A Microinterferometry Study"

Langmuir 34, 14046–14057 (2018).

5. M. Tsuchiya, Y. Hara*, M. Okuda, K. Itoh, R. Nishioka, A. Shiomi, K. Nagao, M. Mori, Y. Mori, J. Ikenouchi, **R. Suzuki**, **M. Tanaka**, T. Ohwada, J. Aoki, M. Kanagawa, T. Toda, Y. Nagata, R. Matsuda, Y. Takayama, M. Tominaga and M. Umeda*
"Cell surface flip-flop of phosphatidylserine is critical for PIEZO1-mediated myotube formation"

Nat. Commun. 9, 2049 (2018).

6. L. Yu, J. Li, J. Hong, Y. Takashima, N. Fujimoto, M. Nakajima, **A. Yamamoto**, X. Dong, Y. Dang, Y. Hou, W. Yang, I. Minami, K. Okita, **M. Tanaka**, C. Luo, F. Tang, Y. Chen, C. Tang, H. Kotera and L. Liu*
"Low Cell-Matrix Adhesion Reveals Two Subtypes of Human Pluripotent Stem Cells"

Stem Cell Rep. 11, 142 (2018).

7. C. Lansche, A. K. Dasanna, K. Quadt, B. Fröhlich, D. Missirlis, M. Tétard, B. Gamain, B. Buchholz, C. P. Sanchez, **M. Tanaka**, U. S. Schwarz* and M. Lanzer*
"The sickle cell trait affects contact dynamics and endothelial cell activation in *Plasmodium falciparum*-infected erythrocytes"

Commun. Biol. 1, 211 (2018).

8. M. Lamas-Murua, B. Stolp, S. Kaw, J. Thoma, N. Tsopoulidis, B. Trautz, I. Ambiel, T. Reif, S. Arora, A. Imle, N. Tibroni, J. Wu, G. Cui, J. V. Stein, **M. Tanaka**, R. Lyck and O. T. Fackler
"HIV-1 Nef Disrupts $CD4^+$ T Lymphocyte Polarity, Extravasation, and Homing to Lymph Nodes via Its Nef-Associated Kinase Complex Interface"

J. Immunol. 201, 2731–2743 (2018).

9. S. Masuda, S. Mielke, F. Amadei, **A. Yamamoto**, P. Wang, T. Taniguchi, **K. Yoshikawa**, K. Tamada* and **M. Tanaka***
"Nonlinear Viscoelasticity of Highly Ordered, Two-Dimensional Assemblies of Metal Nanoparticles Confined at the Air/Water Interface"

Langmuir 34, 13025–13034 (2018).

10. J. Massiot, V. Rosilio, N. Ibrahim, **A. Yamamoto**, V. Nicolas, O. Konovalov, **M. Tanaka** and A. Makky*
"Newly Synthesized Lipid-Porphyrin Conjugates: Evaluation of Their Self-Assembling Properties, Their Miscibility with Phospholipids and Their Photodynamic Activity In Vitro"

Chem. A Eur. J. 24, 19179–19194 (2018).

11. H. Sakuta, S. Seo, S. Kimura, M. Hörning, K. Sadakane, T. Kenmotsu, **M. Tanaka** and **K. Yoshikawa***
"Optical Fluid Pump: Generation of Directional Flow via Microphase Segregation/ Homogenization"

J. Phys. Chem. Lett. 9, 5792–5796 (2018).

12. M. Eshrati, F. Amadei, T. van de Wiele, M. Veschgini, S. Kaufmann and **M. Tanaka***
"Biopolymer-Based Minimal Formulations Boost Viability and Metabolic Functionality of Probiotics Lactobacillus rhamnosus GG through Gastrointestinal Passage"

Langmuir 34, 11167–11175 (2018).

13. I. A. Pavel, M. Giradon, S. El Hajj, S. Parant, F. Amadei, S. Kaufmann, **M. Tanaka**, V. Fierro, A. Celzard, N. Canilho and A. Pasc*
"Lipid-coated mesoporous silica microparticles for controlled delivery of β-galactosidase into intestine"

J. Mater. Chem. B 6, 5633–5639 (2018).

14. L. Huber, **R. Suzuki**, T. Krüger, E. Frey* and A. R. Bausch*
"Emergence of coexisting ordered states in active matter systems"

Science 361, 255–258 (2018).

15. S. Mielke, T. Habe, M. Veschgini, X. Liu, **K. Yoshikawa**, M. P. Krafft* and **M. Tanaka***
"Emergence of Strong Nonlinear Viscoelastic Response of Semifluorinated Alkane Monolayers"

Langmuir 34, 2489–2496 (2018).

16. **K. Hayashi**, T. S. Yamamoto and N. Ueno*
"Intracellular calcium signal at the leading edge regulates mesodermal sheet migration during *Xenopus* gastrulation"

Sci. Rep. 8, 2433 (2018).

17. X. Fan, A. Korytowski, A. Makky, **M. Tanaka** and M. Wink*
"Ib-AMP4 insertion causes surface rearrangement in the phospholipid bilayer of biomembranes: Implications from quartz-crystal microbalance with dissipation"

Biochim. Biophys. Acta (BBA) – Biomembranes 1860, 617–623 (2018).

18. S. Mehlhose, N. Frenkel, H. Uji, S. Hölzel, G. Müntze, D. Stock, S. Neugebauer, A. Dadgar, W. Abuillan, M. Eickhoff*, S. Kimura* and **M. Tanaka***
"Flexible Modulation of Electronic Band Structures of Wide Band Gap GaN Semiconductors Using Bioinspired, Nonbiological Helical Peptides"

Adv. Funct. Mater. 28, 1704034 (2018).

19. X. Liu, S. Mielke, C. Contal, D. Favier, **A. Yamamoto**, **M. Tanaka** and M. P. Krafft*
"2D Spherulites of a Semi-Fluorinated Alkane: Controlled Access to Either Radial Or Ring-Banded Morphologies"

Chem. Phys. Chem. 19, 29–33 (2018).

2019 年

20. **A. Yamamoto**, H. Tanaka, M. Toda, C. Sotozono, J. Hamuro, S. Kinoshita, M. Ueno* and **M. Tanaka***
"A physical biomarker of the quality of cultured corneal endothelial cells and of the long-term prognosis of corneal restoration in patients"

Nat. Biomed. Eng. 3, 953–960 (2019).

21. B. Fröhlich, J. Jäger, C. Lansche, C. P. Sanchez, M. Cyrklaff, B. Buchholz, S. T. Soubeiga, J. Simpore, H. Ito, U. S. Schwarz*, M. Lanzer* and **M. Tanaka***
"Hemoglobin S and C affect biomechanical membrane properties of *P. falciparum*-infected erythrocytes"

Commun. Biol. 2, 311 (2019).

22. P. Linke, **R. Suzuki**, **A. Yamamoto**, M. Nakahata, M. Kengaku, T. Fujiwara, T. Ohzono and **M. Tanaka***
"Dynamic Contact Guidance of Myoblasts by Feature Size and Reversible Switching of Substrate Topography: Orchestration of Cell Shape, Orientation, and Nematic Ordering of Actin Cytoskeletons"

Langmuir 35, 7538–551 (2019).

23. **M. Tanaka**, F. Brochard-Wyart, F. M. Winnik and A. Takahara
"Preface to the Interfaces and Biology: Mechanobiology Special Issue"

Langmuir 35, 7333–7334 (2019).

24. G. S. G. Balta, C. Monzel, S. Kleber, J. Beaudouin, T. Kaindl, M. Thiemann, C. R. Wirtz, **M. Tanaka*** and A. Martin-Villalba*
"3D cellular architecture modulates tyrosine kinase activity thereby acting as a switch between CD95 mediated apoptosis and survival in cancer"

Cell Rep. 29, 2295–2306 (2019).

25. T. Bentele, F. Amadei, E. Kimmle, M. Veschgini, P. Linke, M. S. Gonzales, J. Tennigkeit, **A. D. Ho**, S. Özbek* and **M. Tanaka***
"New Class of Crosslinker-Free Nanofiber Biomaterials from Hydra Nematocyst Proteins"

Sci. Rep. 9, 19116 (2019).

26. M. Eshrati, F. Amadei, S. Staffer, W. Stremmel and **M. Tanaka***
"Shear-Enhanced Dynamic Adhesion of Lactobacillus rhamnosus GG on Intestinal Epithelia: Correlative Effect of Protein Expression and Interface Mechanics"

Langmuir 35, 529–537 (2019).

27. H. Tanaka, **A. Yamamoto**, M. Toda, C. Sotozono, J. Hamuro, S. Kinoshita, M. Ueno* and **M. Tanaka***
"A Non-Invasive Physical Biomarker for Evaluation of Corneal Endothelial Cells"

Invest. Ophth. Vis. Sci. 60, 2156 (2019).

28. **M. Tanaka***
"In Vitro Dynamic Phenotyping for Testing Novel Mobilizing Agents"

In: Klein G., Wuchter P. (eds) ***Stem Cell Mobilization*** pp11-27.

Methods in Molecular Biology, vol. 2017. Humana, New York (2019).

29. S. Mielke, W. Abuillan, M. Veschgini, X. Liu, O. Konovalov, M. P. Krafft* and **M. Tanaka***
"Influence of perfluorohexane-enriched atmosphere on the viscoelasticity and structural order of self-assembled nanodomains of semifluorinated alkanes at the air/water interface"

Chem. Phys. Chem. 20, 1698–1705 (2019).

30. H. Umeshima, K. Nomura, S. Yoshikawa, M. Hörning, **M. Tanaka**, S. Sakuma, F. Arai, M. Kaneko and M. Kengaku*
"Local traction force in the proximal leading process triggers nuclear translocation during neuronal migration"

Neurosci. Res. 142, 38–48 (2019).

31. C. Y. Falco, F. Amadei, S. K. Dhayal, M. Cárdenas, **M. Tanaka** and J. Risbo*
"Hybrid Coating of Alginate Microbeads based on Protein-Biopolymer Multilayers for Encapsulation of Probiotics"

Biotechnol. Progr. 35, e2806 (2019).

32. W. Abuillan, M. Veschgini, S. Mielke, **A. Yamamoto**, X. Liu, O. Konovalov, M. P. Krafft* and **M. Tanaka***

"Long-Range Lateral Correlation between Self-Assembled Domains of Fluorocarbon-Hydrocarbon Tetrablocks by Quantitative GISAXS"

Chem. Phys. Chem. 20, 898–904 (2019).

33. M. Hippler, E. Blasco, J. Qu, **M. Tanaka**, C. Barner-Kowollik, M. Wegener* and **M. Bastmeyer***
"Controlling the Shape of 3D Microstructures by Temperature and Light"

Nat. Commun. 10, 232 (2019).

2020 年

34. M. Hippler, K. Weißenbruch, K. Richler, E. D. Lemma, M. Nakahata, B. Richter, C. Barner-Kowollik, Y. Takashima, A. Harada, E. Blasco, M. Wegener*, **M. Tanaka*** and **M. Bastmeyer***
"Mechanical stimulation of single cells by reversible host-guest interactions in 3D microscaffolds"

Sci. Adv. 6, eabc2648 (2020).

35. B. Fröhlich, Y. Yang, J. Thomas, J. Czajor, C. Lansche, C. Sanchez, M. Lanzer, P. Cloetens* and **M. Tanaka***
"Nano-Focused Scanning X-ray Fluorescence Microscopy Reveals an Effect of Hemoglobin S and C on Biochemical Activities in *P. falciparum*-Infected Erythrocytes"

Anal. Chem. 92, 5765–5771 (2020).

36. F. Amadei, J. Thoma, J. Czajor, E. Kimmle, **A. Yamamoto**, W. Abuillan, O. V. Konovalov, Y. Chushkin* and **M. Tanaka***
"Ion-Mediated Cross-linking of Biopolymers Confined at Liquid/Liquid Interfaces Probed by In Situ High-Energy Grazing Incidence X-ray Photon Correlation Spectroscopy"

J. Phys. Chem. B 124, 8937–8942 (2020).

37. J. Thoma, W. Abuillan, I. Furikado, T. Habe, **A. Yamamoto**, S. Gierlich, S. Kaufmann, K. Brandenburg, T. Gutsmann, O. Konobalov, S. Inoue* and **M. Tanaka***
"Specific localisation of ions in bacterial membranes unravels physical mechanism of effective bacteria killing by sanitizer"

Sci. Rep. 10, 12302 (2020).

38. L. Poisa-Beiro, J. Thoma, J. Landry, S. Sauer, **A. Yamamoto**, V. Eckstein, N. Romanov, S. Raffel, G. F. Hoffmann, P. Bork, V. Benes, A. C. Gavin, **M. Tanaka*** and **A. D. Ho***
"Glycogen accumulation, central carbon metabolism, and aging of hematopoietic stem and progenitor cells"

Sci. Rep. 10, 11597 (2020).

39. **M. Tanaka***, M. Nakahata*, P. Linke and S. Kaufmann

"Stimuli-responsive hydrogels as a model of the dynamic cellular micro-environment"

Polymer J. 52, 861–870 (2020).

40. **M. Tanaka***
"Interplays of Interfacial Forces Modulate Structure and Function of Soft and Biological Matters in Aquatic Environments"

Front. Chem. 8, 165 (2020).

41. **M. Tanaka** and H. Seto
"Interfacial Water: A Physical Chemistry Perspective"

Front. Chem. 8, 760 (2020).

42. S. Mielke, X. Liu, M. P. Krafft and **M. Tanaka***
"Influence of Semifluorinated Alkane Surface Domains on Phase Behavior and Linear and Nonlinear Viscoelasticity of Phospholipid Monolayers"

Langmuir 36, 781–788 (2020).

43. R. Kubota, M. Makuta, **R. Suzuki**, M. Ichikawa, **M. Tanaka** and I. Hamachi*
"Force generation by a propagating wave of supramolecular nanofibers"

Nat. Commun. 11, 3541 (2020).

2021 年

44. A. Shiomi, K. Nagao*, N. Yokota, M. Tsuchiya, U. Kato, N. Juni, Y. Hara, M. X. Mori, Y. Mori, K. Ui-Tei, M. Murate, T. Kobayashi, Y. Nishino, A. Miyazawa, **A. Yamamoto**, **R. Suzuki**, S. Kaufmann, **M. Tanaka**, K. Tatsumi, K. Nakabe, H. Shintaku, S. Yesylevsky, M. Bogdanov and M. Umeda*
"Extreme deformability of insect cell membranes is governed by phospholipid scrambling"

Cell Rep. 35, 109219 (2021).

45. J. Czajor, W. Abuillan, D. V. Nguyen, C. Heidebrecht, E. A. Mondarte, O. V. Konovalov, T. Hayashi, D. Felder-Flesch, S. Kaufmann and **M. Tanaka***
"Dendronized oligoethylene glycols with phosphonate tweezers for cell-repellent coating of oxide surfaces: coarse-scale and nanoscopic interfacial forces"

RSC Adv. 11, 17727–17733 (2021).

46. G. Sedlmeier, V. Al-Rawi, J. Buchert, K. Yserentant, M. Rothley, A. Steshina, S. Gräßle, R. L. Wu, T. Hurrle, W. Richer, C. Decraene, W. Thiele, J. Utikal, W. Abuillan, **M. Tanaka**, D. P. Herten, C. S. Hill, B. K. Garvalov, N. Jung, S. Bräse and J. P. Sleeman*
"Id1 and Id3 Are Regulated Through Matrix-Assisted Autocrine BMP Signaling and Represent Therapeutic Targets in Melanoma"

Adv. Ther. 4, 2000065 (2021).

47. **M. Tanaka*** and **A. Yamamoto**
"Physical Concepts Toward Cell-Material Integration"

Cell-Inspired Materials and Engineering, *Fundamental Biomedical Technologies*, 199–215, *Springer* (2021).

48. E. Sackmann* and **M. Tanaka***
"Critical role of lipid membranes in polarization and migration of cells: a biophysical view"

Biophys. Rev. 13, 123–138 (2021).

49. B. Fröhlich, A. Dsassana, C. Lansche, J. Czajor, C. Sanchez, M. Cyrklaff, **A. Yamamoto**, A. Craig, U. S. Schwarz*, M. Lanzer* and **M. Tanaka***

"Functionalized supported membranes for quantifying adhesion of *P. falciparum*-infected erythrocytes"

Biophys. J. 120, 3315–3328 (2021).

50. B. Kav, B. Demé, C. Gege, **M. Tanaka**, E. Schneck* and T. R. Weikl*
"Interplay of *Trans*- and *Cis*-Interactions of Glycolipids in Membrane Adhesion"

Front. Mol. Biosci. 8, 754654 (2021).

2022 年

51. **A. Yamamoto**, Y. Higaki, J. Thoma, E. Kimmle, R. Ishige, B. Demé, A. Takahara* and **M. Tanaka***
"Water modulates the lamellar structure and interlayer correlation of poly(perfluorooctyl acrylate) films: a specular and off-specular neutron scattering study"

Polym. J. 54, 57–65 (2022).

52. P. Ravat, H. Uchida, R. Sekine, K. Kamei, **A. Yamamoto**, O. Konovalov, **M. Tanaka***, T. Yamada*, K. Harano*, E. Nakamura*
"De Novo Synthesis of Free-Standing Flexible 2-D Intercalated Nanofilm Uniform over Tens of cm^2"

Adv. Mater. 34, 2106465 (2022).

53. L. He, C. Arnold, J. Thoma, C. Rohde, M. Kholmatov, S. Garg, C. -C. Hsiao, L. Viol, K. Zhang, R. Sun, C. Schmidt, M. Janssen, T. MacRae, K. Huber, C. Thiede, J. Hébert, G. Sauvageau, J. Spratte, H. Fluhr, G. Aust, C. Müller-Tidow, C. Niehrs, G. Pereira, J. Hamann, **M. Tanaka**, J. B. Zaugg and C. Pabst*
"CDK7/12/13 inhibition targets an oscillating leukemia stem cell network and synergizes with venetoclax in acute myeloid leukemia"

EMBO Mol. Med. 14, e14990 (2022).

54. L. Poisa-Beiro, J. J. M. Landry, S. Raffel, **M. Tanaka**, J. Zaugg, A. -C. Gavin and **A. D. Ho***
"Glucose Metabolism and Aging of Hematopoietic Stem and Progenitor Cells"

Int. J. Mol. Sci. 23, 3028 (2022).

55. **K. Hayashi**, M. Matsuda, N. Mitake, M. Nakahata, N. Munding, A. Harada, S. Kaufmann, Y. Takashima* and **M. Tanaka***
"One-Step Synthesis of Gelatin-Conjugated Supramolecular Hydrogels for Dynamic Regulation of Adhesion Contact and Morphology of Myoblasts"

ACS Appl. Polym. Mater. 4, 2595–2603 (2022).

56. C. Schreiber, A. Gruber, S. Roßwag, S. Saraswati, S. Harkins, W. Thiele, Z. H. Foroushani, N. Munding, A. Schmaus, M. Rothley, A. Dimmler, **M. Tanaka**, B. K. Garvalov* and J.

P. Sleeman*
"Loss of ASAP1 in the MMTV-PyMT model of luminal breast cancer activates AKT, accelerates tumorigenesis, and promotes metastasis"

Cancer Lett. 533, 215600 (2022).

57. M. Ueno, M. Toda, K. Numa, H. Tanaka, K. Imai, J. Bush, S. Teramukai, N. Okumura, N. Koizumi, **A. Yamamoto**, **M. Tanaka**, C. Sotozono, J. Hamuro and S. Kinoshita*
"Superiority of Mature Differentiated Cultured Human Corneal Endothelial Cell Injection Therapy for Corneal Endothelial Failure"

Am. J. Ophthalmol. 237, 267–277 (2022).

58. T. Kimura, T. Aoyama, M. Nakahata, Y. Takashima, **M. Tanaka**, A. Harada and K. Urayama*
"Time–strain inseparability in multiaxial stress relaxation of supramolecular gels formed *via* host–guest interactions"

Soft Matter 18, 4953–4962 (2022).

59. **A. Yamamoto**, **K. Hayashi**, A. Sumiya, F. Weissenfeld, S. Hinatsu, W. Abuillan, M. Nakahata* and **M. Tanaka***
"Modulation of viscoelasticity and interfacial potential of polyelectrolyte brush by Ion-specific interactions"

Front. Soft Matter 2, 959542 (2022).

60. **M. Tanaka** and M. Lanzer*
"Receptor-Functionalized Lipid Membranes as Biomimetic Surfaces for Adhesion of Plasmodium falciparum-Infected Erythrocytes"

Malaria Immunology: Targeting the Surface of Infected Erythrocytes, 601–613, *Springer Protocols* (2022).

61. **A. Yamamoto***, T. Ikarashi, T. Fukuma, **R. Suzuki**, M. Nakahata, K. Miyata* and **M. Tanaka***
"Ion-specific nanoscale compaction of cysteine-modified poly(acrylic acid) brushes revealed by 3D scanning force microscopy with frequency modulation detection"

Nanoscale Adv. 4, 5027–5036 (2022).

62. **K. Hayashi**, M. Matsuda, M. Nakahata, Y. Takashima* and **M. Tanaka***
"Stimulus-Responsive, Gelatin-Containing Supramolecular Nanofibers as Switchable 3D Microenvironments for Cells"

Polymers 14, 4407 (2022).

63. E. Kimmle, Z. H. Foroushani, S. Keppler, J. Thoma, **K. Hayashi**, **A. Yamamoto**, **M. Bastmeyer** and **M. Tanaka***
"Discreteness of cell–surface contacts affects spatio-temporal dynamics, adhesion, and proliferation of mouse embryonic stem cells"

Front. Phys. 10, 1052106 (2022).

2023 年

64. F. Weissenfeld, L. Wesenberg, M. Nakahata, M. Müller and **M. Tanaka***
"Modulation of wetting of stimulus responsive polymer brushes by lipid vesicles: experiments and simulations"

Soft Matter 19, 2491–2504 (2023).

65. M. Veschgini, **R. Suzuki**, S. Kling, H. O. Petersen, B. G. Bergheim, W. Abuillan, P. Linke, S. Kaufmann, M. Burghammer, U. Engel, F. Stein, Suat Özbek, **T. W. Holstein***, and **M. Tanaka***
"Wnt/β-catenin signaling induces axial elasticity patterns of Hydra extracellular matrix"

iScience 26, 106416 (2023).

66. **M. Tanaka***, M. P. Krafft and A. Pasc
"Higher-order mesoscopic self-assembly of fluorinated surfactants on water surfaces"

NPG Asia Mater. 15, 23 (2023).

67. R. Link, K. Weißenbruch, **M. Tanaka**, **M. Bastmeyer*** and U. S. Schwarz*
"Cell Shape and Forces in Elastic and Structured Environments: From Single Cells to Organoids"

Adv. Funct. Mater. 34, 2302145 (2023).

68. **M. Tanaka***, J. Thoma, L. Poisa-Beiro, P. Wuchter, V. Eckstein, S. Dietrich, C. Pabst, C. Müller-Tidow, **T. Ohta**, **A. D. Ho***
"Physical biomarkers for human hematopoietic stem and progenitor cells"

Cells Dev. 174, 203845 (2023).

69. I. Furikado, T. Habe, S. Inoue* and **M. Tanaka***
"Thermodynamics and Viscoelastic Property of Interface Unravel Combined Functions of Cationic Surfactant and Aromatic Alcohol against Gram-Negative Bacteria"

Langmuir 39, 8523–8531 (2023).

70. N. Munding, M. Fladung, Y. Chen, M. Hippler, **A. D. Ho**, M. Wegener*, **M. Bastmeyer*** and **M. Tanaka***
"Bio-Metamaterials for Mechano-Regulation of Mesenchymal Stem Cells"

Adv. Funct. Mater. 34, 2301133 (2023).

71. P. Zhang, M. Maruoka, **R. Suzuki**, H. Katani, Y. Dou, D. M. Packwood, H. Kosako, **M. Tanaka** and J. Suzuki*
"Extracellular calcium functions as a molecular glue for transmembrane helices to activate the scramblase Xkr4"

Nat. Commun. 14, 5592 (2023).

72. J. Risbo*, T. Nylander* and **M. Tanaka***
"Delivery of probiotics and enzymes in self-assemblies of lipids and biopolymers based on colloidal principles"

Front. Soft Matter 3, 1257688 (2023).

73. T. Serizawa*, S. Yamaguchi, K. Sugiura, R. Marten, **A. Yamamoto**, Y. Hata, T. Sawada, H. Tanaka and **M. Tanaka**
"Antibacterial Synthetic Nanocelluloses Synergizing with a Metal-Chelating Agent"

ACS Appl. Bio. Mater. 7, 246–255 (2023).

74. M. K. Saghafi, S. K. Vasantham, N. Hussain, G. Mathew, F. Colombo, B. Schamberger, E. Pohl, G. C. Marques, B. Breitung, **M. Tanaka**, **M. Bastmeyer**, C. Selhuber-Unkel, U. Schepers, M. Hirtz* and J. Aghassi-Hagmann*
"Printed Electronic Devices and Systems for Interfacing with Single Cells up to Organoids"

Adv. Funct. Mater. 34, 2308613 (2023).

2024 年

75. P. Linke, N. Munding, E. Kimmle, S. Kaufmann, **K. Hayashi**, M. Nakahata, Y. Takashima, M. Sano, **M. Bastmeyer**, **T. Holstein**, S. Dietrich, C. Müller-Tidow, A. Harada, **A. D. Ho** and **M. Tanaka***
"Reversible Host–Guest Crosslinks in Supramolecular Hydrogels for On-Demand Mechanical Stimulation of Human Mesenchymal Stem Cells"

Adv. Healthc. Mater. 13, 2302607 (2024).

76. M. Wang*, M. Kono, Y. Yamaguchi, J. Islam, S. Shoji, Y. Kitagawa, K. Fushimi, S. Watanabe, G. Matsuba, **A. Yamamoto**, **M. Tanaka**, M. Tsuda, S. Tanaka and Y. Hasegawa*
"Structure-changeable luminescent Eu(III) complex as a human cancer grade probing system for brain tumor diagnosis"

Sci. Rep. 14, 778 (2024).

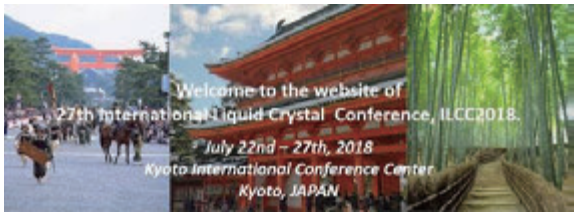
招待講演・学会発表リスト

招待講演・口頭発表

田中　求

1. Motomu Tanaka
   “Coherent X-Ray Diffraction Imaging of Frozen Hydrated Human Erythrocytes Infected by Malaria Parasites”（招待講演）
   16th European Powder Diffraction Conference, University of Edinburgh, Edinburgh, UK, July 2, 2018.

2. Motomu Tanaka
   “Cell Membranes as Liquid Crystals: Impact of Surface Carbohydrates on Mechanics and Biological Functions”（招待講演）
   27th International Liquid Crystal Conference, Kyoto International Conference Center, Kyoto, Japan, July 24, 2018.



3. Motomu Tanaka
   “Influence of Genetic Mutation and Disease on Membrane Electrostatics, Mechanics and Dynamics”（Opening Lecture）
   Workshop - Dynamics of membranes and their constituents, Lund University, Lund, Sweden, September 12, 2018.

4. Motomu Tanaka
   “Pioneering New Physical Platforms Tackling Clinically Relevant Problems”（招待講演）
   RIKEN RCSTH Seminar, Wako, Japan, February 27, 2019.

5. Motomu Tanaka,

“Supported membranes as a platform for dynamic phenotyping of primary human cells: Quantifying the effect of intrinsic and extrinsic factors”（招待講演）
American Chemical Society Spring Meeting, Orange County Convention Center, Orlando, USA, April 2, 2019.

6. Motomu Tanaka
“Supported Membranes: Platform for Dynamic Phenotyping of Diseases”（招待講演）
Institute Colloquium, Institut Charles Sadron, Strasbourg, France, May 7, 2019.

7. Motomu Tanaka and Akihisa Yamamoto
“Human Corneal Endothelium as 2D Colloidal Assembly”（Keynote）
Okinawa Colloids 2019, Bankoku Shunryokan, Nago, Japan, November 5, 2019.

8. Motomu Tanaka
“Nano-to-Meso Confinement Regulates the Fate of Cells”（招待講演）
Debugging Nanobio-Interfaces to Promote Clinical Translation, Universitätsmedizin Mainz, Mainz, Germany, December 6, 2019.

9. Motomu Tanaka
“Hierarchical Structure, Element-Specific Spectroscopy, and Dynamics of Interfaces Probed by Grazing Incidence Illumination”（招待講演）
The 9th Japan-Taiwan Joint Meeting on Neutron and X-ray Scattering, Kitakyushu International Conference Center, Kitakyushu, Japan, April 12, 2020.

10. Motomu Tanaka
“Physical Modeling of Cell Surfaces: Interfacial Forces and Mechanics”（特別講義）
Swedish Neutron Graduate School (SWEDNESS) Summer Symposium “Neutrons in Life Science and Biomaterials” (Online), June 17, 2021.

11. 田中　求
“臨床へとつながる真の医学物理学の開拓”（招待講演）
関西眼疾患研究会、京都市・京都府立医科大学、2018 年 4 月 4 日.

12. 田中　求
“界面ダイナミクスから読み取る疾患”（招待講演）
第 1 回 京大 - ハイデルベルク大 - 理研ワークショップ
「数理と医学」、京都市・京都大学、2019 年 10 月 10 日.

13. 田中　求
“臨床医学の課題に切り込む数物科学”（招待講演）
京都大学 MACS コロキウム、オンライン開催、
2020 年 7 月 17 日.

14. 田中　求
“殺菌・抗菌の物理化学：界面から読み解くケミカルの機能”（招待講演）
CSJ 化学フェスタ、オンライン開催、2020 年 10 月 21 日.

15. 田中　求
“斜入射角 X 線を用いた界面微細構造・水圏静電相互作用・界面ダイナミクスの精密計測”
（招待講演）
ソフト界面科学研究会 2020、オンライン開催、2021 年 3 月 16 日.

16. 田中　求
“界面から読み解く抗菌・殺菌の物理化学:感染症と向き合う
社会に貢献する分析科学”（招待講演）
大阪大学基礎工学研究科・次世代分析科学を考える会、
オンライン開催、2021 年 7 月 20 日.

17. 田中　求
“Biological Interfaces out of Equilibrium-New Challenges in Soft Interface Science”
（招待講演）
九州大学・国際セミナーシリーズ「Soft Interface Seminar」、
オンライン開催、2021 年 10 月 22 日.

18. 田中　求
“生物物理・ソフトマター物理と医学の接点を探る”（招待講演）

第 59 回日本生物物理学会年会 シンポジウム、オンライン開催、
2021 年 11 月 25 日

19. 田中　求
“界面から解き明かす生命現象のダイナミクス”（招待講演）
第 73 回コロイドおよび界面化学討論会 - 異分野融合・学際領域として拡がるコロイド・界面科学、東広島市・広島大学、2022 年 9 月 21 日.

20. 田中　求
“Spatio-temporal analysis of infected cells reveals the protection of HbS carriers from severe malaria”（招待講演）
第三回「医学と数理」研究会　京大－ハイデルベルク大－理研ワークショップ、京都市・京都大学、2022 年 9 月 30 日.

21. 田中　求
“Quantitative biomarkers for human diseases: from collective cell order, spatio-temporal dynamics, to modeling”　（招待講演）
Special Tea Time、仙台市・東北大学 材料科学高等研究所、
2023 年 3 月 28 日

22. Motomu Tanaka
“Bio-metamaterials: Mechanical Regulation of Single Mesenchymal Stem Cells by Unit Cell Arrangement”（基調講演）
Metamaterials 2023:The 17th International Congress on Artificial Materials for Novel Wave Phenomena, Minoa Palace Hotel, Chania, Greece, September 13, 2023.

23. Motomu Tanaka
“New Experimental Analytical Platforms Answering Clinically Relevant Questions”
Kyoto Winter School 2024 “Towards Holistic Understanding of Life”,
京都市・京都大学, 2024 年 2 月 27 日

山本暁久

1. Akihisa Yamamoto
   “A Non-Invasive Physical Biomarker for Restoring Human Corneal Endothelium”（招待講演）
   Kyoto Winter School 2019 “Quantifying Dynamics of Life”, Kyoto University, Kyoto, Japan, March 15, 2019.

2. 山本 暁久
   “細胞集団挙動の定量による培養細胞と再生ヒト角膜内皮の予測的診断法の開発”（招待講演）
   第 1 回「数理が紡ぐ新しい科学研究」連携ワークショップ―生命医科学と数理科学―、札幌市・北海道大学、2019 年 8 月 19 日.

3. 山本 暁久
   “統計的手法による細胞・組織の定量評価：ヒト角膜内皮の再生医療・消化器細胞の癌化と自発運動”（招待講演）
   第 1 回京大高等研究院－Heidelberg 大学－理研 iTHEMS workshop「数理と医学」、京都市・京都大学、2019 年 10 月 10 日.

4. 山本 暁久
   “細胞集団秩序の定量によるヒト角膜内皮の培養細胞と再生組織の予後予測法の開発”（招待講演）
   メカノバイオロジー研究を学ぶ、京都市・京都大学、2019 年 11 月 15 日.

5. 山本 暁久
   “ヒト角膜内皮再生医療における細胞品質・予後予測の統合的バイオマーカーの開発”（招待講演）
   第 69 回高分子討論会、オンライン開催、2020 年 9 月 17 日.

6. 山本 暁久
   “細胞の変形・運動モードの定量によるマウス膵癌前癌病変の判別”（招待講演）
   第 2 回京大－ハイデルベルク大―理研ワークショップ「医学と数理」、オンライン開催、2020 年 9 月 18 日.

7. 山本 暁久
“ヒト角膜内皮の培養細胞と再生組織における細胞集団秩序に基づいた予測的診断法の開発”（招待講演）
第 2 回京大－ハイデルベルク大―理研ワークショップ「医学と数理」、オンライン開催、2020 年 9 月 19 日.

8. 山本 暁久
“パーシステントホモロジーで見るヒト角膜内皮再生組織の局所的秩序構造と組織機能の関係”（招待講演）
TDA-MI workshop 2020、オンライン開催、2020 年 11 月 14 日.

9. Akihisa Yamamoto
“Differentiation State of Cells and Organoids: Evaluation of Morphology Dynamics and Control by Cellular Scaffolds”（招待講演）
The joint Kyoto Univ. – KIT meeting (Online), December 11, 2020.

10. 山本暁久
“不妊治療をアシストする卵子の硬さ／柔らかさの定量評価技術”（招待講演）
京都大学新技術説明会、オンライン開催、2022 年 6 月 28 日.

11. Akihisa Yamamoto
“Spatio-temporal pattern of deformation and migration of pancreatic cells from different precancerous lesions” （招待講演）
YITP workshop “25th Anniversary Symposium of German-Japanese Joint Research Project on Nonequilibrium Statistical Physics - Perspectives for Future Collaboration”, Kyoto University, Kyoto, Japan, October 13, 2022.

12. 山本暁久
“位相的データ解析による肺気腫モデルにおける構造破壊の特徴抽出”（招待講演）
第 3 回 京大-ハイデルベルク大-理研 ワークショップ「医学と数理」、京都市・京都大学、2022 年 9 月 30 日.

13. 山本暁久
“細胞集団秩序に基づくヒト角膜内皮組織再生の長期予後評価”（招待講演）
第 3 回 京大-ハイデルベルク大-理研 ワークショップ「医学と数理」、京都市・京都大学、2022 年 10 月 1 日.

14. Akihisa Yamamoto
“Morphological dynamics of mouse pancreatic cells from different precancerous lesions” （招待講演）
Physics of Soft and Active Matter in Different Spatio-Temporal Domains, 京都市・京都大学, 2023 年 3 月 9 日.

15. Akihisa Yamamoto
“Morphological dynamics of mouse pancreatic cells from different precancerous lesions”
STATPHYS28, 千代田区・東京大学, 2023 年 8 月 8 日.

16. 山本暁久
“物理と数理で『測り』臨床医学につなげる細胞運動と組織秩序” （招待講演）
基礎臨床社会医学統合講義　医学を創る〜数理・工学で切り開く医学〜, 千代田区・東京大学, 2023 年 8 月 29 日.

17. 山本暁久
“異なる前癌病変に由来するマウス膵癌細胞の変形運動ダイナミクス”
日本物理学会第 78 回年会, 仙台市・東北大学, 2023 年 9 月 18 日.

18. 山本暁久
“京大 MACS 教育プログラム「疾患における集団的細胞挙動の数理モデルの開拓」の取り組み” （招待講演）
第 4 回「医学と数理」ワークショップ, 仙台市・東北大学, 2023 年 9 月 29 日

19. Akihisa Yamamoto
“The collective order of human corneal endothelial cells for cultured cells and regenerated tissues: Creation of a novel biomarker and mathematical characterization” （招待講演）
Kyoto Winter School 2024 “Towards Holistic Understanding of Life”, 京都市・京都大学, 2024 年 2 月 27 日

鈴木　量

1. Ryo Suzuki
   “Deformation as a Quantitative Tool to Understanding Self-Organisation in Multi-cellular Organisms: Development and Diseases”（招待講演）
   Kyoto Winter School 2019 “Quantifying Dynamics of Life”, Kyoto University, Kyoto, Japan, March 20, 2019.

2. 鈴木 量
   “細胞集団の自発変形から生命現象を理解する―ヒドラの再生と癌オルガノイド―”（招待講演）
   第 1 回京大高等研究院－Heidelberg 大学－理研 iTHEMS workshop「数理と医学」、京都市・京都大学、2019 年 10 月 10 日.

3. 鈴木 量
   “動的変形解析を用いた大腸癌オルガノイドの転移能の定量評価”（招待講演）
   第 2 回京大－ハイデルベルク大―理研ワークショップ「医学と数理」、オンライン開催、2020 年 9 月 18 日.

4. 鈴木 量
   “慢性閉塞性肺疾患における肺胞の力学特性測定”（招待講演）
   第 2 回京大－ハイデルベルク大―理研ワークショップ「医学と数理」、オンライン開催、2020 年 9 月 18 日.

5. 鈴木 量
   “ヒドラの再生過程における初期体軸形成と組織変形－自発変形のモード解析および Wnt シグナル経路の摂動実験－”（招待講演）
   第 3 回京大－ハイデルベルク大―理研ワークショップ「医学と数理」、京都市・京都大学、2022 年 10 月 1 日.

6. 鈴木 量
   “ヒドラの再生過程における初期体軸形成と組織変形”
   日本物理学会 2023 年春季大会、オンライン開催、2023 年 3 月 23 日.

7. 鈴木 量
   “アクトミオシン再構成系における運動形態の異なる秩序状態の共存”
   日本物理学会 2023 年春季大会、オンライン開催、2023 年 3 月 25 日.

8. Ryo Suzuki
   “Emergence of coexisting ordered states in an active filament system”（招待講演）
   YITP workshop “25th Anniversary Symposium of German-Japanese Joint Research Project on Nonequilibrium Statistical Physics - Perspectives for Future Collaboration”, Kyoto University, Kyoto, Japan, October 13, 2022.

9. Ryo Suzuki
   “Defining axis formation of Hydra regeneration via active deformation and Wnt signalling”
   The 7th International Soft Matter Conference, ISMC 2023, Grand Cube Osaka (Osaka International Convention Center), Osaka, Japan, September 6, 2023.

10. 鈴木 量
    “アクトミオシン再構成系における集団パターンの形成メカニズム”
    日本物理学会 第 78 回年次大会、仙台市・東北大学、2023 年 9 月 17 日.

11. 鈴木 量
    “京大 MACS 教育プログラム「疾患における集団的細胞挙動の数理モデルの開拓」の取り組み”（招待講演）
    第 4 回「医学と数理」ワークショップ, 仙台市・東北大学, 2023 年 9 月 29 日

12. Ryo Suzuki
    “Active tissue deformation as a quantitative tool for the understanding of self-organisation in multi-cellular organisms”（招待講演）
    The 24th iCeMS International Symposium “Self-Assembly Science for Unlocking Life’s Secrets”, Kyoto University, Kyoto, Japan, January 12, 2024.

13. Ryo Suzuki
    “Physics of Regenerating *Hydra*”（招待講演）
    Kyoto Winter School 2024 “Towards Holistic Understanding of Life”, Kyoto University, Kyoto, Japan, February 27, 2024.

林　健太郎

1. Kentaro Hayashi
   “The influence of substrate stiffness on collective cell behavior in neural stem cells”
   Kyoto Winter School 2019 “Quantifying Dynamics of Life”、京都大学、2019/3/18

ポスター発表

山本暁久

1. ○Akihisa Yamamoto, Yusuke Sakamaki, Tatsuaki Tsuruyama, Motomu Tanaka
   “Change in Shape Fluctuation and Migration of Human Gastric Cells Induced by Cancer Progression”
   第 70 回日本細胞生物学会大会　第 51 回日本発生生物学会合同大会、タワーホール船堀、2018/6/7

2. ○山本 暁久
   “中性子非鏡面散乱法を用いた水圏界面の力学特性の定量”
   「水圏機能材料」第 1 回若手スクール、兵庫県立大学・志んぐ荘・Spring-8/SACLA、2019/11/12

3. ○Akihisa Yamamoto, Yusuke Sakamaki, Yuichi Fukunaga, Kentaro Hayashi, Akihisa Fukuda, Hiroshi Seno, Tatsuaki Tsuruyama, Motomu Tanaka
   “Alteration of Spatio-Temporal Pattern of Deformation and Migration of Human Gastric Cells Induced by Cancer Progression”
   International conference on systems biology of human disease、オンライン、2021/7/5

4. ○Akihisa Yamamoto, Yusuke Sakamaki, Yuichi Fukunaga, Kentaro Hayashi, Akihisa Fukuda, Hiroshi Seno, Tatsuaki Tsuruyama, Motomu Tanaka
   “Supported Membranes for Discriminating Cancer Progression of Human Gastric Cells”
   Tethered Membranes: Fundamentals and Applications (TETHMEM)，オンライン, 2021 年 8 月 30 日.

5. ○Akihisa Yamamoto, Kazuaki Furukawa, Rebecca Wright, Tetsuhiko Teshima, Takashi Taniguchi, and Motomu Tanaka
"Dissipative self-spreading of lipid membranes and instantaneous freezing by zwitter-ionic choline phosphate"
Physics of Soft Active Matter in Different Spatio-Temporal Domains, 京都市・京都大学, 2023 年 3 月 9 日.

6. ○山本 暁久、大谷 暢彦、大林 一平、上野 盛夫、田中 求
"位相的データ解析によるヒト角膜内皮細胞の局所構造評価"
第 4 回「医学と数理」ワークショップ, 仙台市・東北大学, 2023 年 9 月 29 日

鈴木　量

1. ○鈴木 量、鶴山 竜昭、田中 求
"原子間力顕微鏡 AFM を用いた子宮頸癌病理サンプルの力学特性測定"
第 4 回「医学と数理」ワークショップ, 仙台市・東北大学, 2023 年 9 月 29 日

林　健太郎

1. ○Kentaro Hayashi, Takamasa S. Yamamoto, Naoto Ueno,
"Analysis of intracellular calcium dynamics and its functional implication at leading edge mesoderm during gastrulation"
第 70 回日本細胞生物学会大会　第 51 回日本発生生物学会合同大会、タワーホール船堀、2018/6/7

2. ○ Kentaro Hayashi, Ryo Suzuki, Akihisa Yamamoto, Masaki Nakahata, Yoshinori Takashima, Akira Harada, Masaki Sano, Ryoichiro Kageyama, Motomu Tanaka
"The influence of substrate stiffness on collective cell behavior in neural stem cells"
Kyoto Winter School 2019 "Quantifying Dynamics of Life" 、京都大学、2019/3/18

3. ○Yoriko Ando, Kentaro Hayashi, Eijiro Maeda, Ryo Tsunoda, Hiroaki Tanaka, Kohei

Murase, Naoto Ueno, Takeo Matsumoto
“Clearing of Xenopus laevis Tailbud Embryos and Quantification of their 3D-tissue Structure toward Finite Element Analysis”
Asian-Pacific Association for Biomechanics, Taiwan, 2019/11/1-3

4. ○松田 茉美、林 健太郎、三竹 のどか、高島 義徳、中畑 雅樹、山口 浩靖、原田 明、田中 求
“Gelatin を基盤とする超分子材料の開発と三次元足場としての応用”
第 69 回高分子討論会、オンライン、2020/9/17

5. ○林 健太郎、山本 暁久、長谷川 光一、中畑 雅樹、高島 義徳、田中 求
“ヒト iPS 細胞のメカノバイオロジー：数理モデルとの連携の可能性”
第 4 回「医学と数理」ワークショップ, 仙台市・東北大学, 2023 年 9 月 29 日

国内・国外のメディア報道

国内メディア

2019 年

1. 田中 求, “培養細胞の増殖 精密制御”
   日経産業新聞, 2019 年 5 月 16 日. “新聞”

2. 山本暁久, 田中 求, “京大と京都府立医大　移植用角膜の品質、評価の新指標”
   日本経済新聞, 2019 年 7 月 23 日. “新聞”

3. 田中 求, 山本暁久, “角膜再生、画像で評価　京大、細胞品質の指標開発”
   日刊工業新聞 New ウェーブ 21, 2019 年 7 月 23 日. “新聞”

4. 山本暁久, 田中 求, “角膜再生、画像で評価　京大、細胞品質の指標開発”
   日刊工業新聞, 2019 年 7 月 23 日. “新聞”

5. 田中 求, 山本暁久, “京大と京都府立医大　移植用角膜の品質、評価の新指標”
   日本経済新聞電子版, 2019 年 7 月 23 日. “新聞”

6. 田中 求, 山本暁久, “角膜内皮再生医療の新しい数値指標の開発に成功 －物理マーカーで予後の予測を可能に－”
   京都大学プレスリリース, 2019 年 7 月 23 日. “プレスリリース”

7. 田中 求, 山本暁久, “京大と京都府立医大　目に移植の角膜、品質評価に新指標”
   日本経済新聞(科学技術掲載), 2019 年 7 月 29 日. “新聞”

8. 山本暁久, 田中 求, “培養細胞の評価、総合的に”
   日経サイエンス 2019 年 10 月号, 2019 年 10 月 1 日. “雑誌”

2020 年

1. 田中 求, 山本暁久, “角膜内皮再生医療における新しい細胞品質評価指標を開発”
   電子情報通信学会ニュース解説, 2020 年 1 月 1 日. “ネットニュース”

2. 田中 求, “界面活性剤と芳香族アルコールによる抗菌作用メカニズムを原子・分子スケールで解明”
   花王株式会社ニュースリリース, 2020 年 10 月 20 日. “プレスリリース”

3. 田中 求, “花王、菌の最表層に対する抗菌剤の作用メカニズムを詳細に解明”
   週刊粧業, 2020 年 10 月 28 日. “雑誌”

海外メディア

2019 年

1. Akihisa Yamamoto, Motomu Tanaka, “Quantitative Biomarker to Test Corneal Cell Quality and Life”
   Medindia, https://www.medindia.net/news/quantitative-biomarker-to-test-corneal-cell-quality-and-life-189094-1.htm, 2019 年 7 月 23 日. “ネットニュース”
2. Akihisa Yamamoto, Motomu Tanaka, “New quantitative biomarker helps assess quality of corneal cells”
   The Medical News, https://www.news-medical.net/news/20190723/New-quantitative-biomarker-helps-assess-quality-of-corneal-cells.aspx, 2019 年 7 月 23 日. “ネットニュース”
3. Akihisa Yamamoto, Motomu Tanaka, “Scientists develop a physical biomarker for cornea restoration therapy”
   MedicalXpress, https://medicalxpress.com/news/2019-07-scientists-physical-biomarker-cornea-therapy.html?src_id=alt, 2019 年 7 月 22 日. “ネットニュース”
4. Akihisa Yamamoto, Motomu Tanaka, “Testing corneal cell quality? Apply physics”
   EurekaAlert!, https://www.eurekalert.org/news-releases/724870, 2019 年 7 月 22 日. “ネットニュース”

2020 年

1. Motomu Tanaka, “Researchers use stimuli-responsive 3D printed scaffolds to stretch individual cells”

3D Printing Industry, https://3dprintingindustry.com/news/researchers-use-stimuli-responsive-3d-printed-scaffolds-to-stretch-individual-cells-176862/, 2020 年 10 月 6 日. “ネットニュース”

2. Motomu Tanaka, “'Stretching Rack' for Cells developed”
   Technology Networks, https://www.technologynetworks.com/tn/news/stretching-rack-for-cells-developed-340879, 2020 年 9 月 28 日. “ネットニュース”

3. Motomu Tanaka, “'Stretching Rack' for Cells”
   Bionity, https://www.bionity.com/en/news/1168088/stretching-rack-for-cells.html?WT.mc_id=ca0068, 2020 年 9 月 28 日. “ネットニュース”

4. Motomu Tanaka, “New device helps study the reaction of individual cells to mechanical stress”
   The Medical News, https://www.news-medical.net/news/20200925/New-device-helps-study-the-reaction-of-individual-cells-to-mechanical-stress.aspx, 2020 年 9 月 26 日. “ネットニュース”

5. Motomu Tanaka, “'Stretching rack' for cells”
   ScienMag, https://scienmag.com/stretching-rack-for-cells/, 2020 年 9 月 25 日. “ネットニュース”

6. Motomu Tanaka, “'Stretching rack' for cells”
   Bioengineer.org, https://bioengineer.org/stretching-rack-for-cells/, 2020 年 9 月 25 日. “ネットニュース”

7. Motomu Tanaka, “Streckbank für Zellen”
   VBIO, https://www.vbio.de/aktuelles/wissenschaft/streckbank-fuer-zellen/, 2020 年 9 月 25 日. “ネットニュース”

8. Motomu Tanaka, “'Stretching Rack' for Cells”
   EurekAlert!, https://www.eurekalert.org/pub_releases/2020-09/kift-rf092520.php, 2020 年 9 月 25 日. “ネットニュース”

9. Motomu Tanaka, “'Stretching Rack' for Cells”
   カールスルーエ工科大学プレスリリース, 2020 年 9 月 24 日. “プレスリリース”

10. Motomu Tanaka, “Researchers develop a 'stretching rack' for cells”
    Phys.org, https://phys.org/news/2020-09-rack-cells.html, 2020 年 9 月 24 日. “ネットニュース”

11. Motomu Tanaka, “Streckbank für Zellen”
    AlphaGalileo, https://www.alphagalileo.org/en-gb/Item-Display/ItemId/197671?returnurl=https://www.alphagalileo.org/en-gb/Item-Display/ItemId/197671, 2020 年 9 月 24 日. “ネットニュース”

12. Motomu Tanaka, “Streckbank für Zellen”
    Informationsdienst Wissenschaft, https://idw-online.de/de/news754693, 2020 年 9 月 24 日. “ネットニュース”

13. Motomu Tanaka, “'Stretching Rack' for Cells”
    Mirage News, https://www.miragenews.com/stretching-rack-for-cells/, 2020 年 9 月 24 日. “ネットニュース”

14. Motomu Tanaka, “'Stretching Rack' for Cells”
    Nanowerk, https://www.nanowerk.com/nanotechnology-news2/newsid=56235.php, 2020 年 9 月 24 日. “ネットニュース”

2023 年

1. Motomu Tanaka, "'Scientific Highlights – De novo formation of non-crystalline fullerene bilayer on water surface"
   https://www.esrf.fr/home/UsersAndScience/Publications/Highlights/esrf-highlights-2022.html, 2023 年 2 月. "ネットニュース"

2. Motomu Tanaka, Ryo Suzuki, "Wnt/β-Catenin Signaling Induces Axial Elasticity Patterns of Hydra Extracellular Matrix"
   Extracellular Matrix News Volume 14.11,
   https://www.stemcellsciencenews.com/news_archive/ extracellular-matrix-news-volume-14-11-mar-23-2023, 2023 年 3 月 23 日."ネットニュース"

ネットワークの構築（１）
医学数物連携勉強会

寄附部門長・田中が発起人となり、2015 年から不定期に「医学数物連携勉強会」を開催してきました。臨床・基礎医学、物理学、数学、情報工学など様々な分野からスピーカーをお招きし、1 時間ほどの話題提供（講演）に引き続きオープンエンドで議論を行っています。当拠点の鈴木助教・山本助教が世話人として運営を担当し、活発な議論が行われています。

京都大学に加え、同志社大学・立命館大学・九州大学・広島市立大学といった他大学の研究者にも参画いただいているだけでなく、企業の研究者にも周知し参加いただいています。参加者が毎回、秘密保持誓約をしたうえで未発表のデータやアイデアも積極的に発表していただくことで新たな研究のシーズを生み出すことを狙います。

実際に、本勉強会での議論からいくつかの共同研究がスタートし、その成果が共著論文に結実しています。今後さらに大きく発展展開することを計画しています。

医数物勉強会の講演リスト

第 8 回　医数物連携勉強会（2018/6/20）

講演タイトル

「肺気腫病変のモデリング:動物実験と数学的アプローチ」

講演者

佐藤 篤靖　助教（京都大学　医学部附属病院　呼吸器内科）

第 9 回　医数物連携勉強会（2018/10/3）

講演タイトル

「産業用カメラを利用した高速度画像記録装置の構築と生命関連科学研究(位相物体観測)への応用」

講演者

藤原 久志　准教授

（広島市立大学　情報科学研究科　医用情報科学専攻）

第 10 回　医数物連携勉強会（2019/5/24）

講演タイトル 1

「細胞間接着の親和性と感覚組織のパターン形成」

講演者

富樫 英　助教（神戸大学　大学院医学研究科）

講演タイトル 2

「細胞接着・細胞選別の理解に向けた数理的アプローチ」

講演者

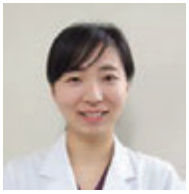
村川 秀樹　准教授

（龍谷大学　理工学部　数理情報学科）

第 11 回　医学数物連携勉強会（2019/10/3）

講演タイトル

「外的刺激で誘発した気道収縮がマウス肺気腫表現型に及ぼす影響」



講演者

濱川 瑶子　医師

（京都大学　大学院医学研究科　呼吸器内科学）

第 12 回　医数物連携勉強会（2020/2/17）

講演タイトル

「作用素論的データ解析によるダイナミクス抽出 ～ 非線形力学系のデータ駆動モデリングへのアプローチ」

講演者

河原 吉伸　教授（九州大学　マス・フォア・インダストリ研究所 / 理化学研究所　革新知能統合研究センター）

第 13 回　医数物連携勉強会（2022/4/13）

講演タイトル

「ライブイメージングによる内耳有毛細胞 Centriole の観察」

講演者

十名 洋介　助教

（京都大学　大学院医学研究科　耳鼻咽喉科・頭頸部外科）

第 14 回　医数物連携勉強会（2022/12/7）

講演タイトル

「表皮構造の数理モデルとその応用」

講演者

長山 雅晴　教授（北海道大学　電子科学研究所）

2018 年

第8回 医学数物連携勉強会のご案内

日時: 平成30年6月20日(水)
午後5時より
場所: iCeMS研究棟隣(下記地図#32)
総合研究1号館119号室

肺気腫病変のモデリング:
動物実験と数学的アプローチ

佐藤 篤靖 助教
(京都大学医学部附属病院 呼吸器内科)

ショートトーク: Karel Svadlenka 准教授
(京都大学 理学研究科 数学・数理解析専攻)
鈴木 量
(京都大学高等研究院 医学物理・医工計測グローバル拠点)

世話人
鈴木量 (rsuzuki@icems.kyoto-u.ac.jp)
山本暁久 (ayamamoto@icems.kyoto-u.ac.jp)

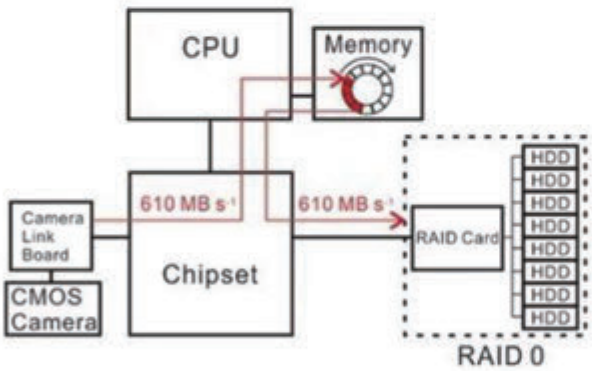
Supported by NAKATANI FOUNDATION

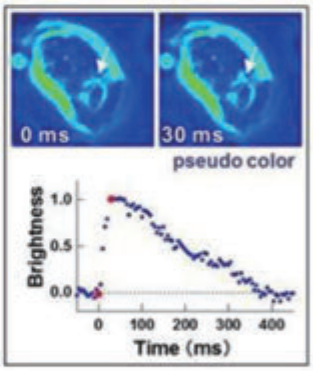
第9回 医学数物連携勉強会のご案内

日時： 平成30年10月3日（水）
午後5時より
場所： 高等研究院本館（下記地図#77）
セミナールーム2F

産業用カメラを利用した高速度画像記録装置の構築と生命関連科学研究（位相物体観測）への応用

藤原 久志 准教授
（広島市立大学 情報科学研究科 医用情報科学専攻）





世話人

鈴木量
(suzuki.ryo.8z@kyoto-u.ac.jp)
山本暁久
(yamamoto.akihisa.6w@kyoto-u.ac.jp)

Supported by NAKATANI FOUNDATION

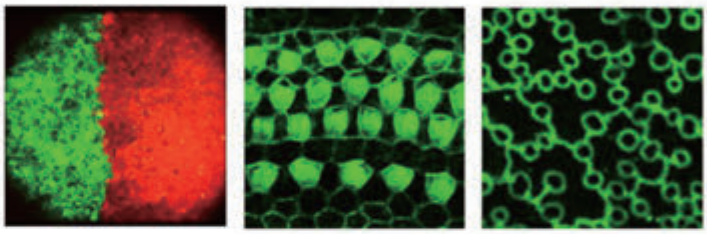
2019 年

第10回 医数物連携勉強会のご案内

日時： 令和元年5月24日（金） 午後3時より
場所： 高等研究院本館（下記地図＃77）
4F会議室

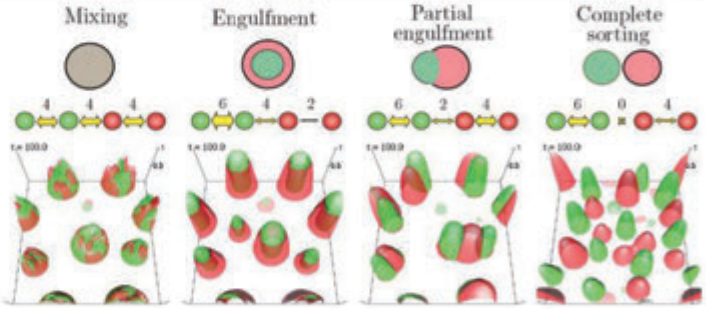
細胞間接着の親和性と感覚組織のパターン形成

富樫 英 助教
神戸大学大学院
医学研究科
分子細胞生物学



細胞接着・細胞選別の理解に向けた数理的アプローチ

村川 秀樹 准教授
龍谷大学
理工学部
数理情報学科



世話人

鈴木量 (suzuki.ryo.8z@kyoto-u.ac.jp)
山本暁久 (yamamoto.akihisa.6w@kyoto-u.ac.jp)

Supported by NAKATANI FOUNDATION

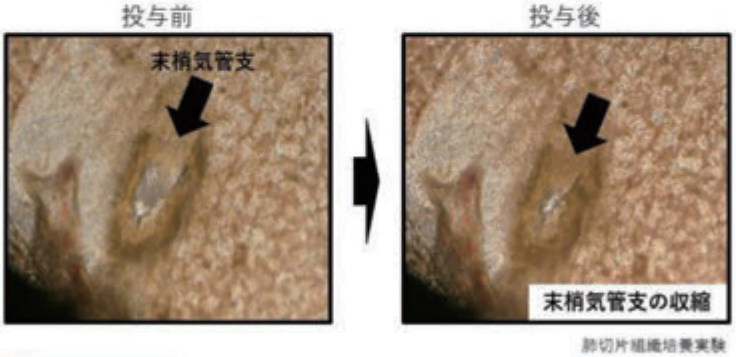
第11回 医学数物連携勉強会のご案内

日時: 令和元年10月3日(木)
午後6時より
場所: 高等研究院本館(下記地図#77)
4F 会議室

外的刺激で誘発した気道収縮が マウス肺気腫表現型に及ぼす影響

濱川 瑶子 氏
(京都大学大学院 医学研究科 呼吸器内科学)

薬剤(carbachol)投与による気道収縮



肺切片組織培養実験

世話人

鈴木量 (suzuki.ryo.8z@kyoto-u.ac.jp)
山本暁久 (yamamoto.akihisa.6w@kyoto-u.ac.jp)

高等研究院 医学物理・医工計測グローバル拠点

Supported by NAKATANI FOUNDATION

2020 年

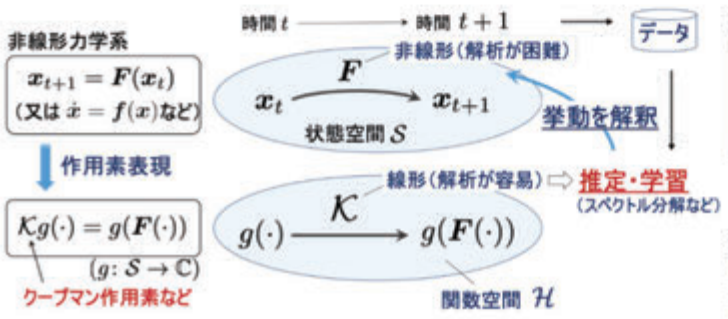
MACS SG9／第12回医数物連携勉強会 合同セミナー

日時：　令和2年2月17日（月）午後6時より
場所：　京都大学高等研究院本館（地図#77）
2階セミナールーム（207）

作用素論的データ解析によるダイナミクス抽出
～　非線形力学系のデータ駆動モデリングへのアプローチ

河原吉伸　教授
九州大学　マス・フォア・インダストリ研究所
理化学研究所　革新知能統合研究センター

本講演では、多くの科学・工学分野において重要となる、データ駆動による動的なプロセスの解析に関して、力学系の作用素論的解析と機械学習に基づいた研究について紹介する。近年、力学系の作用素表現に基づく解析、特にクープマン作用素を用いた解析は、その汎用性や物理的概念とのつながり、また動的モード分解などの推定法の発展もあり多くの分野で注目を集めている。ここでは、力学系の作用素表現やそのスペクトルの推定問題について着目し、最近の話題を中心に紹介する。特に、機械学習分野でよく用いられる方法論に基づいた動的モード分解の拡張や、力学系上の計量の導出や学習への利用などについて 述べる。この中で、我々が取り組んでいるものを中心に、いくつかの応用事例についてもふれる。



共催・協力

MACS SG9
（理学研究科）

中谷医工計測
技術振興財団

世話人

Karel Svadlenka (karel@math.kyoto-u.ac.jp)
鈴木 量 (suzuki.ryo.8z@Kyoto-u.ac.jp)
山本暁久 (yamamoto.akihisa.6w@kyoto-u.ac.jp)

2022 年

第13回 医数物連携勉強会のご案内

日時： 令和4年4月13日（水）
午後6時半より
場所： オンライン開催

ライブイメージングによる
内耳有毛細胞Centrioleの観察

十名 洋介 助教
（京都大学 大学院医学研究科 耳鼻咽喉科・頭頸部外科）

世話人

鈴木 量 (suzuki.ryo.8z@kyoto-u.ac.jp)
山本暁久 (yamamoto.akihisa.6w@kyoto-u.ac.jp)

Supported by NAKATANI FOUNDATION
for advancement of measuring technologies in biomedical engineering

MACS SG7／
第14回医数物連携勉強会
合同セミナー

日時： 令和4年12月7日（水）午後4時45分より
場所： 京都大学高等研究院本館（地図#77）
2階セミナールーム（207号室）

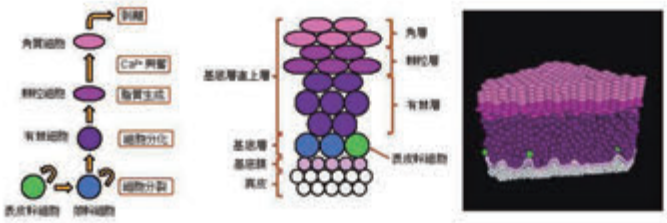
表皮構造の数理モデルとその応用

長山 雅晴　教授
北海道大学電子科学研究所

皮膚は生命に内外を分ける境界としてだけでなく、外界からの情報を体内に伝える働きや外界から体内への異物の侵入を防ぐ働き、体内の水分を外界に漏らさない働き（保水機能）をしている。このような働きは皮膚の最も外層にある表皮が重要な役割を担っており、角層バリア機能と呼ばれている。

この研究では、表皮構造を再現する数理モデルの構築を行い、角層バリア機能の恒常性維持について考察した。その結果、基底層からの細胞供給量に依存すること、および真皮が硬くなることによって表皮が薄くなり、角層バリア機能が低下することを示した。さらに、増殖亢進と急速なターンオーバーを仮定すると「魚の目」として知られる病態が再現できることがわかった。また、ヒトの「魚の目」病理検体データを解析した結果、数理モデル上の仮定を示唆していることもわかった。

この講演では、表皮構造モデルの構築、その病態再現への挑戦、そして数理モデルの器官形成モデルへの拡張について説明する。



共催・協力

MACS SG7
（理学研究科）

中谷医工計測
技術振興財団

世話人

Karel Svadlenka (karel@math.kyoto-u.ac.jp)
鈴木 量 (suzuki.ryo.8z@kyoto-u.ac.jp)
山本暁久 (yamamoto.akihisa.6w@kyoto-u.ac.jp)

ネットワークの構築（２）
KUIAS-ハイデルベルク-理研ワークショップ
「医学と数理」

寄附部門長・田中と理化学研究所・数理創造プログラム（iTHEMS）初田ディレクター、京都大学理学部サイエンス連携探索センター（SACRA）坂上部門長が世話人となり、「医学と数理」をテーマにした分野融合型のワークショップを 2019 年にスタートさせました。

2019 年 10 月に開催した第 1 回目の研究会は、森重文・高等研究院長にもご出席いただき、数学と物理の若手中堅研究者が集まって最新の成果を紹介するという形式で主に数理解析やモデルに関する議論を行いました。そこでの議論をさらに大きく展開するべく、第 2 回目では実際に学際的な共同研究を行っている、臨床医学・基礎医学の研究者と数学・物理学の研究者に「チーム」として研究紹介をお願いしました。2020 年 3 月のオンサイトでの開催は新型コロナウイルス感染拡大の状況を鑑みて断念せざるを得ませんでしたが、2020 年 9 月にオンラインで開催しました。開会に当たっては、京都大学・湊プロボスト（現総長）と森重文・高等研究院長から激励のお言葉をいただきました。オンラインの長所を活かして、日ごろ一堂に会することが難しい国内外の非常に多様な研究者からご講演をいただくことができました。200 人を超える方に参加登録をいただき、非常に活発な議論を行う事ができました。

この研究会を起点として国内外に新たな学問分野を提案し、その成果を発展させていきたいと世話人一同意気込んでいます。

第1回（2019 年 10 月）

第2回（2020 年 9 月）

第二回「医学と数理」ワークショップ

プログラム

9 月 18 日

9:30-9:40　開会のご挨拶・趣旨説明　田中　求　(ハイデルベルグ大/京大)

9:40-9:50　医学と数理の連携について　森　重文（京大高等研究院）

9:50-10:00　医学と数理の連携について　湊　長博（京大）

テーマ１：消化管がん診断へ向けた数理解析

10:00-10:30　妹尾　浩（京大消化器内科・教授）

10:30-11:00　福田晃久（京大消化器内科・講師）

11:00-11:15　山本暁久（京大高等研究院・助教）

11:15-11:30　鈴木　量（京大高等研究院・助教）

11:40-12:20　玉野井冬彦（京大高等研究院・教授）

昼休み

テーマ２：呼吸器障害への数物系アプローチ

13:30-14:00　冨永循哉（東北大放射線科・講師）

14:00-14:30　水藤　寛（東北大 AIMR・教授）

14:40-15:00　佐藤　晋（京大リハビリテーション科・助教）

15:00-15:20　佐藤篤靖（京大呼吸器内科・助教）

15:20-15:40　鈴木　量（京大高等研究院・助教）

15:40-16:10　Karel Svadlenka（京大数学科・准教授）

16:20-16:40　田辺直也（京大地域医療システム学・助教）

16:40-17:10　鍛冶静雄（九大マス・フォア・インダストリ研究所・准教授）

9 月 19 日

テーマ３：再生医療のための数理バイオマーカー

10:00-10:30　上野盛夫（京都府立医大眼科・講師）

10:30-11:00　山本暁久（京大高等研究院・助教）

テーマ 4：数理モデルを活用した画像診断

11:10-11:50　古徳純一（帝京診療放射線学科・教授）

昼休み

13:30-14:10　鶴山竜昭（京大創薬医学・教授）

テーマ 5：循環器障害と数理モデル

14:20-14:50　板谷慶一（京都府立医大循環器外科・講師）

14:50-15:20　坂上貴之（京大数学科・教授）

15:30-15:50　参加者による議論、今後の展望について

15:50　　閉会のご挨拶　　初田哲男（理研）

共催：

京大高等研究院(KUIAS) 医学物理・医工計測グローバル拠点

理研数理創造プログラム(iTHEMS)

京大理学研究科附属サイエンス連携探索センター(SACRA)

第三回「医学と数理」ワークショップ

プログラム

9 月 30 日

9:25-9:30　開会のご挨拶・趣旨説明　田中　求（ハイデルベルグ大/京大）

9:30-9:40　医学と数理の連携について　湊　長博（京大）

9:40-9:50　医学と数理の連携について　森　重文（京大）

9:50-10:00　医学と数理の連携について　小安重夫（理研）

テーマ１：がんと数理・新たな治療

10:00-10:40　石川文彦（理研・チームリーダー）

10:40-10:50　議論

10:50-11:15　妹尾　浩（京大医・教授）

11:15-11:30　福田晃久（京大医・講師）

11:30-11:40　議論

11:40-12:05　玉野井冬彦（京大 iCeMS/UCLA・教授）

12:05-12:10　議論

昼休み

テーマ２：呼吸器疾患と数理

13:10-13:30　平井豊博（京大医・教授）

13:30-13:50　田辺直也（京大医・助教）

13:50-14:05　山本暁久（京大 CiMPhy・助教）

14:05-14:15　議論

14:15-14:40　古徳純一（帝京大医・教授）

14:40-14:45　議論

テーマ３：**Medicine and Numerical Analysis – Activities in Heidelberg -**

15:00-15:35　Thomas Hoefer（DKFZ/Heidelberg・教授）

15:35-15:40　議論

15:40-15:55　Anil Kumar Dasanna（Heidelberg/Saarbruecken・博士研究員）

15:55-16:00　議論

16:00-16:35　Anna Marciniak-Czochra（Heidelberg・教授）

16:35-16:40　議論

15:40-15:55　Judith Thoma（Heidelberg・博士課程）

16:40-17:10　議論

10 月 1 日

テーマ４：発生と数理

9:00-9:40　影山龍一郎（理研・チームリーダー）

9:40-9:50　議論

テーマ５：多様な解析・モデルの可能性

9:50-10:00　水藤　寛（東北大 AIMR・教授）

10:00-10:20　Jiawei Liu（東北大 AIMR・助教）

10:20-10:30　議論

10:30-10:55　坂上貴之（京大理・教授）

10:55-11:00　議論

11:00-11:25　望月敦史（京大医・教授）

11:25-11:30　議論

11:30-12:00　ショートトーク

鷹取　慧（同志社大生命医・研究員）

兼松佑典（広島大理・助教）

昼休み

13:00-13:25　鍛冶静雄（九大 MFI・教授）

13:25-13:30　議論

13:30-13:50　鶴山竜昭（放射線影響研/広大医・研究員）

13:50-13:55　藤﨑碩人（京大理・修士課程）

13:55-14:00　議論

テーマ６：発生と再生

14:00-14:20　鈴木　量（京大 CiMPhy・助教）

14:20-14:40　平岩徹也（シンガポール国立大 MBI・Fellow）

14:40-14:45　議論

14:45-15:05　冨樫　英（神戸大医・助教）

15:05-15:25　Karel Svadlenka（京大理・准教授）

15:25-15:30　議論

15:45-16:05　十名洋介（京大医・助教）

16:05-16:10　永井翔吾（京大理/CiMPhy・修士課程）

16:10-16:15　議論

16:15-16:35　上野盛夫（京都府立医大・講師）

16:35-16:55　山本暁久（京大 CiMPhy・助教）

16:55-17:00　議論

17:00　閉会のご挨拶　初田哲男（理研）

17:05-　意見交換

共催：

京大高等研究院(KUIAS) 医学物理・医工計測グローバル拠点

理研数理創造プログラム(iTHEMS)

京大理学研究科附属サイエンス連携探索センター(SACRA)

第四回「医学と数理」ワークショップ

プログラム

9 月 29 日

9:25-9:30　開会のご挨拶・趣旨説明　田中　求（ハイデルベルグ大/京大）

9:30-9:40　医学と数理の連携について　小谷元子（東北大）

9:40-9:50　医学と数理の連携について　湊　長博（京大）

9:50-10:00　医学と数理の連携について　宮園浩平（理研）

テーマ１：数理による診断・予後予測

10:00-10:30　川上英良（千葉大医/理研・教授）

10:30-10:40　議論

10:50-11:20　増谷佳孝（東北大医・教授）

11:20-11:30　議論

テーマ２：がんと数理

11:30-12:00　名和要武（東大医・助教）

12:00-12:10　議論

12:10-12:25　永井翔吾（京大 CiMPhy・修士課程）

12:25-12:35　議論

12:35-12:45　山本暁久・鈴木　量（京大 CiMPhy・助教）

12:45-12:50　議論

昼休み

14:00-14:30　金道敏樹（金沢工大情報・教授）

14:30-14:40　議論

テーマ３：循環・物質輸送の数理

14:40-15:10　新妻邦泰（東北大医・教授）

15:10-15:20　議論

テーマ４：**Medicine and Numerical Analysis**

15:25-15:30　Motomu Tanaka（Heidelberg/Kyoto）

15:30-16:00　Thomas Stiehl（Aachen）

16:00-16:10　Discussion

16:10-16:40　Stefan Kallenberger（Heidelberg）

16:40-16:50　Discussion

16:50-17:20　Catherine Beauchemin（RIKEN）

17:20-17:30　Discussion

9 月 30 日

テーマ２：がんと数理（続き）

9:00-9:30　石川俊平（京大医・教授）

9:30-9:40　議論

テーマ３：循環・物質輸送の数理（続き）

9:40-10:10　石川拓司（東北大工・教授）

10:10-10:20　議論

10:45-11:15　藤生克仁（東大医・教授）

11:15-11:25　議論

ポスターセッション＆昼休み

テーマ５：多様な解析・モデルの可能性

14:00-14:30　李　聖林（京大 ASHBi・教授）

14:30-14:40　議論

14:40-15:10　尾崎　翔（弘前大工・助教）

15:10-15:20　議論

15:20-15:50　岡村裕彦（岡山大医・教授）

15:50-16:00　議論

16:20-16:50　西條芳文（東北大医工・教授）

16:50-17:00　議論

17:00-17:10　閉会のご挨拶　　初田哲男（理研）

共催：

京大高等研究院(KUIAS) 医学物理・医工計測グローバル拠点

京大理学研究科附属サイエンス連携探索センター(SACRA)

東北大学知の創出センター

理研数理創造プログラム(iTHEMS)

