General Information

http://conference.uni-leipzig.de/poc/2018/

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1. connect with "https://www.eduroam.org/"
2. open Browser -> portal page
3. POC-Conference, password: 9874d-2018

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Imprint

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City of Leipzig


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Leipzig is a vibrant metropolis in the heart of former East Germany. It is well known for its cultural, especially musical, history and famous for its trade fairs and exhibitions. Leipzig played a significant role in the peaceful revolution of 1989, which led to the fall of the Berlin Wall and finally of communism in Eastern Europe.

The *University of Leipzig*, being one of Europe's oldest universities, looks back to a long tradition. Many famous names, including Bach, Mendelssohn, Goethe, Lessing, Leibniz, Debye, Ostwald, Bloch, Hertz, and Heisenberg, are associated with Leipzig and its university.

Please check out **www.uni-leipzig.de** and **www.leipzig.travel** for more information.

Leipzig's Public Transport System

The city of Leipzig and its surrounding areas are part of *MDV local public transport association*. It consists of **tram and bus lines** as well as a metro-like railway called **S-Bahn** (and some regional trains). Trams and buses are operated by the *LVB*, while the S-Bahn is operated by *DB (Deutsche Bahn)*. However, they all share the same ticket system. Ticket fees are distance-based (zones).

Tickets are bought at ticket machines located on most platforms and in some trams as well as directly from bus drivers. The machines accept cash only. Validate your ticket inside the vehicle when using trams or buses. In S-Bahn, tickets have to be validated prior travelling using the stamping machines located on the platforms.

General information on Leipzig's public transportation system, timetables, and a connection planner can be found at **www.l.de/verkehrsbetriebe**. There, you also find network maps for day and night.

In recent years, renting a bike has become very popular. If you are tempted to explore Leipzig by bike, you should go to the following websites to find out the location of a rentable bike and to find out the commercial terms: **https://www.nextbike.de** or **www.lipzitours.de**.

General Information

Conference Venues

The "Physics of Cancer" symposium will take place at:

Felix-Klein-Lecture Hall
Paulinum, main building
5th floor
University of Leipzig
Augustusplatz 10-11
04109 Leipzig
Germany

(Swen Reichhold/Universität Leipzig

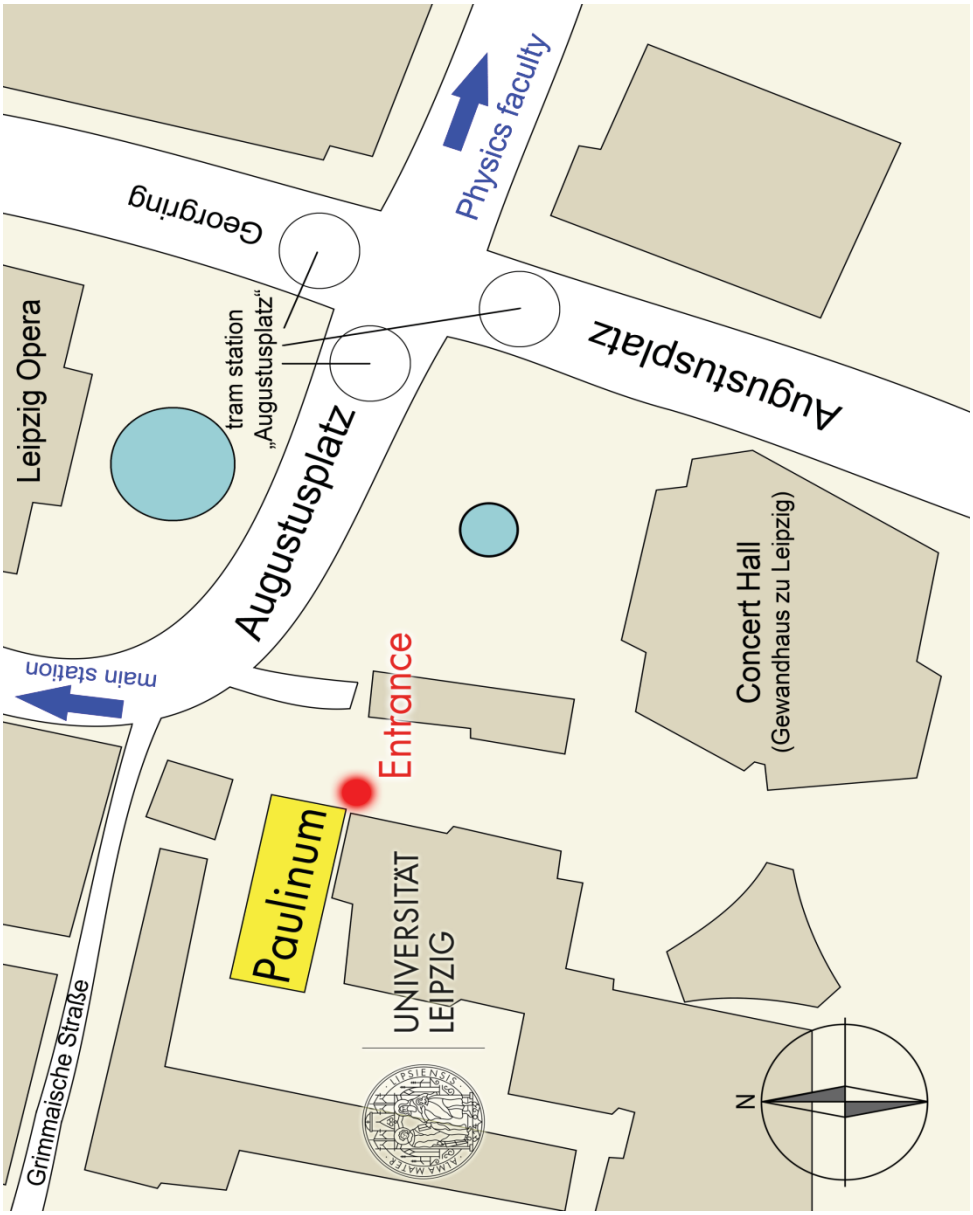
Klaus F. Linscheid, Architektur und Medien

and

University of Leipzig
Faculty of Physics and Earth Sciences/ Aula
Linnéstr. 5
04103 Leipzig, Germany
first floor

The Poster Session on September 25, 2018 will take place at the Facutlty of Physics and Earth Sciences. You may go by tram no. 16 for two stops in direction "Lößnig" (leave train at "Johannisallee"). You may as well walk for approx. 20 min., starting from "Augustusplatz" and walking along "Prager Straße".
We will offer you a guide, if you prefer walking.

Please have a look at the next page to see a map with both venues.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Physics faculty
Augustusplatz
Leipzig Opera
tram station
„Augustusplatz“
Augustusplatz
Concert Hall
(Gewandhaus zu Leipzig)
main station
Entrance
Paulinum
UNIVERSITÄT
LEIPZIG
Grimmaische Straße
N

General Information

Presentations

Scientific presentations will be held either orally (talk) or by poster.

Talk sessions will take place in the Felix Klein lecture hall of the Paulinum/ University campus. The room is equipped with a video projector with VGA input. Contributed talks are allocated 15 min (including discussion), whereas invited talks are allocated 20 min plus 10 min discussion.

The poster session will be on Tuesday, September 25th, 2018 from 12:30 – 15:00 at the Faculty of Physics and Earth Sciences *(Linnéstr. 5, 04103 Leipzig)*. During this session, a lunch buffet will be provided for all participants. Poster boards will be marked with numbers according to the scientific program. Push pins for mounting will be provided. Please remove your poster after the Postersession.

Young Scientist Award

For the first time in the course of all Physics of Cancer symposia,
we are delighted to be able to honor the best poster presentation with the amount of
EUR 1000 on Tuesday, September 25, 2018.
This is kindly funded by the **German Society for Cell Biology (DGZ)**.

In Case of Questions...

... or any problems, do not hesitate to ask the conference organizers and assistants for help. You will recognize them by their name badges with names printed in red (in contrast to the black printing of normal name badges).

Monday, September 24, 2018

AGENDA

11:00 – 13:00 *Conference check-in and on-site registration*

13:00 – 13:15 ***Opening | Welcome Words***

Session I: Cell Mechanics & Migration

13:15 – 13:45 **The cancer-associated adhesion-protein ß-parvin functions as mechanoresponsive signaling hub that regulates cell size, shape, and contractility**
INGO THIEVESSEN (Friedrich Alexander University Erlangen-Nuremberg, Germany)

13:45 – 14:15 **Feeling the tension: Cell-induced stresses in the extracellular matrix**
CHASE BROEDERSZ (Ludwig Maximilians University Munich, Germany)

14:15 – 14:45 **Role of phosphoinositide signaling in mechanoresponse of liver cancer cells**
PAUL JANMEY (University of Pennsylvania, USA)

14:45 – 15:00 **Microenvironmental mechanics contribute to glioblastoma cell behaviour**
KATARZYNA POGODA
(Institute of Nuclear Physics Polish Academy of Sciences, Krákow, Poland)

15:00 – 15:30 Coffee break

15:30 – 16:00 **Focal adhesion - hemidesmosome crosstalk in migrating keratinocytes**
RUDOLF LEUBE (RWTH Aachen University, Germany)

16:00 – 16:30 **Virtual fluidic channels: From single cell rheology to tissue mechanics**
OLIVER OTTO (University of Greifswald, Germany)

16:30 – 17:00 **Polarized dynamics of intermediate filament in glial cell migration**
CÉCILE LEDUC (The Institut Pasteur, France)

17:00 – 17:15 **Mechanical cyclic stretching inhibits cancer cell growth but promotes normal cell growth**
AJAY TIJORE (National University of Singapore, Singapore)

17:30 ***Welcome Dinner / Round Table***

Tuesday, September 25, 2018

Session II: Membranes

09:00 – 09:30 **Modulation of cortical actin assembly dynamics**
ANNE–CÉCILE REYMANN
(Institute of Genetics and Molecular and Cellular Biology, France)

09:30 – 10:00 **Physics of cell adhesion:**
The role of the membrane in the protein recognition process
ANA-SUNCANA SMITH
(Friedrich-Alexander-University of Erlangen-Nuremberg, Germany)

10:00 – 10:15 **Collective motion attenuates natural selection in crowded cellular populations**
JONA KAYSER (University of California – Berkeley, USA)

10:15 – 10:45 ***Coffee break***

Session III: Matrix

10:45 – 11:15 **New peptide probes to map the tensional states of ECM fibers in tumour tissues**
VIOLA VOGEL (ETH Zurich, Switzerland)

11:15 – 11:45 **Mechanics matters for cells: From extracellular matrix via cytoskeleton to the nucleus**
FLORIAN REHFELDT (University of Göttingen, Germany)

11:45 – 12:15 **Control of mechanosensitivity by integrin-ECM binding and nucleocytoplasmic shuttling kinetics**
PERE ROCA-CUSACHS (Institute for Bioengineering of Catalonia, Spain)

12:15 – 12:30 **Biochemical and nanomechanical fingerprints of melanoma development**
JUSTYNA BOBROWSKA (Polish Academy of Sciences, Kraków, Poland)

12:30 – 15:00 **POSTER SESSION**
- YOUNG SCIENTIST AWARD -

Afternoon **Social Event for Invited Speakers**
(*private concert at Bach-museum, followed by dinner at "Ratskeller Leipzig"*)

Poster Session

12:30 – 15:00 *Presentation of the contributed posters with discussions and lunch buffet.*

1 **Mechanical cyclic stretching inhibits cancer cell growth but promotes normal cell growth**
AJAY TIJORE (National University of Singapore, Singapore)

2 **Human glioblastoma mechanics: Substrate stiffness alters traction forces and cell morphology**
FRANCESCO GIOVANNI BARONE (University of Cambridge, GB)

3 **Loss of vimentin increases motility and nuclear damage in confined spaces**
ALISON PATTESON (University of Pennsylvania, Philadelphia, USA)

4 **Migration of cancer cells in predefined 3D collagen matrices**
FLORIAN GEIGER (Ludwigs-Maximilians-University Munich, Germany)

5 **EMT-induced changes of cortical contractility and stiffness in breast epithelial cells**
KAMRAN HOSSEINI (TU Dresden, Germany)

6 **Uncovering the dynamic precursors to contraction**
JOSÉ ALVARADO (University of Texas at Austin, USA)

7 **Real Tumor Pieces and Model Cell-Aggregates Act Alike on Collagen Gels**
FRANK SAUER (University of Leipzig, Germany)

8 **Role of N-Cadherin during the Epithelial-Mesenchymal Transition**
HANNAH MARIE SCHOLZ-MARGGRAF (University of Leipzig, Germany)

9 **Human aorta under tensile stress**
SABRINA FRIEBE (University of Leipzig, Germany)

10 **Comparison of HER2, estrogen and progesterone receptor expression profiles of primary tumor and synchronous axillary lymph node metastases in early breast cancer patients.**
LAURA WEYDANDT (University Hospital Leipzig, Germany)

Tuesday, September 25, 2018

11 **Natural killer cells switch between mesenchymal and amoeboid migration in adhesive vs. non-adhesive 3D environments**
TINA CZERWINSKI (Friedrich Alexander University Erlangen-Nuremberg, Germany)

12 **Electron-Irradiated Hydrogels: Reagent-Free Modification towards Biomedical Applications**
STEFANIE RIEDEL (Leibniz Institute for Surface Modification, Germany)

13 **Shear stress and cellular behaviour in 3 D biofabrication assays**
LENA FISCHER (Friedrich Alexander University Erlangen-Nuremberg, Germany)

