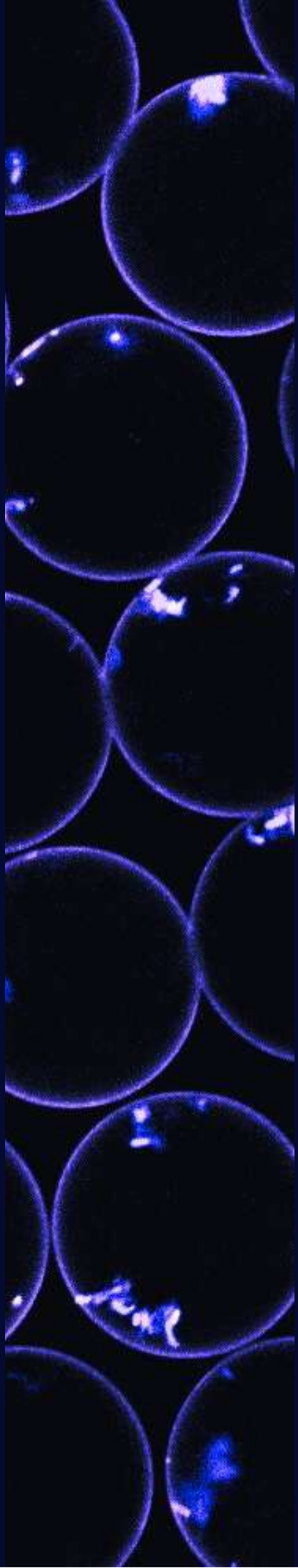

Book of Abstracts

1ST MOLECULAR SYSTEMS ENGINEERING FOR BIOAPPLICATION CONFERENCE

Heidelberger Akademie der Wissenschaften

October 2022

MSEB

PREFACE

This conference will cover a range of molecular systems engineering approaches in biomaterials science and their applications. Molecular systems engineering tries to capture the inherent complexity in biology and is concerned with the behavior of materials on the micro/nano-scale. Molecular engineering is becoming an increasingly expanding field because of the ability to tailor properties of molecule-functionalized biomaterials by selecting and modifying their molecular constituents using biological, physical, and chemical strategies.

As a field, molecular systems engineering is highly interdisciplinary by nature, combining aspects of biology, chemistry, biophysics, materials science and bioengineering. Given the highly fundamental nature of molecular interactions, there is a plethora of potential application areas, which include the design of advanced biomaterials, localized drug delivery, restorations of physiological functions or tissue regeneration. Some of the early successes of molecular engineering have come in the fields of immunotherapy, synthetic biology and printable electronics. Understanding molecular properties and behaviors helps to design and assemble better materials, systems, and processes. Molecular engineering employs theoretical, experimental, and computational approaches to apply those understandings. The Royal Society of Chemistry states "Molecular Systems Design & Engineering provides a hub for research into new understanding of molecular systems and the use of this understanding in applications of technological significance that help address global challenges" (citation: https://www.rsc.org/journals-books-databases/about-journals/msde/). Innovation unlocked by molecular systems engineering in biomedical research will pave the way for advanced bioproducts as diagnostic tools and for the restoration of desired cellular or organ functions.

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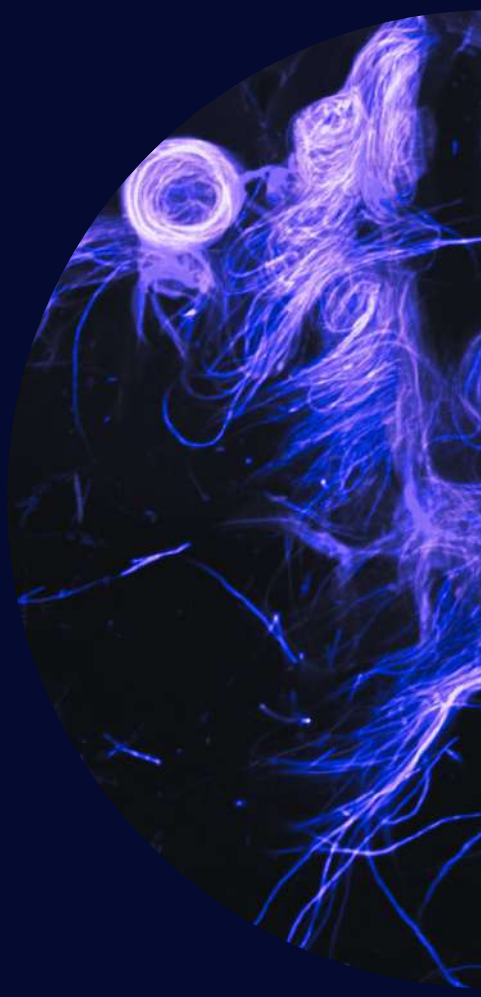


WEDNESDAY 19.10.22

8:00 AM - 9:30 AM	Registration
9:30 AM - 9:45 AM	Introductory comments
	Session 1A: Engineering Molecular Systems for Designing Biomaterials Keynote speaker: Michael A. Nash Chair: Eva Blasco
9:45 AM - 10:30 AM	Deep Mutational Scanning for Therapeutic Enzyme Engineering: Insights into Folding Stability and Catalysis **Michael Nash**
10:30 AM - 10:45 AM	Single cell confinement (SCC) as mechanoregulators to study stem cell fate **Castro Johnbosco**
10:45 AM - 11:00 AM	Steady-state operation of a cell-free genetic band-detection circuit **Anna Jäkel**
11:00 AM - 11:30 AM	**Coffee Break** One-on-one chat with Editors 
	Session 1B: Controlling the Mechanical Properties of Materials Keynote speaker: Aranzazu del Campo Becares Chair: Eva Blasco
11:30 AM - 12:15 PM	Mechanopharmacology with Living Therapeutic Hydrogels **Aránzazu Del Campo**
12:15 PM - 12:45 PM	Droplet-based microfluidics for the generation of extracellular matrix protein-based microcapsules **Sadaf Pashapour**
1:00 PM - 2:00 PM	**Lunch and Roundtable Discussion** 

Session 1C: Advanced Biomaterials Keynote speaker: Matthew Tirrell Chair: Mohammadreza Taale	
02:00 PM - 02:45 PM	Biological implications and biomedical applications of polyelectrolyte complexation **Matthew Tirrell**
02:45 PM - 03:15 PM	Molecularly engineering smart hydrogels using firefly luciferin-bioinspired chemistry **Julieta Paez**
03:15 PM - 03:30 PM	Artificial tumors, or how to asses a highly complex and heterogeneous pathology in vitro **Yasmin Antonelli, I Chen**
3:30 PM - 4:15 PM	**Coffee Break / Poster presentation I** 
Session 1D: 3D Bioprinting Keynote speaker: Tal Dvir Chair: Mohammadreza Taale	
04:15 PM - 05:00 PM	Engineering personalized tissue implants: From 3D printing to bionic organs **Tal Dvir**
5:00 PM - 5:30 PM	Melt electrowriting for the reconstruction of hierarchical tissues **Malgorzata Włodarczyk-Biegun**
5:30 PM - 6:00 PM	**Coffee Break** 
6:00 PM - 8:00 PM	 **Walking tour of Heidelberg's old town**
8:00 PM - 10:00 PM	**Dinner and Roundtable Discussion** 

THURSDAY 20.10.22

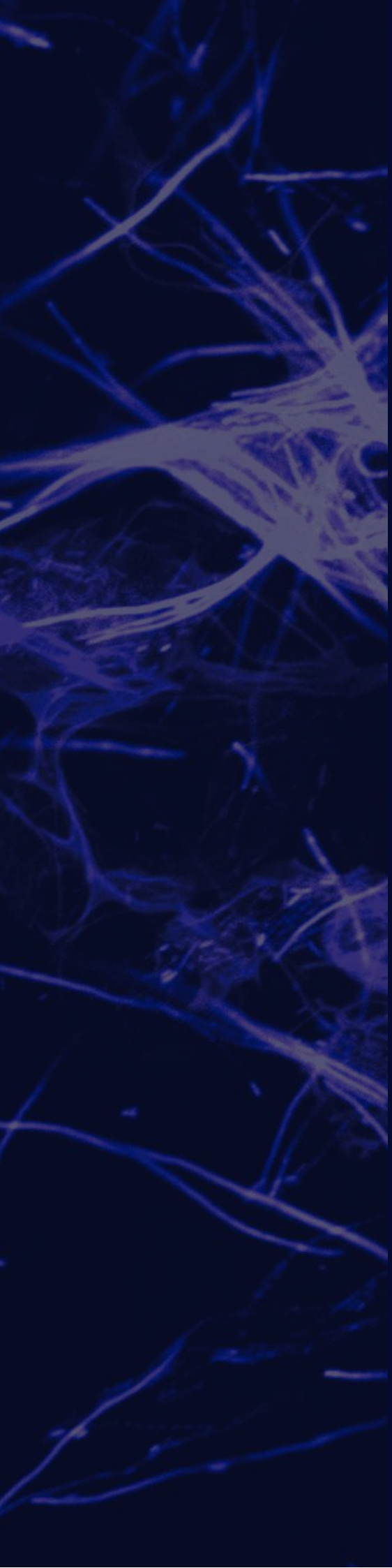
	Session 2A: Synthetic Environment for Cells Keynote Speaker: Cornelia Lee-Thediek Chair: Kerstin Göpfrich
9:00 AM - 9:45 AM	Artificial stem cell niches: on the role of biomaterials in unlocking hematopoietic stem cell applications **Cornelia Lee-Thedieck**
9:45 AM - 10:15 AM	Fibronectin Anchoring on viscoelastic substrates controls cell mechanosensing **Dimitris Missirlis**
10:15 AM - 10:30 AM	A bottom-up approach to study front-rear cell polarization **Andreas Fink**
10:30 AM - 11:15 AM	**Coffee Break / Poster Presentation II** 
	Session 2B: Cell-material Interactions Keynote speaker: Joachim Spatz Chair: Kerstin Göpfrich
11:15 AM - 12:00 PM	Mechanopharmacology with Living Therapeutic Hydrogels **Joachim Spatz**
12:00 PM - 12:30 PM	Droplet-based microfluidics for the generation of extracellular matrix protein-based microcapsules **Nicolas Moreno Gomez**
12:30 PM - 2:30 PM	 **Conference Lunch**
	Session 2C: Soft Implants & Tissue Engineering Keynote speaker: Andres Garcia Chair: Federico Colombo
2:30 PM - 3:15 PM	Bioengineered Synthetic Hydrogels for Regenerative Medicine **Andres Garcia**

THURSDAY 20.10.22

3:15 PM - 3:45 PM	Synthetic Tumour Immune Microenvironments **Oskar Staufer**
3:45 PM - 4:00 PM	**Coffee Break** 
	Session 2D: Bioapplications & Drug Delivery Keynote speaker: Dan Peer Chair: Federico Colombo
4:00 PM - 4:45 PM	RNA Therapeutics is Going Beyond the Liver: From Gene Silencing to Gene Editing **Dan Peer**
4:45 PM - 5:00 PM	Bottom-up assembly of synthetic SARS-CoV-2 minimal virions for the investigation of viral infectivity **Ana Yagüe Relimpio**
5:00 PM - 5:45 PM	**Coffee Break** 
	Session 2E: Bioelectronics - Biorobotics Keynote speaker: George Malliaras Chair: Maria Villiou
5:45 PM - 6:30 PM	Technology for Bioelectronic Medicine **George Malliaras**
6:30 PM - 7:00 PM	Bioelectronic devices and Therapeutic applications: The PNS stimulation as a paradigm of the new bioelectronic medicine era **Dimitrios Koutsouras**
7:00 PM - 9:00 PM	 **Awards Ceremony** **Conference Dinner** 

FRIDAY 21.10.22

9:00 AM - 9:45 AM	Publishing with Impact **Maria Southall** Chair: Trevor Kalkus
9:45 AM - 10:30 AM	Writing a Manuscript **Federico Colombo** Chair: Trevor Kalkus
10:30 AM - 11:00 AM	**Coffee Break** 
10:30 AM - 12:30 AM	 **Invited speakers' guided tour of the Castle**
11:00 AM - 11:45 AM	Writing a Proposal **Trevor Kalkus** Chair: Mohammadreza Taale
11:00 AM - 11:30 AM	Making a Good Presentation **Kerstin Göpfrich** Chair: Mohammadreza Taale
12:30 PM - 2:00 PM	 **Lunch and Roundtable Discussions**
2:00 PM - 3:30 PM	Stress Management **Chrysavgi Zarnakoupi** Chair: Maria Villiou
3:30 PM - 4:15 PM	Career Developement **Nadanai Laohakunakorn** Chair: Maria Villiou
4:15 PM - 4:30 PM	**Coffee Break** 
4:30 PM - 6:00 PM	First Steps in CAD Design - 3D Printing **Tobias Spratte**
6:00 PM - 6:15 PM	**Closing Remarks** 

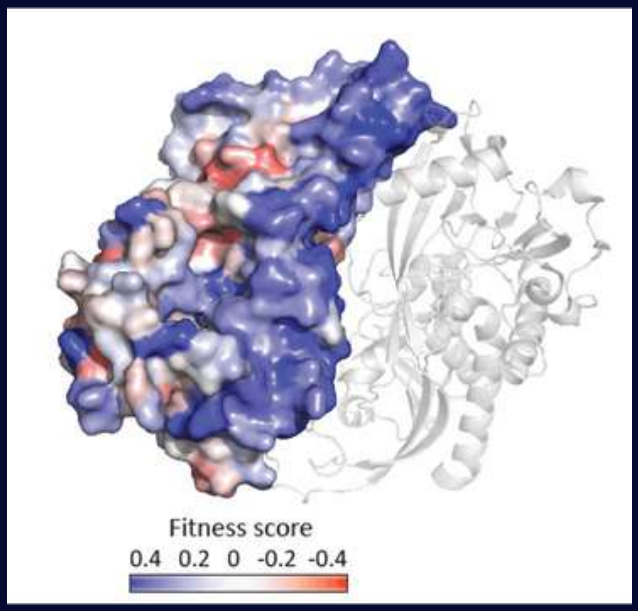


TALKS' ABSTRACTS

DEEP MUTATIONAL SCANNING FOR THERAPEUTIC ENZYME ENGINEERING: INSIGHTS INTO FOLDING STABILITY AND CATALYSIS

Michael Nash
University of Basel/ETH Zurich

Deep mutational scanning refers to a suite of related bio-analytical methods relying on artificial genetic diversity coupled with high-throughput screening/selection and next-generation DNA sequencing. By analyzing the influence of large numbers (>10^4) of mutations on enzyme performance under an artificial in vitro selection pressure, we gain insights into structural and sequence features that control phenotypic properties such as folding stability and catalytic efficiency. In this talk, I will present recent work from my lab developing a biophysical screening and bioinformatic analysis pipeline to enable parallel testing of folding stability and catalytic activity on large numbers of variants of the promising cancer therapeutic enzyme D-amino acid oxidase (DAOx). By taking advantage of the native yeast secretion and display pathway machinery to select for properly folded variants, and coupling it with a pooled single-cell enzyme activity assay, we show how this pipeline can reveal structural, catalytic, and evolutionary properties of this therapeutic enzyme candidate.

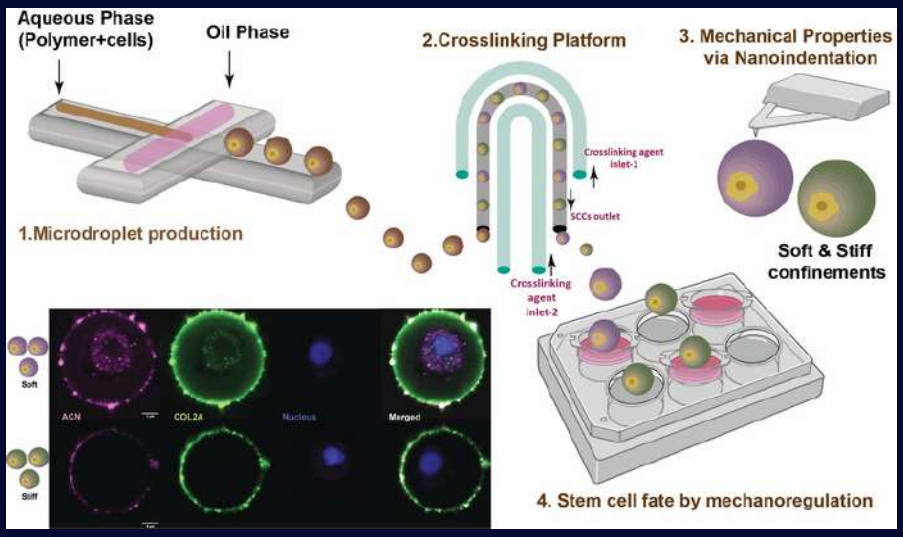


WED
19 OCT
Session 1A

SINGLE CELL CONFINEMENT (SCC) AS MECHANOREGULATORS TO STUDY STEM CELL FATE

Castro Johnbosco, Tom Kamperman, Jeroen Leijten, Malin Becker1, Kannan Govindaraj
University of Twente

Pericellular matrix (PCM) acts as a dynamic temporally tuned mediator in determining the mechanotransduction from ECM to the inner cell membrane. Nascent proteins at micron scale further effect the downstream stem cell biology. Thus, interplay between microenvironmental mechanics and cellular biology effectively guides cell function and fate. However, such orchestration of varying mechanical properties through tunable systems have been explored, single-cell resolution data due to heterogeneity of stem cell population in mechanobiology has remained scarce. Moreover, mechanotransduction within three-dimensional environments occurs distinctly from the 2D environments on which most of our knowledge relies. Hence, a robust system to study mechanoregulation in 3D microenvironments and associated gene regulated outcomes at the single-cell level is required. Hence, we here propose a miniaturized system based on coating individual cells within an engineered pericellular matrix to scrutinize the mechanistic interaction of mechanotransduction on stem cell fate within 3D environments at single-cell resolution.

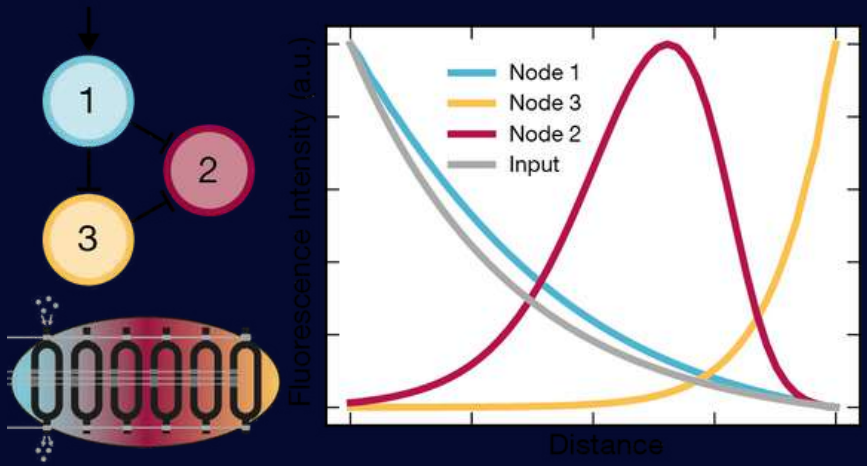


WED
19 OCT
Session 1A

STEADY-STATE OPERATION OF A CELL-FREE GENETIC BAND-DETECTION CIRCUIT

Anna Jäkel, Lukas Aufinger, Friedrich Simmel
TUM

Over the past decade, synthetic gene networks have been used extensively to explore principles of biological pattern formation as they play a decisive role during biological growth and development processes. Pattern-forming circuits are also of great interest for the development of future biomaterials that respond to and differentiate autonomously with respect to their environment.Here, we report on a bottom-up approach to design and analyze a cell-free genetic circuit based on an incoherent feed forward loop (IFFL-2), which is expected to produce a three-stripe pattern in response to an input gradient. In our work, we first simulated the behavior of the circuit and explored relevant parameters using a genetic algorithm approach. We then separately investigated the behavior of the three nodes comprising the IFFL-2 network in a bacterial cell-free gene expression system which was produced from a genome-engineered bacterial strain lacking LacI expression. We showed that the genetic circuit functioned as expected under non-equilibrium conditions in microfluidic ring reactors, whereas it fails to perform in bulk experiments in closed reactors. We showed that the non-equilibrium conditions are of necessity to establish the double-repression cascade which was the essential element of the genetic circuit. We used six neighboring ring reactors to establish a "virtual" morphogen gradient by supplying the reactors with decreasing amounts of the transcription factor σ28, corresponding to the different positions within an exponential morphogen gradient. We finally demonstrated that our IFFL-2 circuit, when operated in the microfluidic system, shows the correct gene expression response that is required for stripe-formation in a spatial context.As the operation in microfluidic reactors would be at least laborious and time consuming to use for the realization of biomaterials that can differentiate autonomously in response to externally supplied chemical cues, the next step is to work on materials with simple and efficient supply lines (like vasculature). Those will be needed to implement cell-free metabolic processes and self-regeneration to enable operation of these systems over longer periods of time under non-equilibrium conditions.