ネットワークの構築（３）
国内・国外他大学からの研究者受入

当拠点では、国内外の他大学・研究機関からトップクラスの研究者を短期または長期で受け入れ、グローバルな連携を行ってきました。

【当拠点客員教授】

Martin Bastmeyer 教授

Department for Cell- and Neurobiology, Zoological Institute,
Karlsruhe Institute of Technology

滞在：2018 年 4 月、2019 年 3－4 月（学術振興会 BRIDGE 再招聘プログラム）、
2024 年 2 月

吉川 研一　教授

京都大学　名誉教授

同志社大学　研究開発推進機構　自己組織化科学研究センター

定期ミーティング

Thomas W. Holstein 教授

Molecular Evolution and Genomics, Centre for Organismal
Studies, Heidelberg University

Ex-President, Heidelberg Academy of Science

滞在：2018 年 4 月、2019 年 3 月（ドイツ科学イノベーションフォーラム）、
2024 年 2 月

太田 隆夫　教授

京都大学　名誉教授

元 豊田理化学研究所フェロー

定期ミーティング

Anthony D. Ho 教授

Department of Medicine V, Heidelberg University

Emeritus Professor

滞在：2018 年 4 月、2019 年 3 月、2024 年 2 月

【客員研究員】

鶴山 竜昭　教授

京都大学医学研究科創薬医学講座
現・放射線影響研究所
病理画像の機械学習と病理試料の力学の相関
2018 年度、2019 年度

杉村 佳織　博士

島津製作所　基盤技術研究所
人工授精における非侵襲卵子評価技術
2019 年度、2020 年度

上野 盛夫　准教授

京都府立医科大学　眼科学教室
角膜再生医療の物理的バイオマーカー開発
定期ミーティング

田中 寛　助教

京都府立医科大学　眼科学教室
角膜再生医療の物理的バイオマーカー開発
2018 年度

【受け入れ研究者（海外）】

Erwin Frey 教授

Arnold Sommerfeld Center for Theoretical Physics and Center for NanoScience, Department of Physics, LMU Munich

セミナー講演と拠点メンバーとの議論

滞在：2018 年 11 月

Chwen-Yang Shew 教授

Department of Chemistry, City University of New York

セミナー講演（京都大学理学部・市川正敏講師、同志社大学生命医科学部・吉川研一教授と共催）

滞在：2019 年 7 月

Helmut R. Brand 教授

Department of Physics, University of Bayreuth

拠点メンバーとの議論、日独非平衡統計物理ネットワークに関する打ち合わせ

滞在：2019 年 8 月、2023 年 3 月、2023 年 10 月

Ole G. Mouritsen 教授

Department of Food Science, Copenhagen University

市民講座「和食の科学」を時計台記念ホールで開催

滞在：2019 年 9 月

Uwe Thiele 教授

Institute for Theoretical Physics, Münster University

在外研究

滞在：2023 年 5－7 月

Marcus Müller 教授

Institute for Theoretical Physics, Göttingen University

拠点メンバーとの議論

滞在：2023 年 7 月

【受け入れ研究者（国内）】

高島 義徳　教授

大阪大学　高等共創研究院　理学研究科 高分子科学専攻
超分子材料による細胞制御
定期ミーティング

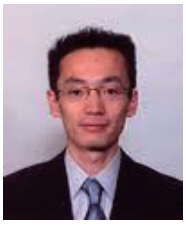
檜垣 勇次　准教授

大分大学　理工学部　共創理工学科
双イオン性高分子ブラシの界面物性
2019 年 3 月

手島 哲彦　博士

NTT 物性研究所
微小流路を用いた脂質膜の自発展開観測
2019 年 11 月

原 雄二　教授



静岡県立大学　薬学部
（前・京都大学工学研究科准教授）
筋管形成のコンタクトガイダンス
定期ミーティング

吉川 洋史　教授

大阪大学　工学研究科　応用物理学科
（前・埼玉大学理学部教授）
パルスレーザーを用いた細胞力学計測（技術指導）
2019 年 3 月

古川 一暁　教授

明星大学　理工学部　物理学系
（前・NTT 物性研究所）
脂質膜の自発展開の観測
2018 年 4 月

谷口 貴志　准教授

京都大学　工学研究科　化学工学科
散逸的脂質膜展開の理論モデル
定期ミーティング

上野 祐子　教授

中央大学　理工学部　応用化学科
（前・NTT 物性研究所）
グラフェンと DNA 脂質膜の融合材料の創製
2018 年 4 月

中畑 雅樹　助教

大阪大学　大学院基礎工学研究科　物質創成専攻　化学工学領域
生物着想型分子認識ポリマーの創製
定期ミーティング

浦山 健司　教授

京都大学　大学院工学研究科　材料化学専攻　高分子機能物性分野
肺胞上皮の in vitro モデルを用いた COPD 進行メカニズムの解明
定期ミーティング

若林 里衣　准教授

九州大学　大学院工学研究院　応用化学部門　分子教室
ペプチド自己会合ナノファイバーによる細胞接着基板の開発
定期ミーティング

児島 千恵　准教授

大阪公立大学　工学研究科　応用化学分野
アニオン性末端デンドリマーと脂質膜の相互作用
定期ミーティング

平岩 徹也　Associate Research Fellow

Academia Sinica（台湾） Institute of Physics
Theoretical Physical Biology Group
再生ヒドラの体軸形成メカニズム
定期ミーティング

【医数物セミナー・学外講師】

藤原 久志　准教授
広島市立大学　情報科学研究科　医用情報科学専攻

富樫 英　助教
神戸大学　大学院医学研究科　分子細胞生物学

村川 秀樹　准教授
龍谷大学　理工学部　数理情報学科

河原 吉伸　教授
九州大学　マス-フォア-インダストリ研究所
理化学研究所　革新知能統合研究センター

長山 雅晴　教授
北海道大学　電子科学研究所

ネットワークの構築（４）
共同研究パートナー

ダイナミックな融合研究によって新たなサイエンスを生み出すことが我々の真骨頂です。ここでは京都拠点のメンバーのそれぞれが主なコンタクトパーソンとなった共同研究をリストアップしました。

国や分野を超えた共同研究ネットワークが大きく展開し、それぞれのテーマでメンバーが着実に成果を上げている事を見ていただければ幸いです。

山本暁久

- 「ヒト角膜内皮組織再建医療のための物理的バイオマーカーの開発」
  木下 茂　教授・外園 千恵　教授・上野 盛夫　講師ら
  （京都府立医科大学・眼科学）
  Nature Biomedical Engineering (2019)、*American Journal of Ophthalmology* (2022)
- 「中性子非鏡面散乱法を用いた疎水性フッ化ポリマー積層構造の水分子による構造変調」
  高原 淳　教授　（九州大学）、桧垣 勇次　准教授　（大分大学）
  Bruno Demé　博士 (Institut Laue-Langevin, France)
  Polymer J. (2022)
- 「フラーレン誘導体自己組織化膜の精密構造解析」
  中村 栄一　教授・原野 幸治　准教授（東京大学・理学系研究科）
  Oleg Konovalov　博士 (European Synchrotron Radiation Facility, France)
  Advanced Materials (2021)
- 「ゼラチンナノファイバーに対するヒト iPS 細胞の接着力と表現型に関する研究」
  小寺 秀俊　教授・劉 莉　准教授（京都大学・工学研究科）
  Yong Chen　教授 (Ecole Normale Supérieure, France)
  Stem Cell Reports (2018)
- 「造血幹細胞・前駆細胞の老化と糖蓄積、炭素代謝の定量解析」
  Anthony D. Ho　教授(Heidelberg University, Germany)
  Scientific Reports (2020)
- 「放射光を用いた新規ポルフィリン共役分子膜の精密構造計測」
  Ali Makky　准教授 (Université Paris-Sacley, France)
  ※ Makky 准教授はハイデルベルク田中研のポスドク OB
  Oleg Konovalov　博士 (European Synchrotron Radiation Facility, France)
  Chemistry - A European Journal (2019)
- 「微小角 X 線光子相関分光法を用いた液体／液体界面におけるゾル - ゲル転移」
  Oleg V. Konovalov　博士・Yuriy Chushkin　博士
  (European Synchrotron Radiation Facility, France)
  The Journal of Physical Chemistry B (2020)

- 「半フッ化アルカン分子の自己組織化による二次元球晶の構造物性解析」
  Marie Pierre Krafft 教授 (University of Strasbourg, France)
  ChemPhysChem (2018)

- 「微小角 X 線蛍光法による抗菌剤のバクテリア表面に対する作用機序の解明」
  井上 滋登 博士ら（花王）
  Oleg V. Konovalov 博士 (ESRF, France)
  Scientific Reports (2020)

- 「気／液界面における金属ナノ粒子の 2 次元自己集合体の秩序構造と非線形粘弾性」
  玉田 薫 教授（九州大学・先導物質化学研究所）
  谷口 貴志 准教授 （京都大学・工学研究科）
  吉川 研一 教授 （同志社大学・生命医科学部）
  Langmuir (2018)

- 「微小角 X 線小角散乱法を用いた分子自己集合体の長距離相関解析」
  Marie Pierre Krafft 教授(University of Strasbourg, France)
  Oleg V. Konovalov 博士 (ESRF, France)
  ChemPhysChem (2019)

- 「固体支持脂質二分子膜の自発展開と凍結の可逆的スイッチング」
  古川 一暁 教授 （明星大学・理工学部）
  谷口 貴志 准教授 （京都大学・大学院工学研究科）
  投稿準備中

- 「消化器がん進行度と細胞の変形・運動モードの相関」
  鶴山 竜昭 教授 （放射線影響研究所、広島大学・医学研究科）
  投稿準備中

- 「ファイトケラチン着想高分子による重金属イオンの選択的捕捉メカニズム」
  中畑 雅樹 助教 （大阪大学・大学院基礎工学研究科）
  池本 夕佳 主幹研究員 （JASRI）
  投稿準備中

- 「トポロジカル解析を駆使した肺気腫に特有な構造の同定」
  平井 豊博 教授・佐藤 篤靖 助教・田辺 直也 助教ら （京都大学・医学研究科）
  投稿準備中

- 「不妊治療における顕微授精のためのバイオマーカーの開発」
  杉村 佳織　博士 （島津製作所）
  古賀 敏文　院長 （古賀敏文ウイメンズクリニック）
  特許出願準備中

- 「患者由来がんオルガノイド動態の数理解析」
  妹尾 浩 教授、福田 晃久 准教授 （京都大学・医学研究科）
  投稿準備中

- 「膵癌前癌病変由来細胞の変形運動モード解析」
  妹尾 浩　教授、福田 晃久　准教授 （京都大学・医学研究科）
  投稿準備中

- 「ヒト脳腫瘍グリオーマモデル細胞の悪性度を評価する発光分子プローブの界面物性評価」
  長谷川 靖哉 教授 （北海道大学・工学研究科）
  田中 伸哉 教授、津田 真寿美 准教授 （北海道大学・医学研究科）
  Scientific Reports (2023)

- 「π 共役両親媒性有機材料の分子薄膜の電気化学特性評価」
  辻 勇人 教授 （神奈川大学・理学研究科）
  竹谷 純一 教授、渡邉 峻一郎 准教授 （東京大学・新領域創成科学研究科）
  投稿準備中

- 「抗菌性を示す合成ナノセルロースとモデルバクテリア膜表面との相互作用」
  芹澤 武 教授 （東京工業大学・物質理工学院）ら
  ACS Applied Bio Materials (2023)

- 「3 次元周波数変調走査型顕微鏡を用いたファイトケラチン着想高分子ブラシの重金属イオン依存的な表面構造物性変化の定量」
  宮田 一輝 准教授、福間 武 教授 （金沢大学）
  中畑 雅樹助教 （大阪大学）
  Nanoscale Advances (2022)

- 「ヒトブラストイドモデルの誘導効率に対するマトリックス力学特性の影響」
  亀井 謙一郎 准教授 （ニューヨーク大学アブダビ校、京都大学・iCeMS）
  論文投稿中

鈴木　量

- 「ヒドラの再生過程における対称性の破れと自発変形の関係」
  Thomas Holstein 教授・Suat Özbek 教授
  （Heidelberg University, Germany）
  平岩 徹也 博士 （Mechanobiology Institute, National University of Singapore, Singapore）
  投稿準備中
- 「可逆的に変調可能なしわ基板を用いた筋管形成の動的制御技術」
  梅田 眞郷 教授 （京都大学・工学研究科）
  原 雄二 教授 （静岡県立大学・薬学部）
  大園 拓哉 主任研究員 （産業技術総合研究所）
  Langmuir (2019)
- 「人工超分子からなるファイバーの進行波が生み出す力の計測」
  浜地 格 教授（京都大学・工学研究科）
  市川 正敏 講師（京都大学・理学研究科物理学専攻）
  Nature Communications (2020)
- 「外的刺激で誘発した気道収縮がマウス肺気腫表現型に及ぼす影響」
  平井 豊博 教授・佐藤 篤靖 助教・田辺 直也 助教ら
  （京都大学・医学研究科）
  Karel Svadlenka 准教授 （東京都立大学・数理科学）
  投稿準備中
- 「動的変形解析を用いた癌オルガノイドの不均一な遺伝型変異と転移能の定量指標」
  佐藤 俊朗 教授（慶應義塾大学・医学部）

投稿準備中

- 「病理サンプルの硬さと機械学習に基づく癌の進行度の診断」
  鶴山 竜昭 教授 （放射線影響研究所、広島大学・医学研究科）
  再投稿準備中
- 「基板硬さによる神経前駆細胞の集団的細胞運動の応答」
  影山 龍一郎 教授 （理化学研究所）
  佐野 雅己 教授 （上海交通大学）
  中畑 雅樹 助教 （大阪大学・大学院基礎工学研究科）
  投稿準備中
- 「患者由来がんオルガノイド動態の数理解析」
  妹尾 浩 教授、福田 晃久　准教授ら （京都大学・医学研究科）
  投稿準備中
- 「細胞外カルシウムによるスクランブラーゼ Xkr4 の活性化メカニズム」
  鈴木 淳 教授（京都大学・iCeMS）
  Nature Communications (2024)

林　健太郎

- 「超分子側鎖を導入したゼラチン材料による動的細胞操作技術の開発」
  高島 義徳 教授（大阪大学・高等共創研究院）
  ACS Appl. Polym. Mater (2022), Polymers (2022)
- 「三次元足場とタンパクナノファイバーの融合による幹細胞分化誘導システムの開発」
  Martin Bastmeyer 教授（Zoological Institute, Karlsruhe Institute of Technology, Germany）
  Front. Phys (2022)
- 「基板硬さによる神経前駆細胞の集団的細胞運動の応答」
  影山 龍一郎 教授 （理化学研究所）
  佐野 雅己 教授 （上海交通大学）
  中畑 雅樹 助教 （大阪大学・大学院基礎工学研究科）
  投稿準備中

国際連携（１）
日独６大学連合（HeKKSaGOn Alliance）

HeKKSaGOn Alliance はハイデルベルク大学がドイツ・ボッシュ財団の支援を受けて、主幹校として 2010 年にスタートさせた日独学術交流プログラムです。

部門長・田中はハイデルベルク大学 Eitel 総長の特命補佐として、2008 年のメンバー校選抜からこのプログラムに関わり、2010 年の第一回会議（於・ハイデルベルク）以来、作業部会 WG1「Life and Natural Science Fusion」の代表を 10 年以上にわたって務め、日独の研究人脈を最大限に活かして活発な学術交流・人材育成を主導してきました。これらの業績を認められて 2014 年にはドイツ連邦・Gauck 大統領（当時）から Siebold 賞を大統領宮殿にて授与されました。また Eitel 総長は日独学術交流への貢献によって 2021 年に旭日大綬章を受章されています。

2020 年に WG の再編成が行われた際には、拠点客員教授のカールスルーエ工科大学・Bastmeyer 教授、東北大学・水藤寛教授に副代表をお願いして医工・医数物連携を前面に打ち出した新たな WG「New-Generation Biomedical Science」を代表として提案、審査委員から最高得票を得てスタートさせました。

ドイツエクセレンスクラスターや WPI プログラム、新学術領域といった既存の大型プロジェクトをうまく紐づけることにより個人のネットワークを超えた Center-to-Center の国際連携を展開しています。

HeKKSaGOn Alliance の歩み（2010 年～）

「HeKKSaGOn Alliance」とは **He**idelberg, **K**yoto, **K**arlsruhe, **S**endai, **G**öttingen, **O**saka の頭文字からとったた 6 大学連合の愛称です。

部門長・田中が Siebold 賞をドイツ連邦共和国・Gauck 大統領より授与（2014 年）

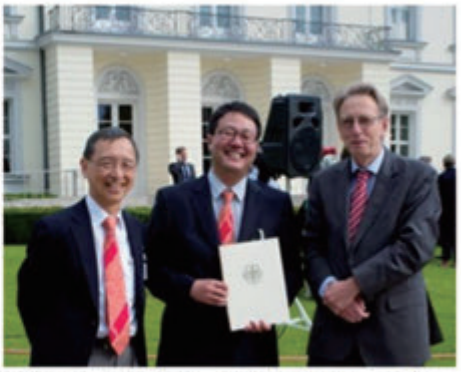
ジーボルト賞を受賞（2014年6月）

於・ドイツ大統領宮殿（ベルリン）

大統領宮殿Schloss Bellveu貴賓室でのセレモニー

受賞者・田中の答礼

ドイツ連邦共和国 J. Gauck大統領と



お祝いに駆けつけてくれた、当拠点客員教授・Ho教授（左）とHolstein教授（右）と宮殿の前庭で

2018 年　第 6 回 WG 会議（於・大阪）

寄附部門のキックオフ翌日から開かれた本会議では、ドイツサイドから田中と Ho 教授、Holstein 教授がプロジェクトリーダーを務める幹細胞に関する Collaborative Research Center CRC873 や Bastmeyer 教授がプロジェクトリーダーを務めるヘルムホルツプログラム Biointerface を紹介し、日本サイドからは新たに加わった東北大・水藤教授が WPI 拠点 AIMR を、大阪大・紀ノ岡教授が材料としての細胞品質の管理システムなどについて紹介しました。

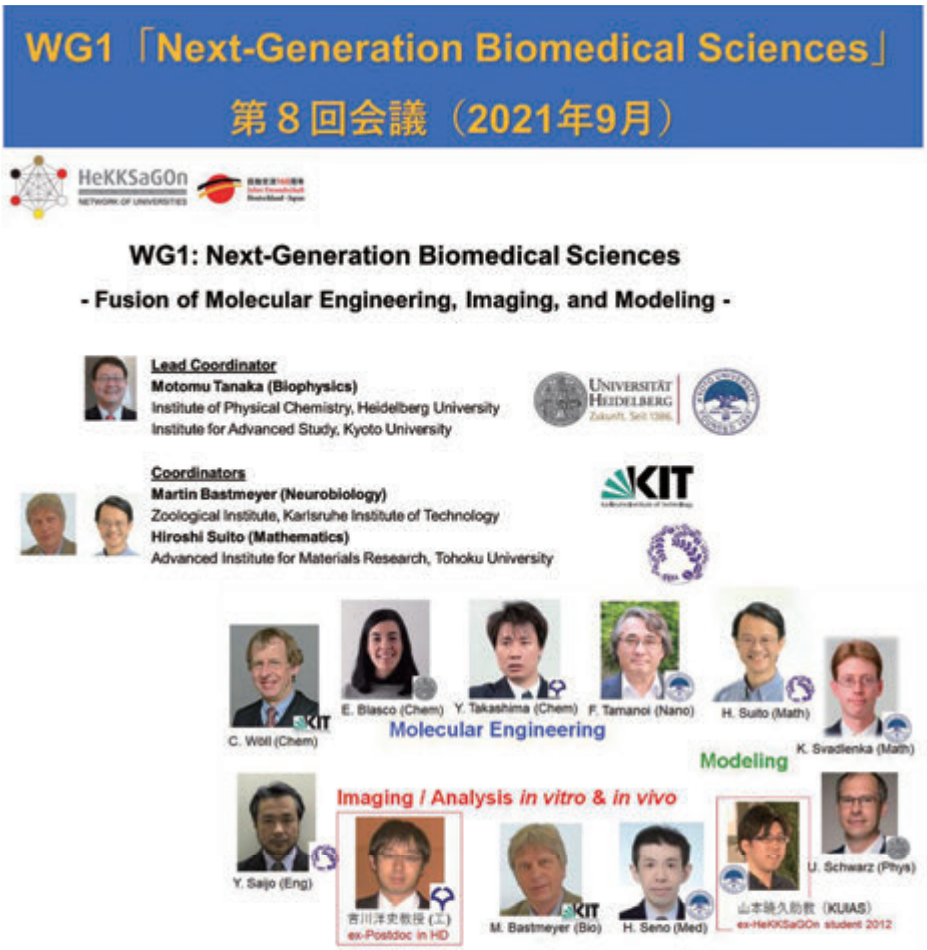
また京都大からは、武田教授（医学部）が学部生海外派遣プログラムについてハイデルベルク田中研はじめいくつかの例を挙げて紹介、Svadlenka 准教授（理学部）が数学を基盤とする MACS 教育プログラムを紹介するなど、人材育成や学生レベルでの交流活動についても議論しました。ここではドイツに学生・ポスドクとして留学経験がある、大阪大・中畑助教（化学工学）や当拠点の山本・鈴木両助教も自らの経験を参加した若手教員らに共有しました。

2019 年　第 7 回 WG 会議（於・ハイデルベルク）

6 大学を一巡して 2 周目に入った本会議では、学長レベルでは今後の展開やビジョンに関する議論が行われ、WG のリニューアルについての議論が行われました。我々の WG では、ドイツで Bastmeyer 教授と田中が運営委員を務めるエクセレンスクラスター「3D Matter Made to Order」がスタートした事、また日本では田中が計画研究班長を務める新学術領域「水圏機能材料」がスタートした事が紹介されました。これを踏まえて議論した結果、「医学」「数理」「材料工学」によりフォーカスする事、その総括を田中が務め、Bastmeyer 教授（生物学）と水藤教授（数学）が副代表としてこれを補佐することが基本方針として決まりました。これに沿って田中・Basmeyer・水藤が 2020 年に提案した新たな WG「New-Generation Biomedical Science」は最高評価を得て 2021 年にスタートしました。

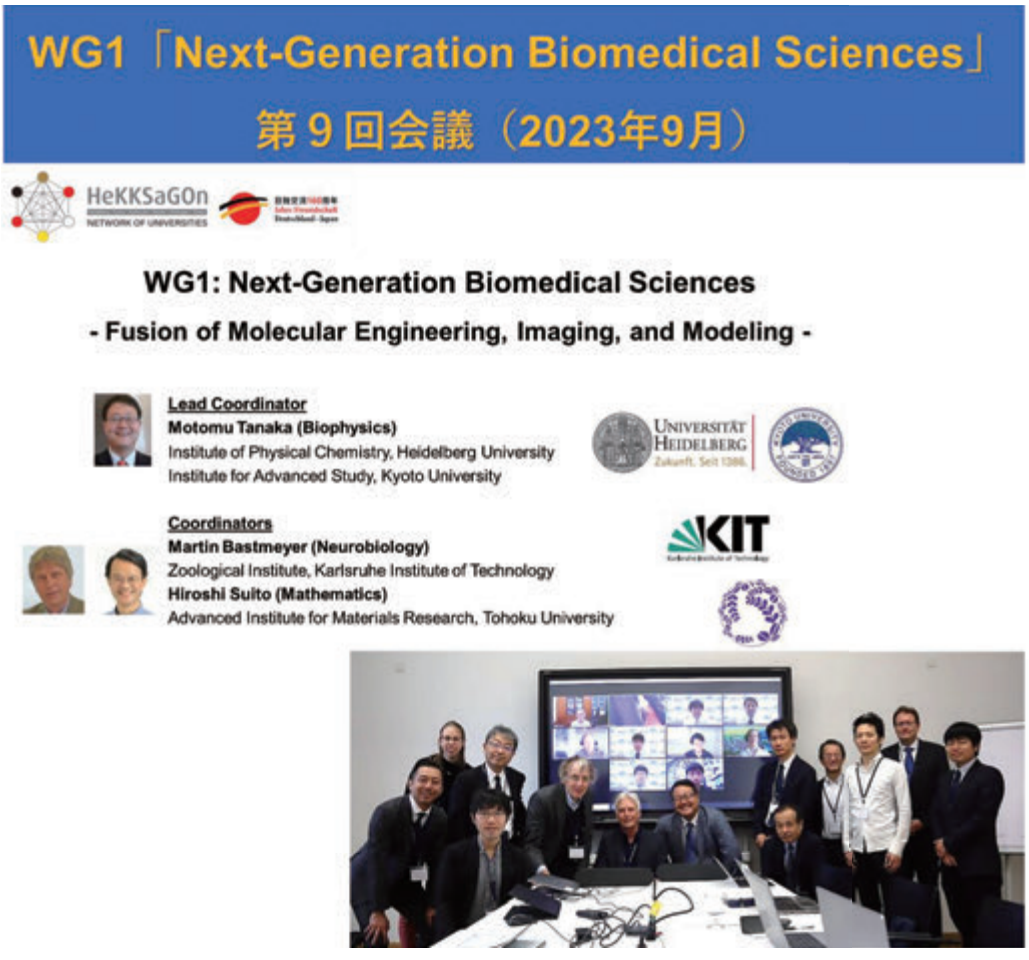
2021 年　第 8 回 WG 会議（於・東北大学、オンライン）

コロナ禍の中迎え東北大学によって主催された第 8 回学長会議では、一部のプログラムがオンラインによって開催されました。Bastmeyer 教授（生物学）・水藤教授（数学）とともに 2020 年に提案し新たに始動した WG「New-Generation Biomedical Science」の活動内容や、分子工学、in vitro 系と in vivo 系の双方に適したイメージング・解析技術、数理モデルといった手法を特色とした新体制について、田中がプレナリーセッションにおいて報告を行いました。また、当拠点の山本助教が Virtual poster session for early-career researchers および連動した口頭発表で、自身のドイツ留学経験やその後の日独二国間連携について活動報告を行いました。



2023 年　第 9 回 WG 会議（於・ゲッティンゲン）

コロナによる行動制限が緩和されはじめた第 9 回学長会議は、ゲッティンゲン大学において対面・オンラインのハイブリッド形式で開催されました。田中が 2 日間にわたり議長を務めた WG「New-Generation Biomedical Science」のミーティングでは、両日とも約 15 名の現地参加者に約 10 名のオンライン参加者を加え、各自の研究内容の紹介だけでなく、若手育成や人材交流についても議論を行いました。2 日目には、当拠点の鈴木助教・山本助教・林助教・永井氏も、それぞれの研究内容や渡独による研究交流、日本における大学院生の受入れや研究指導・共同研究等の経験について報告しました。また、学長会議前にはハイデルベルク大学において”New-Generation Biomedical Science”と題したワークショップを開催し、東北大・水藤教授（数学）、ハイデルベルク大・Salg 医師（医学）、大阪大・中畑助教（化学工学）、大阪大・藤原助教（小児発達学）による講演と議論を通じた、研究に立脚する国際ネットワークの更なる強化を行いました。



国際連携（２）
非平衡統計物理学分野における国際連携

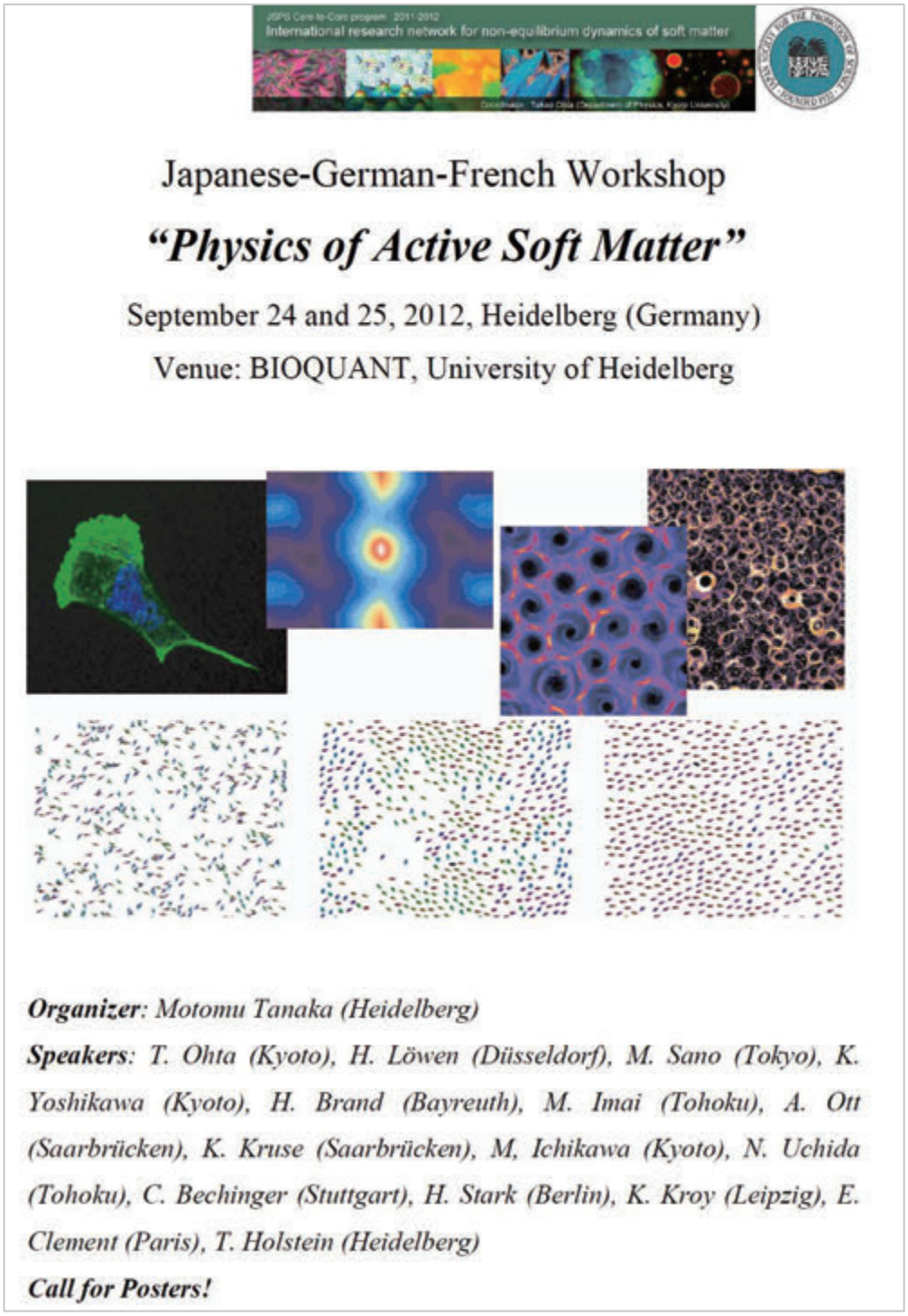
部門長・田中は、独立グループリーダーとして研究を行っていたミュンヘン工科大学物理学部において広島大学（当時）太田隆夫教授（後に京都大学、現・当拠点客員教授）が 2002 年に講演されたのをきっかけに、太田教授や Müller-Krumbhaar 教授（ユーリッヒ国立研究所）が主導する、日本とドイツの非平衡統計物理学における学術交流のネットワークに生命物理・ソフトマター物理のドイツ側若手として参画してきました。

特に先端研究拠点事業（国際戦略型）「ソフトマターと情報に関する非平衡ダイナミクス」（2013 – 2016、代表・京都大学 佐々真一教授）の連携先である EU FP7「Non-equilibrium dynamics of soft and active matter」（2012 – 2016、代表・CEA Hugues Chaté 教授）においてはプロジェクトリーダー兼ドイツ参画機関のとりまとめを務め、2012 年にはハイデルベルクにおいて日独仏シンポジウム「Physics of Active Soft Matter」を開催しました。

1995 年にスタートした日独の非平衡統計物理ネットワークの 25 周年に当たる 2020 年を記念して、日独シンポジウムを京都大学基礎物理学研究所で開催するべく、田中が世話人の中心として準備を進めていたがコロナ禍で一年延期となり、2021 年度もしくは 2022 年度の開催を計画しています。

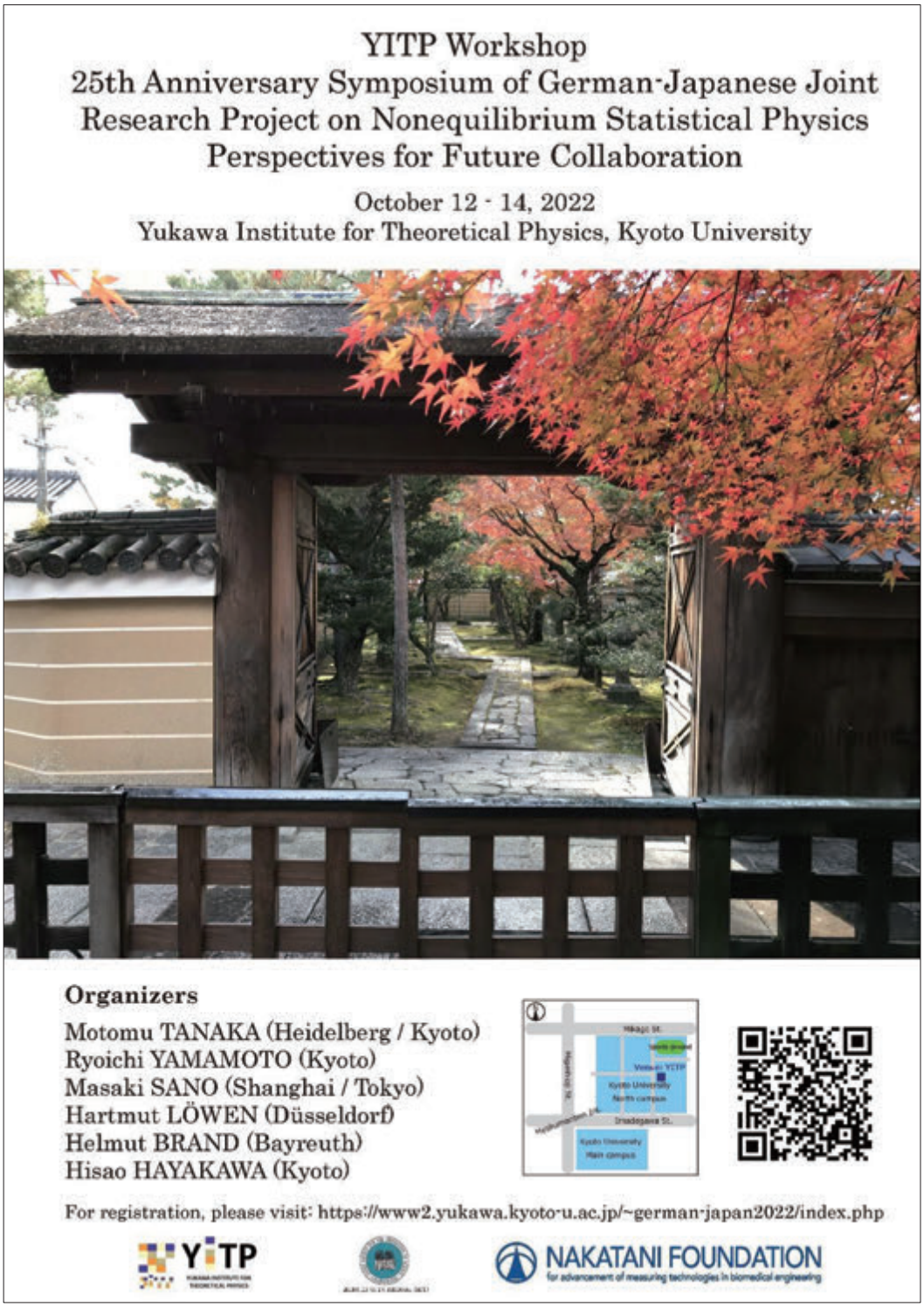
日仏独ワークショップ「Physics of Active Soft Matter」

2012 年 9 月　於・ハイデルベルク大学



日独 非平衡統計物理ネットワーク 25 周年記念シンポジウム

2022 年 10 月　於・京都大学



国際連携（３）

新学術領域『水圏機能材料』とドイツエクセレンスクラスター『3D Matter Made to Order』の連携

部門長・田中と Bastmeyer 教授（当拠点客員教授）は、2019 年にカールスルーエ工科大学とハイデルベルク大学が共同で設立した、ドイツエクセレンスクラスター『3DMatter Made to Order』を設立、現在も運営委員として拠点の運営に携わっています。さらに田中は同年に代表・加藤隆史教授（東京大学）のもとスタートした、新学術領域『水圏機能材料』にも計画研究班長として参加しています。

田中は二つの拠点の得意とする分野が相補的であることに着目し、日独の卓越した拠点同士をつなぐことでシナジーが生まれるのではと考えました。その第一歩として、日独国際シンポジウム「Aquatic Materials Made to Order」を企画、実行委員長としてハイデルベルクでの開催にむけ準備を進めました。残念ながらコロナ禍のため開催 5 日前に日本側メンバーが渡航を断念する状況となり、紙上開催となってしまいましたが、「超分子ゲルと 3 次元微細構造を融合させて一細胞を力学的に操作する」という高島・田中・Bastmeyer の共同研究は国際誌 Science Advances 誌に国際共著論文の形で結実しました（研究ハイライト参照）。田中と Bastmeyer はさらに DAAD（ドイツ学術交流支援機構）と京都大学のパートナーシッププログラムを活用するなどさらなる連携強化を進めています。また山本助教は田畑修教授（京都大学名誉教授、現京都先端科学大学工学部長）が代表を務める国際共同研究強化 B『生体外モデルデバイスの細胞代謝リアルタイムモニタリング技術に関する日独共同研究』の分担研究者として機械工学の J. Korvink 教授（カールスルーエ工大）らと共同研究を行うなど、独自の国際ネットワークの開拓に取り組んでいます。

2020 年

German-Japanese Worksop 「Aquatic Materials Made to Order」 （3月4・5日）

於　ハイデルベルク大学

文部科学省科学研究費補助金新学術領域研究（研究領域提案型）
「水圏機能材料：環境に調和・応答するマテリアル構築学の創成」

MEXT Grant-in-Aid for Scientific Research on Innovative Areas
Area Number: 6104, FY2019-FY2023

Aquatic Functional Materials

領域代表
加藤隆史教授
（東京大学）

田中 求 は計画研究A03（機能開拓班）班長

ドイツ科学財団（Deutsche Forschungsgemainschaft）
German Excellence Cluster「3D Matter Made to Order」

3D MATTER
MADE TO ORDER

Germany's Excellence Strategy
- 2082/1 – 390761711

領域代表

Martin Wegener 教授
（カールスルーエ工科大学）

Uwe Bunz 教授
（ハイデルベルク大学）

田中 求とM. Bastmeyer 教授（拠点客員教授）は共に
設立メンバー・運営委委員

田中が実行委員長として二つの異分野融合型の大型拠点をつなぎ日独間のネットワークづくりを目指したが、コロナ禍のため開催5日前にオンサイトでの開催を断念（紙面開催）

German-Japanese Workshop

“Aquatic Materials Made to Order”

March 4 & 5, 2020

Heidelberg University (Germany)

Jointly Organized by

MEXT Grant-in-Aid for Scientific Research on Innovative Areas

“*Aquatic Functional Materials*”

&

German Excellence Cluster

“*3D Matter Made to Order*”

Aquatic Functional Materials

MEXT Grant-in-Aid for Scientific Research on Innovative Areas
Project Leader: Takashi Kato
Area Number: 6104, FY2019-FY2023

3D MATTER MADE TO ORDER

Germany’s Excellence Strategy
- 2082/1 – 390761711
Spokespersons:
Martin Wegener and Uwe Bunz

人材育成（１）
国際ウィンタースクール

部門長・田中は日独６大学連合（HeKKSaGOn Alliance）の枠組みの中で2012年9月に第一回日独国際サマースクール『CROSSING BORDERS: UNRAVELING PRINCIPLES OF LIFE WITH QUANTITATIVE TOOLS』をボッシュ財団とバーデンヴュルテンベルク州の支援を受けてハイデルベルクで開催しました。これはHeKKSaGOn Allianceのメンバー校の大学院生と若手研究員を対象としたもので、日本とドイツから計40名ほどの学生が参加しました。

その後、京都大学総長裁量経費事業の支援の下、2016年3月に第二回目の国際ウィンタースクール『From Materials to Life: Multidisciplinary Challenges』を京都大学で開催しました。ここではHeKKSaGOn Allianceの枠を超えて、南洋理工大学（シンガポール）はじめ他大学からの参加を募り、より国際色豊かなスクールとなりました。

第三回目の国際ウィンタースクール『Unraveling Dynamics of Life』は中谷財団やドイツ 科学・イノベーション フォーラム 東京（DWIH Tokyo）などの支援のもとに2019年3月に高等研究院で開催しました。拠点長・田中とミュンヘン工科大学でともに研鑽を積んだJoachim Raedler教授（ミュンヘン大学）や20年以上にわたって交流のあるAtul Parikh教授（カリフォルニア大学デービス校）など、名だたる研究者が講師を務め、参加学生たちと議論していただく貴重な機会となりました。

第四回目のスクール『Towards Holistic Understanding of Life』はコロナ禍で延期を余儀なくされましたが、2024年2月に中谷財団に加え「医学と数理」研究会でも連携してきた理研iTHEMSからも支援をいただいて開催することができました。第四回目のスクールには、拠点長・田中が設立メンバーとして参画したドイツ・エクセレンスクラスター「3D Matter Made to Order」のMartin Wegenerセンター長（カールスルーエ工科大）はじめ主要メンバーに講師を務めていただき、工学分野をはじめさらに幅広い視野から

新たなバイオメディカルエンジニアリング創出へ向けた議論を参加学生たちと行うことができました。

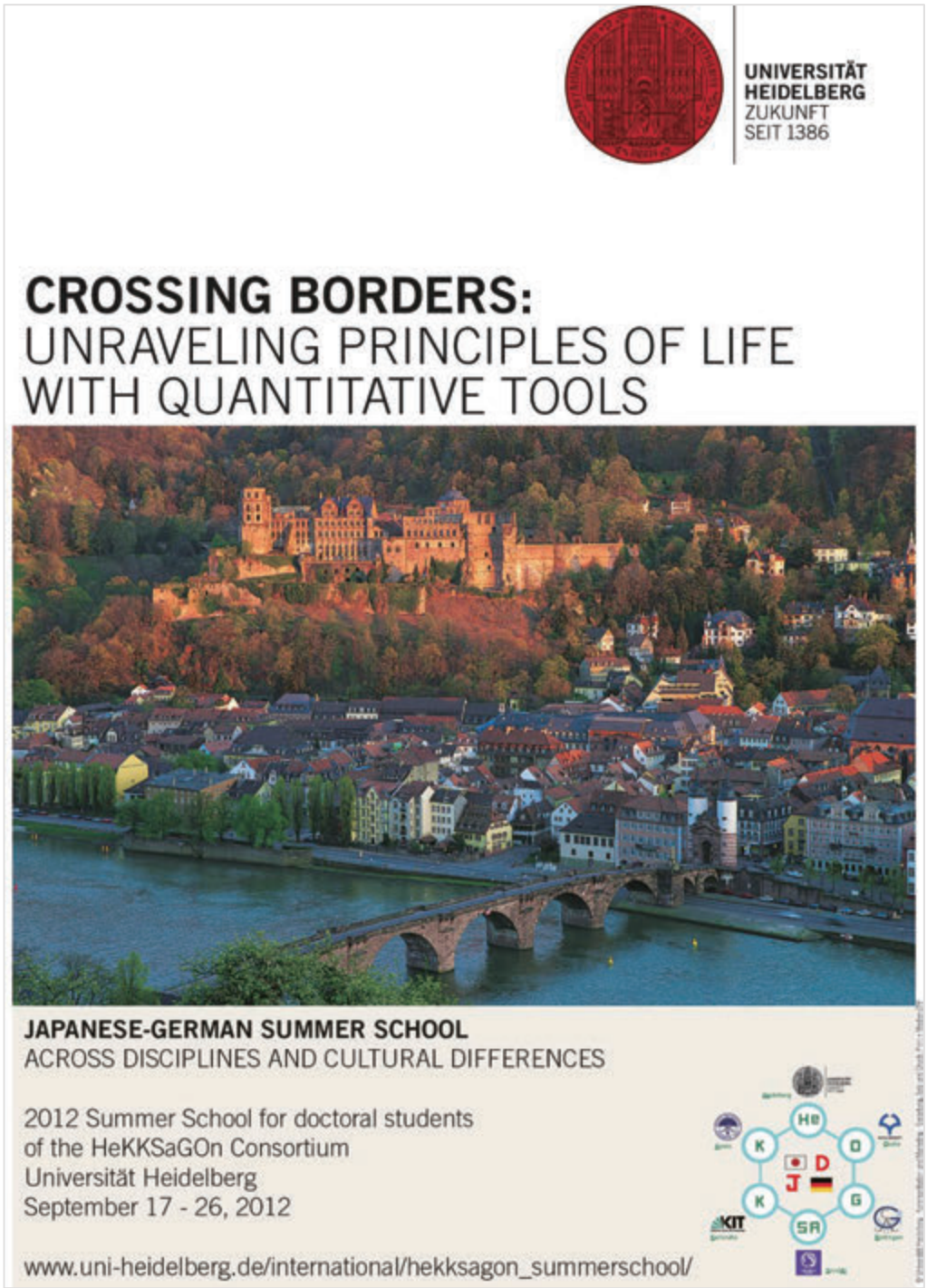
第一回目からずっと変わらない我々のスクールの特徴は、当拠点の客員教授を始め臨床医学・工学・化学・物理学・数学といった幅広い分野の一流の講師陣に講義をお願いするだけでなく、全ての参加者に口頭とポスターで自分の研究を紹介する機会を設けて講師や他の参加者と議論をする時間を多くとっている事、またサイエンスだけでなく『ドイツでドイツ文化を学ぶ』『日本（京都）で日本文化を学ぶ』のようにより広く開催地の文化に触れてもらうプログラムを提供している事があげられます。

第一回目のスクールに学生として参加した当拠点の山本助教が第三回・第四回目のスクールでは講義を担当し、第四回のスクールではハイデルベルク大・田中研でポスドクとして約四年にわたって研鑽を積んだ吉川洋史教授（阪大工）が講義を担当してくださるなど、異分野融合型の研究を通じて育った人材が次の世代の育成に貢献することが感じられた場でもありました。

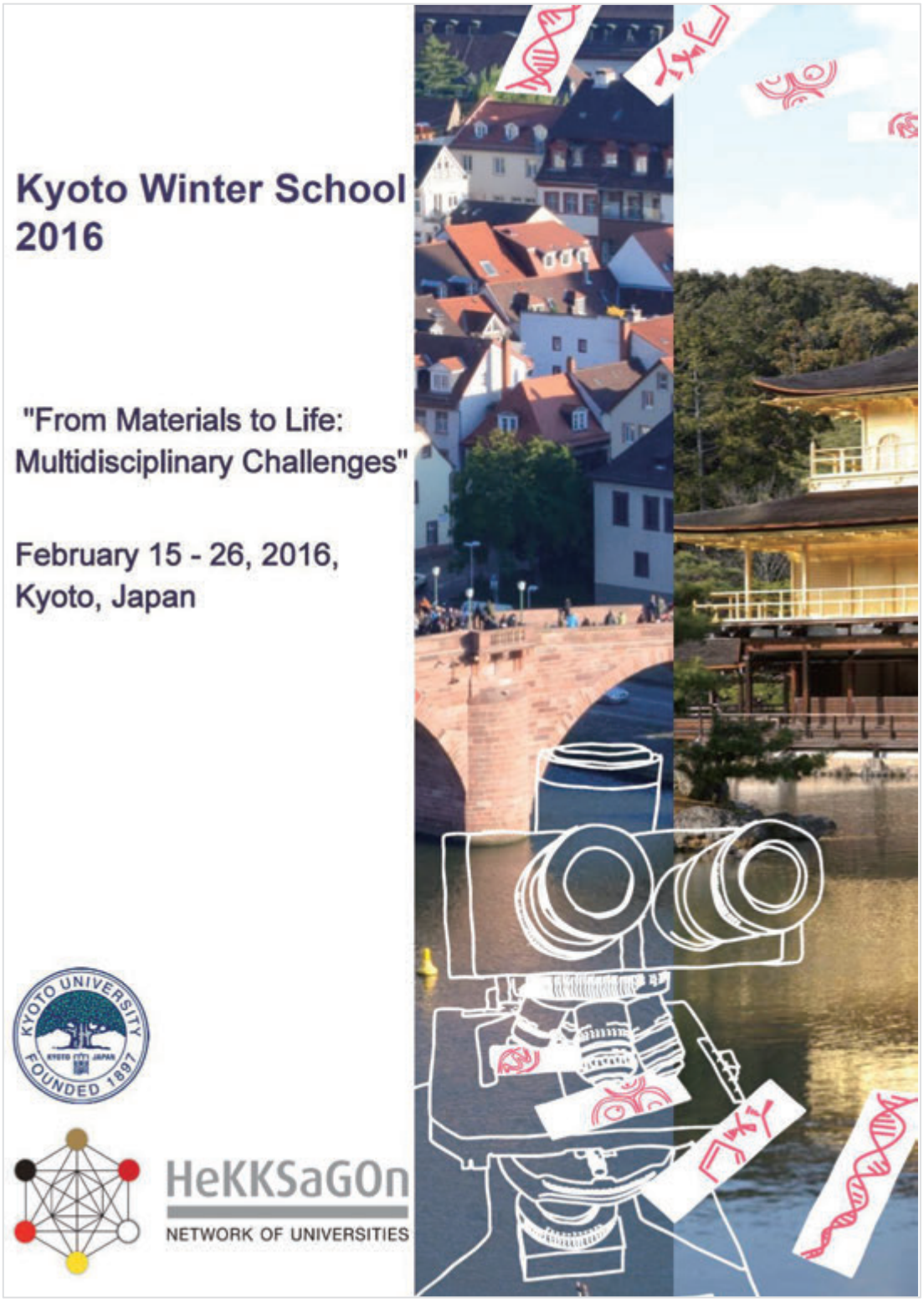
また講師同志・参加者同士がこのスクールでの出会いや議論をきっかけにその後ネットワークを広げて連携したりと、日本にこれまでなかった「顔の見える国際ネットワーク」を基盤にした我々の人材育成のへの取り組みは着実にグローバルな人材の育成としての成果を挙げました。

過去のサマー/ウィンタースクール

第一回（2012年9月・ハイデルベルク）



第二回（2016年2月・京都大学）



第三回（2019年3月・京都大学）

第三回国際ウィンタースクール（2019年3月）

於・京都大学吉田国際交流会館

Kyoto Winter School

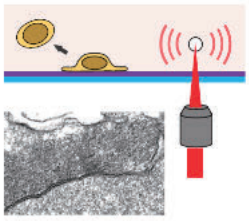
"Quantifying Dynamics of Life"

March 11 – 20, 2019

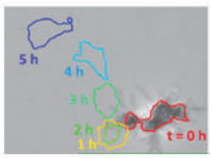
Center for Integrative Medicine and Physics

Institute for Advanced Study, Kyoto University

KUIAS



$$\frac{d}{dt}v_i = \gamma v_i - |v^2|v_i - aS_{ij}v_j$$



Aim:

Cross-disciplinary, international winter school for graduate students and junior researchers from medicine, physics, mathematics, chemistry, biology, and engineering sciences, etc.

Confirmed lecturers:

T. Holstein (Heidelberg), A. Parikh (Davis), M. Bastmeyer (Karlsruhe), J. Rädler (Munich), J. Korvink (Karlsruhe), A. D. Ho (Heidelberg), K. Yoshikawa (Doshisha), S. Kinoshita (KPUM), A. Harada (Osaka), S. Takeuchi (Tokyo), H. Suito (Tohoku), S. Deguchi (JAMSTEC), R. Nagatomi (Tohoku), S. Kidoaki (Kyushu), O. Tabata (Kyoto), K. Svadlenka (Kyoto), T. Tsuruyama (Kyoto), H. Wada (Ritsumeikan), T. Hayashi (Tokyo Tech), H. Y. Yoshikawa (Saitama), M. Sano (Tokyo) F. Tamanoi (Kyoto / UCLA), K. Kodaira (NAOJ)

Organizer:

M. Tanaka (Kyoto / Heidelberg)

Local committee:

A. Yamamoto, R. Suzuki

M. Yoshida

Supported by

NAKATANI FOUNDATION
for advancement of measuring technologies in biomedical engineering

HeKKSaGOn
NETWORK OF UNIVERSITIES

DWIH Tokyo
Land der Ideen

KYOTO WINTER SCHOOL 2019 PROGRAM
"QUANTIFYING DYNAMICS OF LIFE"

Date: March 11 – 20, 2019
Venue: 2nd floor Seminar Room, KUIAS/iCeMS Main Building (#77)
Kyoto University
Yoshida Ushinomiya-cho, Sakyo-ku, Kyoto

PROGRAM

Monday, March 11

8:45 – 9:45 **Welcome & Orientation**
Introduction of the Program

9:45 – 10:45 **Lecture 1 "Physics of Life"**
Prof. Kenichi Yoshikawa (Doshisha University)
10:45 – 11:00 ***Break***
11:00 – 12:00 **Lecture 2 "Towards Medicine-Physics Integration"**
Prof. Motomu Tanaka (Kyoto University / Heidelberg University)
12:00 – 13:30 ***Lunch Break***
13:30 – 14:30 **Lecture 3 "MALDI TOF for Medical Imaging"**
Prof. Tatsuaki Tsuruyama (Kyoto University)
14:30 – 15:30 **Basic Japanese 1**
Mr. Kei Kubo
15:30 – 15:45 ***Break***
15:45 – 16:45 **Campus Tour escorted by KU student ambassadors**
18:00 – 20:00 **Welcome Reception at KUIAS main building**

Tuesday, March 12

8:45 – 9:45 **Lecture 4 "Cell Migration on Microarrays"**
Prof. Joachim Rädler (LMU München)
9:45 – 10:45 **Lecture 5 "Origin of Life out of Equilibrium"**
Prof. Atul Parikh (UC Davis)
10:45 – 11:00 ***Break***
11:00 – 12:00 **Lecture 6 "Life Under Extreme Conditions"**
Prof. Shigeru Deguchi (JAMSTEC)
12:00 – 13:30 ***Lunch Break***
13:30 – **Presentation 1: PhD projects – Session A**

Wednesday, March 13

8:45 – 9:45	**Lecture 7 "Stem Cell Research at Crossroads"**
	Prof. Anthony Ho (Heidelberg University)
9:45 – 10:45	**Lecture 8 "Micro-NMR for Metabolomics"**
	Prof. Jan Korvink (Karlsruhe Institute of Technology)
10:45 – 11:00	***Break***
11:00 – 12:00	**Lecture 9 "Modeling Flows"**
	Prof. Hiroshi Suito (Tohoku University)
12:00 – 13:30	***Lunch Break***
13:30 – 14:30	**Lecture 10 "MEMS Technology for Biohybrid"**
	Prof. Shoji Takeuchi (The University of Tokyo)
14:45 – 16:45	**Japanese Calligraphy**
	Ms. Kazumi Torii assisted by Ms. Hisako Mouri
	At multi-purpose hall (International Seminar House)

Thursday, March 14

8:45 – 9:45	**Lecture 11 "Cell Based Therapy for Cornea Restoration"**
	Prof. Shigeru Kinoshita (Kyoto Prefectural University of Medicine)
9:45 – 10:45	**Lecture 12 "Mechano-Regulation of Stem Cells"**
	Prof. Satoru Kidoaki (Kyushu University)
10:45 – 11:00	***Break***
11:00 – 12:00	**Lecture 13 "The Hydra Stem Cell System"**
	Prof. Thomas Holstein (Heidelberg University)
12:00 – 13:30	***Lunch Break***
13:30 – 14:30	**Basic Japanese 2**
	Mr. Kei Kubo
14:30 –	**Presentation 2: PhD projects – Session B**

Friday, March 15

8:45 – 9:45	**Lecture 14 "Modeling Materials"**
	Prof. Tomohiro Hayashi (Tokyo Institute of Technology)
9:45 – 10:45	**Lecture 15 "Methodology for Control of Self-Organizing Systems"**
	Prof. Hiroshi Yoshikawa (Saitama University)
10:45 – 11:00	***Break***
11:00 – 12:00	**Special Program (1): Lectures by Junior Faculties**
	"Life-inspired Self-sorting Supramolecular Hydrogels"
	Dr. Ryou Kubota (Kyoto University)
	"A Non-Invasive Physical Biomarker for Restoring Human Corneal Endothelium"
	Dr. Akihisa Yamamoto (Kyoto University)
12:00 – 13:30	***Lunch Break***

13:30 – 14:30 **Special Lecture: Transcultural Study**
"The Aesthetics and Sensitivities of the Japanese as seen through Classical Japanese Literature"
Prof. Shikiko Yukawa

14:30 – **1. Gekkeikan Sake company**
2. Fushimi Inari Taisha
(For details, see attachment)

Saturday, March 16

Social Program
(For details, see attachment)

Sunday, March 17

No Program

Monday, March 18

8:45 – 9:45 **Lecture 16 "Dynamics of Cells and Cell Ensembles"**
Prof. Masaki Sano (The University of Tokyo)

9:45 – 10:45 **Lecture 17 "Interface Growth and Morphogenesis"**
Prof. Karel Švadlenka (Kyoto University)

10:45 – 11:00 ***Break***

11:00 – 12:00 **Lecture 18 "Life Shaped by Mechanics"**
Prof. Hirofumi Wada (Ritsumeikan University)

12:00 – 13:30 ***Lunch Break***

13:30 – **Presentation 3: PhD projects – Session C**

Tuesday, March 19

8:45 – 9:45 **Lecture 19 "Materials and Life: Supramolecular Materials"**
Prof. Akira Harada (Osaka University)

9:45 – 10:45 **Lecture 20 "Cellular Mechanobiology"**
Prof. Martin Bastmeyer (Karlsruhe Institute of Technology)

10:45 – 11:00 ***Break***

11:00 – 12:00 **Lecture 21 "Mechanics of Skeletal Muscles"**
Prof. Ryoichi Nagatomi (Tohoku University)

12:00 – 13:30 ***Lunch Break***

13:30 – **Free Time**

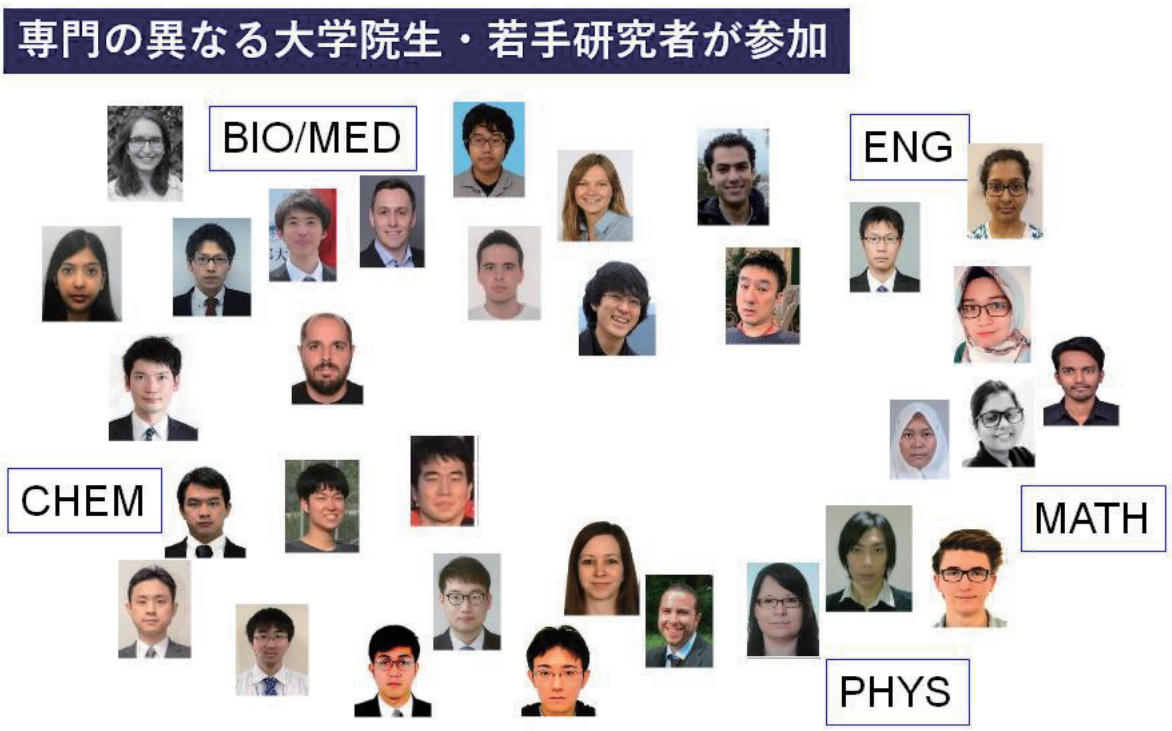
Wednesday, March 20

8:45 – 9:45	**Lecture 22 "MEMS and DNA Nanotechnology for Medicine and Biology"** Prof. Osamu Tabata (Kyoto University)
9:45 – 10:45	**Special Program (2): Lectures by Junior Faculties** **"Charged Polymer Brushes: Dynamic Modulation of Hydration States and Interactions"** Prof. Yuji Higaki (Oita University) **"Deformation as a Quantitative Tool to Understanding Self-Organisation in Multicellular Organisms: Development and Diseases"** Dr. Ryo Suzuki (Kyoto University)
10:45 – 11:00	***Break***
11:00 – 12:00	**Lecture 23 "Precision Medicine and Cancer Nanotherapy"** Prof. Fuyuhiko Tamanoi (Kyoto University / UCLA)
12:00 – 13:30	***Lunch Break***
13:30 – 14:30	**Special Lecture: "Half Century of my Astronomy: From a Star to Galaxies"** Prof. Keiichi Kodaira (NAOJ / MPIfR)
14:30 –	**Discussion & Evaluation**
18:00 – 20:00	**Farewell Party at Camphora** Farewell Speech Prof. Nagahiro Minato, Provost / Executive Vice-President, Kyoto University Prof. Keiichi Kodaira, National Astronomical Observatory of Japan / Max-Planck Institute for Radio-Astronomy

Thursday, March 21

Departure

End of the Kyoto Winter School 2019 Program



単にトップ研究者の講義を聴くにとどまらず、参加者全員に研究発表（口頭・ポスター）してもらい、議論することで視野を広げる機会を提供することを目指しました。

Academic Program（講師・参加者間の議論を重視）

Cultural Program（京都で日本文化に触れる）

サイエンスだけでなく、日本の古都である京都で日本文化に触れてもらうことで、参加者の日本そのものへの理解を深めることを目指しました。

特別講義　小平 桂一 教授

元国立天文台長（すばる天文台設立）
元総合研究大学院大学長

キール大学（独）と東京大学で学位を取得
前JSPSボンオフィス所長として日独の学術交流を10年以上にわたって主導
科学の『Grenzübergänger（越境者）』から若手研究者へのメッセージ

フェアウェルパーティー

湊理事から修了の祝辞

小平教授による乾杯の発声

一人一人に修了証を授与

参加学生からスタッフにプレゼント

大学近くの居酒屋での二次会

国際ウィンタースクール「Quantifying Dynamics of Life」

講師（国外）7 名

氏名：　田中　求
タイトル：　Prof. Dr.
大学：　Ruprecht-Karls-Universität Heidelberg
　/ 国立大学法人　京都大学
所属：　Institute of Physical Chemistry, Physical Chemistry of Biosystems
　医学物理・医工計測グローバル拠点

氏名：　Atul N. Parikh
タイトル：　Prof. Dr.
大学：　University of California, Davis
　/ Nanyang Technological University
所属：　Department of Biomedical Engineering
　Department of Materials Science & Engineering

氏名：　Joachim Rädler
タイトル：　Prof. Dr.
大学：　Ludwig-Maximilians-Universität München
所属：　Faculty of Physics

氏名：　Jan Gerrit Korvink
タイトル：　Prof. Dr.
大学：　Karlsruher Institut für Technologie
所属：　Institute of Microstructure Technology

氏名：　Anthony D. Ho
タイトル：　Prof. Dr.
大学：　Ruprecht-Karls-Universität Heidelberg
所属：　University Hospital
Department of Hematology and Oncology

氏名：　Thomas Holstein
タイトル：　Prof. Dr.
大学：　Ruprecht-Karls-Universität Heidelberg
所属：　Centre for Organismal Studies (COS) Heidelberg

氏名：　Martin Bastmeyer
タイトル：　Prof. Dr.
大学：　Karlsruher Institut für Technologie
所属：　Zoologisches Institut

講師（国内）学外　13 名

氏名：　吉川 研一
タイトル：　教授
大学：　学校法人同志社　同志社大学
所属：　生命医科学部

氏名：　林 智宏
タイトル：　准教授
大学：　国立大学法人　東京工業大学
所属：　大学院 ライフエンジニアリングコース(材料系)

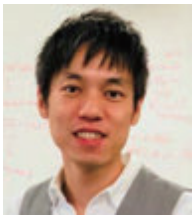
氏名：　吉川 洋史
タイトル：　准教授
大学：　国立大学法人　埼玉大学
所属：　大学院理工学研究科

氏名：　水藤 寛
タイトル：　教授
大学：　国立大学法人　東北大学
所属：　材料科学高等研究所

氏名：　木下 茂
タイトル：　教授
大学：　京都府公立大学法人　京都府立医科大学
所属：　特任講座感覚器未来医療学

氏名：　原田 明
タイトル：　教授
大学：　国立大学法人　大阪大学
所属：　大学院理学研究科

氏名：　和田 浩史
タイトル：　教授
大学：　学校法人立命館　立命館大学
所属：　理工学部　物理科学科



氏名：　木戸秋 悟
タイトル：　教授
大学：　国立大学法人　九州大学
所属：　先導物質化学研究所 分子集積化学部門 医用生物物理化学分野

氏名：　竹内 昌治
タイトル：　教授
大学：　国立大学法人　東京大学
所属：　生産技術研究所
　マイクロメカトロニクス国際研究センター

氏名：　永富 良一
タイトル：　教授
大学：　国立大学法人　東北大学
所属：　医工学研究科

氏名：　出口 茂
タイトル：　センター長
大学：　国立研究開発法人　海洋研究開発機構
所属：　海洋生命理工学研究開発センター

氏名：　佐野 雅己
タイトル：　教授
大学：　国立大学法人　東京大学
所属：　理学系研究科　物理学専攻　物理学科

氏名：　小平　桂一
タイトル：　教授
大学：　大学共同利用機関法人 自然科学研究機構
所属：　国立天文台

講師（国内）学内　4 名

氏名：　Karel Svadlenka
タイトル：　准教授
大学：　国立大学法人　京都大学
所属：　理学研究科 数学教室

氏名：　鶴山 竜昭
タイトル：　教授
大学：　国立大学法人　京都大学
所属：　医学研究科　創薬医学講座

氏名：　田畑 修
タイトル：　教授
大学：　国立大学法人　京都大学
所属：　工学研究科／マイクロエンジニアリング専攻ナノシステム創成工学講座

氏名：　玉野井 冬彦
タイトル：　教授
大学：　国立大学法人　京都大学
／ University of California, Los Angels
所属：　物質－細胞統合システム拠点

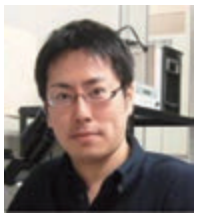
若手講師　4 名

氏名：　山本　暁久
タイトル：　助教
大学：　国立大学法人　京都大学
所属：　医学物理・医工計測グローバル拠点

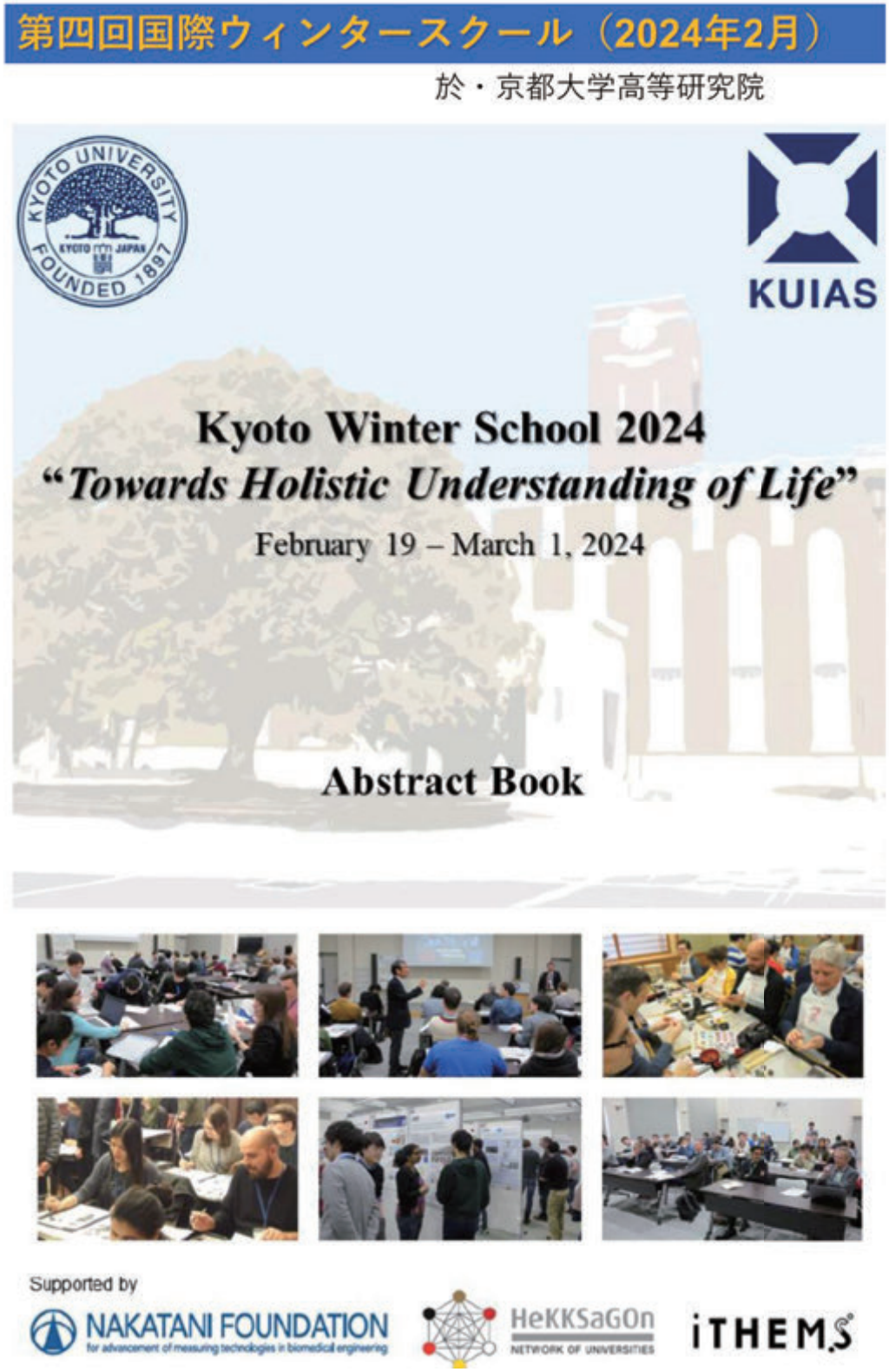
氏名：　鈴木　量
タイトル：　助教
大学：　国立大学法人　京都大学
所属：　医学物理・医工計測グローバル拠点

氏名：　檜垣　勇次
タイトル：　准教授
大学：　国立大学法人　大分大学
所属：　理工学部 共創理工学科 応用化学コース

氏名：　窪田　亮
タイトル：　助教
大学：　国立大学法人　京都大学
所属：　工学研究科　合成・生物化学専攻



第四回（2024年2月・京都大学）



KYOTO WINTER SCHOOL 2024 PROGRAM
— TOWARDS HOLISTIC UNDERSTANDING OF LIFE —

Date: February 19 – March 1, 2024
Venue: 2nd floor Seminar Room, KUIAS Main Building
Kyoto University
Yoshida Ushinomiya-cho, Sakyo-ku, Kyoto

PROGRAM

Monday, February 19

9:45 – 10:45	**Welcome & Orientation**
10:45 – 11:00	***Break***
11:00 – 12:00	**Lecture 1 "A Hitchhiker's Guide to the Bottom of the Ocean for Chemists"** Prof. Shigeru Deguchi (JAMSTEC)
12:00 – 13:30	***Lunch Break***
13:30 – 14:30	**Lecture 2 "Form of life through successive invasion processes and transitions: the invasion analysis"** Dr. Ryosuke Iritani (RIKEN)
14:30 – 14:45	***Break***
14:45 – 15:45	**Lecture 3 "How Sensory Epithelia Shape Their Cellular Patterns"** Prof. Karel Švadlenka (Tokyo Metropolitan University)
15:45 – 16:45	**Campus Tour escorted by KU students**
18:00 – 20:00	**Welcome Reception at KUIAS main building**

Tuesday, February 20

9:45 – 10:45	**Lecture 4 "3D Cellular Microenvironments to Study Cell Mechanics"** Prof. Martin Bastmeyer (Karlsruhe Institute of Technology)
10:45 – 11:00	***Break***
11:00 – 12:00	**Lecture 5 "Cytoskeletons and cortical development: How does the neocortex develop to establish the prototype of neuronal circuits during development by neuronal migration and collateral formation?"** Prof. Makoto Sato (Osaka University)
12:00 – 13:30	***Lunch Break***
13:30 – 14:30	**Basic Japanese 1**
14:30 – 16:45	**Presentations 1: Session A flashtalks + posters**

Wednesday, February 21

9:45 – 10:45	**Lecture 6 "Models for digestive organ tumors: from precursor to intractable cancer"** Prof. Hiroshi Seno (Kyoto University)

10:45 – 11:00 *Break*
11:00 – 12:00 **Lecture 7 "Stem Cells and regeneration in *Hydra*"**
Prof. Thomas Holstein (Heidelberg University)
12:00 – 13:30 *Lunch Break*
13:30 – 14:30 **Lecture 8 "Cancer Radiation Therapy in Japan"**
Prof. Fuyuhiko Tamanoi (Kyoto University)
14:30 – 16:45 **Japanese Calligraphy**

Thursday, February 22

Venue: Seminar room 1, Shirankaikan Annex (few minutes walk from KUIAS main building)

9:45 – 10:45 **Lecture 9 "3D printing with light"**
Prof. Martin Wegener (Karlsruhe Institute of Technology)
10:45 – 11:00 *Break*
11:00 – 12:00 **Lecture 10 "Design and Functions of Supramolecular Materials with Reversible and Movable Cross-Links"**
Prof. Yoshinori Takashima (Osaka University)
12:00 – 13:30 *Lunch Break*
13:30 – 14:30 **Lecture 11 "Investigating Actomyosin Contractility-driven Adhesion Modulation by Complementary High-speed AFM and Fluorescence Microscopy"**
Prof. Clemens Franz (Kanazawa University)
14:30 – 14:45 *Break*
14:45 – 15:45 **Lecture 12 "Advanced laser processing and manipulation techniques for life/material sciences"**
Prof. Hiroshi Yoshikawa (Osaka University)
15:45 – 16:45 **Basic Japanese 2**

Friday, February 23

Social Program
(For details, see attachment)

Saturday, February 24

No Program

Sunday, February 25

No Program

Monday, February 26

9:45 – 10:45 **Lecture 13 "Fluid Dynamics of Swimming Microorganisms"**
Prof. Takuji Ishikawa (Tohoku University)
10:45 – 11:00 *Break*
11:00 – 12:00 **Lecture 14 "Emergence of bio mimicry movements of micro swimmers"**
Dr. Masatoshi Ichikawa (Kyoto University)
12:00 – 13:30 *Lunch Break*
13:30 – 14:30 **Lecture 15 "Overcoming FFPE Sample Challenges in Biomarker Discovery: Innovations in Mass Spectrometry Imaging"**
Prof. Tatsuaki Tsuruyama (Hiroshima University)