14 **Electron irradiated Elastin/Collagen Hydrogels**
NILS WILHARM (Leibniz Institute for Surface Modification, Germany)

15 **The role of stickiness in the rheology of semiflexible polymers**
TOM GOLDE (University of Leipzig, Germany)

16 **Collective motion attenuates natural selection in crowded cellular populations**
JONA KAYSER (University of California – Berkeley, USA)

17 **AFM-based assessment of antitumor drugs on prostate cancer cells**
ANDRZEJ KUBIAK (Polish Academy of Sciences, Poland)

18 **Biomechanics of glioblastoma cells by atomic force microscopy**
TOMASZ ZIELINSKI (Polish Academy of Sciences, Poland)

19 **Non-linear compliance of elastic layers to indentation**
JUSTYNA BOBROWSKA (Polish Academy of Sciences, Poland)

20 **Roadmap to Local Tumor Growth: Insights from Cervical Cancer**
HANS KUBITSCHKE (University of Leipzig, Germany)

Carbon implantation of TiO2 nanotubes for biomedical applications
21 ASTRID WEIDT (University of Leipzig, Germany)

22 **Cancer cell motility study in micro-constriction chips**
CARLOTTA FICORELLA (University of Leipzig, Germany)

23 **Fluid and jammed behaviour in cell spheroids**
STEFFEN GROSSER (University of Leipzig, Germany)

24 **Dynamics of Cell Jamming: Disentangling the Shape and Density Dependences**
JÜRGEN LIPPOLDT (University of Leipzig, Germany)

25 **Exploring tumor heterogeneity – cancer development and invasive traits in primary carcinoma samples**
ERIK W. MORAWETZ (University of Leipzig, Germany)

26 **Collective forces of tumor spheroids in three-dimensional biopolymer networks**
CHRISTOPH MARK (Friedrich Alexander University Erlangen-Nuremberg, Germany)

27 **Friction in isotropic polymer networks**
PAUL MOLLENKOPF (University of Leipzig, Germany)

28 **Reptation in semiflexible polymer networks**
TINA HÄNDLER (University of Leipzig, Germany)

29 **Cortical Actin Contractility of Single Suspended Cells**
ENRICO WARMT (University of Leipzig, Germany)

30 **Microenvironmental mechanics contribute to glioblastoma cell behaviour**
KATARZYNA POGODA (Polish Academy of Sciences, Poland)

31 **Systematic altering of semiflexible biolpolymer networks via tunable cross-linking**
MARTIN GLASER (University of Leipzig, Germany)

32 **Fractional Dynamics in Bioscience and Biomedicine and the Physics of Cancer**
HOSEIN NASROLAHPOUR (Tarbiat Modares University, Iran)

Wednesday, September 26, 2018

Session IV: Vasculature

08:30 – 09:00 **Search and kill - the immune response to cancer cells**
HEIKO RIEGER (Saarland University, Germany)

09:00 – 09:30 **Probing the physiology of physical transport inside cells and developing tissues**
MORITZ KREYSING
(Max Planck Institute of Molecular Cell Biology and Genetics, Germany)

09:30 – 10:00 **Mechanisms of cellular penetration of vascular basement membranes - how biophysics could help us better understand this process**
LYDIA SOROKIN (University of Münster, Germany)

10:00 – 10:15 **Loss of vimentin increases motility and nuclear damage in confined spaces**
ALISON PATTESON (University of Pennsylvania, Philadelphia, USA)

10:15 – 10:45 ***Coffee break***

Session V: Tissue Organization

10:45 – 11:15 **Ratchetaxis and cytokinesis**
DANIEL RIVELINE (Institut de Génétique et de Biologie Moléculaire et Cellulaire, France)

11:15 – 11:45 **PC3-epi prostate cancer cells become polyploid, resistant and mesenchymal on a docetaxel gradient**
BOB AUSTIN (Princeton University, USA)

11:45 – 12:15 **Different modes of fluidization in Human Bronchial Epithelial Cells – the Unjamming Transition vs. the Epithelial-Mesenchymal Transition**
DAPENG BI (Northeastern University, USA)

12:15 – 12:30 **Biomechanics of glioblastoma cells by atomic force microscopy**
TOMASZ ZIELINSKI (Polish Academy of Sciences, Kraków, Poland)

12:30 – 13:30 ***Lunch break***

Session VI: Cancer and Embryology

13:30 – 14:00 **Cancer resection within morphogenetic fields**
BENJAMIN WOLF (University Hospital Leipzig)

14:00 – 14:30 **Coordination of tissue growth by cell mechanics**
MARYAM ALIEE (Friedrich-Alexander University of Erlangen-Nuremberg, Germany)

14:30 – 15:00 **WHY CANCER TREATMENT CAN BACKFIRE – From non-linear dynamics to single-cell transcriptomics of cell state transitions to preclinical studies**
SUI HUANG (Institute for Systems Biology, USA)

15:00 – 15:15 **Collective forces of tumor spheroids in three-dimensional biopolymer networks**
CHRISTOPH MARK (Friedrich-Alexander University of Erlangen-Nuremberg, Germany)

15:15 – 15:45 ***Coffee break***

Session VII: Translational medicine

15:45 – 16:15 **Catch me if you can: Circulating and disseminated tumor cells in breast cancer patients**
BAHRIYE AKTAS (University Hospital Leipzig, Germany)

16:15 – 16:45 **Integrated optofluidic devices for cancer cell analysis and imaging**
ROBERTO OSELLAME (University of Milan, Italy)

17:30 ***Prospective end***

Abstracts

Session I:

Cell Mechanics & Migration

Invited Talk Mo 13:15

The cancer-associated adhesion-protein β-parvin functions as mechanoresponsive signaling hub that regulates cell size, shape, and contractility

INGO THIEVESSEN – Friedrich-August University Erlangen-Nuremberg, Germany, Biophysics Group Center for Medical Physics and Technology, Henkestraße 91 91052 Erlangen Germany

The mechanical environment of cancer cells has critical impact on their motile and proliferative behavior. Why disseminated cancer cells predominantly colonize specific target tissues to form metastases is only poorly understood. The integrin associated adhesion protein β-parvin is upregulated in various cancer types and was shown to support metastatic colonization of breast cancer cells by strengthening the adhesion of filopodium-like protrusions to the extracellular matrix. We addressed the molecular mechanisms of β-parvin mediated cell adhesion in the context of cardiomyocyte mechanics and hypertrophy. We found that β-parvin promotes the formation of sarcomere-containing protrusions in hypertrophic neonatal rat ventricular cardiomyocytes (NRVC) through α/β-PIX mediated activation of Rac1. We further observed that cyclic, uni-axial stretch and physiological substrate stiffness promoted the elongation of hypertrophic NRVC in a β-parvin dependent manner, and that β-parvin is required for the maturation and contractile force generation of three-dimensional cardiac microtissues assembled from NRVC. These data suggest that β-parvin is required for the mechanosensitivity and force generation of myocardial tissue. Consistent with this, application of cardiac volume- and pressure-overload in mice revealed that β-parvin is essential for the development of physiological, but not pathological, cardiac hypertrophy. Moreover, β-parvin activates STAT3 in response to cardiac volume-overload, which in turn mediates VEGF-expression and myocardial vascularization. These data show that β-parvin functions as mechanoresponsive signaling hub that induces cardiac hypertrophy specifically upon increased physiological hemodynamic load. Our study highlights the relevance of common basic cell adhesion processes for different types of human diseases.

Invited Talk Mo 13:45

Feeling the tension: Cell-induced stresses in the extracellular matrix

CHASE BROEDERSZ - Ludwig-Maximilians-University Munich, Faculty of Physics, Theresienstr. 37 D-80333 Munich, Germany

Living cells typically grow in a three dimensional fibrous matrix. At the macroscopic level, these biopolymer matrices exhibit striking nonlinear mechanical responses. However, the implications of this extreme mechanical matrix response for living cells embedded inside the meshwork remain largely unknown. In fact, it is unclear both what the network mechanics looks like from the perspective of such a cell, and how the cell interacts with this network at the microscopic scale to regulate the mechanics of its surrounding matrix. I this talk, I will present our recent progress on characterizing the local changes in the matrix structure and mechanics induced by individual living cells inside a 3D biopolymer matrix. Moreover, I will introduce a method, called Nonlinear Stress Inference Microscopy, with which we can determine the cell-induced local matrix stress from nonlinear microrheology measurements inside the 3D matrix. We will demonstrate this method using a combination of simulations and experiments in collagen, fibrin and matrigel without requiring knowledge of the material constitutive relation of these systems.

Invited Talk Mon 14:15

Role of phosphoinositide signaling in mechanoresponse of liver cancer cells

PAUL JANMEY - University of Pennsylvania, Institute for Medicine and Engineering & Department of Physiology, 1010 Vagelos Research Labs 3340 Smith Walk Philadelphia, PA 19104-6393, USA

Several cytoskeletal regulators, including talin, ezrin, alpha-actinin, and vinculin, that are activated by tension arising when cells are grown on stiff substrates, are also

activated by polyphosphoinositide lipids, in particular PIP2, in the absence of force. These dual mechanisms of activation appear to relate to the finding that some cell types, including the human hepatocellular carcinoma cell Huh7, adopt a phenotype characteristic of adhesion to stiff substrates when they attach to very soft substrates formed by hyaluronic acid (HA) and an integrin ligand such as collagen or fibronectin. Cells that spread on very soft HA-collagen gels exert very low traction stresses compared to cells on stiff 30 kPa substrates, even though cells on both substrates have large spread areas, extensive focal adhesions, and actin bundles. Inhibition of polyphosphoinositide turnover causes Huh7 cells to decrease spreading and detach from HA-collagen substrates, whereas cells on stiffer substrates show almost no response.

Contributed Talk Mon 14:45

Microenvironmental mechanics contribute to glioblastoma cell behaviour

KATARZYNA POGODA[1], PAUL JANMEY[2]—

1 Institute of Nuclear Physics
Polish Academy of Sciences, Krakow, Poland
2 University of Pennsylvania, Philadelphia, PA, USA

Glioblastomas (GBM) are diffuse and highly invasive tumors that originate in brain and make up about 50% of all primary brain and CNS tumors. Unlike solid tumors glioblastomas are characterized by high intratumor heterogeneity and consist of regions with multiple subpopulations of the cells with various extracellular matrix compositions that support development of resistance to radiation and chemotherapy. GBM possess unique soft matter properties, which discriminate them from other soft tissue-derived tumors with relatively low content of fibrous proteins even in high grade tumors. Moreover, the boundary between tumor and normal tissue is not sharp, and single glioma cells rapidly infiltrate different brain regions and proliferate, which leads to recurrence after surgical resection of the primary tumor [1]. For this reason, one of the central therapeutic goals is to limit cell migration and division, and thereby identify molecular regulators of GBM cell motility and proliferation in vitro and in vivo. Although glioblastoma development is not accompanied by increased stiffening of tumor stroma, as is observed for breast or liver cancer, single glioma cells increase in proliferation, motility and invasiveness when cultured on a soft environment [2]. Hyaluronic acid – the main glycosaminoglycan that occupies a large volume of brain ECM - can form highly hydrated matrices that mimic the stiffness and composition of brain and glioblastoma ECM if supplemented with adhesive ligands like collagen I and laminin. These matrices can be used as a cell culture platform. Single glioblastoma cells respond to the presence of crosslinked hyaluronan of stiffness comparable to human brain by changing their morphology, motility, proliferation and secretory properties similarly as they respond to substrate stiffening reported for cells grown on polyacrylamide hydrogels with different rigidities. This outcome suggests that hyaluronic acid can trigger the same cellular response as can be obtained by mechanical force transduced from a stiff environment and is a first evidence that chemical and mechanical features can induce equivalent structural reaction in cells [3].

Reference:

[1] Pogoda, K., & Janmey, P. A.: Glial Tissue Mechanics and Mechanosensing by Glial Cells., Frontiers in Cellular Neuroscience (2018)

[2] Pogoda, K., Chin, L., Georges, P. C., Byfield, F. J., Bucki, R., Kim, R., … Janmey, P. A.: Compression stiffening of brain and its effect on mechanosensing by glioma cells., New Journal of Physics (2014)

[3] Pogoda, K., Bucki, R., Byfield, F. J., Cruz, K., Lee, T., Marcinkiewicz, C., & Janmey, P. A.: Soft Substrates Containing Hyaluronan Mimic the Effects of Increased Stiffness on Morphology, Motility, and Proliferation of Glioma Cells., Biomacromolecules (2017)

Invited Talk Mon 15:30

Focal adhesion - hemidesmosome crosstalk in migrating keratinocytes

ANNE PORA, REINHARD WINDOFFER, RUDOLF E. LEUBE

Institute of Molecular and Cellular Anatomy, RWTH Aachen University, 52074 Aachen

Keratin-anchoring hemidesmosomal cell-matrix anchoring sites contribute to the mechanical integrity of epithelia. Their role in epithelial cell migration, however, remains unclear. We find that hemidesmosomes cluster in migrating human primary keratinocytes as arrays consisting of multiple chevrons that are flanked by actin-associated focal adhesions. The arrays extend from the cell rear to the cell front. New hemidesmosomal chev-

rons form subsequent to focal adhesion assembly at the cell's leading front whereas chevrons and associated focal adhesions disassemble at the cell rear. The bulk of the hemidesmosome-focal adhesion composite, however, remains in place during cell translocation. Similar hemidesmosome-focal adhesion patterns emerge during substrate adhesion and cell spreading. We further find that hemidesmosomes and focal adhesions affect each other's distribution. Our results provide evidence that both junctions are separate but linked entities that treadmill coordinately to support efficient directed cell migration. They further suggest that both junctions cooperate to coordinate the dynamic interplay between the keratin and actin cytoskeleton.