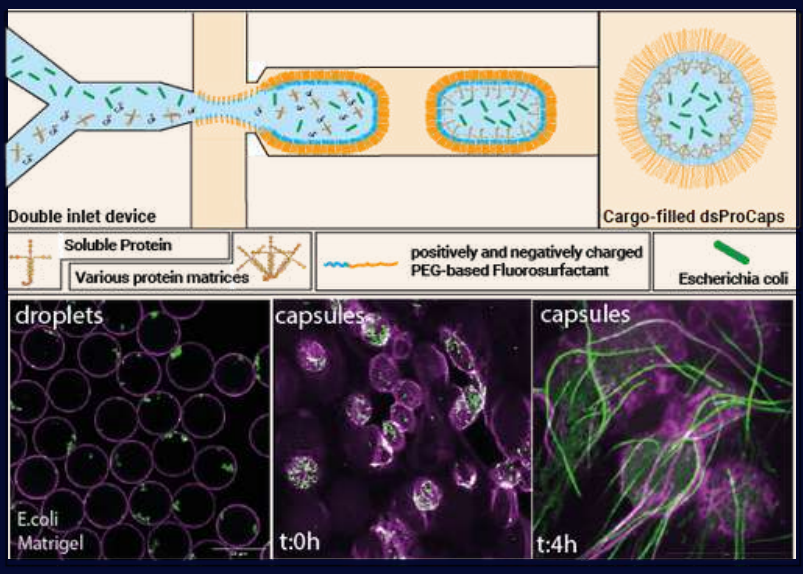


WED
19 OCT
Session 1A

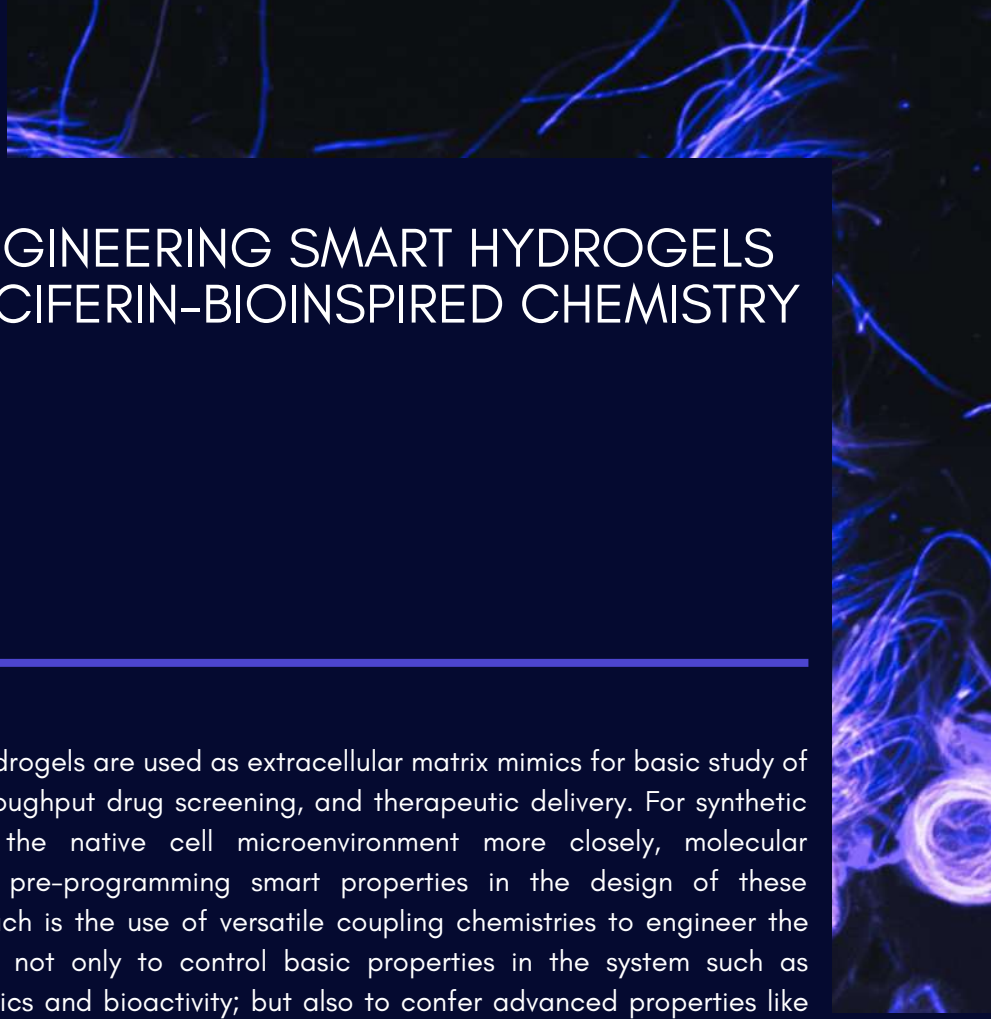
DROPLET-BASED MICROFLUIDICS FOR THE GENERATION OF EXTRACELLULAR MATRIX PROTEIN-BASED MICROCAPSULES

Sadaf Pashapour[1], Christine Selhuber-Unkel[1], Kerstin Göpfrich[2], Michael Platten[3], Joachim Spatz[4]
[1]Institute for Molecular Systems Engineering and Advanced Materials (IMSEAM), University of Heidelberg
[2]Department for Biophysical Engineering of Life, Max Planck Institute for Medical Research, Heidelberg
[3]Department of Neurology, University Medical Centre Mannheim, Medical Faculty Mannheim, Heidelberg University
[4]Department for Cellular Biophysics, Max Planck Institute for Medical Research, Heidelberg

Cell-extracellular matrix (ECM) interactions play a central role in health and disease. Therefore, engineering 3D ECM niche systems to investigate, control and manipulate living organisms within their natural environment has gained increasing interest. In this talk, I will present a novel droplet-based microfluidic approach for the controlled assembly of ECM-based protein microcapsules encapsulating Escherichia coli (E. coli). Towards this end, ECM proteins are polymerized at the inner periphery of E. coli-laden water-in-oil droplets. Sequential release of the assembled ECM protein-based microcapsules into a physiological environment allows for the analysis of bacterial behavior in 3D ECM-based microenvironments. This application of droplet-based microfluidics, which is a subdiscipline of microfluidics, is only one of many various opportunities of this powerful technology. Microfluidics not only allows for the analysis of cells in flow or the production of synthetic cells, but it also helps mimicking several in vivo functions by means of organ-on-a-chip systems. In order to provide accessibility to this technology to a vast majority of research groups, we are currently establishing a microfluidic core facility at the Institute for Molecular Systems Engineering and Advanced Materials (IMSEAM). Hereby, we support prospective research groups with the necessary knowledge and equipment to design and conduct experiments using microfluidic devices.



WED
19 OCT
Session 1B



MOLECULARLY ENGINEERING SMART HYDROGELS USING FIREFLY LUCIFERIN-BIOINSPIRED CHEMISTRY

Minye Jin, **Julieta Paez**
University of Twente

Cell-encapsulating hydrogels are used as extracellular matrix mimics for basic study of cell function, high-throughput drug screening, and therapeutic delivery. For synthetic hydrogels to mimic the native cell microenvironment more closely, molecular engineering aims at pre-programming smart properties in the design of these matrices. One approach is the use of versatile coupling chemistries to engineer the network crosslinks, to not only to control basic properties in the system such as gelation rate, mechanics and bioactivity; but also to confer advanced properties like self-healing, stimuli-responsiveness, adaptability and good processability.

In this presentation, the use of firefly luciferin-bioinspired chemistry to molecularly engineer smart hydrogels for cell encapsulation will be showcased. In a first molecular design, bioinspired covalent chemistry enables the fabrication of tunable and inexpensive hydrogels for 3D cell culture [1]. This platform exhibits advantages like rapid gelation rate and tunability of mechanical and biological properties. In a second molecular design, stimuli-responsive hydrogels are proposed to widen the application range of this synthetic platform [2]. The introduction of redox triggers to the network allows fine control of the gelation onset and gelation rate, which can be used to modulate the injectability of these materials. Finally, the development of reversible hydrogels with self-healing and stress-relaxing properties is presented [3]. In conclusion, firefly luciferin-bioinspired hydrogels are a robust and versatile platform for cell culture, enabling easy adaptation of properties to perform in diverse biomedical situations.

References:

1. Jin, M.; Kocer, G.; Paez, J.I. ACS Appl. Mater. Interfaces 2022, 14, 5017

WED
19 OCT
Session 1C

ARTIFICIAL TUMORS, OR HOW TO ASSESS A HIGHLY COMPLEX AND HETEROGENEOUS PATHOLOGY IN VITRO

Yasmin Antonelli, I Chen
Institute for Molecular Systems Engineering and Advanced Materials, Heidelberg University

When discussing about human diseases, cancer represents the first cause of mortality worldwide. This pathology is traditionally characterized by the presence of semi-solid lumps, known as lumps. Tumors are confining cancer cells, submitting them to a strong mechanical stress. This triggers the expression of highly malignant responses, such as the upregulation of markers for proliferative, invasion and metastasis.

However, one of the major problems to understand the progression of cancer pathologies in vitro, is mostly due to the lack of proper three-dimensional tumors models, and those unchaining the expression of such pathological responses in vitro. In order to solve this scientific and technical challenge, during the last years our teams have been focused on designing, performing and validating new types of tumor-like scaffolds and methods to analyze the behavior of neoplastic cells, considering special features, such as tumor biomechanics, topographic properties of the neoplastic milieus and/or the existence of intratumor heterogeneity, To name a few.

Among others, we are currently studying the confinement and culture of MDA-MB-231 breast cancer cells in hydrogel-based microcapsules having an elasticity of around 25 kPa (measured as Young's Moduli; 600 µm in diameter), followed by the analysis of cell migration onto 1D patterned surfaces. This strategy enables us to understand several processes involved in cancer malignancy, such as tumorigenicity, invasion, intravasation and generation of heterogeneous populations.

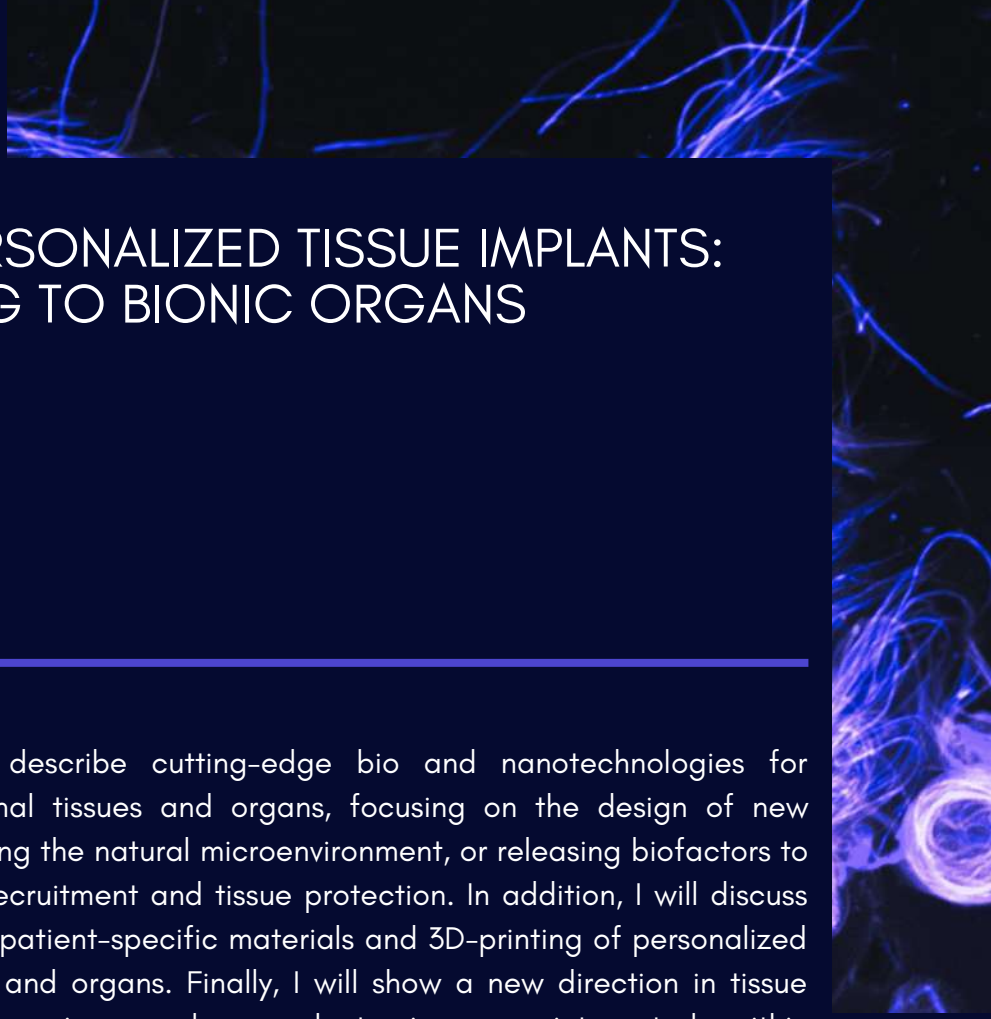
Using this 3D-1D system, we found that cells cultured in a three-dimensional milieu are expressing resistance to anticancer cells (i.e. Cisplatin), tuning the presence of polyploid cells, as well as the cell-matrix attachment properties of cancer cells.

According to our knowledge, the 3D-1D system represents an easy, cheap and highly reliable strategy to study the behavior of cancer cells in vitro, in a micro-environment similar to those found in primary tumors.

References:

1. Ertekin Ö. et al., (2022). Acta Biomaterialia. 142, 208.
2. Leal-Egaña A. et al., (2020). Trends in Biotechnology. 38, P142.
3. Leal-Egaña A. et al., (2017). Molecular Biology of the Cell. 28, 1612.

WED
19 OCT
Session 1C

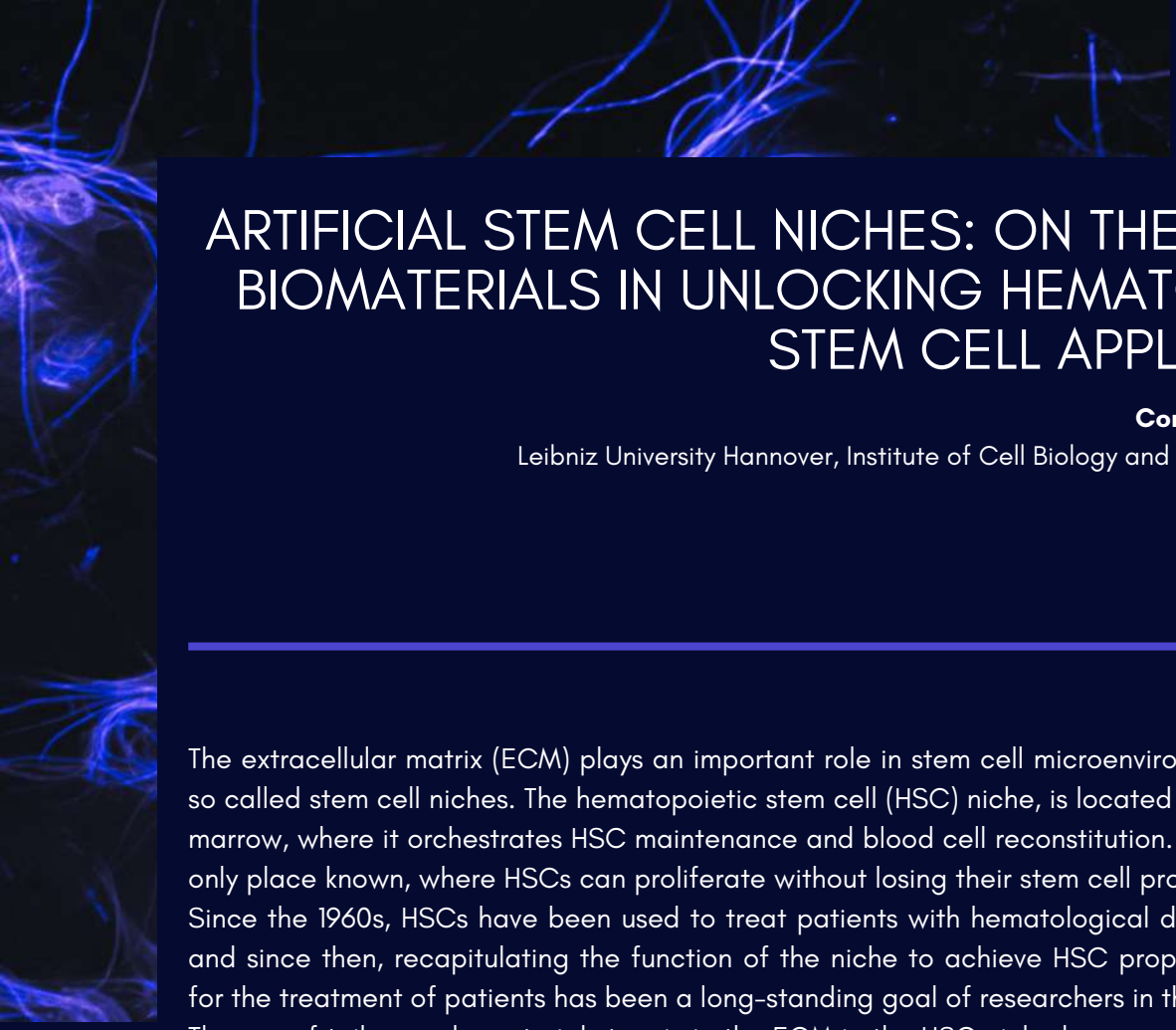


ENGINEERING PERSONALIZED TISSUE IMPLANTS: FROM 3D PRINTING TO BIONIC ORGANS

Tal Dvir
Tel Aviv University

In this talk I will describe cutting-edge bio and nanotechnologies for engineering functional tissues and organs, focusing on the design of new biomaterials mimicking the natural microenvironment, or releasing biofactors to promote stem cell recruitment and tissue protection. In addition, I will discuss the development of patient-specific materials and 3D-printing of personalized vascularized tissues and organs. Finally, I will show a new direction in tissue engineering, where, micro and nanoelectronics are integrated within engineered tissues to form cyborg tissues and bionic organs.

WED
19 OCT
Session 1D



ARTIFICIAL STEM CELL NICHES: ON THE ROLE OF BIOMATERIALS IN UNLOCKING HEMATOPOIETIC STEM CELL APPLICATIONS

Cornelia Lee-Thedieck
Leibniz University Hannover, Institute of Cell Biology and Biophysics, Hannover

The extracellular matrix (ECM) plays an important role in stem cell microenvironments, so called stem cell niches. The hematopoietic stem cell (HSC) niche, is located in bone marrow, where it orchestrates HSC maintenance and blood cell reconstitution. It is the only place known, where HSCs can proliferate without losing their stem cell properties. Since the 1960s, HSCs have been used to treat patients with hematological diseases, and since then, recapitulating the function of the niche to achieve HSC propagation for the treatment of patients has been a long-standing goal of researchers in the field. The use of tailor-made materials to mimic the ECM in the HSC niche has proven to be a promising approach toward this goal. Such materials allow to study the influence of biochemical and physical properties of the matrix on HSC behaviour. This knowledge is used to design artificial stem cell niches for fundamental research and for applications ranging from targeted cell expansion and differentiation for cellular therapies to platforms for drug testing. In this way, innovative ECM-mimetic biomaterials open the avenue toward potential stem cell applications.