14:30 – 14:45 *Break*
14:45 – 16:45 **Presentations 2: Session B flashtalks + posters**

Tuesday, February 27

9:45 – 10:45 **Lecture 16 "Microscale NMR for the dynamics of life"**
Prof. Jan Korvink (Karlsruhe Institute of Technology)
10:45 – 11:00 *Break*
11:00 – 12:00 **Lecture 17 "New Experimental Analytical Platforms Answering Clinically Relevant Questions"**
Prof. Motomu Tanaka (Kyoto University / Heidelberg University)
12:00 – 13:30 *Lunch Break*
13:30 – 14:00 **Short Lecture 1 "Physics of Regenerating *Hydra*"**
Dr. Ryo Suzuki (Kyoto University)
14:00 – 14:30 **Short Lecture 2 "The collective order of human corneal endothelial cells for cultured cells and regenerated tissues: Creation of a novel biomarker and mathematical characterization"**
Dr. Akihisa Yamamoto (Kyoto University)
14:30 – 14:45 *Break*
14:45 – 15:45 **Special Lecture 1 "Beyond "What is Life?" - Amusements with Real-World Modeling"**
Prof. Kenichi Yoshikawa (Doshisha University)
15:45 – 16:45 **Special Lecture 2 "Scripting an Eco-system for Precision Medicine: Navigating the Journey to Bridge Boundaries for Synergistic Integration?"**
Dr. Ganesh Pandian Namasivayam (Kyoto University)

Wednesday, February 28

9:45 – 10:45 **Lecture 18 "Synthetic Nanocelluloses: Molecularly Designable Cellulose Assemblies"**
Prof. Takeshi Serizawa (Tokyo Institute of Technology)
10:45 – 11:00 *Break*
11:00 – 12:00 **Lecture 19 "Experimental Advancements in Nonlinear and Fracture Mechanics of Polymer Soft Materials"**
Prof. Kenji Urayama (Kyoto University)
12:00 – 13:30 *Lunch Break*
13:30 – 14:00 **Short Lecture 3 "Development of Polymeric Materials Based on Bio-Inspired Design, Bio-Synthetic Interaction, and Bio-Synthetic Fusion"**
Dr. Masaki Nakahata (Osaka University)
14:00 – 14:30 **Short Lecture 4 "Exploring Periodic Entangled Structures in Material Science Through Knot Theory"**
Dr. Sonia Mahmoudi (Tohoku University)
14:30 – 14:45 *Break*
14:45 – 16:45 **Presentations 3: Session C flashtalks + posters**

Thursday, February 29

9:45 – 10:45 **Lecture 20 "Towards the clinical application of a holistic understanding of cancer"**
Prof. Jonathan Sleeman (Heidelberg University)

10:45 – 11:00 *Break*

11:00 – 12:00 **Lecture 21 "Extracellular vesicles derived from periodontal disease affect systemic diseases"**
Prof. Hirohiko Okamura (Okayama University)

12:00 – 13:30 *Lunch Break*

13:30 – 15:00 **Free time**

15:00 – 17:30 **CiMPhy Final Symposium at Inamori Hall, Shirankaikan**
Activity report "Creation of a New Research Field by Fusion of Medicine, Physics, and Mathematics – from Japan to the World"
Prof. Motomu Tanaka (Kyoto University / Heidelberg University)
Special talk 1 "The Healing Power within Yourself"
Prof. Anthony Ho (Heidelberg University)
Special talk 2 "Our circulatory system through the lens of applied mathematics"
Prof. Hiroshi Suito (Tohoku University)

18:00 – 20:00 **CiMPhy Final Symposium Reception at Restaurant La Tour, Kyoto University Clock Tower Centennial Hall**

Friday, March 1

9:45 – 10:45 **Lecture 22 "Mechanisms of phospholipid scrambling"**
Prof. Jun Suzuki (Kyoto University)

10:45 – 11:00 *Break*

11:00 – 12:00 **Lecture 23 "Theoretical Modeling and Computational Simulations on Dynamic Self-Organization of Migrating Cells"**
Dr. Tetsuya Hiraiwa (Academia Sinica)

12:00 – 13:30 *Lunch Break*

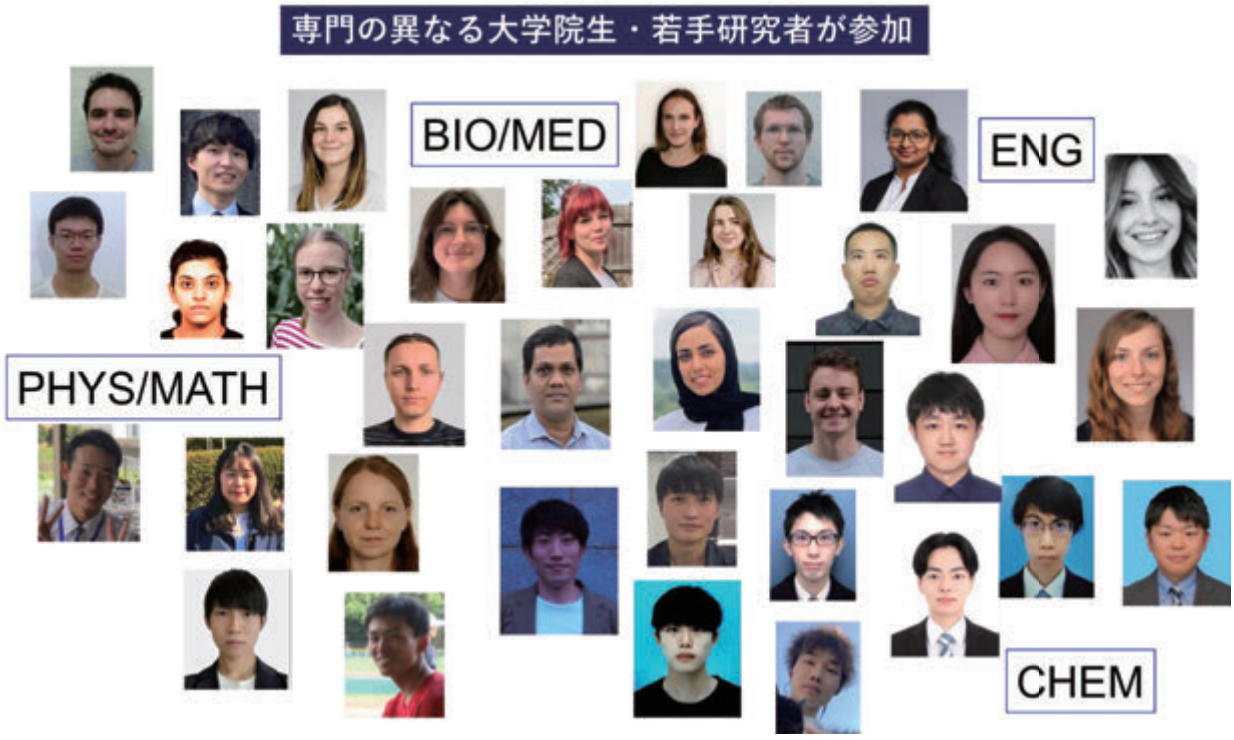
13:30 – 14:30 **Special Lecture 3 "Bio-inspired nanomaterials for biomedical applications"**
Prof. Kazunari Akiyoshi (Kyoto University)

14:30 – **Discussion & Evaluation**

18:00 – 20:00 **Farewell Party at KUIAS main building**

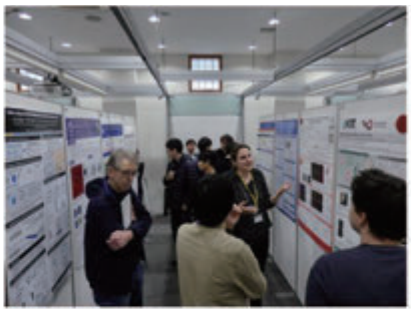
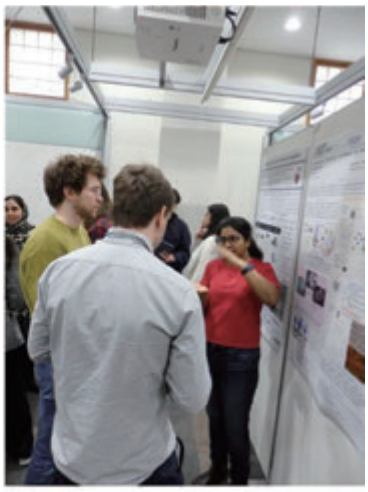
Saturday, March 2

Departure
End of the Kyoto Winter School 2024 Program



講義の後にたっぷりと議論の時間を設けたほか、参加者全員に研究発表（口頭・ポスター）してもらい、互いに議論して視野を広げる機会を提供しました。

スクールの様子

第四回では鈴木量助教（現・慶応義塾大学講師）、山本暁久助教（現・理研 iTHEMS 特別研究員）が実際の運営を一手に担当しました。

Dr. Ryo Suzuki
鈴木量　助教

Dr. Aki Yamamoto
山本暁久　助教

国際ウィンタースクール「Quantifying Dynamics of Life」

講師（国外）8 名

氏名：　田中　求
タイトル：　Prof. Dr.
大学：　Ruprecht-Karls-Universität Heidelberg
　　国立大学法人　京都大学
所属：　Institute of Physical Chemistry, Physical Chemistry of Biosystems
　　医学物理・医工計測グローバル拠点

氏名：　Martin Wegener
タイトル：　Prof. Dr.
大学：　Karlsruhe Institute of Technology
所属：　Institute of Applied Physics
　　Institute of Nanotechnology

氏名：　Jonathan Sleeman
タイトル：　Prof. Dr.
大学：　Ruprecht-Karls-Universität Heidelberg
所属：　Medical Faculty Mannheim

氏名：　Jan Gerrit Korvink
タイトル：　Prof. Dr.
大学：　Karlsruher Institut für Technologie
所属：　Institute of Microstructure Technology

氏名：　平岩徹也
タイトル：　Prof.
大学：　Academia Sinica
所属：　Institute of Physics

氏名：　Anthony D. Ho
タイトル：　Prof. Dr.
大学：　Ruprecht-Karls-Universität Heidelberg
所属：　University Hospital
Department of Hematology and Oncology

氏名：　Thomas Holstein
タイトル：　Prof. Dr.
大学：　Ruprecht-Karls-Universität Heidelberg
所属：　Centre for Organismal Studies (COS) Heidelberg

氏名：　Martin Bastmeyer
タイトル：　Prof. Dr.
大学：　Karlsruher Institut für Technologie
所属：　Zoologisches Institut

講師（国内）学外　10 名

氏名：　出口 茂
タイトル：　センター長
大学：　国立研究開発法人　海洋研究開発機構
所属：　海洋生命理工学研究開発センター

氏名：　高島 義徳
タイトル：　教授
大学：　国立大学法人　大阪大学
所属：　大学院理学研究科

氏名：　芹澤 武
タイトル：　教授
大学：　国立大学法人　東京工業大学
所属：　物質理工学院

氏名：　Karel Svadlenka
タイトル：　教授
大学：　公立大学法人　東京都立大学
所属：　理学研究科 数学教室

氏名：　吉川 洋史
タイトル：　教授
大学：　国立大学法人　大阪大学
所属：　大学院工学研究科

氏名：　水藤 寛
タイトル：　教授
大学：　国立大学法人　東北大学
所属：　材料科学高等研究所

氏名：　鶴山 竜昭
タイトル：　教授
大学：　国立大学法人　広島大学
所属：　医学研究科　病理学講座

氏名：　入谷 亮介
タイトル：　上級研究員
大学：　学校法人立命館　理化学研究所
所属：　iTHEMS

氏名：　佐藤 真
タイトル：　教授
大学：　国立大学法人　大阪大学
所属：　医学研究科　神経機能形態学講座

氏名：　Clemens Franz
タイトル：　准教授
大学：　国立大学法人　金沢大学
所属：　WPI nanoLSI

氏名：　石川 拓司
タイトル：　教授
大学：　国立大学法人　東北大学
所属：　医工学研究科

氏名：　岡村 裕彦
タイトル：　教授
大学：　国立大学法人　岡山大学
所属：　医歯薬研究科　口腔形態学講座

講師（国内）学内　4 名

氏名：　妹尾 浩
タイトル：　教授
大学：　国立大学法人　京都大学
所属：　医学研究科　消化器内科学講座

氏名：　市川 正敏
タイトル：　光子
大学：　国立大学法人　京都大学
所属：　理学研究科　物理学専攻

氏名：　鈴木 淳
タイトル：　教授
大学：　国立大学法人　京都大学
所属：　物質－細胞統合システム拠点

氏名：　玉野井 冬彦
タイトル：　教授
大学：　国立大学法人　京都大学
／ University of California, Los Angels
所属：　物質－細胞統合システム拠点

若手講師　4 名

氏名：　Sonia Mahnoudi
タイトル：　助教
大学：　国立大学法人　東北大学
所属：　材料科学高等研究所

氏名：　中畑　雅樹
タイトル：　助教
大学：　国立大学法人　大阪大学
所属：　理学研究科　高分子化学専攻

氏名：　鈴木　量
タイトル：　助教
大学：　国立大学法人　京都大学
所属：　医学物理・医工計測グローバル拠点

氏名：　山本　暁久
タイトル：　助教
大学：　国立大学法人　京都大学
所属：　医学物理・医工計測グローバル拠点

特別講師　4 名

氏名：　Ganesh Pandian Namasivayam

タイトル：　准教授

大学：　国立大学法人　京都大学

所属：　物質－細胞統合システム拠点

氏名：　吉川 研一

タイトル：　名誉教授

大学：　国立大学法人　京都大学

所属：　理学研究科　物理学専攻

氏名：　秋吉 一成

タイトル：　名誉教授

大学：　国立大学法人　京都大学

所属：　工学研究科　高分子化学専攻

人材育成（２）
MACS プログラム

MACS は **Ma**thematics-based **C**reation of **S**cience の頭文字を取った「数理を基盤として新分野の自発的創出を促す理学教育プログラム」の略称で、京都大学理学研究科が主催する教育プログラムです。

部門長・田中と鈴木助教、山本助教は、理学部数学科・Svadlenka 准教授（代表）と医学部創薬医学・鶴山教授（現・放射線影響研究所）と協力して、スタディグループ SG「疾患における集団的細胞挙動の数理モデルの開拓」を 2018 年に開講しました。

われわれの SG ではヒト病理画像を用いて、個々の細胞やその集団秩序構造の乱れを物理学的に解析し、これを数理モデリングとリンクさせることで定量化し、読み解くことを目指します。参加者は数学・物理・医学の三つの研究グループを回って、講義だけでなく実際のデータを前にした実習を通じて解析やモデリングを習得し、そこで得られた成果や直面した疑問・問題点をセミナーで発表し、議論しています。

このような「先端研究に立脚した教育・人材育成」は、ヨーロッパなど海外では『研究インターンシップ』の形で広く行われており、例えばハイデルベルク大学・田中研では毎年年間 20 人以上の学生を世界から受け入れています。これを MACS プログラムの枠組みで京都大学に取り入れようというのが我々の SG の狙いです。

学部生から博士課程の大学院生まで、また理学部だけでなく医学部の学生も参加するなど、毎年意欲ある学生たちによって活発な活動を展開しているだけでなく、SG からのスピンオフ（機械学習によるがん組織のパターン識別と、原子間力顕微鏡を用いた弾性率マッピング）が論文として結実しつつあるなど「分野横断型の医学物理・医工計測研究を基盤とした人材育成」を体現する活動であると自負しています。

MACS プログラムの概要

スタディグループ「疾患における集団的細胞挙動の数理モデルの開拓」

SG「疾患における集団的細胞挙動の数理モデルの開拓」（2018年～）

SGが目指すもの

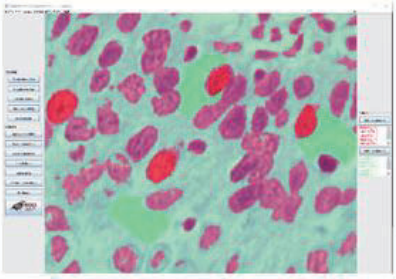
ヒト病理画像を用いて、個々の細胞やその集団秩序構造の乱れを物理学的に解析し、これを数理モデリングとリンクさせることで定量化し、読み解く

SGの運営メンバーと実際の流れ

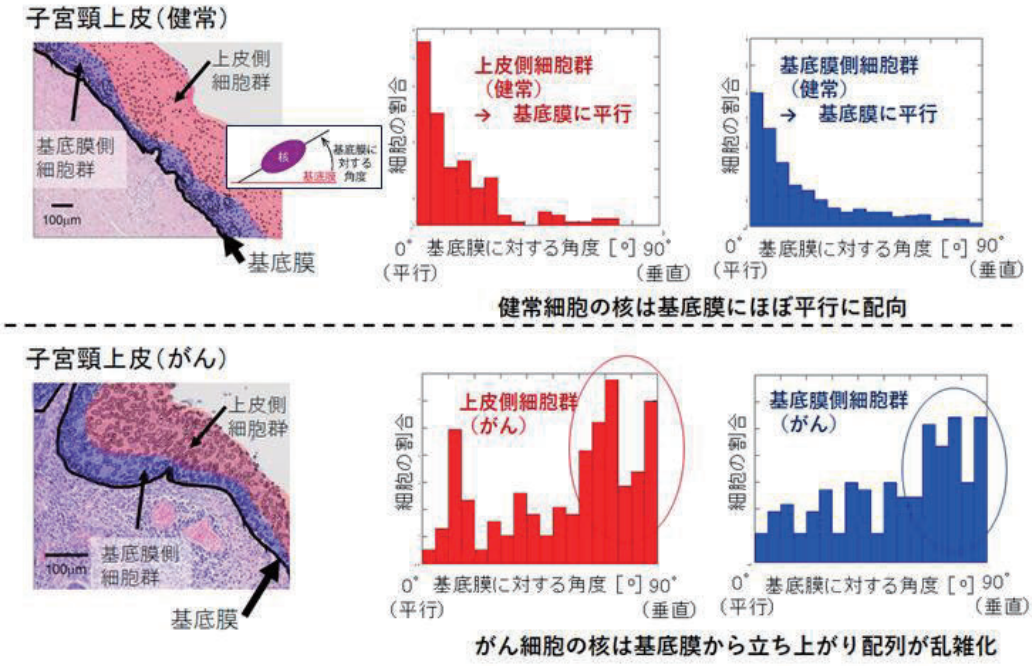
スタディグループ活動の様子

病理試料の画像撮影

機械学習による細胞核抽出



2019年度成果報告より
子宮頸がんによる細胞核配向秩序パターンの変調



MACS プログラム「疾患における集団的細胞挙動の数理モデルの開拓」担当教員

- Karel Svadlenka（代表）京都大学理学部数学科・准教授
  （現・東京都立大学 理学研究科 数理科学専攻・教授）
- 田中　求　京都大学高等研究院・教授、ハイデルベルク大学・教授
- 山本暁久　京都大学高等研究院・助教
- 鈴木　量　京都大学高等研究院・助教
- 鶴山竜昭　京都大学医学部・教授
  （現・放射線影響研究所・主任研究員）
- 坂上貴之　京都大学理学部数学科・教授

過去メンバー

- 平塚拓也　京都大学医学部・講師（現・済生会茨木病院・病理部長）

MACS プログラム「疾患における集団的細胞挙動の数理モデルの開拓」参加学生

【2018 年度】　　計 14 名、大学院生 7 名・学部生 7 名

- 大野　邦久　（理学研究科 生物科学専攻：D3）
- 幕田　将宏　（理学研究科 物理学・宇宙物理学専攻：D3）
- 橋谷　文貴　（理学研究科 化学専攻：D3）
- 向井　大智　（理学研究科 数学・数理解析専攻 数理解析系：D2）
- 浅倉　祥文　（生命科学研究科：D1）
- 矢ヶ崎　怜　（理学研究科 生物科学専攻：M1）
- 小倉　将紘　（理学研究科 物理学・宇宙物理学専攻：M1）
- 太田　友　　（生命科学研究科：B4）
- 親川　晃一　（生命科学研究科：B4）
- 小池　元　　（理学研究科 数学・数理解析専攻 数学系：B3）

- 多胡　徹也　（理学研究科 生物科学専攻：B3）
- 石田　祐　（理学部：B2）
- 藤﨑　碩人　（理学部：B2）
- 妹尾　歩　（理学部：B2）

【2019 年度】　計 11 名、大学院生 8 名・学部生 3 名

- 村上　知暉　（理学研究科 生物科学専攻：M1）
- 大野　邦久　（理学研究科 生物科学専攻：D3）
- 高野　友篤　（理学研究科 生物科学専攻：M1）
- 大谷　暢宏　（医学部 医学科：B2）
- 川上　航　（医学部 医学科：B2）
- 浅倉　祥文　（生命科学研究科 高次生命科学専攻：D2）
- 幕田　将宏　（理学研究科 物理学・宇宙物理学専攻：D4）
- 吉田　純生　（理学研究科 生物科学専攻：M1）
- 上野　賢也　（理学研究科 生物科学専攻：D2）
- 松田　京子　（理学研究科 生物科学専攻：B3）
- 糀谷　暁　（理学研究科 化学専攻：M1）

【2020 年度】　計 8 名、大学院生 3 名・学部生 5 名

- 大谷　暢宏　（医学部 医学科：B3）
- 司　怜央　（医学部 医学科：B3）
- 糀谷　暁　（理学研究科 化学専攻：M2）
- 林　大寿　（理学研究科 物理学・宇宙物理学専攻：M2）
- 長岡　高広　（理学研究科 数学・数理解析専攻：D3）
- 權　俊河　（理学研究科 数学・数理解析専攻：B4）
- 田谷　直亮　（理学研究科 数学・数理解析専攻：B4）
- 藤﨑　碩人　（理学研究科 数学・数理解析専攻：B4）

【2021 年度】　　計 7 名、大学院生 5 名・学部生 2 名

- 糀谷　暁　　（理学研究科 化学専攻：M2）
- 司　怜央　　（医学部 医学科：B4）
- 奥山　紘平　（理学研究科 物理学・宇宙物理学専攻：M2）
- 藤﨑　碩人　（理学研究科 数学・数理解析専攻：M1）
- 石川　陽　　（理学研究科 数学・数理解析専攻：M1）
- 大谷　暢宏　（医学部 医学科：B4）
- 大野　邦久　（理学研究科 生物科学専攻：D3、休学中）

【2022 年度】　　計 13 名、大学院生 7 名・学部生 6 名

- 天野　玲　　（理学研究科 物理学・宇宙物理学専攻：M1）
- 石川　陽　　（理学研究科 数学・数理解析専攻：M2）
- 奥山　紘平　（理学研究科 物理学・宇宙物理学専攻：D1）
- 小山　泰生　（生命科学研究科：D2）
- 加々尾萌絵　（医学研究科 医科学専攻：M1）
- 河本　理来　（医学部 医学科：B1）
- 島本草太朗　（理学部 数学・数理解析専攻：B3）
- 田渕　辰悟　（理学部 物理学・宇宙物理学専攻：B4）
- 司　怜央　　（医学部 医学科：B5）
- 永井　翔吾　（理学研究科 物理学・宇宙物理学専攻：M1）
- 吉田　智紀　（医学部 医学科：B1）
- 藤﨑　碩人　（理学研究科 数学・数理解析専攻：M2）
- 大谷　暢宏　（医学部 医学科：B5）

【2023 年度】　　計 8 名、大学院生 5 名・学部生 3 名

- 奥山　紘平　（理学研究科 物理学・宇宙物理学専攻：D2）
- 小山　泰生　（生命科学研究科：D3）
- 加藤　幹也　（理学研究科 生物科学専攻：B4）
- 司　怜央　（医学部 医学科：B6）
- 永井　翔吾　（理学研究科 物理学・宇宙物理学専攻：M2）
- 似内　奏太　（理学部：B2）
- 林　大寿　（理学研究科 化学専攻：D2）
- 三ツ井梨真　（生命科学研究科：M1）

人材育成（３）
理学部物理科学課題演習

当拠点は特定の学部に属していないため、いわゆる講座配属の対象にはなっていません。そこで部門長・田中は、物理学科の学生に物理学に立脚した最先端の融合研究を紹介するため、理学部物理学第一教室の学内非常勤講師として学部３回生の「物理科学課題演習」を物理学科・市川正敏講師との連携という形で担当してきました。研究室における実際の指導は山本助教・鈴木助教にお願いしています。

『研究インターンシップ』というには期間や頻度も短いものですが、参加学生は当拠点の研究プロジェクトに参加することで、それまで講義で耳にした素粒子物理や高エネルギー物理、固体物理などとは一味違った物理の醍醐味を感じているようです。「分野横断型の医学物理」を京都大学の学生たちに紹介するために奮闘してくれている助教のお二人に感謝します。

物理科学課題演習 参加学生

( )内は直接指導教員

【2019 年度】　　1 名

- 澤崎義仁「ガン細胞の時空間パターンに基づく進行度の同定」
  （山本暁久）

【2020 年度】　　2 名

- 松宮香子「マウス大腸癌オルガノイドの変形と機能の関係性の定量解析」
  （鈴木　量）
- 大橋拓弥「ヒト角膜内皮細胞に対する shape index の分析と課題」
  （山本暁久）

【2021 年度】　　2 名

- 埴村圭吾「マウス腸腫瘍オルガノイドの形成能を変形能から理解する」
  （鈴木　量）
- 池邉凌「ヒト角膜内皮移植組織における細胞配列秩序の時間変化」
  （山本暁久）

【2022 年度】　　3 名

- 森田隆介「神経幹細胞を用いた基板の硬さと細胞の集団挙動との関係の
  定量評価」
  （鈴木　量）
- 篠田遼太郎「マウス膵癌前癌病変細胞の変形モードの振動特性解析」
  （山本暁久）
- 堤雅範「膵臓がんの前駆病変に対する細胞の形状変化の定量的評価と深層学習の
  応用」
  （山本暁久）

人材育成（４）
中谷 RIES プログラム

部門長・田中は、中谷財団の依頼を受けて 2019 年から「国際学生交流プログラム（中谷 RIES プログラム）」のアカデミックコーディネーターを隔年で務めています（2021 年度募集はコロナ禍のため中止）。

これは、日本全国から選抜された学生たちを、ドイツのトップ大学であるハイデルベルク大学とカールスルーエ工科大学の研究室へ派遣し、研究に携わりながら見聞を広めてもらうという『日本からドイツへの派遣』と、ドイツのハイデルベルク大学とカールスルーエ工科大学から選ばれた学生を日本の大学へと派遣するという『ドイツから日本への派遣』という、双方向的な学生交流プログラムです。

2019 年度は、日本から 12 名・ドイツから 12 名、計 24 名の学生が様々な分野から参加したため、24 名分のアカデミックホストを日本とドイツで見つける、ということはなかなか大変でした。初回はいろいろ大変であったため、日本での受け入れがしやすいように受け入れ先を京都大学に一本化して事務手続きを簡略化しました。

8 月から 9 月にかけてという、なかなか受け入れには難しい時期にもかかわらず学生の受け入れを快諾いただいた日本とドイツの同僚の先生方、また積極的に研究テーマに取り組み、研究室のスタッフや学生たちとコミュニケーションをとるなど奮闘してくれた参加学生たちに深く感謝する次第です。

当拠点では、カールスルーエ工科大の Moritz Tremmel さん（生物学・修士）が山本助教の指導のもと、マウス膵がんの細胞動態解析から転移性を識別するというテーマ（京都大学病院消化器内科・妹尾 浩 先生との共同研究）、ハイデルベルク大学の Marlene Ganslmeier さん（生物学・修士）が鈴木助教の指導のもとで配向秩序を制御したナノファイバーを用いた筋管形成のメカニズム（京都大学工学部・梅田 真郷 先生との共同研究）に取り組みました。

募集の Flyer（ドイツ→日本）

2019 Fellowship for Research Internship in Japan for Students of Heidelberg University and Karlsruhe Institute of Technology (*Nakatani RIES Program*)

The Nakatani RIES: Research & International Experiences for Students connects undergraduates with the best of science & engineering research in Japan through a fully funded summer program abroad. The program serves as a catalyst for students interested in future graduate study and research, contributing to vibrant international research collaborations in the future.
About 10 students will be selected by the selection committee, and the successful candidates will be assigned to the host institutions, including Kyoto University and Osaka University.

The Nakatani RIES Fellowship is organized by the Nakatani Foundation (https://www.nakatani-foundation.jp/en/), one of the largest Foundation supporting the Advancement of Biomedical Engineering, and coordinated by Prof. Dr. Motomu Tanaka, Heidelberg University

Eligibility Requirements
- BSc or MSc students of Heidelberg University or Karlsruhe Institute of Technology, from all the disciplines of natural, life, and engineering sciences

2019 Schedule

Duration: 6 - 8 weeks, starting from August 6, 2019
Applications Due: April 12, 2019

How to apply?

Applications should include the following information
(A4 max. 1 page, Arial 12 pt, single line spacing)

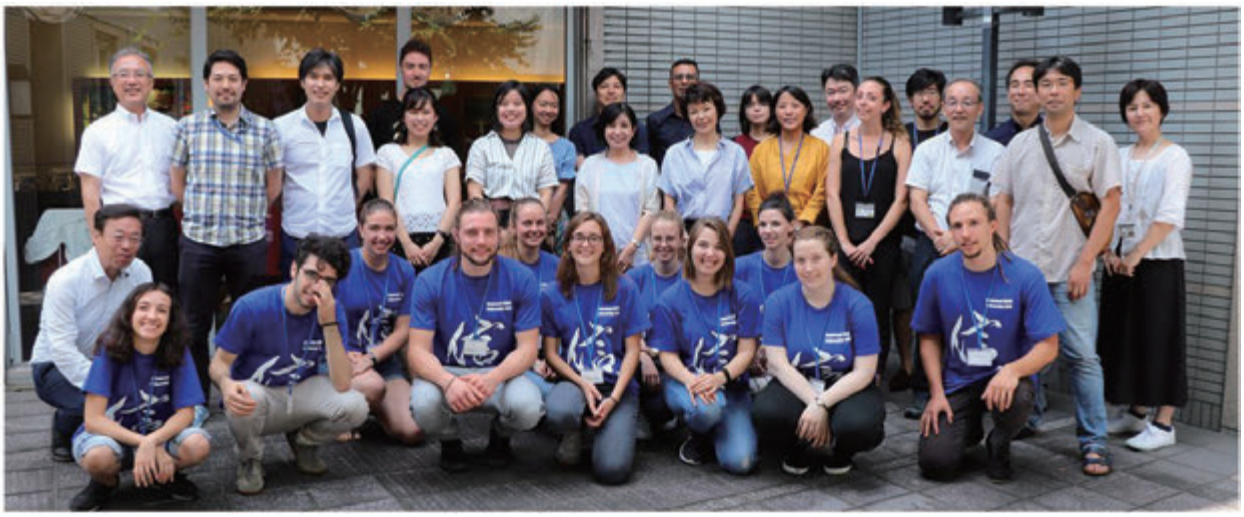
- *Name*
- *Major*
- *Address, e-mail*
- *Semester (as of SS 2019)*
- *Desired subjects (up to 5)*

Applications with the subject line "Summer Program in Japan" should be submitted to kyotointernship@gmail.com

Funding Provided
- International Airfare
- Housing & Partial Meal Stipend
- International Health Insurance
- School Tuition & Fees

募集の Flyer（日本→ドイツ）

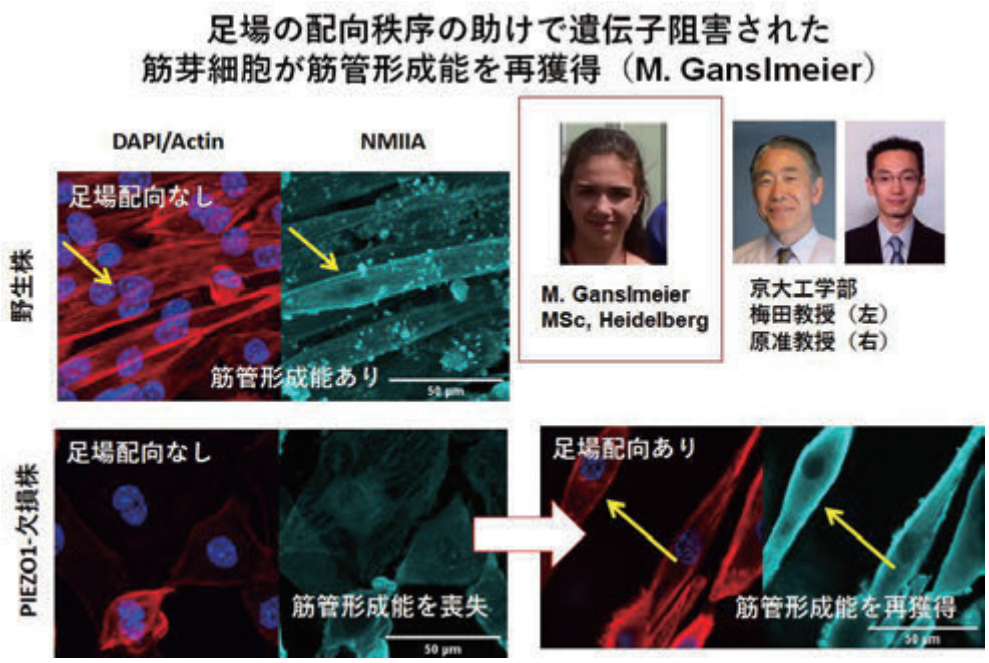
中谷RIESプログラム2019

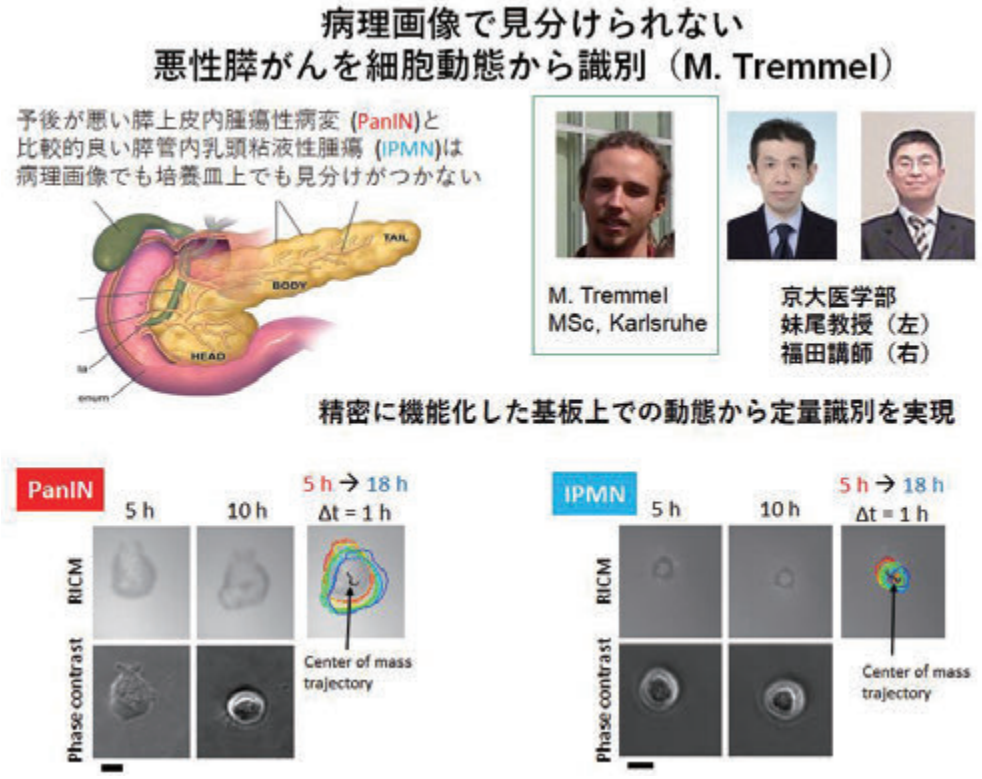


ドイツから日本へ来た学生たちとホスト研究室の教員の集合写真（上）
京都大学高等研究院にて

日本からドイツへ来た学生たち（左）
歴史あるハイデルベルク大学の
旧講堂（Alte Aura）にて

京都拠点で受け入れた学生の活動





日本からの参加学生と受入研究室

Ms. Ayano Tada	Osaka Prefectural University	Prof. Dr. Petra Tegeder Institute of Physical Chemistry, Heidelberg University tegeder@uni-heidelberg.de https://www.uni-heidelberg.de/fakultaeten/chemgeo/pci/tegeder/	Molecular Processes at Interface
Ms. Haruki Hagiwara	Tokyo Institute of Technology	Prof. Dr. Jan Korvink Institute for Microtechnology, Karlsruhe Institute of Technology jan.korvink@kit.edu https://www.imt.kit.edu/index.php	MEMS Technology
Ms. Kyoto Muto	University of Tokyo	Prof. Dr. Anna Marciniak Czochra Center for Interdisciplinary Scientific Calculation (IWR), Heidelberg University Anna.marciniak@iwr.uni-heidelberg.de https://wwwproxy.iwr.uni-heidelberg.de/groups/amj/People/Anna.Marciniak/index.html	Applied Mathematics
Mr. Narutoshi Suto	University of Tokyo	Prof. Dr. Motomu Tanaka Institute of Physical Chemistry, Heidelberg University tanaka@uni-heidelberg.de, wasim.abuillan@gmx.de https://www.pci.uni-heidelberg.de/bpc2/index.html	Medical Physics
Mr. Masaya Watanabe	University of Tokyo	Prof. Dr. Thomas Höfer German Cancer Research Center (DKFZ) and Heidelberg University T.Hoefer@Dkfz-Heidelberg.de https://www.dkfz.de/en/modellierung-biologischer-systeme/	Theoretical Systems Biology
Ms. Moeka Natori	Tohoku University	Prof. Dr. Stefan Wölfl Institute for Molecular Biotechnology (IPMB), Heidelberg University wolfl@uni-hd.de https://www.ipmb.uni-heidelberg.de/biologie/woelfl/index.html	Pharmaceutical Biology
Ms. Yukina Chiba	Nagoya University	Prof. Dr. Thomas Holstein Centre for Organismal Study (COS), Heidelberg University Thomas.holstein@cos.uni-heidelberg.de https://www.cos.uni-heidelberg.de/index.php/t.holstein?l=_e	Molecular Evolution and Genomics
Mr. Ryota Yanagisawa	Osaka University	Prof. Dr. Jan Korvink jan.korvink@kit.edu Institute for Microtechnology, Karlsruhe Institute of Technology https://www.imt.kit.edu/index.php	Bioanalytical Imaging
Ms. Kanako Matsumoto	Osaka University	Prof. Dr. Martin Bastmeyer Institute for Zoology, Karlsruhe Institute of Technology https://znbio.zoo.kit.edu/Startseite.php	Biomaterials, Mechanobiology
Mr. Rimpei Kuroiwa	Osaka University	Prof. Dr. Joachim Wittbrodt Centre for Organismal Study (COS) https://www.cos.uni-heidelberg.de/index.php/j.wittbrodt?l=_e	Animal Physiology
Mr. Koki Asami	Ritsumeikan University	Prof. Dr. Jan Korvink jan.korvink@kit.edu, dario.mager@kit.edu Institute for Microtechnology, Karlsruhe Institute of Technology https://www.imt.kit.edu/index.php	Bio MEMS
Mr. Kenta Toyoda	Waseda University	Prof. Dr. Martin Bastmeyer Institute for Zoology, Karlsruhe Institute of Technology martin.bastmeyer@kit.edu https://znbio.zoo.kit.edu/Startseite.php	Cell and Neurobiology

ドイツからの参加学生と受入研究室

	Name	University	Host	e-mail
1	Lea Ballenberger	HD	Prof. Mineko Kengaku, iCeMS	leaballenberger@gmail.com
2	Marie Blicking	HD	Prof. Osamu Tabata, Engineering Assoc. Prof. Kenichiro Kamei, iCeMS	marie.blickling@yahoo.com
3	Marika Trumm	HD		marika.trumm@stud.uni-heidelberg.de
4	Vasselina Sadovska	HD	Prof. Dan Ohtan Wang, iCeMS	v.sadovska@stud.uni-heidelberg.de
5	Elisa Cappio Barazzone	HD	Prof. Keizo Tomonaga, Inst. Front. Med. Life Sci.	Cappio@stud.uni-heidelberg.de
6	Nils Chaplin	HD	Prof. Naoki Watanabe, Medicine	cl228@stud.uni-heidelberg.de
7	Melanie Ganslmeier	HD	Assist. Prof. Ryo Suzuki, KUIAS	ganslmeier.marlene@gmail.com
8	Noemi Flubacher	KIT	Prof. Takayuki Kohchi, Biology	noemi.flubacher@student.kit.edu
9	Moritz Tremmel	KIT	Assist. Prof. Akihisa Yamamoto, KUIAS	moritz-tremmel@t-online.de
10	Janina Breining	KIT	Prof. Fuyuhiko Tamanoi, iCeMS	breining.j.97@gmail.com
11	Matteo Spatuzzi	HD	Prof. Atsushi Mochizuki, Inst. Front. Med. Life Sci.	matteo.spatuzzi@gmail.com
12	Christina Cramer von Clausbruch	KIT	Prof. Tatsuo Kurihara, Inst. Chem. Res.	christina-cvc@gmx.de

HD: ハイデルベルク大学

KIT： カールスルーエ工科大学

人材育成（５）
京都大学医学部マイコースプログラム
留学生の欧州拠点への受入

京都大学医学部では、4 回生の秋学期期間にすべての科目講義や試験を実施せず、学生が自分の適性に合った研究活動に専念する「マイコース」を実施しています。部門長・田中は第二回のウィンタースクール（2016 年）期間中にコーディネーターである武田俊一教授（医学研究科・放射線遺伝学）からマイコースについてご説明をいただき、その趣旨に賛成して多くの医学生をハイデルベルク大学の欧州拠点に受け入れてきました。

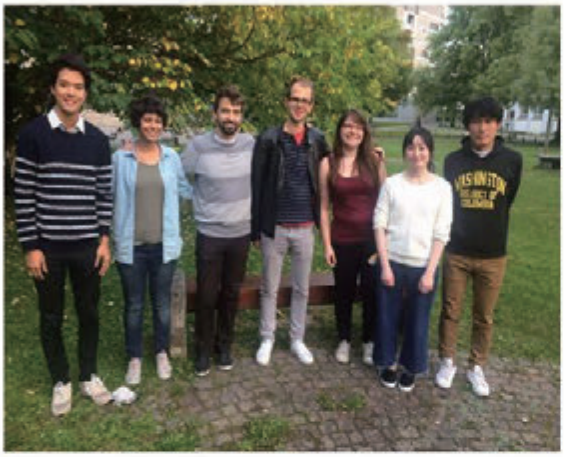
欧州拠点では夏から秋にかけて、ドイツを始め世界中から様々な分野のインターンシップの学生を受け入れます。京大医学部の学生たちも、欧州拠点の教員や博士院生の直接の指導の元、医学と物理の融合テーマに関わる研究に取り組み、終了時には研究室のセミナーでスタッフ・学生全員の前で報告を行い、医学・物理の融合研究に取り組んできました。

医学生を受け入れ指導することは、ハイデルベルク大学の物理や化学の学生やスタッフにとっても大きな刺激となっており、双方向的に「トップクラスの融合研究を基盤にした人材育成」を体現した活動となっています。

京大医学部マイコースプログラム

コーディネーター
武田俊一教授
山田ゆかり講師

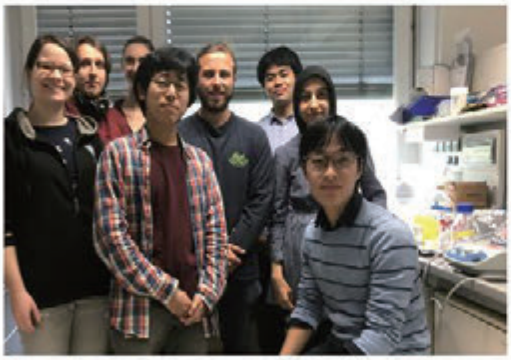
- 京大医学部生が基礎研究に興味を持つよう、4回生を2か月海外の研究室に派遣
- フルタイムで海外のトップラボにおける研究に従事
- 欧州ハブ拠点では2017年以降これまで7名を受入



2017年受入
北野貴暉（左端）、渡辺岳之（右端）

研究テーマ
Probiotics の大腸上皮への定着に関する流体力学的研究

ハイデルベルク大学病院
消化器内科部長
W. Stremmel 教授との共同研究



2019年受入
牧原史尚（中央）、森一斗（右）

2020年・2021年はコロナ禍のため派遣停止

研究テーマ
GPR56欠損が白血病モデル細胞の骨髄nicheへの接着能と動態に与える影響の定量解析

ハイデルベルク大学病院
血液内科部長
C. Mueller Tidow 教授との共同研究

京都大学医学部マイコース受入学生

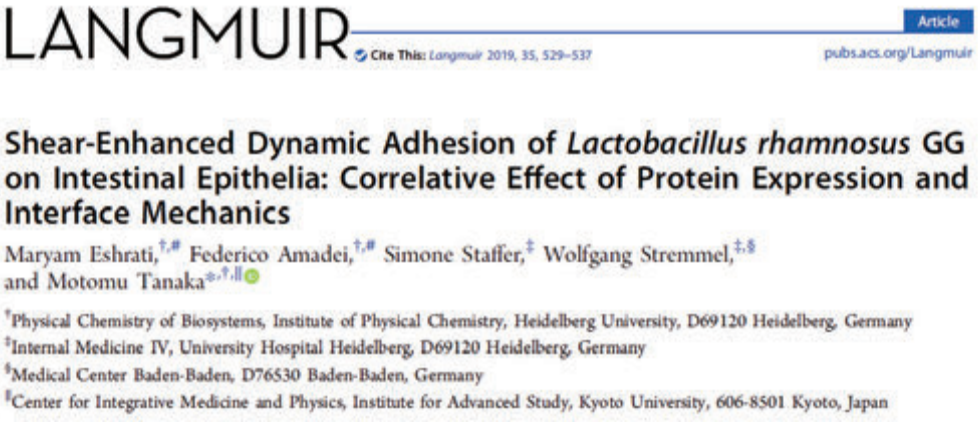
【2017 年度】

北野　貴暉、渡邊　岳之

研究テーマ　「大腸上皮モデルへの乳酸菌定着への流体効果の定量計測・解析」

共同研究先　ハイデルベルク大学消化器内科・Wolfgang Stremmel 教授

研究指導　　Federico Amadei, MSc (Physics), Philipp Linke, MSc (Physics)



LANGMUIR　Article

Cite This: Langmuir 2019, 35, 529−537　pubs.acs.org/Langmuir

Shear-Enhanced Dynamic Adhesion of *Lactobacillus rhamnosus* GG on Intestinal Epithelia: Correlative Effect of Protein Expression and Interface Mechanics

Maryam Eshrati,[†,#] Federico Amadei,[†,#] Simone Staffer,[‡] Wolfgang Stremmel,[‡,§] and Motomu Tanaka[*,†,∥]

[†]Physical Chemistry of Biosystems, Institute of Physical Chemistry, Heidelberg University, D69120 Heidelberg, Germany
[‡]Internal Medicine IV, University Hospital Heidelberg, D69120 Heidelberg, Germany
[§]Medical Center Baden-Baden, D76530 Baden-Baden, Germany
[∥]Center for Integrative Medicine and Physics, Institute for Advanced Study, Kyoto University, 606-8501 Kyoto, Japan

Stremmel 教授との共著論文への貢献を謝辞にて感謝

■ ACKNOWLEDGMENTS

M.E. and F.A. thank C. Dominguez, T. Kitano, T. Watanabe, F. Lasitschka, and P. Linke for experimental assistance, and S. Kaufmann for helpful suggestions. M.T. thanks EU FP7 under REA grant agreement no. 606713 BIBAFOODS and Nakatani Foundation for support.

【2018 年度】

岩本　健太郎、緑谷　創

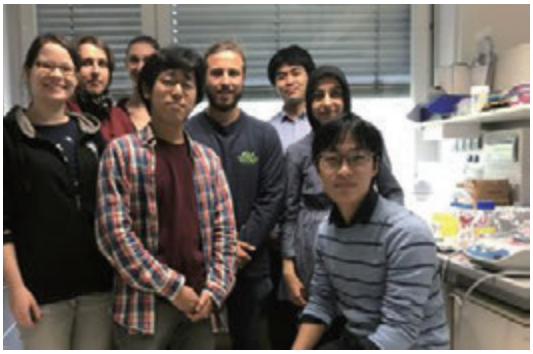
研究テーマ　「加齢による造血幹細胞の代謝スイッチの定量解析」

共同研究先　ハイデルベルク大学血液内科・Anthony Ho 名誉教授

研究指導　　Judith Thoma, MSc (Physics), Dr. Stefan Kaufmann (Biology)

【2019 年度】

牧原　史尚、森　一斗



研究テーマ　「GPR56 が白血病造血幹細胞モデルの骨髄内動態に与える影響の定量」

共同研究先　ハイデルベルク大学血液内科・Carsten Mueller Tidow 教授

研究指導　　Judith Thoma, MSc (Physics), Dr. Caroline Pabst (Medicine)

【2020 年度】

コロナにより中止

【2021 年度】

コロナの渡航規制により、京都で受け入れ

大谷　暢宏

研究テーマ　「パーシステントホモロジーによるヒト角膜内皮再生組織の局所的秩序構造と組織機能の関係に関する研究」

共同研究先　岡山大学　AI・数理データサイエンスセンター　大林　一平　教授

研究指導　山本暁久（助教）

山本　大智

研究テーマ　「２種類の異なる膵癌前駆病変 IPMN と PanIN の細胞運動及び変形の比較」

共同研究先　京都大学　医学研究科　妹尾　浩　教授

研究指導　山本暁久（助教）

【2022 年度】

堀内　力

研究テーマ　「筋管形成における遺伝子変異の力学的刺激による克服」

研究指導　　Dannyu Egic, MSc (Biology)

近藤　竜

研究テーマ　「接着強度を用いた特異的なマラリア感染赤血球の検出」

共同研究先　ハイデルベルク大学感染症研究所　Michael Lanzer 教授

研究指導　　Katharina Scholz, MSc (Chemistry)

【2023 年度】

松下　哲也

研究テーマ　「小児マラリアにおけるホスト細胞の脂質組成の影響に関する研究」

共同研究先　コペンハーゲン大学熱帯医学研究所　Thomas Lavsten 教授

研究指導　　Katharina Scholz, MSc (Chemistry)

人材育成（６）
国内・国外他大学からの学生の受入・研究指導

当拠点では、国内外の他大学から様々な分野の学生や若手研究者を数多く受け入れ、医学物理、医工計測をテーマに分野融合型の先端研究を行ってきました。ここでは京都の拠点を訪れ我々と研究した学生たちの活動について紹介します。

Philipp Linke

PhD student (Physics), Physical Chemistry of Biosystems,
Institute of Physical Chemistry, Heidelberg University

周期と配向を自在に制御できるしわ基板を用いた筋芽細胞の動的制御

滞在期間： 4 か月（2018 年）
Heidelberg 大学総長奨学金

主たる受入研究者　田中 求、大園拓也（産総研）
Langmuir (2019) Cover Article

一野 陽希、朴 峻秀

大阪大学　高等共創研究院　理学研究科 高分子科学専攻
修士課程（一野）、博士課程（朴）

光応答性高分子材料の細胞工学への応用

滞在期間：3 日間（2018）

主たる受入研究者　林健太郎

Danny M. Egic

MSc student, Molecular Biotechnology,
Heidelberg University

人工材料を用いた遺伝子欠損株の筋管形成能再獲得
メカニズム

滞在期間：5 か月（2019）DAAD PROMOS Fellowship

主たる受入研究者　梅田真郷（京大工）、鈴木 量

三竹 のどか、Garry Sinawang

修士課程（三竹）、博士課程（Sinawang）

大阪大学　高等共創研究院　理学研究科 高分子科学専攻

超分子生体材料を用いた細胞操作技術の開発

滞在期間：3 日間（2019）

主たる受入研究者　林健太郎

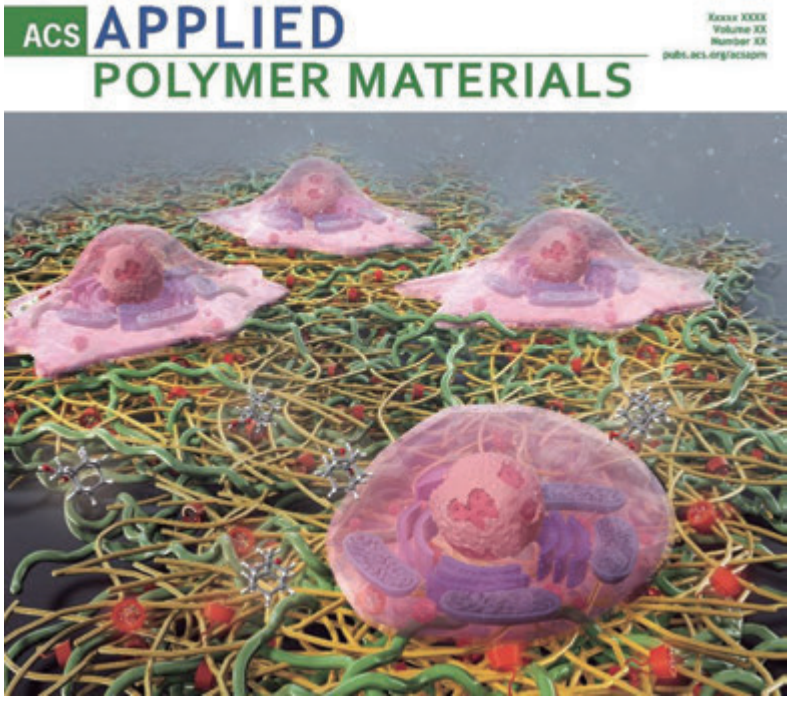
ACS Appl Polymer Mater (2022) cover

ACS APPLIED POLYMER MATERIALS

pubs.acs.org/acsapm Article

One-Step Synthesis of Gelatin-Conjugated Supramolecular Hydrogels for Dynamic Regulation of Adhesion Contact and Morphology of Myoblasts

Kentaro Hayashi, Mami Matsuda, Nodoka Mitake, Masaki Nakahata, Natalie Munding, Akira Harada, Stefan Kaufmann, Yoshinori Takashima,* and Motomu Tanaka*



Judith Thoma

PhD student (Physics), Physical Chemistry of Biosystems, Institute of Physical Chemistry, Heidelberg University


細胞変形と運動の理論モデル

滞在期間：6 週間（2019）HeKKSaGOn 旅費支援

主たる受入研究者　田中 求、佐野雅己（東大理）

Ronja Rappolt

MSc Thesis student (Molecular Biotechnology),
Physical Chemistry of Biosystems, Institute of Physical Chemistry, Heidelberg University

ナノファイバーの配向性がヒト iPS 細胞の動態に与える影響の研究

滞在期間：6 週間（2019）DAAD PROMOS Fellowship

主たる受入研究者　鈴木 量

Julian Czajor

PhD student (Physics), Physical Chemistry of Biosystems, Institute of Physical Chemistry, Heidelberg University


デンドリマーによる血液防汚性表面の表面物理

滞在期間：2 か月（2019）EU FP7

主たる受入研究者
田中 求、林智広（東工大）

RSC Advances (2021)


ROYAL SOCIETY OF CHEMISTRY

RSC Advances

PAPER

Check for updates

Cite this: RSC Adv., 2021, 11, 17727

Dendronized oligoethylene glycols with phosphonate *tweezers* for cell-repellent coating of oxide surfaces: coarse-scale and nanoscopic interfacial forces†

Julian Czajor,‡[a] Wasim Abuillan,‡[a] Dinh Vu Nguyen,[b] Christopher Heidebrecht,[a] Evan A. Mondarte,[c] Oleg V. Konovalov,[d] Tomohiro Hayashi,[ce] Delphine Felder-Flesch,[bf] Stefan Kaufmann[a] and Motomu Tanaka[ag]

Monsur Islam

PhD student (Engineering), Institute for Microstructure Technology, Karlsruhe Institute of Technology

滞在期間：1 週間（2019 年）

ナノファイバーの配向性制御技術の研究調査

主たる受入研究者　鈴木 量

Esther Kimmle

PhD student (Chemistry), Physical Chemistry of Biosystems, Institute of Physical Chemistry, Heidelberg University

ヒト iPS 細胞のメカノセンシングを制御する材料の創製

滞在期間：6 週間（2019）

主たる受入研究者　林健太郎

松田 茉美

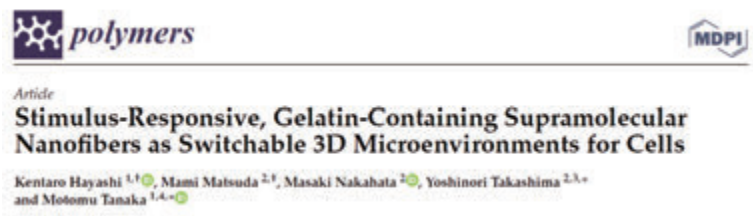
大阪大学　高等共創研究院　理学研究科 高分子科学専攻

刺激応答性たんぱく質ナノファイバーの創製

滞在期間：のべ 3 週間（2019 －）

主たる受入研究者　林健太郎

Polymers (2022)


polymers

MDPI

Article

Stimulus-Responsive, Gelatin-Containing Supramolecular Nanofibers as Switchable 3D Microenvironments for Cells

Kentaro Hayashi [1,†], Mami Matsuda [2,†], Masaki Nakahata [2], Yoshinori Takashima [2,3,*] and Motomu Tanaka [1,4,*]

Ramona Marten



MSc student, Chemistry,
Heidelberg University

固体表面に担持したナノゲルおよび生物着想型機能性高分子の物理化学的特性の計測

滞在期間：5 カ月（2022）

主たる受入研究者　秋吉一成（京大工）、佐々木善浩（京大工）、山本暁久

Christopher Heidebrecht

MSc student, Molecular Biotechnology, Heidelberg University

ヒト iPS 細胞の基板の硬さに対するメカノ応答性の評価

滞在期間：3 カ月（2022）

主たる受入研究者　林健太郎

Lukas Krohne

MSc student, Biochemistry, Heidelberg University

ゼラチン・ナノファイバーを用いた遺伝子阻害された筋芽細胞の筋管形成能再獲得メカニズム

滞在期間：3 カ月（2022）

主たる受入研究者　鈴木 量

Bahareh E. Pour

PhD student (Chemistry), Institute of Physical Chemistry, Heidelberg University

生物着想型材料で機能化された窒化ガリウムデバイスを用いた有害金属イオンのセンシング

滞在期間：2 カ月（2022）

主たる受入研究者　山本暁久

Natalie Munding

PhD student (Chemistry), Institute of Physical Chemistry, Heidelberg University

可逆的な弾性率スイッチングが可能な光応答性水和ゲルの開発

滞在期間：2 カ月（2023）

主たる受入研究者　高島義徳（阪大理）、水藤寛（東北大）

杉浦 開

東京工業大学　物質理工学院　応用化学系

セロオリゴ糖化合物を活用した幹細胞の運命制御技術の開発

滞在期間：京都 1 週間、ハイデルベルク 3 カ月（2023）

主たる受入研究者　山本暁久（京都）、田中 求（ハイデルベルク）

Danny M. Egic

PhD student (Biology), Physical Chemistry of Biosystems,
Institute of Physical Chemistry, Heidelberg University

しわ基板上における筋管再生能の動的制御

滞在期間：2 カ月（2024）

主たる受入研究者　鈴木 量

Magdalena Fladung

PhD student (Biology), Department of Cell and Neurobiology,
Zoological Institute, Karlsruhe Institute of Technology

ナノファイバーの配向性制御技術の最適化

滞在期間：6 週間（2024）

主たる受入研究者　鈴木 量

Elisa Genthner

PhD student (Biology), Department of Cell and Neurobiology,
Zoological Institute, Karlsruhe Institute of Technology

可逆的な弾性率スイッチングが可能な水和ゲル上での
ヒト iPS 細胞のメカノコンプライアンス評価

滞在期間：6 週間（2024）

主たる受入研究者　鈴木 量

研究成果の社会実装・社会への発信（１）
社会実装・産業界との連携

当拠点の研究で得られた成果は、単に論文として発表し、知財として特許出願するだけに留まらず、TLO 京都などの支援のもと産業界と連携し、社会実装を実現することで社会へと還元することを積極的に行っています。
実際に国内・国外の企業と実施許諾（ライセンス契約）に至った発明もすでにＸ件を数え、「研究室から社会へ」の道筋を確立しつつあります。

【特許】

実施許諾

発明の名称：細胞評価方法、細胞評価装置、及び細胞評価プログラム

出願番号：　特願 2017-027247
公開番号：　WO2018/151223
特許番号：　特許第 6985684 号
出願日：　2017/2/16
公開日：　2018/8/23
登録日：　2021/11/30
発明者：　田中求、山本暁久、上野盛夫、羽室淳爾、木下茂、田中寛、戸田宗豊、外園千恵
出願人：　国立大学法人京都大学、京都府公立大学法人
実施許諾の状況：

1　トーメーコーポレーション：日本非独占実施許諾。締結日・2019 年 11 月 25 日、2022 年 3 月末日まで有効。2021 年 7 月 1 5 日に製品販売開始。
2　CorneaGen Inc.：海外独占および日本非独占実施許諾。Effective date（契約有効日）・2019 年 7 月 30 日。

日本では第 6985684 号（発行日：2021 年 12 月 22 日）、米国では No. 11436719（2022 年 9 月 6 日）として特許を取得。

発明の名称：培地用高分子ゲル、培地、細胞の培養方法及びキット

出願番号：　特願 2016-148725
公開番号：　WO2018/021289
特許番号：　特許第 6975427 号
出願日：　2016/7/28
公開日：　2018/2/1
登録日：　2021/11/10
発明者：　原田明、髙島義徳、中畑雅樹、田中求、ホールニング・マルセル
出願人：　国立大学法人大阪大学、国立大学法人京都大学
出願国：日本、米国、欧州（出願中の状態）

実施許諾の状況：

1　ibidi GmbH：独占的実施許諾。締結日・2021 年 7 月 30 日、2021 年 7 月 1 日から 5 年間有効。

日本では第 6975427 号（発行日：2021 年 12 月 1 日）として特許を取得。

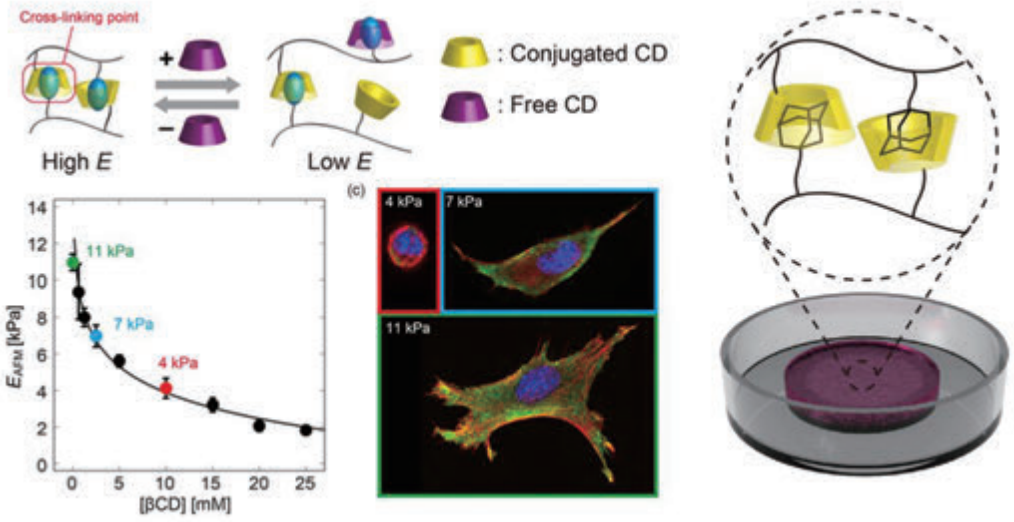
中谷財団第１回技術開発研究助成【特別研究】
で支援いただいた研究が実用化！

実施許諾の例2:「培地用高分子ゲル、培地、細胞の培養方法及びキット」

出願人（発明者）
京都大学（田中 求、M. Horning）
大阪大学（原田明、髙島義徳、中畑雅樹）




実施許諾（日本欧米独占）:ibidi（Germany）



原田・田中らが開発した、細胞活性に影響を与えることなく自在に基板の硬さを変調可能な超分子ゲルを知財化・2021年8月に実施許諾の最終合意にいたる

Dr. Roman Zantl

President ibidi GmbH, Martinsried

Since Motomu and I met first at Erich Sackmann's Institute for Experimental Physics in 1998, we were immediately connected by the fascination of biophysical and biochemical techniques including surface architectures. During our lively discussions and intense intercultural exchange it became clear that Motomu's scientific enthusiasm and personal open mindedness were already connecting the Asian and European scientific communities. Congratulations for this new and exciting institute and good luck with pushing forward physical chemistry in the direction of medical relevance!