Invited Talk Mon 16:00

Virtual fluidic channels: from single cell rheology to tissue mechanics

OLIVER OTTO— ZIK HIKE, University of Greifswald, Centre for Innovation Competence - Humoral Immune Reactions in Cardiovascular Diseases Biomechanics, Fleischmannstraße 42-44 17489 Greifswald, Germany

The mechanical properties of cells have long been established as a sensitive label-free biomarker for their function and state. While mechanical cell assays have traditionally been limited to low throughput or small sample size, the introduction of real-time deformability cytometry (RT-DC) increased analysis rates to up to 1,000 cells per second on-the-fly. RT-DC has demonstrated its relevance in basic and fundamental life science research, e.g. by establishing the mechanical fingerprint of whole blood, by describing the biophysics of Malaria pathogenesis and by observing the activation of immune cells. Yet, linking immune cell activation to underlying tissue alterations, e.g. after viral infiltration, has not been possible so far since RT-DC is a microfluidic technology and limited to suspended cells only. Here, we are introducing the concept of virtual fluidic channels to bridge the gap between microscopic and mesoscopic hydrodynamic environments. Virtual channels can be created in almost any geometry using soft lithography as well as cuvettes and can be tailored dynamically to a hydrodynamic stress distribution sufficient to probe the rheology of arbitrary cell sizes. Using HEK293 cells as a 3D culture model, we demonstrate that the Young's modulus of single cells exceeds the one of spheroids and that the elasticity of spheroids increases with size. The availability of a high-throughput assay for mechanical spheroid characterization might lead to a better understanding of tissue rheology and help to reveal e.g. the interplay of virus infiltration and tissue degeneration as well as the role of reactive species for cytoskeletal remodelling in wound healing.

Invited Talk Mon 16:30

Polarized dynamics of intermediate filament in glial cell migration

CÉCILE LEDUC—Institut Pasteur Paris CNRS UMR3691, Cell Polarity, Migration and Cancer Unit, 25 rue du Dr Roux 75724, Paris Cedex 15, France

Intermediate filaments (IFs) are key players in the control of cell morphology and structure as well as in active processes such as cell polarization, migration and mechano-responses. However the regulatory mechanisms controlling IF dynamics and organization in motile cells are still poorly understood. Using a combination of cutting edge quantitative microscopy techniques and theoretical analysis, we investigated the mechanisms leading to the polarized rearrangement of the IF network along the polarity axis during glial cell migration. We show that the spatial distribution of the cytoplasmic IFs results from a continuous turnover based on the cooperation of an actin-dependent retrograde flow and anterograde and retrograde microtubule-dependent transports. During wound-induced polarization, IF transport becomes directionally biased from the cell center towards the cell front. Such asymmetry in the transport is mainly caused by a Cdc42- and aPKC-dependent inhibition of dynein-dependent retrograde transport. Our results show how polarity signaling can affect the dynamic turnover of the IF network to promote the polarization of the network itself.

Contributed Talk Mon 17:00

Mechanical cyclic stretching inhibits cancer cell growth but promotes normal cell growth

AJAY TIJORE[1], YU-HSIU WANG[1], CHWEE TECK LIM[1], MICHAEL SHEETZ[1,2]—

[1] Mechanobiology Institute, National University of Singapore, Singapore 117411

[2] Department of Biological Sciences, Columbia University, New York NY10027

Cancer cells generally ignore cues from the microenvironment and grow indefinitely. Here we report that mechanical cyclic stretching promotes cancer cell apoptosis and inhibits proliferation on both rigid and soft surfaces. In cancer cells, stretch-induced apoptosis is mediated by calcium-activated calpain activity. However, in normal cells, cyclic stretching protects them from apoptosis while, death associated protein kinase1 (DAPK1) triggers apoptosis on non stretched soft surface. Further, the decline in cancer cell proliferation correlates with the absence cytoskeletal protein, tropomyosin 2.1 (TPM2.1). When transformed cancer cells are restored to normal rigidity-dependent growth by restoration of depleted TPM2.1, mechanical stretch activates growth particularly on soft surface. Also, mechanical stretch causes elongation of cancer cells but not of the normal cells or normalized cancer cells. This cell elongation is dependent on both magnitude and frequency of mechanical stretch. Based upon these findings we suggest that the transformed cell state makes cells vulnerable to mechanical stretch and suppresses cancer growth.

Welcome Dinner / Round Table
(17:30, at Felix-Klein Lecture Hall, Paulinum)

Abstracts

Session II: Membranes

Invited Talk Tue 09:00

Modulation of cortical actin assembly dynamics

ANNE-CÉCILE REYMANN — IGBMC - CNRS UMR 7104 - Inserm U 1258, 1 rue Laurent Fries, BP 10142 67404 Illkirch Cedex, CU Strasbourg, France

The cortex is a thin layer of actin filaments attached to the cellular membrane controlling the form and movement of cells through a constant remodeling of its network of filaments. This architecture is modulated by a combination of specific signaling pathways, numerous regulatory proteins, but is also modified through feedbacks with the mechanical properties and dynamics of this gel like material. As a result, the cortical layer is spatially and temporally regulated.

By the use of in vivo endogenous labeling of proteins and state of the art microscopes, we are now able to resolve the dynamics molecular components of the cytoskeleton in the cortical layer of C. elegans embryos. For example, how fast a formin elongates actin filaments or where capping protein blocks these growing ends. We have also investigated how myosin-induced cortical flows directly drive filaments alignment in contractile rings to induce a stable ingression by mechanically remodeling the actin architecture. This brings up the question of the contribution of the mechanics during this initial phase of contractile ring assembly.

Invited Talk Tue 09:30

Physics of cell adhesion: The role of the membrane in the protein recognition process

ANA SUNCANA SMITH[1,2] —

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[2] Institute RuÄ'er BoškoviÄ‡, Division of Physical Chemistry, Bijenicka 54, Zagreb, Croatia

In embryogenesis, vertebrate cells assemble into organized tissues. In metastatic cancer, cells spreading in the circulatory system build cell-cell contacts with the surrounding tissue to establish new tumors. At the root of these life-forming or life-threatening biological phenomena is cell adhesion, the binding of a biological cell to other cells or to extracellular matrix. The most obvious fundamental question to ask is then as follows: What factors control or govern cell adhesion? For a long time, the paradigmatic answer to this question was that specific protein molecules embedded in the cell wall (or membrane) were responsible for cell adhesion, in either a key-lock fashion (in cell-cell adhesion) or a suction-cup fashion (in cell-matrix adhesion). But, a new realization has emerged during the past two decades that physical mechanisms, promoted by the cell membrane, play an unavoidable, yet not fully understood role. Although these physical elements, namely membrane fluctuations and ability to change shape, do not at all depend on any specific proteins, they can have a major impact on the protein-mediated adhesion, and can be viewed as mechanism that controls the binding affinity to the cell-adhesion molecules. In my talk I will show how these mechanisms can be studied in mimetic models both experimentally and theoretically, the result of which will be discussed in the cellular context.

Contributed Talk Tue 10:00

Collective motion attenuates natural selection in crowded cellular populations

JONA KAYSER, CARL SCHRECK, MATTI GRALKA, DIANA FUSCO, OSKAR HALLATSCHEK – University of California - Berkeley, Physics Department, Stanley Hall, Berkeley, CA 94720, USA

The successive acquisition of mutations is the primary driver of oncogenesis and cancer progression. Throughout the growth process, arising mutant clones have to compete with ancestral genotypes via natural selection. Yet, for dense cellular assemblies, such as solid tumors, little is known about how these evolutionary forces are shaped by the inherent mechanical cell-cell interactions underlying spatial population expansion. Here, by tracking slower-growing clones in a microbial model system, I show that the collective motion of cells can attenuate selection pressures, preventing costly mutations from being weeded out rapidly.

The presented observations can be understood in the framework of an effective surface tension. Using a combination of microbial experiments and computational models I demonstrate that the intrinsic cooperative nature of growth-induced forces suppress the differential displacements required for selection to act. This mechanical screening of fitness differences facilitates the prolonged persistence of costly drug resistant mutations, a primary cause of cancer treatment failure.

Session III: Matrix

Invited Talk Tue 10:45

New peptide probes to map the tensional states of ECM fibers in tumour tissues

VIOLA VOGEL— Laboratory of Applied Mechanobiology, Institute of Translational Medicine, Department for Health Sciences and Technology, ETH Zurich, CH-8093 Zürich, Switzerland

Major transformations of extracellular matrix (ECM) composition, architecture as well as of its mechanical properties accompany inflammatory diseases and cancer progression. While considerable evidence has emerged in recent years that the stretching of ECM fibers can either activate or destroy molecular binding sites, little is known how this alters outside-in cell signaling. As the ECM acts as reservoir for a plethora of growth factors and cytokines, some of which bind to ECM fibers, gaining knowledge on the mechanical strain of ECM fibers in healthy and diseased tissue is thus urgently needed. To address this challenge, we have recently developed mechanosensitive peptide probes which specifically bind to relaxed, but not to stretched fibronectin fibers. Novel insights will be discussed that we obtained in a first set of tissues via spatial correlative assessments in relationship to other biomarkers. Recapitulating de novo tissue growth processes in microtissue platforms gave further insights into mechanisms by which ECM fiber tension might affect tissue growth processes and the fibroblast-to-myofibroblast transition.

Invited Talk Tue 11:15

Mechanics matters for cells: From extracellular matrix via cytoskeleton to the nucleus

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The mechanical properties of microenvironments in our body vary over a broad range and are as important for cells as biochemical cues. An especially striking experiment of this mechano-sensitivity demonstrated that systematic variation of the Young's elastic modulus E of the substrate can direct the lineage differentiation of human mesenchymal stem cells (hMSCs) (1).

To elucidate the complex interplay of physical and biochemical mechanisms of cellular mechano-sensing, well-defined extracellular matrix (ECM) models are essential. While elastic substrates made of polyacrylamide (PA) are widely in use, they have the potential drawback that the precursors are cytotoxic and therefore do not allow for 3D culture systems. Here, a novel biomimetic ECM model based on hyaluronic acid (HA) was successfully established that exhibits a widely tuneable and well-defined elasticity E, allows for 2D and 3D cell culture and enables us to mimic a variety of distinct in vivo microenvironments (2). Quantitative analysis of the structure of acto-myosin fibers of hMSCs on elastic substrates by an order parameter S, reveals that the stress fiber morphology is an early morphological marker of mechano-guided differentiation and can be understood using a classical mechanics model (3). Furthermore, the cytoskeleton also dictates the shape of the nucleus and lends support to a direct mechanical matrix-myosin-nucleus pathway (4).
I will also highlight some of our recent approaches to quantify the cytoskeleton structure during massively parallel life cell imaging with our new tool filament sensor (5), by scanning x-ray microscopy (6), and about elucidating the 3D architecture of focal adhesions using metal induced energy transfer (MIET) combined with FRET (7).

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Invited Talk Tue 11:45

Control of mechanosensitivity by integrin-ECM binding and nucleocytoplasmic shuttling kinetics

PERE ROCA CUSACHS – Institute for Bioengineering of Catalonia, Parc Científic de Barcelona (PCB): Edifici Hèlix c/ Baldiri Reixac 15-21 08028 Barcelona, Spain

Cell proliferation and differentiation, as well as key processes in development, tumorigenesis, and wound healing, are strongly determined by the rigidity of the extracellular matrix (ECM). In this talk, I will explain how we combine molecular biology, biophysical measurements, and theoretical modelling to understand the mechanisms by which cells sense and respond to matrix rigidity. I will discuss how the properties under force of integrin-ECM bonds, and of the adaptor protein talin, drive and regulate rigidity sensing. I will further discuss how this sensing can be understood through a computational molecular clutch model, which can quantitatively predict the role of integrins, talin, myosin, and ECM receptors, and their effect on cell response. Finally, I will analyze how signals triggered by rigidity at cell-ECM adhesions are transmitted to the nucleus, leading to the activation of the transcriptional regulator YAP.

Contributed Talk Tue 12:15

Collectively Emerging Nematic Order in Populations of Fibroblasts

JUSTYNA BOBROWSKA[1], JOANNA PABIJAN[1], JAKUB RYSZ[2], KAMIL AWSIUK[2], ANDRZEJ BUDKOWSKI[2], MAÅ,GORZATA LEKKA[1]

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Searching for new biomarkers is still a great challenge because, so far, there is no single biomarker which has an ability to detect cancers of different organs with high specificity and sensitivity. That is why interdisciplinary approach combining complimentary techniques and the convergence of diverse disciplines can accelerate the progress in cancer diagnosis and therapy. One of the emerging directions is to correlate cellular biomechanics with biochemical and biophysical properties of single cells. The main aim of the studies presented here is to demonstrate that a combination of two techniques, atomic force microscopy (AFM) and time of flight secondary ions mass spectrometry (ToF SIMS) delivers biochemical and nanomechanical fingerprints of mela-

noma progression. To realize it, the mechanical and surface chemical properties of melanoma cell lines originating from various stages of melanoma progression were evaluated. Measurements were carried out for three groups encompassing cells originating from VGP primary tumor sites and those derived from skin and lung metastasis.