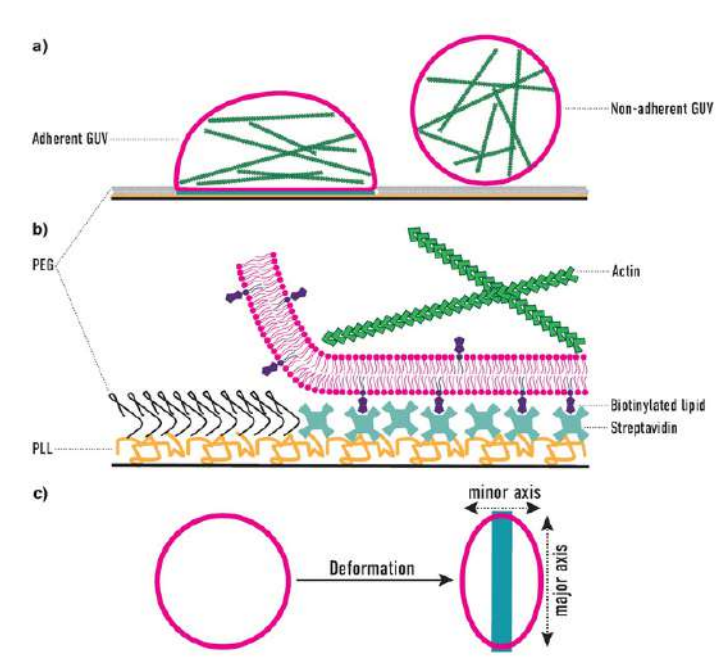
THUR
20 OCT
Session 2A

A BOTTOM-UP APPROACH TO STUDY FRONT-REAR CELL POLARIZATION

Andreas Fink[1,2], Charlotte Doll[2], Sergio Lembo[3], Anusha Bargavi Gopalan[3], Ana Yagüe Relimpio[1,2], Alba Diz-Muñoz[3], Joachim Spatz[1,2], Kerstin Göpfrich[4], Ada Cavalcanti-Adam[1,2]

[1] MPI for medical research
[2] Heidelberg University
[3] Cell Biology and Biophysics Units, European Molecular Biology Laboratory
[4] Biophysical Engineering Group, MPI for medical research

Spontaneous and induced front-rear polarization leading to cell movement is a key process involved in a variety of physiological and pathological events. A current challenge is to uncouple the effect of adhesion and shape from the contribution of the cytoskeleton in regulating the onset of polarization. Here, we presend a minimal model system to study front-rear polarization using Giant Unilamellar Vesicles (GUVs) adhering onto crossbow and line micropatterned surfaces. To further investigate the effects of GUV shape on cytoskeletal organization, actin filaments are polymerized together with bundeling proteins inside of GUVs. In the future, this bottom-up approach will allow to identify the major components needed to create a polarized cytoskeleton, giving a better understanding of polarity in minimal systems.



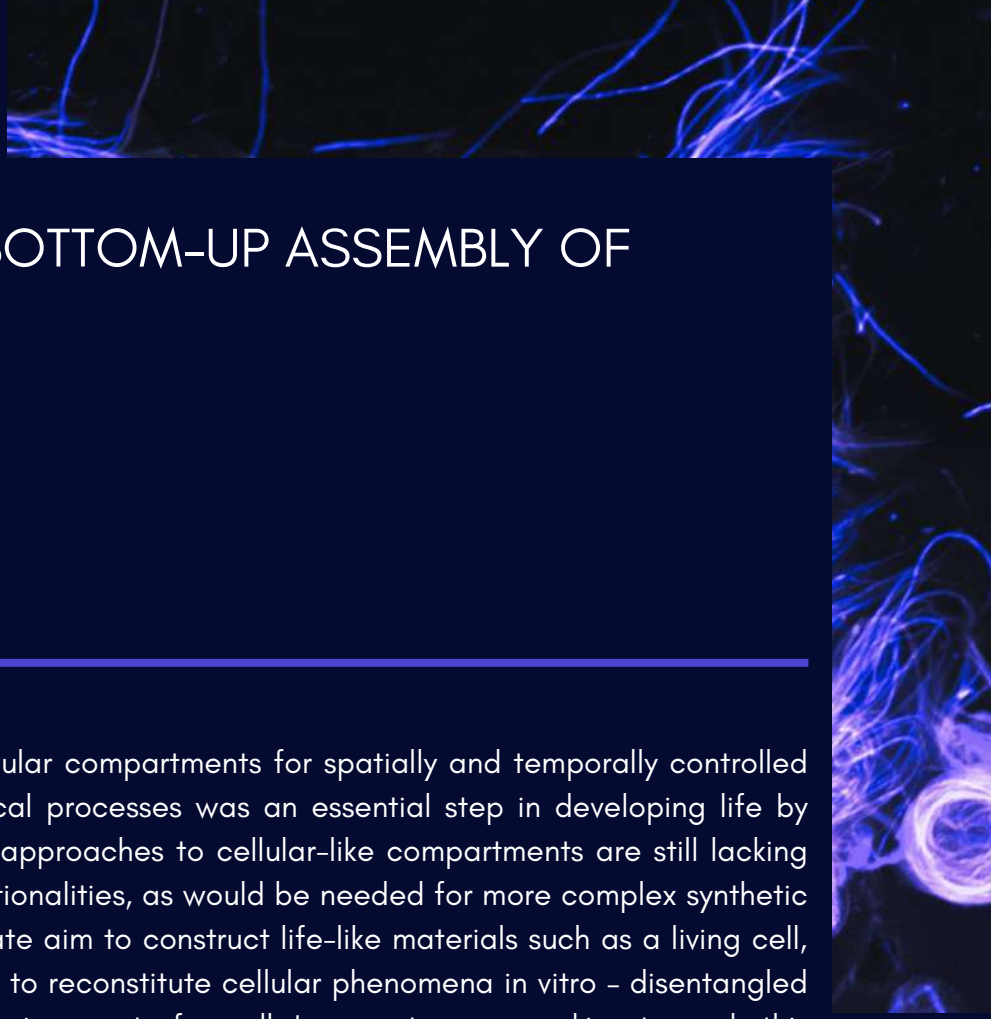
THUR
20 OCT
Session 2A

FIBRONECTIN ANCHORING ON VISCOELASTIC SUBSTRATES CONTROLS CELL MECHANOSENSING

Dimitris Missirli,[1] Tamás Haraszti,[2] Joachim Spatzs[1]
[1]Max-Planck-Institute for Medical Research, Heidelberg
[2]DWI-Leibniz Institute for Interactive Materials

The mechanical properties of the extracellular matrix (ECM) regulate cell physiology in a number of diseases, prompting efforts to elucidate cell mechanosensing mechanisms at the molecular and cellular scale. Here, we present insights on such mechanisms through the use of fibronectin-functionalized silicone elastomers that exhibit considerable frequency-dependence in viscoelastic properties, but no viscoplasiticity at short time scales. The hydrophobic character of the material enabled physical adsorption of the ECM, which formed a homogeneous coating independent of substrate stiffness. Surprisingly, weakly-crosslinked elastomers with shear moduli in the order of tens of Pa supported efficient focal adhesion maturation and fibroblast spreading similar to stiff controls. Careful characterization of surface mechanics revealed that this was attributed to an apparent stiff surface layer originating from solid surface tension and a tight anchoring of fibronectin to the substrate. However, cells did not polarise their cytoskeleton and could not migrate with directional persistence on softer substrates: elastomers with high cross-linking and low deformability were required for polarization. Our results suggest as underlying reason for this behavior the inability of soft elastomer substrates to resist traction forces, rather than a lack of sufficient traction force generation. Accordingly, mild inhibition of actomyosin contractility rescued fibroblast polarization even on the softer elastomers. Additionally, when the anchoring of fibronectin to the elastomer was weakened through modification of surface hydrophilicity, cells recovered the ability to polarise even on the softer substrates. Overall, our findings indicate the regulation of different cellular mechanosensing processes, namely focal adhesion assembly and actin cytoskeleton polarization, by distinct substrate mechanical properties and provide a premise to reconcile previously proposed local and global models of cell mechanosensing.

THUR
20 OCT
Session 2A



MATTER TO LIFE: BOTTOM-UP ASSEMBLY OF SYNTHETIC CELLS

Joachim Spatz
MPI for medical Research

The evolution of cellular compartments for spatially and temporally controlled assembly of biological processes was an essential step in developing life by evolution. Synthetic approaches to cellular-like compartments are still lacking well-controlled functionalities, as would be needed for more complex synthetic cells. With the ultimate aim to construct life-like materials such as a living cell, matter-to-life strives to reconstitute cellular phenomena in vitro - disentangled from the complex environment of a cell. In recent years, working towards this ambitious goal gave new insights into the mechanisms governing life. With the fast-growing library of functional modules assembled for synthetic cells, their classification and integration become increasingly important. We will discuss strategies to reverse-engineer and recombine functional parts for synthetic eukaryotes, mimicking the characteristics of nature's own prototype. Particularly, we will focus on large outer compartments, complex endomembrane systems with organelles and versatile cytoskeletons as hallmarks of eukaryotic life. Moreover, we identify microfluidics and DNA nanotechnology as two highly promising technologies which can achieve the integration of these functional modules into sophisticated multifunctional synthetic cells.

THUR
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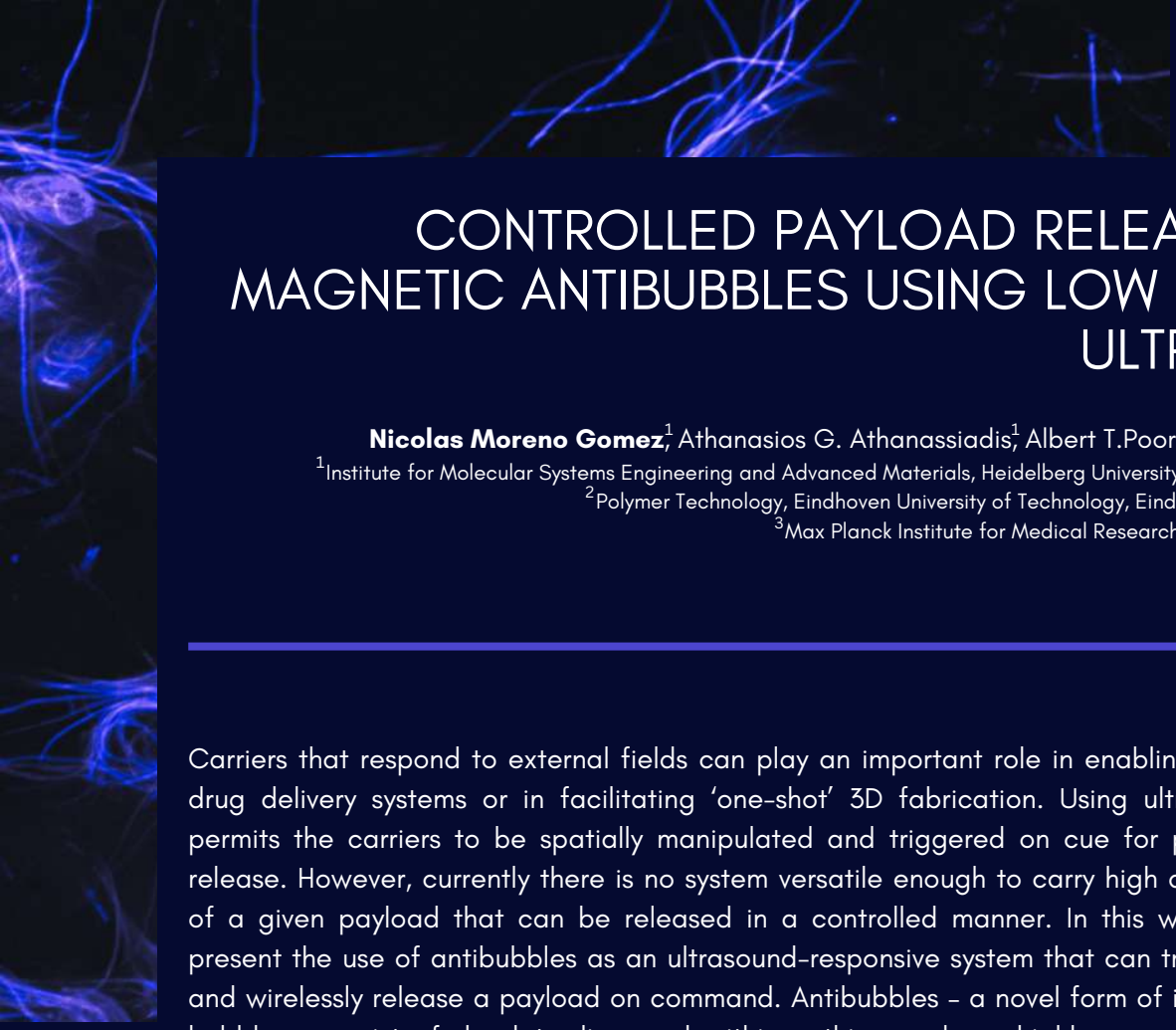
Session 2B



CONTROLLED PAYLOAD RELEASE FROM MAGNETIC ANTIBUBBLES USING LOW INTENSITY ULTRASOUND

Nicolas Moreno Gomez[1], Athanasios G. Athanassiadis[1], Albert T.Poortinga[2], Peer Fischer[1,3]
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[2]Polymer Technology, Eindhoven University of Technology, Eindhoven, the Netherlands
[3]Max Planck Institute for Medical Research, Heidelberg, Germany

Carriers that respond to external fields can play an important role in enabling smart drug delivery systems or in facilitating 'one-shot' 3D fabrication. Using ultrasound permits the carriers to be spatially manipulated and triggered on cue for payload release. However, currently there is no system versatile enough to carry high amounts of a given payload that can be released in a controlled manner. In this work, we present the use of antibubbles as an ultrasound-responsive system that can transport and wirelessly release a payload on command. Antibubbles – a novel form of inverted bubble – consist of droplets dispersed within a thin gas layer highly responsive to ultrasound. Here, we describe how to tailor the acoustic response of antibubbles by modifying their size and the composition of the external surface during fabrication. We find that for different types of antibubbles, the required acoustic pressure to release the loaded calcein is only on the order of a few kPa and varies among different formulations. Additionally, the different external surface composition also modifies the release profile between a single event and a step-wise behavior. We explore different strategies to use our results to further investigate how to control the spatial and temporal antibubble response in complex environments. The combination of antibubbles with new technologies such as acoustic holograms and magnetic inclusions is also discussed. We anticipate that antibubbles can be used as components for ultrasound responsive smart materials, owing to the simplicity to load them during fabrication, their high carrying capacity, and the ability to manipulate them using ultrasound and burst them using low acoustic pressures.

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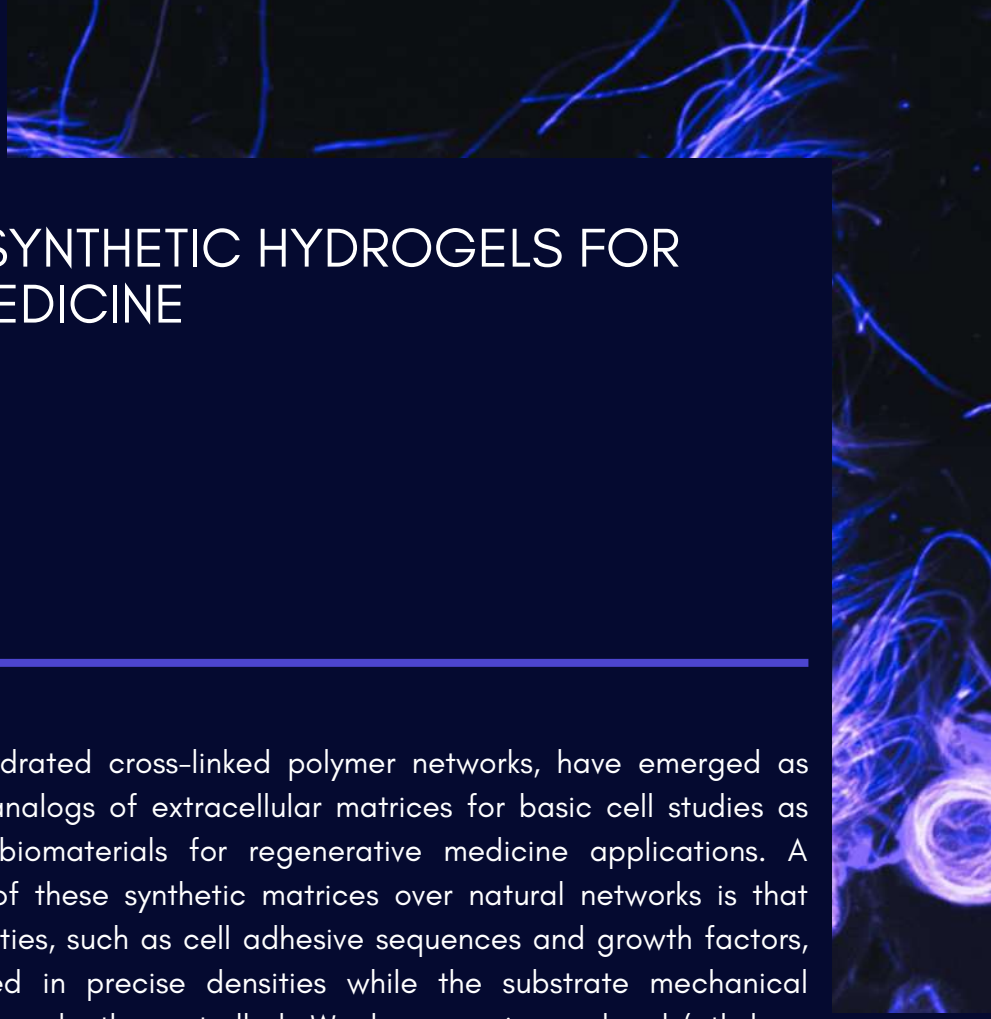
Session 2B



BIOENGINEERED SYNTHETIC HYDROGELS FOR REGENERATIVE MEDICINE

Andres Garcia
Georgia Institute of Technology

Hydrogels, highly hydrated cross-linked polymer networks, have emerged as powerful synthetic analogs of extracellular matrices for basic cell studies as well as promising biomaterials for regenerative medicine applications. A critical advantage of these synthetic matrices over natural networks is that bioactive functionalities, such as cell adhesive sequences and growth factors, can be incorporated in precise densities while the substrate mechanical properties are independently controlled. We have engineered poly(ethylene glycol) [PEG]-maleimide hydrogels for local delivery of therapeutic proteins and cells in several regenerative medicine applications. For example, synthetic hydrogels with optimal biochemical and biophysical properties have been engineered to direct human stem cell-derived intestinal organoid growth and differentiation, and these biomaterials serve as injectable delivery vehicles that promote organoid engraftment and repair of intestinal wounds. In another application, hydrogels presenting immunomodulatory proteins induce immune acceptance of allogeneic pancreatic islets and reverse hyperglycemia in models of type 1 diabetes. Finally, injectable hydrogels delivering anti-microbial proteins eradicate bone-associated bacterial infections and support bone repair. These studies establish these biofunctional hydrogels as promising platforms for basic science studies and biomaterial carriers for cell delivery, engraftment and enhanced tissue repair.