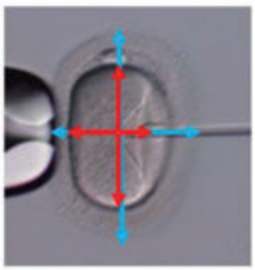
部門長・田中とibidi のZantl CEOは23年前にミュンヘン工科大学の同じ研究所で出会って以来の友人で、寄附部門の開設にあたってもメッセージを寄せてくれた

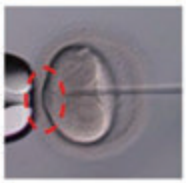
実装へ向け進行中:「卵子評価方法、卵子評価装置、及び卵子評価用プログラム」

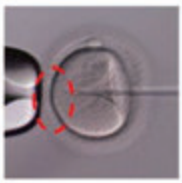
SHIMADZU

出願人（発明者）
京都大学（田中 求、山本暁久）
島津製作所（杉村佳織）
古賀文敏ウィメンズクリニック
（古賀文敏、北上茂樹）

古賀文敏ウイメンズクリニック
KOGA FUMITOSHI WOMEN'S CLINIC







- ピペット側の吸い込みによる変形の有無

- 透明帯の縦横比（縦／横）
- 細胞膜の縦横比（縦／横）を測定

山本・杉村・田中らが開発した、顕微授精の記録動画から卵子の力学特性を抽出し、患者データと合わせて受精の成功率を予測する手法を知財化・2022年には古賀クリニックとの臨床共同研究、2023年からドイツの顕微鏡メーカーとの共同研究を推進

登録済み

発明の名称：検出方法及びデバイス
出願番号：　特願 2016-211569
公開番号：　特開 2018-072134
出願日：　2016/10/28
公開日：　2018/5/10
発明者：　上野祐子、古川一暁、田中求
出願人：　日本電信電話株式会社

発明の名称：生体分子移動制御方法およびデバイス
出願番号：　特願 2017-237175
公開番号：　特開 2019-105484
出願日：　2017/12/11
公開日：　2019/6/27
発明者：　上野祐子、手島哲彦、田中求
出願人：　日本電信電話株式会社 国立大学法人京都大学

発明の名称：脂質二重膜基板におけるリンカー層の制御方法、並びに、脂質二重膜基板及びその製造方法
出願番号：　特願 2018-117219
公開番号：　特開 2019-216660
出願日：　2018/6/20
公開日：　2019/12/26
発明者：　上野祐子、樫村吉晃、大嶋梓、田中求、山本暁久
出願人：　日本電信電話株式会社 国立大学法人京都大学

発明の名称：生体分子の支持体とその製造方法
出願番号：　特願 2019-195481

公開番号：　特開 2021-65200
出願日：　2019/10/28
公開日：　2021/4/30
発明者：　上野祐子、樫村吉晃、大嶋梓、田中求、山本暁久
出願人：　日本電信電話株式会社 国立大学法人京都大学

発明の名称：イオン制御バイオデバイスとその製造方法
出願番号：　特願 2020-116340
公開番号：　特開 2022-14150
出願日：　2020/7/6
公開日：　2022/1/9
発明者：　上野祐子、樫村吉晃、大嶋梓、田中求、山本暁久
出願人：　日本電信電話株式会社 国立大学法人京都大学

発明の名称：卵子評価方法、卵子評価装置、及び卵子評価用プログラム
出願番号：　特願 2021-168634
公開番号：　WO2023/063099
出願日：　2021/10/14
公開日：　2023/4/20
発明者：田中求、山本暁久、杉村佳織、古賀文敏、北上茂樹
出願人：国立大学法人京都大学、株式会社島津製作所、医療法人古賀文敏ウイメンズクリニック

出願中

発明の名称：組織画像の評価方法、評価装置および評価用プログラム

出願番号：特願 2024-192013

出願日：2024/10/31

発明者：田中求、山本暁久、鈴木量、カレル　シュワドレンカ、鶴山竜昭、藤﨑碩人

出願人：国立大学法人京都大学

研究成果の社会実装・社会への発信（２）
プレスリリースなど

当拠点では、医学・物理学・材料科学・数学など分野融合型の研究で得られた成果をプレスリリースや一般向け解説記事のような形で社会へ発信しています。
ここではいくつかの例を挙げて、我々の活動を紹介します。

2019 年

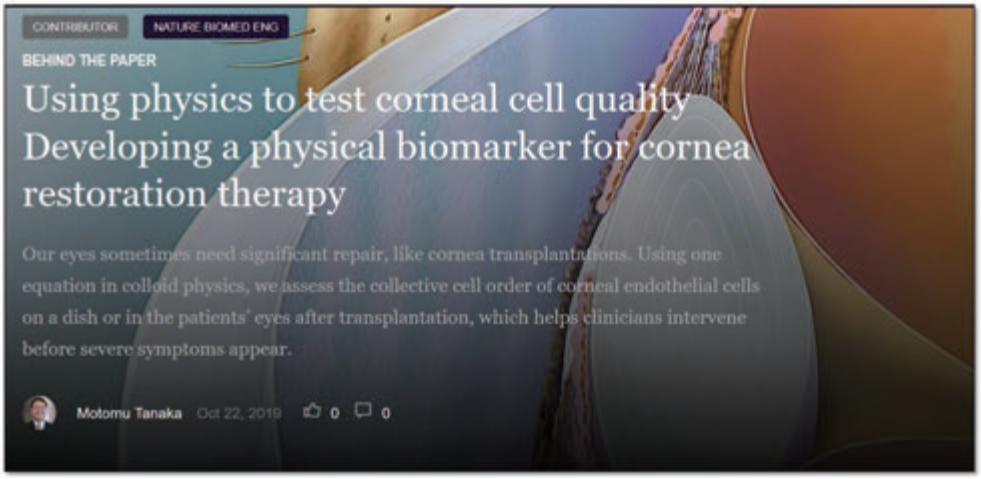
プレスリリース（コロイド物理を活用した革新的角膜内皮細胞評価技術）

2019年5月29日　於・京都大学高等研究院

上段左から　中谷財団・實田事務局長、筆頭著者・山本助教、京都府立医大眼科・外園教授、下段左から　共責任著者・上野講師（京都府立医大、拠点客員研究員）、部門長・田中

日経サイエンス（2019年10月号・12－13頁）

オンラインニュース記事（Nature Blog）



日刊工業新聞（7月23日29面）、日本経済新聞（7月29日29面）、電子情報通信学会学会誌（2020年1月号）など

2020 年

プレスリリース「3Dプリンタと超分子ゲルによる一細胞操作」

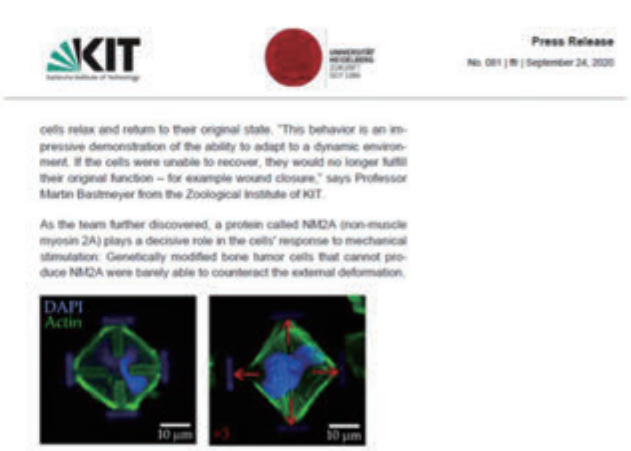
2020年9月24日　カールスルーエ工科大プレス発表

SCIENCE ADVANCES | RESEARCH ARTICLE

MATERIALS SCIENCE

Mechanical stimulation of single cells by reversible host-guest interactions in 3D microscaffolds

Marc Hippler[1,2]*, Kai Weißenbruch[2,3], Kai Richler[2], Enrico D. Lemma[2], Masaki Nakahata[4], Benjamin Richter[2], Christopher Barner-Kowollik[5,6,7], Yoshinori Takashima[8], Akira Harada[8], Eva Blasco[7,9], Martin Wegener[1,9]*, Motomu Tanaka[10,11]*, Martin Bastmeyer[2,3]*



ドイツエクセレンスクラスター「3D Matter Made to Order」（田中と拠点客員・Bastmeyer教授は運営委員メンバー）と新学術領域「水圏機能材料（田中と阪大・高島教授は総括班メンバー）」という日独の大型拠点間の共同研究の成果

その後、京都大学・ハイデルベルク大学もこの情報をウェブサイトでリリース
多数のメディア・ウェブニュースで取り上げられた

プレスリリース「抗菌剤の働くメカニズムを分子・原子レベルで解明」

2020年10月20日　花王株式会社ニュースリリース

欧州放射光機構（ESRF, Grenoble, France）で行った国際共同実験

SCIENTIFIC REPORTS
nature research


田中　求*


J. Thoma (HD)


山本暁久（京大）

OPEN **Specific localisation of ions in bacterial membranes unravels physical mechanism of effective bacteria killing by sanitiser**

Judith Thoma[1,7], Wasim Abuillan[1,2,7], Ippei Furikado[3], Taichi Habe[3], Akihisa Yamamoto[3], Simone Gierlich[3], Stefan Kaufmann[3], Klaus Brandenburg[4,5], Thomas Gutsmann[4], Oleg Konovalov[6], Shigeto Inoue[2,3] & Motomu Tanaka[1,2]


井上滋登*（花王）


振角一平（花王）


波部太一（花王）

News Release

花王株式会社 広報部

kao

〒103-8210 東京都中央区日本橋茅場町1-14-10 TEL 03-3660-7041･7042 FAX 03-3660-7044　www.kao.com/jp/

＜発表資料＞　2020 年 9 月 xx 日 20xxx

界面活性剤と芳香族アルコールによる抗菌作用メカニズムを原子･分子スケールで解明

花王株式会社（社長･澤田道隆）解析科学研究所とドイツ　ハイデルベルク大学　物理化学研究所　田中求教授（京都大学高等研究院特任教授）の研究グループは、細菌の一番外側の表面を覆う層に対する抗菌剤の作用メカニズムを、放射光 X 線を用いた精密解析によって原子･分子スケールで明らかにしました。

今回の研究成果は、*Nature* 誌のオープンアクセスジャーナルである *Scientific Reports* に掲載されました[*1]。

*1　Specific localisation of ions in bacterial membranes unravels physical mechanism of effective bacteria killing by sanitizer
https://doi.org/10.1038/s41598-020-69064-1

その後、週間粧業・医薬通信社など複数のメディアで取り上げられた

2021 年

「現代化学」9 月号

新学術領域の一般向け広告記事が掲載

広告

水圏機能材料

シリーズ
第5回

研究項目 機能開拓班　計画研究 水圏機能材料の電子・イオン機能開拓

生物にならい生物を超える水圏機能材料を働かせる

研究代表者 田中 求・京都大学高等研究院 特任教授・ハイデルベルク大学物理化学研究所 教授
研究分担者 中畑雅樹・大阪大学大学院基礎工学研究科 助教

水は人間の体重の6割以上を占めています。そのため生体中の分子の多く（例えばDNAなど）は、鉄やガラス、プラスチックなどとは違い、水の存在下で特有の構造をとることで環境の変化を検知し、それに順応・対応しています。高い感度と選択性を備えた生体分子に着想を得た材料を合成して、その機能を活用するには、水中の分子構造を精密に制御して水と材料の界面を最適につなぐことが必要です。

分野融合で実現した細胞用超小型ストレッチマシン

田中教授と中畑助教は、生物の機能にならい生物の機能を超える水圏電子・イオン材料の開拓を目指しています。生物は水環境で分子やイオンを選択的に高感度で認識することができます。

中畑助教は、生物に着想を得た新たな人工材料を設計し、合成しています。田中教授は、材料が水分子と出会う界面における材料の構造と機能を精密制御して、その機能を最大限に発揮させる研究を進めています。最終的には、このような材料を超高集積化して、水中の有害イオンを捉えたり、イオンや電子についての認識を半導体材料によって電子信号として選択的に取り出したいと考えています。

図に示したのは、最先端の超精密3Dプリンターで作製したミクロサイズの足場と水環境で分子を選択的に認識する超分子ゲルを融合させた細胞のストレッチマシンです（左）。高分子鎖の架橋を緩めるような低分子水溶液を入れると、水分子が入り込んでゲル（黄色部分）が膨らみ、枠を外へと押し出します（右）。普通の培養液に戻せば、この水分子が抜けて高分子鎖ネットワークが縮小するので、細胞（緑部分）は元の状態に戻ります（中央）。こうして生きた細胞を引っ張ったり緩めたりすることができます。

この研究の意義は、力学的なストレスに対して個々の細胞がどう応答するかを追跡できることにあります。血管、筋肉、消化管のような収縮性の大きな組織の再生医療などに展開する可能性が考えられます。

幅広い知識と技術が必要なストレッチマシンの創作を可能にしたのは、京都大学、大阪大学、ハイデルベルク大学、カールスルーエ工科大学の日独共同研究でした。田中教授は、長くドイツの大学を拠点に研究活動を行い、日独の大学コンソーシアムを率いるなど、両国の学術交流の架け橋として活躍しています。化学物理・生命物理などを専門とする田中教授が、超分子化学を専門とする中畑助教や高島義徳教授（大阪大学高等共創研究院）らと機能開拓グループで進めてきた国際共同研究が生み出した成果です。

(*Sci. Adv.*, 2020, 6, eabc2648)

材料を理詰めで創成する基盤づくり

材料の開発では、従来は最適な材料や作動条件を試行錯誤して探すのが一般的でした。しかし田中教授は、これを理詰めで行うことでより優れた材料をより効率的に作りたいと考えています。水の中で使う材料を理論的に開発するのは容易ではありません。水は単に空隙を埋める溶媒ではなく、材料の機能発現に影響を与えたり、ゲルや水和性高分子の構造に能動的に関わっているからです。

この共同研究がスタートしてから、田中教授と中畑助教はそれぞれの得意分野を生かして、水圏機能材料開発のための理論的な技術基盤づくりを進めてきました。水との親和性が生物にどのように機能を発揮させているかを理解して、水環境で高い機能を発揮し、生物を凌駕する強靭性を持つ材料を生み出すのが目標です。

田中教授は並行して、水との界面で分子が自発的に配列して構築する超分子ス

「現代化学」９月号

有賀教授（物質・材料研究機構）の連載で田中へのインタビューが紹介

研究者に必要なコミュ力とは？

有賀克彦

隠しているんではないかと思います．おもしろい例は，素粒子理論で有名なFeynmanが書いた量子物理の教科書はわかりやすい論理を積み上げていって難しい量子力学を教えています．日本語の哲学書などは特にわかりにくく書く傾向があります．英訳を見てあぁそういうことかと理解できる場合もあります．

「日本人から見ると，米国人の方がコミュニケーション力が高いように感じますが，実際のところ，米国大学や研究現場で働いていてどうでしたか？」

日本の学生にいつも言っていたのは，抽象化した結果を言うのではなく，具体的意味は何かを意識して書くなり話すなりすること．わかりやすい例としてあげると，若い学生が「愛しています」と告白したとします．この中身は好きだ，会いたい，話したい，大切にしたい，などなどいろんな具体的感情がまとめて抽象化されているんですよね．計測器がよく動かないときに不具合があるというのではなくて，電流が通じないとかおかしい電圧が出るとか，具体的に言うことが必要．

「米国の研究者はどうやってコミュニケーションをとっているですか？」

訓練の結果ですね．日常的に自分の言葉で発表，討論することが訓練になっています．日本語では曖昧にぼやかしてものを言うことが日常化しているので，それが科学の論文や口頭発表にも出てきます．菅首相の記者会見や国会答弁を聞いていると，総合的に判断するとか，前向きに検討するとか，中身のない言葉の羅列です．僕が記者だったり議員だったりしたら具体的にはどうするの？と聞きたいですね．日本ではそんな失礼なことは聞くものではないと顰蹙を買うかも．これは日本語の「偉い人」という観念に関係しているようです．英語では「偉い」という言葉はないんじゃないかな？Greatかな？ほかに思いつきませんね．

「コミュニケーション力が高いことによるメリット，デメリットはありますか？」

メリットは中身のあるコミュニケーションが効率的にとれて，相談事などは具体的な実行に移せること．日本ではデメリットとしてはっきりものを言いすぎると嫌がられること．英語でもやんわりと批判したり反対したりはできるのですが……．この「ですが……．」は言っていることに自信がなくてnon-committalな表現ですね．英語ではこのように宙ぶらりんの表現は少ないようです．昔三井物産の役員会は英語でやって曖昧な発言を少なくしようとしたという話がありました．

「コミュニケーション力を高めるにはどうしたらよいか？」

発表，討論などの練習をすること．そのとき，わかりにくい発言には遠慮なく具体的な意味を尋ねること，わからないときは率先して質問すること．でもいつもこれを実行すると，日本では嫌がられそうです．日本の会合ではなかなか質問が出ないのははかの人はわかって黙っているのだと思ってしまうこと．実はわからないと認めないで済むように誰かが質問してくれるのを待っている人が多いんですがね．

ドイツ・ハイデルベルグ大学の
田中 求先生

ドイツで20年以上にわたって研究生活を送ってきましたが，研究上のコミュニケーションで深刻なギャップは感じたことがありません．ただ，国民性でしょうか，いくつか違いを感じることはあります．

ドイツの研究者について概していえるのは，批判も含めた議論が非常に直線的であることです．日本では気をつかって言わないようなクリティカルなコメント・質問も，ドイツ人は（立場に関係なく）ズバッとしてくる印象があります．また教授の役割としては，学会や研究会，会議などで質問や発言をすることが求められます．私もドイツ語で行われる教授会では相変わらず「借りてきた猫」状態ですが，研究会では「必ず前列に座って，いい質問をするよう心掛けながら講演（発表）を聞くのが教授の仕事」だという，ミュンヘン時代の師であるE. Sackmann先生の教えを守るようにしています．

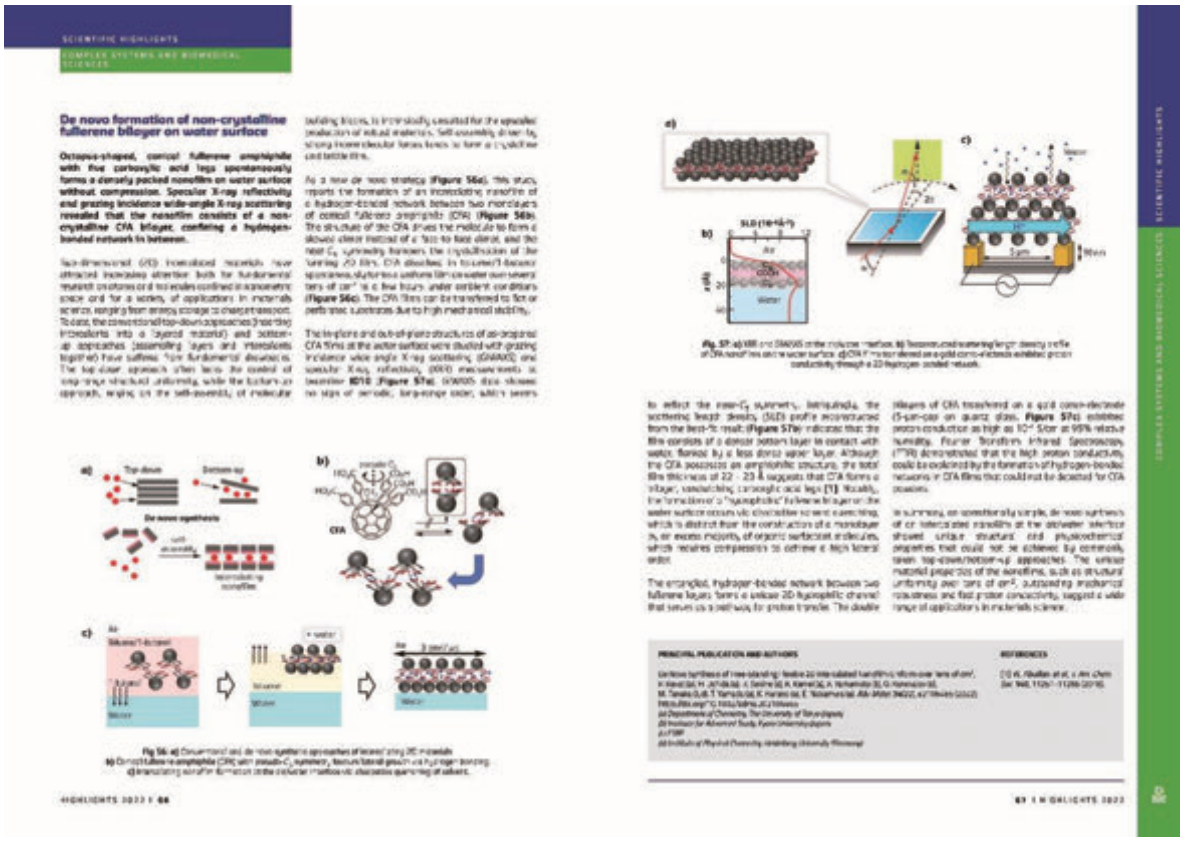
それに対して日本では「批判的なコメントをすると相手に失礼に当たる」という気づかいがあるのか，研究会で議論が白熱することや会議で異なる意見を交わすことが少ないように思います．そういえば，私も日本での研究会や会議でわりとはっきりとモノを言ったせいで，「田中さんはガイジンだ」と言われたことが何度もあります．ドイツ式の振舞いが身に沁みついたのかもしれません．礼儀正しい・奥ゆかしいというのは日本人の優れた美徳であるので，大切にすべき部分だと思います．一方で日本の研究者，特に若手の方の講演を国際学会などで見ていて，議論が弱いという印象を受けることが多いのも事実です．「ガイジンは口（英語）が達者で得している」とかいうレベルの話ではありません．

どちらが優れているというのではなく，相手の長所を認めてうまく取入れられるといいのですが，なかなか難しいですね．

これらの意見を見ると，「受けの名手」として相手の話を聞くということだけではなく，積極的かつ具体性をもって意見を言う「攻めの姿勢」の重要性が国

2022 年

欧州シンクロトロン放射光研究所年次報告書「ESRF Highlights 2022」
**　中村栄一教授（東京大学）、原野幸治主幹研究員（物質・材料研究機構）らとの共同研究に関する成果がハイライトとして選出・紹介**



SCIENTIFIC HIGHLIGHTS

COMPLEX SYSTEMS AND BIOMEDICAL SCIENCES

De novo formation of non-crystalline fullerene bilayer on water surface

Octopus-shaped, conical fullerene amphiphile with five carboxylic acid legs spontaneously forms a densely packed nanofilm on water surface without compression. Specular X-ray reflectivity and grazing incidence wide-angle X-ray scattering revealed that the nanofilm consists of a non-crystalline C70A bilayer, confining a hydrogen-bonded network in between.

HIGHLIGHTS 2022 | 84

SCIENTIFIC HIGHLIGHTS

COMPLEX SYSTEMS AND BIOMEDICAL SCIENCES

85 | HIGHLIGHTS 2022

研究成果の社会実装・社会への発信（３）
アウトリーチ活動など

当拠点では、医学・物理学・材料科学・数学など分野融合型の研究で得られた成果を、企業や市民向けの講演会のような形でより広く社会へ発信することを積極的に行っています。
また次世代の科学を担う中高生を対象に研究紹介を行うなどアウトリーチ活動にも取り組んでいます。

2018 年

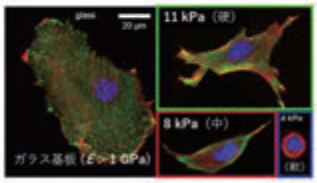
※ここでの議論をきっかけに島津製作所との共同研究がスタート

2019 年

企業向け講演・メディカルジャパン2019

2019.02.21 メディカルジャパン（大阪）

「硬さ」を簡便・自在に制御できる
細胞培養基材



分子認識に基づく可逆的結合で
新機能材料を創出

京都大学・ハイデルベルク大学
田中　求

大阪大学
原田　明、高島義徳、中畑雅樹

※講演後 5 社と企業面談を行うも最後はドイツの ibidi 社とライセンス契約

洛星高校　研究室訪問

2019年6月8日　於・京都大学高等研究院


鈴木助教による研究紹介

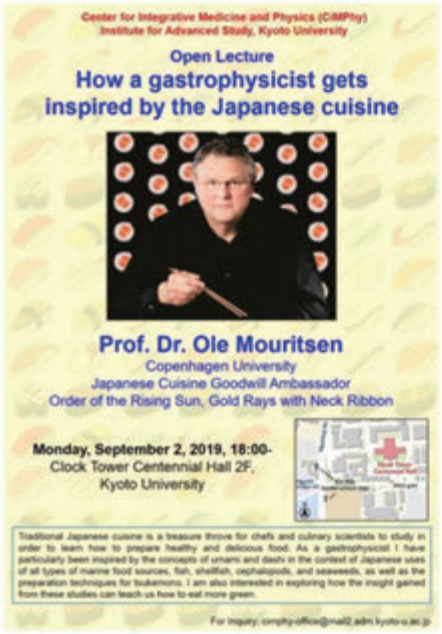
私立洛星高校では「大学で何を専攻するか」を考えるヒントとして、先輩（部門長・田中など）の研究室を訪問して体験する機会を設けている。

田中研究室では、2015年から毎年、鈴木・山本両助教が10－15人を受け入れてきた。

山本助教によるピコ秒パルスレーザーを使った細胞接着強度測定装置の説明

市民講座『和食の科学』物理学と和食の幸せな出会い

2019年9月2日　於・京都大学百周年時計台記念館



講師
コペンハーゲン大学
Ole G. Mouritsen 教授

旭日中授章
農水省・日本食親善大使

南デンマーク大学・膜物理学センター・
設立拠点長
部門長 田中を学生時代に受入・指導

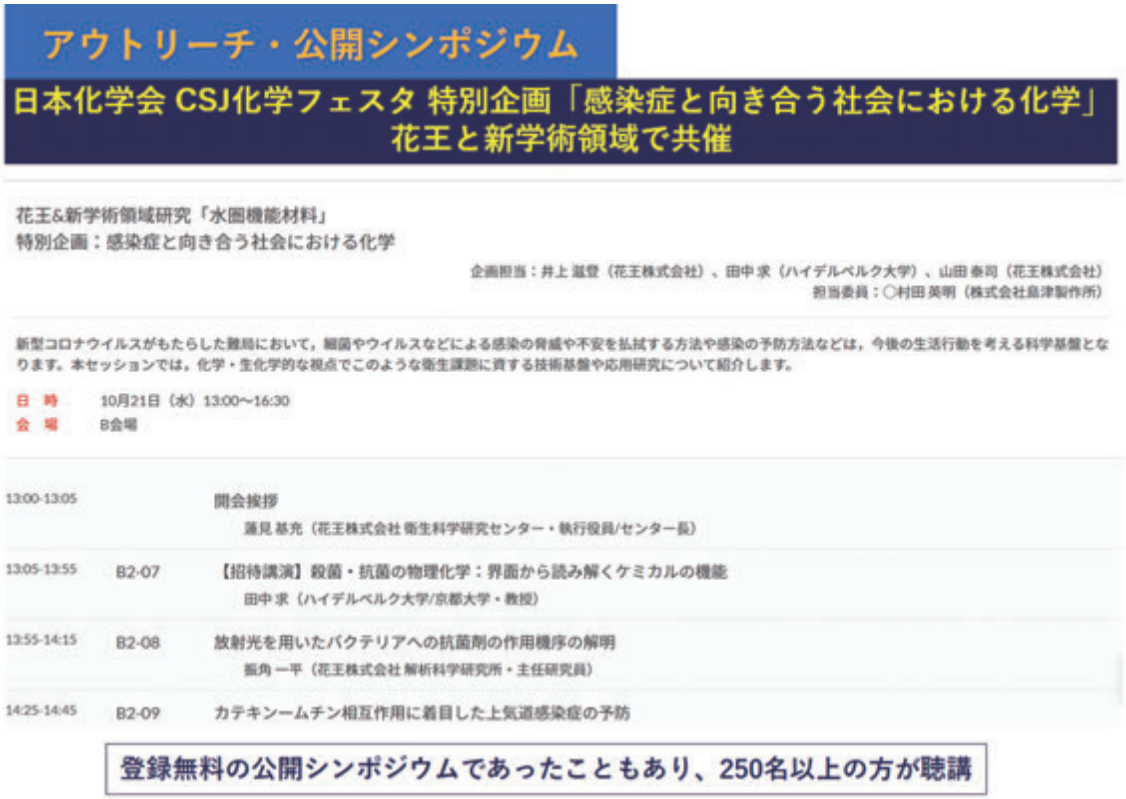
多くの留学生も参加

市民・中高生など百人以上が聴講

食を通じた教育の実践例

ノートルダム女子中高の生徒と

2020 年



アウトリーチ・公開シンポジウム

日本化学会 CSJ化学フェスタ 特別企画「感染症と向き合う社会における化学」
花王と新学術領域で共催

花王&新学術領域研究「水圏機能材料」
特別企画：感染症と向き合う社会における化学

企画担当：井上 滋登（花王株式会社）、田中 求（ハイデルベルク大学）、山田 泰司（花王株式会社）
担当委員：○村田 英明（株式会社島津製作所）

新型コロナウイルスがもたらした難局において，細菌やウイルスなどによる感染の脅威や不安を払拭する方法や感染の予防方法などは，今後の生活行動を考える科学基盤となります。本セッションでは，化学・生化学的な視点でこのような衛生課題に資する技術基盤や応用研究について紹介します。

日 時　10月21日（水）13:00～16:30
会 場　B会場

13:00-13:05		開会挨拶 蓮見 基充（花王株式会社 衛生科学研究センター・執行役員/センター長）
13:05-13:55	B2-07	【招待講演】殺菌・抗菌の物理化学：界面から読み解くケミカルの機能 田中 求（ハイデルベルク大学/京都大学・教授）
13:55-14:15	B2-08	放射光を用いたバクテリアへの抗菌剤の作用機序の解明 振角 一平（花王株式会社 解析科学研究所・主任研究員）
14:25-14:45	B2-09	カテキン−ムチン相互作用に着目した上気道感染症の予防

登録無料の公開シンポジウムであったこともあり、250名以上の方が聴講

※2021 年もオンラインで開催

2022 年

洛星高校　研究室訪問
2022 年 6 月 4 日　於・京都大学高等研究院本館
コロナ禍による行動制限が緩和され、鈴木・山本が研究テーマ紹介と実験室ツアーを対面で開催した

2023 年

洛星高校　研究室訪問
2023 年 6 月 3 日　於・京都大学高等研究院本館
コロナ禍による行動制限が緩和され、鈴木・山本が研究テーマ紹介と実験室ツアーを対面で開催した

東京大学　医学部医学科「基礎臨床社会医学統合講義」
2023 年 8 月 29 日　於・東京大学 医・教育研究棟
学生が自主的にテーマ・プログラムの決定と講師の招待を行うユニークな集中講義プログラムで、医学部 3 年生・4 年生に向けて山本が講義を行った

2024 年

拠点最終報告会

2024 年 2 月 29 日　於・京都大学 芝蘭会館 稲盛ホール

湊長博 京都大学総長、家次恒 中谷医工計測技術財団代表理事のご両名からご挨拶をいただいた後、部門長の田中が拠点におけるこれまでの取り組みと成果について講演を行った。

また、特別講演として、Anthony D. Ho 名誉教授（ハイデルベルク大学医学部附属病院前血液内科部長・寄附部門客員教授）より「The Healing Power within Yourself（あなたの中に宿る治癒するパワー）」、水藤寛 教授（東北大学材料科学高等研究所　副所長）より「Our circulatory system through the lens of applied mathematics（応用数学の目で視る我々の血液循環）」と題してそれぞれご講演いただいた。

国内外から大学関係者、企業研究者、一般市民などを合わせて 80 名を超える参加者が

あり、盛会となった。


京都大学高等研究院特設寄附部門
医学物理・医工計測
グローバル拠点
最終報告会
日 時 2024年2月29日(木)
15：00~17：30
会 場 京都大学芝蘭会館 稲盛ホール
Creation of a New Research Field by Fusion of Medicine, Physics, and Mathematics - from Japan to the World
The Healing Power within Yourself
Anthony D. Ho
Our circulatory system through the lens of applied mathematics

アウトリーチ活動

2018 年

1. 田中　求, “物理で病気を診断する-先攻医療への展望”
   けいはんなリサーチコンプレックス企業向 Cutting Edge 特別講義, 京都府・けいはんなオープンイノベーションセンター, 2018 年 9 月 20 日.

2019 年

1. 田中　求, “「硬さ」を簡便・自在に制御できる細胞培養基材”
   医療と介護の総合展 大阪（メディカル ジャパン 大阪）, 関西広域連合 研究成果企業化促進セミナー, 大阪府・インテックス大阪, 2019 年 2 月 21 日.
2. 山本暁久, “ヒト角膜内皮細胞の集団秩序構造から機能を評価する”, 洛星高校 1 年生に研究紹介, 京都府・京都大学, 2019 年 7 月 8 日.
3. 鈴木　量, “癌オルガノイドの変形から転移能を評価する”, 洛星高校 1 年生に研究紹介, 京都府・京都大学, 2019 年 7 月 8 日.
4. 田中　求（司会）,市民講座『和食の科学』　講師　Ole G. Mouritsen 教授（コペンハーゲン大学）, 京都府・京都大学百周年時計台記念館, 2019 年 9 月 2 日.

2020 年

1. 田中　求（共同世話人）花王・新学術領域コラボ企画『感染症と向き合う社会における化学』CSJ 化学フェスタ, オンライン開催, 2020 年 10 月 21 日
2. 田中　求, “物理科学で生命の謎を解明する”
   高校生のためのサイエンスセミナー, オンライン開催, 2020 年 10 月 31 日.

2021 年

1. 田中　求, “新しい学問を切り開く：物理と数学で解明する生命の謎”
   高校生のためのサイエンスセミナー, オンライン開催, 2021 年 6 月 5 日.

2022 年

1. 山本暁久, “ヒト角膜内皮細胞の「秩序」と機能”, 洛星高校 1 年生に研究紹介, 京都府・京都大学, 2022 年 6 月 4 日.
2. 鈴木　量, “癌オルガノイドの変形から転移能を評価する”, 洛星高校 1 年生に研究紹介, 京都府・京都大学, 2022 年 6 月 4 日.

2023 年

1. 山本暁久, “ヒト角膜内皮細胞の「秩序」と機能”, 洛星高校 1 年生に研究紹介, 京都府・京都大学, 2023 年 6 月 3 日.
2. 鈴木　量, “癌オルガノイドの変形から転移能を評価する”, 洛星高校 1 年生に研究紹介, 京都府・京都大学, 2023 年 6 月 3 日.
3. 山本　暁久, “物理と数理で『測り』臨床医学につなげる細胞運動と組織秩序”, 東京大学医学部 3 年生・4 年生に特別講義「基礎臨床社会医学統合講義」で講義, 東京都・東京大学 医・教育研究棟, 2023 年 8 月 29 日.

2024 年

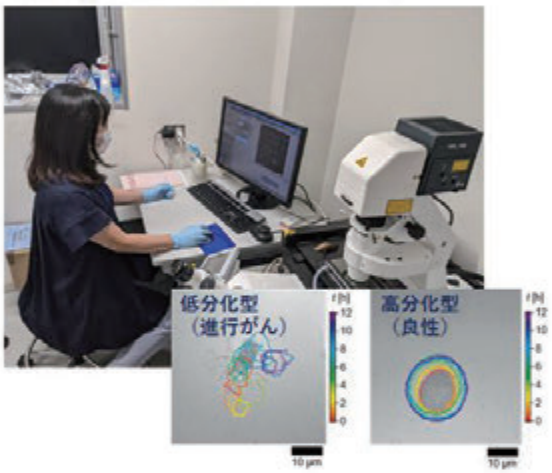
1. 田中　求, “医学と数物融合による新たな学問領域の創出と世界への発信”, 京都大学高等研究院特設寄附部門　医学物理・医工計測グローバル拠点最終報告会, 京都府・京都大学芝蘭会館 稲盛ホール, 2024 年 2 月 29 日.

補足資料（１）
日々の研究風景

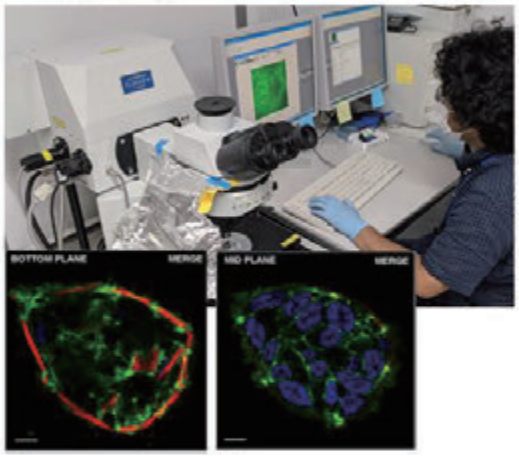
当拠点では、物理学から生物学まで幅広いバックグラウンドをもつ研究者が協力して一つのチームとして分野横断型の研究を行っています。我々の研究の流れと実際に日々の研究を行っている様子をここではご紹介します。

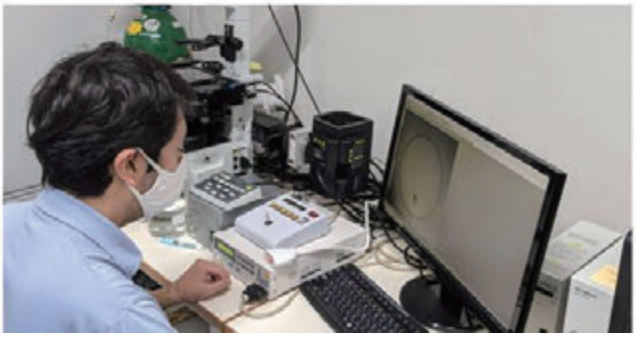
『観る』　事象を正しく理解し解析する『観測』は我々の研究の基盤です

反射干渉顕微鏡を用いた
がん細胞のライブイメージング



共焦点蛍光顕微鏡を用いた
多能性幹細胞コロニーのイメージング



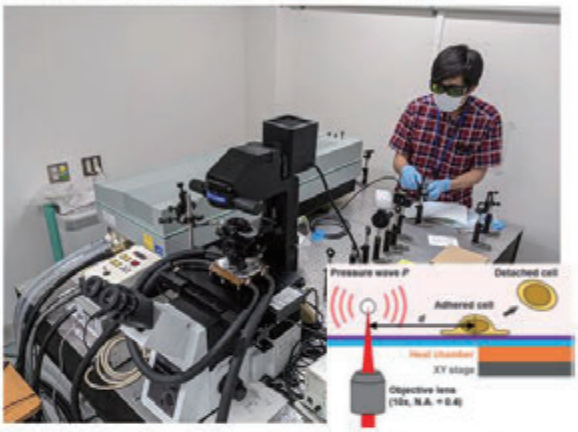


明視野顕微鏡を用いた
組織再生のライブイメージング

『測る』

新たな医工計測技術を開発し、「測れそうに思えない物理量を数値化する」ことでブレークスルーを産み出すことを目指します

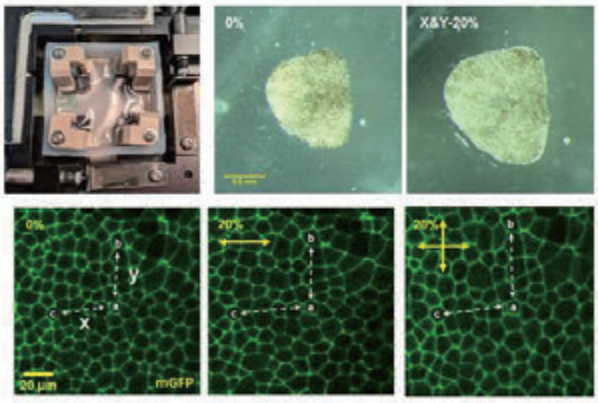
ピコ秒レーザーで誘起した衝撃波で細胞接着強度を高スループット計測



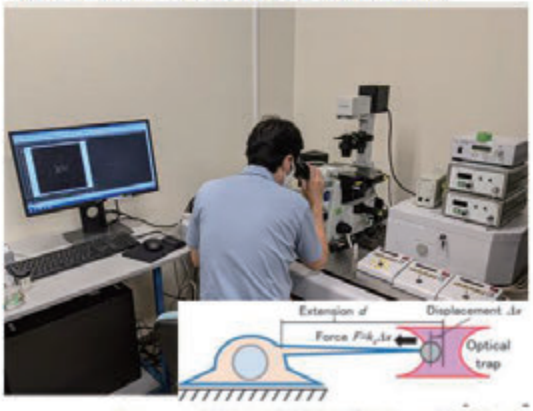
Stem Cell Rep. (2018), *Biophys. J.* (2021)

原子間力顕微鏡でタンパク質ナノファイバーの局所的硬さを計測

2軸独立牽引装置で組織切片の力学応答を計測



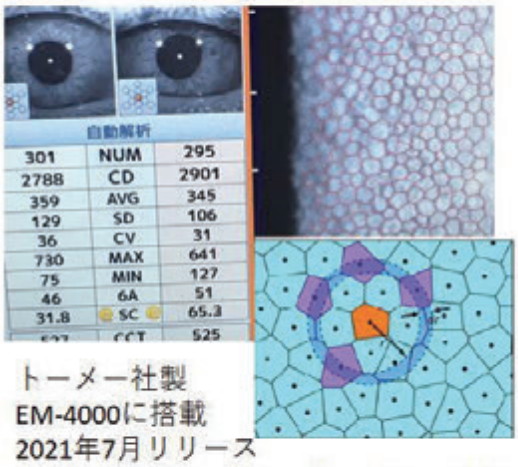
光ピンセットで細胞膜の張力を計測



Nature Comm. (2018), *Nature Comm.* (2021)

『解析する』 得られた画像・データを精密に解析する事で観測した事象を より普遍的な数式や指標にすることで、実用化を目指します

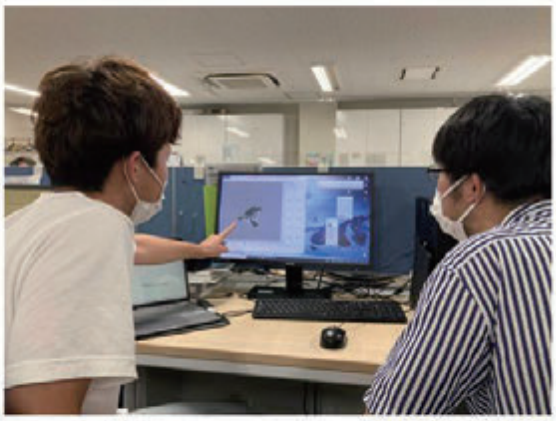
コロイド物理の原理を活かした ヒト角膜の診断評価指標を確立



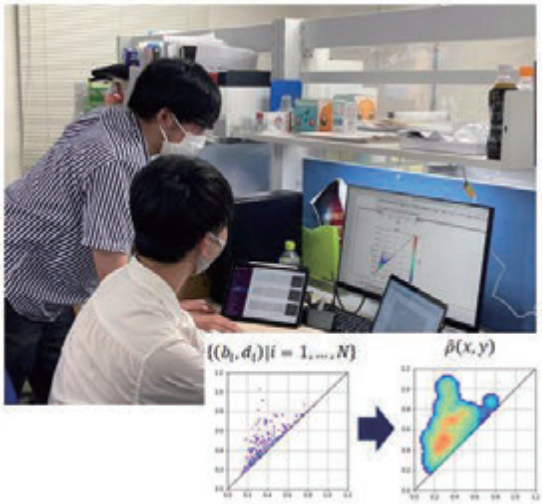
トーメー社製
EM-4000に搭載
2021年7月リリース

Nature Biomed. Eng. (2019)

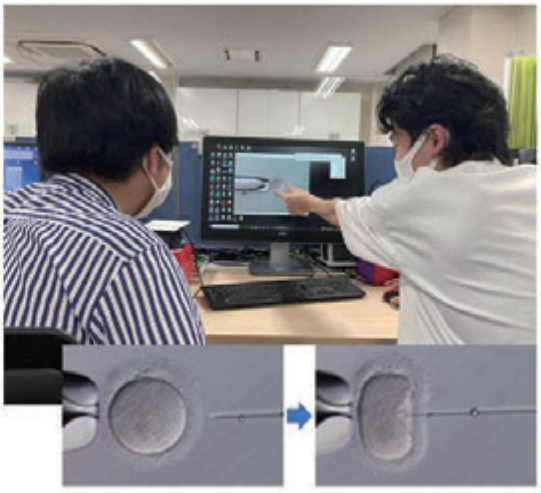
細胞ダイナミクスの時空間解析を駆使して 見た目ではわからないがんの予後を識別



トポロジカル解析でヒト角膜内の 細胞秩序を数値化し品質を精密に評価



顕微授精の記録動画解析から 卵子の品質を非侵襲的に評価する

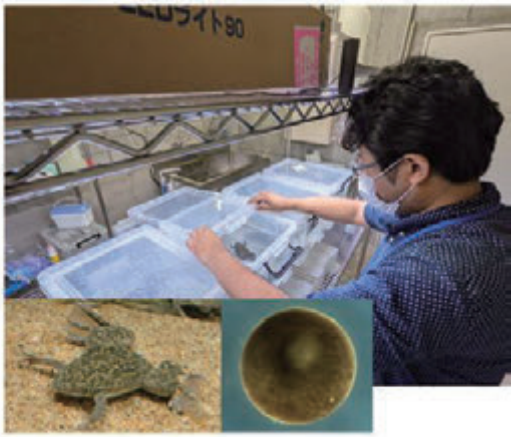


『育てる』

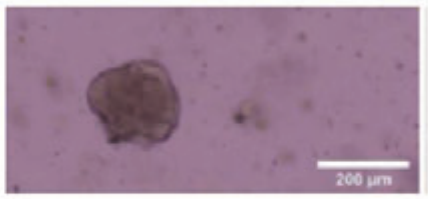
モデル動物（ヒドラ・アフリカツメガエル）から患者由来の
がんオルガノイドまで自分たちで培養系を確立し実験します

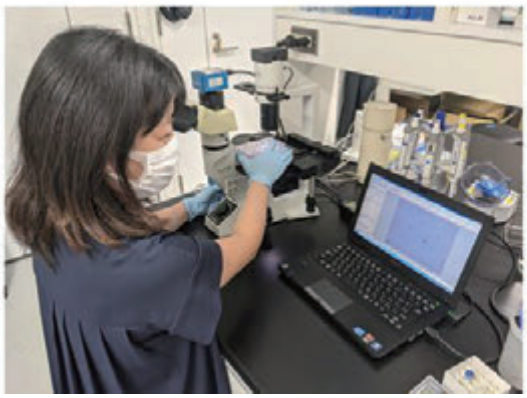
ヒドラ

アフリカツメガエル



患者由来がんオルガノイド





補足資料（２）
出版した論文の第１ページ

JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Cite This: J. Am. Chem. Soc. 2018, 140, 11261−11266
Article
pubs.acs.org/JACS

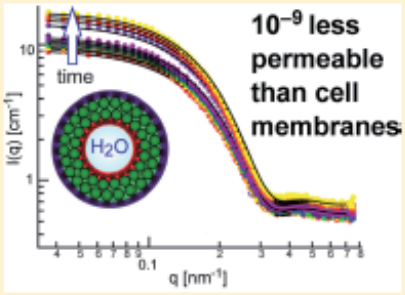
Neutron Scattering Reveals Water Confined in a Watertight Bilayer Vesicle

Wasim Abuillan,[†,#] Alexandra S. Becker,[†] Bruno Demé,[‡] Tatsuya Homma,[§] Hiroyuki Isobe,[§] Koji Harano,*[,§] Eiichi Nakamura,*[,§] and Motomu Tanaka*[,†,∥]

[†]Physical Chemistry of Biosystems, Institute of Physical Chemistry, Heidelberg University, D69120 Heidelberg, Germany
[‡]Institut Laue−Langevin (ILL), CS20156, 38042 Grenoble, France
[§]Department of Chemistry, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, 113-0033 Tokyo, Japan
[∥]Center for Integrative Medicine and Physics, Institute for Advanced Study, Kyoto University, 606-8501 Kyoto, Japan

Supporting Information

ABSTRACT: Water molecules confined in a nanocavity possess distinctly different characteristics from those in bulk, yet the preparation of such nanocavities is still a major experimental challenge. We report here a self-assembled vesicle of an anionic perfluoroalkylated [60]fullerene, unique for its outstanding stability and water tightness, containing water not bound to the membranes. Small-angle neutron scattering revealed that a vesicle of 14 nm outer radius contains a 2 nm thick fullerene bilayer, inside of which is a 3 nm thick membrane-bound water and unbound water in the 4 nm innermost cavity. The vesicle shows astonishingly low water permeability that is 6 to 9 orders of magnitude smaller than that of a lipid vesicle. As a result, a single vesicle isolated on a substrate can retain the interior water in air or even under high vacuum, indicating that the vesicle cavity provides a new tool for physicochemical studies of confined water as well as ions and molecules dissolved in it.



INTRODUCTION

Water molecule confined in a nanocavity is attracting much attention for its characteristics distinct from that in bulk as implied by theoretical studies.[1−3] Water bound on the interior surface of carbon nanotubes,[4−8] layered graphenes,[9,10] and nanopore materials[11,12] has been studied. For instance, the structure and dynamics of water molecules confined in carbon nanotubes have been investigated by neutron and X-ray scattering experiments.[13,14] With the aid of molecular dynamics (MD) simulations, these studies suggested that the water in carbon nanotubes comprises an ice sheet wrapped into a cylinder near the wall and chain-like configurations in the middle.[13] A more recent MD study suggested that the alignment of hydrophilic peptides in large carbon nanotubes enhances the mobility of water molecules inside.[15] However, experimental studies on water free from binding to the nanocavity surface still remain a challenge.

Unlike lipid vesicles,[16] which are irregular in size, mechanically unstable, and leaky against water permeation,[17] a nanometer-sized bilayer vesicle spontaneously made from perfluoroalkylated [60]fullerene (**F8K**, R = C_8F_{17}, Figure 1a,b)[18] is mechanically robust and watertight,[19−21] and their radius can be precisely tuned between 10 and 30 nm by changing the molecular structure and preparation conditions. Although it possibly contains free water in its interior, no information has thus far been available on the internal structure, or on the characteristics, of water in the vesicle. We report herein a small-angle neutron scattering (SANS, Supporting Information Figure S1) and contrast variation study of the **F8K** vesicle in bulk water at 293 K (Figure 1c) that reveals a three-shell structure of the vesicle that confines water in the center (Figure 1d). This water core (light blue) is 4.29 nm in radius and surrounded by 2.99 nm thick membrane-bound water (deep blue), which is then encapsulated in a 2.38 nm thick fullerene bilayer (gray) bearing a 4.48 nm thick outer membrane-bound water (deep blue). Water permeability through this three-shell membrane was monitored through the change in SANS signals over time, utilizing a strong contrast in the scattering length density (SLD) between H_2O and D_2O. The **F8K** membrane prevents water loss extremely well, rendering an osmotic permeability constant in H_2O as small as $P_{water} = (2.6 \pm 0.5) \times 10^{-13}$ m s^{-1}, and the half-lifetime of the water exchange between the interior and bulk is as long as 280 min. This permeability constant is 6 to 9 orders of magnitude smaller than the permeability of a lipid membrane ($P = 10^{-6}$−10^{-4} m s^{-1}). It should be noted that the diffusion coefficient of water in lipid membranes, 10^{-14}−10^{-12} m^2 s^{-1},[22] is comparable to that of a nylon-6 film, 4×10^{-14} m^2 s^{-1}.[23] Most remarkably, when a single vesicle is isolated and

Received: April 16, 2018
Published: August 17, 2018

DOI: 10.1021/jacs.8b04066
J. Am. Chem. Soc. 2018, 140, 11261−11266

SCIENTIFIC REPORTS

OPEN

Simple Physical Model Unravels Influences of Chemokine on Shape Deformation and Migration of Human Hematopoietic Stem Cells

Received: 8 January 2018
Accepted: 29 June 2018
Published online: 13 July 2018

Takao Ohta[1,2,3], Cornelia Monzel[4,6], Alexandra S. Becker[4], Anthony D. Ho[5] & Motomu Tanaka[3,4]

We studied the dynamic behavior of human hematopoietic stem cells (HSC) on the *in vitro* model of bone marrow surfaces in the absence and presence of chemokine (SDF1α). The deformation and migration of cells were investigated by varying the chemokine concentration and surface density of ligand molecules. Since HSC used in this study were primary cells extracted from the human umbilical cord blood, it is not possible to introduce molecular reporter systems before or during the live cell imaging. To account for the experimental observations, we propose a simple and general theoretical model for cell crawling. In contrast to other theoretical models reported previously, our model focuses on the nonlinear coupling between shape deformation and translational motion and is free from any molecular-level process. Therefore, it is ideally suited for the comparison with our experimental results. We have demonstrated that the results in the absence of SDF1α were well recapitulated by the linear model, while the nonlinear model is necessary to reproduce the elongated migration observed in the presence of SDF1α. The combination of the simple theoretical model and the label-free, live cell observations of human primary cells opens a large potential to numerically identify the differential effects of extrinsic factors such as chemokines, growth factors, and clinical drugs on dynamic phenotypes of primary cells.

The balance between self-renewal and differentiation of somatic stem cells is regulated by their microenvironment (called stem cell "niche"). For example, the dormancy of the most primitive hematopoietic stem cells (HSC) is maintained by adhesion to and interaction with the bone marrow niche[1–3]. Interactions of stem cells with the marrow niche actually play crucial roles in blood cancers. In acute myeloid leukemia, leukemia initiating cells remain dormant in the marrow niche and thus can hardly be eliminated by chemotherapy[4–6]. HSC-niche interactions are regulated by a chemokine, stromal cell-derived factor 1α (SDF1α), secreted in the bone marrow, which is specifically identified by CXCR4 protein expressed on HSC[7–10].

To date, several clinical drugs interfering with SDF1α-CXCR4 interactions have been approved for cancer treatment. However, the exact mode of function of such drugs (antagonist, agonist, or inhibitor) compared to naturally occurring SDF1α still remains controversial, because the drugs might harm the function of HSC through off-target effects. Therefore, it is highly important to develop a novel tool to quantitatively assess the influence of chemokines and drugs on human HSC functions beyond the commonly used cell phenotypes.

Recently, we fabricated the surrogate niche model surface based on planar lipid membranes displaying precisely defined concentrations of ligand molecules SDF1α or N-cadherin[11]. By means of a self-developed force measurement assay, we have quantitatively discriminated the adhesion strength of healthy HSC from that of

[1]Department of Physics, The University of Tokyo, Tokyo, 113-0033, Japan. [2]Toyota Physical and Chemical Research Institute, Nagakute, Aichi, 480-1192, Japan. [3]Center for Integrative Medicine and Physics, Institute for Advanced Studies, Kyoto University, 606-8501, Kyoto, Japan. [4]Physical Chemistry of Biosystems, Institute of Physical Chemistry, Heidelberg University, D69210, Heidelberg, Germany. [5]Department of Medicine V, Heidelberg University, D69120, Heidelberg, Germany. [6]Present address: Experimental Medical Physics, Heinrich-Heine University Düsseldorf, 40225, Düsseldorf, Germany. Takao Ohta and Cornelia Monzel contributed equally to this work. Correspondence and requests for materials should be addressed to T.O. (email: ohta@daisy.phys.s.u-tokyo.ac.jp) or M.T. (email: tanaka@uni-heidelberg.de)

SCIENTIFIC REPORTS

Correction: Author Correction

OPEN

Dynamic cellular phenotyping defines specific mobilization mechanisms of human hematopoietic stem and progenitor cells induced by SDF1α versus synthetic agents

Received: 26 October 2017
Accepted: 3 January 2018
Published online: 30 January 2018

Cornelia Monzel[1,4], Alexandra S. Becker[1], Rainer Saffrich[2,5], Patrick Wuchter[2,5], Volker Eckstein[2], Anthony D. Ho[2] & Motomu Tanaka[1,3]

Efficient mobilization of hematopoietic stem and progenitor cells (HSPC) is one of the most crucial issues for harvesting an adequate amount of peripheral HSPC for successful clinical transplantation. Applying well-defined surrogate models for the bone marrow niche, live cell imaging techniques, and novel tools in statistical physics, we have quantified the functionality of two mobilization agents that have been applied in the clinic, NOX-A12 and AMD3100 (plerixafor), as compared to a naturally occurring chemokine in the bone marrow, SDF1α. We found that NOX-A12, an L-enantiomeric RNA oligonucleotide to SDF1, significantly reduced the adhesion of HSPC to the niche surface mediated via the CXCR4-SDF1α axis, and stretched the migration trajectories of the HSPC. We found that the stretching of trajectories by NOX-A12 was more prominent than that by SDF1α. In contrast, plerixafor exhibited no detectable interference with adhesion and migration. We also found that the deformation of HSPC induced by SDF1α or plerixafor was also drastically suppressed in the presence of NOX-A12. This novel technology of quantitative assessment of "dynamic phenotypes" by physical tools has therefore enabled us to define different mechanisms of function for various extrinsic factors compared to naturally occurring chemokines.

Functions of somatic stem cells are strictly governed by an appropriate balance between self-renewal and differentiation. This balance is in turn regulated by interactions between stem cells and their microenvironment-the so-called "niche". In the case of hematopoietic stem and progenitor cells, the dormancy of the most primitive HSPC is maintained by the bone marrow niche by means of several key molecular interactions between receptor-ligand pairs[1–3]. For example, it has been suggested that homophilic, N-cadherin-mediated adhesion between HSPC and mesenchymal stem cells (MSC) supports long-term maintenance of the primitive HSPC pool[4–6]. Another key molecular axis is the interaction between stromal cell-derived factor 1α (SDF1α or CXCL12) and its receptor CXCR4, expressed on the cell surface of HSPC. This axis plays a significant role in homing and migration of HSPC[7–15].

In recent years, peripheral HSPC have largely replaced bone marrow-derived cells for autologous transplants, and they have become the major source of stem cells also for allogeneic transplantations[16–21]. Efficient

[1]Physical Chemistry of Biosystems, Institute of Physical Chemistry, Heidelberg University, 69120, Heidelberg, Germany. [2]Department of Medicine V, Heidelberg University, 69120, Heidelberg, Germany. [3]Institute for Integrated Cell-Material Sciences, Kyoto University, 606-8501, Kyoto, Japan. [4]Present address: Laboratoire Physico-Chimie, Institut Curie, CNRS UMR168, 75005, Paris, France. [5]Present address: Institute of Transfusion Medicine and Immunology, Medical Faculty Mannheim, Heidelberg University, German Red Cross Blood Service Baden-Württemberg – Hessen, 68167, Mannheim, Germany. Correspondence and requests for materials should be addressed to A.D.H. (email: anthony_dick.ho@urz.uni-heidelberg.de) or M.T. (email: tanaka@uni-heidelberg.de)

LANGMUIR
Article
Cite This: Langmuir 2018, 34, 14046−14057
pubs.acs.org/Langmuir

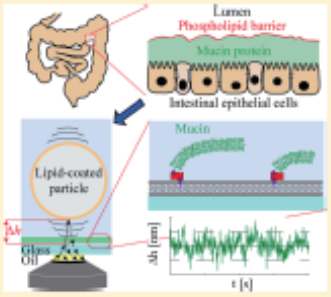
Nonclassical Interactions of Phosphatidylcholine with Mucin Protect Intestinal Surfaces: A Microinterferometry Study

Federico Amadei,[†] Benjamin Fröhlich,[†] Wolfgang Stremmel,[‡,§] and Motomu Tanaka*[,†,∥]

[†]Physical Chemistry of Biosystems, Institute of Physical Chemistry, Heidelberg University, D69120 Heidelberg, Germany
[‡]Medical Center Baden-Baden, D76530 Baden-Baden, Germany
[§]Internal Medicine IV, University Hospital Heidelberg, D69120 Heidelberg, Germany
[∥]Center for Integrative Medicine and Physics, Institute for Advanced Study, Kyoto University, 606-8501 Kyoto, Japan

Supporting Information

ABSTRACT: Albeit many studies demonstrated that the accumulation of phospholipids in the intestinal mucosal surfaces is essential for the protection of colon epithelia against pathogenic bacteria, the mechanism of interactions between phospholipids and the surface protein mucin is not well understood. In this study, the significance of interfacial interactions between phospholipids and mucin proteins was quantified by the combination of an *in vitro* intestinal surface model and label-free microinterferometry. The model of intestinal surfaces consists of planar lipid membranes deposited on solid substrates (supported membranes) that display mucin proteins at defined surface densities. Following the quantitative characterization of the systems, we monitored the vertical fluctuation of 10 μm-large particles on model intestinal surfaces by using microinterferometry, and calculated the effective interfacial interaction potentials by analytically solving the Langevin equation. We found that the spring constant of interfacial potentials calculated based on a harmonic approximation increased concomitantly with the increase in surface potentials, indicating the dominant role of electrostatic interactions. Intriguingly, the spring constants of particles coated with phospholipids do not follow electrostatic interactions. The spring constant of particles coated with zwitterionic phosphatidylcholine was larger compared to membranes incorporating positively or negatively charged lipids. Our data suggested the presence of another underlying molecular level interaction, such as phosphocholine−saccharide interactions. The fact that phosphatidylcholine sustains the binding capability to enzymatically degraded mucin suggests that the direct delivery of phosphatidylcholine to the damaged mucus is a promising strategy for the better treatment of patients affected by inflammatory bowel diseases.



INTRODUCTION

The colon epithelial cells in the gastrointestinal tract are exposed to a huge bacterial load (approx. one trillion bacteria per gram of stool), but they are protected from the physical abrasion and the attack of pathogenic bacteria by a mucus layer.[1] The scaffold of mucus layers is the family of highly glycosylated proteins, called mucins.[2] The major constituent, mucin2, is secreted either by specialized submucosal glands, or by goblet cells embedded in the underlying gastrointestinal epithelial layer.[3] Mucin proteins possess one or several central domains enriched with O-linked oligosaccharides such as negatively charged sialic acid and sulfate residues, whereas the N- and C-termini are mostly nonglycosylated and even hypothesized to be hydrophobic.[4,5]

However, mucin per se is not able to protect intestinal epithelia against the bacterial invasion. A mounting piece of evidence has suggested that the layer of phospholipids serves as a protective barrier (Scheme 1a).[6,7] Among various phospholipids secreted in the intestinal mucus, phosphatidylcholine (PC) and lyso-phosphatidylcholine (lyso-PC) account for more than 90%.[8] Recent studies have demonstrated that the secretion of PC and lyso-PC in luminal mucosa occurs as a result of the selective paracellular transport of PC/lyso-PC across the lateral tight junction between intestinal epithelia via a cystic fibrosis transmembrane conductance regulator.[9] Finally, PC and lyso-PC bind to the surface of mucin2, which moves distally to the rectum.

Once the PC/lyso-PC coating is thinned or damaged by the enzymatic degradation of PCs by ectophospholipase in the colonic microbiota, these regions become the most vulnerable area for bacterial invasion.[6] In inflammatory bowel diseases, such as Crohn's disease and ulcerative colitis, PC secretion is intrinsically impaired, resulting in a 70% reduction of its content in mucus.[8,10] As a consequence, the bacterial invasion and hence the mucosal inflammation starts in rectum and extends proximally. Moreover, although it has been reported

Received: September 6, 2018
Revised: October 25, 2018
Published: October 25, 2018

DOI: 10.1021/acs.langmuir.8b03035
Langmuir 2018, 34, 14046−14057

nature COMMUNICATIONS

ARTICLE

DOI: 10.1038/s41467-018-04436-w OPEN

Cell surface flip-flop of phosphatidylserine is critical for PIEZO1-mediated myotube formation

Masaki Tsuchiya[1], Yuji Hara[1,2], Masaki Okuda[1], Karin Itoh[1], Ryotaro Nishioka[1], Akifumi Shiomi[1], Kohjiro Nagao[1], Masayuki Mori[1], Yasuo Mori[1], Junichi Ikenouchi[3], Ryo Suzuki[4,13], Motomu Tanaka[4,5,13], Tomohiko Ohwada[6], Junken Aoki[7], Motoi Kanagawa[8], Tatsushi Toda[9], Yosuke Nagata[10], Ryoichi Matsuda[11], Yasunori Takayama[12], Makoto Tominaga[12] & Masato Umeda[1]

Myotube formation by fusion of myoblasts and subsequent elongation of the syncytia is essential for skeletal muscle formation. However, molecules that regulate myotube formation remain elusive. Here we identify PIEZO1, a mechanosensitive Ca^{2+} channel, as a key regulator of myotube formation. During myotube formation, phosphatidylserine, a phospholipid that resides in the inner leaflet of the plasma membrane, is transiently exposed to cell surface and promotes myoblast fusion. We show that cell surface phosphatidylserine inhibits PIEZO1 and that the inward translocation of phosphatidylserine, which is driven by the phospholipid flippase complex of ATP11A and CDC50A, is required for PIEZO1 activation. PIEZO1-mediated Ca^{2+} influx promotes RhoA/ROCK-mediated actomyosin assemblies at the lateral cortex of myotubes, thus preventing uncontrolled fusion of myotubes and leading to polarized elongation during myotube formation. These results suggest that cell surface flip-flop of phosphatidylserine acts as a molecular switch for PIEZO1 activation that governs proper morphogenesis during myotube formation.

[1] Department of Synthetic Chemistry and Biological Chemistry, Graduate School of Engineering, Kyoto University, Kyoto 615-8510, Japan. [2] AMED-PRIME, Japan Agency for Medical Research and Development, Tokyo 100-0004, Japan. [3] Department of Biology, Faculty of Sciences, Kyushu University, Fukuoka 819-0395, Japan. [4] Institute for Integrated Cell-Material Sciences (WPI iCeMS), Kyoto University, Kyoto 606-8501, Japan. [5] Physical Chemistry of Biosystems, Institute of Physical Chemistry, University of Heidelberg, Heidelberg 69120, Germany. [6] Laboratory of Organic and Medicinal Chemistry, Graduate School of Pharmaceutical Sciences, The University of Tokyo, Tokyo 115-0033, Japan. [7] Department of Molecular and Cellular Biochemistry, Graduate School of Pharmaceutical Sciences, Tohoku University, Miyagi 980-8578, Japan. [8] Division of Neurology/Molecular Brain Science, Kobe University Graduate School of Medicine, Hyogo 650-0017, Japan. [9] Department of Neurology, Division of Neuroscience, Graduate School of Medicine, The University of Tokyo, Tokyo 113-8655, Japan. [10] Department of Life Science, Faculty of Science, Okayama University of Science, Okayama 700-0005, Japan. [11] Department of Life Sciences, Graduate School of Arts and Sciences, The University of Tokyo, Tokyo 153-8902, Japan. [12] Division of Cell Signaling, Okazaki Institute for Integrative Bioscience, Aichi 444-8787, Japan. [13] Present address: Center for Integrative Medicine and Physics, Institute for Advanced Study, Kyoto University, Kyoto 606-8501, Japan. Correspondence and requests for materials should be addressed to Y.H. (email: hara@sbchem.kyoto-u.ac.jp) or to M.U. (email: umeda@sbchem.kyoto-u.ac.jp)

Stem Cell Reports
Article
ISSCR
OPEN ACCESS

Low Cell-Matrix Adhesion Reveals Two Subtypes of Human Pluripotent Stem Cells

Leqian Yu,[1,2] Junjun Li,[1,3] Jiayin Hong,[4] Yasuhiro Takashima,[5] Nanae Fujimoto,[1,2] Minako Nakajima,[1,2] Akihisa Yamamoto,[1,11] Xiaofeng Dong,[4] Yujiao Dang,[6] Yu Hou,[6] Wei Yang,[7] Itsunari Minami,[8] Keisuke Okita,[5] Motomu Tanaka,[1,9,11] Chunxiong Luo,[7] Fuchou Tang,[6] Yong Chen,[1,7,10] Chao Tang,[4,*] Hidetoshi Kotera,[1,2,12,*] and Li Liu[1,3,*]

[1]Institutes for Integrated Cell-Material Sciences (WPI-iCeMS), Kyoto University, Kyoto 606-8501, Japan
[2]Nanometrics Laboratory, Department of Micro Engineering, Kyoto University, Kyoto 615-8540, Japan
[3]Department of Cardiovascular Surgery, Osaka University Graduate School of Medicine, Osaka 565-0871, Japan
[4]Center for Quantitative Biology and Peking-Tsinghua Center for Life Sciences, Academy for Advanced Interdisciplinary Studies, Peking University, Beijing 100871, China
[5]Center for iPS Cell Research and Application (CiRA), Kyoto University, Kyoto 606-8507, Japan
[6]Biodynamic Optical Imaging Center (BIOPIC), Peking University, Beijing 100876, China
[7]Center for Quantitative Biology, Academy for Advanced Interdisciplinary Studies, Peking University, Beijing 100871, China
[8]Department of Cell Design for Tissue Construction Faculty of Medicine, Osaka University, Osaka 565-0871, Japan
[9]Physical Chemistry of Biosystems, Institute for Physical Chemistry, Heidelberg University, Heidelberg D69120, Germany
[10]Ecole Normale Supérieure, CNRS-ENS-UPMC UMR 8640, 24 Rue Lhomond, Paris 75005, France
[11]Present address: Center for Integrative Medicine and Physics, Institute for Advanced Study, Kyoto University, Kyoto 606-8501, Japan
[12]Present address: RIKEN, 2-1 Hirosawa, Wako, Saitama 351-0198, Japan
*Correspondence: tangc@pku.edu.cn (C.T.), kotera.hidetoshi.7e@kyoto-u.jp (H.K.), li-liu@surg1.med.osaka-u.ac.jp (L.L.)
https://doi.org/10.1016/j.stemcr.2018.06.003

SUMMARY

We show that a human pluripotent stem cell (hPSC) population cultured on a low-adhesion substrate developed two hPSC subtypes with different colony morphologies: flat and domed. Notably, the dome-like cells showed higher active proliferation capacity and increased several pluripotent genes' expression compared with the flat monolayer cells. We further demonstrated that cell-matrix adhesion mediates the interaction between cell morphology and expression of *KLF4* and *KLF5* through a serum response factor (SRF)-based regulatory double loop. Our results provide a mechanistic view on the coupling among adhesion, stem cell morphology, and pluripotency, shedding light on the critical role of cell-matrix adhesion in the induction and maintenance of hPSC.

INTRODUCTION

Somatic cells can be reprogrammed to induced pluripotent stem cells (iPSCs) by ectopic expression of four transcription factors (Oct4, Sox2, Klf4, and c-Myc [OSKM]) (Takahashi and Yamanaka, 2006). During the reprogramming process of iPSCs, the endogenous expression of OCT4, SOX2, and KLF4 increased sharply in the early phase and dropped moderately in the late phase, while the cell-matrix adhesion (represented by the focal adhesion (FA) proteins which link cells with their surrounding matrix) demonstrated exactly the opposite variation trend: downregulated in the early phase and upregulated in the late phase (Hansson et al., 2012). In the pluripotent state, iPSCs showed low adhesive strength to surrounding matrix compared with their parental somatic cells (Singh et al., 2013) and their lineage differentiated cells (Narve et al., 2017; Singh et al., 2013), indicating that pluripotency is associated with altered cell-matrix adhesion and motility. On the other hand, in contrast with cell-matrix adhesion, the cell-cell adhesion-related protein epithelial-cadherin (E-cadherin) was upregulated during the reprogramming process (Hansson et al., 2012). It has been reported that elimination of E-cadherin prevents somatic cells from reprogramming to pluripotency (Li et al., 2009) and that enhancement of E-cadherin can elevate the reprogramming efficiency of iPSCs (Chen et al., 2010) and can even replace the need for Oct4 (the most critical factor in OSKM) during iPSC reprogramming (Redmer et al., 2011; Sakurai et al., 2014). In addition, compact colonies and E-cadherin-mediated cell-cell adhesion are required for iPSC survival and stemness (Ohgushi et al., 2010). Furthermore, substantial remodeling of cell adhesive microenvironment is a prerequisite for reprogramming. For example, high cell-matrix adhesion represents a barrier toward iPSC reprogramming (Qin et al., 2014), while cell-cell adhesion promotes iPSC reprogramming (Caiazzo et al., 2016; Downing et al., 2013). Collectively, the above studies suggested that low cell-matrix adhesion and strong cell-cell adhesion are hallmarks of high pluripotency, and that both features are intimately coupled to the reprogramming process.

To further investigate how cell adhesion properties affect the hPSC culture and pluripotency, in this work, we employed a nanofibrous substrate (Liu et al., 2014) and platform for single-cell isolation and culture. We revealed that there exist two distinct subtypes of cells in the conventional PSC population, which differ in their morphology, gene expression pattern, cell-matrix and cell-cell adhesion,

COMMUNICATIONS BIOLOGY

ARTICLE

DOI: 10.1038/s42003-018-0223-3 OPEN

The sickle cell trait affects contact dynamics and endothelial cell activation in *Plasmodium falciparum*-infected erythrocytes

Christine Lansche[1], Anil K. Dasanna[2], Katharina Quadt[1], Benjamin Fröhlich[3], Dimitris Missirlis[4], Marilou Tétard[5], Benoit Gamain[5], Bernd Buchholz[6], Cecilia P. Sanchez[1], Motomu Tanaka[3], Ulrich S. Schwarz[2] & Michael Lanzer[1]

Sickle cell trait, a common hereditary blood disorder, protects carriers from severe disease in infections with the human malaria parasite *Plasmodium falciparum*. Protection is associated with a reduced capacity of parasitized erythrocytes to cytoadhere to the microvascular endothelium and cause vaso-occlusive events. However, the underpinning cellular and biomechanical processes are only partly understood and the impact on endothelial cell activation is unclear. Here, we show, by combining quantitative flow chamber experiments with multiscale computer simulations of deformable cells in hydrodynamic flow, that parasitized erythrocytes containing the sickle cell haemoglobin displayed altered adhesion dynamics, resulting in restricted contact footprints on the endothelium. Main determinants were cell shape, knob density and membrane bending. As a consequence, the extent of endothelial cell activation was decreased. Our findings provide a quantitative understanding of how the sickle cell trait affects the dynamic cytoadhesion behavior of parasitized erythrocytes and, in turn, endothelial cell activation.

[1] Department of Infectious Diseases, Parasitology, Universitätsklinikum Heidelberg, Im Neuenheimer Feld 324, 69120 Heidelberg, Germany. [2] Institute for Theoretical Physics and BioQuant-Center for Quantitative Biology, Heidelberg University, 69120 Heidelberg, Germany. [3] Physical Chemistry of Biosystems, University of Heidelberg, 69120 Heidelberg, Germany. [4] Department of Cellular Biophysics, Max Planck Institute for Medical Research, 69120 Heidelberg, Germany. [5] Université Sorbonne Paris Cité, Université Paris Diderot, Inserm, INTS, Unité Biologie Intégrée du Globule Rouge, UMR S1134, Severe Malaria Pathogenesis Group, Laboratoire d'Excellence GR-Ex, Paris 75739, France. [6] Department of Hematology and Oncology, University Children's Hospital, Medical Faculty Mannheim, 68167 Mannheim, Germany. These authors contributed equally: Christine Lansche, Anil K. Dasanna. Correspondence and requests for materials should be addressed to U.S.S. (email: schwarz@thphys.uni-heidelberg.de) or to M.L. (email: michael.lanzer@med.uni-heidelberg.de)

HIV-1 Nef Disrupts CD4$^+$ T Lymphocyte Polarity, Extravasation, and Homing to Lymph Nodes via Its Nef-Associated Kinase Complex Interface

Miguel Lamas-Murua,*,[1] Bettina Stolp,*,[1] Sheetal Kaw,* Judith Thoma,[†] Nikolaos Tsopoulidis,* Birthe Trautz,* Ina Ambiel,* Tatjana Reif,* Sakshi Arora,* Andrea Imle,* Nadine Tibroni,* Jingxia Wu,[‡] Guoliang Cui,[‡] Jens V. Stein,[§] Motomu Tanaka,[†,¶] Ruth Lyck,[§] and Oliver T. Fackler*

HIV-1 Nef is a multifunctional protein that optimizes virus spread and promotes immune evasion of infected cells to accelerate disease progression in AIDS patients. As one of its activities, Nef reduces the motility of infected CD4$^+$ T lymphocytes in confined space. In vivo, Nef restricts T lymphocyte homing to lymph nodes as it reduces the ability for extravasation at the diapedesis step. Effects of Nef on T lymphocyte motility are typically mediated by its ability to reduce actin remodeling. However, interference with diapedesis does not depend on residues in Nef required for inhibition of host cell actin dynamics. In search for an alternative mechanism by which Nef could alter T lymphocyte extravasation, we noted that the viral protein interferes with the polarization of primary human CD4$^+$ T lymphocytes upon infection with HIV-1. Expression of Nef alone is sufficient to disrupt T cell polarization, and this effect is conserved among lentiviral Nef proteins. Nef acts by arresting the oscillation of CD4$^+$ T cells between polarized and nonpolarized morphologies. Mapping studies identified the binding site for the Nef-associated kinase complex (NAKC) as critical determinant of this Nef activity and a NAKC-binding–deficient Nef variant fails to impair CD4$^+$ T lymphocyte extravasation and homing to lymph nodes. These results thus imply the disruption of T lymphocyte polarity via its NAKC binding site as a novel mechanism by which lentiviral Nef proteins alter T lymphocyte migration in vivo. ***The Journal of Immunology*****, 2018, 201: 2731–2743.**

Negative factor (Nef) is a 25–34-kDa myristoylated accessory protein encoded by the primate lentiviruses HIV-1, HIV-2, and SIV. Although Nef is not needed for virus replication in cell culture, it optimizes virus replication in the infected host and thus significantly contributes to disease progression to AIDS. To mediate this critical function in AIDS pathogenesis, Nef acts as versatile protein interaction adaptor that manipulates a remarkable range of host cell processes, including signal transduction and vesicular transport pathways, by genetically separable but incompletely defined molecular mechanisms (1–5). Nef mediates its functions via various interactions with host cell proteins, thereby inducing changes in central intracellular transport and signaling pathways of HIV-infected cells (2, 6). This includes reducing cell surface densities of transmembrane receptors and peripheral membrane proteins by molecular mechanisms that affect endocytosis, anterograde transport, and/or protein stability (7–12). By modulating surface exposure of cell-surface receptors such as MHC class I and II, CD4, chemokine receptors, costimulatory molecules such as CD80 and CD86, tetraspanins, and NK cell ligands, Nef acts to evade host cell immune responses and prevents superinfection of infected cells (8, 10–17). In addition, Nef affects activation state and responsiveness of T lymphocytes to TCR signaling by modifying their vesicular transport and actin remodeling pathways (18–26). These alterations reduce activation-induced cell death and thus prolong the survival of productively infected cells (27). Finally, Nef enhances the infectivity of HIV particles by antagonizing the restriction factors SERINC 3 and 5 via yet to be determined mechanisms (28–31).

*Department of Infectious Diseases, Integrative Virology, University Hospital Heidelberg, 69120 Heidelberg, Germany; [†]Physical Chemistry of Biosystems, University of Heidelberg, 69120 Heidelberg, Germany; [‡]T Cell Metabolism (D140), German Cancer Research Centre, 69120 Heidelberg, Germany; [§]Theodor Kocher Institute, University of Bern, 3012 Bern, Switzerland; and [¶]Center for Integrative Medicine and Physics, Institute for Advanced Study, Kyoto University, Kyoto 606-8501, Japan

[1]M.L.-M. and B.S. contributed equally to this work.

ORCIDs: 0000-0002-8819-4350 (N. Tsopoulidis); 0000-0002-4347-480X (S.A.); 0000-0001-5559-7957 (G.C.); 0000-0002-6479-4837 (R.L.); 0000-0003-2982-4209 (O.T.F.).

Received for publication October 12, 2017. Accepted for publication August 21, 2018.

This work was supported by Deutsche Forschungsgemeinschaft Grants FA378/10-2 and SFB1129 (to O.T.F.) and SFB1129 (to M.T.), and the Nakatani Foundation (to M.T.). N. Tsopoulidis was supported by a Heidelberg Biosciences International Graduate School fellowship. O.T.F. and M.T. are members of the CellNetworks Cluster of Excellence (EXC81).

O.T.F. designed the study, interpreted results, and wrote the manuscript together with B.S. M.L.-M. conducted and analyzed the experiments shown in Figs. 1–3 and 5. S.K. conducted and analyzed the in vivo homing experiments. B.S. carried out the transendothelial migration experiments together with R.L., conducted the Seahorse analyses with help from J.W. and G.C., and analyzed the data. N. Tsopoulidis recorded the movies analyzed in Figs. 4 and 5. J.T. and M.T. generated and interpreted the power spectrum analyses (Fig. 4B–G). S.K., N. Tsopoulidis, B.T., T.R., S.A., A.I., and N. Tibroni tracked movies. A.I. and J.V.S. provided essential expertise. All authors read and edited the manuscript.

Address correspondence and reprint requests to Dr. Oliver T. Fackler, Department of Infectious Diseases, Integrative Virology, Center for Integrative Infectious Disease Research, University Hospital Heidelberg, Im Neuenheimer Feld 344, 69120 Heidelberg, Germany. E-mail address: oliver.fackler@med.uni-heidelberg.de

The online version of this article contains supplemental material.

Abbreviations used in this article: ACF, autocorrelation function; CMM, complete mouse medium; D, donor; ECAR, extracellular acidification rate; MLV, murine leukemia virus; NAKC, Nef-associated kinase complex; OCR, oxygen consumption rate; pMBMEC, primary mouse brain microvascular endothelial cell; WT, wild type.

www.jimmunol.org/cgi/doi/10.4049/jimmunol.1701420

LANGMUIR
Article
Cite This: Langmuir 2018, 34, 13025−13034
pubs.acs.org/Langmuir

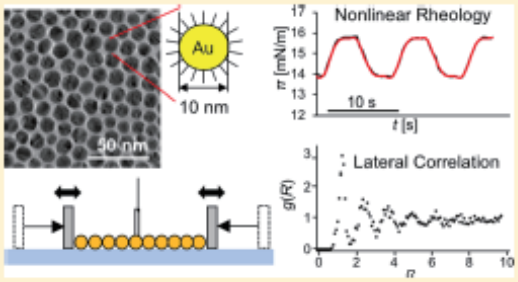
Nonlinear Viscoelasticity of Highly Ordered, Two-Dimensional Assemblies of Metal Nanoparticles Confined at the Air/Water Interface

Shihomi Masuda,[†,‡,#] Salomé Mielke,[†,#] Federico Amadei,[†] Akihisa Yamamoto,[§] Pangpang Wang,[○,‡] Takashi Taniguchi,[∥] Kenichi Yoshikawa,[§,⊥] Kaoru Tamada,*[,‡] and Motomu Tanaka*[,†,§]

[†]Physical Chemistry of Biosystems, Institute of Physical Chemistry, Heidelberg University, D69120 Heidelberg, Germany
[‡]Institute for Materials Chemistry and Engineering (IMCE), Kyushu University, 819-0395 Fukuoka, Japan
[§]Center for Integrative Medicine and Physics, Institute for Advanced Study, Kyoto University, 606-8501 Kyoto, Japan
[∥]Department of Chemical Engineering, Graduate School of Engineering, Kyoto University, 615-8510 Kyoto, Japan
[⊥]Faculty of Life and Medical Sciences, Doshisha University, 610-0321 Kyotanabe, Japan

Supporting Information

ABSTRACT: In this study, we investigated the viscoelastic properties of metal nanoparticle monolayers at the air/water interface by dilational rheology under periodic oscillation of surface area. Au nanoparticles capped with oleylamine form a stable, dense monolayer on a Langmuir film balance. The stress response function of a nanoparticle monolayer was first analyzed using the classical Kelvin−Voigt model, yielding the spring constant and viscosity. The obtained results suggest that the monolayer of nanoparticles is predominantly elastic, forming a two-dimensional physical gel. As the global shape of the signal exhibited a clear nonlinearity, we further analyzed the data with the higher modes in the Fourier series expansion. The imaginary part of the higher mode signal was stronger than the real part, suggesting that the dissipative term mainly causes the nonlinearity. Intriguingly, the response function measured at larger strain amplitude became asymmetric, accompanied by the emergence of even modes. The significance of interactions between nanoparticles was quantitatively assessed by calculating the potential of mean force, indicating that the lateral correlation could reach up to the distance much larger than the particle diameter. The influence of surface chemical functions and core metal has also been examined by using Au nanoparticles capped with partially fluorinated alkanethiolate and Ag nanoparticles capped with myristic acid. The combination of dilational rheology and correlation analyses can help us precisely control two-dimensional colloidal assembly of metal nanoparticles with fine-adjustable localized surface plasmon resonance.