AFM has become a well-established method in the research of biological materials ranging from single proteins to living cells, as it allows not only for the topography measurements with a very good spatial resolution but it enables also the analysis of the elastic properties of various materials, including single cells. While the majority of solid tumors is more rigid than their surrounding environment, it is known that individual cancer cells are more deformable than their benign counterparts. In our studies, based on the elasticity measurements, the melanoma cells biomechanics was quantified by the Young's modulus [1]. The biochemical properties of melanoma cell surfaces were investigated using Time-of-Flight Secondary Ion Mass Spectrometry (ToF SIMS). Since the ToF-SIMS experiments have to be carried out in high vacuum conditions, biological samples like cells require a special treatment [2]. Subsequently, high resolution mass spectra were collected for each melanoma cell type and analyzed by means of Principal Component Analysis (PCA) [3]. Our findings show that both characteristics of cancer-related changes, nanomechanical and biochemical fingerprints, increase with a stage of melanoma progression. Simultaneously, proposed methodology of AFM and ToF SIMS measurements can be successfully implemented in the studies on increasing the effectiveness of anticancer drugs.

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Abstracts

Poster Session

Poster 1

Mechanical cyclic stretching inhibits cancer cell growth but promotes normal cell growth

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Cancer cells generally ignore cues from the microenvironment and grow indefinitely. Here we report that mechanical cyclic stretching promotes cancer cell apoptosis and inhibits proliferation on both rigid and soft surfaces. In cancer cells, stretch-induced apoptosis is mediated by calcium-activated calpain activity. However, in normal cells, cyclic stretching protects them from apoptosis while, death associated protein kinase1 (DAPK1) triggers apoptosis on non stretched soft surface. Further, the decline in cancer cell proliferation correlates with the absence cytoskeletal protein, tropomyosin 2.1 (TPM2.1). When transformed cancer cells are restored to normal rigidity-dependent growth by restoration of depleted TPM2.1, mechanical stretch activates growth particularly on soft surface. Also, mechanical stretch causes elongation of cancer cells but not of the normal cells or normalized cancer cells. This cell elongation is dependent on both magnitude and frequency of mechanical stretch. Based upon these findings we suggest that the transformed cell state makes cells vulnerable to mechanical stretch and suppresses cancer growth.

Poster 2

Human glioblastoma mechanics: substrate stiffness alters traction forces and cell morphology

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Glioblastoma is the most invasive and lethal primary brain tumour in adults accompanied by a poor prognosis and short survival time from the time of diagnosis. This is the result of the high heterogeneity of the genetic landscape accompanied by the absence of specific molecular therapeutic targets. The majority of glioblastoma is initiated from astrocytes, the most prevalent glial cells in the central nervous system (CNS). While the pathophysiology of astrocytes and patient-derived glioblastoma cells has so far been extensively characterized in terms of genetics, biochemistry and molecular biology, the effect of mechanical cues on these cells is poorly understood. Here, we cultured these cells on polyacrylamide hydrogels and studied the influence of the mechanical environment on cellular traction forces and morphology. Primary glioblastoma cells were derived by distinct spatially tumour fractions from three different patients. Glioblastoma cells showed significant differences in traction stresses (force per unit area). In addition, actin network architecture for both glioblastoma cells and astrocytes depended on substrate stiffness. On stiffer substrates, cells displayed a more complex actin network architecture accompanied by an increase in cell spread area. Finally, substrate stiffness regulated the nuclear vs cytoplasmic localization of oligodendrocyte transcription factor 2 (Olig2), which is a key transcription factor in glioblastoma stemness, linked with

proliferation and invasion capacity. Our results suggest that different tumour fractions of this high-grade glioma may be distinguished according to their traction stresses.

Poster 3

Loss of vimentin increases motility and nuclear damage in confined spaces

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The migration of cells through tight constricting spaces or along fibrous tracks in tissues is important for biological processes, such as embryogenesis, wound healing, and cancer metastasis, and depends on the mechanical properties of the cytoskeleton. Migratory cells often express and upregulate the intermediate filament protein vimentin. The viscoelasticity of vimentin networks in shear deformation has been documented, but its role in motility is largely unexplored. We studied the effects of vimentin on cell motility and nuclear damage using mouse embryo fibroblasts derived from wild-type and vimentin-null mice. We find that loss of vimentin increases motility in confining environments, such as micro-fluidic channels and collagen matrices, that mimic interstitial spaces in tissues. Loss of vimentin leads to accumulated nuclear damage, in the form of blebs, nuclear envelope rupture, and enhanced DNA damage, which accompanies the migration of cells through small pores. Atomic force microscopy measurements reveal that the presence of vimentin enhances the perinuclear stiffness of the cell, to an extent that depends on surface ligand presentation and therefore signaling from extracellular matrix receptors. Together, our findings indicate that vimentin hinders three-dimensional motility by providing mechanical resistance against large strains and thereby protects the structural integrity of the cell and the nucleus. Reference:
https://doi.org/10.1101/371047

Poster 4

Migration of cancer cells in predefined 3D collagen matrice

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The metastasis of tumor cells is one of the biggest threats of cancer. The mobility of tumor cells is influenced by the structure of the surrounding tissue.[1] To study this influence, we designed several artificial tissue gels with different structures using collagen I as model system. The movement of invasive MDA-MB-231 breast cancer cells was tracked and analyzed in these gels, to determine which gel structure enhances or hinders cell migration and to further improve the understanding of the mechanisms behind the migration of these cells in connective tissue.[2]

The collagen fiber length is controlled via temperature during the gelation process. Without further modification, gels consist of randomly oriented collagen fibers. To achieve an alignment of the fibers two different methods with different rates of alignment were developed; an alignment via Surface Acoustic Waves and via magnetic beads.

The resulting gels were then used to measure the movement of MDA-MB-231 cancer cells in different surroundings. The results of these measurements revealed a different behaviour of the cells in the gels depending on the fiber length. The cells show a hindered, subdiffusive migration in short collagen fibers without alignment, changing to a diffusive migration mode in long unoriented gels. In a collagen gel with long fibers and a high rate of alignment the movement even becomes superdiffusive.

These results suggest that long and aligned fibers promote invasion of tumor cells into connective tissue, as opposed to small, randomly oriented fibers, which hinder it. The cells also might use the collagen fibers as

anchor points to push themselves through the matrix, hence a more rigid collagen network should promote the cell movement.

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Poster 5

EMT-induced changes of cortical contractility and stiffness in breast epithelial cells

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Cancer cells have been reported to show a softer phenotype. At the same time, it has been speculated that invasive cancer cells are particularly contractile. Epithelial mesenchymal transition (EMT) has been previously identified as a key process in cancer progression and metastasis, suggesting that EMT reduces cell stiffness and enhances cell contractility. To test this hypothesis, we probed breast epithelial cells mechanically before and after chemically induced epithelial mesenchymal transition (EMT). We uniaxially compressed isolated suspended cells in a parallel plate confinement assay using an atomic force microscope in conjunction with a wedged cantilever. In this way, we measured cortical contractility and cortical stiffness. We find that cell stiffness is decreasing jointly with cortical contractility through EMT in suspended cells.

Poster 6

Uncovering the dynamic precursors to contraction

JOSÉ ALVARADO – University of Texas at Austin, USA

Cells and tissues have the remarkable ability to actively generate the forces required to change their shape. This active mechanical behavior is largely mediated by the actin cytoskeleton, a crosslinked network of actin filaments that is contracted by myosin motors. Experiments and active gel theories have established that the length scale over which gel contraction occurs is governed by a balance between motor activity and crosslink density. By contrast, the dynamics that govern the contractile activity of the cytoskeleton remain poorly understood. Here we investigate the dynamics of reconstituted actin-myosin networks by simultaneous real-space video and Fourier-space dynamic light scattering. Light scattering reveals rich and unanticipated dynamics at the microscopic scale that evolve with sample age. We uncover two dynamical precursors that precede macroscopic contraction of the gel. The first precursor is characterized by stress-induced rearrangements that slowly accelerate. The second precursor proceeds via sudden rearrangements that depend on network adhesion to the boundaries and are characteristic of heterogeneous dynamics. These microscopic dynamics reveal an interesting analogy between internally driven rupture and collapse of active gels and delayed rupture of passive gels under external loads.

Poster 7

Real Tumor Pieces and Model Cell-Aggregates Act Alike on Collagen Gels

FRANK SAUER[1], STEFFEN GROSSER[1], ERIK MORAWETZ[1], SUSANNE BRIEST[3], LARS-CHRISTIAN HORN[4], BAHRIYE AKTAS[3], CLAUDIA T. MIERKE[2], JOSEF A. KÄS[1]

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A central paradox in physics of cancer is that tumors are stiff, whereas the single cancer cells are softer than their healthy counterparts. Since tumor progression is usually paralleled with a restructuring of the surrounding extracellular matrix (ECM), understanding the basic mechanical features of cell-ECM interactions is quintessential to that.
We analyze the effects of cell aggregates on collagen gels to quantify matrix deformations and to identify further noticeable alterations. In cooperation with the university hospital Leipzig we compare established stable model systems such as aggregates from cultured cell lines against more physiological samples: primary tumor extracts.
Our results indicate that primary samples show comparable systematic tissue-ECM interactions as the cell line model systems and that they might be rated on a common malignancy scale.

Poster 8

Role of N-Cadherin during the Epithelial-Mesenchymal Transition

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The aim is to find a marker for differentiation of normal tissue and cancerous tissue. The analysis of cadherin, aims the characterization of a possible marker for differentiation of normal tissue and cancerous tissue. Cadherin are adhesion proteins, which are important for cell-cell junction. In order to verify and quantify cadherin in the cell, it is necessary to stain the
cell with a specific fluorescence marker for N- and E-cadherin. In the picture below, the staining methods are illustrated. It is possible to stain E-cadherine in living cells with one existing solution, containing stain and fluorescence tag. For N-cadherin staining doesn't exist a living stain method for. Therefor, it was necessary to evaluate the primary and secondary
antibody solutions, and the fluorescent tag, to find a fitting staining method. The fluorescence imaging were done with the Optical Stretcher.

Poster 9

Human aorta under tensile stress

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An aortic aneurysm is an enlargement of the aorta. In most cases, no symptoms appear and aneurysm is identified as incidental finding. About 36 of 100.00 people suffer from that disease and received the diagnosis every year [1]. Occurrence of this disease strongly depends on age, gender and distinct risk factors as smoking, overweight, hypertension and increased level of blood lipids. In case of an increasing aneurysm diameter, a rupture within the aortic wall threatens, so called aortic dissection, or at worst a rupture of the entire aorta, so called aortic rupture. In both cases, there is an acute danger to life. In cooperation with the Herzzentrum Leipzig, we investigate aortic samples from patients which suffer from an aortic aneurysm with regard to their mechanical properties. Therefore, a tubular aortic portion were harvested from patients and cut into rectangular shapes, originated from convex and concave part of the aorta, and stretched until rupture using uniaxial tensile tests. Clinical data of patients as

age, aortic diameter, arterial hypertension, elastin content or type of aortic valve (bicuspid- or tricuspid aortic valve) were correlated with the elastic modulus to contribute to a better understanding of the role of pathological factors in mechanical properties of aorta.
[1] Gesundheitsberichterstattung des Bundes, 2018

Poster 10

Comparison of HER2, estrogen and progesterone receptor expression profiles of primary tumor and synchronous axillary lymph node metastases in early breast cancer patients.

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Background:
Targeted systemic therapy in early breast cancer with synchronous lymph node metastases (LNM) is currently based on the expression of the hormone receptors (ER/PR ≥1%) and overexpression of HER2 in the primary tumor. However, the expression of these predictive markers on LNM has not yet been taken into account. The aim of the present study was to compare the HER2/ER/PR expression profiles of primary tumors and synchronous LNM.

Patients and Methods:
177 patients with early breast cancer were enrolled in this study. Formalin-fixed and paraffin-embedded archival tissues of the primary tumors and the lymph node metastases were analyzed by two pathologists. ER, PR and HER2 expression was assessed by fully-automated immunohistochemistry (Ventana medical Systems, Tucson, AZ, USA) and HER2/CEN17 dual chromogenic in situ hybridization (Zytomed Systems, Berlin, Germany) according to modified ASCO/CAP guidelines (2010 and 2013, respectively).

Results:
The discordance rates between primary tumors and axillary LNM were 13% (22/177) for HER2, 9% (14/177) for ER and 19% (32/177) for PR. The intrinsic subtypes between primary tumors and LNM changed in 20% of all cases (35/177 patients; gain of HER2 in 5/35, activation of HRs in 3/35 cases, loss of HER2 in 17/35 and loss of HRs in 10/35 cases becoming triple negative).

Conclusion: Our preliminarily results demonstrate, that changes in subtypes are the rule rather than the exception. Subtype shift may be of essential therapeutic significance for individual patients, larger studies should be enrolled to validate these data.

Poster 11

Natural Killer cells switch between mesenchymal and amoeboid migration in adhesive vs. non-adhesive 3D environments

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For migration in dense three dimensional environments, immune cells including Natural Killer (NK) cells are believed to employ integrin-independent amoeboid migration mechanisms characterized by weak adhesion, fast changes in cell morphology, and high migration speeds exceeding 10 µm/min. By contrast, strong adhesion with the matrix is thought to lead to slow-down or complete arrest of cell migration. In this study, we

measure the traction forces that migrating NK cells exert on their 3D environment and compare migration mechanisms in differently adhesive matrices.