THUR
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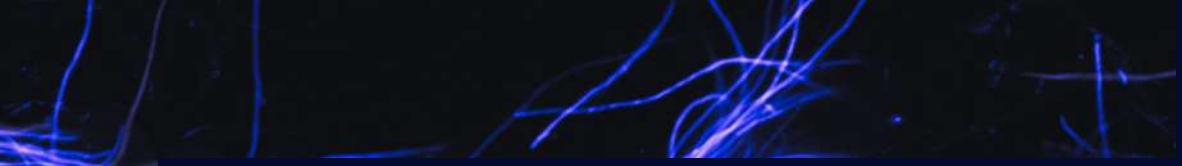
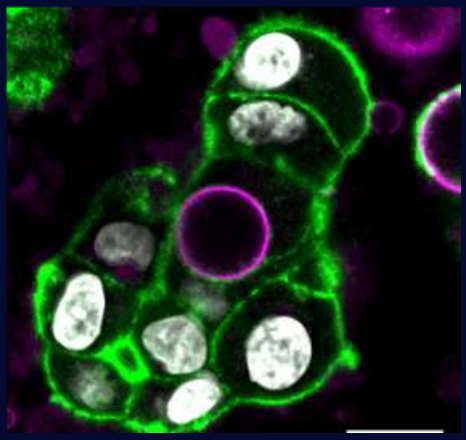
Session 2C



SYNTHETIC TUMOUR IMMUNE MICROENVIRONMENTS

Oskar Staufer
University of Oxford

The microenvironment of tumors comprises multiple types of immune cells, rendering the tumour immune-microenvironment (TIME) exceedingly complex in structure and function. Although some deceptively simple signaling axis (e.g. PD 1, LAG3 etc) have been pinpointed, empiric investigations of this multipartite system have proven to be ineffective, currently impending improvement of immune-targeted cancer therapies. Systematically combining the mosaic of functional immune parts for bottom-up engineering of an artificial TIME (ART-TIME), that exhibits key characteristics of tumor-immune interactions, opens up new perspectives towards rational analysis of TIME and its influence on tumor initiation, progression and treatment.
I will present how immune cells, the defining elements of a TIME, can be recreated as synthetic cells by bottom-up assembly. The programmable synthetic cells are introduced into tumor organoids to function as lifelike leukocyte mimics inside in vitro tumors. By this, a molecularly defined immune environment is created. Multi-parametric screening is applied to assess organoid development as well as immunotherapy response as a function of the ART-TIME configuration. This links TIME architectures to cancer adaptation and therapy resistance. ART-TIME strives to deconvolute the dynamic complexity of immune microenvironments towards a rational dissection. Moreover, ART-TIME contributes concepts for the assembly of hybrid biomaterials and insights on tumour immunology using programmable man-made materials. This interdisciplinary approach opens up perspectives for synthetic cells capable of manipulating tissue patterns by creating hybrid materials at the vanishing boarders between the living and non-living world.



THUR
20 OCT
Session 2C

RNA THERAPEUTICS IS GOING BEYOND THE LIVER: FROM GENE SILENCING TO GENE EDITING

Dan Peer
Laboratory of Precision NanoMedicine, Tel Aviv University

Accumulating work points out relevant genes and signaling pathways hampered in human disorders as potential candidates for therapeutics. Developing nucleic acid-based tools to manipulate gene expression, such as siRNAs, mRNA and genome editing strategies, open up opportunities for personalized medicine. Yet, although major progress was achieved in developing RNA targeted delivery carriers, mainly by utilizing monoclonal antibodies (mAbs) for targeting, their clinical translation has not occurred. In part because of massive development and production requirements and high batch-to-batch variability of current technologies, which relies on chemical conjugation. Here we present a self-assembled modular platform that enables to construct theoretically unlimited repertoire of RNA targeted carriers. The platform self-assembly is based on a membrane-anchored lipoprotein, incorporated into RNA-loaded novel, unique lipid nanoparticles that interact with the antibody Fc domain. We show that a simple switch of 8 different mAbs, redirects specific uptake of siRNAs by diverse leukocyte subsets in vivo. The platform therapeutic potential is demonstrated in an inflammatory bowel disease model, by targeting colon macrophages to reduce inflammatory symptoms, and in Mantle Cell Lymphoma xenograft model, by targeting cancer cells to induce cell death and improve survival. In addition, I will discuss novel approach for delivering modified mRNA to specific cell types in vivo utilizing this platform. I will also share some data on mRNA vaccines for COVID19 and Finally, I will share new data showing very high efficiency genome editing in glioma and metastatic ovarian cancer. This modular delivery platform can serve as a milestone in turning precision medicine feasible.

THUR
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Session 2D

BOTTOM-UP ASSEMBLY OF SYNTHETIC SARS-COV-2 MINIMAL VIRIONS FOR THE INVESTIGATION OF VIRAL INFECTIVITY

Ana Yagüe Relimpio,[1,2] Oskar Staufer[1,2,3,4], Andreas Fink[1], Alessia Ruggieri[5], Imre Berger[3], Ilia Platzman[1,2], Joachim P. Spatz[1,2,3,4]

[1]Department for Cellular Biophysics, Max Planck Institute for Medical Research
[2]Institute for Molecular Systems Engineering, Heidelberg University
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[4]Max Planck School Matter to Life,
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SARS-CoV-2 is the betacoronavirus responsible for the still ongoing COVID-19 pandemic, which still remains a major global health concern. Due to the high mutagenicity of the virus, well-controlled studies of its infectivity are challenging. Furthermore, performing research with natural viruses is often dangerous and complex, and they are restricted to high biosafety facilities. We developed a technology for the bottom-up assembly of modular minimal SARS-CoV-2-like virions with molecularly defined composition. The bottom-up synthesis of synthetic virions consisted of the creation of small unilamellar vesicles (SUVs) with a lipid composition that resembles that of the SARS-CoV-2 virus. The vesicles were further functionalized with spike glycoprotein. Under low biosafety conditions we performed a systematic screening of spike-functionalized SUV binding to target cells under well-defined free fatty acid conditions. We found that unsaturated fatty acid binding to the spike reduced spike-mediated SARS-CoV-2 infectivity. Importantly, our technology could be modulated to study the infectivity of different SARS-CoV-2 variants of concern, as well as to assess the direct impact of FDA-approved drugs on spike protein cell-binding activities. Additionally, we aim to decipher the effect of the lipid composition - both on the cell and on the virus membrane - on viral infectivity. Specifically in the case of SARS-CoV-2, the importance of cholesterol and sphingomyelin have been highlighted as a key element for the infectivity of the virus. The developed technology allowed us to circumvent the current limitations associated with studies of natural SARS-CoV-2 viruses for potential therapeutical applications.

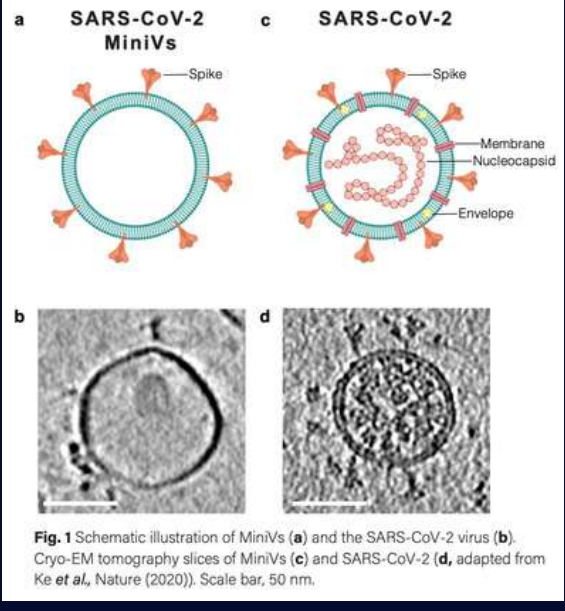


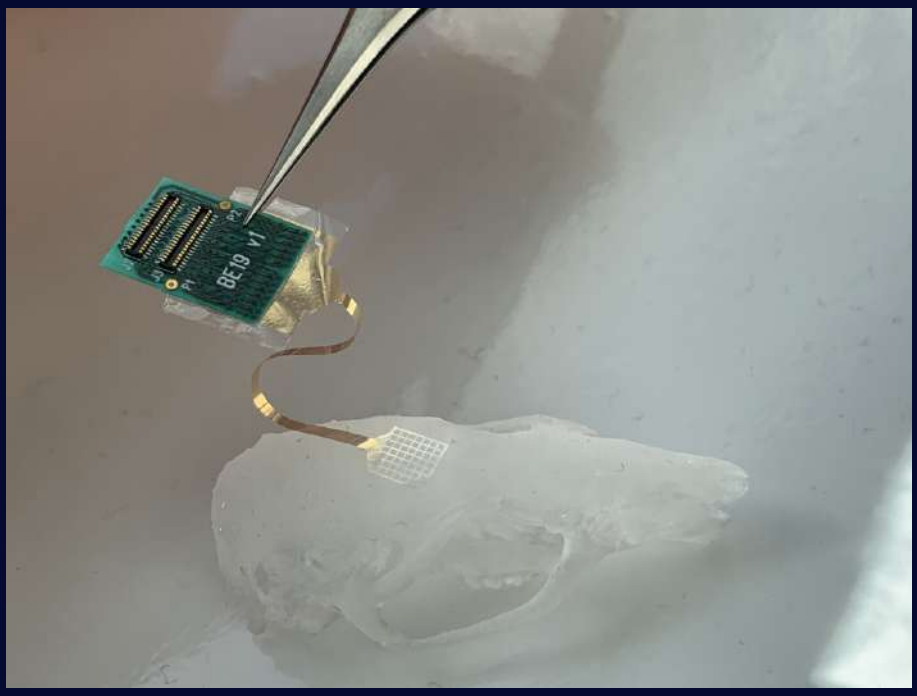
Fig. 1 Schematic illustration of MiniVs (**a**) and the SARS-CoV-2 virus (**b**). Cryo-EM tomography slices of MiniVs (**c**) and SARS-CoV-2 (**d,** adapted from Ke *et al.*, Nature (2020)). Scale bar, 50 nm.

THUR
20 OCT
Session 2D

TECHNOLOGY FOR BIOELECTRONIC MEDICINE

George Malliaras
University of Cambridge

Bioelectronic medicine provides a new means of addressing disease via the electrical stimulation of tissues: Deep brain stimulation, for example, has shown exceptional promise in the treatment of neurological and neuropsychiatric disorders, while stimulation of peripheral nerves is being explored to treat autoimmune disorders. To bring these technologies to patients at scale, however, significant challenges remain to be addressed. Key among these is our ability to establish stable and efficient interfaces between electronics and the human body. I will show examples of how this can be achieved using new organic electronic materials and devices engineered to communicate with the body and evolve with it.



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Session 2E

BIOELECTRONIC DEVICES AND THERAPEUTIC APPLICATIONS: THE PNS STIMULATION AS A PARADIGM OF THE NEW BIOELECTRONIC MEDICINE ERA

Dimitrios Koutsouras, Evelien Hermeling, Lucas Lindeboom, Fabian Beutel, Jesse Kling, Nicolo Rossetti, Mark Fichman, Vojkan Mihajlovic, Geert Langereis1
imec The Netherlands

The global population is aging, and the growing health awareness has created an imperative need for more efficient approaches to address today's increasing health-related demands. Biomedical devices play a crucial role in this pursuit as they can offer novel solutions to incurable or chronic diseases. In this context, during the last couple of decades, bioelectronic devices have gained great attention as a way of establishing a communication pathway, between the worlds of biology and electronics. The overall goal is for technology to bestow new tools to clinicians which can translate them into state-of-the-art healthcare solutions. Especially the nervous system (NS), despite being the most important system in the human body, remains the least understood one. At the same time, it offers numerous opportunities for application of modern therapeutic approaches which harness the neural wiring of the body. The Peripheral Nervous System (PNS) in particular, has recently become the target of intense research activity worldwide. This research aspires to complement, or even replace, chemical drugs with neuromodulation therapies giving rise to a new class of therapeutic approaches known as bioelectronic medicine. The benefit is the creation of targeted, effective, adaptive, and personalized treatments with minimized side effects compared to the traditional pharmaceutical ones. The Vagus Nerve (VN), as the main parasympathetic nerve of the autonomic division of the PNS, is responsible for the, throughout the torso, organ innervation, and therefore the regulation of a variety of sensory, motor, and physiological functions. As such, it is believed to hold the key to alleviating many ailments, including several chronic ones. Our work focuses on developing new Vagus Nerve Stimulation (VNS) approaches and incorporating closed-loop therapies in biomedical devices. Overall, it paves new routes towards novel and drug-free remedies

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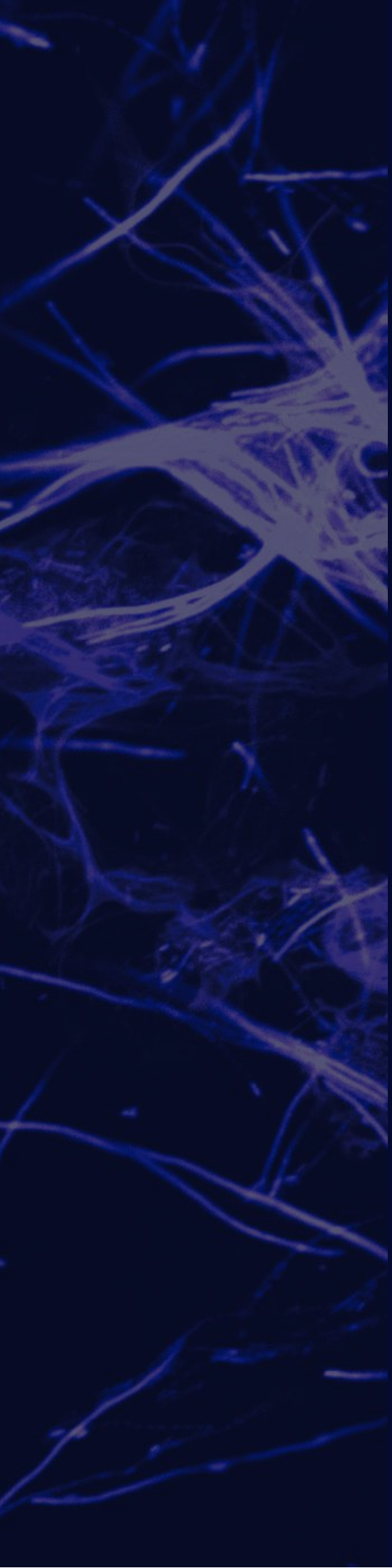


POSTER SESSION I

19.10.2022
3:30 PM – 4:15 PM
Heidelberger Akademie der Wissenschaften

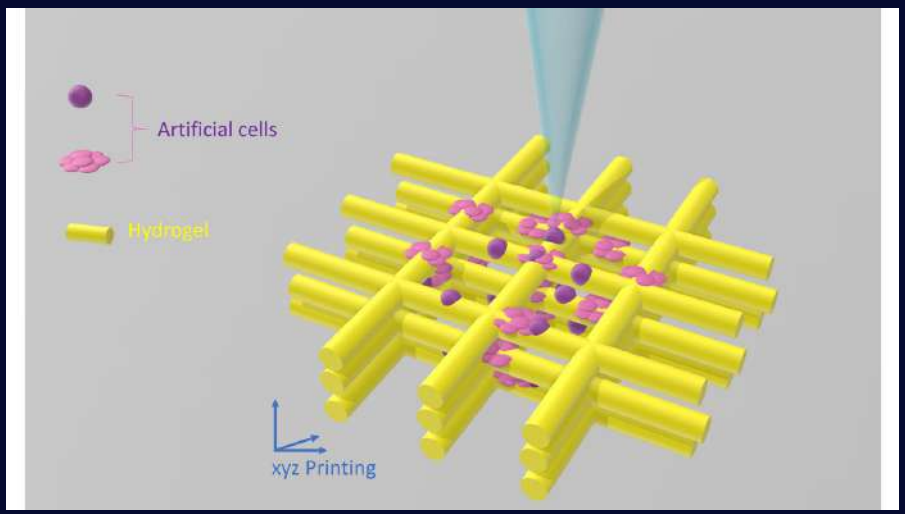
ARTIFICIAL TISSUE ENGINEERING: 3D BIOPRINTING MEETS SYNTHETIC CELLS

Yiğitcan Sümbelli,[1] Léocadie Edet[2], Alexander F. Mason[3], Jan C.M. van Hest[1]

[1]Eindhoven University of Technology
[2]École de Biologie Industrielle
[3]University of New South Wales

Developing functional tissue models to be used as a replacement for damaged tissues is one of the main goals of tissue engineering. While these replacing tissue models can be (bio)fabricated via a variety of different techniques, 2 components of the process are always required: native cells and biomolecular cues. The relationship between native cells and biomolecular cues is however highly dependent on the physicochemical properties of the surrounding biomaterial, which is the most important limiting factor for such engineering approaches. In addition to that, the directed interaction between different cell types, and controlled deposition of biomolecular cues remain as a major issue.

3D bioprinting is an advanced technique that can be used for such studies, by regulating the physicochemical properties of the selected biomaterials and by achieving spatiotemporal control over cellular deposition and display of biochemical cues. Within this field of science, synthetic cell studies in relationship with biomaterials are a rising focus of interest. As simplified mimics of living cells, they can be programmed to interact with their environment in a controlled fashion, for example via the local and time-resolved release of bioactive components. Understanding the synthetic cell behaviour when integrated with traditional tissue engineering approaches can be seen as one of the fundamental topics to investigate the characteristics of artificial tissue mimics for further developments. In this study, 3D printed ECM-like materials that carried synthetic cellswere developed. Terpolymer stabilized carbohydrate-based coacervates were embedded into protein - carbohydrate, and modified protein-based biomaterial ink combinations, respectively. The mechanical behaviour of the biomaterial inks and synthetic cell behaviour within the 3D printed structures are the main point of interests of the study.



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STIMULI RESPONSIVE HYDROGEL ACTUATORS FOR MICROFLUIDIC SORTING IN BIOAPPLICATIONS

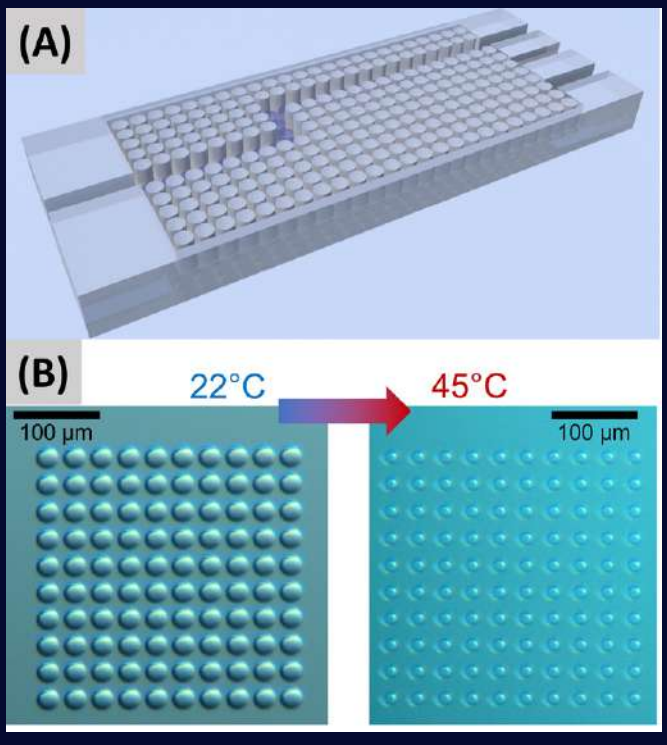
Tobias Spratte[1], Anastasia Dudin[1], Aldo Leal-Egaña[1], Sophie Geiger[1], Li-Yun Hsu[2], Eva Blasco[2], Christine Selhuber-Unkel[1]

[1]Institute for Molecular Systems Engineering and Advanced Materials, Heidelberg University
[2]Organic Chemistry Institute and Center for Advanced Materials, Heidelberg University

The ability to purify cell mixtures by sorting or even isolating single cells from a suspension has become an essential tool in research fields such as biology, biophysics, or medicine. To fulfill such tasks, responsive soft and deformable materials are required, which allow for precise and gentle handling of fragile microscale biological objects. Among those materials, poly(N-isopropylacrylamide) (pNIPAM) hydrogel is an excellent candidate to design thermoresponsive soft actuators.