■ INTRODUCTION

A number of studies have demonstrated that micrometer-scale particles form two-dimensional (2D) colloidal assemblies,[1] whose phases can be modulated by salts, surfactants, and polymers.[2−4] To date, 2D assemblies of nanometer-scaled particles have been investigated mostly using metal or semiconductor nanoparticles taking spherical or rodlike structures.[5] Highly ordered assemblies of these nanoparticles have been drawing attention toward the optoelectronic device applications utilizing localized surface plasmon resonance (LSPR).[6−9] Although the precise control of interparticle distance is crucial for the fabrication of LSPR materials, the fabrication of macroscopically uniform 2D sheets of Au or Ag nanoparticles remained challenging. Recently, Tamada and co-workers succeeded in the fabrication of 2D sheets of Ag[10] and Au nanoparticles.[11] Monodispersive metal nanoparticles capped by organic molecules form an ordered monolayer at the air/water interface, which can be transferred onto a transmission electron microscopy (TEM) grid by the Langmuir−Schaefer (LS) method. Such nanoparticle monolayers can be applied not only for understanding the fundamental principle of LSPR but also for various applications, such as high-resolution imaging in the close proximity of the surface.[12,13]

Like other surfactant molecules, nanoparticles residing at the air/water interface reduce the surface tension and make the interface more elastic. Here, the mechanical properties of the interface depend on the phase behavior and hence the lateral

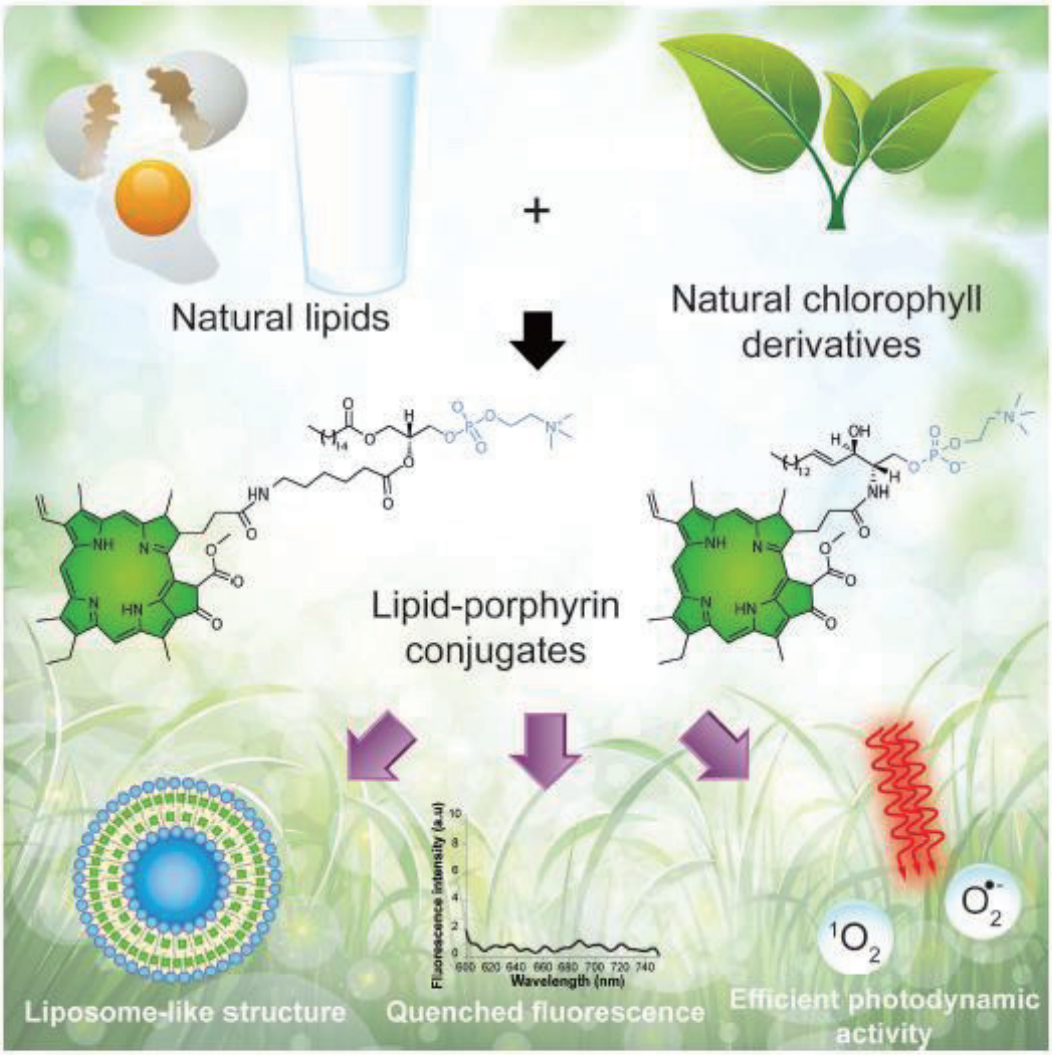
Received: August 10, 2018
Revised: September 27, 2018
Published: September 28, 2018

DOI: 10.1021/acs.langmuir.8b02713
Langmuir 2018, 34, 13025−13034

ChemPubSoc Europe
DOI: 10.1002/chem.201804865
CHEMISTRY A European Journal Full Paper

Newly Synthesized Lipid–Porphyrin Conjugates: Evaluation of Their Self-Assembling Properties, Their Miscibility with Phospholipids and Their Photodynamic Activity In Vitro

Julien Massiot,[a] Véronique Rosilio,[a] Nada Ibrahim,[a] Akihisa Yamamoto,[b] Valérie Nicolas,[c] Oleg Konovalov,[d] Motomu Tanaka,[b, e] and Ali Makky*[a]



THE JOURNAL OF PHYSICAL CHEMISTRY Letters

Cite This: J. Phys. Chem. Lett. 2018, 9, 5792−5796

Letter

pubs.acs.org/JPCL

Optical Fluid Pump: Generation of Directional Flow via Microphase Segregation/Homogenization

Hiroki Sakuta,[†] Shunsuke Seo,[†] Shuto Kimura,[†] Marcel Hörning,[‡,¶] Koichiro Sadakane,[†] Takahiro Kenmotsu,[†] Motomu Tanaka,[§,¶,∥] and Kenichi Yoshikawa*[,†]

[†]Faculty of Life and Medical Sciences, Doshisha University, Kyotanabe 610-0394, Japan

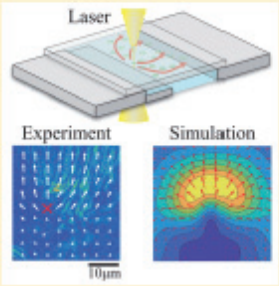
[‡]Institute of Biomaterials and Biomolecular Systems, University of Stuttgart, Stuttgart 70569, Germany

[¶]Institute for Integrated Cell-Material Sciences, Kyoto University, Kyoto 606-8501, Japan

[§]Institute of Physical Chemistry, University of Heidelberg, Heidelberg 69120, Germany

[∥]Center for Integrative Medicine and Physics Institute for Advanced Study, Kyoto University, Kyoto 606-8501, Japan

ABSTRACT: We report the successful generation of directional liquid-flow under stationary laser irradiation at a fixed position in a chamber. We adopt a homogeneous solution consisting of a mixture of water and triethylamine (TEA), with a composition near the critical point for phase segregation. When geometrical asymmetry is introduced around the laser focus in the chamber, continuous directional flow is generated, accompanied by the emergence of water-rich microdroplets at the laser focus. The emerging microdroplets tend to escape toward the surrounding bulk solution and then merge/annihilate into the homogeneous solution. The essential features of the directional flow are reproduced through a simple numerical simulation using fluid dynamic equations.



In general, oil/water systems exist as either a homogeneous solution or a macroscopically segregated solution,[1−3] which can be interpreted in terms of a first-order phase transition. The phase coexistence on a microscopic scale is intrinsically unstable in the absence of a surfactant under equilibricity. This implies the possible occurrence of dynamic phenomena, including the emergence and annihilation of microscopic segregation under thermodynamically open conditions. Recently, it has been shown that a focused laser can generate microscopic phase-separation in a homogeneous solution composed of oil and water under a condition that is near the critical point for a phase transition.[4−14] When the homogeneous solution is enriched with oil near the bimodal line in the phase diagram, water-rich microdroplets successively emerge from the laser focus under constant laser irradiation.[15−19] The generated water-rich microdroplets tend to escape from the focus because of the lower dielectricity compared to that of the oil-rich medium. As they travel into the periphery, the microdroplets disappear by merging into the homogeneous bulk in the absence of a laser-induced dielectric potential. Here, it is expected that the emergence of several microdroplets at the laser focus will cause an increase in local pressure due to a transient increase in the total oil/water interfacial area, which is incommensurate with molecular packing. In this article, we propose a new methodology for producing an optically driven micropump by applying such kind of dynamical phenomenon with the emergence/annihilation of microdroplets caused by a focused laser.

There has been growing interest[20−22] in the subject of micropumps below the millimeter scale in the medical and microengineering fields, such as in the use of micropumps in biosensors, small fuel cells, and drug-delivery equipment. However, micropumps smaller than a micrometer scale do not seem to be available for practical application. Trials that involve the downsizing of existing pump have encounterd serious difficulties because of the relatively greater effects of viscosity and friction in a microscopic system. However, it is well-known that laser trapping is a useful tool for transporting objects smaller than the scale of several tens of micrometers.[10,23−26] Several studies have shown that centimeter-sized objects at an interface can be transported by laser through a thermocapillary effect.[27−32] Thus, methods for transporting objects on a scale between several millimeters and several tens of micrometers are needed.[2] Recently, Wang et al. reported that directional flow on the scale of several cm is generated by the use of a laser beam, through the photoacoustic effect.[33] The driving force is attributed to the generation of cavity caused by laser irradiation. Although this methodology seems to be interesting, we have to consider the possible effect of chemical damage induced by the breakage shock of the cavity.[34]

Received: June 15, 2018
Accepted: September 17, 2018
Published: September 17, 2018

DOI: 10.1021/acs.jpclett.8b01876
J. Phys. Chem. Lett. 2018, 9, 5792−5796

LANGMUIR
Article
Cite This: Langmuir 2018, 34, 11167−11175
pubs.acs.org/Langmuir

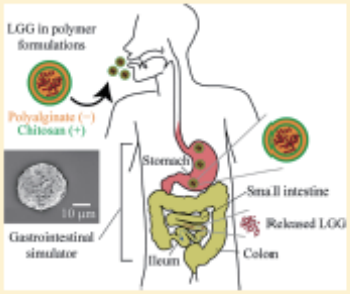
Biopolymer-Based Minimal Formulations Boost Viability and Metabolic Functionality of Probiotics *Lactobacillus rhamnosus* GG through Gastrointestinal Passage

Maryam Eshrati,[†] Federico Amadei,[†] Tom Van de Wiele,[‡] Mariam Veschgini,[†] Stefan Kaufmann,*[†] and Motomu Tanaka*[,†,§]

[†]Physical Chemistry of Biosystems, Institute of Physical Chemistry, Heidelberg University, 69120 Heidelberg, Germany
[‡]Center for Microbial Ecology and Technology (CMET), Faculty of Bioscience Engineering, Ghent University, 9000 Ghent, Belgium
[§]Center for Integrative Medicine and Physics, Institute for Advanced Studies, Kyoto University, 606-8501 Kyoto, Japan

Supporting Information

ABSTRACT: The delivery of probiotic microorganisms as food additives via oral administration is a straightforward strategy to improve the intestinal microbiota. To protect probiotics from the harsh environments in the stomach and small intestine, it is necessary to formulate them in biocompatible carriers, which finally release them in the ileum and colon without losing their viability and functions. Despite major progresses in various polymer-based formulations, many of them are highly heterogeneous and too large in size and hence often "felt" by the tongue. In this study, we established a new formulation for probiotics *Lactobacillus rhamnosus* GG (LGG) and systematically correlated the physicochemical properties of formulations with the functions of probiotics after the delivery to different gastrointestinal compartments. By reducing the stirring speed by 1 order of magnitude during the emulsification of polyalginate in the presence of xanthan gum, we fabricated microparticles with a size well below the limit of human oral sensory systems. To improve the chemical stability, we deposited chitosan and polyalginate layers on particle surfaces and found that the deposition of a 20 nm-thick layer is already sufficient to perfectly sustain the viability of all LGG. Compared to free LGG, the colony-forming units of LGG in these formulations were by factors of 10^3 larger in stomach fluid and 10^4 larger in small intestine fluid. The metabolic functionality of LGG in polymer formulations was assessed by measuring the amount of lactate produced by LGG in a human gastrointestinal simulator, showing 5 orders of magnitude larger values compared to free LGG. The obtained results have demonstrated that the minimal formulation of LGG established here boosts not only the viability but also the metabolic functionality of probiotics throughout oral uptake, passage through the gastrointestinal tract, and delivery to the ileum and colon.



INTRODUCTION

The human colonic lumen contains a large number of bacteria, amounting to 1 trillion per g of stool, that live in a symbiotic relationship with their host. Dysregulations of the natural intestinal microbiota can lead to severe, potentially fatal disorders like inflammatory bowel diseases such as Crohn's disease and ulcerative colitis.[1,2] A healthy intestinal microbiota can be supported by an uptake of probiotic microorganisms, whose metabolic activity supports the natural gastrointestinal microbiota.[3] The beneficial effects of probiotics are (1) inhibition of binding and growth of pathogens either by blocking their binding sites or by secretion of antimicrobial substances like lactic acid, (2) improvement of the intestinal epithelial barrier, and (3) modulation of the host immune response by sustaining the homeostasis of intestinal microbiota.[3−5] It is known that colon epithelial cells are protected from physical abrasion and the attack of pathogenic bacteria by a mucus layer consisting of mucin proteins, whose surface is covered by phospholipid layers.[6,7] However, once the homeostasis of gastrointestinal microbiota is broken, pathogenic bacteria start producing phospholipase that degrades phospholipids. As a consequence, the mucus layer can no longer hold its barrier function. According to the International Scientific Association for Probiotics and Prebiotics, the maximum benefit is obtained by a minimum probiotics amount of 10^9 colony-forming units (CFU) administrated per day.[8] Probiotics have been used widely as food additives in a large scale since the 1980s, and the most commercially available probiotics are *Lactobacillus* or *Bifidobacterium*.[8,9]

One of the major problems in the delivery of probiotics via oral administration is that a substantial amount of the bacteria cannot survive under harsh environments in the upper

Received: June 7, 2018
Revised: August 21, 2018
Published: August 21, 2018

DOI: 10.1021/acs.langmuir.8b01915
Langmuir 2018, 34, 11167−11175

Journal of
Materials Chemistry B

PAPER

View Article Online
View Journal | View Issue

Cite this: J. Mater. Chem. B, 2018, 6, 5633

Lipid-coated mesoporous silica microparticles for the controlled delivery of β-galactosidase into intestines†

Ileana-Alexandra Pavel,[a] Maxime Girardon,[a] Sarah El Hajj,[a] Stéphane Parant,[a] Federico Amadei,[b] Stefan Kaufmann,[b] Motomu Tanaka,[bc] Vanessa Fierro,[d] Alain Celzard,[d] Nadia Canilho[a] and Andreea Pasc*[a]

Received 27th April 2018,
Accepted 6th August 2018

DOI: 10.1039/c8tb01114a

rsc.li/materials-b

β-Galactosidase has been drawing increasing attention for the treatment of lactose intolerance, but its delivery has been impeded by degradation under gastric conditions. We have demonstrated that the coating of mesoporous silica microparticles (diameter ≈ 9 μm, pore size ≈ 25 nm) with dioleoylphosphatidylcholine membranes significantly improved the loading capability and protected the enzymes from the loss of function under simulated gastric conditions. Once the particles are transferred to simulated intestinal conditions, the digestion of phosphatidylcholine with pancreatin led to the release of functional β-galactosidase. The coating of mesoporous silica nanoparticles with a single phospholipid bilayer opens up a large potential towards the controlled release of orally administrated drugs or enzymes to the intestines.

Introduction

β-Galactosidase (β-Gal) is found in animals, plants and microorganisms[1] wherein it is responsible for the hydrolysis of terminal glycosidic bonds of polysaccharides, mainly lactose, into glucose and galactose residues. Its deficiency in the small intestine causes a worldwide common disease called lactose intolerance.[2] To overcome the inconvenience of this disease while continuing consumption of dairy products, patients need to either eat lactose-free foods or take lactase supplements as tablets or as functional food.[3,4] However, the development of food containing β-Gal is challenging, since the enzyme can lose its activity through pH and temperature changes, during processing, but also after ingestion, all along the gastrointestinal transit.

To improve its activity in food, encapsulation of β-Gal was proposed. For instance, encapsulation into organic (*e.g.* carrageenan-based hydrogels)[5] or inorganic (*e.g.* SiO_2 and $CaCO_3$) particles was suggested to provide protective matrices for β-Gal, in which the latter is shown to be more pH-tolerant and have higher thermal stability.[6] Among these, silica carriers are gaining increased interest in oral delivery,[7] including for the delivery of active ingredients[8] or probiotics.[9–11] According to the US Food and Drug Administration (FDA) and the European Food Safety Authority (EFSA), amorphous forms of silica and silicates are generally recognized as safe for oral administration in amounts of up to 1500 mg.[12] Because of their tuneable pore size, high pore volume and large surface area, amorphous silica can entrap not only organic drugs, but also enzymes.[13,14] This fact is also related to the presence of silanol groups (Si-OH) on the pore walls, which can physisorb various compounds through H-bonding.[15,16]

The design of "smart" carriers for drug delivery through oral administration requires not only the biocompatibility of the matrix but also responsiveness to endogenous stimuli such as pH, temperature or enzymes. The biocompatibility and safety of silica can be improved by functionalization with various chemical groups, such as polyethylene glycols,[17] or by coating with lipid bilayers.[18] The biocompatibility and the half-life of lipid-coated silica were observed to be 10-fold higher than those of bare silica.[18] On the other hand, silica particles coated with lactose derivatives were capable of releasing their load in the small intestine, triggered by β-galactosidase.[19] Another responsive material was designed by Popat *et al.* and concerns dual pH- and enzyme-triggered release from mesoporous silica particles coated with succinylated soy protein isolate.[20] Specific release of the encapsulated drug occured upon digestion of the protein coating in simulated intestinal fluids containing pancreatin.

Some of the authors have reported the coating of porous silica particles with synthetic lipid membranes,[21] sarcoplasmic membranes from rabbit muscle,[22] and human red blood cell

[a] Université de Lorraine, CNRS, L2CM, F-54506 Nancy, France. E-mail: andreea.pasc@univ-lorraine.fr
[b] Physical Chemistry of Biosystems, Heidelberg University, Im Neuenheimer Feld 253, 69120 Heidelberg, Germany
[c] Center for Integrative Medicine and Physics, Institute for Advanced Study, Kyoto University, 606-8501 Kyoto, Japan
[d] Université de Lorraine, CNRS, IJL, F-88000 Epinal, France

† Electronic supplementary information (ESI) available: Thermogravimetric analysis.. See DOI: 10.1039/c8tb01114a

ACTIVE MATTER

Emergence of coexisting ordered states in active matter systems

L. Huber[1*], R. Suzuki[2,3,4*†], T. Krüger[1*], E. Frey[1‡], A. R. Bausch[2‡]

Active systems can produce a far greater variety of ordered patterns than conventional equilibrium systems. In particular, transitions between disorder and either polar- or nematically ordered phases have been predicted and observed in two-dimensional active systems. However, coexistence between phases of different types of order has not been reported. We demonstrate the emergence of dynamic coexistence of ordered states with fluctuating nematic and polar symmetry in an actomyosin motility assay. Combining experiments with agent-based simulations, we identify sufficiently weak interactions that lack a clear alignment symmetry as a prerequisite for coexistence. Thus, the symmetry of macroscopic order becomes an emergent and dynamic property of the active system. These results provide a pathway by which living systems can express different types of order by using identical building blocks.

The distinctive feature of active matter is the local supply of energy that is transduced into mechanical motion. Examples include assemblies of self-propelled colloidal particles (*1*–*5*), self-organizing systems composed of biopolymers and molecular motors (*6*–*9*), and layers of migrating cells (*10*, *11*). These systems exhibit a rich phenomenology of collective phenomena and emergent properties, with features absent in passive equilibrium systems. Self-propelled colloidal particles interacting solely by steric repulsion have been predicted (*12*, *13*) to show phase separation into an ordered, solid-like phase with a disordered gas-like phase, similar to experimental observations (*2*–*4*). Active systems composed of rod-shaped particles, cytoskeletal filaments, or colloidal particles with velocity alignment interactions show an even broader range of collective behavior, including polar clusters (*1*, *5*–*7*), nematic lanes (*9*), and vortex patterns (*8*, *14*), which, in all cases, phase-separate with a dilute isotropic, disordered background. Theoretical studies have shown that, in principle, alignment interactions can explain how these different types of orientational order and the transitions between them emerge on the basis of either agent-based (*15*–*27*) or mean-field models (*20*–*28*). All these studies tacitly assume that, as in systems in thermal equilibrium, the symmetry of the observed macroscopic order is largely dictated by the symmetry of local alignment interactions. But to what degree is the symmetry of the macroscopic order constrained by the symmetry of the microscopic interactions? More broadly, can active systems depart from these constraints and express a multitude of different ordering simultaneously, as is the case for living systems such as actin stress fibers and filopodia (*29*, *30*)?

To study these fundamental questions, we use the high-density actomyosin motility assay (Fig. 1A), which is ideally suited to address the microscopic processes that underlie pattern formation in active systems (*6*, *7*, *31*–*34*). By sensitively tuning the interactions between the myosin-driven filaments with a depletion agent, we can observe the emergence of a phase in which nematic and polar order stably coexist. The complete phase diagram is recovered from agent-based simulations of self-propelled filaments, in which weak alignment interactions quantitatively reproduce the experimentally determined microscopic collision statistics. We show that sufficiently weak interactions generically lead to dynamic coexistence of three phases (isotropic, nematic, and polar).

In the actomyosin motility assay, hydrolysis of adenosine triphosphate (ATP) enables actin filaments to actively glide over a lawn of non-processive heavy meromyosin motor proteins (*31*, *32*). Previous studies have shown that increasing the filament density beyond a critical value results in the emergence of polar clusters and waves (*6*, *7*) (Fig. 2A). These patterns are produced by collisions in which filaments may align in a polar or nematic fashion. The degree and symmetry of the alignment depends on the change in the relative orientation of the interacting filaments, $\Delta = \theta_{out} - \theta_{in}$, where θ_{in} and θ_{out} are the angles before and after a collision event, respectively (Fig. 1B). In theoretical studies (*15*–*28*), these collisions have been idealized by assuming that filaments either align in a strictly polar or strictly nematic fashion upon colliding (Fig. 1C). However, in actual experimental active matter systems (*8*, *9*, *34*, *35*), the degree of alignment caused by a single collision event is weak, that is, the relative change in filament orientation is small, $|\theta_{out} - \theta_{in}| < \pi$ (Fig. 1D). Moreover, the resulting alignment exhibits neither perfectly nematic nor perfectly polar symmetry. Instead, depending on the collision angle θ_{in}, in the motility assay, there is a weak tendency to favor either alignment or anti-alignment of the filaments (Fig. 1, C and D). How, then, can such weak interactions without a clear alignment symmetry on a local scale lead to collective order at the system level, and what features of the local interactions determine the global symmetry of the macroscopic state?

To answer these questions, we tuned the local interactions between the filaments by adding polyethylene glycol (PEG, 35 kDa), a depletion agent, at concentrations of up to 3% (w/v) to the assay (Fig. 1D and fig. S1). The observed change in the binary collision statistics can be attributed to the excluded-volume effect of the PEG molecules, which forces the filaments closer to the bottom surface covered with motors, enabling each to interact with more motors on average, with a concomitant increase in motor processivity (Fig. 1E). This reduces the incidence of collisions where filaments just pass over each other (*9*) and increases the likelihood that filaments will repel each other sterically, thus enhancing the tendency to align nematically [Fig. 1D, (*36*)]. This technique enabled us to continuously modulate the symmetry of alignment interactions at the microscopic level and probe the robustness of pattern formation in the gliding assay at high filament densities. Despite the rather minute changes in interaction characteristics caused by adding PEG at a concentration of 3% (Fig. 1D), we found that polar flocks no longer form. Instead, the moving filaments quickly, within a few minutes, self-organize into a network of "ant trails" (Fig. 2B and movie S1). In contrast to the unidirectional filament motion found within polar clusters, the filaments that form these "lanes" move bi-directionally, as do many colonial ant species (*37*). Because the filaments move along these tracks in either direction with equal probability (Fig. 2C and fig. S2), the overall order is nematic, not polar, and stable; this is quantified by the local nematic order (fig. S2A) and the autocorrelation function of the filament orientations (fig. S2, D and E). Moreover, whereas polar clusters propagate through the system at uniform speed, nematic lanes form static networks with branches spanning up to several hundred micrometers in length (Fig. 2B). Filaments are also seen to continuously leave and enter the trails (Fig. 2D and movie S2), such that these branches remain fixed in orientation and slowly grow and shrink at their ends (fig. S2F). These processes, operating on a time scale of minutes, lead to a slow reorganization of network architecture, with new branches forming (movie S3) while others contract (movie S4). Note that these networks are isotropically oriented and that no notable actin bundling was observed below 3% PEG.

This fundamental qualitative change in macroscopic order, from propagating waves of polar

[1]Arnold Sommerfeld Center for Theoretical Physics and Center for NanoScience, Department of Physics, Ludwig-Maximilians-Universität München, D-80333 Munich, Theresienstrasse 37, Germany. [2]Lehrstuhl for Biophysik (E27), Technische Universität München, James-Franck-Strasse 1, D-85748 Garching, Germany. [3]Graduate School of Medicine, Kyoto University, 606-8501 Kyoto, Japan. [4]Institute for Integrated Cell-Material Sciences, Kyoto University, 606-8501 Kyoto, Japan.
*These authors contributed equally to this work.
†Present address: Center for Integrative Medicine and Physics, Institute for Advanced Study, Kyoto University, 606-8501 Kyoto, Japan.
‡Corresponding author. Email: frey@lmu.de (E.F.); abausch@mytum.de (A.R.B.)

LANGMUIR Article
Cite This: Langmuir 2018, 34, 2489−2496
pubs.acs.org/Langmuir

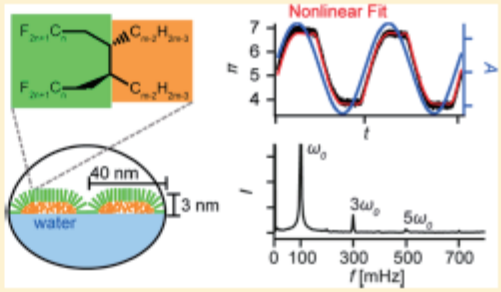
Emergence of Strong Nonlinear Viscoelastic Response of Semifluorinated Alkane Monolayers

Salomé Mielke,[†] Taichi Habe,[†,⊥] Mariam Veschgini,[†] Xianhe Liu,[‡] Kenichi Yoshikawa,[§] Marie Pierre Krafft,[‡] and Motomu Tanaka*[,†,∥]

[†]Institute of Physical Chemistry, University of Heidelberg, 69120 Heidelberg, Germany
[‡]Institut Charles Sadron (CNRS), University of Strasbourg, 67034 Strasbourg, France
[§]Faculty of Life and Medical Sciences, Doshisha University, 610-0321 Kyotanabe, Japan
[∥]Institute for Advanced Study, Kyoto University, 606-8501 Kyoto, Japan

Supporting Information

ABSTRACT: Viscoelasticity of monolayers of fluorocarbon/hydrocarbon tetrablock amphiphiles di(*FnHm*) ($(C_nF_{2n+1}CH_2)$-$(C_{m-2}H_{2m-3})CH$–$CH(C_nF_{2n+1}CH_2)(C_{m-2}H_{2m-3})$) was characterized by interfacial dilational rheology under periodic oscillation of the moving barriers at the air/water interface. Because the frequency dispersion of the response function indicated that di(*FnHm*) form two-dimensional gels at the interface, the viscosity and elasticity of di(*FnHm*) were first analyzed with the classical Kelvin−Voigt model. However, the global shape of stress response functions clearly indicated the emergence of a nonlinearity even at very low surface pressures ($\pi \approx 5$ mN/m) and small strain amplitudes ($u_0 = 1\%$). The Fourier-transformed response function of higher harmonics exhibited a clear increase in the intensity only from odd modes, corresponding to the nonlinear elastic component under reflection because of mirror symmetry. The emergence of strong nonlinear viscoelasticity of di(*FnHm*) at low surface pressures and strain amplitudes is highly unique compared to the nonlinear viscoelasticity of other surfactant systems reported previously, suggesting a large potential of such fluorocarbon/hydrocarbon molecules to modulate the mechanics of interfaces using the self-assembled domains of small molecules.



INTRODUCTION

Microscopic and mesoscopic structural patterns,[1,2] such as stripes and bubbles, can be found in various systems, including noble gas molecules,[3] ferrofluids,[4] block copolymers,[5] and surfactants[6] on substrates. These equilibrium patterns exhibit the modulation of order parameters, resulting from the interplay of various molecular interactions.

The characteristic length scale of patterns (stripe width and domain size) under equilibrium is determined by the competition between interactions among homologous species and the line tension γ. Surfactants with perfluorocarbon blocks have been used for designing new types of colloidal suspensions, targeting versatile medical applications.[7,8] Different from the zigzag conformation formed by hydrocarbon chains, perfluorocarbon chains form helices of six turns because of the larger van der Waals radius of fluorine, 1.35 Å, and behave like a stiff rod.[9] When the surfactants with perfluorocarbon chains are confined at the air/water interface, dipolar interactions between terminal CF_3 groups immersed in the medium with a low dielectric constant (air) tend to elongate the domains, competing against the line tension that tends to minimize the length of the domain boundary.

Previously, we reported that lipids with semifluorinated tails form stripe patterns at the air/water interface near the gas−liquid coexistence phase, whereas the same lipids that only possess hydrocarbon chains form circular domains.[10] Oelke et al. reported that perfluorinated lipids form circular, solid domains when they are incorporated into phospholipids with hydrocarbon chains.[11] Although the size of domains formed by lipids with hydrocarbon chains is heterogeneous because of coalescence of small domains, the domains of perfluorinated lipids seemed highly uniform, showing almost no sign of coalescence. This finding suggested that the interactions between fluorocarbon domains are predominantly repulsive. In fact, the potential of the mean force acting between fluorocarbon domains suggested that the fluorocarbon domains form a hexagonal order and the lateral correlation between the domains can reach over a distance that is 8 times larger than the domain size itself.[11,12] The equilibrium size of domains (0.3−2 μm) exhibited a distinct dependence on the length of

Received: November 21, 2017
Revised: January 11, 2018
Published: January 23, 2018

DOI: 10.1021/acs.langmuir.7b03997
Langmuir 2018, 34, 2489−2496

SCIENTIFIC REPORTS

OPEN

Intracellular calcium signal at the leading edge regulates mesodermal sheet migration during *Xenopus* gastrulation

Received: 20 October 2017
Accepted: 23 January 2018
Published online: 05 February 2018

Kentaro Hayashi[1,2], Takamasa S. Yamamoto[1] & Naoto Ueno[1,2]

During the gastrulation stage in animal embryogenesis, the cells leading the axial mesoderm migrate toward the anterior side of the embryo, vigorously extending cell protrusions such as lamellipodia. It is thought that the leading cells sense gradients of chemoattractants emanating from the ectodermal cells and translate them to initiate and maintain the cell movements necessary for gastrulation. However, it is unclear how the extracellular information is converted to the intracellular chemical reactions that lead to motion. Here we demonstrated that intracellular Ca^{2+} levels in the protrusion-forming leading cells are markedly higher than those of the following cells and the axial mesoderm cells. We also showed that inhibiting the intracellular Ca^{2+} significantly retarded the gastrulation cell movements, while increasing the intracellular Ca^{2+} with an ionophore enhanced the migration. We further found that the ionophore treatment increased the active form of the small GTPase Rac1 in these cells. Our results suggest that transient intracellular Ca^{2+} signals play an essential role in the active cell migration during gastrulation.

Gastrulation is one of the most important processes in the early development of a variety of animals. In vertebrates, this dynamic remodelling process is achieved by the coordinated movements of three germ layers, which contribute to the development of various organs in their proper positions in the body. In the experimental vertebrate model *Xenopus laevis*, the gastrulation movements begin with vegetal rotation of the mesodermal sheet[1]. Subsequently, the leading edge mesoderm (LEM), the most vegetal mesoderm region, touches the inner side of the blastocoel roof (BCR). The LEM then shows directional migration toward the anterior end on the fibronectin-rich BCR[2–5]. During this process, axial mesoderm following the LEM undergoes convergent extension, in which cell movements elongate the embryo proper along the anterior-posterior axis and narrow the tissue mediolaterally, eventually forming the rod-shaped notochord[6]. On the other hand, the prechordal mesoderm that follows the LEM cells plays essential roles in head formation[7,8].

The LEM has an indispensable role in the directional migration of the mesodermal sheet, and disrupting this migration causes severe morphological defects in the embryo, such as abnormal notochord formation and *spina bifida*[9,10]. This anterior tissue migration is thought to be regulated by chemoattractants and/or by cell responses to mechanical signals. As chemoattractants for the directed tissue migration, PDGF[7] and SDF-1[11] secreted from the ectoderm have been implicated, and the LEM cells are thought to receive these chemokine signals via their respective receptors[8,12]. On the other hand, the LEM cells' sensing of local mechanical interactions between the leader cells and follower cells has been reported to determine the asymmetric formation of cell protrusions and the oriented movement of LEM cells[13]. However, how such mechanical signals are interpreted by the cells remains unknown.

Intracellular Ca^{2+} signalling regulates a variety of physiological events, including cell proliferation, apoptosis, differentiation, and cell migration[14]. In cell migration, Ca^{2+} signalling regulates the effectors required for cytoskeletal remodelling and the establishment of focal adhesions[15–18]. Ca^{2+} signalling is essential both for the homeostasis of adult animals and for developmental processes such as organogenesis[19,20]. It is generally thought

[1]Department of Developmental Biology, National Institute for Basic Biology, 38 Nishigonaka, Myodaiji, Okazaki, Aichi, 444-8585, Japan. [2]Department of Basic Biology, School of Life Science, The Graduate University of Advanced Studies (SOKENDAI), 38 Nishigonaka, Myodaiji, Okazaki, Aichi, 444-8585, Japan. Correspondence and requests for materials should be addressed to N.U. (email: nueno@nibb.ac.jp)

BBA - Biomembranes 1860 (2018) 617–623

Contents lists available at ScienceDirect

BBA - Biomembranes

journal homepage: www.elsevier.com/locate/bbamem

Ib-AMP4 insertion causes surface rearrangement in the phospholipid bilayer of biomembranes: Implications from quartz-crystal microbalance with dissipation

Xiaobo Fan[a,b,*], Agatha Korytowski[c], Ali Makky[c], Motomu Tanaka[c], Michael Wink[b,**]

[a] Clinical Diagnostics Department, Medical School, Southeast University, Nanjing, China
[b] Institute of Pharmacy and Molecular Biotechnology, Heidelberg University, Germany
[c] Physical Chemistry Department, Heidelberg University, Germany

ARTICLE INFO

Keywords:
Lipid bilayer
Membrane rearrangement
Wrinkling
Poring
Antimicrobial peptide

ABSTRACT

Most antimicrobial peptides exert their rapid bactericidal activity through a unique mechanism of bacterial membrane disruption. However, the molecular events that underlie this mechanism remain partly unresolved. In this study, the frequency shift (ΔF) obtained through quartz-crystal microbalance with dissipation (QCM–D) indicated that the initial binding of Ib-AMP4 within the lipid membrane started at a critical Ib-AMP4 concentration that exceeded 100 μg/ml. Circular dichroism measurements provided evidence that Ib-AMP4 occurs in a β-sheet configuration which is adapted for insertion into the lipid membrane. Monolayer experiments and the value of dissipation alteration (ΔD) obtained through QCM–D showed that the pressure increased within the phospholipid bilayer upon peptide insertion, and the increase in pressure subsequently forced the bilayer to wrinkle and form pores. However, D continued to increase, indicating that the membrane surface underwent a dramatic morphological transition: the membrane surface likely became porous and uneven as Ib-AMP4 projected from the external surface of the lipid bilayer. Intensive peptide insertion, however, soon plateaued 1 min after the addition of Ib-AMP4. This behaviour corresponded with the results of bactericidal kinetics and liposome leakage assays. A sudden decrease in D accompanied by a negligible decrease in F occurred after replacing the Ib-AMP4 solution with HEPES buffer. This result implied that the bilayer surface rearranged and that poration and wrinkling decreased without further peptide insertion. Transmission electron microscopy results indicated that pore formation occurred during Ib-AMP4 insertion but eventually subsided. Therefore, the mode of action of AMP in bacterial membranes could be elucidated through QCM-D.

1. Introduction

Electrostatic interactions between lysine or arginine residues of peptides with phosphate groups of phospholipids in lipid bilayers are particularly strong [1]. The highly conserved positive charges of basic amino acid residues in antimicrobial peptides (AMPs) provide evidence that electrostatic attraction drives the initial binding of AMPs with their target microbes [2–4].

When AMPs bind to bacterial membranes, they will first undergo a transition stage, during which their membrane-binding affinity change through alterations in their geometric conformations. AMPs then undergo a self-promoting association or multimerization and become perpendicularly oriented to the phospholipids in the bacterial membrane [5,6]. Finally, the membrane becomes leaky through hole or a channel formation.

Different hypotheses have been presented for the AMP transition stage, including the classic barrel–stave, toroid–pore, and carpet theories [6,7]. However, the detailed molecular events involved in AMP transition are far from clear due to the limitations of presently available monitoring techniques. Although electron microscopy has been successfully applied to observe subcellular structures, its tedious sample preparation procedures and/or non-real-time analysis make an application for dynamic processes difficult.

Liposomes are important model systems in this context. Expansion, contraction, and bending are the three main forms of deformation in liposome bilayer [8]. Expansion and contraction are within-plane motions that are evaluated on the basis of compressibility, which corresponds to the change in pressure vs. area per molecule in a membrane.

* Correspondence to: X. Fan, Southeast University, China.
** Correspondence to: M. Wink, IPMB, Heidelberg University, 69120 Heidelberg, Germany.
E-mail addresses: 101011951@seu.edu.cn (X. Fan), wink@uni-hd.de (M. Wink).

https://doi.org/10.1016/j.bbamem.2017.10.025
Received 3 July 2017; Received in revised form 24 October 2017; Accepted 25 October 2017
Available online 26 October 2017

ADVANCED FUNCTIONAL MATERIALS
www.afm-journal.de

Flexible Modulation of Electronic Band Structures of Wide Band Gap GaN Semiconductors Using Bioinspired, Nonbiological Helical Peptides

Sven Mehlhose, Nataliya Frenkel, Hirotaka Uji, Sara Hölzel, Gesche Müntze, Daniel Stock, Silvio Neugebauer, Armin Dadgar, Wasim Abuillan, Martin Eickhoff, Shunsaku Kimura, and Motomu Tanaka**

Modulation of the electronic band profiles of wide band gap GaN semiconductors is achieved by the macromolecular dipole potentials exerted from ordered monolayers of synthetic, nonbiological aldehyde terminated helical peptides deposited on wet chemically oxidized GaN surfaces functionalized with aminosilanes. The selective coupling of either N- or C-terminal to the amino-terminated surface enables one to control the direction of the dipole moment, while the number of amino acids determines its magnitude. After confirming the formation of highly ordered peptide monolayers, the impact of macromolecular dipole potentials is quantified by electrochemical impedance spectroscopy. Moreover, the chronoamperometry measurements of ferrocene-terminated peptides suggest that the transfer of electrons injected from ferrocene follows inelastic hopping, while the current responses of peptides with no ferrocene moieties are purely capacitive. Finally, the same functionalization steps are transferred to GaN/AlGaN/GaN high electron mobility transistor structures. Stable and quantitative modulation of the current–voltage characteristics of the 2D electron gas by the deposition of bioinspired peptides is a promising strategy for the macromolecular dipole engineering of GaN semiconductors.

1. Introduction

The chemical coupling of organic molecules to semiconductors has been drawing increasing attention as a method to provide semiconductors with new and controllable surface properties, such as hydrophilicity/hydrophobicity, lubrication, antibiofouling capability, and biocompatibility.[1] For example, the deposition of densely packed, organic monomolecular films stabilizes GaAs surfaces against oxidation in ambient atmosphere as well as in aqueous environments by the suppression of surface states.[2] The grafting of organic molecules does not only change the surface but also alters surface charges (monopoles) and dipoles, which results in changes in electron affinity and band bending.[3] This offers much larger degrees of freedom in tuning material properties of semiconductors compared to the classical inorganic doping and the deposition of additional inorganic layers.

For example, the dipole moment of an organic molecule projected in the direction normal to the surface $\rho_{\perp}$ causes a change in the surface dipole potential, $\Delta\Psi \propto \rho_{\perp}/A$, where A is the area per molecule. This concept was demonstrated by the use of electrolyte-gate field-effect transistors with gate surfaces functionalized with small molecules.[2a,3d,4] For example, the lateral resistance of GaAs/AlGaAs heterostructures was linearly proportional to the projected dipole moments of 4′-4-mercaptobiphynels

S. Mehlhose, Dr. N. Frenkel, Dr. W. Abuillan,[+] Prof. M. Tanaka
Physical Chemistry of Biosystems
Institute of Physical Chemistry
Heidelberg University
D69120 Heidelberg, Germany
E-mail: tanaka@uni-heidelberg.de
S. Mehlhose, Dr. N. Frenkel, Dr. H. Uji, Prof. S. Kimura
Department of Material Chemistry
Graduate School of Engineering
Kyoto University
6158510 Kyoto, Japan
E-mail: shun@scl.kyoto-u.ac.jp
The ORCID identification number(s) for the author(s) of this article can be found under https://doi.org/10.1002/adfm.201704034.
[+]Present Address: Institute of Industrial Science, The University of Tokyo, Tokyo 153-8505, Japan
S. Hölzel, Dr. G. Müntze, D. Stock, Prof. M. Eickhoff
I Physikalisches Institut
Justus-Liebig-Universität Gießen
Heinrich-Buff-Ring 16, D35392 Gießen, Germany
S. Neugebauer, Prof. A. Dadgar
Otto-von-Guericke Universität Madgeburg
Abteilung Halbleiterepitaxie
Postfach 4120, D39016 Magdeburg, Germany
Prof. M. Eickhoff
Institut für Festkörperphysik
Universität Bremen
Otto-Hahn-Allee, D28359 Bremen, Germany
Prof. M. Tanaka
Institute for Integrated Cell-Material Science (WPI iCeMS)
Kyoto University
6068501 Kyoto, Japan

DOI: 10.1002/adfm.201704034

ChemPubSoc Europe

DOI: 10.1002/cphc.201701064

CHEMPHYSCHEM Communications

2D Spherulites of a Semi-Fluorinated Alkane: Controlled Access to Either Radial Or Ring-Banded Morphologies

Xianhe Liu,[a] Salomé Mielke,[b] Christophe Contal,[a] Damien Favier,[a] Akihisa Yamamoto,[c] Motomu Tanaka,*[b, c] and Marie Pierre Krafft*[a]

Thin films of a semi-fluorinated alkane cast onto solid substrates consist of well-formed two-dimensional non-birefringent ring-banded and/or radial spherulites. Controlling the experimental conditions allows orientation of the crystallization toward either radial-only or ring-banded-only morphologies. Intermediate states were also captured in which both radial and ring-banded spherulites coexist. Monitoring of the formation of these intermediate states brought evidence for a first crystallization mode that sweeps radially outwards from a central nucleus until the propagating front edge experiences a second crystallization mode that proceeds through a diffusion-controlled rhythmic crystallization mechanism that leads to high (≈2 μm) concentric ridges. These 2D spherulites were investigated by optical and atomic force microscopies, interferometric profilometry, and off-specular neutron scattering.

Polycrystalline aggregates with an essentially spherical outer boundary, called spherulites, are observed to form from a large variety of compounds, including organic compounds and minerals.[1] Two-dimensional spherulites have been characterized in films resulting, for example, from solvent evaporation during casting of liquid drops of solutions of such materials on solid substrates. Concentric ring-banded spherulites constitute an intensely investigated sub-class of spherulites that usually possess chiroptical properties. Such ring-banded spherulites are formed by polymers (e.g. polyethylene and poly(ethylene adipate)),[2] but also by various small organic molecules (e.g. phthalic acid,[3] aspirin,[4] hippuric acid,[5] mannitol,[6] testosterone propionate[7]), and by inorganic compounds (e.g. potassium dichromate and boric acid[8]). A major distinction needs to be made between spherulites that have a twisted crystal morphology, which is responsible for the „banded" optical texture, and spherulites that have a real wave-like topography with actual valleys separated by ridges. The former do not necessarily have a „real" relief, while the latter can exhibit extinction bands or not. Lately, substantial interest has focused on non-birefringent ring-banded spherulites.[9] The latter have only been observed with a few polymers and never with small molecules. Improving control over the morphology of 2D spherulites and understanding their mechanisms of formation, which can involve a twisting of the crystal or a rhythmic crystallization process, both being able to act in interplay, are needed in order to tailor new material characteristics.

Here we report first that a simple semi-fluorinated alkane, $C_{10}F_{21}C_{16}H_{33}$ (*F10H16*), when deposited as a thin film on solid surfaces (glass or silicon wafers), forms non-birefringent 2D spherulites. To the best of our knowledge, this is one of the rare examples of non-birefringent 2D spherulites obtained with small organic molecules. Remarkably, depending on the experimental conditions, we could obtain radial-*only*, or ring-banded-*only* spherulites. We attained control of the morphology of the spherulites by adjusting key experimental parameters that govern crystallization. We provide evidence for two crystallization events that include an initial outwards crystallization starting from a nucleus that generates radial fibrous spherulites, followed by a rhythmical precipitation that produces concentric rings.

$C_nF_{2n+1}C_mH_{2m+1}$ (*FnHm*) diblocks are highly hydrophobic amphiphilic, amphistetic and amphidynamic molecules that display a marked propensity for self-assembly, nanocompartmentation and nanostructuration.[10] In their bulk solid state they form fibers, liquid crystals and gels.[11] *FnHm* diblock *mono*layers actually consist of highly monodisperse, disk-like domains (20–40 nm in diameter) that form ordered hexagonal lattices.[12] Such diblocks have also been used as film and shell components for modifying and controlling film phase behavior, emulsion stability, liposome stability and permeability, and fiber formation.[13] No spherulite was ever reported to form from *FnHm* diblocks.

Films of $C_{10}F_{21}C_{16}H_{33}$ (*F10H16*) were prepared by casting chloroform/ethanol solutions of the compound on glass plates or silicon wafers. Two different film thicknesses, 1.5 and 3.5 ± 0.2 μm, as determined by interferometric profilometry, were obtained by setting the concentrations of the solutions at 1 and 4 mg mL^{-1}, respectively. When the films were heated above the isotropic temperature of *F10H16* (74 ± 2 °C, as determined by differential scanning calorimetry, see Supporting In-

[a] X. Liu, C. Contal, D. Favier, Dr. M. P. Krafft
University of Strasbourg
Institut Charles Sadron (ICS CNRS)
23 rue du Loess, 67034 Strasbourg (France)
E-mail: krafft@unistra.fr

[b] S. Mielke, Prof. M. Tanaka
Physical Chemistry of Biosystems
Institute of Physical Chemistry
University of Heidelberg
Im Neuenheimer Feld 253, 69120 Heidelberg (Germany)

[c] A. Yamamoto, Prof. M. Tanaka
Institute for Integrated Cell-Material Science (WPI iCeMS)
Kyoto University
606-8501 Kyoto (Japan)

Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under: https://doi.org/10.1002/cphc.201701064.

2019 年

nature biomedical engineering

ARTICLES

https://doi.org/10.1038/s41551-019-0429-9

A physical biomarker of the quality of cultured corneal endothelial cells and of the long-term prognosis of corneal restoration in patients

Akihisa Yamamoto[1,5], Hiroshi Tanaka[2,5], Munetoyo Toda[2], Chie Sotozono[2], Junji Hamuro[2], Shigeru Kinoshita[3], Morio Ueno[2*] and Motomu Tanaka[1,4*]

Dysfunction of the corneal endothelium reduces the transparency of the cornea and can cause blindness. Because corneal endothelial cells have an extremely limited proliferative ability in vivo, treatment for corneal endothelial dysfunction involves the transplantation of donor corneal tissue. Corneal endothelium can also be restored via intraocular injection of endothelial cells in suspension after their expansion in vitro. Yet, because quality assessment during the expansion of the cells is a destructive process, a substantial number of the cultured cells are lost. Here, we show that the 'spring constant' of the effective interaction potential between endothelial cells in a confluent monolayer serves as a biomarker of the quality of corneal endothelial cells in vitro and of the long-term prognosis of corneal restoration in patients treated with culture-expanded endothelial cells or with transplanted corneas. The biomarker can be measured from phase contrast imaging in vitro and from specular microscopy in vivo, and may enable a shift from passive monitoring to pre-emptive intervention in patients with severe corneal disorders.

The cornea is a layer of transparent tissue that forms the anterior portion of the outer casing of the eye, and its posterior surface is lined by a monolayer of corneal endothelial cells that keep corneal transparency maintained by regulating the flow of water into the cornea. Pathological damage or corneal disorders such as Fuchs' endothelial corneal dystrophy, accompanied by the subsequent loss of corneal endothelial cells, is compensated for by the natural spread of the remaining corneal endothelial cells[1]. However, when the corneal endothelial cell density decreases from the normal level ($\geq$2,000 cells mm^{-2})[2] to fewer than 400 cells mm^{-2}, this event leads to an abnormal swelling and thickening of the cornea, known as corneal endothelial dysfunction; its severe type is termed bullous keratopathy[3]. Ultimately, this can result in a loss of visual acuity (Fig. 1a).

Annually, approximately 200,000 corneal transplantations are performed in more than 100 countries[4], and more than half of these cases are corneal endothelial dysfunction, including bullous keratopathy. At present, the surgical treatments for bullous keratopathy include penetrating keratoplasty[5], Descemet's stripping automated endothelial keratoplasty[6,7] and Descemet's membrane endothelial keratoplasty[8]. Since human corneal endothelial cells have extremely limited proliferative ability in vivo, all of the treatments mentioned above inevitably involve the use of a fresh, donor corneal tissue, including endothelium[4,9–14].

In 2009, the presence of a rho-associated protein kinase (ROCK) inhibitor was found to significantly promote the proliferation of primate corneal endothelial cells in vitro[15], which enabled the cultivation of human corneal endothelial cells from donor corneas in vitro (Fig. 1b). A strategy was then developed to restore human corneal endothelium by injecting the suspension of cultured corneal endothelial cells (Fig. 1c)[16]. Briefly, after the removal of the deteriorated corneal endothelial cells and abnormal extracellular matrix from the basement membrane of the patient's cornea, the suspension of cultivated cells is injected into the anterior chamber of the patient's eye with a ROCK inhibitor. With the patient then being placed in a prone position, the injected cells sediment, adhere onto the posterior surface of the cornea, and successfully restore a corneal endothelial cell layer via self-organization. This therapy leads to the recovery of corneal transparency and thickness and, hence, good visual acuity (Fig. 1c). Compared with the widely used corneal transplantations, the restoration of cornea via cell injection is less invasive and less stressful for the patient, which clearly indicates the sophistication of the procedure. Since 2013, over 50 clinical trial cases have been performed, resulting in the restoration of corneal endothelium via this cell injection therapy.

At present, the quality of in vitro cultured human corneal endothelial cells is assessed by flow cytometry, with surface markers following the previously reported protocol[17–19]. As shown in Supplementary Fig. 1, CD166$^+$/CD24$^-$/CD105$^-$/CD44$^-$ cells are currently defined as 'effector cells' for corneal endothelial cell injection therapy[17–19]. Since effector cells share several common phenotypes that resemble those of healthy human corneal endothelial cells in vivo[16], the percentage of effector cells, $\chi_{effector}$, is used as an indicator to classify the quality of cultivated human corneal endothelial cells (Fig. 1d). However, little is understood about how the expression of surface markers is correlated with the restoration functions of endothelial cells. Hence, a function-based quality assessment of in vitro cultured cells is still a challenge. In contrast, transplanted donor corneal endothelium after keratoplasty has been evaluated by specular microscopy (Supplementary Fig. 2)[20,21] using some parameters based on clinical findings, such as the cell density, its coefficient of variation, and the proportion of hexagonal cells[22,23]. In fact, several recent studies have suggested the importance of 'uniformity' in phenotypes; however, they remained as phenomenological observations[19,24].

[1]Center for Integrative Medicine and Physics, Institute for Advanced Study, Kyoto University, Kyoto, Japan. [2]Department of Ophthalmology, Kyoto Prefectural University of Medicine, Kyoto, Japan. [3]Department of Frontier Medical Science and Technology for Ophthalmology, Kyoto Prefectural University of Medicine, Kyoto, Japan. [4]Physical Chemistry of Biosystems, Institute of Physical Chemistry, Heidelberg University, Heidelberg, Germany. [5]These authors contributed equally: Akihisa Yamamoto, Hiroshi Tanaka. *e-mail: mueno@koto.kpu-m.ac.jp; tanaka@uni-heidelberg.de

Yamamoto et al., *Nat. Biomed. Eng.*
Editorial と News & Views で紹介

editorial

Forceful biomarkers

The physical properties of living tissues are a compelling source of biomarkers of health and disease.

Biomarkers come in all sizes, shapes and colours. Step counts are a biomarker for physical activity, blood pressure is a clinical biomarker for hypertension (and a risk factor for stroke), and haemoglobin concentration for anaemia. Most biomarkers of disease — such as the concentration of chloride in sweat for cystic fibrosis, serum levels of the prostate-specific antigen for the prognosis of prostate cancer and mutations in the *BRCA* genes for breast-cancer risk — are biochemical, cellular or genomic. This is a direct result of staggering advances in technologies for biosensing, single-cell analyses and genomics. In comparison, the physical properties of ensembles of cells and the extracellular matrix making up living tissues — that is, the properties that affect their morphology, structure and mechanical properties — have been a much less prolific source of specific biomarkers.

Many physical diseases have tissue-level hallmarks, and more of such microscopic-to-macroscopic biomarkers (rather than of the molecular or cellular kind) could aid the understanding of disease risk, or help with diagnosis, prognosis or patient monitoring. For instance, carcinomas — malignancies of epithelial tissue that account for more than 80% of all cases of cancer

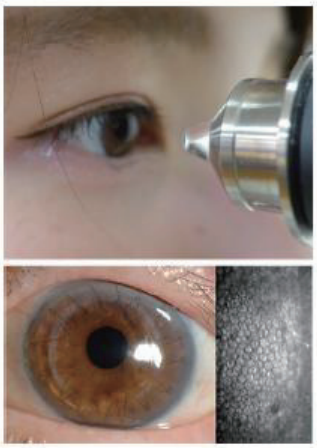


Figure adapted from. Yamamoto, A. et al. *Nat. Biomed. Eng.* https://doi.org/10.1038/s41551-019-0429-9 (2019), Springer Nature Ltd.

analyses). When biopsied tissue is not abnormal mechanical properties, such as solid stress and stored elastic energy, which only recently have been quantitatively mapped in excised human tissues. And as shown earlier this year, for some types of brain tumour, solid stress is also a biomarker of the neurological dysfunction caused by the tumour's compression of adjacent brain tissue, which then experiences reduced blood perfusion (as seen with magnetic resonance imaging in patients).

This issue includes an exemplary discovery of a new tissue-level biomarker for the health status of corneal endothelium: a measure of the average 'spring-like' force that a cell in the endothelial monolayer experiences as a consequence of its interaction with the cell's immediate neighbours. The balance of forces that the cells experience and exert affect how the cells in the monolayer arrange themselves and thus their collective degree of order. This can be modelled by using basic concepts in statistical mechanics, as shown by Motomu Tanaka, Morio Ueno and colleagues in an Article. In particular, the researchers measured such a spring-like force by calculating the second derivative around the minimum

news & views

TISSUE TRANSPLANTS

A prognostic biomarker of corneal repair

A non-invasive biomarker of the degree of collective order of monolayers of corneal endothelial cells cultured for transplantation predicts the long-term prognosis of corneal restoration in patients.

Jodhbir S. Mehta, Viridiana Kocaba and Gary S. Peh

In clinical practice, the most common type of tissue transplant is that of the cornea. Corneal transplants usually replace dysfunctional corneal endothelial tissue — the cornea's innermost cellular monolayer. Advances over the past two decades have refined the transplantation methods for such tissue: penetrating keratoplasties (the replacement of the entire cornea) are being gradually substituted by safer and selective transplantation methods that replace only a layer of cells[1] (such as Descemet stripping automated endothelial keratoplasty and Descemet membrane endothelial keratoplasty), and more recently the injection of tissue-engineered corneal-endothelial cells[1,2] has been tested in patients. These newer procedures all rely on allogenic tissue transfer, and their most serious consequences are long-term endothelial-cell attrition[3] (a natural ageing process where the endothelial-cell monolayer progressively thins) and tissue rejection (however, rejection risks are drastically less than that for penetrating keratoplasty). Cellular attrition following corneal transplantation increases steeply in the first year, followed by continual endothelial cell loss at a rate of 5–10% per annum[3]. Current methods to assessing in vivo endothelial cell loss involve specular microscopy (Fig. 1a) or in vivo confocal

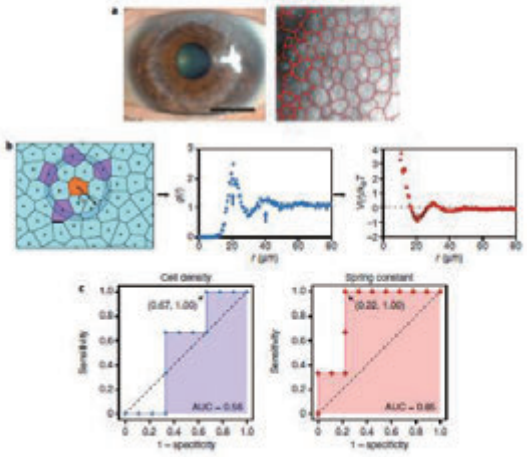


Fig. 1 | **A non-invasive prognostic biomarker of corneal restoration. a**, Photograph of the cornea (left), and a section of a specular microscopy image of it with cell boundaries overlaid (right), of a patient who underwent penetrating keratoplasty. Scale bar, 100μm. **b**, The 'spring constant' biomarker corresponds to

COMMUNICATIONS BIOLOGY

ARTICLE

https://doi.org/10.1038/s42003-019-0556-6 OPEN

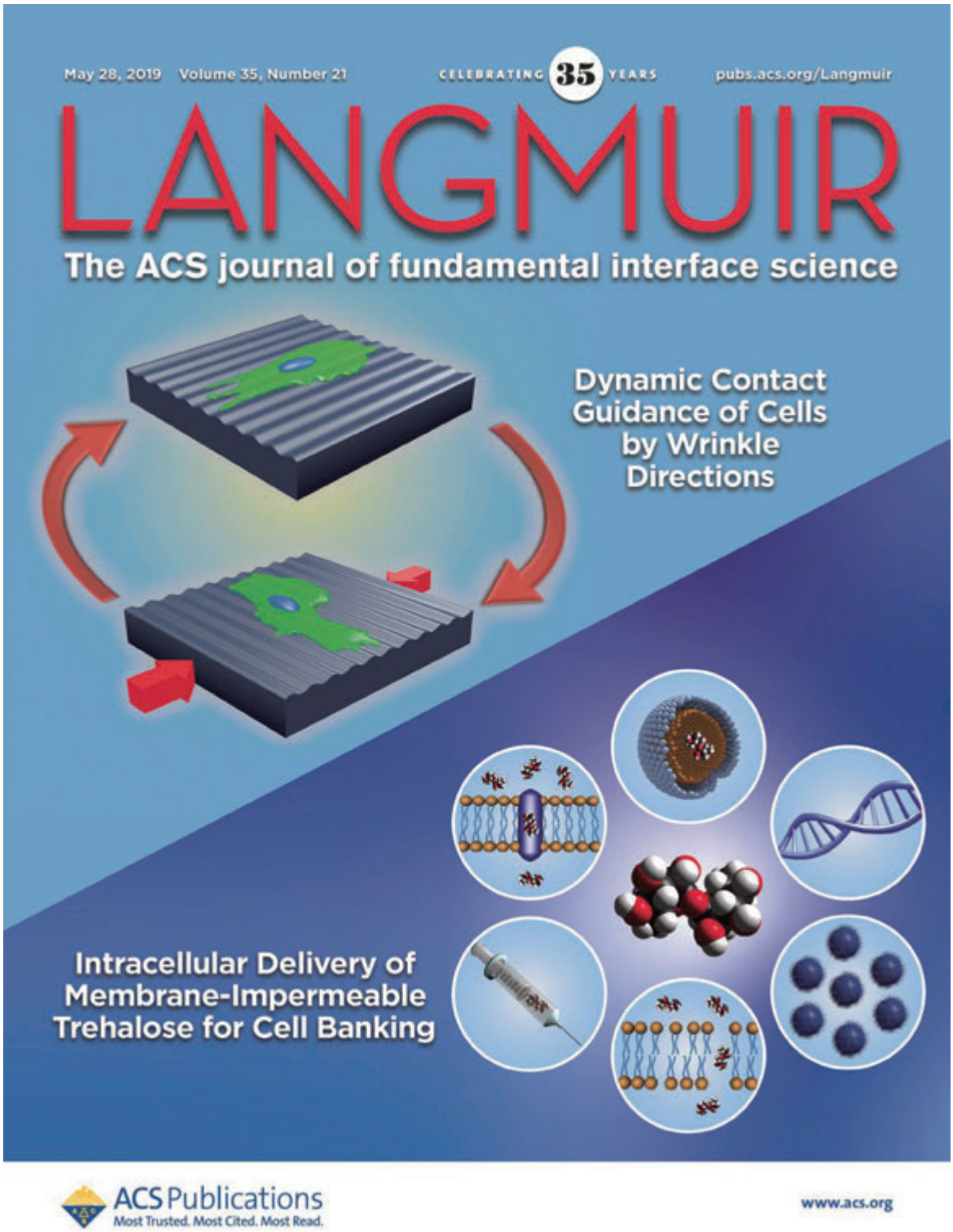
Hemoglobin S and C affect biomechanical membrane properties of *P. falciparum*-infected erythrocytes

Benjamin Fröhlich[1], Julia Jäger[2], Christine Lansche[3], Cecilia P. Sanchez[3], Marek Cyrklaff[3], Bernd Buchholz[4], Serge Theophile Soubeiga[5], Jacque Simpore[5], Hiroaki Ito[6], Ulrich S. Schwarz[2], Michael Lanzer[3] & Motomu Tanaka[1,7]

During intraerythrocytic development, the human malaria parasite *Plasmodium falciparum* alters the mechanical deformability of its host cell. The underpinning biological processes involve gain in parasite mass, changes in the membrane protein compositions, reorganization of the cytoskeletons and its coupling to the plasma membrane, and formation of membrane protrusions, termed knobs. The hemoglobinopathies S and C are known to partially protect carriers from severe malaria, possibly through additional changes in the erythrocyte biomechanics, but a detailed quantification of cell mechanics is still missing. Here, we combined flicker spectroscopy and a mathematical model and demonstrated that knob formation strongly suppresses membrane fluctuations by increasing membrane-cytoskeleton coupling. We found that the confinement increased with hemoglobin S but decreases with hemoglobin C in spite of comparable knob densities and diameters. We further found that the membrane bending modulus strongly depends on the hemoglobinopathetic variant, suggesting increased amounts of irreversibly oxidized hemichromes bound to membranes.

[1] Physical Chemistry of Biosystems, Heidelberg University, Im Neuenheimer Feld 253, 69120 Heidelberg, Germany. [2] Institute for Theoretical Physics and BioQuant-Center for Quantitative Biology, Philosophenweg 19, Heidelberg University, 69120 Heidelberg, Germany. [3] Department of Infectious Diseases, Parasitology, Universitätsklinikum Heidelberg, Im Neuenheimer Feld 324, 69120 Heidelberg, Germany. [4] Department of Hematology and Oncology, University Children's Hospital, Medical Faculty Mannheim, 68167 Mannheim, Germany. [5] Biomolecular ResearchCenter Pietro Annigoni, University of Ouagadougou, 01 BP 364 Ouagadougou, Burkina Faso. [6] Department of Mechanical Engineering, Osaka University, Suita, Osaka 565-0871, Japan. [7] Center for Integrative Medicine and Physics, Institute for Advanced Study, Kyoto University, Kyoto 606-8501, Japan. Correspondence and requests for materials should be addressed to U.S.S. (email: schwarz@thphys.uni-heidelberg.de) or to M.L. (email: michael.lanzer@med.uni-heidelberg.de) or to M.T. (email: tanaka@uni-heidelberg.de)

Linke et al., *Langmuir*
雑誌の特集号の表紙に選出



LANGMUIR
Cite This: Langmuir 2019, 35, 7538−7551
Article
pubs.acs.org/Langmuir

Dynamic Contact Guidance of Myoblasts by Feature Size and Reversible Switching of Substrate Topography: Orchestration of Cell Shape, Orientation, and Nematic Ordering of Actin Cytoskeletons

Philipp Linke,[†,‡] Ryo Suzuki,[†] Akihisa Yamamoto,[†] Masaki Nakahata,[§] Mineko Kengaku,[∥] Takahiro Fujiwara,[∥] Takuya Ohzono,*[,⊥] and Motomu Tanaka*[,†,‡]

[†]Center for Integrative Medicine and Physics, Institute for Advanced Study and [∥]Institute for Integrated Cell-Material Sciences, Kyoto University, 606-8501 Kyoto, Japan

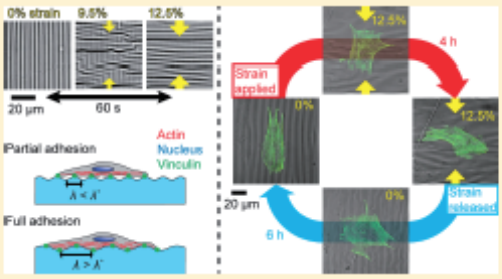
[‡]Physical Chemistry of Biosystems, Institute of Physical Chemistry, Heidelberg University, D69120 Heidelberg, Germany

[§]Department of Material Engineering Science, Graduate School of Engineering Science, Osaka University, 560-8531 Osaka, Japan

[⊥]Electronics and Photonics Research Institute, National Institute for Advanced Industrial Science and Technology, 305-8505 Tsukuba, Japan

Supporting Information

ABSTRACT: Biological cells in tissues alter their shapes, positions, and orientations in response to dynamic changes in their physical microenvironments. Here, we investigated the dynamic response of myoblast cells by fabricating substrates displaying microwrinkles that can reversibly change their direction within 60 s by axial compression and relaxation. To quantitatively assess the collective order of cells, we introduced the nematic order parameter of cells that takes not only the distribution of cell-wrinkle angles but also the degree of cell elongation into account. On the subcellular level, we also calculated the nematic order parameter of actin cytoskeletons that takes the rearrangement of actin filaments into consideration. The results obtained on substrates with different wrinkle wavelengths implied the presence of a characteristic wavelength beyond which the order parameters of both cells and actin cytoskeletons level off. Immunofluorescence labeling of vinculin showed that the focal adhesions were all concentrated on the peaks of wrinkles when the wavelength is below the characteristic value. On the other hand, we found focal adhesions on both the peaks and the troughs of wrinkles when the wavelength exceeds the characteristic level. The emergence of collective ordering of cytoskeletons and the adaptation of cell shapes and orientations were monitored by live cell imaging after the seeding of cells from suspensions. After the cells had reached the steady state, the orientation of wrinkles was abruptly changed by 90°. The dynamic response of myoblasts to the drastic change in surface topography was monitored, demonstrating the coordination of the shape and orientation of cells and the nematic ordering of actin cytoskeletons. The "dynamic" substrates established in this study can be used as a powerful tool in mechanobiology that helps us understand how cytoskeletons, cells, and cell ensembles respond to dynamic contact guidance cues.



INTRODUCTION

Mounting evidence suggests that biological cells not only transduce chemical signals from the surrounding environment but also adapt their shapes and functions to the physical microenvironment, such as mechanical properties of extracellular matrixes (ECMs).[1−3] For example, the mechanosensing of stem cells has drawn increasing attention due to its crucial role in the maintenance of stem cell functions and the regulation of lineage-specific differentiation.[4−8] ECMs often show highly anisotropic topography that influences the morphology, directional order, and migration behavior of cells, which is called contact guidance.[9−11] For instance, fibrous ECMs made out of collagen type I play major roles in guiding the alignment and migration of various cells.[12,13] One of the straightforward ways to model contact guidance in vitro is to fabricate two-dimensional substrates displaying anisotropic patterns possessing different biochemical functions[14−17] or mechanical properties.[18−20] As an alternative strategy, substrates displaying parallelly aligned wrinkles, ridges, and

Special Issue: Interfaces and Biology 1: Mechanobiology and Cryobiology

Received: September 1, 2018
Revised: October 29, 2018
Published: October 30, 2018

DOI: 10.1021/acs.langmuir.8b02972
Langmuir 2019, 35, 7538−7551

Langmuir 特集号の Preface を
Guest Editor として執筆

LANGMUIR Cite This: *Langmuir* 2019, 35, 7333−7334 Preface pubs.acs.org/Langmuir

Preface to the Interfaces and Biology 1: Mechanobiology Special Issue

Ideas that forces can regulate tissue development emerged in the late 1800s from observations by Wolff on the adaptation of bone tissue to mechanical stress,[1] corroborated by Roux[2] and Thompson[3] in their studies of embryonic development. Tools to test these hypotheses did not exist until the early 21st century when it became possible to measure and to manipulate physical forces in living cell. Mechanobiology was "rediscovered". Nowadays, there is ample evidence that most cells can sense the mechanical properties of their environment and that mechanical forces modulate biological processes in cells. This special issue of *Langmuir* is a testimony to the vibrancy of this field, especially from the viewpoint of interfacial phenomena.

In this issue, Janmey and colleagues discuss how the machinery that drives cellular processes, such as motility, division, and differentiation, changes in response to signals that originate on interfaces within cells or between cells and the surrounding matrix.[4] Tanaka et al. report that cells cultured on dynamic substrates orchestrate the dynamics through changes in their shape and cytoskeletal order.[5] Kidoaki and Moriyama determine the critical stiffness gradient in a cell culture matrix necessary to induce cellular durotaxis.[6] Using micro- and nanopillar arrays as cell culture substrates, Ding and colleagues investigate how the topography of the substrate affects the size of the cell nucleus.[7] Atomic force microscopy (AFM) coupled with advanced computational techniques allow Stadler et al. to gain new insights into the biomechanical heterogeneity of living cells.[8] Liu et al. applied magnetic AFM to reveal the evolution of biofilms formed on substrates of different stiffness.[9] Merkel et al. monitor how an applied cyclic strain affects neuronal outgrowth,[10] Sokabe et al. observe that cell adhesion proteins accumulate in cells upon application of a tensile load on actin,[11] while Tay et al. describe the mechanoregulation of a cancer-associated fibroblast phenotype within 3D hydrogel networks.[12]

The importance of membranes that define the interface between cytoplasmic and exoplasmic spaces is highlighted in several articles collected in this issue. For instance, on the basis of an all-atom molecular dynamics study Sokabe et al. demonstrate that several biophysical mechanisms depend on the membrane thickness.[13] Zhang et al. synthesized a π-conjugation-based rigid molecule for plasma membrane insertion to regulate the cancer cell membrane permeability.[14] Okamoto and Tokunou observed the mechanomodulation of cofactor alignments in a multiheme membrane protein complex, altering its binding affinity to minerals.[15]

In vivo, cells are tightly connected to each other via cell−cell adhesive junctions that act as mechanosensing complexes in multicellular architectures. These complexes tend to respond collectively to mechanical cues. Casademunt and colleagues report that the wetting transition from a 3D cell aggregate to a cell monolayer is affected by the substrate stiffness,[16] while Winnik et al. observe that nanoparticles reduce the extent of spreading of 3D cell aggregates on a substrate.[17] Using photoactivable hydrogels, Nakanishi et al. assess the interplay of chemical, mechanical, and topographical regulation during the collective migration of cells.[18]

We hope that this *Langmuir* issue, which stresses the importance of interfaces and surfaces in mechanobiology, will entice biologists and surface scientists to work together in a quest to resolve the interrelations between mechanical cues and cellular behavior for isolated single cells and ensembles of cells found in connective tissues. We thank the authors and reviewers who contributed to this issue, the *Langmuir* editorial office, and the staff from ACS Publications for their assistance and support during the preparation and publication of this special issue.

Motomu Tanaka, Guest Editor
Heidelberg University, Heidelberg, Germany
Kyoto University, Kyoto, Japan
Francoise Brochard-Wyart, Guest Editor
Institut Curie, Paris, France
Francoise M. Winnik, Editor-in-Chief
University of Helsinki, Helsinki, Finland
National Institute for Materials Science, Tsukuba, Japan
Atsushi Takahara, Senior Editor
Kyushu University, Fukuoka, Japan

AUTHOR INFORMATION

ORCID
Motomu Tanaka: 0000-0003-3663-9554
Francoise M. Winnik: 0000-0001-5844-6687
Atsushi Takahara: 0000-0002-0584-1525

Notes

Views expressed in this editorial are those of the authors and not necessarily the views of the ACS.

REFERENCES

(1) Wolff, J. *The Law of Bone Remodelling*; Springer-Verlag: Berlin, 1986.
(2) Roux, W. *Gesammelte Abhandlungen über Entwicklungsmechanick*; W. Engelmann: Leipzig, 1895.
(3) Thompson, D. W. *On Growth and Form*; Cambridge University Press: Cambridge, U.K., 1917.
(4) Leiphart, R. J.; Chen, D.; Peredo, A. P.; Loneker, A. E.; Janmey, P. A. Mechanosensing at Cellular Interfaces. *Langmuir* **2018**, DOI: 10.1021/acs.langmuir.8b02841.
(5) Linke, P.; Suzuki, R.; Yamamoto, A.; Nakahata, M.; Kengaku, M.; Fujiwara, T.; Ohzono, T.; Tanaka, M. Dynamic Contact Guidance of Myoblasts by Feature Size and Reversible Switching of Substrate Topography: Orchestration of Cell Shape, Orientation, and

Special Issue: Interfaces and Biology 1: Mechanobiology and Cryobiology
Published: June 11, 2019

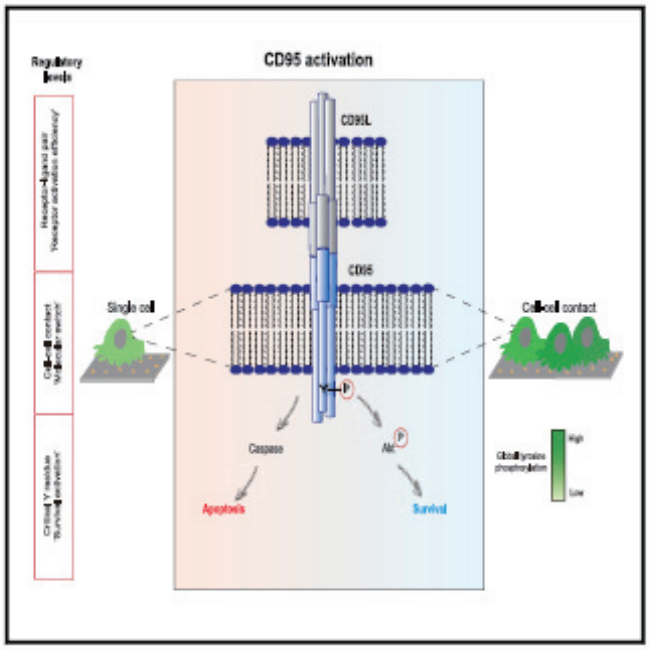
   DOI: 10.1021/acs.langmuir.9b01206
Langmuir 2019, 35, 7333−7334

Article

Cell Reports

3D Cellular Architecture Modulates Tyrosine Kinase Activity, Thereby Switching CD95-Mediated Apoptosis to Survival

Graphical Abstract



Authors

Gülce S. Gülcüler Balta, Cornelia Monzel, Susanne Kleber, ..., Yvonne Samstag, Motomu Tanaka, Ana Martin-Villalba

Correspondence

tanaka@uni-heidelberg.de (M.T.), a.martin-villalba@dkfz-heidelberg.de (A.M.-V.)

In Brief

Gülcüler Balta et al. show that CD95 receptor activation is determined through the presentation of its ligand at a certain intermolecular distance. The type of signaling triggered by CD95 is, however, decided by the cellular environment. CD95 triggers survival in cancer cells in contact with other cells and death in isolated ones.