NK cells derived from peripheral blood of healthy donors are ex vivo expanded for 14 days in the presence of IL-2 and NK cell-sensitive tumor cells (K562) transfected with membrane-bound IL-15 and 4-1BBLigand. Cells are suspended in an adhesive or non-adhesive hydrogel. Cell shape changes and movements are recorded using bright-field microscopy image stacks with a frame rate of one stack every 15 seconds. From each cell trajectory, we compute migration speed and directional persistence (average cosine of the turning angle between two consecutive time steps; persistence is +1 for ballistic migration, 0 for random migration, and -1 for stationary cells). As an adhesive tissue, we use collagen networks (concentration 1.2 mg/ml) with average pore size of 3.8 µm and stiffness of 180 Pa. We image the deformation of the collagen matrix around cells using confocal reflection microscopy and estimate contractile forces using 3D traction microscopy. As a non-adhesive hydrogel, we use copolymer networks of acrylic acid and alkyl-methacrylate (carbomer) with 100 nm mesh size and a yield stress of ~10 Pa.

We find similar migration speed (v) and directional persistence (dp) of cells in both hydrogels (v=7.0 µm/min, dp=0.6 in collagen versus v=7.1 µm/min, dp=0.4 in carbomer. These small differences are not statistically significant due to high variability between different donors. In both environments, cell shape and morphodynamics are similar, with elongated cells that form short-lived pseudopods. In collagen, we observe large (>1 µm) long-range (> 30 µm) deformations of the network fibers surrounding the cells, indicating that NK cell migration in collagen is predominantly mesenchymal and driven by large, highly dynamic contractile forces of ~5 nN. To our knowledge, this is the first report demonstrating a high-adhesion mesenchymal migration mechanism for leukocytes in a 3D porous environment. However, in a non-adhesive environment that prevents the transmission of contractile forces to the environment, cells switch to an amoeboid migration mode and achieve similarly high speeds and directional persistence.

Poster 12

Electron-Irradiated Hydrogels: Reagent-Free Modification towards Biomedical Applications

Stefanie Riedel[1,2], Catharina Krömmelbein[2], Katharina Bela[1,2], Carl Suckfüll[1,2], Joachim Zajadacz[1], Stefan G. Mayr[1,2]

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Collagen and gelatin hydrogels have attracted considerable interest in biology and medicine during the past years. Due to their strong biocompatibility and biodegradability, they are highly attractive materials for biomedical applications such as extracellular matrix components. Thereby, precise adaption of structure and mechanics as well as stimuli-response is an interesting aspect of the modification of these materials. Reagent-free modification of hydrogels can be achieved by utilizing high energy electron irradiation inducing crosslinking. We will demonstrate how crosslinking with high-energetic electrons allows fine-tuning of materials properties such as structure, mechanics and swelling. Furthermore, we will present the development of stimuli-responsive systems as well as topographically and mechanically patterned hydrogel substrates for biomedical applications.

Poster 13

Shear stress and cellular behaviour in 3 D biofabrication assays

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The mechanical environment of cancer cells has critical impact on their proliferative and motile behaviour. However, how mechanical parameters such as substrate stiffness or shear forces affect intracellular signalling processes that control cancer cell behaviour is only partially understood. Using alginate-based 3D bioprinting in combination with fluorescent chemical dye and lentiviral reporters we investigate the effects of shear forces and ECM-stiffness on cell stress and behaviour. Preliminary data show that the incorporation of the fluorescent styryl-dye FM 1-43 by NIH3T3 cells increased with the pneumatic pressure (50 - 600 kPa) used to drive the piston of the printer, demonstrating that shear stress can perturb plasma membrane integrity. We will modulate additional parameters such as matrix stiffness and needle diameter, and correlate the effects on plasma membrane integrity with experimental data on immediate cell death, longterm proliferation and apoptosis using lentiviral reporters, as well as with mathematical modelling data of shear forces exerted onto the cells during needle passage. We are planning to conduct experiments in cancer as well as stem cells. We anticipate our results to provide deeper insights into the relationship between the mechanical properties of the ECM and the behaviour of embedded cells in 3D bioprinting models.

Poster 14

Electron irradiated Elastin/Collagen Hydrogels

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Collagen matrices are common tissue models in the field of cancer research which constantly advance the understanding of processes such as (cancer) cell migration and nonlinear mechanics of tissue. However, some types of connective tissue exhibit a distinct proportion of the protein elastin of up to 50 weight-%. Thus, the creation of a tissue model with a tunable ratio of elastin to collagen and tunable rheological and topological properties can open new ways of precisely mimicking physiological environments.
This work aims to create an elastin/collagen tissue model by means of electron irradiation and will thereby benefit progresses in regenerative medicine and tissue engineering.

Poster 15

The role of stickiness in the rheology of semiflexible polymers

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A variety of semiflexible polymers form central structures in biological material. Modeling approaches usually neglect the influence of polymer-specific molecular features aiming to describe semiflexible polymers in a universal frame. Here, we investigate the influence of such molecular details on networks assembled from filamentous actin, intermediate filaments (IF), and synthetic double-crossover DNA nanotubes. In contrast to prevalent theoretical assumptions, we noticed an arising stickiness during network maturation. This effect is caused by various inter-filament interactions, which

can be merged into a single parameter quantifying the direct impact of this interplay on the molecular level to mechanical bulk properties. The interpretation of this parameter as a polymer-specific stickiness is consistent with observations from macro-rheological properties and reptation behavior. These results are well captured within the glassy wormlike chain model revealing that IF are more than twice as sticky as actin filaments and DNA nanotubes. Our findings demonstrate that stickiness should not be ignored in modeling approaches concerning semiflexible polymer networks.

Poster 16

Collective motion attenuates natural selection in crowded cellular populations

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The successive acquisition of mutations is the primary driver of oncogenesis and cancer progression. Throughout the growth process, arising mutant clones have to compete with ancestral genotypes via natural selection. Yet, for dense cellular assemblies, such as solid tumors, little is known about how these evolutionary forces are shaped by the inherent mechanical cell-cell interactions underlying spatial population expansion. Here, by tracking slower-growing clones in a microbial model system, I show that the collective motion of cells can attenuate selection pressures, preventing costly mutations from being weeded out rapidly. The presented observations can be understood in the framework of an effective surface tension. Using a combination of microbial experiments and computational models I demonstrate that the intrinsic cooperative nature of growth-induced forces suppress the differential displacements required for selection to act. This mechanical screening of fitness differences facilitates the prolonged persistence of costly drug resistant mutations, a primary cause of cancer treatment failure.

Poster 17

AFM-based assessment of antitumor drugs on prostate cancer cells

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Cancer is still one of the most common cause of a death in human. Apart from capability to infinite proliferation, cancer cells are characterized by ability to invade and to metastase that has been shown to be linked with altered biomechanical properties [1], [2]. Evidence shows that cancer cells are softer than their healthy counterparts what makes them easier to move in a complex microenvironment of the extracellular matrix [2]. Deformability of cells and tissues is mostly connected with cytoskeletal elements and extracellular matrix proteins, mainly with actin filaments that have been shown to participate in cell migration. Disintegration of actin cytoskeleton leads to the depletion of motility and robust cells softening. Cytoskeletal network composed of microtubules is an important target for anticancer drugs due to its crucial role in mitosis [3]. However, their contribution to a deformability of cancerous cells and thereby the role of biomechanics in antitumor drug action is less known. The main aim of our study was to elaborate how disruption of microtubule network affects the efficiency of antitumor drugs and how it is manifested in cellular deformability.
As a model cellular system, Du145 prostate cancer cells derived from brain metastasis were chosen. Cells were cultured in media without antibiotics to exclude their potential interaction with anticancer drugs. Microtubules organization was affected by chemotherapeutic agents vinflunine. It binds to vinca binding site on tubulin dimers leading to microtubule cytoskeleton destabilization [3]. Drug concentration was assessed by MTT

cytotoxicity assay to establish noncytotoxic and cytotoxic drug doses. Nanoindentation experiments were carried out using atomic force microscopy (AFM) working in a force spectroscopy mode. Based on Hertz model [4], elastic (Young's) modulus of prostate cells was determined for two doses of the vinflunine. Namely, 100 nM showing no cytotoxicity and 750 nM with clearly visible cytotoxic effect. Treatment with vinflunine changes cellular deformability in a dose-dependent manner. Stiffening of cells upon treatment with cytotoxic dose of vinflunine might be caused by aggregation of tubulin in central area of cells. Results show that AFM might be successfully used to investigate effect of chemotherapeutic agent on cancerous cells, especially in search of effective, low drug concentrations.

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Poster 18

Biomechanics of glioblastoma cells by atomic force microscopy

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Glioblastoma is a one of most deadly cancers, thus, understanding mechanisms governing its invasion is important for the development of novel treatment approaches. Nanomechanics of living cells is one of essential cues shown to play a role in glioblastoma migration and metastasis[1], [2]. Various studies, carried so far, have shown that the main structure responsible for mechanical properties of cells is a cytoskeleton, in particular, actin filaments [3], [4].

In our studies, we focused on nanomechanical properties of glioblastoma cells in relation to changes induced in actin filament organization upon cytochalasin D treatment. Two cell lines with distinct morphologies were chosen, namely, U118 and U138 possessing fibroblast and keratinocyte-like characteristics, respectively. Elastic properties of cells (quantified through the Young's modulus, [4]) and F-actin organization in cells were obtained by applying atomic force and fluorescence microscopes. Results identify that these glioblastoma response to cytochalasin D (5μg/ml) in a time(dose)-dependent manner resulted in both softening and stiffening of cells. Fibroblasts-like cells (U118) increase their deformability (Young's modulus decreases) after 10 minutes of cytochalasin D incubation. As Young's modulus decreases for all probed indentations (from 200 nm to 800 nm), softening of cells, we can postulate that cytochalasin D re-organization proceeds within a whole actin filament network. Keratinocyte-like U138 cells respond differently. For the same incubation time, there was no changes in elastic properties while increasing the time of cytochalasin D exposure to 30 minutes induced stiffening of these cells. They become more rigid within a whole indentation depth. These finding are analogous to that recently published showing pronounced effect of cytochalasin D on fibroblasts and no effect for keratinocytes [5]. Summarizing, the fact that U118 glioblastoma cells are stiffer than U138 ones can be explained by well-differentiated network of actin filaments with the presence of stress fibres in U118 and lack of them in U138. Exposure to cytochalasin D shows that elastic properties of fibroblast-like U118 are govern by actin filaments while their role in deformability of U138 is less significant.

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Poster 19

Biochemical and nanomechanical fingerprints of melanoma development

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Searching for new biomarkers is still a great challenge because, so far, there is no single biomarker which has an ability to detect cancers of different organs with high specificity and sensitivity. That is why interdisciplinary approach combining complimentary techniques and the convergence of diverse disciplines can accelerate the progress in cancer diagnosis and therapy. One of the emerging directions is to correlate cellular biomechanics with biochemical and biophysical properties of single cells. The main aim of the studies presented here is to demonstrate that a combination of two techniques, atomic force microscopy (AFM) and time of flight secondary ions mass spectrometry (ToF SIMS) delivers biochemical and nanomechanical fingerprints of melanoma progression. To realize it, the mechanical and surface chemical properties of melanoma cell lines originating from various stages of melanoma progression were evaluated. Measurements were carried out for three groups encompassing cells originating from VGP primary tumor sites and those derived from skin and lung metastasis.

AFM has become a well-established method in the research of biological materials ranging from single proteins to living cells, as it allows not only for the topography measurements with a very good spatial resolution but it enables also the analysis of the elastic properties of various materials, including single cells. While the majority of solid tumors is more rigid than their surrounding environment, it is known that individual cancer cells are more deformable than their benign counterparts. In our studies, based on the elasticity measurements, the melanoma cells biomechanics was quantified by the Young's modulus [1]. The biochemical properties of melanoma cell surfaces were investigated using Time-of-Flight Secondary Ion Mass Spectrometry (ToF SIMS). Since the ToF-SIMS experiments have to be carried out in high vacuum conditions, biological samples like cells require a special treatment [2]. Subsequently, high resolution mass spectra were collected for each melanoma cell type and analyzed by means of Principal Component Analysis (PCA) [3]. Our findings show that both characteristics of cancer-related changes, nanomechanical and biochemical fingerprints, increase with a stage of melanoma progression. Simultaneously, proposed methodology of AFM and ToF SIMS measurements can be successfully implemented in the studies on increasing the effectiveness of anticancer drugs.

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Poster 20

Roadmap to Local Tumor Growth: Insights from Cervical Cancer

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Wide tumour excision – i.e. the resection of a malignant neoplasm with a metrically defined circumferential margin of healthy tissue – is currently the standard approach to the surgical treatment of solid cancers including carcinomas of the lower genital tract. This strategy is based on the premise that tumours grow isotropically.

We reviewed the local spreading patterns of 518 carcinomas of the uterine cervix. The data was collected prospectively as part of the ongoing cancer field resection trials at our institution. We used area-proportional Euler diagrams to detect ordered patterns of tumour spread and applied computational modelling techniques to simulate local tumour spread in order to identify parameters influencing preferred infiltration patterns.

Some anatomical structures such as the urinary bladder and its support structures were significantly more likely to be infiltrated by cervical cancer than other structures such as the ureter or the rectum with its support structures. Computational tumour spread models assuming isotropic growth could not explain these infiltration patterns. Introducing ontogenetic tissue properties as an additional parameter led to accurate prediction of the clinically observed tissue specific infiltration likelihoods. The calculation of area-proportional Euler diagrams indicates that the successive infiltration likelihoods of ontogenetically increasingly distant tissues are nearly perfect subsets of the ontogenetically more proximal tissues.