Many current sorting methods, such as microfluidics, exhibit a limited functionality due to predefined and static geometries. This project focusses on the development of a soft and dynamic microfluidic chip, consisting of a pNIPAM micropillar array, which can form various channel configurations to guide biological loads, such as cells (cf. Figure 1).

A high-resolution fabrication method is needed for precise control about the microstructures. Here, we focus on a direct laser writing (DLW) process based on two photon polymerization (2PP) in order to design the responsive micropillar arrays. These hydrogel structures can be actuated remotely, for instance via locally varying the environmental temperature (~37°C), which results in a high degree of flexibility and manifold usage in various experimental setups. Further, we investigate the interaction between living cells and the hydrogel material.



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CO-AXIAL 3D BIOPRINTING FOR BIOMIMETIC MULTIFIBER SKELETAL MUSCLE-BASED BIOACTUATORS

Judith Fuentes, Rafael Mestre, Maria Guix, Ibstissam Ghailan, Samuel Sánchez

Institute for Bioengineering of Catalonia (IBEC)

Recent advances in three-dimensional (3D) bioprinting and tissue engineering have opened new possibilities in the fabrication of bioengineered muscle models able to mimic the complex hierarchical organization and functional properties from the native tissues [1]. The combination of skeletal muscle tissue and artificial elements has led to a wide variety of innovative solutions to create bio-hybrid robotic systems and bioactuators [2] that offer the opportunity to study processes of interest in the biomedical field, such as muscle development and regeneration However, one key problem in tissue engineering is the poor oxygen and nutrients supply in the inner regions of the printed scaffold, leading to a reduced cell viability.

In our work, we explored co-axial 3D bioprinting [3] as a novel strategy towards overcoming the nutrient diffusion problem by creating individual, non-fused fibers with defined thickness. Therefore, we aim to develop a 3D bioengineered skeletal muscle bioactuator with biomimetic design in terms of structure and functionality. In comparison with conventional 3D-bioprinting, where a single syringe containing the cell-laden bioink is used, in co-axial 3D-bioprinting an outer layer of sacrificial material (pluronic acid in this study) allows a physical confinement on the inner layer (i.e bioink), obtaining thin independent printed fibers that can be hierarchically organized. Such technique is generally implemented in the fabrication of vascular systems [4]. The use of bioprinting techniques allow the fabrication of bioengineered muscle-based actuators that present highly aligned myotubes with contractile capabilities. However, the formation of thinner and individual fibers obtained by co-axial 3D-printing resulted in an enhanced diffusion of nutrients during the muscle maturation process, improving cell differentiation and obtaining stronger bioactuators which present an increased force output in comparison with the actuators fabricated by using conventional printing.

After exploring the potential of 3D bioprinting for fabricating 3D bioengineered skeletal muscle bioactuators, our interests are currently focused on exploiting the regenerative capabilities of muscle tissue to integrate self-healing properties to living actuators [5] and create more biomimetic in vitro muscle models for biomedical applications.

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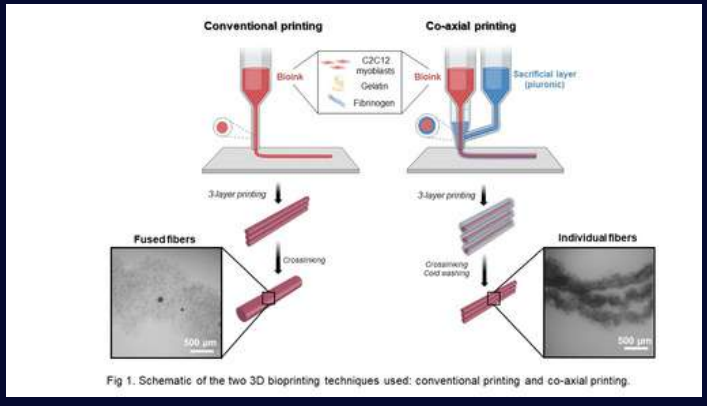

Fig 1. Schematic of the two 3D bioprinting techniques used: conventional printing and co-axial printing.

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P1.03

DESIGN OF STIMULI-RESPONSIVE MULTICOMPARTMENT VESICLES FOR IMMUNOLOGICAL APPLICATIONS

Anastassiya Schramm, Ilia Platzman, Joachim Spatz
Max Planck Institute for Medical Research

Programmed Death-Ligand 1 (PD-L1) protein together with its receptor, Programmed Cell-Death Protein 1 (PD-1) are crucial members of an immune checkpoint PDL1-PD1. PD-L1 is commonly expressed by antigen-presenting cells, such as B cells and macrophages. This ligand plays a major role in suppresing immune system to avoid auto-immunity upon binding to its receptor PD-1, which is expressed on the T-cells. A wide range of tumors have evolved to express this protein on their surface in order to evade the immune system response. Furthermore, certain tumor cells can upregulate the expression of the PD-L1 on the surface of the exosomes, that they secrete. When a T-cell is surrounded by the PD-L1 presenting exosomes, it becomes "exhausted" or simply non-funtional due to the constant blocking of its PD-1 receptors.

In this project we propose a modular multicompartment trigger-responsive system that can potentially inhibit PD-L1 on the tumor and its exosomes. The system will consist of a unilamellar lipid vesicle, functionalized with NIR-responsive gold nanorods, magnetic nanoparticles, PEG, CD47 and tumor recognition ligand (Figure 1). The system would be injected in proximity to the tumor and could further be moved to a precise location by means of magnetic field. Upon rupturing the vesicle with NIR light, PD-L1 blocking components will be released, which could restore the activity of the T-cells.

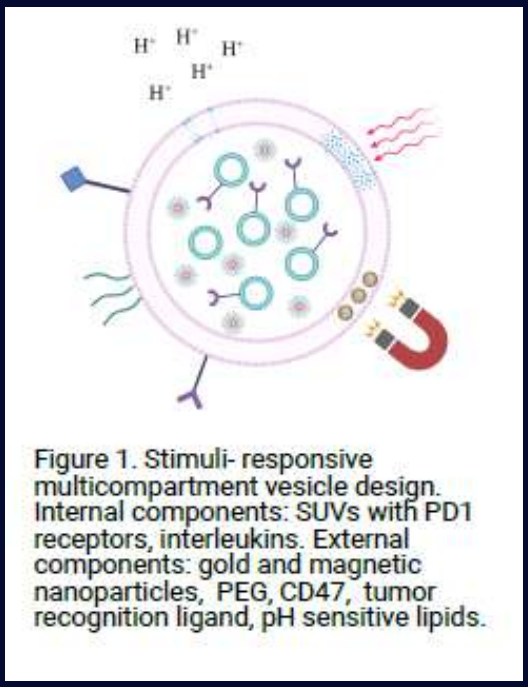

Figure 1. Stimuli- responsive multicompartment vesicle design. Internal components: SUVs with PD1 receptors, interleukins. External components: gold and magnetic nanoparticles, PEG, CD47, tumor recognition ligand, pH sensitive lipids.

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P1.04

MAPPING ELECTROTAXIS IN CANCER

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[3]Department of Microsystems Engineering, University of Freiburg
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[5]Freiburg Institute for Advanced Studies (FRIAS), University of Freiburg
[6]Department of Microtechnology and Nanoscience, Chalmers University of Technology

Being one of the deadliest diseases worldwide cancer constitutes a major societal burden. High mortality rates among terminal cancer patients that suffer from metastasis demonstrates the obstacles of traditional therapies which are incapable of efficiently targeting solely malignant cells and end up causing systemic damage. The development of truly selective cancer therapeutics will only progress if we start identifying and disentangling unique properties and signaling mechanisms of metastasis. This is where this project sets in by focusing on electromigratory (electrotaxis) behavior of malignant cancer cells along direct current electric fields (DCEFs). Directional migration along DCEFs has been observed in most mammalian cells.1 However, malignant cells distinguish themselves by their higher sensitivity and ability to respond also at moderate field strengths.2,3,4,5 The stronger tendency of malignant cells to electromigrate is likely linked to their increased expression of ion channels and overall, more mobile phenotype. A key finding has been that the higher the metastatic potential of a cell line, the more pronounced was the electrotactic response, giving rise to the hypothesis that electrical signaling may be a critical driver of metastasis by contributing to its invasiveness.6 However the underlying biochemical mechanisms that initiate electrotaxis in cells are not well understood. To close this knowledge gap we aim to map the electrotaxis of malignant cells using model microfluidic devices and elucidate the biochemical mechanisms involved in the cell migration via Raman spectroscopy.

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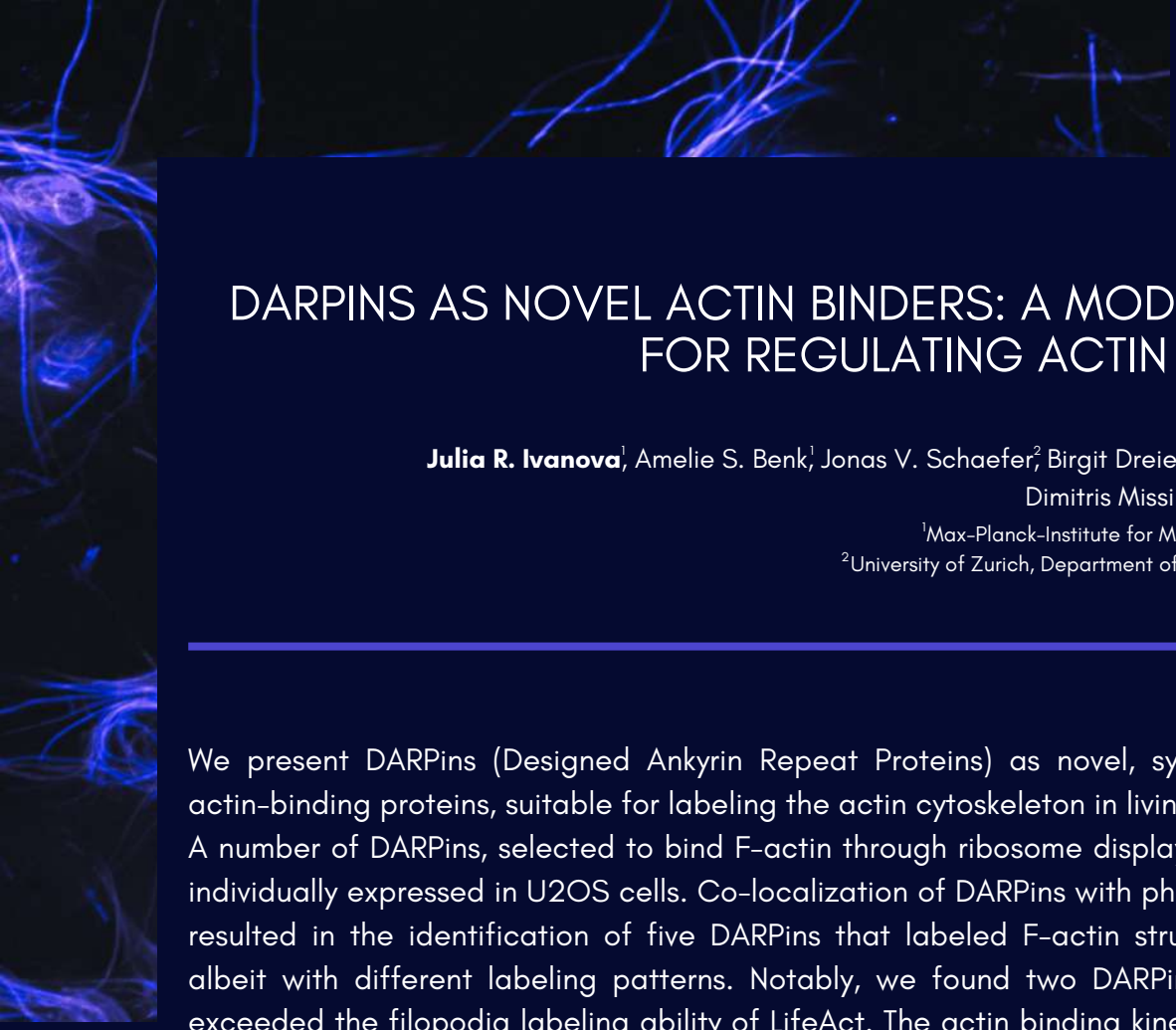

DARPINS AS NOVEL ACTIN BINDERS: A MODULAR TOOL FOR REGULATING ACTIN DYNAMICS

Julia R. Ivanova[1], Amelie S. Benk[1], Jonas V. Schaefer[2], Birgit Dreier[2], Andreas Plückthun[2], Dimitris Missirlis[1], Joachim P. Spatz[1]

[1]Max-Planck-Institute for Medical Research, Germany
[2]University of Zurich, Department of Biochemistry, Switzerland

We present DARPins (Designed Ankyrin Repeat Proteins) as novel, synthetic actin-binding proteins, suitable for labeling the actin cytoskeleton in living cells. A number of DARPins, selected to bind F-actin through ribosome display, were individually expressed in U2OS cells. Co-localization of DARPins with phalloidin resulted in the identification of five DARPins that labeled F-actin structures, albeit with different labeling patterns. Notably, we found two DARPins that exceeded the filopodia labeling ability of LifeAct. The actin binding kinetics as measured by FRAP correlated with DARPin accumulation in dynamic actin structures: The higher the DARPin turnover, the more the DARPins accumulated to lamellipodia/filopodia compared to stress fibers. This led to the hypothesis that the localization of actin probes depends on the inherent dynamics of the actin structures, e.g. the retrograde flow in lamellipodia and slower polymerization in stress fibers. To test this, the actin dynamics were arrested in living cells with a drug cocktail: fast re-localization of a DARPin to lamellipodia was observed. In sum, we propose DARPins as promising new actin labels in living cells and are now exploring the construction of modular, in cellulo actin cross-linkers.

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P1.06

KIRIGAMI BASED DYNAMIC SYSTEMS FOR IN VITRO CELL STUDIES

Gaurav Dave, Florine Sessler, Christine Selhuber-Unkel

Institute for Molecular Systems Engineering and Advanced Materials (IMSEAM), Heidelberg University

It is well known that cells respond to their environment, as well as, have an active role in shaping the environment they are in. Biochemical and biomechanical cues have been known to impact the cell behavior in a scaffold significantly. Novel and complex ideas on how mechanical cues such as stiffness, topography and porosity can be manipulated to tune cell behaviour or; taking an opposite approach were structures can be designed to respond to the mechanical stimulus by cells, are of much interest.
In this project, kirigami based design has been showcased. This design shows a novel strain deformation. The straining is supported by junctions bending rather than stretching of the material in the tiles. Such structure can be used for a scaffold with strain to porosity response. Additionally, such geometry in a cylindrical structure can be used to study cell migration behaviour for different structural stiffness, and showcase how cells can push and shape the structure.
The aim of this project is to design and fabricate such structures via the help of two-photon polymerization based 3D printing and further apply them to study cell mechanics and cell migration.

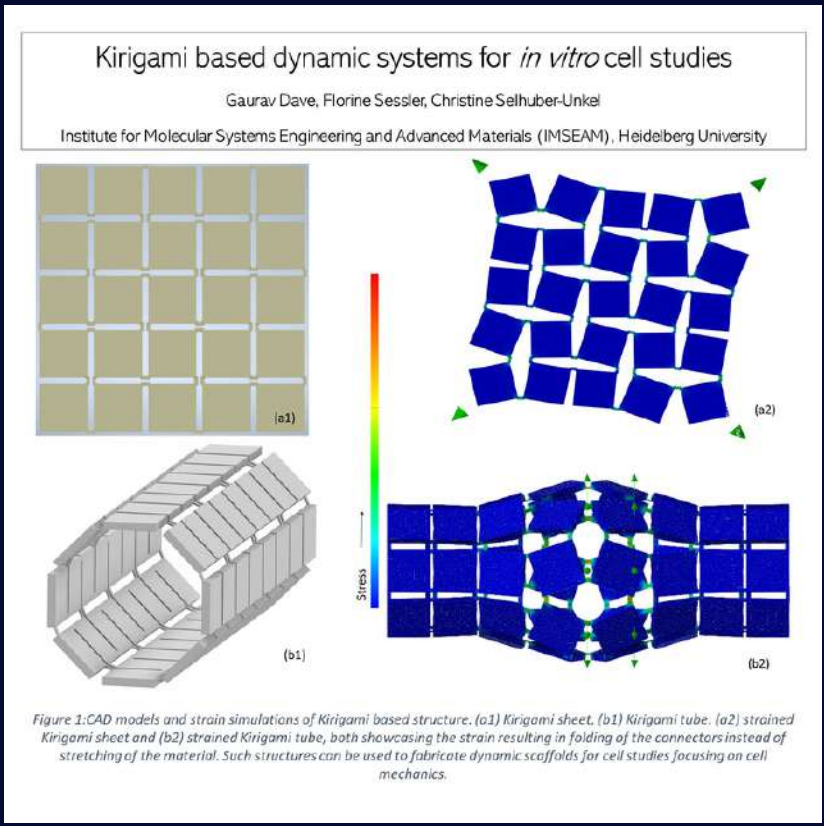


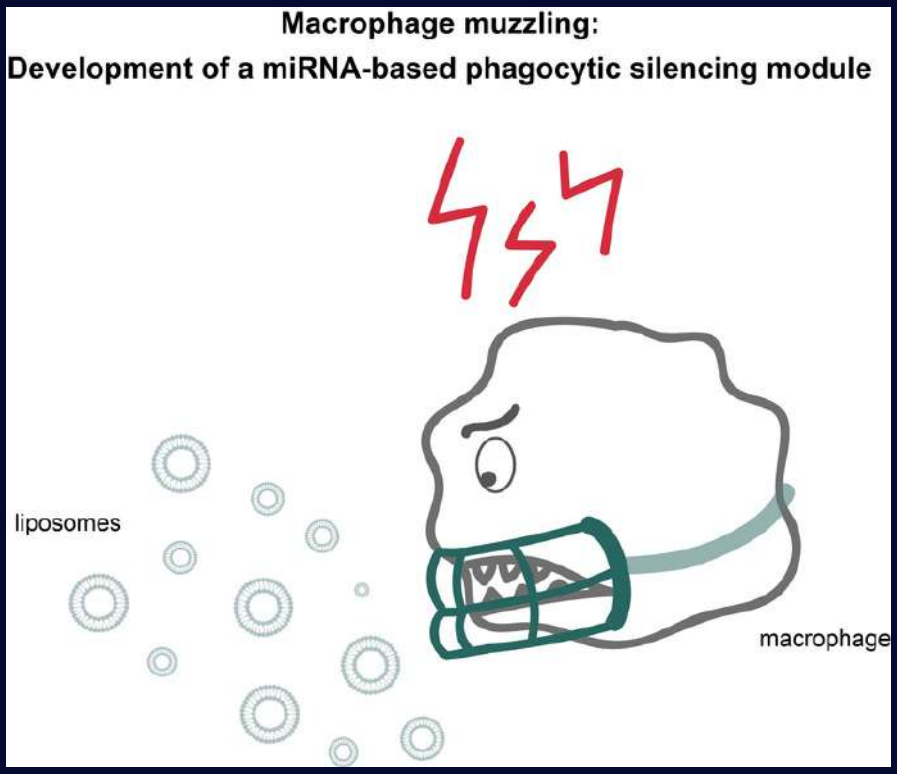
Figure 1:CAD models and strain simulations of Kirigami based structure. (a1) Kirigami sheet, (b1) Kirigami tube. (a2) strained Kirigami sheet and (b2) strained Kirigami tube, both showcasing the strain resulting in folding of the connectors instead of stretching of the material. Such structures can be used to fabricate dynamic scaffolds for cell studies focusing on cell mechanics.

WED
19 OCT
P1.07

MACROPHAGE MUZZLING: DEVELOPMENT OF A MIRNA-BASED PHAGOCYTIC SILENCING MODULE

Ann-Kathrin Gelmroth
Max Planck Institute for Medical Research

Nanoparticle-based drug delivery systems emerged as promising therapeutic vehicles in the last years. Particularly lipid-based particles stand out with their low, toxicity, high biocompartibility and synthetic formulation and modification simplicicity. However, adequate bloodstream persistence and low disposal rates through immune cells as well as targeted cell delivery are the major issues facing these drug delivery systems. To circumvent biological barriers, lipid vehicles are equipped with immunogenic polymers and ligands. Though, long circulating nanoparticles still display a challenge.
Here, a novel liposome-based tool towards prolonged persistance and blood circulation time is presented. Muzzling of macrophages is performed with this micro-RNA (miRNA)-containing module via downregulation of phagocytic important genes and the direct interference into the cellular transcriptome.