Highlights

- Specific intermolecular spacing of CD95Ligand induces efficient CD95 clustering
- CD95 clustering triggers apoptotic and survival signaling
- CD95 signals survival in the presence of cell-cell contact
- Cell-cell contact increases levels of phosphotyrosinated proteins including CD95

Gülcüler Balta et al., 2019, Cell Reports 29, 2295–2306
November 19, 2019 © 2019 The Authors.
https://doi.org/10.1016/j.celrep.2019.10.054

CellPress

www.nature.com/scientificreports

SCIENTIFIC REPORTS
natureresearch

OPEN

New Class of Crosslinker-Free Nanofiber Biomaterials from *Hydra* Nematocyst Proteins

Theresa Bentele[1,6], Federico Amadei[2,6], Esther Kimmle[2], Mariam Veschgini[2], Philipp Linke[2], Mariana Sontag-González[2,5], Jutta Tennigkeit[1], Anthony D. Ho[3,4], Suat Özbek[1*] & Motomu Tanaka[2,4*]

Nematocysts, the stinging organelles of cnidarians, have remarkable mechanical properties. *Hydra* nematocyst capsules undergo volume changes of 50% during their explosive exocytosis and withstand osmotic pressures of beyond 100 bar. Recently, two novel protein components building up the nematocyst capsule wall in *Hydra* were identified. The cnidarian proline-rich protein 1 (CPP-1) characterized by a "rigid" polyproline motif and the elastic Cnidoin possessing a silk-like domain were shown to be part of the capsule structure via short cysteine-rich domains that spontaneously crosslink the proteins via disulfide bonds. In this study, recombinant Cnidoin and CPP-1 are expressed in *E. coli* and the elastic modulus of spontaneously crosslinked bulk proteins is compared with that of isolated nematocysts. For the fabrication of uniform protein nanofibers by electrospinning, the preparative conditions are systematically optimized. Both fibers remain stable even after rigorous washing and immersion into bulk water owing to the simultaneous crosslinking of cysteine-rich domains. This makes our nanofibers clearly different from other protein nanofibers that are not stable without chemical crosslinkers. Following the quantitative assessment of mechanical properties, the potential of Cnidoin and CPP-1 nanofibers is examined towards the maintenance of human mesenchymal stem cells.

Nematocysts are harpoon-like organelles characteristic of the cnidarian phylum[1]. The development of *Hydra* nematocysts, which comprise four different types, occurs in the body column of the polyps in specialized cells, called nematocytes. After maturation, nematocytes migrate towards the tentacles and are mounted in so called "battery cells" (Fig. 1a)[2]. Nematocysts consist of a hollow capsule body, to which an inverted tubule is attached that in the case of the large "stenothele" type of nematocyst has a stylet used to perforate the prey's integument and allow injection of peptide toxins to paralyze the prey (Fig. 1b)[3–6].

As biomaterials, one of the unique characteristics of nematocysts is the outstanding mechanical toughness of the capsule wall structure. Maturation of the capsule involves "wall hardening" and build-up of an internal osmotic pressure of about 150 bar. After discharge, the elastically stretched nematocyst capsule shrinks to 50% of its original volume signifying the release of kinetic energy during the explosive exocytosis[7]. Actually, the nematocyst discharge is one of the fastest events in the animal kingdom, generating an acceleration of more than 5 million g[8,9]. The nematocyst capsule comprises protein complexes crosslinked by intermolecular disulfide bonds between cysteine-rich domains (CRDs), which are found at both C- and N-termini of various nematocyst proteins (Fig. 1c)[10]. Among those, minicollagens are major structural proteins possessing short collagen sequences (Gly-X-Y) flanked by polyproline stretches and terminal CRDs[11]. Previous data on nematocyst proteins containing CRDs have demonstrated that these are tightly integrated due to disulfide reshuffling into the capsule polymer and can only be released as monomers by reducing agents[7,12–15]. We have recently demonstrated that the CRD can be used as a versatile crosslinker module to create linear or branched polymers from diverse proteins[10].

[1]Centre for Organismal Studies, Department of Molecular Evolution and Genomics, Heidelberg University, 69120, Heidelberg, Germany. [2]Physical Chemistry of Biosystems, Institute of Physical Chemistry, Heidelberg University, 69120, Heidelberg, Germany. [3]Department of Medicine V, University of Heidelberg, 69120, Heidelberg, Germany. [4]Center for Integrative Medicine and Physics, Institute for Advanced Study, Kyoto University, 606-8501, Kyoto, Japan. [5]Present address: School of Earth and Environmental Sciences, Science Medicine and Health, University of Wollongong, NSW 2522, Wollongong, Australia. [6]These authors contributed equally: Theresa Bentele and Federico Amadei. *email: suat.oezbek@cos.uni-heidelberg.de; tanaka@uni-heidelberg.de

LANGMUIR
Cite This: Langmuir 2019, 35, 529−537
Article
pubs.acs.org/Langmuir

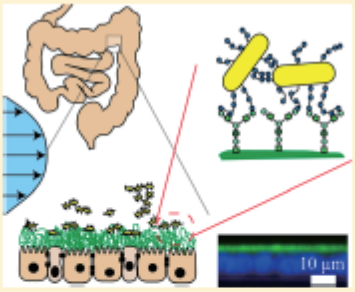
Shear-Enhanced Dynamic Adhesion of *Lactobacillus rhamnosus* GG on Intestinal Epithelia: Correlative Effect of Protein Expression and Interface Mechanics

Maryam Eshrati,[†,#] Federico Amadei,[†,#] Simone Staffer,[‡] Wolfgang Stremmel,[‡,§] and Motomu Tanaka*[,†,∥]

[†]Physical Chemistry of Biosystems, Institute of Physical Chemistry, Heidelberg University, D69120 Heidelberg, Germany
[‡]Internal Medicine IV, University Hospital Heidelberg, D69120 Heidelberg, Germany
[§]Medical Center Baden-Baden, D76530 Baden-Baden, Germany
[∥]Center for Integrative Medicine and Physics, Institute for Advanced Study, Kyoto University, 606-8501 Kyoto, Japan

Supporting Information

ABSTRACT: The oral uptake of probiotic microorganisms as food additives is one widely used strategy to sustain and improve the homeostasis of intestinal microbiota that protect the intestinal epithelia from attack by pathogenic bacteria. Once delivered to the ileum and colon, probiotics must adhere and form colonies on mucus that coats the surface of intestinal epithelial cells. Although an increasing amount of knowledge about the genetic and molecular level mechanisms of probiotics−mucus interactions has been accumulated, little is known about the physicochemical aspects of probiotics−mucus interactions under physiological shear in intestines. In this study, we established well-defined models of intestinal epithelial cell monolayers based on two major constituents of gut epithelia, enterocytes and goblet cells. First, the formation of a polarized cell monolayer sealed by tight junctions was monitored by transepithelial electrical resistance over time. The establishment of tight junctions and secretion of mucus proteins (mucin) was confirmed by immunofluorescence staining. In the next step, we measured the elasticity of cell monolayer surfaces by indentation using particle-assisted atomic force microscopy. The effective elastic modulus of goblet cell-like cells was 30 times smaller compared to that of enterocyte-like cells, which can be attributed to the secretion of a 3 μm thick mucin layer. As probiotics, we used *Lactobacillus rhamnosus* GG (LGG), which is one of the most widely used strains as food additives. To investigate the dynamic adhesion of LGG to the intestine model surface, we transferred the epithelial cell monolayer into a microfluidic chamber. A distinct difference in dynamic adhesion between two cell types was observed, which could be attributed to the difference in the mucin expression amount. Remarkably, we found that the dynamic LGG adhesion is enhanced by the increase in shear stress, showing a maximum binding efficiency at 0.3 Pa. Finally, we examined the persistence of LGG adhesion by a stepwise increase in the shear stress exerted on adherent LGG, demonstrating that LGG could withstand high shear stress even beyond that of physiological stress. The obtained results present a large potential to quantitatively understand the influence of engineered foods and probiotics on the homeostasis of microbiota on the surface of intestinal epithelia.

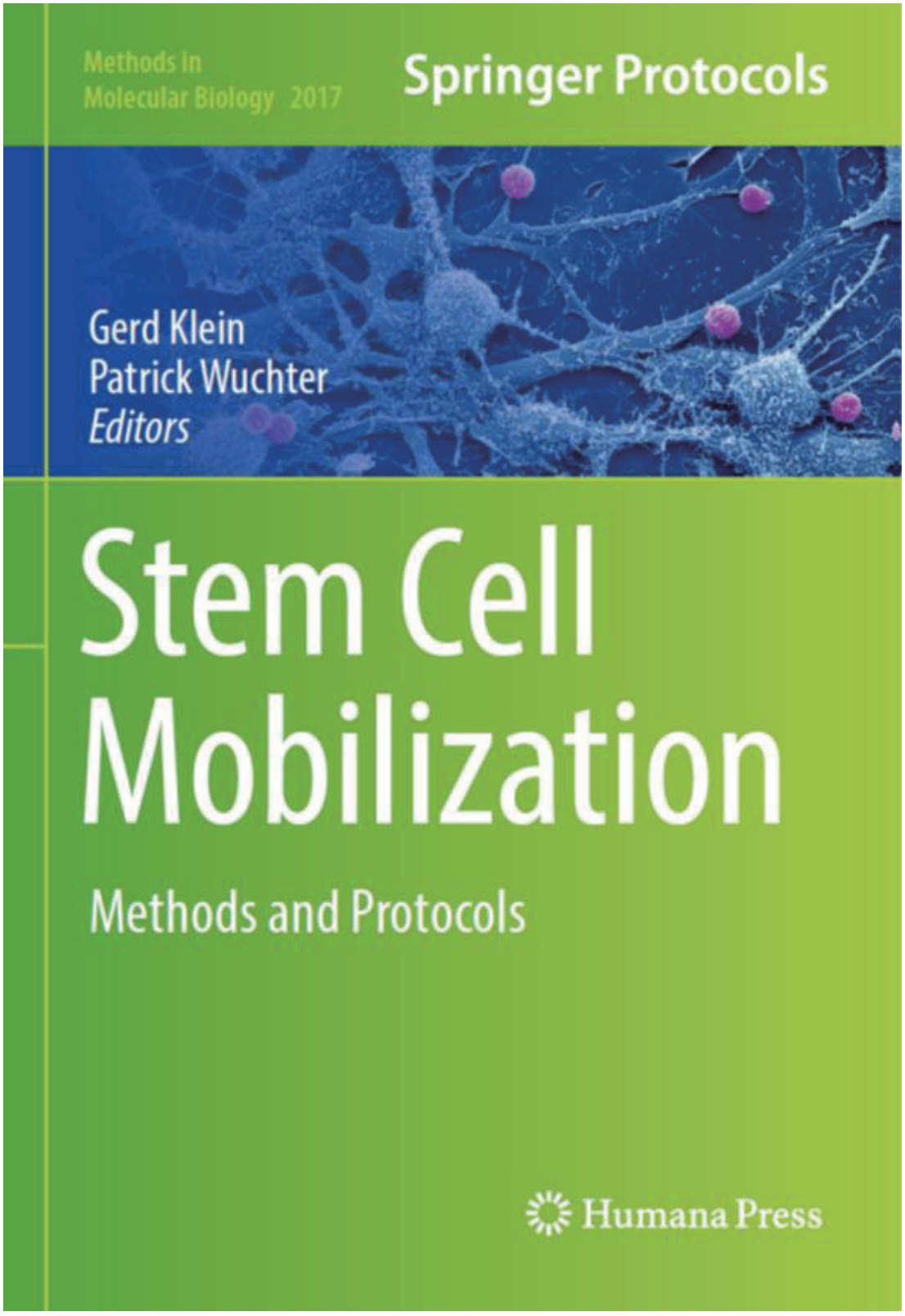


■ INTRODUCTION

The human gastrointestinal tract is the largest organ in the body formed by a single layer of intestinal epithelial cells, possessing a surface area of 300 m^2.[1] The surface of gastrointestinal epithelia is exposed to an extremely high bacterial load, ranging from thousands to trillions of bacteria per milliliter of luminal contents from stomach to colon.[2] In intestinal epithelia, individual cells are connected by tight junctions and anchored on the basement membrane by hemidesmosomes.[3] The most abundant epithelial cells throughout the intestine are enterocytes serving as the primary surface for nutrient absorption, whose apical surface is covered with microvilli.[4] Enterocytes are interspersed with goblet cells,[5] which secrete high molecular weight glycoproteins, mucins (≈2 × 10^6 Da).[5] Among different mucin proteins, mucin 2 (MUC2) is a major constituent of mucus layers that builds up a protective barrier on the epithelial surfaces against pathogens and toxins.[3,4,6] It is notable that mucin alone is not able to protect intestinal epithelia against the bacterial invasion. The layer of phospholipids serves as a protective barrier, among which phosphatidylcholine (PC) and lyso-phosphatidylcholine (lyso-PC) account for more than 90%.[7] It has been reported

Received: August 28, 2018
Revised: November 8, 2018
Published: December 19, 2018

DOI: 10.1021/acs.langmuir.8b02931
Langmuir 2019, 35, 529−537


Methods in
Molecular Biology 2017
Springer Protocols
Gerd Klein
Patrick Wuchter
Editors
Stem Cell
Mobilization
Methods and Protocols
Humana Press

Chapter 2

In Vitro Dynamic Phenotyping for Testing Novel Mobilizing Agents

Motomu Tanaka

Abstract

A new method to quantify the influence of mobilization agents on the dynamics of human hematopoietic stem and progenitor cells (HSPC) is introduced. Different from the microscopy-based high-content screening relying on multiple staining, machine learning, and molecular-level perturbation, the proposed method sheds light on the "dynamics" of HSPC in the presence of extrinsic factors, including SDF1α and mobilization agents. A well-defined model of the bone marrow niche is fabricated by the deposition of planar lipid membranes on glass slides (called supported membranes) displaying ligand molecules at precisely controlled surface densities. The dynamics of human HSPC, $CD34^+$ cells from umbilical cord blood or peripheral blood, are monitored by time-lapse, live cell imaging with a standard phase-contrast microscopy or a specially designed microinterferometry in the absence or presence of mobilization agents. After extracting the contour of each cell, one can analyze the dynamics of cell "shapes" step-by-step, yielding various levels of information ranging from the principal mode of deformation, the persistence of deformation patterns, and the energy consumption by HSPC in the absence and presence of mobilization agents. Moreover, by tracking the migration trajectories of HSPC, one can gain insight how mobilization agents influence the "motion" of HSPC. As these readouts can be connected to a theoretical model, this strategy enables one to classify the influence of not only mobilization agents but also target-specific inhibitors or other treatments in quantitative indices.

Key words Supported membrane, Cell adhesion, Cell migration, Theoretical model

1 Introduction

The dormancy of the most primitive hematopoietic stem and progenitor cells (HSPC) is maintained by the bone marrow niche via several ligand-receptor interactions. Mounting evidence suggests that mesenchymal stem or stromal cells (MSC) play key roles in sustaining the niche functions [1, 2]. One of the important molecular axes is the homophilic interaction between N-cadherin molecules expressed on both HSPC and MSC, which supports the long-term maintenance of the primitive HSPC pool in the bone marrow niche [3–5]. On the other hand, CXCR4 expressed on HSPC specifically recognizes stromal cell-derived factor 1α (SDF1α or

Gerd Klein and Patrick Wuchter (eds.), *Stem Cell Mobilization: Methods and Protocols*, Methods in Molecular Biology, vol. 2017, https://doi.org/10.1007/978-1-4939-9574-5_2,

ChemPubSoc Europe

DOI: 10.1002/cphc.201900316

CHEMPHYSCHEM Articles

Check for updates

Influence of Perfluorohexane-Enriched Atmosphere on Viscoelasticity and Structural Order of Self-Assembled Semifluorinated Alkanes at the Air-Water Interface

Salomé Mielke,[a] Wasim Abuillan,[a, b] Mariam Veschgini,[a] Xianhe Liu,[c] Oleg Konovalov,[d] Marie Pierre Krafft,*[c] and Motomu Tanaka*[a, e]

Abstract: Semifluorinated alkanes *FnHm* self-assemble into nanometer-sized surface micelles at the air-water interface. In this study, we investigated how an atmosphere enriched with perfluorohexane (PFH) influences the interfacial viscoelasticity and structural order of a monolayer of *FnHm* by the combination of dilational rheology and grazing-incidence small-angle X-ray scattering (GISAXS). The monolayers behaved predominantly elastic which can be attributed to the strong dipole repulsions of the surface domains. Enrichment of the atmosphere with PFH lead to an increase of the compressibility and a decrease of the elastic modulus without altering the structural ordering of the *FnHm* molecules into highly correlated nanodomains, suggesting the adsorption of PFH molecules to the free spaces between the domains. The capability of *FnHm* domains to retain the structural integrity in the presence of PFH gas is promising for the fabrication of stable microbubbles for sonographic imaging.

1. Introduction

Perfluorocarbon compounds have been draining increased attention because of their unique physical and chemical properties.[1–3] The strong C–F bond makes fluorocarbon compounds very stable compared to hydrocarbon compounds. The low polarizability of fluorine atoms is the reason for very low cohesive forces between fluorocarbon segments. Moreover, perfluorocarbons are known to be inert to biological systems, which allows for a diversity of biomedical applications.[1–7]

The weak intermolecular cohesion is one of the unique physical characteristics of fluorocarbons. It makes the solubility of respiratory gases very high.[2] Therefore, perfluorocarbons enriched with oxygen could help patients with acute respiratory distress syndrome (ARDS) continue breathing.[8,9] They have also potential for lung surfactant replacement.[10–12] To date, several studies have shown how fluorocarbons interact with interfaces. For example, fluorocarbon gases reduce the tension at the air/water interface by 2–5 mN/m, suggesting their adsorption.[13] More recently, we reported that perfluorohexane (PFH) gas facilitates the displacement of albumin by phospholipids,[14] suggesting that PFH gas can potentially be used to improve the therapeutic treatment of ARDS patients as it allows phospholipids to reach the alveolar surface by removing the serum proteins.

Another unique characteristic of PFH is its extremely low water solubility, (2.7×10^{-4} mol m^{-3} for perfluorohexane), which is two orders of magnitude lower than the water solubility of nitrogen or oxygen (0.48 mol/m^3).[15,16] This property makes microbubbles of PFH vapor attractive for ultrasonic image diagnostics.[17] In general, microbubbles used in sonographic imaging suffer from the collapse of bubbles due to the dissolution of standard gases into water.[17,18] Owing to their extremely poor water solubility, PFH gases are expected to significantly increase the lifetime of microbubbles.[19,20] However, the microbubbles of perfluorocarbon gas alone are not stable enough in physiological fluids. They need to be further stabilized by coating the vapor/water interface by surfactant molecules.[17] PFH was found to exert a co-surfactant role with regards to phospholipids forming monolayers at the gas/water interface.[21]

Promising candidates as bubble shell components are semifluorinated alkanes $C_nF_{2n+1}C_mH_{2m+1}$ (*FnHm* diblocks). Previous studies showed their capability to stabilize phospholipid vesicles[22,23] as well as fluorocarbon-in-water emulsions.[24] At the air/water interface, *FnHm* molecules form highly monodisperse domains with the size of 28–34 nm.[25] Recently, we employed grazing incidence small angle X-ray scattering (GISAXS)[26–28] and demonstrated that these compounds spontaneously self-assemble into hemispherical domains taking hex-

[a] S. Mielke, Dr. W. Abuillan, Dr. M. Veschgini, Prof. Dr. M. Tanaka
Physical Chemistry of Biosystems, Institute of Physical Chemistry
Heidelberg University, D-69120 Heidelberg (Germany)
E-mail: tanaka@uni-heidelberg.de
[b] Dr. W. Abuillan
Institute of Industrial Science, The University of Tokyo
153-0041 Tokyo (Japan)
[c] Dr. X. Liu, Prof. Dr. M. P. Krafft
Institut Charles Sadron (CNRS UPR 22)
University of Strasbourg, 23 rue du Loess
F-67034 Strasbourg Cedex (France)
E-mail: krafft@unistra.fr
[d] Dr. O. Konovalov
European Synchrotron Radiation Facility (ESRF)
Grenoble Cedex 9 38053 (France)
[e] Prof. Dr. M. Tanaka
Center for Integrative Medicine and Physics
Institute for Advanced Study, Kyoto University
606-8501 Kyoto (Japan)

Supporting information for this article is available on the WWW under https://doi.org/10.1002/cphc.201900316

Neuroscience Research 142 (2019) 38–48

Contents lists available at ScienceDirect

Neuroscience Research

journal homepage: www.elsevier.com/locate/neures

Local traction force in the proximal leading process triggers nuclear translocation during neuronal migration

Hiroki Umeshima[a,*], Ken-ichi Nomura[c], Shuhei Yoshikawa[c], Marcel Hörning[a,1], Motomu Tanaka[a,e], Shinya Sakuma[d], Fumihito Arai[d], Makoto Kaneko[c], Mineko Kengaku[a,b]

[a] Institute for Integrated Cell-Material Sciences (WPI-iCeMS), Kyoto University, Yoshida-Honmachi, Sakyo-ku, Kyoto, 606-8501, Japan
[b] Graduate School of Biostudies, Kyoto University, Yoshida-Honmachi, Sakyo-ku, Kyoto, 606-8501, Japan
[c] Graduate School of Engineering, Osaka University 2-1, Yamadaoka, Suita, Osaka, 565-0871, Japan
[d] Dept. of Micro-Nano Mechanical Science & Engineering, Nagoya University, Furo-cho, Chikusa-ku, Nagoya, 464-8603, Japan
[e] Physical Chemistry of Biosystems, University of Heidelberg, D69120, Heidelberg, Germany

ARTICLE INFO

Article history:
Received 22 February 2018
Received in revised form 31 March 2018
Accepted 2 April 2018
Available online 5 April 2018

Keywords:
Neuronal migration
Nucleus
Traction force
Actin
Myosin-II
Swelling
Nesprin

ABSTRACT

Somal translocation in long bipolar neurons is regulated by actomyosin contractile forces, yet the precise spatiotemporal sites of force generation are unknown. Here we investigate the force dynamics generated during somal translocation using traction force microscopy. Neurons with a short leading process generated a traction force in the growth cone and counteracting forces in the leading and trailing processes. In contrast, neurons with a long leading process generated a force dipole with opposing traction forces in the proximal leading process during nuclear translocation. Transient accumulation of actin filaments was observed at the dipole center of the two opposing forces, which was abolished by inhibition of myosin II activity. A swelling in the leading process emerged and generated a traction force that pulled the nucleus when nuclear translocation was physically hampered. The traction force in the leading process swelling was uncoupled from somal translocation in neurons expressing a dominant negative mutant of the KASH protein, which disrupts the interaction between cytoskeletal components and the nuclear envelope. Our results suggest that the leading process is the site of generation of actomyosin-dependent traction force in long bipolar neurons, and that the traction force is transmitted to the nucleus via KASH proteins.

1. Introduction

Neuronal migration is a fundamental step of mammalian brain development. Post-mitotic neurons, arising from neural progenitor cells in the proliferative zone, extend a leading process toward their migrating direction and translocate the nucleus and other organelles into the leading process until they reach their final destination in the brain (Cooper, 2013). Defects in neuronal migration thus cause brain malformation and severe neurological disorders (Gleeson and Walsh, 2000). Extensive studies have implicated a synergistic interplay between the actin and microtubule cytoskeletons in nuclear translocation as well as neurite outgrowth during neuronal migration. It has been reported that the centrosome is positioned in a transient cytoplasmic swelling or dilation in the proximal leading process before nuclear translocation, where it organizes polarized arrays of peri-nuclear microtubules (Tsai et al., 2007). The minus-end directed motor dynein then transports the nucleus along the microtubule arrays toward the centrosome in the leading process (Shu et al., 2004; Tanaka et al., 2004). On the other hand, contractile forces exerted by actin and non-muscle myosin-II are also indispensable for nuclear translocation (Bellion et al., 2005; He et al., 2010; Martini and Valdeolmillos, 2010; Schaar and McConnell, 2005; Solecki et al., 2009). However, the precise sites of actomyosin force generation remain controversial, and may drive a pulling force at the nuclear front or a pushing force at the cell rear depending on cell type and context.

Generally, actomyosin forces are transmitted to the underlying substrate via cell adhesions, and are converted to traction forces that drive cell movement (Case and Waterman, 2015; Munevar et al., 2001). Traction force microscopy (TFM) allows for quantitative assessment of the direction and extent of cellular forces transmitted to the substrate. Recent studies using TFM have

* Corresponding author.
E-mail address: umeshima@icems.kyoto-u.ac.jp (H. Umeshima).
[1] Present address: Institute of Biomaterials and Biomolecular Systems (IBBS), University of Stuttgart, Stuttgart, 70569, Germany.

https://doi.org/10.1016/j.neures.2018.04.001
0168-0102/

Received: 29 November 2018 | Revised and accepted: 8 March 2019
DOI: 10.1002/btpr.2806

RESEARCH ARTICLE

BIOTECHNOLOGY PROGRESS

Hybrid coating of alginate microbeads based on protein-biopolymer multilayers for encapsulation of probiotics

Cigdem Yucel Falco[1] | Federico Amadei[2] | Surender K. Dhayal[3] | Marité Cárdenas[4] | Motomu Tanaka[2] | Jens Risbo[1]

[1]University of Copenhagen, Department of Food Science, Copenhagen, Denmark
[2]Heidelberg University, Institute for Physical Chemistry, Heidelberg, Germany
[3]Research & Development, Chr. Hansen A/S, Hoersholm, Denmark
[4]Biomedical Laboratory Science and Biofilm Research Center for Biointerfaces, Faculty of Health and Society, Malmö University, Malmö, Sweden

Correspondence
Jens Risbo, Department of Food Science, University of Copenhagen, Rolighedsvej 30, DK-1958, Copenhagen, Denmark.
Email: jri@food.ku.dk

Funding Information
People Programme (Marie Curie Actions) of the European Union's Seventh Framework Programme FP7/2007-2013/, Grant/Award Number: 606713

Abstract

A hybrid coating based on multilayers of proteins and biopolymers was developed to enhance the protection performance of alginate microbeads against acidic conditions for delivery of probiotics (*Lactobacillus rhamnosus* GG). Zeta potential measurements and quartz crystal microbalance with dissipation confirmed layer-by-layer deposition of protein-polymer layers. The stability of protein-based coatings during simulated gastric fluid (SGF) treatment was monitored by microscopy. Protein-coated microbeads were partially dismantled, whereas polymer-coated microbeads were intact after a sequential treatment in simulated gastric and intestinal fluids. This suggests that hybrid formulation offers an advantage over the coatings based on biopolymer multilayers in terms of better release of bacteria. Uncoated alginate microbeads completely dissolved and could not protect bacteria after SGF treatment whereas microbeads with hybrid coating showed increased physical stability and a modest decrease of culturability of 3.8 log units. Therefore, this work provides a concept for future protein-based hybrid coatings for bacterial delivery systems.

KEYWORDS
alginate, chitosan, lactoferrin, layer-by-layer, microencapsulation of probiotics

1 | INTRODUCTION

The encapsulation of probiotics has been a subject of a growing interest in the scientific and commercial platforms in the past decade because of the vulnerability of probiotic bacteria to low pH of stomach[1] in the absence of a successful delivery system.

Alginate-based microbeads are one of the most studied encapsulation systems for delivery of probiotics[2–7] due to the ability of alginate to form hydrogel by calcium crosslinking at mild conditions.[8] However, the alginate hydrogel matrix is not physically stable, especially in acidic pH of the stomach due to protonation of carboxylic groups of alginate below the pKa of alginate (3.4–3.7)[9] and subsequent matrix dissolution. Moreover, it can be destabilized easily with chelators such as phosphate, lactate, and citrate as well as non-gelling cations such as sodium and magnesium ions which are present in the human body.[10]

To improve the stability of alginate particles, one approach could be forming a protective and stable membrane on the surface of alginate microbeads via the layer-by-layer (LbL) technique using natural colloidal materials. LbL offers tailorable properties of the end coating such as thickness, structure, and surface properties.[11] Therefore, such surface modification can reduce the porosity of alginate microbeads, and limit the permeation of acids into microbeads during the gastric passage.[12]

The vast majority of studies investigated coating alginate beads with chitosan[1,13–21] due to its cationic nature at pH below its pKa around 6.5.[22] However, chitosan is not a food approved ingredient by EU, and has an antimicrobial effect which is a matter of debate.[23,24]

In the context of LbL coatings of bacteria containing alginate beads, milk proteins with varying isoelectric point (pI) could also be considered. Lactoferrin can be considered as an alternative to chitosan due to its net positive surface charge at neutral pH (pI is around 8–9[25,26]). Sodium

ChemPubSoc Europe

DOI: 10.1002/cphc.201800967

CHEMPHYSCHEM Articles

Check for updates

Long-Range Lateral Correlation between Self-Assembled Domains of Fluorocarbon-Hydrocarbon Tetrablocks by Quantitative GISAXS**

Wasim Abuillan+,[a, e] Mariam Veschgini+,[a] Salomé Mielke,[a] Akihisa Yamamoto,[b] Xianhe Liu,[c] Oleg Konovalov,[d] Marie Pierre Krafft,*[c] and Motomu Tanaka*[a, b]

The structure and lateral correlation of fluorocarbon-hydrocarbon tetrablock di(*F*10*Hm*) domains at the air/water interface have been determined by quantitative analysis of grazing incidence small-angle X-ray scattering (GISAXS) data. The measured GISAXS signals can be well represented by the full calculation of the form and structure factors. The form factor suggests that di(*F*10*Hm*) domains take a hemiellipsoid shape. Both major and minor axes of the hemiellipsoids monotonically increased in response to the elongation of the hydrocarbon blocks, which can be explained by the concominant increase in van der Waals interaction. The structure factor calculated from the GISAXS signals suggests that the domains take an orthorhombic lattice. Remarkably, the lateral correlation can reach over a distance that is more than 14 times longer than the distance to the nearest neighbors. Our data suggest that quantitative GISAXS enables the optimal design of mesoscopic self-assemblies at the air/water interface by fine-tuning of the structures of molecular building blocks.

1. Introduction

Spontaneous formation of hierarchical patterns by self-assembly of small molecules is one of the key strategies that biological systems utilize.[1,2] An increasing number of studies have been conducted to understand the basic principles of self-assembly, since the controlled assembly and positioning of nanoscale objects is highly relevant in supramolecular chemistry[3,4] and nanotechnology.[5–7] In particular, the self-assembly at the air/water or oil/water interface enables to confine the building blocks and hence the patterns in a two-dimensional space. Mouting evidence has indicated that the shape, size and uniformity of self-assembled patterns strongly depend on the chemical structures of molecular building blocks, such as low molecular weight surfactants[8,9] and amphiphilic block copolymers.[10,11]

Surfactants with perfluorocarbon blocks have been used to design new types of colloidal systems, targeting versatile medical applications.[12–14] Owing to the larger van der Waals radius of fluorine, 1.35 Å, perfluorocarbon chains form helices of six turns with larger cross-sectional area (~0.3 nm^2) compared to hydrocarbon chains (~0.2 nm^2). This results in a stiff, rod-like conformation that is distinctly different from the zigzag conformation taken by hydrocarbon chains.[15,16] As fluorine has a lower polarizability compared to hydrogen, the cohesion between fluorocarbon chains is weaker than the cohesion between hydrocarbon chains. Interestingly, fluoro- and hydrocarbon chains are very poorly miscible, although both chains are highly hydrophobic. It has been reported that the "diblocks", linearly connected fluoro- and hydrocarbon chains, form self-assembled micelles in both fluorocarbon and hydrocarbon solvents,[14,17,18] and forming a stable monolayer at the air/water interface.

A previous atomic force microscopy (AFM) study showed that *FnHm* monolayers transferred from the air/water interface onto solid substrates consist of highly monodisperse domains.[12,19,20] The grazing incidence small-angle X-ray scattering (GISAXS) yielded the lattice parameters of *FnHm* domains, denoting that 20 to 40 nm-large domains take a hexagonal lattice. The systematic dependence of the domain diameter on the block ratio between *Fn* and *Hm*[21–23] was corroborated by theoretical investigations.[24] However, the calculation of the lateral correlation distance between *FnHm* domains from the peak width might be erroneous, when each domain does not consist of a single crystallite. We overcame this problem by the quantitative calculation of structure and form factors. Our quantitative GISAXS analysis revealed that the correlation between *FnHm* domains can actually reach over a distance,

[a] Dr. W. Abuillan,+ Dr. M. Veschgini,+ S. Mielke, Prof. Dr. M. Tanaka
Physical Chemistry of Biosystems, Institute of Physical Chemistry, Heidelberg University, D-69120 Heidelberg (Germany)
E-mail: tanaka@uni-heidelberg.de
[b] Dr. A. Yamamoto, Prof. Dr. M. Tanaka
Center for Integrative Medicine and Physics, Institute for Advanced Study, Kyoto University, 606-8501 Kyoto (Japan)
[c] X. Liu, Prof. Dr. M. P. Krafft
Institut Charles Sadron (CNRS UPR 22)
University of Strasbourg, 23 rue du Loess
F-67034 Strasbourg Cedex (France)
E-mail: krafft@unistra.fr
[d] Dr. O. Konovalov
European Synchrotron Radiation Facility (ESRF)
Grenoble Cedex 9 38053 (France)
[e] Dr. W. Abuillan+
Current address: Institute of Industrial Science, The University of Tokyo, 153–0041 Tokyo (Japan)

[+] These Authors contributed equally to this work.

[**] GISAXS: Grazing Incidence Small-angle X-ray Scattering

Supporting information for this article is available on the WWW under https://doi.org/10.1002/cphc.201800967

nature COMMUNICATIONS

ARTICLE

https://doi.org/10.1038/s41467-018-08175-w OPEN

Controlling the shape of 3D microstructures by temperature and light

Marc Hippler[1,2], Eva Blasco[3], Jingyuan Qu[2,4], Motomu Tanaka[5,6], Christopher Barner-Kowollik[3,7], Martin Wegener[2,4] & Martin Bastmeyer[1,8]

Stimuli-responsive microstructures are critical to create adaptable systems in soft robotics and biosciences. For such applications, the materials must be compatible with aqueous environments and enable the manufacturing of three-dimensional structures. Poly(*N*-isopropylacrylamide) (pNIPAM) is a well-established polymer, exhibiting a substantial response to changes in temperature close to its lower critical solution temperature. To create complex actuation patterns, materials that react differently with respect to a stimulus are required. Here, we introduce functional three-dimensional hetero-microstructures based on pNIPAM. By variation of the local exposure dose in three-dimensional laser lithography, we demonstrate that the material parameters can be altered on demand in a single resist formulation. We explore this concept for sophisticated three-dimensional architectures with large-amplitude and complex responses. The experimental results are consistent with numerical calculations, able to predict the actuation response. Furthermore, a spatially controlled response is achieved by inducing a local temperature increase by two-photon absorption of focused light.

[1] Zoologisches Institut, Zell- und Neurobiologie, Karlsruhe Institute of Technology (KIT), Fritz-Haber-Weg 4, 76131 Karlsruhe, Germany. [2] Institut für Angewandte Physik, Karlsruhe Institute of Technology (KIT), Wolfgang-Gaede-Straße 1, 76131 Karlsruhe, Germany. [3] Macromolecular Architectures, Institut für Technische Chemie und Polymerchemie, Karlsruhe Institute of Technology (KIT), Engesserstrasse 18, 76128 Karlsruhe, Germany. [4] Institut für Nanotechnologie, Karlsruhe Institute of Technology (KIT), Hermann-von-Helmholtz-Platz 1, 76344 Eggenstein-Leopoldshafen, Germany. [5] Physical Chemistry of Biosystems, Institute of Physical Chemistry, Heidelberg University, Im Neuenheimer Feld 253, 69120 Heidelberg, Germany. [6] Institute for Integrated Cell-Materials Science (WPI iCeMS), Kyoto University, Kyoto 606-8501, Japan. [7] School of Chemistry, Physics and Mechanical Engineering, Queensland University of Technology (QUT), 2 George Street, Brisbane, QLD 4000, Australia. [8] Institut für Funktionelle Grenzflächen, Karlsruhe Institute of Technology (KIT), Hermann-von-Helmholtz-Platz 1, 76344 Eggenstein-Leopoldshafen, Germany. Correspondence and requests for materials should be addressed to M.W. (email: martin.wegener@kit.edu) or to M.B. (email: bastmeyer@kit.edu)

2020 年

Hippler et al., *Sci. Adv.*

ハイデルベルク大学・カールスルーエ工科大学・京都大学プレスリースで紹介

SCIENCE ADVANCES | RESEARCH ARTICLE

MATERIALS SCIENCE

Mechanical stimulation of single cells by reversible host-guest interactions in 3D microscaffolds

Marc Hippler[1,2]*, Kai Weißenbruch[2,3], Kai Richler[2], Enrico D. Lemma[2], Masaki Nakahata[4], Benjamin Richter[2], Christopher Barner-Kowollik[5,6,7], Yoshinori Takashima[8], Akira Harada[8], Eva Blasco[7,9], Martin Wegener[1,9]*, Motomu Tanaka[10,11]*, Martin Bastmeyer[2,3]*

Many essential cellular processes are regulated by mechanical properties of their microenvironment. Here, we introduce stimuli-responsive composite scaffolds fabricated by three-dimensional (3D) laser lithography to simultaneously stretch large numbers of single cells in tailored 3D microenvironments. The key material is a stimuli-responsive photoresist containing cross-links formed by noncovalent, directional interactions between β-cyclodextrin (host) and adamantane (guest). This allows reversible actuation under physiological conditions by application of soluble competitive guests. Cells adhering in these scaffolds build up initial traction forces of ~80 nN. After application of an equibiaxial stretch of up to 25%, cells remodel their actin cytoskeleton, double their traction forces, and equilibrate at a new dynamic set point within 30 min. When the stretch is released, traction forces gradually decrease until the initial set point is retrieved. Pharmacological inhibition or knockout of nonmuscle myosin 2A prevents these adjustments, suggesting that cellular tensional homeostasis strongly depends on functional myosin motors.

INTRODUCTION

In cell biological research, more and more attention is drawn to biophysical cues that influence cellular behavior in addition to biochemical cues (*1*). For example, adherent cells have been found to be more spread, more polarized, and more contractile in stiffer environments, they migrate differently, and stem cells differentiate into different cell types (*2*). Cells are able to recognize and transduce mechanical stress and strain patterns by mechanosensitive modules such as ion channels, cell adhesion sites, and the cytoskeleton (*3*). The mechanical input is ultimately converted to biochemical signals that guide not only the dynamic rearrangement of actin stress fibers and the actin cortex (*4*) but also gene expression and the response to soluble ligands. Although several approaches have been established to stretch cells, it remains challenging to monitor the cell response to mechanical stimuli.

Mechanical stimulation of cells is most commonly performed by pneumatic, piezoelectric, or electromagnetic stretching of deformable polydimethylsiloxane substrates or thin membranes (*5*). Here, cells are typically adhering to two-dimensional (2D) substrates in random morphologies. Other approaches such as optical tweezers, atomic force microscopy (*6*), microplates (*7*), or micromanipulators (*8*) offer precise displacements in 3D, but these techniques are hardly scalable to study a large number of cells. In addition, a fixation of cells in the stretched state is not possible. Moreover, all available techniques require complex setups to trigger and control the stimulation. A detailed description and comparison of these methods can be found in several reviews (*9*, *10*). Here, we propose a different approach using 3D scaffolds based on stimuli-responsive, supramolecular polymers to simultaneously stretch a large number of single cells in tailored 3D microenvironments.

In the past, 3D laser lithography has successfully been used to manufacture cell scaffolds with tailored geometry and spatially functionalized surfaces (*11*). However, the transition from passive to active systems requires responsive materials that can be stimulated on demand (*12*). In recent years, a large number of these material systems with numerous applications in the macroscopic (*13*) and microscopic (*14*, *15*) regime have been investigated and extensively reviewed (*16*, *17*). One crucial constraint for the application in cell biology is a specific physiological stimulus of the material that does not influence or alter the behavior of the cells. Despite a number of studies demonstrating the dynamic control of cells using hydrogels responsive to temperature (*18*), pH (*19*), enzymes (*20*), or illumination with ultraviolet light (*21*), these applications are limited because the formation and cleavage of bonds are often performed under harsh conditions. Supramolecular polymers (*22*, *23*) could provide an advantage over the abovementioned materials, if appropriate host or guest molecules are selected for the stimulation (*24*).

In the following, we first present a stimuli-responsive photoresist containing cross-links formed by noncovalent, directional interactions between β-cyclodextrin (host) and adamantane (guest) moieties. The resulting hydrogel microstructures fabricated by 3D laser lithography exhibit large volume changes by stimulation with the soluble low–molecular weight guest molecules under physiological conditions. Next, we combine this material with conventional photoresists to fabricate composite scaffolds consisting of protein-repellent base structures, protein-adhesive parts, and the stimuli-responsive

[1]Institute of Applied Physics, Karlsruhe Institute of Technology (KIT), 76128 Karlsruhe, Germany. [2]Zoological Institute, Karlsruhe Institute of Technology (KIT), 76128 Karlsruhe, Germany. [3]Institute of Functional Interfaces, Karlsruhe Institute of Technology (KIT), 76128 Karlsruhe, Germany. [4]Department of Materials Engineering Science, Graduate School of Engineering Science, Osaka University, Toyonaka, Osaka 560-8531, Japan. [5]Centre for Materials Science, Queensland University of Technology (QUT), 2 George Street, Brisbane, QLD 4000, Australia. [6]School of Chemistry and Physics, Queensland University of Technology (QUT), 2 George Street, Brisbane, QLD 4000, Australia. [7]Institute of Nanotechnology, Karlsruhe Institute of Technology (KIT), 76128 Karlsruhe, Germany. [8]Department of Macromolecular Science, Graduate School of Science, Osaka University, 1-1 Machikaneyama-cho, Toyonaka, Osaka 560-0043, Japan. [9]Institute for Chemical Technology and Polymer Chemistry, Karlsruhe Institute of Technology (KIT), 76128 Karlsruhe, Germany. [10]Institute of Physical Chemistry, Heidelberg University, Im Neuenheimer Feld 253, 69120 Heidelberg, Germany. [11]Center for Integrative Medicine and Physics, Institute for Advanced Study, Kyoto University, Kyoto 606-8501, Japan.
*Corresponding author. Email: marc.hippler@kit.edu (M.H.); martin.wegener@kit.edu (M.W.); tanaka@uni-heidelberg.de (M.T.), martin.bastmeyer@kit.edu (M.B.)

analytical chemistry

pubs.acs.org/ac Article

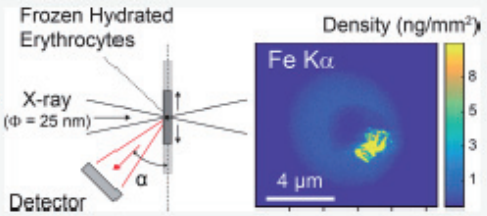
Nanofocused Scanning X-ray Fluorescence Microscopy Revealing an Effect of Heterozygous Hemoglobin S and C on Biochemical Activities in *Plasmodium falciparum*-Infected Erythrocytes

Benjamin Fröhlich, Yang Yang, Judith Thoma, Julian Czajor, Christine Lansche, Cecilia Sanchez, Michael Lanzer, Peter Cloetens, and Motomu Tanaka*

Cite This: *Anal. Chem.* 2020, 92, 5765−5771 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: While there is ample evidence suggesting that carriers of heterozygous hemoglobin S and C are protected from life-threatening malaria, little is known about the underlying biochemical mechanisms at the single cell level. Using nanofocused scanning X-ray fluorescence microscopy, we quantify the spatial distribution of individual elements in subcellular compartments, including Fe, S, P, Zn, and Cu, in *Plasmodium falciparum*-infected (*P. falciparum*-infected) erythrocytes carrying the wild type or variant hemoglobins. Our data indicate that heterozygous hemoglobin S and C significantly modulate biochemical reactions in parasitized erythrocytes, such as aberrant hemozoin mineralization and a delay in hemoglobin degradation. The label-free scanning X-ray fluorescence imaging has great potential to quantify the spatial distribution of elements in subcellular compartments of *P. falciparum*-infected erythrocytes and unravel the biochemical mechanisms underpinning disease and protective traits.



Malaria still remains a major public health issue caused by some species of intracellular protozoa from the genus *Plasmodium* (*P.*), among which *P. falciparum* is responsible for most of the malaria-related deaths. After a parasite (merozoite) invades a host erythrocyte, the parasite is enclosed in a parasite compartment (PC) and hence separate from the erythrocyte cytoplasm (EC). Hemoglobin constitutes >95% of the erythrocyte dry mass and is a central point of the parasite metabolism.[1] After ≈24 h postinfection, termed as the trophozoite stage, about 40% of hemoglobins (Hb) is degraded in a digestive vacuole (DV), which is a compartment inside PC.[2] The proteolytic digestion of Hb in the DV results in amino acids and heme. The former is utilized for the development and growth of the parasite, while the latter is stored as hemozoin crystals.

Intriguingly, it is widely known that carriers of certain hemoglobinopathies, variant forms of hemoglobin caused by genetic mutations, rarely develop life-threating conditions during a malaria infection. However, the underlying principle of the protection mechanism is only partly understood. Two very common representatives of such hemoglobinopathies are heterozygous hemoglobin S ("sickle cell trait", HbAS) and hemoglobin C (HbAC), both of which are characterized by a single amino acid substitution in one of the β-globin chains, compared with the wild type hemoglobin HbAA.[3] To date, however, the effect of hemoglobinopathies on biochemical reactions in *P. falciparum*-infected erythrocytes has mostly been studied in cell populations and not at the single cell level.

In this study, we quantitatively assessed how the metabolic activity of *P. falciparum* is affected by the hemoglobinopathies HbAS and HbAC using element-specific, scanning X-ray fluorescence microscopy (SXFM).[4−10] The use of a nanofocused synchrotron beam enabled the label-free, chemically imaging inside single red blood cells and the quantification of the spatial, subcellular distributions of target elements with nanometer resolution and trace level sensitivity.[11]

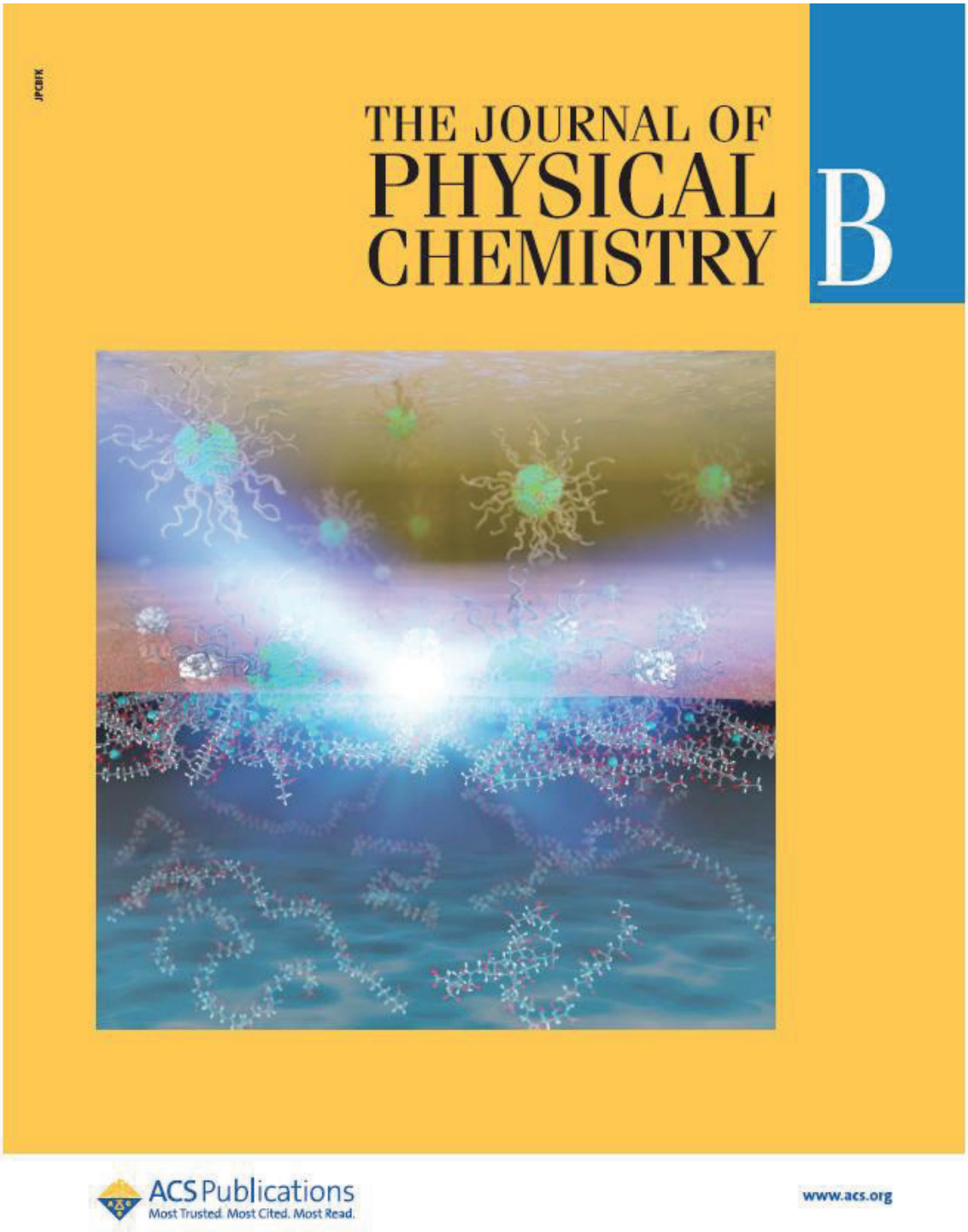
■ RESULTS AND DISCUSSION

As schematically shown in Figure 1a, for fluorescence mapping, the cryofixed sample was continuously scanned with a focused X-ray nanoprobe (17.05 keV) focused down to a beam size of about 27 × 37 nm². On one side of the sample, a multielement SSD detector (Rayspec, U.K.) was placed nearly orthogonal (α = 5°) to the beam path, collecting fluorescence signals. Panels b and c of Figure 1 represent the same infected HbAA erythrocyte at the trophozoite stage (24−36 h postinvasion), as a virtual slice calculated from a phase contrast tomography reconstruction and by fluorescence mapping, respectively. The

Received: November 10, 2019
Accepted: March 23, 2020
Published: March 23, 2020

https://dx.doi.org/10.1021/acs.analchem.9b05111
Anal. Chem. 2020, 92, 5765−5771

Amadei et al., *J. Phys. Chem. B*
雑誌の表紙に選出



THE JOURNAL OF PHYSICAL CHEMISTRY B

pubs.acs.org/JPCB

Article

Ion-Mediated Cross-linking of Biopolymers Confined at Liquid/Liquid Interfaces Probed by In Situ High-Energy Grazing Incidence X-ray Photon Correlation Spectroscopy

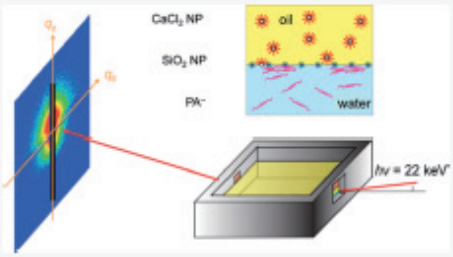
Federico Amadei, Judith Thoma, Julian Czajor, Esther Kimmle, Akihisa Yamamoto, Wasim Abuillan, Oleg V. Konovalov, Yuriy Chushkin,* and Motomu Tanaka*

Cite This: J. Phys. Chem. B 2020, 124, 8937−8942

Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: As manifested in biological cell membranes, the confinement of chemical reactions at the 2D interfaces significantly improves the reaction efficacy. The interface between two liquid phases is used in various key processes in industries, such as in food emulsification and floatation. However, monitoring the changes in the mechanics and dynamics of molecules confined at the liquid/liquid interfaces still remains a scientific challenge because it is nontrivial to access the interface buried under a liquid phase. Herein, we report the in situ monitoring of the cross-linking of polyalginate mediated by Ca^{2+} ions at the oil/water interface by grazing incidence X-ray photon correlation spectroscopy (GIXPCS). We first optimized the reaction conditions with the aid of interfacial shear rheology and then performed GIXPCS using a high-energy synchrotron X-ray beam (22 keV) that guarantees sufficiently high transmittance through the oil phase. The intensity autocorrelation functions implied that the formation of a percolated network of polyalginate is accompanied by increasing relaxation time. Moreover, the relaxation rate scales linearly with the momentum transfer parallel to the interface, suggesting that the process is driven by hyperdiffusive propagation but not by Brownian diffusion. Our data indicated that high-energy GIXPCS has potential for in situ monitoring of changes in the dynamics of polymers confined between two liquid phases.



INTRODUCTION

Confinement of chemical reactions in a 2D space significantly improves the reaction rate and efficiency of the reaction: the relationship between the mean diffusion time for the three-body collision τ and the effective molecular radius r is $\langle \tau_{2D} \rangle \propto -\ln r$ in 2D, while that in 3D is $\langle \tau_{3D} \rangle \propto r^{-1}$.[1] In biological cell membranes, numerous biochemical reactions are confined and regulated in/near the membranes. One obvious example is the catalytic digestion of phospholipids by phospholipase A2 at the membrane/water interface, showing the highest efficiency near the phase separation boundary.[2] Multiphasic catalytic reactions at the liquid/liquid interface are also attractive for catalyst separation and product recovery in organic transformation.[3] To date, various tools, such as emulsions, Janus particles, and microfluidic devices, have been proposed to increase the reaction efficiency.[4] A sol−gel transition at the interface is also an important process for stabilization of food colloids and microencapsulation of enzymes and cells.[5]

Despite a wide variety of applications in different fields, in situ monitoring of changes in the dynamical properties of molecules confined at the liquid/liquid interface is still an experimental challenge because the liquid/liquid interface is not easily accessible. Interface rheology[6] is one of the tools to monitor the change in viscoelasticity of interfaces caused by the formation of films and domains at the liquid/liquid interface by discriminating the interfacial properties from the bulk. However, despite a major progress in recent years, rheological measurements yield response functions averaged over macroscopic length scales, but they are not able to provide insights into the underlying microscopic behaviors. When we look at the time domain, interface rheology measurements can be performed under limited frequency conditions. Therefore, the influence of reactions and structure formation on the dynamics of molecules confined at the liquid/liquid interface is largely unknown.

X-ray photon correlation spectroscopy (XPCS),[7] detecting temporal correlation of scattered photons, has been used to measure the dynamics of disordered systems, such as collective diffusion of colloids near glass transition,[8] aging of metallic glass,[9] and dynamics of polymer chains in solutions and gels.[10]

Received: August 1, 2020
Revised: September 2, 2020
Published: September 2, 2020

https://doi.org/10.1021/acs.jpcb.0c07056
J. Phys. Chem. B 2020, 124, 8937−8942

Thoma et al., *Sci. Rep.*
花王ニュースリリースなどで紹介

www.nature.com/scientificreports

SCIENTIFIC REPORTS
nature research

OPEN

Specific localisation of ions in bacterial membranes unravels physical mechanism of effective bacteria killing by sanitiser

Judith Thoma[1,7], Wasim Abuillan[1,7✉], Ippei Furikado[2], Taichi Habe[2], Akihisa Yamamoto[3], Simone Gierlich[1], Stefan Kaufmann[1], Klaus Brandenburg[4,6], Thomas Gutsmann[4], Oleg Konovalov[5], Shigeto Inoue[2✉] & Motomu Tanaka[1,3✉]

Antimicrobial resistance is a major threat to public health. Although many commercial sanitisers contain a combination of cationic surfactants and aromatic alcohols, the physical mechanisms where these two substances bind to or how they disturb bacterial membranes are still largely unknown. In this study, we designed a well-defined model of Gram-negative bacteria surfaces based on the monolayer of lipopolysaccharides with uniform saccharide head groups. Since commonly used X-ray reflectivity is sensitive to changes in the thickness, roughness and electron density but is not sensitive to elements, we employed grazing incidence X-ray fluorescence. In the absence of Ca^{2+}, cationic surfactants can penetrate into the membrane core with no extra support by disturbing the layer of K^+ coupled to negatively charged saccharide head group at $z = 17$ Å from the air/chain interface. On the other hand, Ca^{2+} confined at $z = 19$ Å crosslink charged saccharides and prevent the incorporation of cationic surfactants. We found that the addition of nonlethal aromatic alcohols facilitate the incorporation of cationic surfactants by the significant roughening of the chain/saccharide interface. Combination of precise localisation of ions and molecular-level structural analysis quantitatively demonstrated the synegtestic interplay of ingredients to achieve a high antibacterial activity.

As stated in a report issued by the World Health Organization in 2014, antimicrobial resistance is a major threat to public health[1–3]. This is due to the overuse of therapeutic agents by over-prescribing antibiotics in the clinical treatment of human patients as well as livestock in the farming industry[4,5]. Although the development of antimicrobial agents is necessary for the sustainable society, it is often overlooked that a proper use of sanitisers already enables us to achieve a sufficient hygiene level as well as to reduce the number of antibiotic treatments[6]. Bacteria, including pathogenic and non-pathogenic species, form colonies, often called biofilms, in households, industry sectors, and hospitals. A recent multicentre study reported patients' bath basins as potential bacterial reservoirs, which may become a source of transmission of nosocomial infections[7].

Currently, chemical sanitisers, such as quaternary ammonium compounds (QACs), bisbiguanides (chlorhexidine), and polymeric biguanides, are among the most commonly used disinfectants[6,8]. For example, benzalkonium chloride (BAC, Fig. 1a) is a cationic surfactant widely used as a sanitiser[9,10]. The mechanism of QAC activity is believed to involve (1) the electrostatic binding of positively charged quaternary nitrogen to negatively charged lipids on bacterial membrane surfaces, (2) the integration of hydrocarbon chains of QACs into the hydrophobic core of bacterial membranes, which results in (3) the disruption of cell membranes and subsequent loss of cytoplasm[6,10,11]. However, although QACs have been extensively used since the 1930s, some bacterial strains have

[1]Physical Chemistry of Biosystems, Institute of Physical Chemistry, University of Heidelberg, 69120 Heidelberg, Germany. [2]Analytical Science Research Laboratories, Kao Corporation, 1334 Minato, Wakayama, Wakayama Prefecture 640-8580, Japan. [3]Center for Integrative Medicine and Physics, Institute for Advanced Study, Kyoto University, Kyoto 606-8501, Japan. [4]Research Center Borstel, Leibniz Lung Center, 23845 Borstel, Germany. [5]European Synchrotron Radiation Facility (ESRF), 38043 Grenoble, France. [6]Present address: Brandenburg Antiinfektiva GmbH, 23845 Borstel, Germany. [7]These authors contributed equally: Judith Thoma and Wasim Abuillan. ✉email: abuillan@uni-heidelberg.de; inoue.shigeto@kao.com; tanaka@uni-heidelberg.de

SCIENTIFIC REPORTS
nature research

Check for updates

OPEN

Glycogen accumulation, central carbon metabolism, and aging of hematopoietic stem and progenitor cells

Laura Poisa-Beiro[1,2,10], Judith Thoma[3,4,10], Jonathan Landry[5], Sven Sauer[6], Akihisa Yamamoto[4], Volker Eckstein[1], Natalie Romanov[7,9], Simon Raffel[1], Georg F. Hoffmann[6], Peer Bork[2,7], Vladimir Benes[5], Anne-Claude Gavin[2,7,8], Motomu Tanaka[3,4]✉ & Anthony D. Ho[1,2,4]✉

Inspired by recent proteomic data demonstrating the upregulation of carbon and glycogen metabolism in aging human hematopoietic stem and progenitor cells (HPCs, CD34+ cells), this report addresses whether this is caused by elevated glycolysis of the HPCs on a per cell basis, or by a subpopulation that has become more glycolytic. The average glycogen content in individual CD34+ cells from older subjects (>50 years) was 3.5 times higher and more heterogeneous compared to younger subjects (<35 years). Representative glycolytic enzyme activities in HPCs confirmed a significant increase in glycolysis in older subjects. The HPCs from older subjects can be fractionated into three distinct subsets with high, intermediate, and low glucose uptake (GU) capacity, while the subset with a high GU capacity could scarcely be detected in younger subjects. Thus, we conclude that upregulated glycolysis in aging HPCs is caused by the expansion of a more glycolytic HPC subset. Since single-cell RNA analysis has also demonstrated that this subpopulation is linked to myeloid differentiation and increased proliferation, isolation and mechanistic characterization of this subpopulation can be utilized to elucidate specific targets for therapeutic interventions to restore the lineage balance of aging HPCs.

Glycogen accumulation upon aging has been reported in cells such as nerves, neurons, astrocytes, and muscle cells[1–5]. Glycogen is the storage polyglucosan (PG) and periodic acid–Schiff (PAS) reaction has been established as the method to detect glycogen and other polysaccharides[6]. Glycogen content is usually low in blood cells but high levels of glycogen are characteristically found in the leukemia cells of patients with acute lymphoblastic leukemia (ALL)[7,8]. Before immuno- and molecular diagnostics for classification of acute leukemias has become routine, PAS-staining constituted an essential histochemical method for the classification of acute leukemias. Glycogen accumulation in form of PAS positive granules was prominently found in the blasts of ALL and was reported to indicate prognostic significance[8].

[1]Department of Medicine V, Heidelberg University, Im Neuenheimer Feld 410, 69120 Heidelberg, Germany. [2]Molecular Medicine Partnership Unit Heidelberg, EMBL and Heidelberg University, 69120 Heidelberg, Germany. [3]Physical Chemistry of Biosystems, Institute of Physical Chemistry, Heidelberg University, Im Neuenheimer Feld 253, 69120 Heidelberg, Germany. [4]Center for Integrative Medicine and Physics, Institute for Advanced Study, Kyoto University, Kyoto 606-8501, Japan. [5]Genomics Core Facility, European Molecular Biology Laboratory (EMBL), Meyerhofstrasse 1, 69117 Heidelberg, Germany. [6]Division of Child Neurology and Metabolic Diseases, Centre for Child and Adolescent Medicine, University Hospital Heidelberg, Im Neuenheimer Feld 430, 69120 Heidelberg, Germany. [7]Structural and Computational Biology Unit, European Molecular Biology Laboratory (EMBL), Meyerhofstrasse 1, 69117 Heidelberg, Germany. [8]Department for Cell Physiology and Metabolism, Centre Medical Universitaire, University of Geneva, Rue Michel-Servet 1, 1211 Geneva 4, Switzerland. [9]Present address: Max Planck Institute of Biophysics, Max-von-Laue Straße 3, 60438 Frankfurt am Main, Germany. [10]These authors contributed equally: Laura Poisa-Beiro and Judith Thoma. ✉email: tanaka@uni-heidelberg.de; anthony_dick.ho@urz.uni-heidelberg.de

Polymer Journal (2020) 52:861–870
https://doi.org/10.1038/s41428-020-0353-6

REVIEW

Stimuli-responsive hydrogels as a model of the dynamic cellular microenvironment

Motomu Tanaka[1,2] · Masaki Nakahata[3] · Philipp Linke[1] · Stefan Kaufmann[1]

Received: 15 January 2020 / Revised: 13 March 2020 / Accepted: 1 April 2020 / Published online: 14 May 2020

Abstract

Ample evidence has demonstrated that biological cells not only react to biochemical cues from the surrounding microenvironments but also sensitively detect the mechanical properties of the extracellular matrix and neighboring cells to adapt their shape, function, and fate. Mechanical aspects in biology, called mechanobiology, have been attracting biologists, chemists, physicists, and mechanical engineers. However, most in vitro studies to date have heavily relied on covalently cross-linked hydrogels with prefixed and hence unchangeable mechanical properties, although the mechanical properties of the cellular microenvironment are never uniform or static. From this context, stimuli-responsive hydrogels are highly attractive as surrogate materials that can simulate dynamic physical microenvironments in vivo. This review tries to provide a comprehensive overview of previous achievements, present pitfalls and challenges, and future perspectives on the recent development of stimuli-responsive hydrogel materials for the dynamic control of cell behavior.

Introduction

During the past two decades, mechanobiology has drawn increasing attention as an interdisciplinary forum for researchers from the fields of materials science and biomedical science. Mounting evidence suggests that biological cells not only passively sense biochemical cues but also actively react to mechanical cues from the surrounding microenvironment [1, 2]. For example, the formation of neurite branches of neuronal cells [3] and the striation of actomyosin bundles in cardiac myotubes [4] is significantly improved on hydrogel substrates possessing elastic moduli comparable to those of the native extracellular matrix. Researchers from regenerative medicine have also suggested the importance of mechanical compliance in the regulation of stem cell differentiation. Mesenchymal stem cells injected into the blood vessels of a lever undergoing fibrosis did not lead to the regeneration of hepatocytes but instead led to misdifferentiation into ductal cells [5]. In 2006, Discher and coworkers showed that the lineage-specific differentiation of somatic stem cells can be regulated by the elasticity of chemically cross-linked polyacrylamide substrates functionalized with type I collagen [6]. Although later studies have shown that substrate elasticity is important but not the only determinant for the fate of stem cells [7, 8], this study made many materials scientists aware of the crucial roles of mechanics in regulating cells. To date, a number of chemically cross-linked hydrogels have been synthesized as models of the extracellular matrix [9]. The fine adjustment of cross-linker concentrations and the reaction time [10, 11] enables the control of bulk elastic moduli (Young's moduli) of hydrogels ex situ. Such materials have been used to gain insights into the roles of elasticity compliance between cells and the extracellular matrix in optimizing cell morphology [4, 12, 13], regulating migratory behavior [14, 15], controlling stem cell differentiation [16], and engineering tissue [17].

However, these ex situ approaches to mechanically regulate biological cells have overlooked one key aspect: the microenvironments of cells are never static but highly dynamic. Dynamic changes in extracellular matrix stiffness significantly influences various cellular functions. A number of studies have

✉ Motomu Tanaka
tanaka@uni-heidelberg.de

✉ Masaki Nakahata
nakahata@cheng.es.osaka-u.ac.jp

[1] Physical Chemistry of Biosystems, Institute of Physical Chemistry, Heidelberg University, 69120 Heidelberg, Germany

[2] Center for Integrative Medicine and Medicine, Institute for Advanced Study, Kyoto University, Kyoto 606-8501, Japan

[3] Department of Materials Engineering Science, Graduate School of Engineering Science, Osaka University, Osaka 560-8531, Japan

frontiers in Chemistry

REVIEW
published: 17 March 2020
doi: 10.3389/fchem.2020.00165

Interplays of Interfacial Forces Modulate Structure and Function of Soft and Biological Matters in Aquatic Environments

Motomu Tanaka [1,2*]

[1] Physical Chemistry of Biosystems, Institute of Physical Chemistry, Heidelberg University, Heidelberg, Germany, [2] Center for Integrative Medicine and Physics, Institute for Advanced Study, Kyoto University, Kyoto, Japan

Water had been considered as a passive matrix that merely fills up the space, supporting the diffusion of solute molecules. In the past several decades, a number of studies have demonstrated that water play vital roles in regulating structural orders of biological systems over several orders of magnitude. Water molecules take versatile structures, many of which are transient. Water molecules act as hydrogen bond donors as well as acceptors and biochemical reactions utilize water molecules as nucleophiles. Needless to say, the same principle holds for the synthetic materials that function under water: the conformation, dynamics and functions of molecules are significantly influenced by the surrounding water. This review sheds light on how the structure and function of soft and biological matter in aquatic environments are modulated by the orchestration of various interfacial forces.

Keywords: soft matter, biosystems, interfacial forces, disjoining pressure, specular reflectivity

OPEN ACCESS

Edited by:
Doo Soo Chung,
Seoul National University, South Korea

Reviewed by:
Rudi Van Eldik,
University of Erlangen Nuremberg, Germany
YounJoon Jung,
Seoul National University, South Korea

****Correspondence:***
Motomu Tanaka
tanaka@uni-heidelberg.de

Specialty section:
This article was submitted to Physical Chemistry and Chemical Physics, a section of the journal Frontiers in Chemistry

Received: *16 August 2019*
Accepted: *25 February 2020*
Published: *17 March 2020*

Citation:
Tanaka M (2020) Interplays of Interfacial Forces Modulate Structure and Function of Soft and Biological Matters in Aquatic Environments. Front. Chem. 8:165. doi: 10.3389/fchem.2020.00165

INTRODUCTION

Water shares about 60–65 wt% of an adult human body, whose most prominent example is cytosolic fluid inside ~100 trillion (10^{14}) cells making up our body. Mounting evidence suggests that water is not a simple continuum supporting passive diffusion of solute molecules. On the contrary, water plays more active roles in controlling the conformation and dynamics of biopolymers and proteins over several orders of magnitude both in space and time (Ball, 2017). For example, ^{2}H spin relaxation studies on bacteria cultured in D_2O showed that about 85 % of water in bacteria has bulk-like dynamics ($\tau \sim 10^{-11}$ s), and the dynamics of the rest of water is slower by one order of magnitude (Persson and Halle, 2008). Most strikingly, a very small fraction of water (~0.1 %) shows a significantly slow dynamics with $\tau \sim 10^{-6}$ s. Thus, if one considers the interafacial interactions between water and biological matter, the interactions inevitably involve both free (bulk) and bound (hydrating) water.

If we look into biological systems, a variety of interfacial interactions are combined to sustain living systems in water (Alberts, 2017). For example, epithelial cells establish stable, specific contacts with neighboring cells. On the other hand, cells in connective tissues, both in loose and dense connective tissues, hardly make any contacts with their neighbors. The intercellular space is filled with various biopolymers, acting as "cushions" and "lubricants" to help tissues withstand compressional and frictional stresses, respectively (**Figure 1A**). Moreover, the layer of oligo- and polysaccharides coating the outer surface of cell membranes, called glycocalyx, plays major roles

Frontiers in Chemistry 特集号の Preface を
Guest Editor として執筆

frontiers in Chemistry

EDITORIAL
published: 02 September 2020
doi: 10.3389/fchem.2020.00760

Editorial: Interfacial Water: A Physical Chemistry Perspective

Motomu Tanaka [1,2]* *and Hideki Seto* [3]*

[1] *Institute of Physical Chemistry, Heidelberg University, Heidelberg, Germany,* [2] *Institute for Advanced Study, Kyoto University, Kyoto, Japan,* [3] *High Energy Accelerator Research Organization, Tsukuba, Japan*

Keywords: interfacial water, hydration, aquatic functional materials, surface and interface, hydrogen bonding, liquid-liquid phase separation

Editorial on the Research Topic

Interfacial Water: A Physical Chemistry Perspective

Earth is called a "water planet," as it is the only planet possessing massive quantities of liquid water on its surface. Water is essential to sustain our life, as 60–65 wt% of a human body consists of water. Because of the increasing demand for more efficient use and management of water, the United Nations defines "Clean Water and Sanitation" as one of the Sustainable Development Goals (SDG 6).

Liquid water is one of the most ubiquitous materials on earth and is closely associated with life. Its anomalous behavior is recognized as the origin of a variety of phenomena in chemistry, biology, and geosciences and the underlying aspects of liquid water have been investigated from the viewpoint of physics. However, for reasons that include a lack of full understanding of liquid water (despite the accumulation of a vast body of experimental and theoretical data), the role of water at interfaces has yet to be fully elucidated. For example, ample evidence suggests that water molecules near the interface take various transient structures depending on the interacting surface, while the presence of water molecules significantly modifies the physical properties of surfaces.

This special issue of *Frontiers in Chemistry—Physical Chemistry and Chemical Physics* aims to shed light on interfacial water from different angles.

Tanaka (article 165) provided a comprehensive review on how the interfacial "forces" are counter-balanced and define the structure and mechanical properties of soft matter and biological matter in aquatic environments. Following the classical concept of *disjoining pressure* described by Derjaguin, this article exemplifies several surface sensitive techniques, such as high energy X-ray reflectivity and specular/off-specular neutron scattering, that enables the quantification of molecular-level structures and significance of interactions in aquatic environments. The perspective article by Cao et al. (article 626) further extends the topic to "looking at water near the solid/liquid interface." They nicely summarize recent progress in non-contact atomic force microscopy and simulations enable to visualize hydrogen bonding network and weakly bonded water clusters. They conclude that the continuous improvement of AFM imaging and AFM modeling will bring about more comprehensive understanding of the structural, mechanical, dynamic, and functional heterogeneity of intricate interfacial water systems.

In this Research Topic, two papers deal with physical properties of water molecules interacting with biological membranes. Hydration of biological membranes is a biologically relevant issue, as many of key biochemical reactions are confined to the close proximity of membrane surfaces. Yamada and Seto's minireview (article 8) provides a compact summary of the application of the quasi-elastic neutron scattering (QENS) technique on hydration between lipid membranes. Such techniques, quantifying the diffusive dynamics in explicit geometry, will help material scientists to unravel the dynamics of water confined in nanochannels, such as polymer-based electrolytes for

OPEN ACCESS

Approved by:
Bretislav Friedrich, Fritz-Haber-Institut, Germany

Correspondence:
Motomu Tanaka
tanaka@uni-heidelberg.de
Hideki Seto
hideki.seto@kek.jp

Specialty section:
This article was submitted to Physical Chemistry and Chemical Physics, a section of the journal Frontiers in Chemistry

Received: *10 July 2020*
Accepted: *22 July 2020*
Published: *02 September 2020*

Citation:
Tanaka M and Seto H (2020) Editorial: Interfacial Water: A Physical Chemistry Perspective. Front. Chem. 8:760. doi: 10.3389/fchem.2020.00760

LANGMUIR

pubs.acs.org/Langmuir Article

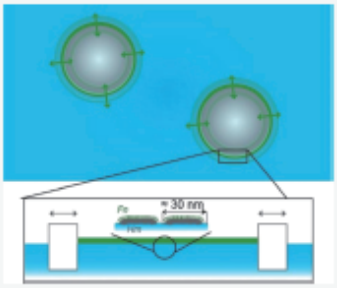
Influence of Semifluorinated Alkane Surface Domains on Phase Behavior and Linear and Nonlinear Viscoelasticity of Phospholipid Monolayers

Salomé Mielke, Xianhe Liu, Marie Pierre Krafft,* and Motomu Tanaka*

Cite This: *Langmuir* 2020, 36, 781−788 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: Semifluorinated alkanes self-assemble into 30−40 nm-large surface domains (hemimicelles) at the air/water interface. They have been drawing increasing attention to stabilize microbubbles coated with lipids, which are used for enhancing the contrast in sonographic imaging. Although previous studies suggested that semifluorinated alkanes increase the stability of phospholipid membranes, little is known about how semifluorinated alkanes influence phase behaviors and mechanical properties of lipid-coated microbubbles. As a well-defined model of microbubble surfaces, we prepared monolayers consisting of a mixture of phospholipids and semifluorinated alkanes at the air/water interface and investigated the influence of hemimicelles of semifluorinated alkanes on the phase behavior and interfacial viscoelastic properties of phospholipid monolayers. Hemimicelles are phase-separated from phospholipids and accumulate at the phase boundary, which strongly modulates the correlation between solid phospholipid domains. Intringuingly, we found that the mixed monolayer of semifluorinated alkanes and phospholipids possesses linear and nonlinear viscoelastic properties comparable to those of phospholipid monolayers. Since the mixing of semifluorinated alkanes and phospholipids enables one to overcome the intrinsically low stability of pure semifluorinated alkanes against the change in the surface area of microbubbles through the partial dissolution of gas into the aqueous phase, this is a promising strategy for the stable coating of microbubbles in ultrasound diagnosis.