The prevailing assumption of isotropic tumour extension has significant shortcomings in the case of cervical cancer. Rather, cervical cancer spread seems to follow ontogenetically defined trajectories. The observations of this study might also be applicable to other cancer entities.

Poster 21

Carbon implantation of TiO2 nanotubes for biomedical applications

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For medical implants, titanium and titanium oxides are materials of first choice. High corrosion resistance and exceptional biocompatibility provide superior conditions for a permanent implantation in the human body. Titanium dioxide (TiO) nanotube arrays show specific surface structures that enhance protein adsorption [1]

and enable long-term culture of adult tissues, without detectable degeneration effects of cells and tissues [2,3]. Thus, they bear a great potential not only for ex vivo tissue culture but also as an implant coating. Implants for electrical stimulation of neuronal tissues are in particular challenging, since the formation of glia scars around the implanted electrode hinders electric coupling to neuronal cells. To resolve this problem, TiO_2 nanotube arrays are employed which support neuronal tissue adhesion for improved electrical stimulation. The electrical conductivity of the TiO_2 nanotube arrays is enhanced by implantation of carbon ions in low fluences of 1×10^{14} ions/cm² with 60 keV to maintain the amorphous TiO_2 phase and to minimize surface damage. Here we observed a reduction of surface roughness and an increase of surface free energy, while the nanotube heights were unchanged. The surface topography changed to smaller nanotube diameters due to increased surface relaxation effects, mainly surface diffusion. Moreover, these carbon implanted TiO_2 nanotubes arrays show a satisfying conductivity, as well as well-defined and tunable surface characteristics and material properties. In this way, a promising surface functionalization method for implant materials with suitable electrical properties applicable for neuroelectrodes is developed.

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Poster 22

Cancer cell motility study in micro-constriction chips

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Compressive stress plays a fundamental role in the physics behind tumor growth and development. It was assumed that compression regulates the selection of metastatic cell populations or even stimulates tumor invasion, as it causes both genetic and phenotypic mutations that are related to malignancy [1]. Previous studies on cancer cell migration in vitro have been performed by using subnucleus-scaled microfluidic channels, collagen matrices, as well as pores of variable width and length, but they have mainly focused on the consequences of nuclear deformation and rupture [2,3].
Here, we investigate the dynamics of breast cancer cells in rigid confinement on a two-dimensional platform. We address the question of how the dynamical restructuring of the filamentous actin cytoskeleton modulates cell migration through narrowing micro-constrictions, and how it changes by altering the geometry of the constrictions. The rigidity of our micro-structures offers an interesting opportunity to screen the deformability of a cell, a fundamental ability in tumor invasion.

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Poster 23

Fluid and jammed behaviour in cell spheroids

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Multicellular organisms require tissues to be able to switch from solid-like to fluid-like behaviour. In cell monolayers, the cell jamming mechanism has been found to implement such a switch. As cells have more degrees of freedom in 3D, it is not clear if these 2D results hold up in 3D.

We compare the structure and dynamics of 3D cell spheroids composed of either cells from a malignant or a non-malignant breast cancer cell line. We use fusion assays and live observation to quantify the global tissue behavior and rates of cell migration in these systems. We find that the malignant cell line is fluid-like, while the non-malignant cell line is partially jammed. Using full 3D image segmentation, we find a strong correlation between cell shape and jamming in the spheroids.

Our results show that 3D cell jamming is related to tissue architecture.

Poster 24

Dynamics of cell jamming: Disentangling the shape and density dependences

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Cellular dynamics have been shown to display characteristics of jamming transitions, which originally had been observed as a function of cell number density (Angelini et al., PNAS 2011). Recently, the Self-Propelled Voronoi (SPV) model has predicted a shape dependent and density-independent jamming transition as a result of the counter play of adhesion and contractile forces (Bi et al., Nat. Phys. 2015).

We use cell tracking combined with Voronoi tessellation of the nuclei to estimate the probability of T1 transitions and neighbourhood exchanges. Thereby, we can describe the local fluidity of a cell layer and look for the onset of cellular jamming. A moderately high density is required for epithelial-like MCF-10A cells to jam. Within this high-density regime, the correlation of fluidity and shape of the individual local cells is stronger than the correlation of fluidity and local density. Mesenchymal-like MDA-MB-231 cells stay fluid even for very high densities and never reach the round configurations that correlate to jamming for epithelial-like MCF-10A. In co-culture, both cell types demix and MDA-MB-231 cells form unjammed islands within the jammed collective of MCF-10A cells.

Poster 25

Exploring tumor heterogeneity – cancer development and invasive traits in primary carcinoma samples

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The large majority of tumor diseases become a fatal threat, once cells start to invade surrounding tissue. Whether cells developed the trait of intravasation and start to form metastases, or the tumor expands as a bulk with diffuse border into the enveloping stroma, it always marks the step from a benign neoplasm to cancer. Treatment by surgery, chemotherapy, and/or radiation therapy is urgent necessity from this point. Biochemical triggers that enable a cancerous cell to leave the primary tumor are well known. Yet the exact physical requirements are still to be pinpointed. A way to access the physical traits of aggressive cancer cells is to acknowledge the high diversity within a single neo-

plasm. Even in aggressive tumors, only a small fraction of the cells will invade surrounding tissue.

We investigate the heterogeneity of cancer in primary samples of carcinomas of the breast and the cervix, provided by the Universitätsklinikum Leipzig. To distinguish between aggressive and non-aggressive cells, known markers for cancer development are the obvious choice. One of the most fundamental and first steps of a malignant transformation in carcinomas is the epithelial to mesenchymal transition (EMT). The EMT is accompanied by a turnover of cellular adhesion, most importantly by the downregulation and deactivation of E-Cadherin (E-Cad). We dissociate living tumor tissue into single cell suspensions to examine the viscoelastic creep response in an optical stretching device. Additional fluorescent staining of E-Cad in the measured cells gives an individualized correlation between progress of the EMT and single cell mechanical behavior. By evaluating not only fluorescence intensity, but also the clustering of E-Cad on the cell surface, we are able to show that subpopulations of cancer cells with different progress in cancer development exist in a single tumor sample. These subpopulations differ not only in their developmental state, but more importantly show a difference in their optical deformability. The deactivation and mobilization of E-Cad in the cell membrane seems to be coupled to a softening of the cell body, as expected for cells with increased aggressiveness.

Poster 26

Collective forces of tumor spheroids in three-dimensional biopolymer networks

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In the pathological process of metastasis, cancer cells leave a primary tumor, either individually or collectively. This invasion process requires that cells exert physical forces onto the surrounding extracellular matrix. We describe a technique for quantifying the contractile forces that tumor spheroids collectively exert on highly nonlinear three-dimensional collagen networks. Building on an existing finite element approach for single-cell traction force microscopy [1], we exploit the spherical symmetry of tumor spheroids to derive a scale-invariant relation between spheroid contractility and the surrounding matrix deformations. The method thus avoids computationally expensive material simulations for the analysis of each individual measurement. Moreover, image acquisition can be done with low resolution (5x objective, NA=0.1) brightfield microscopy. For A172 and U87 glioblastoma spheroids, we find that the collective forces reflect the contractility of individual cells only during the initial contraction phase ($\lesssim$1h), but not on longer time scales. In particular, the large strains induced by the spheroids may significantly alter the mechanical environment of the invading cells, due to strain stiffening and fiber alignment, and thus alter cellular force generation at a collective level. This new assay offers a way to investigate the mechanics behind collective effects in cancer invasion that cannot be measured on a single-cell level.

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Poster 27

Friction in isotropic polymer networks

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The cytoskeleton, which dominates the main mechanical functions of the cell, is a meshwork of different biopolymers. Networks of biopolymers can be described energetically by theoretic models. The predominant

model established in the field is the tube model, which assumes the energy of an individual filament as the sum of its bending energy and its entropic interaction with the surrounding network. Recent experimental studies prompt, that the scaling relations derived from the model are incomplete, as the suggested scaling of the elastic plateau modulus is inconsistent with the experimental results. A possible explanation is, that the model does neglect significant energetic contributions.

In optical tweezers experiments the potential energetic contribution to the total energy of an individual filament by an extensibility term was excluded.

Recent publications highlighted the impact of sliding friction between polymers in an anisotropic configuration. In this project, the impact of inter-polymeric friction is investigated in isotropic network structures by comparing the mechanical properties of networks, consisting of filaments with surface modifications.

Poster 28

Reptation in semiflexible polymer networks

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Studying the mechanics and dynamics of biopolymers has inspired many ideas and theories in polymer physics. One prominent example is actin, being the best-studied semiflexible polymer. Unfortunately, naturally occurring protein-based biopolymers are limited in their properties such as length, stiffness and interaction strengths. This highlights the advantage of having "programmable" model polymers at hand, which give the opportunity to experimentally test parameters otherwise unavailable in natural systems, and therefore expand theoretical approaches.
Nanotubes formed from synthetic DNA strands are ideal model polymers: they are semiflexible over their typical length scale and can be hybridized to have characteristics such as persistence length, which are similar to actin filaments or can be varied in a controllable way. Additionally, DNA nanotubes are extremely stable, making them both favorable for polymer physics experiments and material science applications. We use this model system to directly visualize the dynamics of tracer filaments in semiflexible polymer networks. The results can be used to measure the networks' tube width and mesh size. Furthermore, reptation analysis with our „programmable" filaments enables the test of central assumptions and predictions from the theory of semiflexible polymer networks.

Poster 29

Cortical Actin Contractility of Single Suspended Cells

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Up to now cellular contractility was seen basically as a force dipole requiring adhesion sites and actin stress fibers, mainly necessary during cell migration. In this study, we investigate suspended cells regarding active contractility, lacking stress fibers and adhesion points. Epithelial cells assemble a strong acto-myosin cortex providing pretension forming round cell shape, and exhibiting more contractile behavior during long optical stretcher observation. Cell contractility needs a short mechanical impulse to induce acto-myosin contraction of the cell cortex. Then we explore active cell contraction even below initial cell elongation. We'll focus on how these findings correlate to different migratory and jamming behavior in healthy and mesenchymal cell clusters.

Poster 30

Microenvironmental mechanics contribute to glioblastoma cell behaviour

Katarzyna Pogoda[1], Paul Janmey[2]

[1] Institute of Nuclear Physics Polish Academy of Sciences, Krakow, Poland

[2] University of Pennsylvania, Philadelphia, PA, USA

Glioblastomas (GBM) are diffuse and highly invasive tumors that originate in brain and make up about 50% of all primary brain and CNS tumors. Unlike solid tumors glioblastomas are characterized by high intra-tumor heterogeneity and consist of regions with multiple

subpopulations of the cells with various extracellular matrix compositions that support development of resistance to radiation and chemotherapy. GBM possess unique soft matter properties, which discriminate them from other soft tissue-derived tumors with relatively low content of fibrous proteins even in high grade tumors. Moreover, the boundary between tumor and normal tissue is not sharp, and single glioma cells rapidly infiltrate different brain regions and proliferate, which leads to recurrence after surgical resection of the primary tumor [1]. For this reason, one of the central therapeutic goals is to limit cell migration and division, and thereby identify molecular regulators of GBM cell motility and proliferation in vitro and in vivo.
Although glioblastoma development is not accompanied by increased stiffening of tumor stroma, as is observed for breast or liver cancer, single glioma cells increase in proliferation, motility and invasiveness when cultured on a soft environment [2]. Hyaluronic acid – the main glycosaminoglycan that occupies a large volume of brain ECM - can form highly hydrated matrices that mimic the stiffness and composition of brain and glioblastoma ECM if supplemented with adhesive ligands like collagen I and laminin. These matrices can be used as a cell culture platform. Single glioblastoma cells respond to the presence of crosslinked hyaluronan of stiffness comparable to human brain by changing their morphology, motility, proliferation and secretory properties similarly as they respond to substrate stiffening reported for cells grown on polyacrylamide hydrogels with different rigidities. This outcome suggests that hyaluronic acid can trigger the same cellular response as can be obtained by mechanical force transduced from a stiff environment and is a first evidence that chemical and mechanical features can induce equivalent structural reaction in cells [3].

[1] Pogoda, K., & Janmey, P. A.: Glial Tissue Mechanics and Mechanosensing by Glial Cells., Frontiers in Cellular Neuroscience (2018)

[2] Pogoda, K., Chin, L., Georges, P. C., Byfield, F. J., Bucki, R., Kim, R., … Janmey, P. A.: Compression stiffening of brain and its effect on mechanosensing by glioma cells., New Journal of Physics (2014)

[3] Pogoda, K., Bucki, R., Byfield, F. J., Cruz, K., Lee, T., Marcinkiewicz, C., & Janmey, P. A.: Soft Substrates Containing Hyaluronan Mimic the Effects of Increased Stiffness on Morphology, Motility, and Proliferation of Glioma Cells., Biomacromolecules (2017)

Poster 31

Systematic altering of semiflexible biolpolymer networks via tunable cross-linking

MARTIN GLASER[1,2], JESSICA LORENZ[2], TOM GOLDE[1], JOSEF KÄS[1], JÖRG SCHNAUß[1,2], DAVID SMITH2

[1] Leipzig University, Peter Debye Institute for Soft Matter Physics, Soft Matter Physics Division, Linnéstraße 5, Leipzig, Germany

[2] Fraunhofer Institute for Cell Therapy and Immunology, Department of Diagnostics, DNA Nanodevices Unit, Perlickstraße 1, Leipzig, Germany

The mechanical properties of complex soft matter have been subject to various experimental and theoretical studies. The underlying constituents often cannot be modeled in the classical physical frame of flexible polymers or rigid rods. Polymers in the semiflexible regime, where the finite bending stiffness leads to a non-trivial mechanical contribution, are a highly interesting subclass and can be found in the cytoskeleton of living cells. A natural occurring model system for such polymers is the protein actin.