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19 OCT
P1.08

A BOTTOM-UP APPROACH TO STUDY A MINIMAL ACTIN CORTEX ORGANISATION IN GIANT UNILAMELLAR VESICLES

Sunnatullo Fazliev, Andreas Fink, Elisabetta Ada Cavalcanti-Adam, Joachim Spatz

Max-Planck-Institute for Medical Research, Germany

WED
19 OCT
P1.09

The cytoskeleton of the cell is a remarkable structure that mediates cell shape, adhesion, and motility in response to myriad intra- and extracellular cues. Engineering cytoskeletal elements for synthetic cells is of great interest in basic as well applied research, as it allows to mimic and modulate cell morphogenesis. Here, we employ bottom-up approach to study how actin networks organise depending on membrane shape. Using giant unilamellar vesicles (GUVs) we show that actin filaments can be organised beneath the membrane to form cortex-like structures. This is achieved using a minimal set of components: only actin and crowder molecules. In addition, using a micropatterning approach we adhere GUVs on different patterns to study actin network organisation. Our results shed light on actin network organisation in GUVs of various shapes and provide a minimal system to engineer cortex-like actin structures.

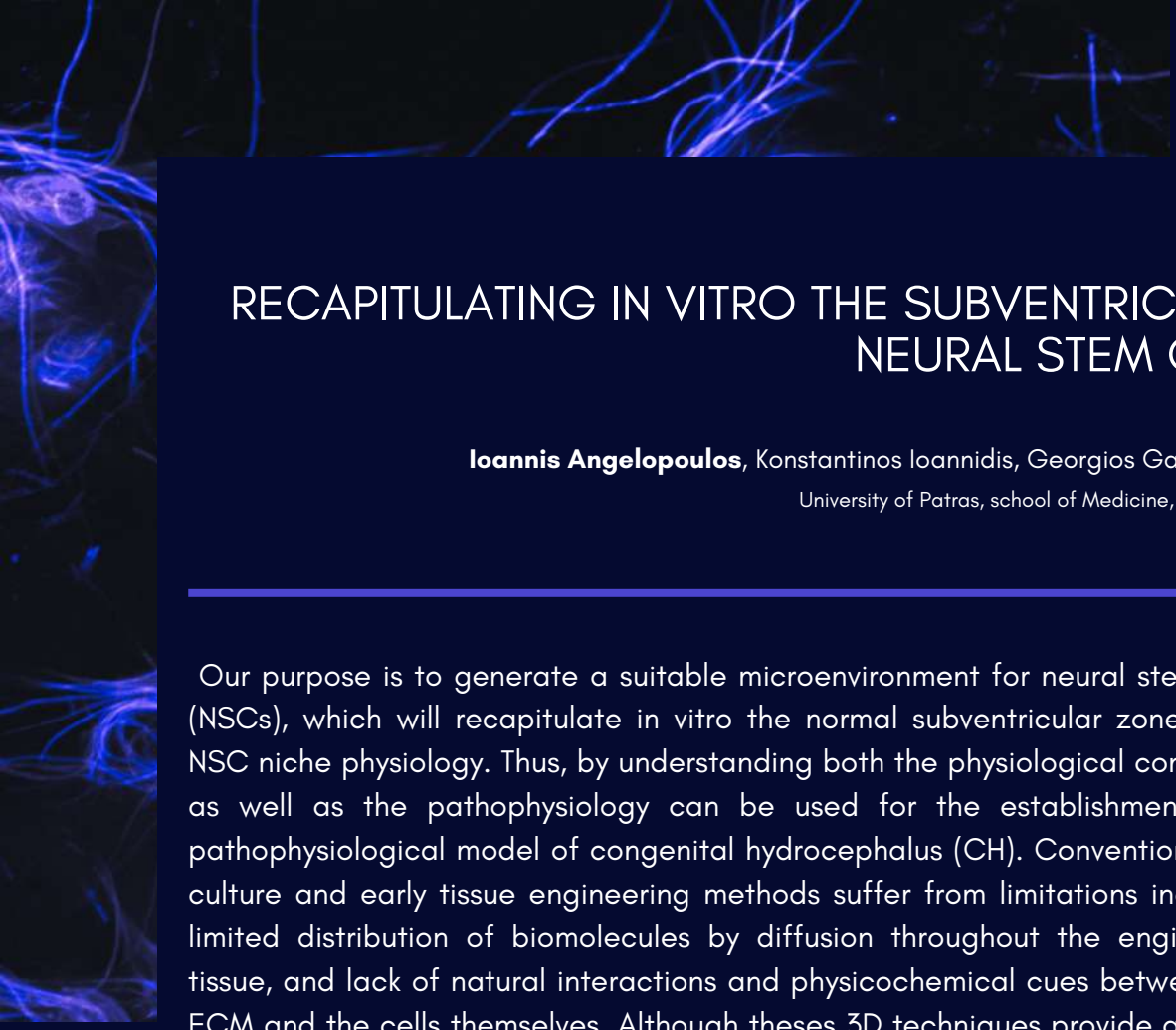
SYNTHESIS OF CELLULOSE BASED COPOLYMERS

Korbinian Sommer

Technische Universität München

WED
19 OCT
P1.10

Cellulose is an almost inexhaustible natural resource, which enables the production of novel hybrid-copolymers based on a renewable raw material. The modification of the hydroxyl groups of the cellulose backbone, either through functional groups to introduce specific reactivities or through linking to polymer side chains, enables the targeted adjustment of properties and functionalities of the resulting materials. By grafting with hydrophobic or hydrophilic macromolecules, e.g. poly(caprolactones) or poly(ethylene glycol), we achieved tailored polymer architectures and properties through regioselective modification of the cellulose backbone. Both the chain length of the cellulose and the degree of substitution and polymerization of the polymer side chains are adjustable parameters that influence the properties of the graft copolymers.
Possible areas of application for these materials include the production of nanoparticles as well as the formation of photonic structures through self-aggregation and phase separation of the copolymers respectively. Depending on the functionalization, the production of crosslinkable hydrogels, e.g. for 3D printing, is also conceivable. Furthermore, an increased biocompatibility is expected from the copolymers, as is already known from the respective pure polymers, while the processability of the copolymers improves considerably in comparison to pure cellulose.



RECAPITULATING IN VITRO THE SUBVENTRICULAR (SVZ) NEURAL STEM CELL NICHE

Ioannis Angelopoulos, Konstantinos Ioannidis, Georgios Gakis, Stavros Taraviras
University of Patras, school of Medicine, department of physiology

Our purpose is to generate a suitable microenvironment for neural stem cells (NSCs), which will recapitulate in vitro the normal subventricular zone (SVZ) NSC niche physiology. Thus, by understanding both the physiological conditions as well as the pathophysiology can be used for the establishment of a pathophysiological model of congenital hydrocephalus (CH). Conventional cell culture and early tissue engineering methods suffer from limitations including limited distribution of biomolecules by diffusion throughout the engineered tissue, and lack of natural interactions and physicochemical cues between the ECM and the cells themselves. Although theses 3D techniques provide a better biomimetic microenvironment for cells and stem cells compared to two-dimensional (2D) cultures, they still have limitations and have encouraged researchers to further develop optimized methods. In our case, we have established a static transwell organotypic culture of the SVZ niche using region specific decellularized matrix, closely mimicking the native SVZ stem cell niche comprising of ependymal cells, radial glial cells (RGC), astrocytes and NSCs. Our preliminary data suggest that further development and usage of a dynamic microfluidic culture would better imitate the physiological analog which requires a constant flow rate of the cerebrospinal fluid as it happens normally in vivo. Our ultimate goal is to establish a pathophysiological model of hydrochephalus, which will lead to translational applications for studying and developing personalized medicine protocols.

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P1.11

MULTI-MATERIAL 3D PRINTING A SOFT POWER SOURCE WITH INTEGRATED BIOLOGY

Trevor Kalkus, Christine Selhuber-Unkel

Institute for Molecular Systems Engineering and Advanced Materials (IMSEAM), Heidelberg University

The engineering field of soft robotics works towards meeting demands for applications that require delicacy, deformation, or biocompatibility, which range from environmental sensors to medical devices and beyond. However, the methods for actuating soft robotics often require rigid power sources or bulky auxiliary equipment. Strongly electric fish, like electric eels, provide bioinspiration for the development of soft and biocompatible power sources. The development of soft power sources has the potential to remove many of the constraints that limit soft robotics. Previously developed soft power sources lack the ability to provide sustained power for long durations, limiting their potential impact. Because these soft power sources harvest salinity gradient power, we are developing methods to generate a sustained ion gradient within the device to provide continuous power production. The use of immobilized urease to produce ammonium cations and hydroxide anions offers a low-risk candidate for an initial proof of concept. Furthermore, we are developing a variety of hydrogel inks for 3D printing to demonstrate that advantages of additive manufacturing for soft and complex devices. By utilizing multi-material 3D printing to create soft power sources, we aim to improve the ease of production and iteration as well as the ability to integrate soft power sources with soft actuators.

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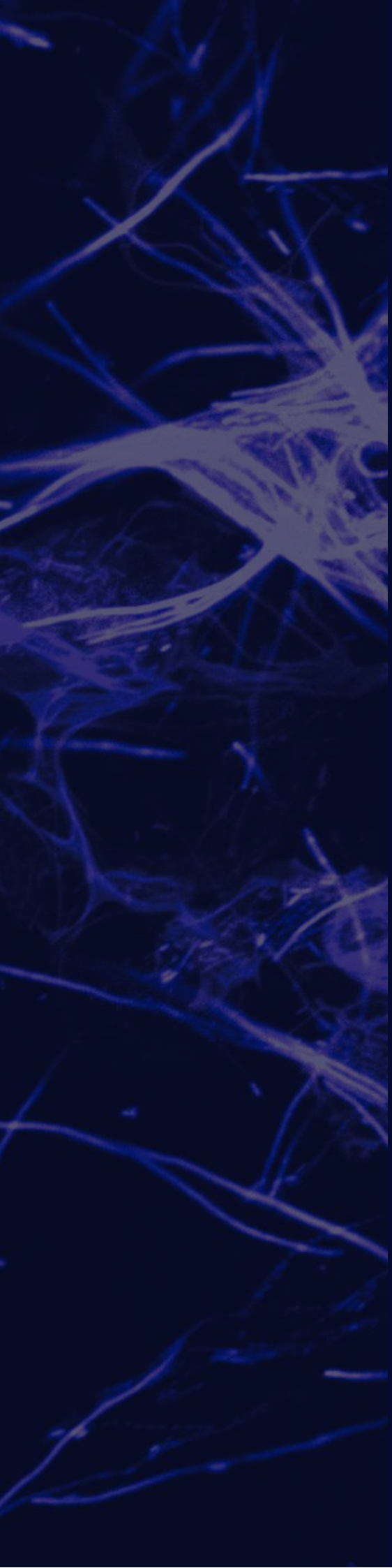
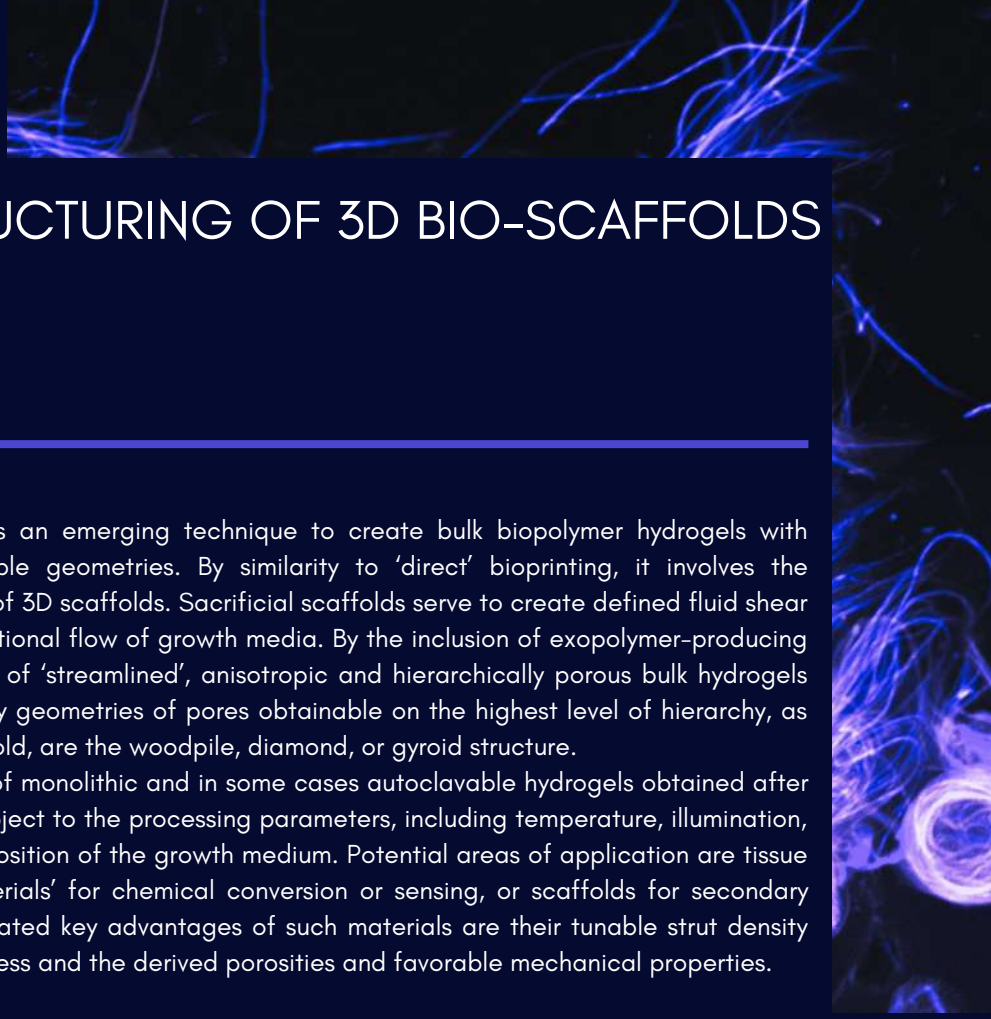


POSTER SESSION II

20.10.2022
10:30 AM – 11:15 AM
Völkerkundemuseum vPST



RHEOTACTIC STRUCTURING OF 3D BIO-SCAFFOLDS

Yvonne Gmach

Technical Univerity of Munich Campus Straubing

THUR
20 OCT
P2.01

Rheotactic structuring is an emerging technique to create bulk biopolymer hydrogels with intricate pre-determinable geometries. By similarity to 'direct' bioprinting, it involves the additive manufacturing of 3D scaffolds. Sacrificial scaffolds serve to create defined fluid shear when subjected to directional flow of growth media. By the inclusion of exopolymer-producing microbes, in situ growth of 'streamlined', anisotropic and hierarchically porous bulk hydrogels can achieved. Exemplary geometries of pores obtainable on the highest level of hierarchy, as determined by the scaffold, are the woodpile, diamond, or gyroid structure.
The physical properties of monolithic and in some cases autoclavable hydrogels obtained after scaffold removal are subject to the processing parameters, including temperature, illumination, flow rate, and the composition of the growth medium. Potential areas of application are tissue engineering, 'living materials' for chemical conversion or sensing, or scaffolds for secondary microbial growth. Postulated key advantages of such materials are their tunable strut density and structural cohesiveness and the derived porosities and favorable mechanical properties.

PHOTOSWITCHABLE AZOBENZENE-BASED 2D/3D SCAFFOLDS FOR CELL DIFFERENTIATION

Qiyang Jiyang

Institute for Molecular Systems Engineering and Advanced Materials, Heigelberg University

THUR
20 OCT
P2.02

Photoswitchable scaffolds are promising platforms for a physical understanding of cells which allow photomechanical stimulation of cellular proteins in molecular lever, thus to control mechanosensing in cells and control cellular functions (e.g. cell adhesion and cell differentiation) in a user-defined manner. Reported examples mainly deal with the response of cell adhesion to forces on the azobenzene-functionalized surface. Moreover, such system was manipulated under UV illumination and the short cis state lifetime of the azobenzene limit the sustainability of the stimulation. Therefore, in this work, we here apply a azobenzene which present a slow thermal back-isomerization and can be switched under near-infrared light. This photoswitchable azobenzene can be incorporated into 2D functional surface and 3D hydrogels which allow for the quantitative probing of mechanical interactions between cellular proteins and photoswitchable azobenzene.

BIOINSPIRED INJECTABLE HYDROGEL WITH REDOX-RESPONSIVENESS FOR CELL-INSTRUCTIVE MATRIX CUES

Minye Jin, Julieta Paez
University of Twente

Hydrogel is a hydrophilic polymer network used as extracellular matrix mimics in biomaterials field. One challenge of developing such biomaterials is the capability to precisely engineer desired properties, while keeping robustness and versatility in the system. Recently, we reported a luciferin-bioinspired hydrogel system as 3D cell culture matrices.1 This platform showed an efficient gelation rate and high tunability in mechanical and biological properties. To further develop this system that allows fine control of the gelation onset for injectable and processable application, novel redo-triggerable macromers were introduced to the molecular design.
In this poster, we exhibit stimuli-responsive hydrogels based on luciferin-bioinspired crosslinking strategy. The hydrogel gelation onset can be well controlled in the presence of mild reductant using protected polymer precursor solutions. The regulation of intrinsic parameters (e.g. structure of protecting group, reductant type) and extrinsic parameters (e.g. pH, temperature) have been investigated to modulate materials properties. This molecular-engineered platform can also be adapted as injectable hydrogel in tissue engineering field.