INTRODUCTION

Semifluorinated alkane diblock molecules ($C_nF_{2n+1}C_mH_{2m+1}$, *FnHm*) have drawn increasing attention during the last decades due to their exceptional physical and chemical properties.[1−4] These include a strong dipole moment resulting mainly from the CH_2−CF_2 junction and the CF_3 terminal group and a highly hydrophobic and oleophobic nature of the molecules.[1,5,6] Long semifluorinated alkanes ($n + m > 22$) form stable Langmuir monolayers at the air/water interface and self-assemble spontaneously into monolayers composed of highly uniform, circular domains with diameters between 30 and 40 nm, so-called surface hemimicelles.[1,7,8] These hemimicelles, schematically represented in Figure 1a (inset), are very stable against coalescence, and their size can be regulated by the balance between fluoro- and hydrocarbon segment lengths.[9,10] Grazing-incidence small-angle X-ray scattering (GISAXS) revealed that the *FnHm* hemimicelles adopt a hexagonal paracrystal lattice on water and that the lateral correlation between the micelles reaches over a distance that is 8−20 times longer than the diameter of one micelle, depending on the length of the *FnHm* molecules.[10]

Recent studies demonstrated that the self-assembled *FnHm* hemimicelles confined at the air/water interface possess unique viscoelastic properties.[3,11−13] Dilational[10] and shear[9] rheology measurements revealed that the system is predominantly elastic, which can be attributed to very poor compressibility (~7 m/N) and strong dipole repulsions between the micelles.[12] A possible explanation for the low interfacial viscosity is the strong hydrophobic nature of the semifluorinated alkanes, which results in a low friction between *FnHm* monolayers and the water subphase.[12]

Such unique mechanical properties of surface domains of semifluorinated alkanes open up a broad variety of biomedical applications. One potential application is to stabilize microbubbles that are used as contrast agents for ultrasound imaging and drug delivery.[14−16] So far, commercial microbubbles used for ultrasound diagnostics are coated with shells made of lipids or albumin.[16,17] However, increasing the control over microbubble size and stability characteristics is a sought after challenge. Pure monolayers made out of *FnHm* hemimicelles possess very low lateral compressibility and thus tend to collapse under a slight decrease in the surface area.[11] Thus, we

Received: November 12, 2019
Revised: December 13, 2019
Published: January 6, 2020

https://doi.org/10.1021/acs.langmuir.9b03521
Langmuir 2020, 36, 781−788

nature COMMUNICATIONS

ARTICLE

https://doi.org/10.1038/s41467-020-17394-z OPEN

Force generation by a propagating wave of supramolecular nanofibers

Ryou Kubota[1], Masahiro Makuta[2], Ryo Suzuki[3], Masatoshi Ichikawa[2], Motomu Tanaka[3,4] & Itaru Hamachi[1,5]✉

Dynamic spatiotemporal patterns that arise from out-of-equilibrium biochemical reactions generate forces in living cells. Despite considerable recent efforts, rational design of spatiotemporal patterns in artificial molecular systems remains at an early stage of development. Here, we describe force generation by a propagating wave of supramolecular nanofibers. Inspired by actin dynamics, a reaction network is designed to control the formation and degradation of nanofibers by two chemically orthogonal stimuli. Real-time fluorescent imaging successfully visualizes the propagating wave based on spatiotemporally coupled generation and collapse of nanofibers. Numerical simulation indicates that the concentration gradient of degradation stimulus and the smaller diffusion coefficient of the nanofiber are critical for wave emergence. Moreover, the force (0.005 pN) generated by chemophoresis and/or depletion force of this propagating wave can move nanobeads along the wave direction.

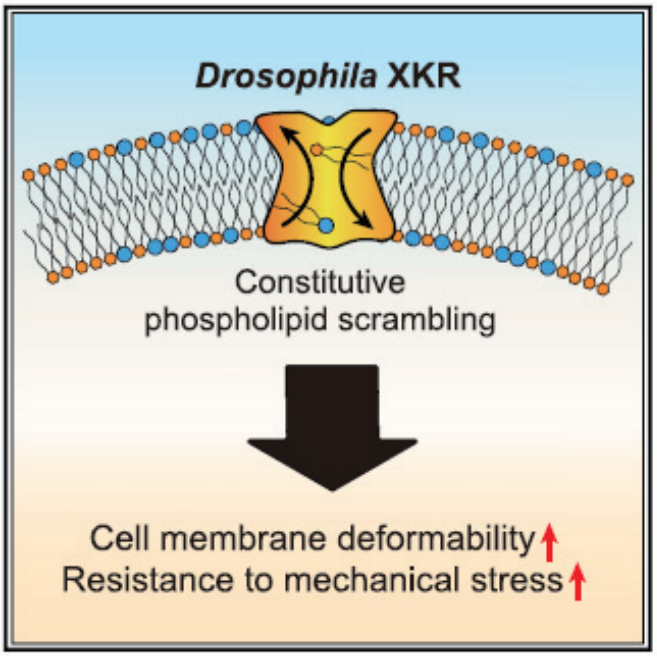
[1] Department of Synthetic Chemistry and Biological Chemistry, Graduate School of Engineering, Kyoto University, Katsura, Nishikyo-ku, Kyoto 615-8510, Japan. [2] Department of Physics, Kyoto University, Sakyo-ku, Kyoto 606-8502, Japan. [3] Center for Integrative Medicine and Physics, Institute for Advanced Study, Kyoto University, Sakyo-ku, Kyoto 606-8501, Japan. [4] Physical Chemistry of Biosystems, Institute of Physical Chemistry, Heidelberg University, 69120 Heidelberg, Germany. [5] JST-ERATO, Hamachi Innovative Molecular Technology for Neuroscience, Kyoto University, Katsura, Nishikyo-ku, Kyoto 615-8530, Japan. ✉email: ihamachi@sbchem.kyoto-u.ac.jp

Article

Cell Reports

Extreme deformability of insect cell membranes is governed by phospholipid scrambling

Graphical abstract



Authors

Akifumi Shiomi, Kohjiro Nagao, Nobuhiro Yokota, ..., Semen Yesylevsky, Mikhail Bogdanov, Masato Umeda

Correspondence

nagao@sbchem.kyoto-u.ac.jp (K.N.), umeda@sbchem.kyoto-u.ac.jp (M.U.)

In brief

Shiomi et al. show that *Drosophila* cells possess a cell membrane with extreme deformability and resistance to mechanical stress, where constitutively active phospholipid scramblase XKR disturbs the asymmetric distribution of phospholipids and promotes the deformability of cell membranes by regulating both actin cortex dynamics and mechanical properties of the phospholipid bilayer.

Highlights

- Compared with mammalian cells, *Drosophila* cells have a highly elastic cell membrane
- *Drosophila* XKR promotes membrane deformation by constitutive phospholipid scrambling
- Phospholipid scrambling affects actin cortex dynamics and lipid bilayer mechanics
- Deformability of mammalian cells can also be enhanced by phospholipid scrambling

Shiomi et al., 2021, Cell Reports 35, 109219
June 8, 2021
https://doi.org/10.1016/j.celrep.2021.109219

CellPress

RSC Advances

PAPER

View Article Online
View Journal | View Issue

Cite this: RSC Adv., 2021, 11, 17727

Dendronized oligoethylene glycols with phosphonate *tweezers* for cell-repellent coating of oxide surfaces: coarse-scale and nanoscopic interfacial forces†

Julian Czajor,‡[a] Wasim Abuillan,‡[a] Dinh Vu Nguyen,[b] Christopher Heidebrecht,[a] Evan A. Mondarte,[c] Oleg V. Konovalov,[d] Tomohiro Hayashi,[ce] Delphine Felder-Flesch,[bf] Stefan Kaufmann[a] and Motomu Tanaka[*ag]

Received 1st April 2021
Accepted 10th May 2021

DOI: 10.1039/d1ra02571f

rsc.li/rsc-advances

Dendronized oligoethylene glycols (dendron OEGs) with two phosphonate groups (phosphonate *tweezers*) have been drawing significant attention as a new class of coating materials for superparamagnetic iron oxide surfaces. However, despite dendron OEGs showing outstanding stability in physiological fluids in previous studies, little is understood about their structure and mechanical properties. Herein we report the surface and internal structures and mechanical properties of dendron OEGs, and quantitatively determine their ability to avoid non-specific adhesion of blood platelets. To gain insight into the interfacial force interactions, we measured the coarse-scale surface force acting on cell-sized particles and mapped the nanoscopic pinning centers by fast force mapping.

Introduction

Owing to their excellent magnetic properties and high transverse relaxation, over the past several decades superparamagnetic iron oxide nanoparticles have been drawing increasing attention for a variety of medical applications, such as contrast enhancement in MRI[1–3] and hyperthermia cancer theranostics.[4,5] A key prerequisite for their medical application is the chemical functionalization of nanoparticles to achieve; (i) high stability in physiological fluids, (ii) control of the particle size below 100 nm, without aggregation, and (iii) the preservation of high saturation magnetization. In the absence of surface coating materials, iron oxide nanoparticles tend to form μm-sized aggregates. In addition, it is clear that iron oxide nanoparticles for medical applications should not non-specifically adhere to vascular endothelial cells or blood cells, particularly platelets. To date, several polymers have been developed for coating the surface of oxide nanoparticles, including polyethylene glycol (PEG),[6] dextran,[7] and polyvinylpyrrolidone, amongst others.[8] However, despite significant progress, a persisting limitation of polymer-based coatings is that high molecular weight polymers tend to form thick organic "shells" that generally increase the hydrodynamic diameter of particles and cause problems following administration.

To increase the grafting density and enable the flexible adjustment of structures and functions, Felder-Flesch and coworkers proposed the grafting of dendritic oligoethylene glycols *via* phosphonate chemistry.[9–11] In contrast to widely-used linear polymer brushes, dendritic molecules allow for the discrete control of entities with monodisperse size and physical properties by changing their generation.[12] Phosphonates were chosen for the surface coupling because they realize a much higher grafting rate[13] and stronger binding than the carboxylate anchors more commonly used for the surface coating of oxide nanoparticles.[14,15] The replacement of carboxylates with phosphonates also offers an advantage in terms of the magnetic properties. In-field Mössbauer spectroscopy and SQUID measurements have suggested that the coating of oxide with carboxylates leads to spin canting in the oxide layer, resulting in a decrease in the net magnetization. In contrast, coating with phosphonate did not screen the magnetic properties.[15] The coating of iron oxide nanoparticles with thin layers of dendronized oligoethylene glycol *via* phosphonate chemistry therefore realized versatile, robust, and high relaxation MRI contrast agents.[10] To date, dendronized

[a]Physical Chemistry of Biosystems, Institute of Physical Chemistry, Heidelberg University, 69120 Heidelberg, Germany. E-mail: tanaka@uni-heidelberg.de
[b]Institut de Physique et Chimie des Matériaux de Strasbourg (IPCMS), University of Strasbourg, 23 rue du Loess, 67034 Strasbourg, France
[c]Department of Materials Science and Engineering, School of Materials and Chemical Technology, Tokyo Institute of Technology, 226-8502, Kanagawa, Japan
[d]European Synchrotron Radiation Facility, CS 40220, 38043, Grenoble, France
[e]JST-PRESTO, 4-1-8 Hon-cho, Kawaguchi, Saitama, 332-0012, Japan
[f]SUPERBRANCHE SAS, IPCMS Bâtiment 69, 23 rue du loess BP 43, 67034 Strasbourg Cedex 2, France
[g]Center for Integrative Medicine and Physics, Institute for Advanced Study, Kyoto University, Kyoto 606-8501, Japan

† Electronic supplementary information (ESI) available. See DOI: 10.1039/d1ra02571f

‡ Equal contributors.

ADVANCED THERAPEUTICS
www.advtherap.com

Id1 and Id3 Are Regulated Through Matrix-Assisted Autocrine BMP Signaling and Represent Therapeutic Targets in Melanoma

*Georg Sedlmeier, Vanessa Al-Rawi, Justyna Buchert, Klaus Yserentant, Melanie Rothley, Anastasia Steshina, Simone Gräßle, Ruo-Lin Wu, Thomas Hurrle, Wilfrid Richer, Charles Decraene, Wilko Thiele, Jochen Utikal, Wasim Abuillan, Motomu Tanaka, Dirk-Peter Herten, Caroline S. Hill, Boyan K. Garvalov, Nicole Jung, Stefan Bräse, and Jonathan P. Sleeman**

The tumorigenicity of cancer cells is highly influenced by the extracellular matrix (ECM) through mechanisms that are poorly understood. Here it is reported that a variety of 3D ECM microenvironments strongly induce expression of Id1 and Id3 in melanoma cells. Genetic ablation of Id1/Id3 impairs melanoma cell outgrowth in 3D Matrigel culture and inhibits melanoma initiation in vivo. Mechanistically, 3D ECM microenvironments hinder diffusion of endogenously produced bone morphogenetic proteins, thereby fostering autocrine signaling and Id1/Id3 expression. A compound screen identifies new coumarin derivatives that potently inhibit both Id1/Id3 expression and melanoma initiation in vivo. Together, the findings reveal a novel mechanism through which the ECM increases tumorigenicity, identify Id1/Id3 as melanoma-relevant therapeutic targets, and characterize inhibitors of Id1/Id3 expression with therapeutic potential.

1. Introduction

Phenotypic plasticity is thought to enable a subpopulation of tumor cells to support the initiation, long-term maintenance and therapy resistance of tumors.[1] Plasticity can be acquired by tumor cells through exposure to appropriate environmental signals.[2] The extracellular matrix (ECM) within the tumor microenvironment, a complex and dynamic network of secreted proteins and polysaccharides that includes collagens, laminins, proteoglycans and hyaluronic acid,[3] is thought to provide such signals through its biochemical and physical properties.[4–6] In mice, the efficiency of tumor initiation increases with the

Dr. G. Sedlmeier, Dr. V. Al-Rawi, Dr. J. Buchert, Dr. M. Rothley, A. Steshina, Dr. R.-L. Wu, Dr. W. Thiele, Dr. B. K. Garvalov, Prof. J. P. Sleeman
European Center for Angioscience (ECAS)
Medical Faculty Mannheim of the University of Heidelberg
Ludolf-Krehl-Strasse 13–17, 68167 Mannheim, Germany
E-mail: jonathan.sleeman@medma.uni-heidelberg.de

Dr. G. Sedlmeier, Dr. W. Thiele, Dr. B. K. Garvalov, Prof. J. P. Sleeman
Mannheim Institute for Innate Immunoscience (MI3)
Medical Faculty Mannheim of the University of Heidelberg
Ludolf-Krehl-Strasse 13–17, 68167 Mannheim, Germany

Dr. V. Al-Rawi, Dr. M. Rothley, Dr. W. Thiele, Prof. J. P. Sleeman
Institute of Biological and Chemical Systems – Biological Information Processing (IBCS-BIP)
Karlsruhe Institute of Technology
Campus North, Building 319, Hermann-von-Helmholtz-Platz 1, 76344 Eggenstein-Leopoldshafen, Germany

The ORCID identification number(s) for the author(s) of this article can be found under https://doi.org/10.1002/adtp.202000065

DOI: 10.1002/adtp.202000065

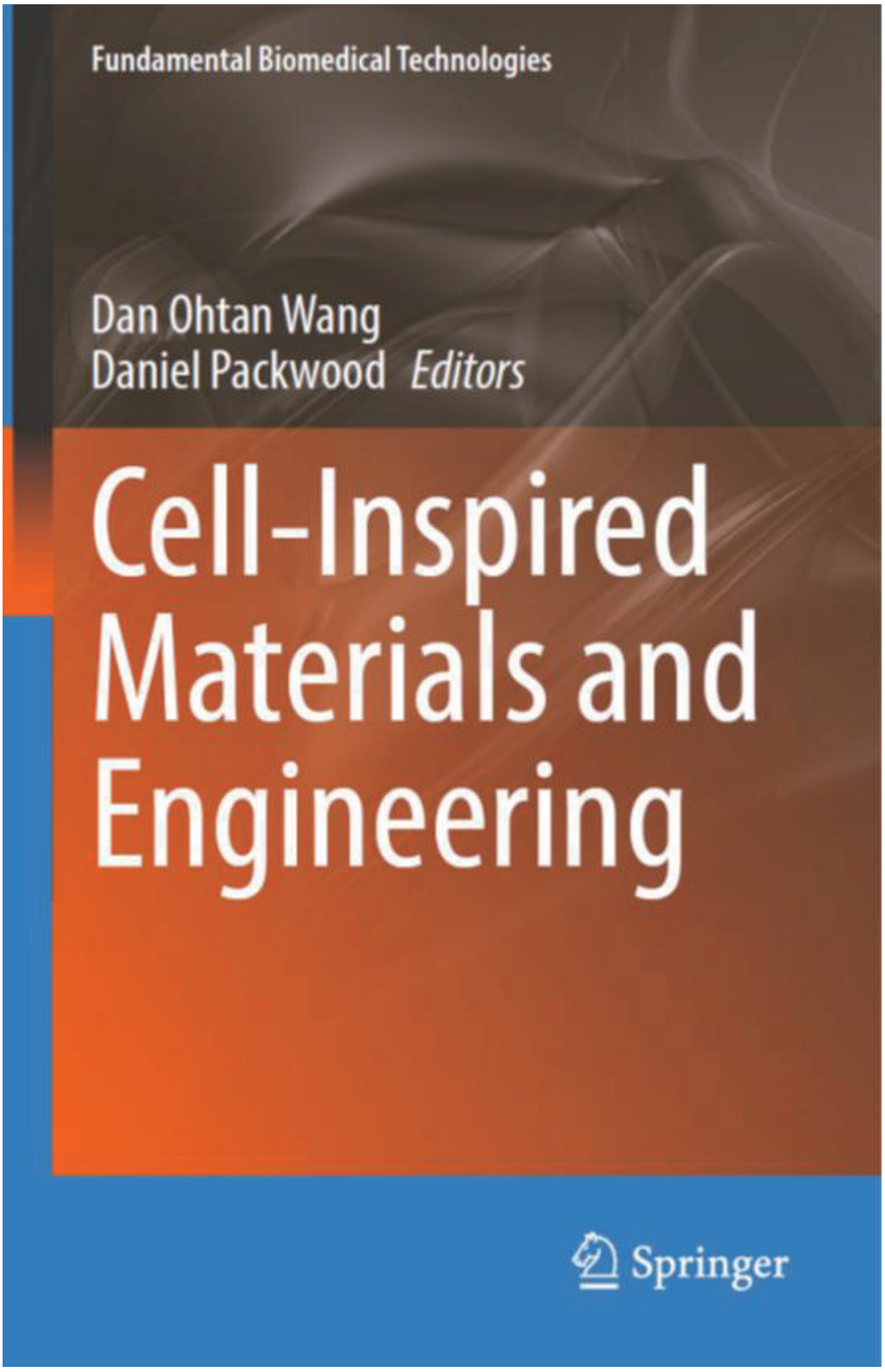
K. Yserentant, Dr. W. Abuillan, Prof. M. Tanaka, Prof. D.-P. Herten
Institute of Physical Chemistry
University of Heidelberg
Im Neuenheimer Feld 229, 69120 Heidelberg, Germany

K. Yserentant, Prof. D.-P. Herten
College of Medical and Dental Sciences & School of Chemistry
University of Birmingham
Birmingham, UK

K. Yserentant, Prof. D.-P. Herten
Centre of Membrane Proteins and Receptors (COMPARE)
Universities of Birmingham and Nottingham
UK

S. Gräßle, Dr. T. Hurrle, Dr. N. Jung, Prof. S. Bräse
Institute of Organic Chemistry (IOC)
Karlsruhe Institute of Technology
Campus South, Building 30.42, Fritz-Haber-Weg 6 76131 Karlsruhe, Germany

S. Gräßle, Dr. N. Jung, Prof. S. Bräse
Institute of Biological and Chemical Systems – Functional Molecular Systems (IBCS-FMS)
Karlsruhe Institute of Technology (KIT)
Hermann-von-Helmholtz-Platz 1 D-76344 Eggenstein-Leopoldshafen Germany


Fundamental Biomedical Technologies
Dan Ohtan Wang
Daniel Packwood Editors
Cell-Inspired Materials and Engineering
Springer

Physical Concepts Toward Cell–Material Integration

Motomu Tanaka and Akihisa Yamamoto

1 Interfaces: Where Materials Meet Cells

One of the most crucial steps in cell–material integration is the optimization of cell–material interactions. Namely, materials should not cause the protein denaturing by nonspecific adhesions or interfere with the endogenous functions of biological cells. Typical examples include stents and artificial heart valves, as the nonspecific adsorption and accumulation (fouling) of serum proteins might cause a serious consequence. On the other hand, cells should not interfere with the structural integrity of materials by irreversible chemical reactions or enzymatic degradation. The place where cells meet materials defines the "interface" between two different worlds.

M. Tanaka (✉)
Physical Chemistry of Biosystems, Institute of Physical Chemistry, Heidelberg University, Heidelberg, Germany

Center for Integrated Medicine and Physics, Institute for Advanced Study, Kyoto University, Kyoto, Japan
e-mail: tanaka@uni-heidelberg.de

A. Yamamoto
Center for Integrated Medicine and Physics, Institute for Advanced Study, Kyoto University, Kyoto, Japan

D. O. Wang, D. Packwood (eds.), *Cell-Inspired Materials and Engineering*, Fundamental Biomedical Technologies, https://doi.org/10.1007/978-3-030-55924-3_9

Biophysical Reviews (2021) 13:123–138
https://doi.org/10.1007/s12551-021-00781-1

REVIEW

Critical role of lipid membranes in polarization and migration of cells: a biophysical view

Erich Sackmann[1] · Motomu Tanaka[2,3]

Received: 19 November 2020 / Accepted: 3 January 2021 / Published online: 11 January 2021

Abstract
Cell migration plays vital roles in many biologically relevant processes such as tissue morphogenesis and cancer metastasis, and it has fascinated biophysicists over the past several decades. However, despite an increasing number of studies highlighting the orchestration of proteins involved in different signaling pathways, the functional roles of lipid membranes have been essentially overlooked. Lipid membranes are generally considered to be a functionless two-dimensional matrix of proteins, although many proteins regulating cell migration gain functions only after they are recruited to the membrane surface and self-organize their functional domains. In this review, we summarize how the logistical recruitment and release of proteins to and from lipid membranes coordinates complex spatiotemporal molecular processes. As predicted from the classical framework of the Smoluchowski equation of diffusion, lipid/protein membranes serve as a 2D reaction hub that contributes to the effective and robust regulation of polarization and migration of cells involving several competing pathways.

Keywords Lipid membranes · Cell adhesion · Cell polarization · Cell migration

Introduction: cell migration driven by membrane protrusion/retraction

Directional migration (crawling) of eukaryotic cells is one of the most relevant processes not only for simple, unicellular organisms like amoeba but also for highly developed metazoans such as mammals (Abercrombie 1980). In general, cell migration can be categorized into two groups: mesenchymal migration and amoeboid movement. Mesenchymal migration is characterized by the formation of actin-containing protrusions, such as lamellipodia, near the spreading front that is followed by retraction of the trailing end. Amoeboid migration is driven by the extension of protrusions at the front side, called pseudopods, which pull cells forward. Pseudopods might consist of actin-free blebs and lamellipodia-like structures, such as uropods of hematopoietic stem cells or invadopodia of cancer cells.

From the viewpoint of nonequilibrium statistical physics, cell migration is also an interesting subject because the front-rear asymmetry is caused by spontaneous symmetry breaking. A simple equation describing instability-driven motion for the movement of a spherical droplet, or a circle in a two-dimensional (2D) projection), including the velocity of center of mass v, friction γ and the deformation tensor S, $dv_i/dt = \gamma v_i - v^2 v_i - aS_{ij}v_j$, is not sufficient to describe cell migration. Cells adhere to the contact surface, such as the extracellular matrix or other cells, generate forces and actively deform while crawling. A number of studies have shown that a cell undergoes rhythmic deformation by protruding and retracting the plasma membrane during migration. Membrane protrusions are formed either by (i) generation of actin networks mediated by the Arp2/3 complex, such as lamellipodia and invadopodia (for cancer cells); (ii) Arp2/3-independent extension of actin bundles, such as filopodia; or (iii) actin-free membrane blebs originating from intracellular hydrodynamic pressures (Schaks et al. 2019).

✉ Motomu Tanaka
tanaka@uni-heidelberg.de

Erich Sackmann
sackmann@ph.tum.de

[1] Physics Department E22/E27, Technical University of Munich, James-Franck-Strasse, 85747 Garching, Germany

[2] Physical Chemistry of Biosystems, Institute of Physical Chemistry, Heidelberg University, 69120 Heidelberg, Germany

[3] Center for Integrative Medicine and Physics, Institute for Advanced Study, Kyoto University, Kyoto 606-8501, Japan

Biophysical Journal
Article

Functionalized supported membranes for quantifying adhesion of *P. falciparum*-infected erythrocytes

Benjamin Fröhlich,[1] Anil K. Dasanna,[2] Christine Lansche,[3] Julian Czajor,[1] Cecilia P. Sanchez,[3] Marek Cyrklaff,[3] Akihisa Yamamoto,[4] Alister Craig,[5] Ulrich S. Schwarz,[2,*] Michael Lanzer,[3,*] and Motomu Tanaka[1,4,*]
[1]Physical Chemistry of Biosystems, Institute of Physical Chemistry and [2]Institute for Theoretical Physics and BioQuant-Center for Quantitative Biology, Heidelberg University, Heidelberg, Germany; [3]Department of Infectious Diseases, Parasitology, Universitätsklinikum Heidelberg, Heidelberg, Germany; [4]Center for Integrative Medicine and Physics, Institute for Advanced Study, Kyoto University, Kyoto, Japan; and [5]Liverpool School of Tropical Medicine, Liverpool, United Kingdom

ABSTRACT The pathology of *Plasmodium falciparum* malaria is largely defined by the cytoadhesion of infected erythrocytes to the microvascular endothelial lining. The complexity of the endothelial surface and the large range of interactions available for the infected erythrocyte via parasite-encoded adhesins make analysis of critical contributions during cytoadherence challenging to define. Here, we have explored supported membranes functionalized with two important adhesion receptors, ICAM1 or CD36, as a quantitative biomimetic surface to help understand the processes involved in cytoadherence. Parasitized erythrocytes bound to the receptor-functionalized membranes with high efficiency and selectivity under both static and flow conditions, with infected wild-type erythrocytes displaying a higher binding capacity than do parasitized heterozygous sickle cells. We further show that the binding efficiency decreased with increasing intermolecular receptor distance and that the cell-surface contacts were highly dynamic and increased with rising wall shear stress as the cell underwent a shape transition. Computer simulations using a deformable cell model explained the wall-shear-stress-induced dynamic changes in cell shape and contact area via the specific physical properties of erythrocytes, the density of adhesins presenting knobs, and the lateral movement of receptors in the supported membrane.

SIGNIFICANCE Adhesion of infected erythrocytes to the microvascular endothelial lining is the key event that defines pathology of *Plasmodium falciparum* malaria. To dissect critical contributions involved in the complex interaction between parasitized erythrocytes and the endothelial surface, supported membranes functionalized with important adhesion receptors ICAM1 or CD36 were used as a well-defined biomimetic surface. In combination with computer simulations, our experiments revealed that the cytoadhesion of parasitized heterozygous sickle cells is reduced compared to infected wild-type erythrocytes not only because of reduced receptor-specific adhesion but also because of changes in the cell shape. Thus, our work highlights how molecular and cellular aspects synergize in the adhesion of *P. falciparum*-infected erythrocytes.

INTRODUCTION

Tropical malaria is an infectious disease caused by the unicellular eukaryotic parasite *Plasmodium falciparum*. An estimated 229 million people were infected with *P. falciparum* in 2019, of which 409,000 patients died of severe complications (1). The pathology of *P. falciparum* malaria is associated with the intraerythrocytic life cycle of the parasite. As the parasite develops within red blood cells, it changes the structure and function of the host cell (2,3). Most notably, infected erythrocytes acquire cytoadhesive properties and sequester in the deep vascular bed by adhering to the endothelial lining of microcapillaries (2,3), thus escaping clearance by the spleen. Sequestered infected erythrocytes can obstruct tissue perfusion and elicit localized inflammatory reactions, among other pathophysiological sequelae, which together contribute to severe disease.

Submitted February 19, 2021, and accepted for publication July 2, 2021.
*Correspondence: schwarz@thphys.uni-heidelberg.de or Michael.Lanzer@med.uni-heidelberg.de or tanaka@uni-heidelberg.de
Anil K. Dasanna's present address is Department of Theoretical Physics, Saarland University, Saarbrücken, Germany.
Editor: Tommy Nylander.
https://doi.org/10.1016/j.bpj.2021.07.003

Fröhlich et al., *Biophys. J.*
New and Notable に紹介

Biophysical Journal
New and Notable

Modeling the effects of malaria on red blood cell binding at the vascular interface

Luke A. Clifton[1,*]
[1]ISIS Pulsed Neutron and Muon Source, Science and Technology Facilities Council, Rutherford Appleton Laboratory, Harwell Science and Innovation Campus, Didcot, Oxford, United Kingdom

Malaria is one of the largest diseases affecting tropical and subtropical regions, with more than 200 million cases and between 400,000 and 500,000 deaths annually, disproportionately afflicting the young, elderly, or immune compromised (1,2). Infamously spread by infected mosquitoes, the disease is caused by several parasitic species of *Plasmodium* (*P. falciparum*, *P. malariae*, *P. vivax*, *P. ovale*, and *P. knowlesi*). Symptoms of the disease can include chills, fever, nausea, anemia, vomiting, and flu-like symptoms, such as body aches and malaise; in extreme cases, it causes seizures, coma, and death. The progress of the disease is directly linked to the life cycle of the parasite. After infection from a mosquito bite the *Plasmodium* enters the liver, where it undergoes asexual reproduction. The parasite then enters the blood stream, where it infects the red blood cells (erythrocytes) and again undergoes asexual reproduction multiple times that eventually results in the bursting (lysis) of the infected cell and release of the *Plasmodium* back into the blood serum, enabling new erythrocyte infections. It is during this stage that male or female forms of the *Plasmodia* can develop, renewing the *Plasmodium* life cycle if ingested by a female mosquito. It is also during this blood stage of the disease that the most symptoms are seen because of the combined effects of the blood cell lysis, the by-products of *Plasmodium* reproduction, and the accumulation of *Plasmodium*-infected red blood cells in capillaries.

Regions infected with malaria show a tendency to have a much higher prevalence of the sickle cell trait in the population. The carriers of this trait have inherited one gene that encodes for normal hemoglobin and one that encodes a version with a single point mutation. If an individual inherits two copies of the sickle cell gene (one from each parent) they will have sickle cell disease, named because of the shape of the red blood cells formed, which causes a number of health complications. If only one copy of the gene is present, the blood cells have a normal appearance at rest but can become sickle shaped under stress conditions. Individuals with the sickle cell gene are more resistant to malaria, meaning this trait confers a genetic advantage, hence its persistence in the population despite the disadvantages it brings. The reason for this resistance is only partly understood.

P. falciparum is responsible for ~50% of malaria cases and causes the most malaria-related deaths. During the blood stage, *P. falciparum*-infected erythrocytes bind to the blood vessel walls (composed of endothelial cells), with the accumulation of infected erythrocytes causing restrictions in blood flow in microvascular tissues, such as capillaries, causing local inflammation and preventing the removal of the infected blood cells in the spleen. The sequestration of infected erythrocytes in the brain it is associated with the severest forms of the disease. *P. falciparum*-infected erythrocytes bind to endothelial cell surfaces because of the manipulation of erythrocyte membrane composition by the parasite. Inside the erythrocyte, the *Plasmodium* produces a protein (*P. falciparum* erythrocyte membrane protein 1 (PfEMP1)) that makes its way to the red blood cell membrane surface, where it is localized in parasite-induced knob-like protrusions on the erythrocyte surface. From here, PfEMP1 can interact with several proteins found in the endothelial cell membranes, anchoring the infected erythrocyte to this.

In this issue of *Biophysical Journal*, Fröhlich et al. (3) have developed planar endothelial membrane models on solid support materials containing the eukaryotic membrane proteins intercellular adhesion molecule 1 (ICAM-1) and cluster of differentiation 36 (CD36), both of which PfEMP1 can utilize as adhesion receptors to bind the infected erythrocytes to the vascular lining. The interaction of

Submitted April 23, 2021, and accepted for publication July 2, 2021.

*Correspondence: luke.clifton@stfc.ac.uk

Editor: Tommy Nylander.
https://doi.org/10.1016/j.bpj.2021.07.004

frontiers in Molecular Biosciences

ORIGINAL RESEARCH
published: 19 November 2021
doi: 10.3389/fmolb.2021.754654

Interplay of *Trans*- and *Cis*-Interactions of Glycolipids in Membrane Adhesion

Batuhan Kav[1], *Bruno Demé*[2], *Christian Gege*[3], *Motomu Tanaka*[3,4], *Emanuel Schneck*[5,6]* *and Thomas R. Weikl*[1]*

[1]*Max Planck Institute of Colloids and Interfaces, Department of Theory and Bio-Systems, Potsdam, Germany,* [2]*Institut Laue-Langevin, Large Scale Structures Group, Grenoble, France,* [3]*Heidelberg University, Institute of Physical Chemistry of Biosystems, Heidelberg, Germany,* [4]*Kyoto University, Institute for Advanced Study, Center for Integrative Medicine and Physics, Kyoto, Japan,* [5]*Max Planck Institute of Colloids and Interfaces, Department of Biomaterials, Potsdam, Germany,* [6]*Technische Universität Darmstadt, Physics Department, Darmstadt, Germany*

Glycolipids mediate stable membrane adhesion of potential biological relevance. In this article, we investigate the *trans*- and *cis*-interactions of glycolipids in molecular dynamics simulations and relate these interactions to the glycolipid-induced average separations of membranes obtained from neutron scattering experiments. We find that the *cis*-interactions between glycolipids in the same membrane leaflet tend to strengthen the *trans*-interactions between glycolipids in apposing leaflets. The *trans*-interactions of the glycolipids in our simulations require local membrane separations that are significantly smaller than the average membrane separations in the neutron scattering experiments, which indicates an important role of membrane shape fluctuations in glycolipid *trans*-binding. Simulations at the experimentally measured average membrane separations provide a molecular picture of the interplay between glycolipid attraction and steric repulsion of the fluctuating membranes probed in the experiments.

Keywords: glycolipids, carbohydrate–carbohydrate interactions, LewisX carbohydrate, membrane adhesion, membrane shape fluctuations, molecular dynamics (MD) simulations, neutron scattering

OPEN ACCESS

Edited by:
Amirhoushang Bahrami, Bilkent University, Turkey

Reviewed by:
Franci Merzel, National Institute of Chemistry, Slovenia
Guang-Kui Xu, Xi'an Jiaotong University, China

***Correspondence:**
Emanuel Schneck
schneck@fkp.tu-darmstadt.de
Thomas R. Weikl
thomas.weikl@mpikg.mpg.de

Specialty section:
This article was submitted to Biophysics, a section of the journal Frontiers in Molecular Biosciences

Received: *06 August 2021*
Accepted: *14 October 2021*
Published: *19 November 2021*

Citation:
Kav B, Demé B, Gege C, Tanaka M, Schneck E and Weikl TR (2021) Interplay of Trans- and Cis-Interactions of Glycolipids in Membrane Adhesion. Front. Mol. Biosci. 8:754654. doi: 10.3389/fmolb.2021.754654

1 INTRODUCTION

Glycolipids are abundant components of biological membranes and play important roles in cell–cell interactions (Schnaar, 2004; Day et al., 2015; Varki, 2017; Poole et al., 2018) and the interactions of stacked membranes in cellular organelles (Stoffel and Bosio, 1997; Boudiere et al., 2014). Besides glycolipid recognition by proteins (Liu and Rabinovich, 2005; Arnaud et al., 2013), glycolipid–glycolipid interactions have been investigated in a variety of reconstituted or synthetic systems including nanoparticles and surfaces functionalized with carbohydrate tips of glycolipids (de la Fuente et al., 2001; Hernáiz and de la Fuente, 2002; de la Fuente et al., 2005), atomic force microscopy setups (Tromas et al., 2001; Bucior et al., 2004; Lorenz et al., 2012; Witt et al., 2016), reconstituted vesicles (Pincet et al., 2001; Gourier et al., 2005; Kunze et al., 2013), as well as supported membranes (Yu et al., 1998), and stacks of membranes (Schneck et al., 2011; Latza et al., 2020) containing glycolipids. Experiments with giant vesicles and stacks of membranes indicate that glycolipids can mediate stable membrane adhesion (Gourier et al., 2005; Schneck et al., 2011; Latza et al., 2020), but a molecular view and quantification of the glycolipid–glycolipid interactions that lead to membrane adhesion is still largely missing.

Polymer Journal (2022) 54:57–65
https://doi.org/10.1038/s41428-021-00555-2

ORIGINAL ARTICLE

Water modulates the lamellar structure and interlayer correlation of poly(perfluorooctyl acrylate) films: a specular and off-specular neutron scattering study

Akihisa Yamamoto[1] · Yuji Higaki[2,7] · Judith Thoma[3] · Esther Kimmle[3] · Ryohei Ishige[4] · Bruno Demé[5] · Atsushi Takahara[2,6] · Motomu Tanaka[1,3]

Received: 6 June 2021 / Revised: 13 July 2021 / Accepted: 11 August 2021 / Published online: 27 September 2021

Abstract

Comb-like polymers with pendant-like perfluorocarbon side chains self-assemble into smectic lamellae and have been extensively used as water-repellent, hydrophobic coating materials characterized by large water contact angles ($\theta > 120°$). As poly(perfluorooctyl acrylate) films are "*apparently hydrophobic*" ($\theta > 120°$), the interaction of such materials and water molecules has been largely overlooked. To unravel the molecular-level interactions between water and apparently hydrophobic polymers, specular and off-specular neutron scattering experiments were conducted at defined osmotic pressure Π_{H2O}. The poly{2-[(perfluorooctylethyl)carbamate]ethyl} acrylate (PFAUr-C_8), which had a carbamate linker, transitioned to another lamellar phase at 89 °C. At $T = 25$ °C; the lamellar periodicity of PFAUr-C_8 slightly increased with decreasing osmotic pressure, while the vertical correlation length increased. However, the poly[(perfluorooctyl)ethyl] acrylate (PFA-C_8) that did not contain a carbamate linker directly transitioned to a disordered phase at 84 °C. The lamellar periodicity of PFA-C_8 was largely independent of the osmotic pressure, suggesting that PFA-C_8 was poorly hydrated. Remarkably, the vertical correlation length decreased with decreasing osmotic pressure. Because hydration facilitated by the linker modulated the smectic lamellae of the poly(perfluoroalkyl acrylate), water molecules could be used to optimize the self-assembly of apparently hydrophobic liquid crystalline polymers.

Introduction

Fluorocarbons and hydrocarbons possess distinct structural and physicochemical properties [1, 2]. The cross-sectional area of fluorocarbons (27–30 Å^2) is larger than that of hydrocarbons (18–21 Å^2). Because of the large steric requirements of fluorine, fluorocarbons adopt a helical conformation and form a rigid, rod-like chain [3]. The cohesion between fluorocarbon chains is weaker than that of their hydrogenated analogs because the polarizability of fluorine is lower than that of hydrogen. Because fluorocarbon chains are both hydrophobic and oleophobic [1], linearly connected fluorocarbon and hydrocarbon chains are amphiphilic. These molecules spread at the air/water

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41428-021-00555-2.

✉ Atsushi Takahara
takahara.atsushi.150@m.kyushu-u.ac.jp

✉ Motomu Tanaka
tanaka@uni-heidelberg.de

[1] Center for Integrative Medicine and Physics, Institute for Advanced Study, Kyoto University, Kyoto 606-8501, Japan

[2] Institute for Materials Chemistry and Engineering, Kyushu University, Fukuoka 819-0395, Japan

[3] Physical Chemistry of Biosystems, Institute of Physical Chemistry, Heidelberg University, D69120 Heidelberg, Germany

[4] Department of Chemical Science and Engineering, School of Materials and Chemical Technology, Tokyo Institute of Technology, Tokyo 152-8552, Japan

[5] Institut Laue-Langevin, 6 rue Jules Horowitz, F38042 Grenoble, Cedex 9, France

[6] Research Center for Negative Emission Technology, Kyushu University, Fukuoka 819-0395, Japan

[7] Present address: Department of Integrated Science and Technology, Faculty of Science and Technology, Oita University, Oita 870-1192, Japan

SPRINGER NATURE

RESEARCH ARTICLE

ADVANCED MATERIALS
www.advmat.de

De Novo Synthesis of Free-Standing Flexible 2D Intercalated Nanofilm Uniform over Tens of cm^2

Prince Ravat, Hikaru Uchida, Ryosuke Sekine, Ko Kamei, Akihisa Yamamoto, Oleg Konovalov, Motomu Tanaka, Teppei Yamada,* Koji Harano,* and Eiichi Nakamura**

Of a variety of intercalated materials, 2D intercalated systems have attracted much attention both as materials per se, and as a platform to study atoms and molecules confined among nanometric layers. High-precision fabrication of such structures has, however, been a difficult task using the conventional top-down and bottom-up approaches. The de novo synthesis of a 3-nm-thick nanofilm intercalating a hydrogen-bonded network between two layers of fullerene molecules is reported here. The two-layered film can be further laminated into a multiply film either in situ or by sequential lamination. The 3 nm film forms uniformly over an area of several tens of cm^2 at an air/water interface and can be transferred to either flat or perforated substrates. A free-standing film in air prepared by transfer to a gold comb electrode shows proton conductivity up to 1.4×10^{-4} S cm^{-1}. Electron-dose-dependent reversible bending of a free-standing 6-nm-thick nanofilm hung in a vacuum is observed under electron beam irradiation.

1. Introduction

Fundamental problems to be solved when designing an ideal synthesis of 2D nanomaterials[1–10] include mild conditions, pre- and postsynthetic structural control, structural uniformity over an area as large as possible, and robustness and flexibility to be free-standing and transferable. These issues rear their head in the fabrication of 2D intercalated nanofilms, as the materials find an increasing number of applications such as charge transporting material, energy storage, electronic device, and battery material.[11–13] However, only a limited level of control has been realized by either of the two conventional approaches: Top-down inserting intercalant to a layered material or bottom-up assembling layers and intercalants together (**Figure 1a**). The top-down approach breaking apart the preformed layered structure of 3D materials provides a quick and scalable access to the locally precise intercalated structure, but lacks the control of long-range structural uniformity as to the thickness and the area of the 2D film. The bottom-up approach, on the other hand, can better control the uniformity of the film. Relying on self-assembly of numerous building blocks, however, it is intrinsically unsuitable for making robust film in a scalable manner. We conceived of a de novo synthesis, where the prelamellar blocks and intercalants spontaneously form a lamellar structure, which is further laminated or intercalated postsynthetically (Figure 1b). To this end, we designed an octopus-like conical fullerene amphiphile (CFA, **1**)[14–16] tangling its sticky legs to form a 2D hydrogen-bonded network (Figure 1c). We report here the synthesis and properties of 3-nm-thick fullerene film (FF) at the air/water interface, which features a hydrogen-bonded water network intercalated between the two CFA layers (Figure 1d). Under ambient conditions during a few hours, the pentapod molecule **1** in toluene/1-butanol/water spontaneously forms a 3-nm-thick uniform film over several tens of cm^2. We can also prepare in situ a multiply film either by using larger amount of **1** or by repeating the whole procedure multiple times (Figure 1b). The latter approach will provide a method for laminating different 2D films sequentially one after another. The film can be transferred to a variety of flat or perforated substrates, and a 6-nm-thick film in humid air on a gold comb electrode shows proton conductivity up to 1.4×10^{-4} S cm^{-1} (Figure 1e). The film in vacuum (Figure 1d) was found to bend reversibly under electron beam irradiation at different electron dose rates (EDRs), suggesting differential charging of top and bottom layers.[17]

P. Ravat, H. Uchida, R. Sekine, K. Kamei, T. Yamada, K. Harano, E. Nakamura
Department of Chemistry
The University of Tokyo
7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan
E-mail: teppei@chem.s.u-tokyo.ac.jp; harano@chem.s.u-tokyo.ac.jp; nakamura@chem.s.u-tokyo.ac.jp
A. Yamamoto, M. Tanaka
Center for Integrative Medicine and Physics
Institute for Advanced Study
Kyoto University
Kyoto 606–8501, Japan
E-mail: tanaka@uni-heidelberg.de
O. Konovalov
European Synchrotron Radiation Facility
Grenoble 38043, France
M. Tanaka
Physical Chemistry of Biosystems
Institute of Physical Chemistry
Heidelberg University
Heidelberg 69120, Germany
The ORCID identification number(s) for the author(s) of this article can be found under https://doi.org/10.1002/adma.202106465.

DOI: 10.1002/adma.202106465

Article

TRANSPARENT PROCESS OPEN ACCESS

EMBO Molecular Medicine

CDK7/12/13 inhibition targets an oscillating leukemia stem cell network and synergizes with venetoclax in acute myeloid leukemia

Lixiazi He[1,2], Christian Arnold[2,3], Judith Thoma[4], Christian Rohde[1,2], Maksim Kholmatov[2,3], Swati Garg[1,2,5], Cheng-Chih Hsiao[6], Linda Viol[7,8], Kaiqing Zhang[9], Rui Sun[9], Christina Schmidt[1], Maike Janssen[1], Tara MacRae[10], Karin Huber[1], Christian Thiede[11], Josée Hébert[12,13,14], Guy Sauvageau[10,13,14], Julia Spratte[15], Herbert Fluhr[15], Gabriela Aust[16], Carsten Müller-Tidow[1,2], Christof Niehrs[9,17], Gislene Pereira[7,8], Jörg Hamann[6], Motomu Tanaka[4,18], Judith B Zaugg[2,3] & Caroline Pabst[1,2,*]

Abstract

The heterogeneous response of acute myeloid leukemia (AML) to current anti-leukemic therapies is only partially explained by mutational heterogeneity. We previously identified GPR56 as a surface marker associated with poor outcome across genetic groups, which characterizes two leukemia stem cell (LSC)-enriched compartments with different self-renewal capacities. How these compartments self-renew remained unclear. Here, we show that GPR56^{+} LSC compartments are promoted in a complex network involving epithelial-to-mesenchymal transition (EMT) regulators besides Rho, Wnt, and Hedgehog (Hh) signaling. Unexpectedly, Wnt pathway inhibition increased the more immature, slowly cycling GPR56^{+}CD34^{+} fraction and Hh/EMT gene expression, while Wnt activation caused opposite effects. Our data suggest that the crucial role of GPR56 lies in its ability to co-activate these opposing signals, thus ensuring the constant supply of both LSC subsets. We show that CDK7 inhibitors suppress both LSC-enriched subsets *in vivo* and synergize with the Bcl-2 inhibitor venetoclax. Our data establish reciprocal transition between LSC compartments as a novel concept underlying the poor outcome in GPR56^{high} AML and propose combined CDK7 and Bcl-2 inhibition as LSC-directed therapy in this disease.

Keywords AML; CDK7 inhibition; GPR56; leukemia stem cell; self-renewal
Subject Categories Cancer; Signal Transduction
DOI 10.15252/emmm.202114990 | Received 14 August 2021 | Revised 6 February 2022 | Accepted 7 February 2022 | Published online 7 March 2022
EMBO Mol Med (2022) 14: e14990

Introduction

Acute myeloid leukemia (AML) is a hematologic malignancy affecting both young and elderly patients, for whom intensive therapies are often not an option (Döhner *et al*, 2015). Assessment of cytogenetic and molecular genetic aberrations has become the gold standard for risk stratification and for guiding therapeutic decisions for AML patients harboring targetable mutations (Döhner *et al*, 2017). Targeting mutated proteins by small molecules such as IDH1/2 or

1 Department of Medicine V, Hematology, Oncology and Rheumatology, University Hospital Heidelberg, Heidelberg, Germany
2 Molecular Medicine Partnership Unit (MMPU), University of Heidelberg and European Molecular Biology Laboratory (EMBL), Heidelberg, Germany
3 European Molecular Biology Laboratory (EMBL), Heidelberg, Germany
4 Physical Chemistry of Biosystems, Institute of Physical Chemistry, Heidelberg University, Heidelberg, Germany
5 Department of Medical Oncology, Dana Farber Cancer Institute, Boston, MA, USA
6 Department of Experimental Immunology, Amsterdam Infection & Immunity Institute, Amsterdam University Medical Centers, Amsterdam, Netherlands
7 Centre for Organismal Studies (COS)/Centre for Cell and Molecular Biology (ZMBH), University of Heidelberg, Heidelberg, Germany
8 German Cancer Research Centre (DKFZ), DKFZ-ZMBH Alliance, Heidelberg, Germany
9 Division of Molecular Embryology, DKFZ-ZMBH Alliance, Heidelberg, Germany
10 Laboratory of Molecular Genetics of Stem Cells, Institute for Research in Immunology and Cancer, University of Montreal, Montreal, Quebec, Canada
11 Department of Internal Medicine I, University Hospital of Dresden Carl Gustav Carus, Dresden, Germany
12 The Quebec Leukemia Cell Bank and Division of Hematology-Oncology, Maisonneuve-Rosemont Hospital, Montréal, Canada
13 Department of Medicine, Faculty of Medicine, Université de Montréal, Montréal, Canada
14 Division of Hematology-Oncology, Maisonneuve-Rosemont Hospital, Montreal, Quebec, Canada
15 Department of Gynecology and Obstetrics, University Hospital Heidelberg, Heidelberg, Germany
16 Department of Surgery, Research Laboratories, Leipzig University, Leipzig, Germany
17 Institute of Molecular Biology (IMB), Mainz, Germany
18 Center for Integrative Medicine and Physics, Institute for Advanced Study, Kyoto University, Kyoto, Japan
*Corresponding author. Tel: +49 6221 56 34121; Fax: +49 6221 56 5419; E-mail: caroline.pabst@med.uni-heidelberg.de

International Journal of
Molecular Sciences

MDPI

Review

Glucose Metabolism and Aging of Hematopoietic Stem and Progenitor Cells

Laura Poisa-Beiro [1,2], Jonathan J. M. Landry [3], Simon Raffel [1], Motomu Tanaka [4], Judith Zaugg [2,5], Anne-Claude Gavin [2,6] and Anthony D. Ho [1,2,*]

1 Department of Medicine V, University of Heidelberg, Im Neuenheimer Feld 410, 69120 Heidelberg, Germany; laura.poisabeiro@med.uni-heidelberg.de (L.P.-B.); simon.raffel@med.uni-heidelberg.de (S.R.)
2 Molecular Medicine Partnership Unit Heidelberg, European Molecular Biology Laboratory (EMBL) & Heidelberg University, 69120 Heidelberg, Germany; judith.zaugg@embl.de (J.Z.); anne-claude.gavin@unige.ch (A.-C.G.)
3 Genomics Core Facility, European Molecular Biology Laboratory (EMBL), Meyerhofstr. 1, 69117 Heidelberg, Germany; jonathan.landry@embl.de
4 Physical Chemistry of Biosystems, Inst, Heidelberg University, Im Neuenheimer Feld 253, 69120 Heidelberg, Germany; tanaka@uni-heidelberg.de
5 European Molecular Biology Laboratory, Meyerhofstr. 1, 69117 Heidelberg, Germany
6 Department for Cell Physiology and Metabolism, Centre Medical Universitaire, University of Geneva, Rue Michel-Servet 1, 1211 Geneva, Switzerland
* Correspondence: anthony_dick.ho@urz.uni-heidelberg.de

Abstract: Comprehensive proteomics studies of human hematopoietic stem and progenitor cells (HSPC) have revealed that aging of the HSPC compartment is characterized by elevated glycolysis. This is in addition to deregulations found in murine transcriptomics studies, such as an increased differentiation bias towards the myeloid lineage, alterations in DNA repair, and a decrease in lymphoid development. The increase in glycolytic enzyme activity is caused by the expansion of a more glycolytic HSPC subset. We therefore developed a method to isolate HSPC into three distinct categories according to their glucose uptake (GU) levels, namely the GU^{high}, GU^{inter} and GU^{low} subsets. Single-cell transcriptomics studies showed that the GU^{high} subset is highly enriched for HSPC with a differentiation bias towards myeloid lineages. Gene set enrichment analysis (GSEA) demonstrated that the gene sets for cell cycle arrest, senescence-associated secretory phenotype, and the anti-apoptosis and P53 pathways are significantly upregulated in the GU^{high} population. With this series of studies, we have produced a comprehensive proteomics and single-cell transcriptomics atlas of molecular changes in human HSPC upon aging. Although many of the molecular deregulations are similar to those found in mice, there are significant differences. The most unique finding is the association of elevated central carbon metabolism with senescence. Due to the lack of specific markers, the isolation and collection of senescent cells have yet to be developed, especially for human HSPC. The GU^{high} subset from the human HSPC compartment possesses all the transcriptome characteristics of senescence. This property may be exploited to accurately enrich, visualize, and trace senescence development in human bone marrow.

Keywords: hematopoietic stem and progenitor cells; aging; senescence signature; central carbon metabolism; glycolysis

Citation: Poisa-Beiro, L.; Landry, J.J.M.; Raffel, S.; Tanaka, M.; Zaugg, J.; Gavin, A.-C.; Ho, A.D. Glucose Metabolism and Aging of Hematopoietic Stem and Progenitor Cells. *Int. J. Mol. Sci.* **2022**, *23*, 3028. https://doi.org/10.3390/ijms23063028

Academic Editor: Jonathan L. Tilly

Received: 19 January 2022
Accepted: 2 March 2022
Published: 11 March 2022

1. Introduction

The regenerative power of a living organism is reflected by the potential of its somatic stem cells to replace damaged tissues, especially in a biological system that is characterized by a high cell turnover such as the hematopoietic system [1,2]. A living organism is hence as old as its somatic stem cells [3].

In murine models, aging of the hematopoietic system is reflected by a decrease in regenerative potential and in the competence of the adaptive immune system [4–10]. The

ACS APPLIED POLYMER MATERIALS

pubs.acs.org/acsapm

Article

One-Step Synthesis of Gelatin-Conjugated Supramolecular Hydrogels for Dynamic Regulation of Adhesion Contact and Morphology of Myoblasts

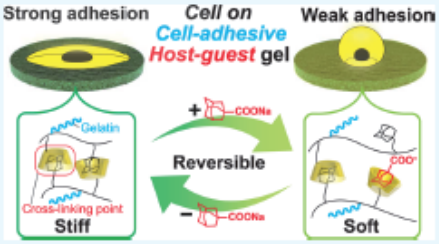
Kentaro Hayashi, Mami Matsuda, Nodoka Mitake, Masaki Nakahata, Natalie Munding, Akira Harada, Stefan Kaufmann, Yoshinori Takashima,* and Motomu Tanaka*

Cite This: *ACS Appl. Polym. Mater.* 2022, 4, 2595−2603

Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: Hydrogels possessing fine-adjustable and switchable elasticity emulate the mechanical microenvironments of biological cells, which are known to change dynamically during development and disease progression. In this study, a supramolecular hydrogel conjugated with gelatin side chains was synthesized. By systematically screening the molar fraction of supramolecular host/guest cross-linkers, Young's modulus of the substrate was fine-adjusted to the level for myoblasts, $E \approx 10$ kPa. C2C12 myoblasts reproducibly and firmly adhered to the gelatin-conjugated hydrogel via focal adhesion contacts consisting of integrin clusters, whereas only a few cells adhered to the gel without gelatin side chains. The elasticity of the gelatin-conjugated hydrogel was switchable to desired levels by simply adding and removing free guest molecules in appropriate concentrations without interfering with cell viability. Immunofluorescence confocal microscopy images of fixed cells confirmed the adaptation of focal adhesions and remodeling of actin cytoskeletons on the gelatin-conjugated hydrogel. Time-lapse phase-contrast images demonstrated the dynamic response of the cells, manifested in their morphology, to an abrupt change in the substrate elasticity. Gelatin-conjugated hydrogels with switchable elasticity enable the direct and reversible mechanical stimulation of cells in one step without tedious surface functionalization with adhesion ligands.



KEYWORDS: *supramolecular hydrogel, gelatin, reversible cross-links, switchable elasticity, mechanosensing*

1. INTRODUCTION

Ample evidence suggested that the fate and functions of biological cells are directed not only by biochemical factors but also by the biophysical properties of the surrounding microenvironment.[1,2] The formation of parallel acto-myosin bundles in myotubes[3] and neurite branches by neuronal cells[4] is optimal on substrates with elasticity similar to that of the native extracellular environment. Using chemically cross-linked polyacrylamide substrates coated with type I collagen, Discher and co-workers demonstrated that the differentiation of mesenchymal stem cells is directed by Young's modulus E of the substrate.[5] Studies conducted over the past two decades indicate that mechanical incompliance between cells and their environments may result in the misdirection of cell fate. For example, mesenchymal stem cells injected into a fibrotic liver differentiate into ductal cells, not hepatocytes, because a fibrotic liver is much stiffer than a healthy liver.[6] Przybyla et al. reported that human embryonic stem cells (hESCs) detect with high sensitivity the elasticity of hydrogel substrates and undergo β-catenin/Wnt-dependent mesoderm differentiation accordingly.[7]

To achieve ideal mechanical compliance between cells and contact substrates, chemically cross-linked hydrogels have been widely used as models of the extracellular matrix (ECM)[8] because Young's modulus of these hydrogels can be fine-adjusted by the cross-linker concentration and reaction time.[9,10] However, polymer networks cross-linked by covalent bonds are not able to alter the elasticity reversibly. It is well established that extracellular microenvironments are not static but highly dynamic both in space and time. The structure and mechanical properties of the ECM are significantly modulated by many diseases. For example, fibrotic stiffening of the bone marrow is characteristic of some blood cancers, such as osteomyeloma,[11] and remodeling of the ECM plays a key role in chronic obstructive pulmonary disease (COPD).[12] Moreover, many metastatic cancers are characterized by the upregulation of matrix metalloproteases that digest and modulate the mechanical properties of the ECM.[13] All these findings indicate that there is a clear demand for a new class of

Received: December 26, 2021
Accepted: February 15, 2022
Published: March 29, 2022

https://doi.org/10.1021/acsapm.1c01902
ACS Appl. Polym. Mater. 2022, 4, 2595−2603

Cancer Letters 533 (2022) 215600

Contents lists available at ScienceDirect

Cancer Letters

journal homepage: www.elsevier.com/locate/canlet

Original Articles

Loss of ASAP1 in the MMTV-PyMT model of luminal breast cancer activates AKT, accelerates tumorigenesis, and promotes metastasis

Caroline Schreiber [a], Annette Gruber [a], Sven Roßwag [a], Supriya Saraswati [a], Shannon Harkins [a], Wilko Thiele [a,b], Zahra Hajian Foroushani [c], Natalie Munding [c], Anja Schmaus [a,b], Melanie Rothley [a,b], Arno Dimmler [d], Motomu Tanaka [c,e], Boyan K. Garvalov [a,**,1], Jonathan P. Sleeman [a,b,*,1]

[a] European Center for Angioscience (ECAS), Medical Faculty Mannheim, Heidelberg University, 68167, Mannheim, Germany
[b] Institute for Biological and Chemical Systems - Biological Information Processing (IBCS-BIP), Karlsruhe Institute of Technology (KIT) Campus North, D-76344 Karlsruhe, Germany
[c] Physical Chemistry of Biosystems, Institute of Physical Chemistry, Heidelberg University, 69120, Heidelberg, Germany
[d] Vincentius-Diakonissen-Kliniken, 76135, Karlsruhe, Germany
[e] Center for Integrative Medicine and Physics, Institute for Advanced Study, Kyoto University, 606-8501, Kyoto, Japan

ARTICLE INFO

Keywords:
ASAP1
Luminal breast cancer
Metastasis
Invasion
AKT
Hyperplasia
MMTV-PyMT

ABSTRACT

ASAP1 is a multi-domain adaptor protein that regulates cytoskeletal dynamics, receptor recycling and intracellular vesicle trafficking. Its expression is associated with poor prognosis in a variety of cancers, and can promote cell migration, invasion and metastasis. Although amplification and expression of ASAP1 has been associated with poor survival in breast cancer, we found that in the autochthonous MMTV-PyMT model of luminal breast cancer, ablation of ASAP1 resulted in an earlier onset of tumor initiation and increased metastasis. This was due to tumor cell-intrinsic effects of ASAP1 deletion, as ASAP1 deficiency in tumor, but not in stromal cells was sufficient to replicate the enhanced tumorigenicity and metastasis observed in the ASAP1-null MMTV-PyMT mice. Loss of ASAP1 in MMTV-PyMT mice had no effect on proliferation, apoptosis, angiogenesis or immune cell infiltration, but enhanced mammary gland hyperplasia and tumor cell invasion, indicating that ASAP1 can accelerate tumor initiation and promote dissemination. Mechanistically, these effects were associated with a potent activation of AKT. Importantly, lower ASAP1 levels correlated with poor prognosis and enhanced AKT activation in human ER+/luminal breast tumors, validating our findings in the MMTV-PyMT mouse model for this subtype of breast cancer. Taken together, our findings reveal that ASAP1 can have distinct functions in different tumor types and demonstrate a tumor suppressive activity for ASAP1 in luminal breast cancer.

1. Introduction

Breast cancer is the most prevalent type of cancer in women in the Western world. Advances in early diagnosis and the development of therapeutic strategies have improved the life expectancy of patients considerably, with the relative 10-year survival of breast cancer patients in Germany currently at 82% [1]. However, around 25% of these women eventually succumb to their disease, mainly due to the consequences of metastasis.

Breast cancers can be stratified into different molecular subtypes based on the expression of the estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) [2,3]. Each subtype has a different prognosis and requires a different treatment regimen [4]. Luminal breast cancer, the most frequent type of breast cancer, is positive for the expression of ER and PR, but is mainly negative for HER2. Luminal breast cancers are subdivided into luminal A and luminal B according to their proliferation rate. Basal tumors, on the other hand, are negative for ER, PR and HER2 (triple negative) and have the worst prognosis of all breast cancer subtypes.

ASAP1 (ArfGAP with SH3 domain, ankyrin repeats and PH domain 1) is a cytoplasmic adaptor protein that is also known as AMAP1 and

* Corresponding author. European Center for Angioscience (ECAS), Medical Faculty Mannheim, Heidelberg University, 68167 Mannheim, Germany.
** Corresponding author.
E-mail addresses: boyan.garvalov@medma.uni-heidelberg.de (B.K. Garvalov), jonathan.sleeman@medma.uni-heidelberg.de (J.P. Sleeman).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.canlet.2022.215600
Received 9 December 2021; Received in revised form 10 February 2022; Accepted 11 February 2022
Available online 15 February 2022

Superiority of Mature Differentiated Cultured Human Corneal Endothelial Cell Injection Therapy for Corneal Endothelial Failure

MORIO UENO, MUNETOYO TODA, KOHSAKU NUMA, HIROSHI TANAKA, KOJIRO IMAI, JOHN BUSH, SATOSHI TERAMUKAI, NAOKI OKUMURA, NORIKO KOIZUMI, AKIHISA YAMAMOTO, MOTOMU TANAKA, CHIE SOTOZONO, JUNJI HAMURO, AND SHIGERU KINOSHITA

• PURPOSE: To investigate the safety and efficacy of cultured human corneal endothelial cell (hCEC) injection therapy with mature differentiated (mature) cell subpopulations (SPs) for corneal endothelial failure (CEF).
• DESIGN: Comparative, interventional case series.
• METHODS: This study involved 18 eyes with CEF that underwent cultured hCEC injection therapy, categorized into 2 groups: (1) 11 eyes administered a relatively lower proportion (0.1 to 76.3%) of mature cell SPs (group 1 [Gr1]), and (2) 7 eyes administered a relatively higher proportion (>90%) of mature cell SPs (group 2 [Gr2]). From 1 week to 3 years postoperation, corneal endothelial cell (CEC) density (CECD), central corneal thickness (CCT), and best-corrected visual acuity (BCVA) were recorded, and the CEC parameter's "spring constant" was calculated. The proportion of mature SPs was evaluated by fluorescence-activated cell sorting analysis based on cell-surface markers.
• RESULTS: At 3 years postoperation, corneal restoration with improved BCVA was attained in 10 of the 11 Gr1 eyes and all Gr2 eyes, the median CECD in Gr2 (3083 cells/mm^2; range, 2182-4417 cells/mm^2) was higher than that in Gr1 (1349 cells/mm^2; range, 746-2104 cells/mm^2) ($P < .001$), and the spring constant verified the superiority of the mature cultured hCECs. From 24 weeks through 3 years postoperation, the median percentage of CECD decrease was 3.2% in Gr2 and 23.6% in Gr1 ($P < .005$). CCT recovery was prompt and constant in Gr2, while diverse in Gr1. No adverse events were observed.
• CONCLUSION: Our findings showed that mature cell SPs for hCEC injection therapy provide rapid recovery of CCT, better CECD, and low CECD attrition over 3 years postsurgery. (Am J Ophthalmol 2022;237: 267–277. © 2021 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/))

CURRENTLY, THE TREATMENTS FOR MODERATE corneal endothelial dysfunction and corneal endothelial failure (CEF), classically termed "bullous keratopathy," include Descemet stripping automated endothelial keratoplasty,[1-3] Descemet membrane endothelial keratoplasty,[4,5] and penetrating keratoplasty,[6,7] all of which require the use of a fresh donor cornea. The postoperative outcomes of Descemet stripping automated endothelial keratoplasty and Descemet membrane endothelial keratoplasty procedures are quite well known.

However, for mild corneal endothelial dysfunction, such as stage 1 or stage 2 Fuchs endothelial corneal dystrophy (FECD),[8] Descemet membrane stripping only (DSO), a surgical procedure that involves the removal of a small central corneal area of the Descemet membrane with guttae and degenerated endothelium, has been proposed.[9] The benefit of DSO is that it does not involve the use of donor corneal tissue, whereas the disadvantage is a relatively low corneal endothelial cell (CEC) density (CECD) postoperatively. Moreover, the long-term efficacy of DSO has yet to be fully elucidated. Previous studies have reported the preliminary findings between the administration, or no administration, of Rho-associated protein kinase (ROCK) inhibitor eye drops following DSO.[10,11]

Ideally, for cases of corneal endothelial dysfunction or CEF, the optimal therapy would be a minimally invasive procedure that reconstructs the cornea with a high CECD of homeostatic ordered CECs, thus maintaining a normal healthy corneal structure for a long-term period post treatment. Toward that end, we previously reported our novel surgical procedure involving the injection of allogeneic cultured human CECs (hCECs) with a ROCK inhibitor into

AJO.com Supplemental Material available at AJO.com.
Accepted for publication November 8, 2021.
From the Department of Ophthalmology, Kyoto Prefectural University of Medicine, Kyoto, Japan (M.U., K.N., H.T., K.I., J.B., C.S., J.H.); Department of Frontier Medical Science and Technology for Ophthalmology, Kyoto Prefectural University of Medicine, Kyoto, Japan (M.To., S.K.); Department of Biostatistics, Kyoto Prefectural University of Medicine, Kyoto, Japan (S.T.); Department of Biomedical Engineering, Doshisha University, Kyotanabe, Japan (N.O., N.K.); Center for Integrative Medicine and Physics, Institute for Advanced Study, Kyoto University, Kyoto, Japan (A.Y., M.Ta.); Physical Chemistry of Biosystems, Institute of Physical Chemistry, Heidelberg University, Heidelberg, Germany (M.Ta.)
Inquiries to Shigeru Kinoshita, Department of Frontier Medical Science and Technology for Ophthalmology, Kyoto Prefectural University of Medicine, 465 Kajii-cho, Hirokoji-agaru, Kawaramachi-dori, Kamigyo-ku, Kyoto 602-0841, Japan.; e-mail: fmstoph@koto.kpu-m.ac.jp

0002-9394/$36.00
https://doi.org/10.1016/j.ajo.2021.11.012

Soft Matter

PAPER

View Article Online
View Journal | View Issue

Cite this: Soft Matter, 2022, 18, 4953

Time–strain inseparability in multiaxial stress relaxation of supramolecular gels formed *via* host–guest interactions†

Takuro Kimura,[a] Takuma Aoyama,[a] Masaki Nakahata,[b] Yoshinori Takashima,[c] Motomu Tanaka,[de] Akira Harada[f] and Kenji Urayama[*ag]

Received 3rd March 2022,
Accepted 9th June 2022

DOI: 10.1039/d2sm00285j

rsc.li/soft-matter-journal

Supramolecular hydrogels utilizing host–guest interactions (HG gels) exhibit large deformability and pronounced viscoelasticity. The inclusion complexes between β-cyclodextrin (host) and adamantane (guest) units on the water-soluble polymers form transient bonds. The HG gels show significant stress relaxation with finite equilibrium stress following the step strain. The stress relaxation process reflects the detachment dynamics of the transient bonds which sustain the initial stress, while the finite equilibrium stress is preserved by the permanent topological cross-links with a rotaxane structure. Nonlinear stress relaxation experiments in biaxial stretching with various combinations of two orthogonal strains unambiguously reveal that time and strain effects on stress are not separable. The relaxation is accelerated for a short time frame ($<10^2$ s) with an increase in the magnitude of strain, whereas it is retarded for a longer time window with an increase in the anisotropy of the imposed biaxial strain. The time–strain inseparability in the HG gels is in contrast to the simple nonlinear viscoelasticity of a dual cross-link gel with covalent and transient cross-links in which the separability was previously validated by the same assessment. We currently interpret that the significant susceptibility of the detachment dynamics to the deformation type results from the structural characteristics of the HG gels, *i.e.*, the host and guest moieties covalently connected to the network chains, the considerably low concentrations (<0.1 M) of these moieties, and the slidability of the permanent rotaxane cross-links.

Introduction

Polymer gels are unique soft solids which possess reversible deformability and the capacity to retain a solvent of several times their own weight. These unparalleled features enable a wide range of possibilities for their utilization in food, cosmetics, and biomedical applications, and tissue engineering;[1,2] however, a major application issue to be overcome is the enhancement of their mechanical toughness.[3] A promising approach for this issue is to utilize temporary bonds (cross-links) which repeat the attachment and detachment processes within a characteristic time for a mechanism of energy dissipation. Several studies[4–7] have demonstrated that polymer gels become pronouncedly tough and viscoelastic by introducing various types of transient bonds. For example, dual cross-linked (DC) poly(vinyl alcohol) (PVA) hydrogels[7] utilize the coordination of free borate ions on hydroxy groups in the network strands as transient bonds, and the polyampholyte physical hydrogels have ionic bonds with a wide distribution of strength.[6]

Harada *et al.* reported a new class of supramolecular gels with high flexibility, toughness, and self-healing capacities utilizing host–guest (HG) interactions between the side chains as transient bonds.[8–10] For example, linear, water-soluble polymer chains possessing few units of β-cyclodextrin (β-CD; host) and adamantane (Ad; guest) can form hydrogels cross-linked by inclusion complexes (Fig. 1a). The HG hydrogels are reversibly extensible while remaining insoluble even in good solvents.

[a] Department of Macromolecular Science and Engineering, Kyoto Institute of Technology, Sakyo-ku, Kyoto 606-8585, Japan
[b] Department of Materials Engineering Science, Graduate School of Engineering Science, Osaka University, 560-8531 Osaka, Japan
[c] Institute for Advanced Co-Creation Studies, Osaka University, Suita Osaka 565-0871, Japan
[d] Center for Integrative Medicine and Physics, Institute for Advanced Study, Kyoto University, 606-8501 Kyoto, Japan
[e] Physical Chemistry of Biosystems, Institute of Physical Chemistry, Heidelberg University, D69120 Heidelberg, Germany
[f] The Institute of Scientific and Industrial Research, Osaka University, Ibaraki, Osaka 567-0047, Japan
[g] Department of Material Chemistry, Graduate School of Engineering, Kyoto University, 615-8510 Kyoto, Japan. E-mail: urayama.kenji.2s@kyoto-u.ac.jp

† Electronic supplementary information (ESI) available: Double logarithmic plots of $\Delta\sigma$ versus t for different types of stretching at various degrees of imposed strain for HGG63-0, the reproducibility of the stress relaxation behavior for HGG63-2, and the fitted results of eqn (4) to the t dependence of f for several types of stretching for HGG63-0. See DOI: https://doi.org/10.1039/d2sm00285j

frontiers | Frontiers in Soft Matter

TYPE Original Research
PUBLISHED 19 July 2022
DOI 10.3389/frsfm.2022.959542

OPEN ACCESS

EDITED BY
Tommy Nylander,
Lund University, Sweden

REVIEWED BY
Yuri Gerelli,
Marche Polytechnic University, Italy
Fabrice Cousin,
UMR12 Laboratoire Léon Brillouin (LLB), France

*CORRESPONDENCE
Masaki Nakahata,
nakahata.masaki.scl@osaka-u.ac.jp
Motomu Tanaka,
tanaka@uni-heidelberg.de

SPECIALTY SECTION
This article was submitted to Self-Assembly and Self-Organisation, a section of the journal Frontiers in Soft Matter

RECEIVED 01 June 2022
ACCEPTED 30 June 2022
PUBLISHED 19 July 2022

CITATION
Yamamoto A, Hayashi K, Sumiya A, Weissenfeld F, Hinatsu S, Abuillan W, Nakahata M and Tanaka M (2022), Modulation of viscoelasticity and interfacial potential of polyelectrolyte brush by ion-specific interactions. *Front. Soft. Matter* 2:959542. doi: 10.3389/frsfm.2022.959542

Modulation of viscoelasticity and interfacial potential of polyelectrolyte brush by Ion-specific interactions

Akihisa Yamamoto[1], Kentaro Hayashi[1], Ai Sumiya[2], Felix Weissenfeld[3], Satoko Hinatsu[1], Wasim Abuillan[3], Masaki Nakahata[2,4]* and Motomu Tanaka[1,3]*

[1]Center for Integrative Medicine and Physics, Institute for Advanced Study, Kyoto University, Kyoto, Japan, [2]Department of Materials Engineering Science, Graduate School of Engineering Science, Osaka University, Osaka, Japan, [3]Physical Chemistry of Biosystems, Institute of Physical Chemistry, Heidelberg University, Heidelberg, Germany, [4]Department of Macromolecular Science, Graduate School of Science, Osaka University, Osaka, Japan

Polyelectrolyte brushes have drawn increasing attention because their physicochemical properties can be modulated by adjustment of the pH and ion concentration. Here, we report the controlled grafting of poly acrylic acid containing cysteine side chains onto supported lipid membranes to allow for the modulation of viscoelasticity as well as interfacial potential by ion-specific interactions, that is, with cadmium ions. Quartz crystal microbalance with dissipation indicated that the resonance frequency increased and the dissipation decreased as the cadmium concentration increased, attributed to the dehydration of brushes. Systematic variation of the molecular structure demonstrated that the coexistence of thiol and carboxyl moieties is necessary for the viscoelastic response, suggesting that these structural features, common with naturally occurring proteins, form complexes with cadmium ions. Analysis of the height fluctuation of colloidal particles by reflection interference contrast microscopy indicated that the change in the viscoelasticity of the polymer brush layer alters the curvature of the effective interfacial potential. Intriguingly, we found that modulation of the viscoelasticity and interfacial potential caused by calcium ions is weak, suggesting that the interaction is ion-specific. Polymer brushes that can alter the interfacial potential through changes in the degree of hydration opens new avenues for the design of smart, adaptable surfaces.

KEYWORDS

polyelectrolyte brush, ion specificity, interface viscoelasticity, quartz crystal microbalance, microinterferometry, interfacial potential

Methods in Molecular Biology 2470

Springer Protocols

Anja Tatiana Ramstedt Jensen
Lars Hviid *Editors*

Malaria Immunology

Targeting the Surface of Infected Erythrocytes

Humana Press

Chapter 45

Receptor-Functionalized Lipid Membranes as Biomimetic Surfaces for Adhesion of *Plasmodium falciparum*-Infected Erythrocytes

Motomu Tanaka and Michael Lanzer

Abstract

Here, we describe a detailed protocol of how to manufacture biomimetic, host receptor-functionalized membranes and how to use them in adhesion assays. Receptor-functionalized membranes have the advantage that the receptor identity and the receptor density can be controlled, which, in turn, enables studies on the kinetics, dynamics and biomechanics of receptor/ligand interactions. Such information is difficult to obtain from currently used in vitro systems, including cultured primary human microvascular endothelial cells or receptor-coated surfaces, which often display either multiple receptors or receptors with uncertain density and arrangement.