A recent study by Lorenz et al. on synthetically crosslinked actin networks has attracted great interest [1]. In order to gain a deeper understanding on the crosslinking of biopolymer networks two additional systems have been established. First, networks of the intermediate filament Vimentin have been modified by synthetic DNA-based crosslinks. Second, networks of entangled DNA nanotubes with comparable persistence length have been crosslinked, acting as a comparable, purely synthetic model system.

Also, the study will allow a deeper insight into the underlying mechanics of biomaterials, such as hydrogels, which are extensively used for in vitro as well as in vivo applications.

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Poster 32

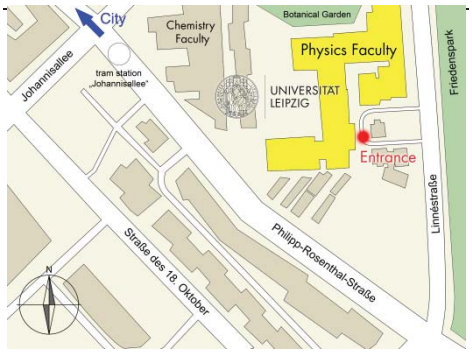
Fractional dynamics in bioscience and biomedicine and the Physics of Cancer

HOSEIN NASROLAHPOUR

Tarbiat Modares University, Tehran, Iran

Almost all phenomena and structures in nature exhibit some degrees of fractionality or fractality. Fractional calculus and fractal theory are two interrelated concepts. In this article we study the memory effects in nature and particularly in biological structures. Based on this fact that natural way to incorporate memory effects in the modeling of various phenomena and dealing with complexities is using of fractional calculus, in this article we present different examples in various branch of science from cosmology to biology and we investigate this idea that are we able to describe all of such these phenomena using the well-known and powerful tool of fractional calculus. In particular we focus on fractional calculus approach as an effective tool for better understanding of physics of living systems and organism and especially physics of cancer.

Location:
Faculty of Physics and Earth Sciences
Linnéstr. 5, 04103 Leipzig



Session IV: Vasculature

Invited Talk Wed 08:30

Search and kill - the immune response to cancer cells

HEIKO RIEGER— Saarland University, Center for Biophysics & Theoretical Physics, Campus, E2 6, 66123 Saarbrücken

Cytotoxic T lymphocytes and natural killer cells are the main cytotoxic killer cells of the human body to eliminate pathogen-infected or tumorigenic cells. Various processes are involved in a successful killing event: activation of the killer cell, migration and search for the target, formation of a synapse and polarization upon contact with the target, transport of cytotoxic agents towards the synapse, and finally elimination of the target via necrosis or apoptosis. In this talk I will review various biophysical aspects of killing that were studied theoretically in collaboration with experimental research groups. Topics include the analysis of search strategies of migrating killer cells; the mechanistic understanding of the molecular motor driven cytoskeleton rotation towards the synapse during polarization; the modulation of the intracellular calcium homoeostasis by mitochondria relocation towards the synapse; the efficiency of the spatial organization of the cytoskeleton for search problems occurring in intra-cellular cargo transport; and the analysis of different killing strategies inducing necrosis or apoptosis.

Invited Talk Wed 09:00

Probing the physiology of physical transport inside cells and developing tissues

MORITZ KREYSING — Max Planck Institute of Molecular Cell Biology and Genetics, Dresden, Center of Systems Biology, Dresden

Throughout the last decades, access to genetic perturbations, fluorescent labels and modern microscopy advanced our molecular understanding of cell-biological processes tremendously.

The spatio-temporal organization of cells, developing embryos and cancers that we observe under these microscopes is widely believed to also depend on physical processes, such as diffusion, motor-driven intracellular flows as well as cell migration. Thus far, however, it often remains a challenge to experimentally test the physiology of these physical transport processes, which is due to the lack of suitable perturbation methods.

Here, we exploit thermoviscous expansion phenomena to optically induce hydrodynamic flow in single cells and developing embryos. By controlling such flows inside the cytoplasm of the C. elegans zygote, we reveal the causal implications of intracellular flows during PAR polarization. Specifically, we show that i) hydrodynamic flows inside the cytoplasm localize PAR-2 proteins at the posterior membrane and drive cell polarization. ii) Induced cortical flows transporte membrane-bound PAR molecules and rotate the membrane polarization, leading to iii) the down-stream phenotype of an inverted body axis.

Furthermore, we utilize flow perturbations for probe-free active micro-rheology of the cytoplasm. From here, I discuss challenges and opportunities how to leverage cancer research by next generation, interactive imaging. In particular we discuss how optically generated extracellular flows could compensate for a lack of vascularization in tumor spheroids, and how to overcome the problem of tissue-induced light scattering, which currently precludes live imaging deep inside cancers.

[1] Mittasch *et al.*, Nat Cell Biol 20 (2018)

[2] Kruse, Chiaruttini, and Roux, Nat Cell Biol 20 (2018)

[3] Weigert *et al.*, PLOS Comp Bio 14 (2018)

Invited Talk Wed 09:30

Mechanisms of cellular penetration of vascular basement membranes - how biophysics could help us better understand this process

Abstracts

XUELI ZHANG, HUIYU WANG, JIAN SONG, LYDIA SOROKIN — University of Muenster, Institute of Physiological Chemistry and Pathobiochemistry, Waldeyerstraße 15 48149 Münster, Germany

While considerable information is available on how leukocytes navigate through the loose interstitial matrix of the stroma of tissues, comparatively little is known about penetration of basement membranes (BMs), tight protein networks that separate tissue compartments and designed to limit the movement of both cells and soluble molecules. In vivo imaging in our laboratory has revealed that penetration of the endothelial BM represents the time limiting step in extravasation, taking up to 40 min compared to the 3-4 min required to penetrate the endothelial monolayer. We have shown that the laminins, integral BMs components, play a critical role in this step. Endothelial BMs of postcapillary venules show ubiquitous distribution of laminin 411 (composed of $\alpha4\beta1\gamma1$ chains) and patchy distribution of laminin 511 ($\alpha5\beta1\gamma1$). In vivo inflammatory models involving T lymphocytes and neutrophils, indicate that sites containing little or no laminin 511 are the preferred sites of leukocyte extravasation. In vitro studies have shown that laminin 511 is highly adhesive for both neutrophils and T cells and inhibits migration in particular of T cells. Laminin 511 is known to self assemble into a 2D network, while laminin 411 has compromised networking ability due to truncated C-terminal domains. Preliminary work from our lab suggests that such structural differences result in differences in BM flexibility. Ex vivo analyses of intact BMs isolated from laminin ï¡4 knockout mice (Lama4-/-) and endothelial specific laminin ï¡5 knockout mice (Tie2cre/Lama5-/-) show that the presence of laminin 511 decreases BM flexibility, raising the possibility that the laminins may also contribute to mechanical signals transduced to leukocytes during extravasation. We are currently addressing this possibility using in vitro microchannel experiments that aim at mimicking the physical constraints that leukocytes undergo during migration across BMs and permit distinction between molecular versus mechanical signals.

Contributed Talk Wed 10:00

Loss of vimentin increases motility and nuclear damage in confined spaces

ALISON PATTESON[1,2], KATARZYNA POGODA[3], PAUL JANMEY[1] —

[1] Institute for Medicine and Engineering, University of Pennsylvania, 3340 Smith Walk, Philadelphia, USA

[2] Department of Physics, Syracuse University, 229C Physics Building, Syracuse, USA

[3] Institute of Nuclear Physics, Polish Academy of Sciences, PL-31342 Krakow, Poland

The migration of cells through tight constricting spaces or along fibrous tracks in tissues is important for biological processes, such as embryogenesis, wound healing, and cancer metastasis, and depends on the mechanical properties of the cytoskeleton. Migratory cells often express and upregulate the intermediate filament protein vimentin. The viscoelasticity of vimentin networks in shear deformation has been documented, but its role in motility is largely unexplored. We studied the effects of vimentin on cell motility and nuclear damage using mouse embryo fibroblasts derived from wild-type and vimentin-null mice. We find that loss of vimentin increases motility in confining environments, such as micro-fluidic channels and collagen matrices, that mimic interstitial spaces in tissues. Loss of vimentin leads to accumulated nuclear damage, in the form of blebs, nuclear envelope rupture, and enhanced DNA damage, which accompanies the migration of cells through small pores. Atomic force microscopy measurements reveal that the presence of vimentin enhances the perinuclear stiffness of the cell, to an extent that depends on surface ligand presentation and therefore signaling from extracellular matrix receptors. Together, our findings indicate that vimentin hinders three-dimensional motility by providing mechanical resistance against large strains and thereby protects the structural integrity of the cell and the nucleus. Reference: https://doi.org/10.1101/371047

Session V: Tissue Organization

Invited Talk Wed 10:45

Ratchetaxis and cytokinesis

DANIEL RIVELINE – IGBMC - CNRS UMR 7104 - Inserm U 1258, 1 rue Laurent Fries / BP 10142 / 67404 Illkirch CEDEX / France

I will present two cell physics phenomena and their characterisations using cell biology, microfabrication, and theory.

Ratchetaxis : Directed cell migration is usually thought to depend on the presence of long-range gradients of either chemoattractants or physical properties such as stiffnessor adhesion. However, in vivo, chemical or mechanical gradients have not systematically been observed. I will report a new type of motility, ratchetaxis, or how local and periodic external cues can direct cell motion.

Cytokinesis : The cytokinetic ring is essential for separating cells during division, but its acto-myosin organisation is still unknown. I will show that the internal structure and dynamics of rings are different from sarcomeres and distinct in different cell types. Using microcavities to orient rings in single focal planes, we found in mammalian cells a transition from a homogeneous distribution to a periodic pattern of myosin clusters at the onset of constriction. In contrast, in fission yeast, myosin clusters rotate prior to and during constriction. Thus, self-organisation under different conditions may be a generic feature for regulating morphogenesis in vivo.

Invited Talk Wed 11:15

PC3-epi prostate cancer cells become polyploid, resistant and mesenchymal on a docetaxel gradient

BOB AUSTIN — Princeton University, Physics Department, Princeton, New Jersey 08544, USA

The ability of a population of prostate PC3-epi cancer cells to become resistant to docetaxel therapy and progress to the mesenchymal state remains a fundamental problem, consisting of several steps which we do not understandwell. These steps occur as movements of generalized cell genotypes and phenotypes over a landscape of the tumor's ecological complexity. Utilizing a microfluidic stress landscape, we observe several of these steps: (1) the emergence of polyploid giant cancer cells (PGCCs) that appear to be important mediators of resistance in response to chemotherapeutic stress ; (2) transition from the epithelial to the mesenchymal state. PC3-epi human prostate cancer cells were exposed to a chemotherapy (docetaxel) gradient and population dynamics as well as morphological and phenotypic variations were monitored as a function of stress, time and space over the stress landscape. In the highest chemotherapy concentration regions, the PGCCs were the primary survivors and replenished by possibly altruistic cells from lower drug regions. The survival of PC3 population in the docetaxel gradient increased compared with the control experiments done in separate wells with corresponding fixed docetaxel concentration. The cell density of PGCCs in docetaxel gradient was also enriched at higher docetaxel concentrations in contrast to that of the control experiments. We argue that when the population was granted the opportunity to migrate in the chemotherapeutic stress landscape, which is a recapitulation of a heterogeneous environment in a tumor, the coexistence of the emerging drug-resistance PGCCs and the possibly altruistic proliferative diploid cells may serve as a survival strategy for the cancer population.

Invited Talk Wed 11:45

Different modes of fluidization in Human Bronchial Epithelial Cells -- the Unjamming Transition vs. the Epithelial-Mesenchymal Transition

DAPENG BI — Northeastern University, Dept. of Physics, College of Science, Dana Research Center 110 Forsyth St. Boston, MA 02115, USA

Epithelial tissues form the lining of every organ surface and cavity in our body. In these tissues the cells are largely confluent with strong apico-basal polarity. They remain non-migratory under homeostatic conditions which has been compared with a jammed system in

recent literature. Using a culture of human lung epithelial tissue we compare a newly discovered mode of fluidization of jammed cells – the unjamming transition (UJT) – with the canonical epithelial-mesenchymal transition (EMT). We show that in the UJT, the cells exhibit large-scale dynamic collective motion when subjected to compressive stress from apical to basal side. To induce EMT, on the other hand, we treat the cells with TGF-beta1 which makes them lose the epithelial character, disrupt the cell-cell junctions and express a host of mesenchymal markers. We show that not only the UJT proceeds without expression of any of these markers, the cell-cell junctions remain intact and the cells preserve their confluent epithelial nature with only some elongation of the apical surfaces. In addition, measurements of cell shapes and cellular dynamics reveal the emergence of large and fast moving nematic swirls accompanying the UJT which are not observed during EMT. We use a dynamic vertex model (DVM) to capture the essential ingredients of these two dynamical behaviors and propose how the UJT could be an alternative route to fluidization of jammed epithelial tissues, independent of EMT. The DVM differs from previous vertex models in that edges can now become curved, tortuous and ruffled, thus reflecting the effects of forces acting on the edge locally, and their competition. These forces include cortical tension, intracellular-pressure differences, and polarized motility forces.