References:

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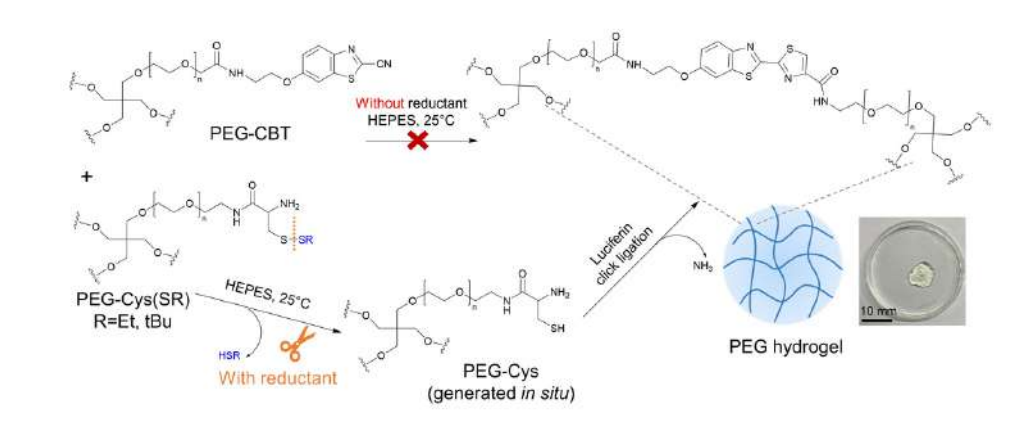

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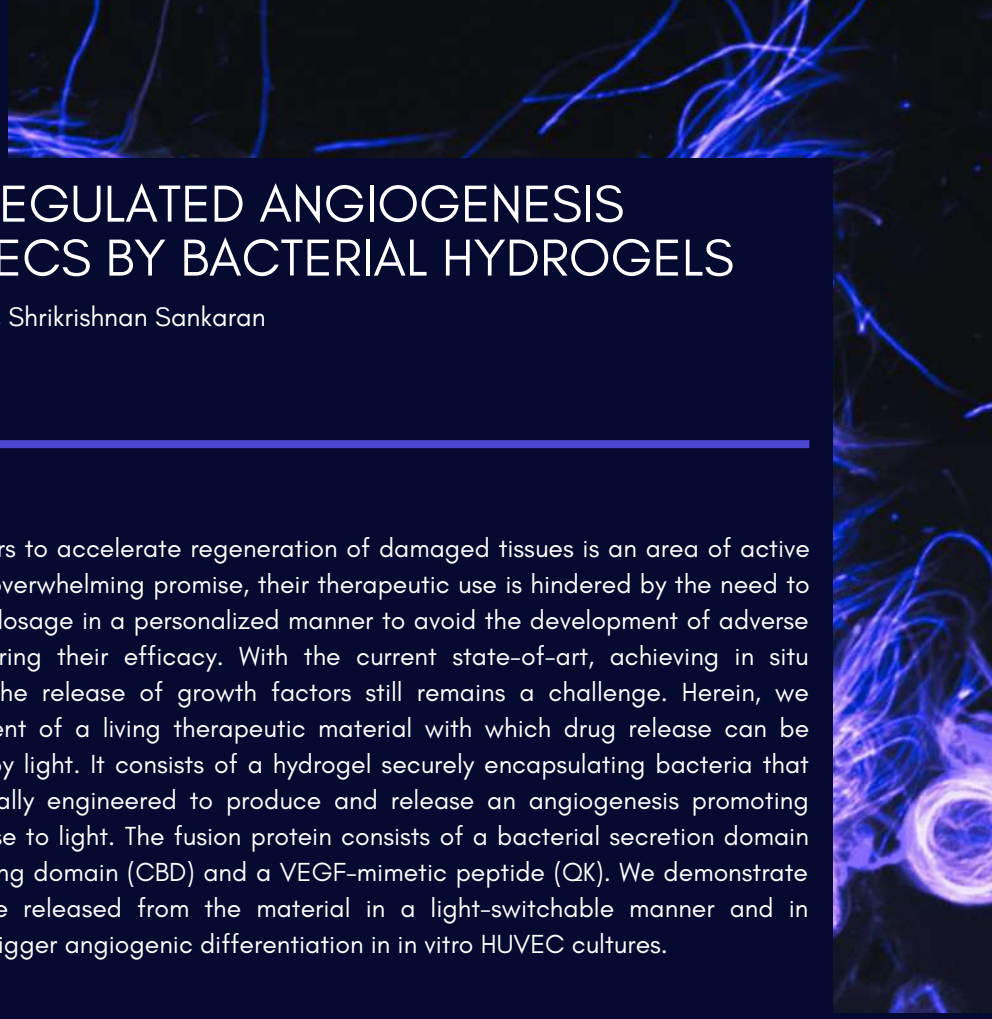

STUDY OF OPTO-REGULATED ANGIOGENESIS INDUCTION IN HUVECS BY BACTERIAL HYDROGELS

Varun Tadimarri, Priyanka Dhakane, Shrikrishnan Sankaran

Leibniz Institute for new materials, Saarbruecken

THUR
20 OCT
P2.04

The use of growth factors to accelerate regeneration of damaged tissues is an area of active research. Despite their overwhelming promise, their therapeutic use is hindered by the need to carefully regulate their dosage in a personalized manner to avoid the development of adverse side-effects while ensuring their efficacy. With the current state-of-art, achieving in situ temporal control over the release of growth factors still remains a challenge. Herein, we describe the development of a living therapeutic material with which drug release can be controlled in real-time by light. It consists of a hydrogel securely encapsulating bacteria that have been optogenetically engineered to produce and release an angiogenesis promoting fusion protein in response to light. The fusion protein consists of a bacterial secretion domain (YebF), a collagen binding domain (CBD) and a VEGF-mimetic peptide (QK). We demonstrate that his protein can be released from the material in a light-switchable manner and in sufficient quantities to trigger angiogenic differentiation in in vitro HUVEC cultures.

IDENTIFYING THE EFFECTS OF CELL-CELL PROXIMITY ON DICTYOSTELIUM DISCOIDEUM DYNAMICS

Carla Kulcsar[1], Fereydoon Taheri[2], Christine Selhuber-Unkel[2]

[1]Faculty of Physics, Heidelberg University
[2]Institute of Molecular Systems Engineering and Advanced Materials, Heidelberg University

THUR
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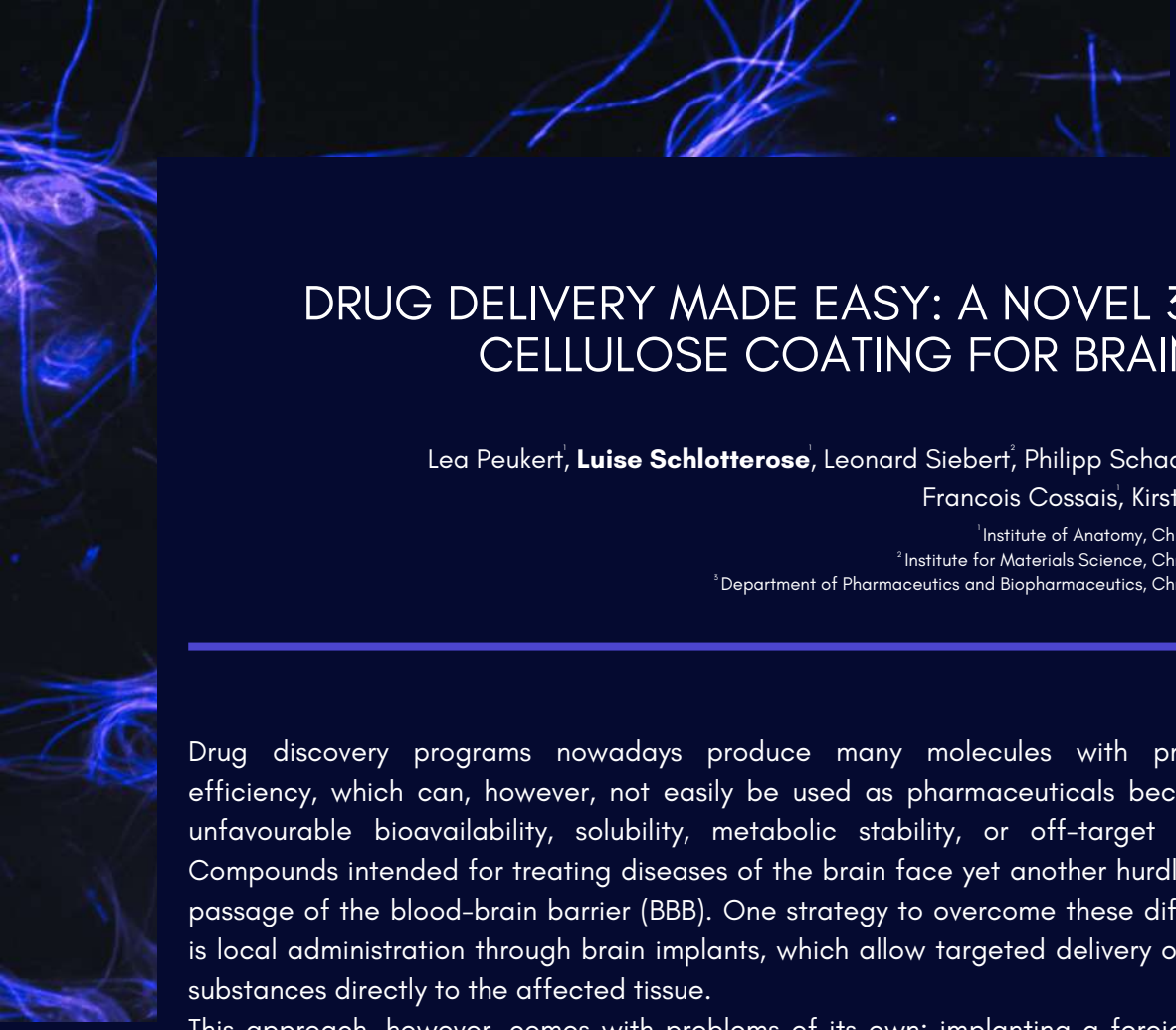
P2.05

Dictyostelium discoideum cells are highly mobile cells living in soil and are often used as model organisms for studying different cellular processes of social cells. We studied the motility of these cells focusing especially on the influence of cell-to-cell distance on their movement.Our Analysis is based on the examination of spontaneous cell movement of over a hundred individual cells for five minutes without adding external signaling cues.We analyzed characteristic quantities of motion such as mean-square-displacement, velocity autocorrelation function and velocity and angular distribution. The data indicate that their motility of a cell is influenced by the proximity to its nearest neighboring cell.



DRUG DELIVERY MADE EASY: A NOVEL 3D-PRINTED CELLULOSE COATING FOR BRAIN IMPLANTS

Lea Peukert[1], **Luise Schlotterose**[1], Leonard Siebert[2], Philipp Schadte[2], Regina Scherließ[3]
Francois Cossais[1], Kirsten Hattermann-Koch[1]

[1]Institute of Anatomy, Christian-Albrechts-University Kiel
[2]Institute for Materials Science, Christian-Albrechts-University Kiel
[3]Department of Pharmaceutics and Biopharmaceutics, Christian-Albrechts-University Kiel

Drug discovery programs nowadays produce many molecules with promising efficiency, which can, however, not easily be used as pharmaceuticals because of unfavourable bioavailability, solubility, metabolic stability, or off-target toxicity. Compounds intended for treating diseases of the brain face yet another hurdle in the passage of the blood-brain barrier (BBB). One strategy to overcome these difficulties is local administration through brain implants, which allow targeted delivery of active substances directly to the affected tissue.

This approach, however, comes with problems of its own: implanting a foreign body into the brain can lead to neuroinflammation and undesirable glial scarring. Here, we present an inexpensive, customizable coating for brain implants, which mildens neuroinflammation and reduces the formation of glial scars.

The coating we produce consists of ethyl cellulose (EC) and hydroxypropyl cellulose (HPMC), which are applied to the implant as a 3D-printable ink. The coating dissolves within 48 hours after implantation, allowing for unimpaired long-time release of active substances.

The printed material can easily be shape-customized to pre-surgical imaging to fit into any cavity. Its porous structure enables the attachment of cells and the drainage of fluid. As we demonstrate, the material is well tolerated by cells constituting brain tissue.

Additionally, drug substances acting against inflammation can be embedded into the coating. Methylene blue was used as a model compound to prove release by zero-order kinetics. Furthermore, we show the beneficial effect of the anti-inflammatory agent resveratrol embedded into the material.

In summary, we have developed a coating material for brain implants with cell-favourable properties. Anti-inflammatory drug substances can be embedded to minimize undesired reactions of the surrounding tissue. The material is inexpensive and can be formed into any shape by 3D printing. These properties make our material valuable in many cases, where pharmaceutical substances are delivered locally through implants, and undesired foreign body reactions need to be suppressed.

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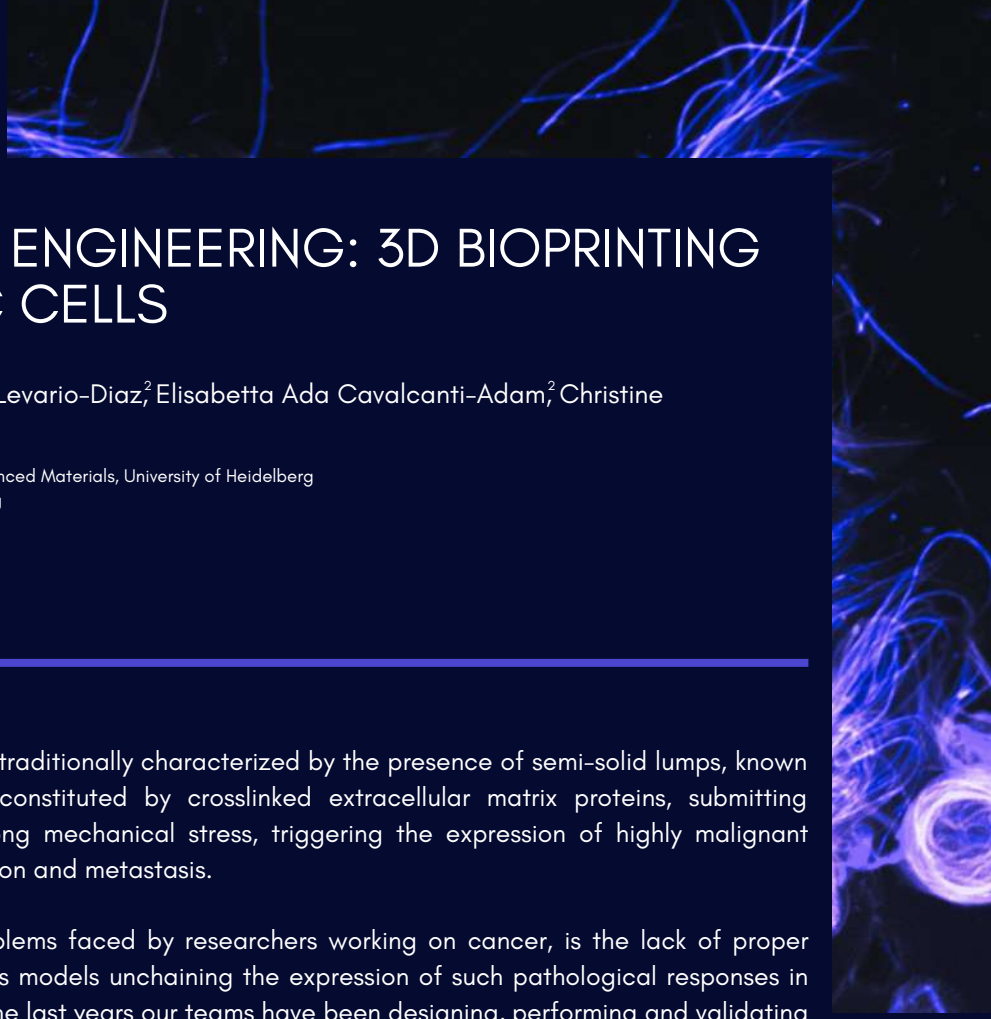

ARTIFICIAL TISSUE ENGINEERING: 3D BIOPRINTING MEETS SYNTHETIC CELLS

Yasmin Antonelli[1], I Chen[2], Victoria Levario-Diaz[2], Elisabetta Ada Cavalcanti-Adam[2], Christine Selhuber-Unkel[1], Aldo Leal-Egaña[1]

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Cancer pathologies are traditionally characterized by the presence of semi-solid lumps, known as lumps. Tumors are constituted by crosslinked extracellular matrix proteins, submitting confined cells to a strong mechanical stress, triggering the expression of highly malignant responses, such as invasion and metastasis.

One of the current problems faced by researchers working on cancer, is the lack of proper three-dimensional tumors models unchaining the expression of such pathological responses in vitro. Therefore, during the last years our teams have been designing, performing and validating new types of tumor-like scaffolds and methods to analyze the behavior of neoplastic cells.

Among others, we have been studying the confinement and culture of MDA-MB-231 breast cancer cells in microcapsules made of alginate and gelatin (1:1), and having an elasticity of around 25 kPa (measured as Young's Moduli; 600 µm in diameter). Since this blend comprise a mixture between a biodegradable and a non-biodegradable polymer, these scaffolds enable the growth and migration of cancer cells under strong mechanical stress, triggering the expression of pathological hallmarks. In order to determine how the biomechanical stress influences the mechanical activity of cancer cells, MDA-MB-231 were isolated and seeded onto flat surfaces pattered with migration guidelines made of collagen type-I (1D scaffolds). These 1D matrices mimic the fibrillar topology sensed by cancer cells during their migration. This strategy enables us understanding several processes involved in cancer malignancy, such as tumorigenicity, invasion, intravasation and generation of heterogeneous populations. Among other relevant results obtained in this research, we detected the expression of resistance to anticancer cells (i.e. Cisplatin), an enhanced presence of polyploid cells, as well as an increased cell-matrix attachment properties of cancer cells isolated from the 3D hydrogels-based microcapsules.

According to our knowledge, the 3D-1D system represents an easy, highly reliable, and cheap strategy to study the behavior of cancer cells in vitro, in a micro-environment similar to the one found in primary tumors.

References:

1. Ertekin Ö. et al., (2022). Acta Biomaterialia. 142, 208.
2. Leal-Egaña A. et al., (2020). Trends in Biotechnology. 38, P142.
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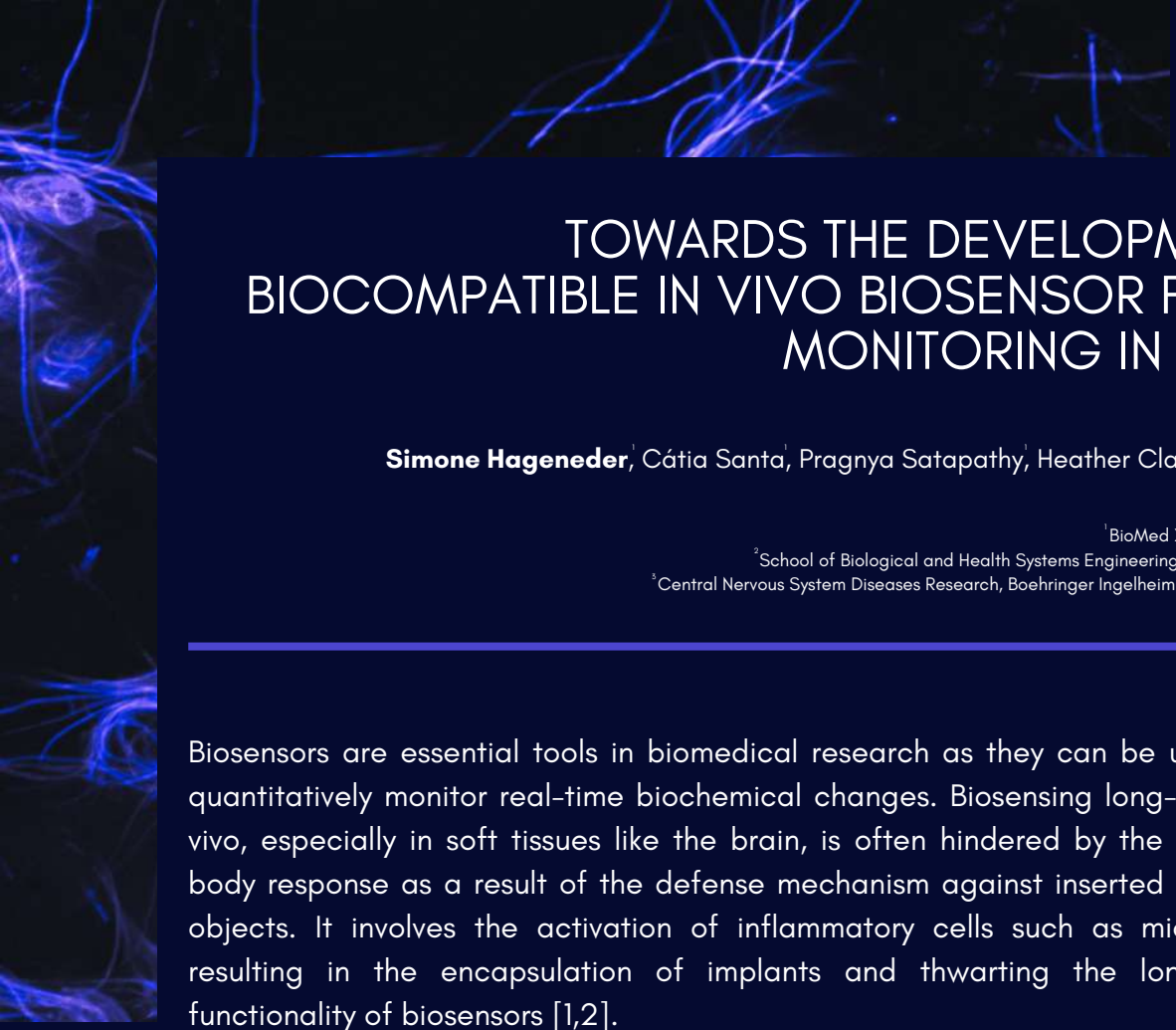

TOWARDS THE DEVELOPMENT OF A BIOCOMPATIBLE IN VIVO BIOSENSOR FOR DRUG MONITORING IN THE BRAIN

Simone Hageneder[1], Cátia Santa[1], Pragnya Satapathy[1], Heather Clark[2], Bastian Hengerer[3], Khulan Sergelen[1]

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Biosensors are essential tools in biomedical research as they can be used to quantitatively monitor real-time biochemical changes. Biosensing long-term in vivo, especially in soft tissues like the brain, is often hindered by the foreign body response as a result of the defense mechanism against inserted foreign objects. It involves the activation of inflammatory cells such as microglia, resulting in the encapsulation of implants and thwarting the long-term functionality of biosensors [1,2].