Key words Cell adhesion, Host receptor, Supported membranes

1 Introduction

Erythrocytes infected with *P. falciparum* acquire cytoadhesive properties and sequester in the microvasculature to avoid clearance in the spleen [1, 2]. While cytoadhesion ensures the survival of the parasite in the human host, it leads to severe clinical manifestation in the patient, e.g., by occluding vessels, disrupting tissue perfusion, and causing microvascular inflammation, which can lead to organ dysfunction and the symptoms associated with cerebral and placental malaria. Recognizing the pivotal role cytoadhesion plays in the pathology of *falciparum* malaria, numerous studies have addressed the underlying pathophysiological mechanisms and identified three families of parasite-encoded, surface-presented variant antigens that can mediate cytoadhesive interactions with host receptors [1, 2]. These are the RIFIN, the STEVOR, and the PfEMP1 families. Both RIFIN and STEVOR antigens can promote rosetting of parasitized erythrocytes with uninfected red blood cells, albeit with different specificities for host receptors—ABO

Anja Tatiana Ramstedt Jensen and Lars Hviid (eds.), *Malaria Immunology: Targeting the Surface of Infected Erythrocytes*, Methods in Molecular Biology, vol. 2470, https://doi.org/10.1007/978-1-0716-2189-9_45,

Nanoscale Advances

ROYAL SOCIETY OF CHEMISTRY

PAPER

View Article Online
View Journal | View Issue

Cite this: *Nanoscale Adv.*, 2022, 4, 5027

Ion-specific nanoscale compaction of cysteine-modified poly(acrylic acid) brushes revealed by 3D scanning force microscopy with frequency modulation detection†

Akihisa Yamamoto, [a] Takahiko Ikarashi, [b] Takeshi Fukuma, [bc] Ryo Suzuki, [a] Masaki Nakahata, [de] Kazuki Miyata [bc] and Motomu Tanaka [af]

Stimuli-responsive polyelectrolyte brushes adapt their physico-chemical properties according to pH and ion concentrations of the solution in contact. We synthesized a poly(acrylic acid) bearing cysteine residues at side chains and a lipid head group at the terminal, and incorporated them into a phospholipid monolayer deposited on a hydrophobic silane monolayer. The ion-specific, nanoscale response of polyelectrolyte brushes was detected by using three-dimensional scanning force microscopy (3D-SFM) combined with frequency modulation detection. The obtained topographic and mechanical landscapes indicated that the brushes were uniformly stretched, undergoing a gradual transition from the brush to the bulk electrolyte in the absence of divalent cations. When 1 mM calcium ions were added, the brushes were uniformly compacted, exhibiting a sharper brush-to-bulk transition. Remarkably, the addition of 1 mM cadmium ions made the brush surface significantly rough and the mechanical landscape highly heterogeneous. Currently, cadmium-specific nanoscale compaction of the brushes is attributed to the coordination of thiol and carboxyl side chains with cadmium ions, as suggested for naturally occurring, heavy metal binding proteins.

Received 2nd June 2022
Accepted 14th September 2022

DOI: 10.1039/d2na00350c

rsc.li/nanoscale-advances

Introduction

Stimuli-responsive polymers have attracted interest for use in various drug delivery and microencapsulation applications because these substances can protect and/or release materials in response to the surrounding environment.[1] In particular, polyelectrolyte brushes have been grafted on surfaces to give the materials adaptable functionalities. In these cases, the physical properties of the surface can be modulated based on the electrostatic properties of the external media (*e.g.*, pH and salt concentrations).[2–4] The structures and mechanical properties of polymer brushes have been measured experimentally using X-ray/neutron reflectivity,[5,6] quartz crystal microbalance with dissipation (QCM-D),[7,8] tribology,[9,10] and microinterferometry.[11,12]

Among the various techniques, atomic force microscopy (AFM) is commonly used to investigate the mechanical properties of polymer brushes *via* nanoindentation.[13,14] Recently, Fukuma *et al.*, developed three-dimensional scanning force microscopy (3D-SFM) based on frequency modulation AFM (FM-AFM),[15] which has been utilized to construct force maps of material surfaces. During the measurement process, a cantilever tip scans in the vicinity of the interface both parallel and perpendicular to the surface, and the frequency shift of the oscillating cantilever is recorded in 3D space. This technique has been successful in visualizing the 3D force maps of the surfaces of various materials in water, *e.g.*, minerals,[16,17] graphene,[18] graphite,[19] and supported phospholipid bilayers.[20] A key advantage of this technique is that it can be used to investigate the density distribution of water at the solid/water interface. By exploiting this unique functionality, 3D-SFM has been applied to observe the ammonia-mediated hydration of poly(vinyl alcohol) coated surfaces.[21] However, to our knowledge, no experimental studies have demonstrated the potential of 3D-SFM to detect dynamic modulations of hydrated polymer brushes driven by external chemical stimuli.

In this study, we functionalized the surface of planar lipid membranes (*i.e.*, supported membranes)[22,23] with poly(acrylic

[a]Center for Integrative Medicine and Physics, Institute for Advanced Study, Kyoto University, Kyoto 606-8501, Japan. E-mail: yamamoto.akihisa.6w@kyoto-u.ac.jp
[b]Division of Nano Life Science, Kanazawa University, Kanazawa 920-1192, Japan. E-mail: k-miyata@staff.kanazawa-u.ac.jp
[c]Nano Life Science Institute (WPI-NanoLSI), Kanazawa University, Kanazawa 920-1192, Japan
[d]Department of Materials Engineering Science, Graduate School of Engineering Science, Osaka University, Osaka 560-8531, Japan
[e]Department of Macromolecular Science, Graduate School of Science, Osaka University, Osaka 560-0043, Japan
[f]Physical Chemistry of Biosystems, Institute of Physical Chemistry, Heidelberg University, 69120 Heidelberg, Germany. E-mail: tanaka@uni-heidelberg.de

† Electronic supplementary information (ESI) available. See https://doi.org/10.1039/d2na00350c

polymers

MDPI

Article

Stimulus-Responsive, Gelatin-Containing Supramolecular Nanofibers as Switchable 3D Microenvironments for Cells

Kentaro Hayashi [1,†], Mami Matsuda [2,†], Masaki Nakahata [2], Yoshinori Takashima [2,3,*] and Motomu Tanaka [1,4,*]

[1] Center for Integrative Medicine and Physics, Institute for Advanced Study, Kyoto University, Kyoto 606-8501, Japan
[2] Department of Macromolecular Science, Graduate School of Science, Osaka University, Osaka 560-0043, Japan
[3] Institute for Advanced Co-Creation Studies, Osaka University, Osaka 565-0871, Japan
[4] Physical Chemistry of Biosystems, Institute of Physical Chemistry, Heidelberg University, 69120 Heidelberg, Germany
* Correspondence: takashima.yoshinori.sci@osaka-u.ac.jp (Y.T.); tanaka@uni-heidelberg.de (M.T.)
† These authors contributed equally to this work.

Abstract: Polymer- and/or protein-based nanofibers that promote stable cell adhesion have drawn increasing attention as well-defined models of the extracellular matrix. In this study, we fabricated two classes of stimulus-responsive fibers containing gelatin and supramolecular crosslinks to emulate the dynamic cellular microenvironment in vivo. Gelatin enabled cells to adhere without additional surface functionalization, while supramolecular crosslinks allowed for the reversible switching of the Young's modulus through changes in the concentration of guest molecules in culture media. The first class of nanofibers was prepared by coupling the host–guest inclusion complex to gelatin before electrospinning (pre-conjugation), while the second class of nanofibers was fabricated by coupling gelatin to polyacrylamide functionalized with host or guest moieties, followed by conjugation in the electrospinning solution (post-conjugation). In situ AFM nano-indentation demonstrated the reversible switching of the Young's modulus between 2–3 kPa and 0.2–0.3 kPa under physiological conditions by adding/removing soluble guest molecules. As the concentration of additives does not affect cell viability, the supramolecular fibers established in this study are a promising candidate for various biomedical applications, such as standardized three-dimensional culture matrices for somatic cells and the regulation of stem cell differentiation.

Keywords: gelatin nanofiber; electrospinning; supramolecular crosslink; in situ AFM nano-indentation; elasticity switching

check for updates

Citation: Hayashi, K.; Matsuda, M.; Nakahata, M.; Takashima, Y.; Tanaka, M. Stimulus-Responsive, Gelatin-Containing Supramolecular Nanofibers as Switchable 3D Microenvironments for Cells. *Polymers* **2022**, *14*, 4407. https://doi.org/10.3390/polym14204407

Academic Editor: Francisco Javier Espinach Orús

Received: 1 October 2022
Accepted: 14 October 2022
Published: 19 October 2022

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

1. Introduction

Tissue homeostasis in multicellular organisms is sustained by the continuous remodeling of cells and extracellular matrix (ECM). Proteolytic degradation of ECM, such as the digestion of fibrous collagen by metalloprotease, enables cancer cells to invasively migrate into tissues [1,2]. In the case of muscle damage, the accumulation of fibrous type I collagen near the damage leads to an increase in ECM elasticity, which activates muscle regeneration through the proliferation of stem cells [3]. To date, matching the mechanical properties of cells and ECM, known as mechano-compliance, has been modeled using hydrogels that exhibit the elasticity of ECM [4]. However, an increasing number of studies have shown that the behavior of cells on two-dimensional (2D) substrates is distinctly different from that on three-dimensional (3D) ECMs in vivo. Moreover, type I collagen and fibronectin, two major classes of ECM proteins, are fibrous and form "mesh-like" 3D microenvironments [5–7].

Polymer- and/or protein-based nanofibers are considered well-defined models of natural 3D ECMs [8–10]. Gelatin, a hydrolysate of collagen, has been widely applied

frontiers | Frontiers in Physics

TYPE Original Research
PUBLISHED 09 December 2022
DOI 10.3389/fphy.2022.1052106

OPEN ACCESS

EDITED BY
Changjin Huang,
Nanyang Technological University, Singapore

REVIEWED BY
Kabir H. Biswas,
Hamad bin Khalifa University, Qatar
Massimiliano Galluzzi,
Shenzhen Institutes of Advanced Technology (CAS), China

*CORRESPONDENCE
Motomu Tanaka,
tanaka@uni-heidelberg.de

SPECIALTY SECTION
This article was submitted to Biophysics, a section of the journal Frontiers in Physics

RECEIVED 23 September 2022
ACCEPTED 28 November 2022
PUBLISHED 09 December 2022

CITATION
Kimmle E, Hajian Foroushani Z, Keppler S, Thoma J, Hayashi K, Yamamoto A, Bastmeyer M and Tanaka M (2022), Discreteness of cell–surface contacts affects spatio-temporal dynamics, adhesion, and proliferation of mouse embryonic stem cells.
Front. Phys. 10:1052106.
doi: 10.3389/fphy.2022.1052106

Discreteness of cell–surface contacts affects spatio-temporal dynamics, adhesion, and proliferation of mouse embryonic stem cells

Esther Kimmle[1], Zahra Hajian Foroushani[1], Stephan Keppler[2], Judith Thoma[1], Kentaro Hayashi[3], Akihisa Yamamoto[3], Martin Bastmeyer[2,3,4] and Motomu Tanaka[1,3]*

[1]Physical Chemistry of Biosystems, Institute of Physical Chemistry, Heidelberg University, Heidelberg, Germany, [2]Zoological Institute, Cell- and Neurobiology, Karlsruhe Institute of Technology, Karlsruhe, Germany, [3]Center for Integrative Medicine and Physics, Institute for Advanced Study, Kyoto University, Kyoto, Japan, [4]Institute for Biological and Chemical Systems - Biological Information Processing (IBCS-BIP), Karlsruhe Institute of Technology, Eggenstein-Leopoldshafen, Germany

The self-renewal and lineage-specific differentiation of stem cells are regulated by interactions with their microenvironments, called stem cell *niche*. Stem cells receive both biochemical and biophysical cues from their *niche*, which leads to the activation of signaling pathways, resulting in the modulation of gene expressions to guide their fate. Most of previous studies are focused on the effect of substrate stiffness using hydrogels with different Young's moduli, and information is lacking on the effect of the discreteness of cell–substrate contacts on stem cells. Using mouse pluripotent, embryonic stem cells (mESCs) as the model system for early development, we quantitatively investigated the migration, dynamic deformation, and adhesion of mESCs on sparse and dense gelatin nanofibers deposited on glass surfaces, with a continuous layer of gelatin coated on glass substrates as the control. After confirming the maintenance of pluripotency on all the surfaces throughout the experiments, the centroid trajectories were monitored using timelapse imaging. The mean square displacement analysis indicated that both the diffusion coefficient and exponent were largest on sparse nanofibers, while the diffusion coefficient of mESCs on dense nanofibers was comparable to that on the control. Moreover, power spectral analysis of the shape deformation in the Fourier mode indicated that mESCs predominantly underwent elliptic deformation (mode 2), with the largest energy dissipation on sparse nanofibers. These data suggest that mESCs can deform and move on sparse nanofibers owing to the discrete cell–surface contact points. Intriguingly, using a self-developed technique based on laser-induced shock waves, a distinctly larger critical pressure was required to detach cells from nanofibers than from continuous gelatin. This finding suggests that the continuous but weak cell-substrate contacts suppress the deformation-driven mESC migration. As one of the key biological functions of stem cells, the proliferation rate of mESCs on these surfaces was determined. Although the observed difference was not statistically significant, the highest proliferation rate was observed on

2023 年

Soft Matter

ROYAL SOCIETY OF CHEMISTRY

PAPER

View Article Online
View Journal | View Issue

Cite this: *Soft Matter*, 2023, 19, 2491

Modulation of wetting of stimulus responsive polymer brushes by lipid vesicles: experiments and simulations†

Felix Weissenfeld,‡[a] Lucia Wesenberg,‡[b] Masaki Nakahata,[cd] Marcus Müller *[b] and Motomu Tanaka *[ae]

Received 20th December 2022,
Accepted 10th February 2023

DOI: 10.1039/d2sm01673g

rsc.li/soft-matter-journal

The interactions between vesicle and substrate have been studied by simulation and experiment. We grafted polyacrylic acid brushes containing cysteine side chains at a defined area density on planar lipid membranes. Specular X-ray reflectivity data indicated that the addition of Cd^{2+} ions induces the compaction of the polymer brush layer and modulates the adhesion of lipid vesicles. Using micro-interferometry imaging, we determined the onset level, $[CdCl_2]$ = 0.25 mM, at which the wetting of the vesicle emerges. The characteristics of the interactions between vesicle and brush were quantitatively evaluated by the shape of the vesicle near the substrate and height fluctuations of the membrane in contact with brushes. To analyze these experiments, we have systematically studied the shape and adhesion of axially symmetric vesicles for finite-range membrane–substrate interaction, *i.e.*, a relevant experimental characteristic, through simulations. The wetting of vesicles sensitively depends on the interaction range and the approximate estimates of the capillary length change significantly, depending on the adhesion strength. We found, however, that the local transversality condition that relates the maximal curvature at the edge of the adhesion zone to the adhesion strength remains rather accurate even for a finite interaction range as long as the vesicle is large compared to the interaction range.

1 Introduction

Physical contact of cells to their neighbors – cell adhesion – plays a key role in a wide variety of biological processes. Cell adhesion modulates a number of biochemical signaling pathways[1,2] and tissue morphogenesis driven by forces acting between neighboring cells.[3] On the other hand, impaired cell adhesion function is often associated with diseases, such as cancer metastasis. A significant reduction of cell–cell and cell–matrix adhesion causes the invasive migration and release of cancer cells into blood circulation.[4] Ample evidence has indicated that cell adhesion is not only a static attachment between cells but also highly dynamic. For example, the freshwater polyp Hydra is able to regenerate the complete body with a new head and foot by *de novo* pattern formation from dissociated single cells by sorting cell–cell contacts.[5,6] On the molecular level, an increasing number of experimental studies have shown that the dynamic rearrangement of adhesion molecules and their ligands plays critical roles in immunological response[7] and cell apoptosis.[8] Such experimental findings have been qualitatively recapitulated by using a phenomenological model of adhesion-induced phase separation[9] or by assuming the presence of strong pinning centers.[10] However, the quantitative combination of experiments and simulations still remains challenging.

Therefore, a large number of studies so far have been performed to physically model cell adhesion using rather simple, artificial lipid vesicles in the presence and absence of specific ligand–receptor-like interaction pairs (stickers). Cell adhesion in equilibrium has been described within the framework of wetting physics, irrespective of the different origins of adhesion on the molecular level.[11–14] In analogy to the shape of liquid drops on substrates, the shape of a cell or a lipid vesicle can be fine-tuned by tailoring the membrane–substrate interaction, $V(z)$, that quantifies the free energy of placing a unit area of the membrane a distance, z, away from the substrate. $V(z)$ is

[a] *Physical Chemistry of Biosystems, Institute of Physical Chemistry, Heidelberg University, 69120 Heidelberg, Germany. E-mail: tanaka@uni-heidelberg.de*
[b] *Institute for Theoretical Physics, Georg-August University, Friedrich-Hund-Platz 1, 37077 Göttingen, Germany. E-mail: mmueller@theorie.physik.uni-goettingen.de*
[c] *Department of Materials Engineering Science, Graduate School of Engineering Science, Osaka University, 560-8531 Osaka, Japan*
[d] *Department of Macromolecular Science, Graduate School of Science, Osaka University, 560-8531 Osaka, Japan*
[e] *Center for Advanced Study, Institute for Advanced Study, Kyoto University, 606-8501 Kyoto, Japan*

† Electronic supplementary information (ESI) available. See DOI: https://doi.org/10.1039/d2sm01673g

‡ These authors contributed equally.

iScience

CellPress
OPEN ACCESS

Article

Wnt/β-catenin signaling induces axial elasticity patterns of *Hydra* extracellular matrix

Mariam Veschgini,[1] Ryo Suzuki,[1,2] Svenja Kling,[3] Hendrik O. Petersen,[3] Bruno Gideon Bergheim,[3] Wasim Abuillan,[1] Philipp Linke,[1] Stefan Kaufmann,[1] Manfred Burghammer,[4] Ulrike Engel,[3,5] Frank Stein,[6] Suat Özbek,[3] Thomas W. Holstein,[2,3,*] and Motomu Tanaka[1,2,7,*]

SUMMARY

The extracellular matrix (ECM) plays crucial roles in animal development and diseases. Here, we report that Wnt/β-catenin signaling induces the ECM remodeling during *Hydra* axis formation. We determined the micro- and nanoscopic arrangement of fibrillar type I collagen along *Hydra*'s body axis using high-resolution microscopy and X-ray scattering. Elasticity mapping of the ECM *ex vivo* revealed distinctive elasticity patterns along the body axis. A proteomic analysis of the ECM showed that these elasticity patterns correlate with a gradient-like distribution of metalloproteases along the body axis. Activation of the Wnt/β-catenin pathway in wild-type and transgenic animals alters these patterns toward low ECM elasticity patterns. This suggests a mechanism whereby high protease activity under control of Wnt/β-catenin signaling causes remodeling and softening of the ECM. This Wnt-dependent spatiotemporal coordination of biochemical and biomechanical cues in ECM formation was likely a central evolutionary innovation for animal tissue morphogenesis.

INTRODUCTION

The extracellular matrix (ECM) regulates the homeostasis of animal tissues, supporting the structural integrity and cell functions.[1] ECM remodeling plays vital roles in regulating not only behaviors of single cells[2] but also the morphogenesis of tissues, where it is accompanied by large-scale deformations, such as tissue invagination during gastrulation or the immigration and convergent extension of cells.[3–5] Many diseases are also characterized by the significant remodeling of ECM, such as the myelofibrosis in bone marrow causing pancytopenia[6] and stiffening of pulmonary ECM in fibrotic lung tissues.[7] However, despite accumulating knowledge on participating proteins and key signaling pathways, little is understood how ECM elasticity correlates with tissue morphogenesis.[3] Barriga et al. indented cut pieces of *Xenopous laevis*' mesoderm with atomic force microscopy (AFM) and demonstrated by using head mesoderm of different age as well as hydrogels that the collective migration of neural crest cells during morphogenesis requires a stiffening of mesoderm.[8,9] However, direct elasticity measurements of the ECM as a function of morphogenesis have not been reported so far. The use of a model animal with a simpler body design is therefore a straightforward strategy.

In this paper, we investigated the temporal progression of ECM elasticity during tissue growth in the freshwater polyp *Hydra*. *Hydra* is a member of the >600 million-years-old phylum Cnidaria and a paradigm for an almost unlimited growth and regeneration capability. Compared to bilaterian animals, it has a simple, sack-like body plan with a body wall composed of an ECM, called mesoglea, which separates two cell layers; an outer ectoderm; and an inner endoderm. Previous accounts showed that the mesoglea plays an important role in asexual reproduction of *Hydra* through budding. Mesoglea undergoes dynamic remodeling in order to support the daughter animal (bud) stemming out of the main body axis of a mother *Hydra*.[10–12] This body axis is an oral-aboral (OA) axis with an oral "head" and an aboral "foot". It is equivalent to the posterior-anterior axis of bilaterians (for details, see the review by Holstein[13]).

Intriguingly, the molecular composition of *Hydra* mesoglea is very similar to that of vertebrate ECM, containing heparan sulfate, laminin, and fibronectin-like molecules as well as fibrillar (type I and II) and non-fibrillar (type IV) collagens.[12,14–16] *Hydra* ECM combines two major ECM functions that are separated

[1]Physical Chemistry of Biosystems, Institute of Physical Chemistry, Heidelberg University, D69120 Heidelberg, Germany

[2]Center for Integrated Medicine and Physics, Institute for Advanced Study, Kyoto University, Kyoto 606-8501, Japan

[3]Molecular Evolution and Genomics, Centre for Organismal Studies, Heidelberg University, D69120 Heidelberg, Germany

[4]European Synchrotron Radiation Facility, F38000 Grenoble, France

[5]Nikon Imaging Center, Heidelberg University, D69120 Heidelberg, Germany

[6]European Molecular Biology Laboratory, Meyerhofstrasse 1, D69117 Heidelberg, Germany

[7]Lead contact

*Correspondence: thomas.holstein@cos.uni-heidelberg.de (T.W.H.), tanaka@uni-heidelberg.de (M.T.)

https://doi.org/10.1016/j.isci.2023.106416

Tanaka et al. *NPG Asia Materials* (2023) 15:23
https://doi.org/10.1038/s41427-023-00466-z

NPG Asia Materials

REVIEW ARTICLE Open Access

Higher-order mesoscopic self-assembly of fluorinated surfactants on water surfaces

Motomu Tanaka[1,2], Marie Pierre Krafft[3] and Andreea Pasc[4]

Abstract

Surfactants containing fluorocarbon chains have been increasingly studied because they self-assemble into a variety of microscopic and mesoscopic domains and tend to form highly ordered patterns at the air/water interface; these patterns are clearly different from those formed by their hydrocarbon analogs. Focusing on the fluorinated surfactants possessing unique physical characteristics, this review describes the relationship between the line tension and dipole interaction, which is the comprehensive principle governing the pattern formation of two-dimensional self-assemblies. This review further discusses several key experimental and analytical techniques that are useful for characterizing the shape, size, correlation, and viscoelasticity of hierarchical self-assemblies on water surfaces. Finally, several biomedical applications, including biomimetic surface coating, multimodal contrast agents in medical diagnostics, and controlled delivery of gases (O_2 and NO) for oxygenation and antimicrobial effects, are introduced to highlight how the unique physicochemical properties of fluorinated self-assemblies can be applied in materials science.

Higher-order pattern formation by molecular self-assemblies is a universal phenomenon

A wide range of organic molecules (including surfactants, liquid crystals, and diblock copolymers) have various hierarchical two- and three-dimensional patterns and textures[1,2]. For example, circular domains, stripes, and chiral crystal structures have been found in Langmuir monolayers of lipids and surfactants at the air/water interface[3,4]. Three-dimensional lamellae, inversed hexagonal micelles, and bicontinuous cubic phase assemblies of lipids[5,6], liquid crystals[7], and diblock copolymers[8–11] have also been found. Notably, a small set of structural parameters leads to very similar patterns, independent of the detailed molecular structures. For example, Israelachivili, Mitchell, and Ninham theoretically accounted for the shape of self-assembled surfactant aggregates using the following geometric packing constraint: $p = v/Al$, where v is the volume of the hydrophobic core, A is the surface area (area occupied by a head group), and l is the axial length of the surfactant molecule[12]. This simple geometric constraint can be applied to predict the morphology of various supramolecular architectures formed by a wide variety of molecules with different sizes and structures, including phospholipids, liquid crystals, and block copolymers. However, the characteristic length scale and periodicity of patterns can range over several orders of magnitude, from tens of nanometers (e.g., periodicity of phospholipid "ripples")[13] to hundreds of micrometers (e.g., stationary patterns driven by chemical reactions)[14]. As comprehensively summarized by Seul and Andelman from a theoretical viewpoint[2], these patterns are stabilized through interplay between competing intermolecular interactions characterized by the spatial variation of order parameters. As described more explicitly in the following sections, this review specifically focuses on two-dimensional assemblies of fluorinated surfactants on water surfaces because the competition of line tension and dipole interaction plays dominant roles in the formation of various hierarchical structures.

Fluorinated surfactants: What make them unique compared with hydrocarbon analogs?

This review aims to provide a comprehensive overview of the physical principles governing the formation of

Correspondence: Motomu Tanaka (tanaka@uni-heidelberg.de)
[1]Center for Integrative Medicine and Physics, Institute for Advanced Study, Kyoto University, Kyoto, Japan
[2]Physical Chemistry of Biosystems, Institute of Physical Chemistry, Heidelberg University, Heidelberg, Germany
Full list of author information is available at the end of the article

ADVANCED FUNCTIONAL MATERIALS
www.afm-journal.de

Cell Shape and Forces in Elastic and Structured Environments: From Single Cells to Organoids

Rabea Link, Kai Weißenbruch, Motomu Tanaka, Martin Bastmeyer, and Ulrich S. Schwarz**

With the advent of mechanobiology, cell shape and forces have emerged as essential elements of cell behavior and fate, in addition to biochemical factors such as growth factors. Cell shape and forces are intrinsically linked to the physical properties of the environment. Extracellular stiffness guides migration of single cells and collectives as well as differentiation and developmental processes. In confined environments, cell division patterns are altered, cell death or extrusion might be initiated, and other modes of cell migration become possible. Tools from materials science such as adhesive micropatterning of soft elastic substrates or direct laser writing of 3D scaffolds have been established to control and quantify cell shape and forces in structured environments. Herein, a review is given on recent experimental and modeling advances in this field, which currently moves from single cells to cell collectives and tissue. A very exciting avenue is the combination of organoids with structured environments, because this will allow one to achieve organotypic function in a controlled setting well suited for long-term and high-throughput culture.

1. Introduction

During the last decades, cell mechanics, forces, and shape have emerged as important elements of the way biological cells interact with their environment.[1] While the importance of control of cells through biochemical ligands such as growth factors, hormones, and cytokines has been appreciated from the very start of cell culture experiments, the insight that spatial control of cell adhesion, the physical properties of the extracellular matrix as well as the mechanics of the cytoskeleton and the nucleus might be equally important for cellular decision making are rather recent insights. Not surprisingly, it was tied to the development of new tools that allowed researchers to control the extracellular environment. This development started by transferring tools from the microfabrication of electronic devices into the life sciences, most notably microcontact printing to generate adhesive islands to control cell adhesion to planar substrates.[2] Pioneering work showed that cell fate can be controlled by the size of the adhesive islands: cells only survived on large islands and triggered apoptosis on small ones.[3] Later it was discovered that this switch is related to the translation of the transcription factor YAP/TAZ into the nucleus in mechanically stressed cells.[4]

Apart from geometry, extracellular stiffness has been found to be a major regulator of cell behavior, and again this insight was tight to advances in materials preparation. Soft elastic substrates were introduced into cell culture mainly to measure cell forces from their deformations.[5,6] However, it was then realized

R. Link, U. S. Schwarz
Institute for Theoretical Physics
Heidelberg University
69120 Heidelberg, Germany
E-mail: ulrich.schwarz@bioquant.uni-heidelberg.de
R. Link, U. S. Schwarz
BioQuant-Center
Heidelberg University
69120 Heidelberg, Germany

K. Weißenbruch, M. Bastmeyer
Zoological Institute
Karlsruhe Institute of Technology (KIT)
76131 Karlsruhe, Germany
E-mail: martin.bastmeyer@kit.edu
K. Weißenbruch, M. Bastmeyer
Institute for Biological and Chemical Systems
Biological Information Processing
Karlsruhe Institute of Technology (KIT)
76344 Karlsruhe, Germany
M. Tanaka
Institute of Physical Chemistry
Heidelberg University
69120 Heidelberg, Germany

The ORCID identification number(s) for the author(s) of this article can be found under https://doi.org/10.1002/adfm.202302145

DOI: 10.1002/adfm.202302145

Cells & Development 174 (2023) 203845

Contents lists available at ScienceDirect

Cells & Development

journal homepage: www.journals.elsevier.com/cells-and-development

Physical biomarkers for human hematopoietic stem and progenitor cells

Motomu Tanaka [a,b,*], Judith Thoma [a,1], Laura Poisa-Beiro [c,1], Patrick Wuchter [c,2], Volker Eckstein [c,1], Sascha Dietrich [c,1], Caroline Pabst [c,1], Carsten Müller-Tidow [c,1], Takao Ohta [b,1], Anthony D. Ho [b,c,d,*]

[a] Physical Chemistry of Biosystems, Institute of Physical Chemistry, INF253, Heidelberg University, 69120 Heidelberg, Germany
[b] Center for Integrative Medicine and Physics, Institute for Advanced Study, Kyoto University, 606-8501 Kyoto, Japan
[c] Department of Medicine V, Heidelberg University, INF410, 69120 Heidelberg, Germany
[d] Molecular Medicine Partnership Unit Heidelberg, European Molecular Biology Laboratory (EMBL), Heidelberg University, 69120 Heidelberg, Germany

ARTICLE INFO

Keywords:
Human hematopoietic stem and progenitor cell
Acute myeloid leukemia
Cell adhesion
Spatio-temporal dynamics
Clinical agent

ABSTRACT

Adhesion of hematopoietic stem and progenitor cells (HSPCs) to the bone marrow niche plays critical roles in the maintenance of the most primitive HSPCs. The interactions of HSPC–niche interactions are clinically relevant in acute myeloid leukemia (AML), because (i) leukemia-initiating cells adhered to the marrow niche are protected from the cytotoxic effect by chemotherapy and (ii) mobilization of HSPCs from healthy donors' bone marrow is crucial for the effective stem cell transplantation. However, although many clinical agents have been developed for the HSPC mobilization, the effects caused by the extrinsic molecular cues were traditionally evaluated based on phenomenological observations. This review highlights the recent interdisciplinary challenges of hematologists, biophysicists and cell biologists towards the design of defined *in vitro* niche models and the development of physical biomarkers for quantitative indexing of differential effects of clinical agents on human HSPCs.

Introduction

Functions of somatic stem cells are tightly controlled by the balance between self-renewal and differentiation. This balance is in turn regulated by interactions between stem cells and their microenvironment, the so-called "niche" (Moore and Lemischka, 2006). In the case of hematopoietic stem and progenitor cells (HSPCs), the adhesion to the bone marrow niche has been shown to maintain the dormancy of the most primitive HSPCs (Fig. 1A). Ample evidence has indicated that mesenchymal stromal cells, osteoblasts, and endothelial cells function as the surrogate niche in the bone marrow, supporting HSPC maintenance (Lapidot et al., 2005; Mendelson and Frenette, 2014; Ho and Wagner, 2007; Morrison and Scadden, 2014). It has been reported that the co-culture of HSPCs and mesenchymal stromal cells increases proliferation and maintenance of HSPCs (Walenda et al., 2010; Wuchter et al., 2022). Furthermore, HSPCs are frequently found in the vicinity of blood vessels, suggesting that HSPCs might be maintained in a vascular niche by endothelial cells. (Kiel et al., 2005; Ding et al., 2012) To date, several key molecular interactions between HSPCs and their cellular niche have been identified. Using mouse models, it has been shown that long-term HSPCs adhere to spindle-shaped osteoblasts expressing N-cadherin, suggesting that the homophilic N-cadherin interactions are involved in the maintenance of dormancy (Zhang et al., 2003; Calvi et al., 2003). Wein et al. showed that the N-cadherin expressed on HSPCs mediates interaction with mesenchymal stem cells (Fig. 1B) (Wein et al., 2010), and Méndez-Ferrer et al. demonstrated that mesenchymal stem cells expressing nestin physically associate with HSPCs and act as niche cells (Méndez-Ferrer et al., 2010). The overexpression of N-cadherin in HSPCs further resulted in the enhancement of cytoadhesion and the suppression of HSPC division *in vitro*, suggesting that N-cadherin-mediated adhesion supports maintenance of long-term pools of HSPCs (Hosokawa et al., 2010). Another key molecular axis is the interaction between stromal cell-derived factor 1α (SDF1α) and its receptor CXCR4, which has been shown to regulate the mobilization of HSPCs (Möhle et al., 1998; Ponomaryov et al., 2000; Lapidot and Kollet, 2002; Dar et al., 2005). SDF1α is a multifunctional cytokine that serves as a

* Corresponding authors at: Center for Integrative Medicine and Physics, Institute for Advanced Study, Kyoto University, 606-8501 Kyoto, Japan.
E-mail addresses: tanaka@uni-heidelberg.de (M. Tanaka), a_d_ho@msn.com (A.D. Ho).
[1] Present address: Department of Hematology, Oncology, and Clinical Immunology, Universitätsklinikum Düsseldorf, 40225 Düsseldorf, Germany.
[2] Present address: Institute of Transfusion Medicine and Immunology, Medical Faculty Mannheim, Heidelberg University, German Red Cross Blood Service Baden-Württemberg – Hessen, 68167 Mannheim, Germany.

https://doi.org/10.1016/j.cdev.2023.203845
Received 13 February 2023; Received in revised form 18 April 2023; Accepted 21 April 2023
Available online 26 April 2023

LANGMUIR

pubs.acs.org/Langmuir Article

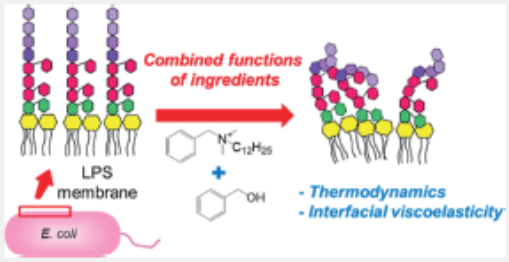
Thermodynamics and Viscoelastic Property of Interface Unravel Combined Functions of Cationic Surfactant and Aromatic Alcohol against Gram-Negative Bacteria

Ippei Furikado, Taichi Habe, Shigeto Inoue,* and Motomu Tanaka*

Cite This: *Langmuir* 2023, 39, 8523–8531 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: Lipopolysaccharides (LPSs), the major constituents of the outer membranes of Gram-negative bacteria, play a key role in protecting bacteria against antibiotics and antibacterial agents. In this study, we investigated how a mixture of cationic surfactants and aromatic alcohols, the base materials of widely used sanitizers, synergistically act on LPSs purified from *Escherichia coli* using isothermal titration calorimetry (ITC), surface tension measurements, and quartz crystal microbalance with dissipation (QCM-D). ITC data measured in the absence of Ca^{2+} ions showed the coexistence of exothermic and endothermic processes. The exotherm can be interpreted as the electrostatic binding of the cationic surfactant to the negatively charged LPS membrane surface, whereas the endotherm indicates the hydrophobic interaction between the hydrocarbon chains of the surfactants and LPSs. In the presence of Ca^{2+} ions, only an exothermic reaction was observed by ITC, and no entropically driven endotherm could be detected. Surface tension experiments further revealed that the co-adsorption of surfactants and LPS was synergistic, while that of surfactants and alcohol was negatively synergistic. Moreover, the QCM-D data indicated that the LPS membrane remained intact when the alcohol alone was added to the system. Intriguingly, the LPS membrane became highly susceptible to the combination of cationic surfactants and aromatic alcohols in the absence of Ca^{2+} ions. The obtained data provide thermodynamic and mechanical insights into the synergistic function of surfactants and alcohols in sanitation, which will enable the identification of the optimal combination of small molecules for a high hygiene level for the post-pandemic society.



INTRODUCTION

Both pathogenic and nonpathogenic bacteria overgrow, secrete extracellular polysaccharides, and form biofilms. An increasing number of studies have shown that biofilms cause many problems in household, medical, and industrial settings. In 2014, the World Health Organization issued a report stating that antimicrobial resistance, caused by the overprescription of antibiotics to human patients in clinics and livestock in farming industries, is a major threat to public health.[1−5] One problem in the medical sector is the transmission of nosocomial infections in hospitals. A recent multicenter study showed that bath basins used by patients are potential bacterial reservoirs that might transmit nosocomial infections.[6] Therefore, there is a strong demand for the development of "new" antimicrobial agents. However, it is often overlooked that we can achieve a sufficient hygiene level and reduce the number of antibiotic treatments if we appropriately use existing sanitizers.[7]

Quaternary ammonium compounds (QACs), bisbiguanides (chlorhexidine), and polymeric biguanides are the most commonly used disinfectants.[7−9] Since the 1930s, benzalkonium chloride (BAC, Figure 1a), a cationic QAC surfactant, has been extensively used as a sanitizing agent.[10,11] The mechanism of BAC activity involves the following steps. First, positively charged quaternary nitrogen atoms bind to negatively charged lipids on bacterial membrane surfaces via electrostatic attraction. Second, the hydrocarbon chains of BACs are integrated into the hydrophobic core of bacterial lipids, which results in membrane disruption and hence bacterial death.[7,11,12]

As the outer surfaces of Gram-negative bacteria display a dense layer of negatively charged glycolipids called lipopolysaccharides (LPSs, Figure 1c), the disruption of the LPS layer by the integration of electrostatically attracted cationic molecules has also been widely accepted as the functional mechanism of cationic antimicrobial peptides. The interaction of cationic antimicrobial peptides has been studied using various methods, such as SPR[13] and ITC,[14] which have

Received: March 31, 2023
Revised: May 24, 2023
Published: June 8, 2023

https://doi.org/10.1021/acs.langmuir.3c00862
Langmuir 2023, 39, 8523−8531

RESEARCH ARTICLE

ADVANCED FUNCTIONAL MATERIALS
www.afm-journal.de

Bio-Metamaterials for Mechano-Regulation of Mesenchymal Stem Cells

Natalie Munding, Magdalena Fladung, Yi Chen, Marc Hippler, Anthony D. Ho, Martin Wegener, Martin Bastmeyer,* and Motomu Tanaka**

Cell behaviors significantly depend on the elastic properties of the microenvironments, which are distinct from commonly used polymer-based substrates. Artificial elastic materials called metamaterials offer large freedom to adjust their effective elastic properties as experienced by cells, provided (i) the metamaterial unit cell is sufficiently small compared to the biological cell size and (ii) the metamaterial is sufficiently soft to deform by the active cell contraction. Thus, metamaterials targeting bio-applications (bio-metamaterials) appear as a promising path toward the mechanical control of stem cells. Herein, human mesenchymal stem cells (hMSCs) are cultured on three different types of planar periodic elastic metamaterials. To fulfill the above two key requirements, microstructured bio-metamaterials have been designed and manufactured based on a silicon elastomer-like photoresist and two-photon laser printing. In addition to the conventional morphometric and immunocytochemical analysis, the traction force that hMSCs exert on metamaterials are inferred by converting the measured displacement-vector fields into force-vector fields. The differential responses of hMSCs, both on the cellular level and the sub-cellular level, correlate with the calculated effective elastic properties of the bio-metamaterials, suggesting the potential of bio-metamaterials toward mechanical regulation of cell behaviors by the arrangement of unit cells.

1. Introduction

Metamaterials are rationally designed artificial solids in that the atoms of ordinary solids are replaced by tailored functional building blocks serving as unit cells that can be arranged into a periodic lattice. This concept allows for obtaining effective metamaterial behavior that goes beyond that of the ingredient materials and that can be highly unusual or even unprecedented. Thereby, metamaterials have enabled novel behavior and potential applications in mechanics,[1] electromagnetism/optics,[2] and transport.[3]

Here, we investigate the possibility of applying metamaterials as bio-materials, called "bio-metamaterials" in the following. The targeted application is to mechanically control the behavior of living cells adhering to the bio-metamaterial via its tailored effective elastic properties. It has been unclear and has been debated whether the effective metamaterial properties have any relevance at all for the behavior of living cells. Moreover, the meaning of effective

N. Munding, M. Tanaka
Physical Chemistry of Biosystems
Institute of Physical Chemistry
Heidelberg University
69120 Heidelberg, Germany
E-mail: tanaka@uni-heidelberg.de

M. Fladung, M. Bastmeyer
Cell and Neurobiology
Zoological Institute
Karlsruhe Institute of Technology (KIT)
76131 Karlsruhe, Germany
E-mail: martin.bastmeyer@kit.edu

Y. Chen, M. Hippler, M. Wegener
Institute of Nanotechnology and Institute of Applied Physics
Karlsruhe Institute of Technology (KIT)
76128 Karlsruhe, Germany
E-mail: martin.wegener@kit.edu

A. D. Ho
Department of Medicine V
Heidelberg University
69120 Heidelberg, Germany

A. D. Ho, M. Bastmeyer, M. Tanaka
Center for Integrative Medicine and Physics
Institute for Advanced Study
Kyoto University
Kyoto 606-8501, Japan

M. Bastmeyer
Institute for Biological and Chemical Systems– Biological Information Processing (IBCS-BIP)
Karlsruhe Institute of Technology (KIT)
76344 Eggenstein-Leopoldshafen, Germany

The ORCID identification number(s) for the author(s) of this article can be found under https://doi.org/10.1002/adfm.202301133

DOI: 10.1002/adfm.202301133

nature communications

Article

https://doi.org/10.1038/s41467-023-40934-2

Extracellular calcium functions as a molecular glue for transmembrane helices to activate the scramblase Xkr4

Received: 24 January 2023

Accepted: 11 August 2023

Published online: 11 September 2023

Check for updates

Panpan Zhang[1,2], Masahiro Maruoka[1,3], Ryo Suzuki[4], Hikaru Katani[1], Yu Dou[1,2], Daniel M. Packwood[1], Hidetaka Kosako[5], Motomu Tanaka[1,4,6] & Jun Suzuki[1,2,3,7]

The "eat me" signal, phosphatidylserine is exposed on the surface of dying cells by phospholipid scrambling. Previously, we showed that the Xkr family protein Xkr4 is activated by caspase-mediated cleavage and binding of the XRCC4 fragment. Here, we show that extracellular calcium is an additional factor needed to activate Xkr4. The constitutively active mutant of Xkr4 is found to induce phospholipid scrambling in an extracellular, but not intracellular, calcium-dependent manner. Importantly, other Xkr family members also require extracellular calcium for activation. Alanine scanning shows that D123 and D127 of TM1 and E310 of TM3 coordinate calcium binding. Moreover, lysine scanning demonstrates that the E310K mutation-mediated salt bridge between TM1 and TM3 bypasses the requirement of calcium. Cysteine scanning proves that disulfide bond formation between TM1 and TM3 also activates phospholipid scrambling without calcium. Collectively, this study shows that extracellular calcium functions as a molecular glue for TM1 and TM3 of Xkr proteins for activation, thus demonstrating a regulatory mechanism for multi-transmembrane region-containing proteins.

Phospholipids are asymmetrically distributed in the lipid bilayer of plasma membranes, wherein phosphatidylserine (PS) and phosphatidylethanolamine (PE) locate at the inner leaflet of the membranes while phosphatidylcholine (PC) and sphingomyelin (SM) locate at the outer leaflet[1,2]. To maintain the asymmetrical distribution of phospholipids, P4-ATPase functions as a flippase to translocate PS and PE from the outer to the inner leaflet in an ATP-dependent manner[3]. However, asymmetrical distribution of phospholipids is altered in various physiological situations to adapt to the environmental changes. For example, PS is exposed on the cell surface of activated platelets by phospholipid scrambling (PLS) and functions as a scaffold for coagulation factors[4]. PS is also exposed on the apoptotic cell surface, where it functions as an "eat me" signal[5,6] for apoptotic cells to be engulfed by phagocytes. In these processes, scramblases non-specifically and bi-directionally translocate phospholipids in the lipid layer without energy consumption[7–9].

We previously identified two families of scramblases: the TMEM16 family[10,11], calcium-dependent scramblases, and the XK-related (Xkr) family[12,13], caspase cleavage-dependent scramblases. The Xkr family proteins are comprised of ten transmembrane (TM) helices including two α-helices which are partly embedded in the membrane: one is positioned between TM2 and TM3, and another between TM6 and

[1]Institute for Integrated Cell-Material Sciences (WPI-iCeMS), Kyoto University, Yoshida-Honmachi, Sakyoku, Kyoto 606-8501, Japan. [2]Graduate School of Biostudies, Kyoto University, Konoe-cho, Yoshida, Sakyoku, Kyoto 606-8501, Japan. [3]Center for Integrated Biosystems, Institute for Biomedical Sciences, Academia Sinica, Taipei, Taiwan. [4]Center for Integrative Medicine and Physics (CiMPhy), Institute for Advanced Study, Kyoto University, Yoshida-Honmachi, Sakyoku, Kyoto 606-8501, Japan. [5]Fujii Memorial Institute of Medical Sciences, Institute of Advanced Medical Sciences, Tokushima University, 3-18-15 Kuramoto-cho, Tokushima 770-8503, Japan. [6]Physical Chemistry of Biosystems, Institute of Physical Chemistry, Heidelberg University, 69120 Heidelberg, Germany. [7]CREST, Japan Science and Technology Agency, Kawaguchi, Saitama 332-0012, Japan. e-mail: jsuzuki@icems.kyoto-u.ac.jp

frontiers | Frontiers in Soft Matter

TYPE Review
PUBLISHED 01 November 2023
DOI 10.3389/fsfm.2023.1257688

OPEN ACCESS

EDITED BY
Kai Yang,
Soochow University, China

REVIEWED BY
Naiyan Lu,
Jiangnan University, China
Laurent Sagalowicz,
Nestle, Switzerland

*CORRESPONDENCE
Jens Risbo,
jri@food.ku.dk
Tommy Nylander,
Tommy.Nylander@fkem1.lu.se
Motomu Tanaka,
tanaka@uni-heidelberg.de

RECEIVED 12 July 2023
ACCEPTED 11 October 2023
PUBLISHED 01 November 2023

CITATION
Risbo J, Nylander T and Tanaka M (2023), Delivery of probiotics and enzymes in self-assemblies of lipids and biopolymers based on colloidal principles.
Front. Soft Matter 3:1257688.
doi: 10.3389/fsfm.2023.1257688

Delivery of probiotics and enzymes in self-assemblies of lipids and biopolymers based on colloidal principles

Jens Risbo[1]*, Tommy Nylander[2,3,4,5]* and Motomu Tanaka[6,7]*

[1]Department of Food Science, University of Copenhagen, Frederiksberg, Denmark, [2]Division of Physical Chemistry, Department of Chemistry, Lund University, Lund, Sweden, [3]NanoLund, Lund University, Lund, Sweden, [4]LINXS Institute of Advanced Neutron and X-Ray Science, Lund, Sweden, [5]School of Chemical Engineering and Translational Nanobioscience Research Center, Sungkyunkwan University, Suwon, Republic of Korea, [6]Physical Chemistry of Biosystems, Institute of Physical Chemistry, Heidelberg University, Heidelberg, Germany, [7]Center for Integrative Medicine and Physics, Institute for Advanced Study, Kyoto University, Kyoto, Japan

Food is a complex soft matter, because various components, such as proteins, lipids, and carbohydrates, are self-assembled via non-covalent, colloidal interactions and form hierarchical structures at multiple length scales. Soft matter scientists have shown an increasing interest in understanding the general principles governing the food structure formation. During the last several decades, an increasing number of studies have shown that the maintenance of healthy gastrointestinal tract and its microbiome is essential for human health and wellbeing. The realization of the importance of the gastrointestinal microbiome has led to the development of *probiotics*, which are defined as living bacteria that confer a health benefit on the host. Probiotic bacteria and enzymes can be delivered to the intestinal system by formulating appropriate carriers and including these into food ingested by humans. Despite this simple statement, it involves many challenges in the field of soft matter science. This review aims to highlight how the key concepts in soft matter science can be used to design, characterize, and evaluate self-assembled formulations of probiotics and enzymes based on lipids and biopolymers. The topics covered in this review includes the emulsification of oil-water mixtures, the self-assembly of lipids and polymers at interfaces, the electrostatics and viscoelasticity of interfaces, and the wetting/adhesion of colloidal particles.

KEYWORDS
self-assembly, lipids, polymers, colloids, probiotics, enzymes, foods

1 Introduction: food science and soft matter

Food is a complex material, consisting of macromolecules, such as proteins, lipids, and carbohydrates, together with water, minerals, and many other minor but nutritionally significant compounds, such as vitamins and polyphenols. These components are self-assembled via colloidal forces and form hierarchical structures at multiple length scales. The understanding of such forces is fundamental to not only understand the structures naturally present in plant and animal tissues, but also how they can be disrupted and reassembled into new structures with higher nutritional value by employing appropriate processing. It is noteworthy that food structures are not constant but are prone to changes during harvesting, storage, distribution, and digestion. Soft matter scientists have shown an increasing interest

ACS APPLIED BIO MATERIALS

www.acsabm.org

Article

Antibacterial Synthetic Nanocelluloses Synergizing with a Metal-Chelating Agent

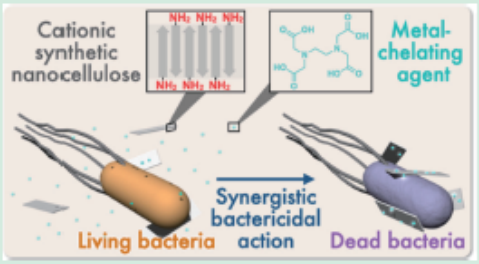
Takeshi Serizawa,* Saeko Yamaguchi, Kai Sugiura, Ramona Marten, Akihisa Yamamoto, Yuuki Hata, Toshiki Sawada, Hiroshi Tanaka, and Motomu Tanaka

Cite This: *ACS Appl. Bio Mater.* 2024, 7, 246–255

Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: Antibacterial materials composed of biodegradable and biocompatible constituents that are produced via eco-friendly synthetic strategies will become an attractive alternative to antibiotics to combat antibiotic-resistant bacteria. In this study, we demonstrated the antibacterial properties of nanosheet-shaped crystalline assemblies of enzymatically synthesized aminated cellulose oligomers (namely, surface-aminated synthetic nanocelluloses) and their synergy with a metal-chelating antibacterial agent, ethylenediaminetetraacetic acid (EDTA). Growth curves and colony counting assays revealed that the surface-aminated cellulose assemblies had an antibacterial effect against Gram-negative *Escherichia coli* (*E. coli*). The cationic assemblies appeared to destabilize the cell wall of *E. coli* through electrostatic interactions with anionic lipopolysaccharide (LPS) molecules on the outer membrane. The antibacterial properties were significantly enhanced by the concurrent use of EDTA, which potentially removed metal ions from LPS molecules, resulting in synergistic bactericidal effects. No antibacterial activity of the surface-aminated cellulose assemblies was observed against Gram-positive *Staphylococcus aureus* even in the presence of EDTA, further supporting the contribution of electrostatic interactions between the cationic assemblies and anionic LPS to the activity against Gram-negative bacteria. Analysis using quartz crystal microbalance with dissipation monitoring revealed the attractive interaction of the surface-aminated cellulose assembly with LPS Ra monolayers artificially produced on the device substrate.



KEYWORDS: *cellulose oligomer, crystalline assembly, antibacterial cationic polymer, bactericidal activity, ethylenediaminetetraacetic acid, synergistic effect*

1. INTRODUCTION

Antibacterial materials that suppress the uncontrolled growth of pathogenic bacteria have attracted considerable attention for preventing bacterial infections or mitigating bacterial virulence in the fields of food, cosmetics, and medicine.[1−4] Due to the unfortunate evolution of antibiotic-resistant bacteria,[5−8] antibacterial synthetic polymers have been developed as alternatives to antibiotics.[9−11] Advantages of antibacterial synthetic polymers include designability of the chemical structure, stability under biological conditions, processability, and low skin penetration compared to low-molecular-weight organic or inorganic antibacterial materials. Antibacterial synthetic polymers typically have cationic and hydrophobic functionalities (e.g., amino and alkyl groups, respectively), which have been designed with inspiration from cationic host defense peptides[12] or biocidal cationic surfactants (e.g., benzalkonium chlorides).[13] Cationic and hydrophobic groups of polymers interact electrostatically and hydrophobically with the anionic lipid bilayer of bacteria, disrupting the membrane structure and thus killing bacteria. An emerging alternative polymer design is the combination of cationic and hydrophilic functionalities.[14−16] Because of the limited attractive interactions between cationic hydrophilic polymers and the zwitterionic lipid bilayer of mammalian cells, novel antibacterial polymers have been shown to exhibit higher biocompatibility than conventional cationic hydrophobic polymers. Nevertheless, few eco-friendly synthetic strategies for producing antibacterial polymers with cationic and hydrophilic characteristics have been developed. Moreover, it is still challenging to obtain cationic polymers that exhibit bactericidal activity and are biocompatible with mammalian cells.

Cellulose is a naturally abundant polysaccharide that exists in nature as crystalline fibers.[17,18] Recently, nanocelluloses, including cellulose nanofibers and cellulose nanocrystals, which

Received: September 21, 2023
Revised: November 2, 2023
Accepted: November 2, 2023
Published: November 15, 2023

https://doi.org/10.1021/acsabm.3c00846
ACS Appl. Bio Mater. 2024, 7, 246–255

ADVANCED FUNCTIONAL MATERIALS
www.afm-journal.de

Printed Electronic Devices and Systems for Interfacing with Single Cells up to Organoids

Mahsa K. Saghafi, Srivatsan K. Vasantham, Navid Hussain, George Mathew, Federico Colombo, Barbara Schamberger, Eric Pohl, Gabriel Cadilha Marques, Ben Breitung, Motomu Tanaka, Martin Bastmeyer, Christine Selhuber-Unkel, Ute Schepers, Michael Hirtz, and Jasmin Aghassi-Hagmann**

The field of bioelectronics with the aim to contact cells, cell clusters, biological tissues and organoids has become a vast enterprise. Currently, it is mainly relying on classical micro- and nanofabrication methods to build devices and systems. Very recently the field is highly pushed by the development of novel printable organic, inorganic and biomaterials as well as advanced digital printing technologies such as laser and inkjet printing employed in this endeavor. Recent advantages in alternative additive manufacturing and 3D printing methods enable interesting new routes, in particular for applications requiring the incorporation of delicate biomaterials or creation of 3D scaffold structures that show a high potential for bioelectronics and building of hybrid bio-/inorganic devices. Here the current state of printed 2D and 3D electronic structures and related lithography techniques for the interfacing of electronic devices with biological systems are reviewed. The focus lies on in vitro applications for interfacing single cell, cell clusters, and organoids. Challenges and future prospects are discussed for all-printed hybrid bio/electronic systems targeting biomedical research, diagnostics, and health monitoring.

1. Introduction

Classical approaches for manufacturing electronic devices in bioelectronics have come a long way and feature an impressive track record in what kind of measurements are feasible nowadays on single cells up to tissues, organoids or even in vivo.[1] In particular, the development in microfabrication for electrodes and microelectrode arrays (MEAs),[2–5] and complementary metal-oxide semiconductors (CMOS) technology[6] have given rise to a myriad of applications in monitoring[7,8] and stimulating[9,10] single and groups of cells. Still, these approaches have inherent difficulties in respect to organic material integration, biocompatibility, and for applications that require flexible devices. Additionally, when biomedical applications are aimed at, disposability and manufacturing

M. K. Saghafi, S. K. Vasantham, N. Hussain, G. Mathew, G. C. Marques, B. Breitung, M. Hirtz, J. Aghassi-Hagmann
Institute of Nanotechnology (INT)
Karlsruhe Institute of Technology (KIT)
Kaiserstraße 12, 76131 Karlsruhe, Germany
E-mail: michael.hirtz@kit.edu; jasmin.aghassi@kit.edu

M. K. Saghafi, S. K. Vasantham, N. Hussain, G. Mathew, M. Hirtz
Karlsruhe Nano Micro Facility (KNMFi)
Karlsruhe Institute of Technology (KIT)
Kaiserstraße 12, 76131 Karlsruhe, Germany

F. Colombo, B. Schamberger, C. Selhuber-Unkel
Institute for Molecular Systems Engineering and Advanced Materials (IMSEAM)
Heidelberg University
Im Neuenheimer Feld 225, 69120 Heidelberg, Germany

E. Pohl, U. Schepers
Institute of Functional Interfaces (IFG)
Karlsruhe Institute of Technology (KIT)
Kaiserstraße 12, 76131 Karlsruhe, Germany

M. Tanaka
Physical Chemistry of Biosystems
Institute of Physical Chemistry
Heidelberg University
69120 Heidelberg, Germany

M. Tanaka
Center for Integrative Medicine and Physics
Institute for Advanced Study
Kyoto University
Kyoto 606-8501, Japan

M. Bastmeyer
Zoological Institute, Cell and Neurobiology
Karlsruhe Institute of Technology
Kaiserstraße 12, 76131 Karlsruhe, Germany

M. Bastmeyer
Institute for Biological and Chemical Systems – Biological Information Processing (IBCS-BIP)
Karlsruhe Institute of Technology (KIT)
Kaiserstraße 12, 76131 Karlsruhe, Germany

The ORCID identification number(s) for the author(s) of this article can be found under https://doi.org/10.1002/adfm.202308613

DOI: 10.1002/adfm.202308613

RESEARCH ARTICLE

ADVANCED HEALTHCARE MATERIALS
www.advhealthmat.de

Reversible Host–Guest Crosslinks in Supramolecular Hydrogels for On-Demand Mechanical Stimulation of Human Mesenchymal Stem Cells

*Philipp Linke, Natalie Munding, Esther Kimmle, Stefan Kaufmann, Kentaro Hayashi, Masaki Nakahata, Yoshinori Takashima, Masaki Sano, Martin Bastmeyer, Thomas Holstein, Sascha Dietrich, Carsten Müller-Tidow, Akira Harada, Anthony D. Ho, and Motomu Tanaka**

Stem cells are regulated not only by biochemical signals but also by biophysical properties of extracellular matrix (ECM). The ECM is constantly monitored and remodeled because the fate of stem cells can be misdirected when the mechanical interaction between cells and ECM is imbalanced. A well-defined ECM model for bone marrow-derived human mesenchymal stem cells (hMSCs) based on supramolecular hydrogels containing reversible host–guest crosslinks is fabricated. The stiffness (Young's modulus E) of the hydrogels can be switched reversibly by altering the concentration of non-cytotoxic, free guest molecules dissolved in the culture medium. Fine-adjustment of substrate stiffness enables the authors to determine the critical stiffness level E^* at which hMSCs turn the mechano-sensory machinery on or off. Next, the substrate stiffness across E^* is switched and the dynamic adaptation characteristics such as morphology, traction force, and YAP/TAZ signaling of hMSCs are monitored. These data demonstrate the instantaneous switching of traction force, which is followed by YAP/TAZ signaling and morphological adaptation. Periodical switching of the substrate stiffness across E^* proves that frequent applications of mechanical stimuli drastically suppress hMSC proliferation. Mechanical stimulation across E^* level using dynamic hydrogels is a promising strategy for the on-demand control of hMSC transcription and proliferation.

1. Introduction

The extracellular matrix (ECM) is a crucial component in maintaining the structural integrity and functionality of cells, as well as regulating the homeostasis of animal tissues.[1] Remodeling of ECM plays a significant role in regulating not only the behavior of single cells but also the morphogenesis of tissues.[2] Cells respond not only to extrinsic biochemical signals, such as gradients of chemokines or growth factors, but also to the biophysical cues from their surrounding microenvironment, including the topography and stiffness of the ECM. The adhesion, morphology, and migration of cells are influenced by the bulk Young's modulus of ECM model substrates when one uses chemically crosslinked hydrogels functionalized with ECM proteins.[3] Myoblasts differentiate into myotubes with pronounced actomyosin striation when cultured on hydrogel substrates possessing a Young's modulus similar to that of the native ECM.[4] The Young's modulus values of hydrogel substrates influence the

P. Linke, N. Munding, E. Kimmle, S. Kaufmann, M. Tanaka
Physical Chemistry of Biosystems
Institute of Physical Chemistry
Heidelberg University
69120 Heidelberg, Germany
E-mail: tanaka@uni-heidelberg.de

K. Hayashi, M. Bastmeyer, T. Holstein, A. D. Ho, M. Tanaka
Center for Integrative Medicine and Physics
Institute for Advanced Study
Kyoto University
Kyoto 606-8501, Japan

M. Nakahata, Y. Takashima
Department of Macromolecular Science
Graduate School of Science
Osaka University
Osaka 560-0043, Japan

M. Sano
Institute of Natural Sciences
Shanghai Jiao Tong University
Shanghai 200240, China

The ORCID identification number(s) for the author(s) of this article can be found under https://doi.org/10.1002/adhm.202302607

DOI: 10.1002/adhm.202302607

scientific reports

Check for updates

OPEN

Structure-changeable luminescent Eu(III) complex as a human cancer grade probing system for brain tumor diagnosis

Mengfei Wang[1,3✉], Masaya Kono[2], Yusaku Yamaguchi[2], Jahidul Islam[3], Sunao Shoji[4], Yuichi Kitagawa[1,3], Koji Fushimi[3], Sora Watanabe[5], Go Matsuba[5], Akihisa Yamamoto[6], Motomu Tanaka[6,7], Masumi Tsuda[1,8], Shinya Tanaka[1,8] & Yasuchika Hasegawa[1,3✉]

Accurate determination of human tumor malignancy is important for choosing efficient and safe therapies. Bioimaging technologies based on luminescent molecules are widely used to localize and distinguish active tumor cells. Here, we report a human cancer grade probing system (GPS) using a water-soluble and structure-changeable Eu(III) complex for the continuous detection of early human brain tumors of different malignancy grades. Time-dependent emission spectra of the Eu(III) complexes in various types of tumor cells were recorded. The radiative rate constants (k_r), which depend on the geometry of the Eu(III) complex, were calculated from the emission spectra. The tendency of the k_r values to vary depended on the tumor cells at different malignancy grades. Between T = 0 and T = 3 h of invasion, the k_r values exhibited an increase of 4% in NHA/TS (benign grade II gliomas), 7% in NHA/TSR (malignant grade III gliomas), and 27% in NHA/TSRA (malignant grade IV gliomas). Tumor cells with high-grade malignancy exhibited a rapid upward trend in k_r values. The cancer GPS employs Eu(III) emissions to provide a new diagnostic method for determining human brain tumor malignancy.

Cancer is a major public health problem in every country of the world[1,2]. Increasing the universal awareness of early cancer diagnosis is key to increasing the chances of successful treatment[3–5]. Bioimaging technologies based on luminescent molecules are powerful approaches for locating and distinguishing tumor cells. Luminescent molecules have been developed as non-invasive probes for early cancer diagnosis. Luminescent organic dyes exhibit tunable fluorescence properties associated with structural modifications. Pu and Yuan summarized recent studies on near-infrared (NIR) shifting fluorescence using structurally modified hemicyanine dyes for the bioimaging and diagnosis of cancers in mice[6,7]. Urano reported a membrane-permeable hydroxymethyl rhodol derivative for fluorescence-guided diagnosis of ovarian cancer in mice[8,9]. Metal-free thermally activated delayed fluorescence (TADF) materials are attractive next-generation organic dyes for biomedical applications. Hudson and Algar described red-emissive TADF polymer dots for time-gated cellular imaging of human liver cancer cells[10,11]. Among luminescent molecules, transition metal complexes show potential advantages in bioimaging and cancer diagnosis owing to their long phosphorescence lifetimes. Ma and Leung developed design strategies for transition-metal-complex-based cancer diagnosis[12,13]. Thomas et al. mainly concentrated on phosphorescent Ru(II) complexes that bind DNA and other biomolecules such as cell probes, therapeutics, and theranostics[14]. Luminescent lanthanide complexes with long-lived 4f–4f transitions have also been reported for biomedical diagnoses[15]. Parker and Bünzli reviewed the current developments in water-soluble lanthanide(III) cyclen- and

[1]Institute for Chemical Reaction Design and Discovery (WPI-ICReDD), Hokkaido University, Sapporo, Hokkaido 001-0021, Japan. [2]Graduate School of Chemical Sciences and Engineering, Hokkaido University, Sapporo, Hokkaido 060-8628, Japan. [3]Faculty of Engineering, Hokkaido University, Sapporo, Hokkaido 060-8628, Japan. [4]Department of Engineering, Nara Women's University, Nara 630-8506, Japan. [5]Graduate School of Organic Material Engineering, Yamagata University, Yonezawa, Yamagata 992-8510, Japan. [6]Center for Integrative Medicine and Physics, Institute for Advanced Study, Kyoto University, Kyoto 606-8501, Japan. [7]Physical Chemistry of Biosystems, Institute of Physical Chemistry, Heidelberg University, 69120 Heidelberg, Germany. [8]Department of Cancer Pathology, Faculty of Medicine, Hokkaido University, Sapporo, Hokkaido 060-8638, Japan. ✉email: wang.mf@icredd.hokudai.ac.jp; hasegaway@eng.hokudai.ac.jp

補足資料（３）

寄附部門運営会議・議事録

寄附部門運営会議・議題リスト

2018 年度

2018/5/9
【審議】
1. 共同研究の受け入れ(2 件について)
2. 寄附研究部門の名称付与に関する内規について
3. 連携教員等の委嘱について

2018/7/30
【審議】
1. 寄附金の受入について

2018/10/10
【審議】
1. 寄附研究部門の運営・管理について
2. 今後の事業計画について
3. その他
【報告】
1. 寄附研究部門の運営・管理状況について
2. 事業の進捗状況
3. 財務執行状況
4. その他

2019/1/29
【審議】
1. 外国人共同研究者の受入れについて

2019/3/7
【審議】
1. 客員・連携教員等の委嘱について
2. ウインタースクール開催に伴う短期交流学生の受入れについて

2019/3/25
【審議】
1. 共同研究の受入れについて

2019 年度

2019/4/15
【審議】
1. 寄附研究部門の運営・管理について
2. 共同研究の受入について
3. 今後の事業計画について
4. その他
【報告】
1. 寄附研究部門の運営・管理状況について
2. 事業の進捗状況
3. 財務執行状況
4. その他

2019/7/16
【審議】
1. 短期交流学生の受入れについて

2019/10/7
【審議】
1. 寄附研究部門の運営・管理について
2. 寄附研究部門の運営計画について
3. 寄附研究部門の事業計画について
4. その他
【報告】
1. 寄附部門の運営状況について
2. 事業の進捗
3. 財務執行状況
4. その他

2019/11/14
【審議】
1. 寄附金の受入れについて

2020/3/4
【審議】
1. 客員・特任教授等の称号付与について

2020 年度

2020/6/3
【審議】
1. 今後の事業計画について
【報告】
1. 寄附研究部門の運営状況について
2. 事業の進捗
3. 執行状況
4. その他

2020/6/15
【審議】
1. 共同研究の受入れについて

2020/11/17
【審議】
1. 今後の事業計画について
【報告】
1. 寄附研究部門の運営状況について
2. 事業の進捗
3. 執行状況
4. その他

2021 年度

2021/5/12
【審議】
1. 今後の事業計画について
    1.1 寄附研究部門の運営計画
    1.2 事業計画
        1.2.1 欧州ハブ拠点との連携
        1.2.2 学内・学外との連携
    1.3 その他

2021/11/12
【審議】
1. 今後の事業計画について
    1.1 寄附研究部門の運営計画
    1.2 事業計画
        1.2.1 欧州ハブ拠点との連携
        1.2.2 DAAD-京大「間」プログラム
    1.3 その他

2022 年度

2022/6/22
【審議】
1. 今後の事業計画について
    1.1 寄附研究部門の運営計画
    1.2 事業計画
        1.2.1 ハイデルベルク大学からの学生受入
    1.3 その他

2022/11/10
【審議】
1. 今後の事業計画について
    1.1 寄附研究部門の運営計画
        1.1.1 林健太郎研究員の特定助教への昇任
    1.2 事業計画
        1.2.1 ミュンスター大学からの研究者受入
    1.3 その他

2023 年度

2023/6/6
【審議】
1. 今後の事業計画について
    1.1 寄附研究部門の運営計画
    1.2 事業計画
        1.2.1 HeKKSSaGOn 日独学長会議
        1.2.2 第 4 回「医学と数理」研究会
        1.2.3 国際 Winter School
    1.3 その他

2023/11/6
【審議】
1. 今後の事業計画について
    1.1 寄附研究部門の運営計画
        1.1.1 最終報告会（2 月 29 日）
    1.2 事業計画
        1.2.1 国際 Winter School
    1.3 その他

補足資料（４）
競争的資金・研究費獲得状況

中谷財団からの長期大型助成以外のものについて記載

田中　求

科研費　基盤研究 A (2017~2019 年度)
『微小環境の動的変化を用いた幹細胞の機能制御技術』
代表　田中　求、分担　吉川洋史（埼玉大学 理学研究科）
（総額）43,550,000 円（直接経費）33,500,000 円（間接経費）10,050,000 円

科研費　特設領域・基盤研究 B (2016~2019 年度)
『脊索中胚葉システムの形態形成における自発運動の力場解析』
代表　田中　求、分担　鈴木　量
（総額）18,460,000 円（直接経費）14,200,000 円（間接経費）4,260,000 円

科研費　新学術領域研究 (2019~2023 年度)
『水圏機能材料の電子・イオン機能開拓』
代表　田中　求、分担　中畑雅樹（大阪大学 大学院基礎工学研究科）
（総額）117,130,000 円（直接経費）90,100,000 円（間接経費）27,030,000 円

科研費　新学術領域研究 (2019~2023 年度)
『水圏機能材料の創成に関する総括研究』
代表　加藤隆史（東京大学 大学院工学系研究科）、分担　田中　求
（総額）158,990,000 円（直接経費）122,300,000 円（間接経費）36,690,000 円

科研費　基盤研究 A (2020~2022 年度)
『がん細胞・オルガノイドの動態を基盤とする物理的バイオマーカーの創出』
代表　田中　求、分担　妹尾　浩（京都大学 医学研究科 消化器内科）
（総額）44,980,000 円（直接経費）34,600,000 円（間接経費）10,380,000 円

寄附金　株式会社島津製作所 (2019~2020 年度)
『卵子の力学特性定量法の開発』
代表　田中　求
（総額）3,692,000 円（直接経費）2,840,000 円（間接経費）852,000 円

寄附金　株式会社島津製作所 (2021 年度)
『卵子の力学特性定量法の開発』
代表　田中　求
（総額）2,431,000 円（直接経費）1,870,000 円（間接経費）561,000 円

日本学術振興会　外国人研究者再招へい事業（JSPS BRIDGE fellowship program）
（2018~2019 年度）
『メカノバイオロジー研究の国際ネットワーク強化』
代表　田中　求
（総額）150,000 円
　　Bastmeyer 教授（拠点客員教授）の招聘事業として実施

HeKKSaGOn Working Group (2021~2023 年度)
“Next-Generation Biomedical Science”
代表　田中　求
（総額）42,400 €　→ 部会全体の交流予算

京都大学・DAAD パートナーシッププログラム「AIDA」（2023 年度）
代表　田中　求
（総額）980,000 円
　　ドイツ側パートナー・Bastmeyer 教授（拠点客員教授）も DAAD より
　　マッチングファンドを取得

科研費　基盤研究 B (2023~2026 年度)
『培養ヒト角膜内皮細胞注入療法から発するリバーストランスレーショナルリサーチ』
代表　木下　茂（京都府立医科大学）、分担　田中　求、北澤耕司（京都府立医科大学）、上野盛夫（京都府立医科大学・眼科、当拠点客員）、戸田宗豊（京都府立医科大学）
（総額）18,850,000 円（直接経費）14,500,000 円（間接経費）4,350,000 円

山本暁久

科研費　基盤研究 C (2016~2019 年度)
『細胞接着の物理の解明に向けた糖脂質膜と幹細胞の力学的相互作用の精密測定』
代表　山本暁久
（総額）4,680,000 円（直接経費）3,600,000 円（間接経費）1,080,000 円

科研費　基盤研究 B (2020~2022 年度)
『二次元細胞集団の相状態とダイナミクス：局所秩序構造の定量手法の開拓』
代表　山本暁久、分担　上野盛夫（京都府立医科大学・眼科、当拠点客員）
（総額）17,680,000 円（直接経費）13,600,000 円（間接経費）4,080,000 円

京都大学　いしずえ（2019 年度）
『細胞形状・運動相関の定量に基づく細胞間相互作用の定式化と集団遊走の数理モデル開拓』
代表　山本暁久
（総額）1,600,000 円（直接経費）1,600,000 円（間接経費）0 円

科研費　国際共同研究加速基金・国際共同研究強化 B (2018~2021 年度)
『生体外モデルデバイスの細胞代謝リアルタイムモニタリング技術に関する日独共同研究』
代表　田畑　修（京都先端科学大学）、分担　山本暁久
（総額）17,940,000 円（直接経費）13,800,000 円（間接経費）4,140,000 円

寄附金　株式会社トーメーコーポレーション (2020 年度)
『細胞の評価方法に関する研究発展のため』
代表　山本暁久
（総額）100,000 円

寄附金　日本電信電話株式会社 (2018~2019 年度)
『グラフェン表面に構築した人工生体膜(支持膜)を用いた界面制御と生体反応の可視化』
代表　山本暁久
（総額）6,000,000 円

寄附金　中谷医工計測技術振興財団 (2019 年度)
『ソフトマター物理・生命物理の研究に対する助成金』
代表　山本暁久
（総額）100,000 円

科研費　基盤研究 B (2023~2026 年度)
『ヒト角膜内皮疾患における細胞外基質の非一様化に対する内皮細胞の応答機構の解明』
代表　山本暁久、分担　上野盛夫（京都府立医科大学・眼科、当拠点客員）
（総額）18,460,000 円（直接経費）14,200,000 円（間接経費）4,260,000 円

鈴木　量

科研費　若手研究 B (2016 ~2019 年度)
『再生ヒドラの揺らぎの全モード解析』
代表　鈴木　量
（総額）4,160,000 円（直接経費）3,200,000 円（間接経費）960,000 円

科研費　基盤研究 C (2019 ~2021 年度)
『可逆的に変調可能なしわ基板を用いた筋管形成の動的制御技術の開拓』
代表　鈴木　量
（総額）4,420,000 円（直接経費）3,400,000 円（間接経費）1,020,000 円

寄附金　中谷医工計測技術振興財団 (2019 年度)
『生命物理学、医学物理学、アクティブマター物理学の研究に対する助成金』
代表　鈴木　量
（総額）100,000 円

科研費　基盤研究 B (2022 ~2024 年度)
『力学的拘束によるヒドラオルガノイドの再生能力制御技術の開拓』
代表　鈴木　量
（総額）17,680,000 円（直接経費）13,600,000 円（間接経費）4,080,000 円

林　健太郎

科研費　若手研究 B (2022 ~2024 年度)
『可逆的な刺激応答性二次元・三次元足場材料を用いたヒト iPS 細胞の動的制御』
代表　林　健太郎
（総額）4,550,000 円（直接経費）3,500,000 円（間接経費）1,050,000 円

公益財団法人 中谷財団

第１回長期大型研究助成　京都大学高等研究院　最終報告書

発　行　令和７年5月
発行所　公益財団法人 中谷財団
〒141-0032　東京都品川区大崎一丁目2番2号　アートヴィレッジ大崎セントラルタワー8階
ＵＲＬ　https://www.nakatani-foundation.jp