Our team aims to develop an in vivo biosensor for continuously monitoring neuropsychiatric drugs in the brain of rodents to elucidate the pharmacokinetics. We focus on reducing biofouling by providing biocompatibility through biological and mechanical matching of our sensor with the brain tissue.

I will present our approach towards achieving biocompatibility using polymeric hydrogels, and strategies for incorporating these materials into optical biosensors to enhance sensitivity.

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[2] Tan, C., Robbins, E. M., Wu, B., & Cui, X. T. (2021). Recent advances in in vivo neurochemical monitoring. Micromachines, 12(2), 208.

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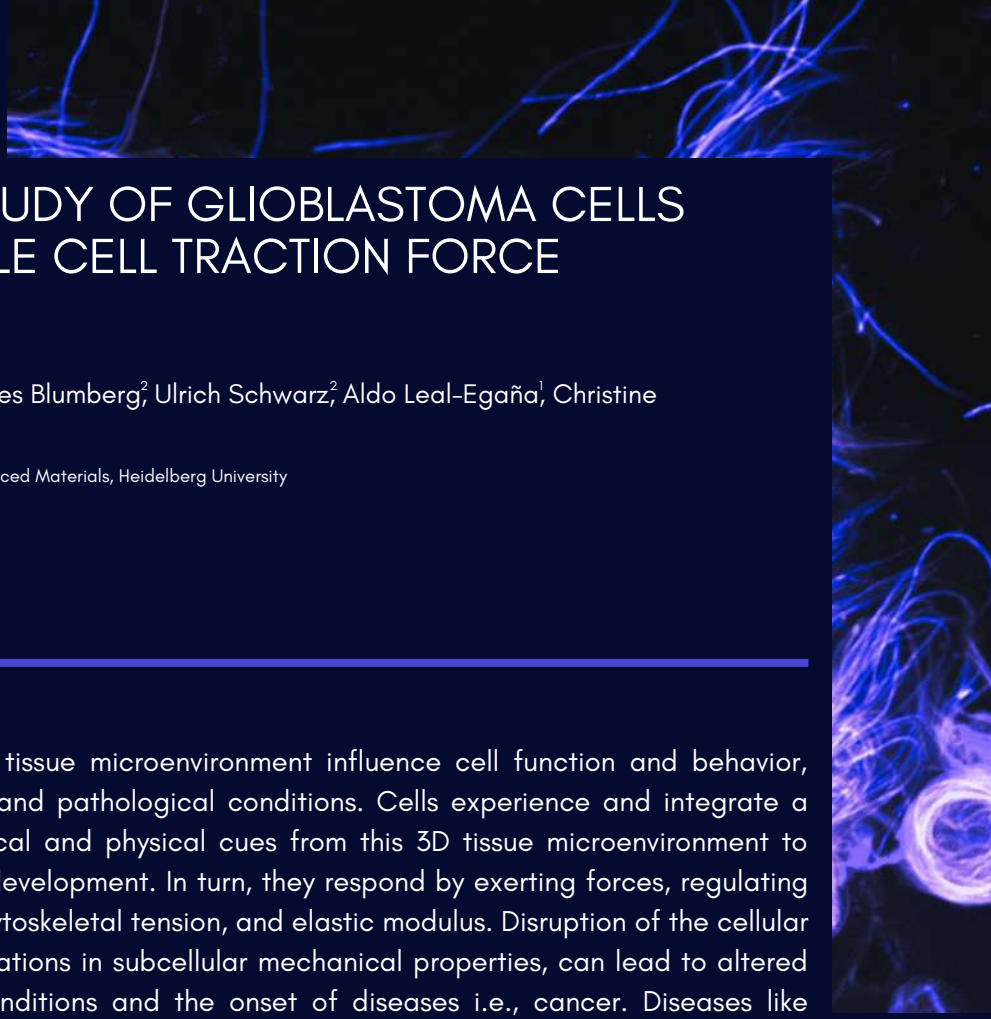

BIOMECHANICAL STUDY OF GLIOBLASTOMA CELLS ANALYZED BY SINGLE CELL TRACTION FORCE MICROSCOPY

Mishal Khan[1], Philipp Kollenz[1], Johannes Blumberg[2], Ulrich Schwarz[2], Aldo Leal-Egaña[1], Christine Selhuber-Unkel[1]

[1]Institute of Molecular Systems Engineering and Advanced Materials, Heidelberg University
[2]Institute for Theoretical Physics, Heidelberg University

The structures of the tissue microenvironment influence cell function and behavior, both in physiological and pathological conditions. Cells experience and integrate a multitude of mechanical and physical cues from this 3D tissue microenvironment to adapt to organismal development. In turn, they respond by exerting forces, regulating their shape, internal cytoskeletal tension, and elastic modulus. Disruption of the cellular forces, as well as variations in subcellular mechanical properties, can lead to altered pathophysiological conditions and the onset of diseases i.e., cancer. Diseases like cancer are characterized by dramatic changes in cell and tissue mechanics, and dysregulation of forces at the cell and tissue level can activate mechanosensing to compromise tissue integrity and function and promote disease progression. Cells can move by exerting traction forces on their environment. These can be assessed by using microfabricated substrates and improved computational approaches, enabling us the characterization of the biomechanical forces generated by single cells cultured in defined microenvironments. This provides valuable insights into the malignancy of cancer cells. However, the conventional microfabricated structures i.e., 2D substrates are far from matching the complexities present in vivo. Hence, there is a need for biomimicking the natural surfaces for cellular applications. We here show the traction forces induced by single glioblastoma cells in three-dimensional (3D) tumor microenvironment-inspired scaffolds i.e., collagen. The dimensionality of cell culture influences cell motility and cellular interaction with the surrounding cells and ECM. As cells grown on 2D scaffolds, adapt to the artificial environment and may no longer display characteristics of the original tumor. An attempt to develop 3D tumor microenvironment-inspired scaffolds and their functionality in unraveling the role of microenvironment on tumor cell behaviors are also examined. Characterizing the cues involved in glioblastoma cell migration could enable the scientific and medical community to develop better strategies to understand and treat brain cancer.

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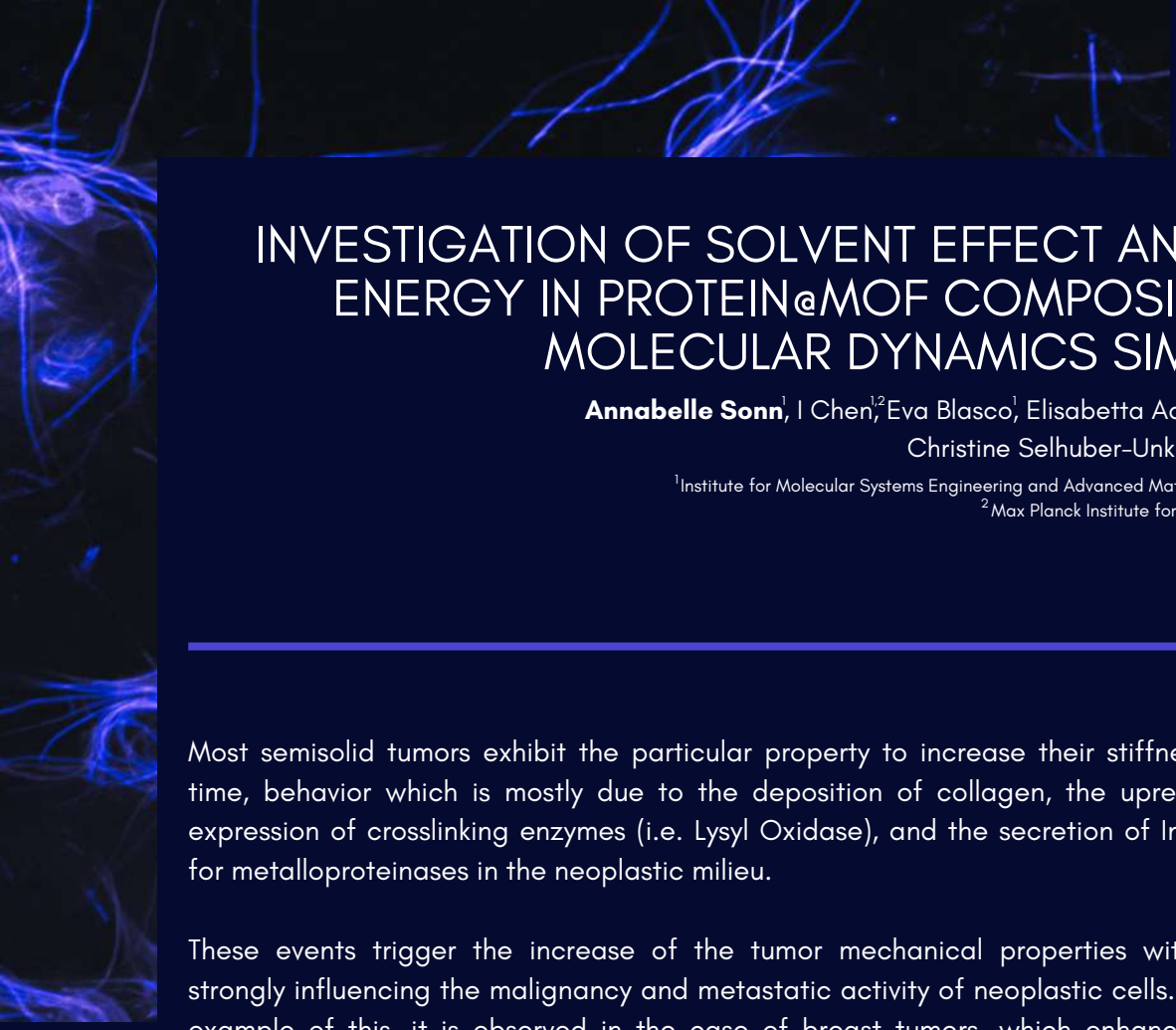

INVESTIGATION OF SOLVENT EFFECT AND BINDING ENERGY IN PROTEIN@MOF COMPOSITES USING MOLECULAR DYNAMICS SIMULATIONS

Annabelle Sonn[1], I Chen[1,2], Eva Blasco[1], Elisabetta Ada Cavalcanti-Adam[2], Christine Selhuber-Unkel[1,2], Aldo Legal-Egaña[1]

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Most semisolid tumors exhibit the particular property to increase their stiffness with time, behavior which is mostly due to the deposition of collagen, the upregulated expression of crosslinking enzymes (i.e. Lysyl Oxidase), and the secretion of Inhibitors for metalloproteinases in the neoplastic milieu.

These events trigger the increase of the tumor mechanical properties with time, strongly influencing the malignancy and metastatic activity of neoplastic cells. A clear example of this, it is observed in the case of breast tumors, which enhances their elasticity from around 4 kPa in early stages of this pathology, up to 80 kPa in advanced phases of cancer progression.

Since most in vitro cancer studies have been carried out with scaffolds keeping their elasticity with time, in this work we focused our research on establishing a new type of 4D culture method (i.e. including time), characterized by its mechanical tunability. This aim has been accomplished after functionalizing polyethylenglycol (PEG) with the light sensitive anthracene, to enable a progressive and controlled crosslinking of the polymer backbones mediated by UV light. The functionalized PEG-anthracene was then merged with gelatin, in order to enhance the biocompatibility of these hydrogels.

Further, this blend was characterized by rheological methods in presence of different expositions to UV light, in order to determine how the mechanical properties of these polymers are tuned. Additionally, preliminary assays of cell-matrix cytotoxicity were carried out.

Our preliminary results are showing that this blend exhibits promising capabilities to be used in 3D cell culture, and in particular for testing the activity of cancer cells in vitro, in a much similar manner to primary tumors than traditional polymer-scaffolds performed up to date.

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THUR
20 OCT
P2.10

GENERATION OF CELL MICRO-FACTORIES FOR 3D NETWORKS

Celine Kesenheimer[1], Maria Villiou[1,2], Reza Taale[1], Christine Selhuber-Unkel[1,2]

[1]Institute of Molecular Systems Engineering and Advanced Materials, Heidelberg University
[2]Max Planck Schools: Matter to Life, University of Heidelberg

Minimalistic 3D models are great tools to study cellular processes, such as differentiation, proliferation, and motility in a more realistic setting in-vitro. Two-photon polymerization method provides a unique possibility to fabricate tunable microstructures with known mechanical properties. Here we simplified the complex microstructure of biological environments to 3D micro-scaffolds from different materials (silicone-based, hydrogel-based) employing this technique. As a result, the effect of physical parameters, e.g., thickness and distance between the columns, their curvature on biological processes from the proliferation to the migration of fibroblasts can be investigated systematically. We vary the structural material features (e.g. columns) of scaffolds by two-photon polymerization in a micrometer scale. A particularly challenging aspect is to reproducibly fabricate these scaffolds at total scaffold sizes in the mm range, which are necessary for large-scale cell cultures.

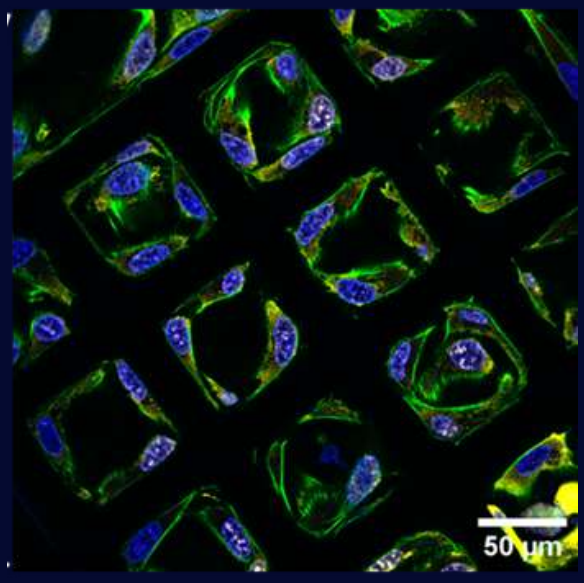

Figure. Confocal image of REF52 WT cells on IP-Visio 3D scaffold after 7 days of migration/proliferation studies. Immunofluorescence staining with DAPI (blue, nucleus), Phalloidin (green, actin filaments), Paxillin (yellow, cytoskeletal protein that is integral to the formation of focal adhesion), ki67 (red, proliferation marker). Scale Bar: 50 µm

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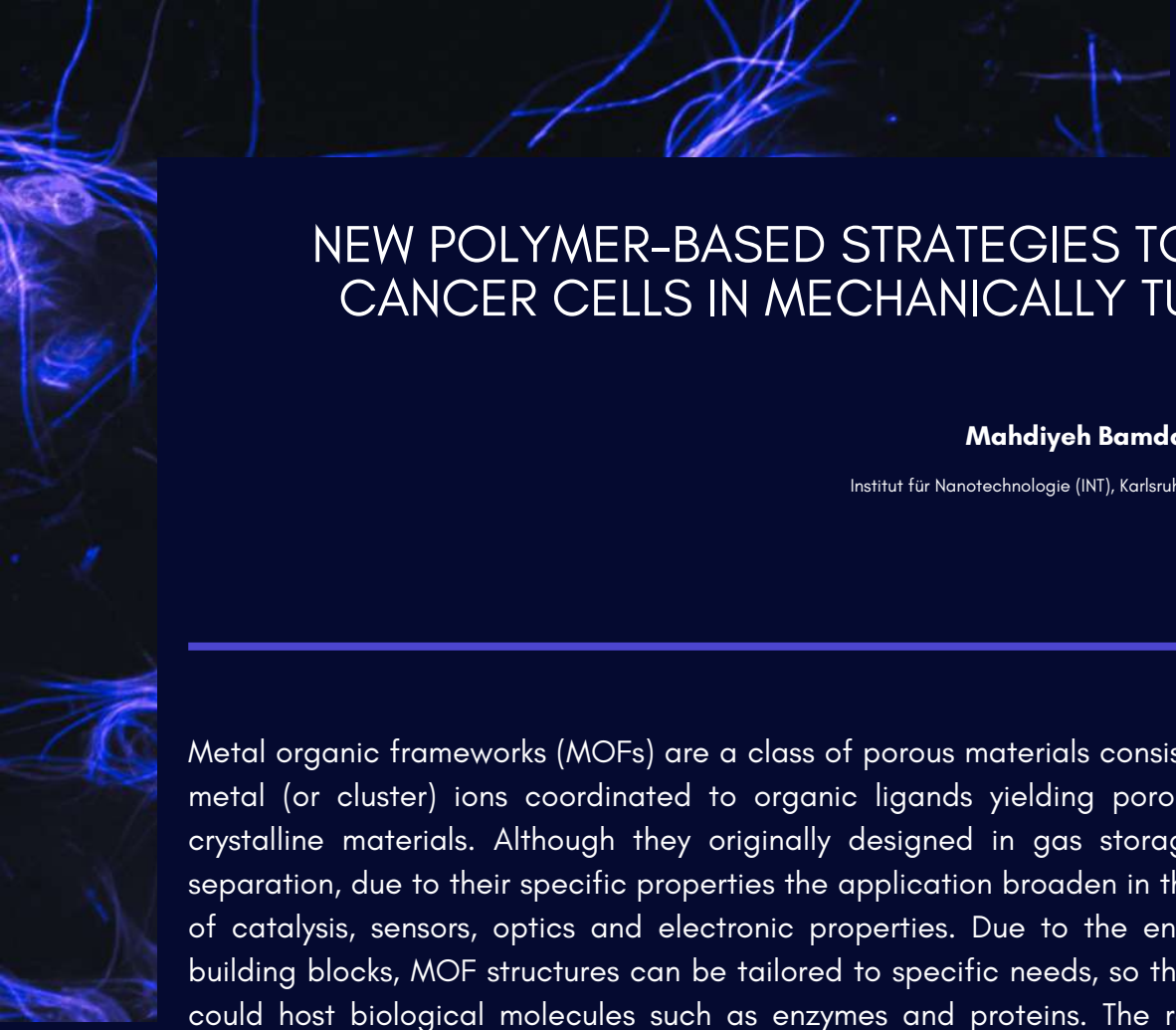

NEW POLYMER-BASED STRATEGIES TO CULTURE CANCER CELLS IN MECHANICALLY TUNABLE 4D MATRICES

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Metal organic frameworks (MOFs) are a class of porous materials consisting of metal (or cluster) ions coordinated to organic ligands yielding porous and crystalline materials. Although they originally designed in gas storage and separation, due to their specific properties the application broaden in the field of catalysis, sensors, optics and electronic properties. Due to the enormous building blocks, MOF structures can be tailored to specific needs, so that they could host biological molecules such as enzymes and proteins. The resulted bio-composite can be used in drug delivery, biosensing, and cell and virus manipulation. Another application of protein@MOFs is as catalysis in reactions. In this case, MOF scaffolds protect embedded protein making it more sustainable and reusable.

There are different challenges to tackle the inherent properties of protein@MOF structures such as the stability of protein embedded in MOF, the effect of different factors such as solvent and temperature on the function of composite.

In this work, we aim to investigate the binding mechanism and effect of different solvents for two protein@MOF composite from the molecular point of view. Molecular dynamics simulation techniques are used to study the binding energy of peroxygenase in NU-1000 MOF. The same approach is used to investigate the effect of different solvents on the interaction between esterase and NU-1000.

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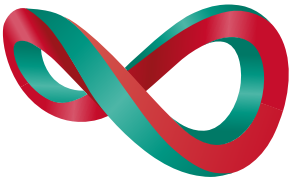

3D MATTER
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