Contributed Talk Wed 12:15

Biomechanics of glioblastoma cells by atomic force microscopy

TOMASZ ZIELINSKI[1], JOANNA ZEMLA[1], KLAUDIA SUCHY[1], JOANNA PERA[2], MALGORZATA LEKKA[1] —

[1] Polish Academy of Sciences, Institute of Nuclear Physics, Department of Biophysical Microstructures, Radzikowskiego 152, PL-31342, Kraków, Poland

[2] Jagiellonian University, Department of Neurology, Botaniczna 3, PL-31503, Kraków, Poland

Glioblastoma is a one of most deadly cancers, thus, understanding mechanisms governing its invasion is important for the development of novel treatment approaches. Nanomechanics of living cells is one of essential cues shown to play a role in glioblastoma migration and metastasis[1], [2]. Various studies, carried so far, have shown that the main structure responsible for mechanical properties of cells is a cytoskeleton, in particular, actin filaments [3], [4].

In our studies, we focused on nanomechanical properties of glioblastoma cells in relation to changes induced in actin filament organization upon cytochalasin D treatment. Two cell lines with distinct morphologies were chosen, namely, U118 and U138 possessing fibroblast and keratinocyte-like characteristics, respectively. Elastic properties of cells (quantified through the Young's modulus, [4]) and F-actin organization in cells were obtained by applying atomic force and fluorescence microscopes. Results identify that these glioblastoma response to cytochalasin D (5μg/ml) in a time(dose)-dependent manner resulted in both softening and stiffening of cells. Fibroblasts-like cells (U118) increase their deformability (Young's modulus decreases) after 10 minutes of cytochalasin D incubation. As Young's modulus decreases for all probed indentations (from 200 nm to 800 nm), softening of cells, we can postulate that cytochalasin D re-organization proceeds within a whole actin filament network. Keratinocyte-like U138 cells respond differently. For the same incubation time, there was no changes in elastic properties while increasing the time of cytochalasin D exposure to 30 minutes induced stiffening of these cells. They become more rigid within a whole indentation depth. These finding are analogous to that recently published showing pronounced effect of cytochalasin D on fibroblasts and no effect for keratinocytes [5]. Summarizing, the fact that U118 glioblastoma cells are stiffer than U138 ones can be explained by well-differentiated network of actin filaments with the presence of stress fibres in U118 and lack of them in U138. Exposure to cytochalasin D shows that elastic properties of fibroblast-like U118 are govern by actin filaments while their role in deformability of U138 is less significant.

[1] K.Pogoda, L.K. Chin, P. C Georges, F.R. J Byfield, R. Bucki, R. Kim, M. Weaver, R. G Wells, C. Marcinkiewicz and P. A Janmey: Compression stiffening of brain and its effect on mechanosensing by glioma cells, New Journal of Physics, 16 075002 (2014)

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[4] Cai X, Xing X, Cai J, Chen Q, Wu S, Huang F: Connection between biomechanics and cytoskeletal structure of lymphocyte and Jurkat cells: An AFM study, Micron 41(3) 257-262 (2010)

[5] Orzechowska B, Pabijan J, Wiltowska-Zuber J, ZemÅ‚a J, Lekka M.: Fibroblasts change spreading capability and mechanical properties in a direct interaction with keratinocytes in conditions mimicking wound healing, J. Biomech. 74 134-142 (2018)

Abstracts

Session VI: Cancer and Embryology

Invited Talk Wed 13:30

Cancer resection within morphogenetic fields

BENJAMIN WOLF — Leipzig University Medical Center, Department of Obstetrics and Gynecology

Wide tumour excision – i.e. the resection of a malignant neoplasm with a metrically defined circumferential margin of healthy tissue – is currently the standard approach to the surgical treatment of solid cancers including carcinomas of the lower genital tract. This strategy is based on the premise that tumours grow isotropically. We reviewed the local spreading patterns of 518 carcinomas of the uterine cervix. We found that some anatomical structures such as the urinary bladder and its support structures were significantly more likely to be infiltrated by cervical cancer than other structures such as the ureter or the rectum with its support structures. Computational tumour spread models assuming isotropic growth could not explain these infiltration patterns. Introducing ontogenetic tissue properties as an additional parameter led to accurate prediction of the clinically observed tissue specific infiltration likelihoods. The prevailing assumption of isotropic tumour extension has significant shortcomings in the case of cervical cancer. Rather, cervical cancer spread seems to follow ontogenetically defined trajectories and cancer resection strategies should be adapted to these findings. Orthotopic tumour transplantation experiments can be used to investigate the mechanistic causes of these ontogenetically determined growth patterns.

Invited Talk Wed 14:00

Coordination of tissue growth by cell mechanics

MARYAM ALIEE – Friedrich-August University Erlangen-Nuremberg, Germany, Nägelsbachstraße 49b, 91054 Erlangen, Germany

Living organisms represent fascinating and precise structures. It is still a big challenge to understand the mechanisms though which cells interact with each other and the environment to form reproducible patterns. We study the challenge of tissue growth with the help of a theoretical model. We develop a continuum model to take into account cell mechanics and growth to study dynamics of tissues. We consider balance of cell number and forces for viscoelastic materials modified by active terms coming from cell division and apoptosis. We solve the equations with analytical and numerical methods. I will present the solutions of these equations for two specific cases. First, I use these equations to understand the nontrivial characteristics of growth of a colony of MDCK cells. In particular, we study the differentiation of the tissue into a dense immobile region surrounded by a moving edge. We also discuss the circumstances under which the accelerating colony border is reproduced.

In the second part, I use this approach to study the case where two cell populations with different homeostatic pressure are separated by an interface. The difference in the homeostatic pressures of two cell types drives the propagation of the interface, corresponding to the invasion of one cell type into the other. The dynamics of the system is described by a generalized version of the Fisher wave equation, which takes into account the coupling between cell number balance and tissue mechanics.

Invited Talk Wed 14:30

WHY CANCER TREATMENT CAN BACKFIRE - From non-linear dynamics to single-cell transcriptomics of cell state transitions to preclinical studiest

SUI HUANG — Institute for Systems Biology,, 401 Terry Avenue North Seattle, WA 98109-5263, USA

The near universally rapid development of therapy resistance in cancers is driven by a treatment-induced cell state transition, from a drug-sensitive to a resilient, stem-cell-like state. This non-genetic active adaptation wins time for the cells before the ensuing slower process of Darwinian selection of cells that "happen" to carry resistance-conferring mutations. The basis of this quasi-discrete drug-induced phenotype switch is a transition from one stable, high-dimensional attractor state (in gene expression state space) into another attractor. We

found that this process is not just a "jump" between attractor states but requires the destabilization of the original attractor as a consequence of which the cancer cells overcome the decreased "energy barrier" and enter the new attractor state that encodes the gene expression profile conferring a resistant, stem-like phenotype. Thus, we propose that in general, a cell state transition between stable attractors rather is a bifurcation event, and therefore, is observable as a critical transition characterized by passage through instability ("regime shift"). In the talk I will show single-cell resolution gene expression profile measurements in cell populations undergoing such cell state transitions. The data is consistent with two predictions: (i) appearance of a new kind of high-dimensional "Early Warning Signals" that precede critical transitions and can be detected in snapshot measurements and (ii) the emergence of "rebellious cells". The latter are cells that due to the multi-attractor nature of the epigenetic landscape and the inherent heterogeneity of cell populations have entered an alternative attractor instead of the one intended by the intervention. This alternative fate can be manifest as a phenotype switch in the direction opposite to the one desired after their attractor has vanished. This would explain why cancer therapy, which seeks to push tumor cells to the apoptotic state, can also generate stem-like cells in the stressed but surviving cells -the source of drug resistance. In biology terms, stress either kills or rejuvenates you. Or as Nietzsche said: "Was mich nicht umbringt, macht mich stärker". Theoretical considerations and experimental results will be presented and practical implications discussed, including on the theoretical limit, due to the inherent backfiring of therapy, of "curability" of cancer.

Contributed Talk Wed 15:00

Collective forces of tumor spheroids in three-dimensional biopolymer networks

CHRISTOPH MARK[1], THOMAS J. GRUNDY[2], DAVID BÖHRINGER[1], JULIAN STEINWACHS[1], GERALDINE M. O'NEILL[2], BEN FABRY[1] —

[1] Friedrich-Alexander University Erlangen-Nürnberg, Department of Physics, Biophysics group, Henkestr. 91, 91052 Erlangen, Germany

[2] University of Sydney, Children's Cancer Research Unit, Focal Adhesion Biology group, Cnr Hawkesbury Rd & Hainsworth St Westmead, NSW 2145, Australia

In the pathological process of metastasis, cancer cells leave a primary tumor, either individually or collectively. This invasion process requires that cells exert physical forces onto the surrounding extracellular matrix. We describe a technique for quantifying the contractile forces that tumor spheroids collectively exert on highly nonlinear three-dimensional collagen networks. Building on an existing finite element approach for single-cell traction force microscopy [1], we exploit the spherical symmetry of tumor spheroids to derive a scale-invariant relation between spheroid contractility and the surrounding matrix deformations. The method thus avoids computationally expensive material simulations for the analysis of each individual measurement. Moreover, image acquisition can be done with low resolution (5x objective, NA=0.1) brightfield microscopy. For A172 and U87 glioblastoma spheroids, we find that the collective forces reflect the contractility of individual cells only during the initial contraction phase (â‰²1h), but not on longer time scales. In particular, the large strains induced by the spheroids may significantly alter the mechanical environment of the invading cells, due to strain stiffening and fiber alignment, and thus alter cellular force generation at a collective level. This new assay offers a way to investigate the mechanics behind collective effects in cancer invasion that cannot be measured on a single-cell level.

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Abstracts

Session VI: Cancer and Embryology

Invited Talk Wed 15:45

Catch me if you can: Circulating and disseminated tumor cells in breast cancer patients

BAHRIYE AKTAS, IVONNE NEL — Universitätsklinikum Leipzig, Klinik und Poliklinik für Gynäkologie, Semmelweisstr. 14, 04103 Leipzig, Germany

Even years after successful treatment of the primary tumor about one third of breast cancer patients are suffering from metastatic relapse. One reason might be hematogenous spread during early disease stages when isolated tumor cells change their physical properties from epithelial to mesenchymal features (EMT) and become able to disseminate from the primary tumor site. After entering the lymphatic system and the blood circulation they can travel to distant organs and seed metastases. Therefore circulating tumor cells (CTCs) might be interesting and easy accessible surrogate markers to monitor disease progression and treatment response in the clinical setting. Discordant receptor status of estrogen-, progesterone and human epidermal growth factor 2 (HER2) between the primary tumor and disseminated cells might play a role regarding resistance to endocrine or targeted therapy. However, their ability to change phenotypical, mechanical as well as functional properties during cancer growth and treatment courses makes it very challenging to characterize CTCs in the blood in order to investigate their prognostic relevance.

Disseminated breast cancer cells preferentially migrate into the bone marrow where they seed micrometastases and become dormant. The so called disseminated tumor cells (DTCs) are persistent against systemic chemotherapeutic treatment due to low proliferation in this "steady state" and may cause metastatic relapse at a later stage by re-circulation into the blood system. DTCs may serve as independent prognostic markers that are associated with impaired overall and disease-free survival. Immunocytochemical detection of DTCs in bone marrow aspirates of breast cancer patients allows detailed characterization of the minimal residual disease. A very promising approach to eradicate DTCs is the use of bisphosphonates (BP). Breast cancer patients that were tested positive for DTCs could benefit from BP intake and hence better prognosis even years after first diagnosis. Based on DTC status, patients with high risk for relapse can be identified and treated accordingly.

Invited Talk Wed 16:15

Integrated optofluidic devices for cancer cell analysis and imaging

ROBERTO OSELLAME — National Research Council (CNR) - Institute for Photonics and Nanotechnologies (IFN), P.zza L. da Vinci 32, 20133 Milano - Italy

Current frontier of cellular biology is the manipulation, analysis and sorting of single cells. Populations of cells in culture and in organisms, although considered nominally identical, often present some heterogeneity that poses a severe challenge for many experimental measurements. In fact, differences among cells of the same population may unravel the complexity of many biological phenomena. Single cell analysis and sorting are powerful tools for the selection of a small group of cells of interest out of a wide and heterogeneous population, such as blood samples, cells from resected tumors or in vitro cultures; the goal of such analysis being the diagnosis of pathological disorders or the separation of specific cells for further analysis.

In recent years, considerable effort has been devoted to the development of integrated and low-cost optofluidic devices able to handle single cells. Such devices usually rely on microfluidic circuits that guarantee a controlled flow of the cells with optical radiations often exploited to probe or manipulate the cells under test. Among the different microfabrication technologies, femtosecond laser micromachining (FLM) [1] is ideally suited for this purpose as it provides the integration of both microfluidic and optical functions on the same glass chip leading to monolithic, perfectly aligned, robust and portable optofluidic devices.

Here we present some integrated optofluidic devices for cell studies, which combine microfluidic and optical technologies to implement the following functionalities in monolithic chips: mechanical phenotyping at the single

cell level by optical stretching [2]; optical sorting triggered by fluorescence signals [3] or mechanical response [4]; high-throughput 3D optical imaging by light-sheet microscopy on-chip [5].

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[3] Bragheri *et al.*: Optofluidic integrated cell sorter fabricated by femtosecond lasers, Lab Chip 12, 3779–3784 ((2012))

[4] T. Yang *et al.*: An integrated optofluidic device for single-cell sorting driven by mechanical properties, Lab Chip 15, 1262 ((2015))

[5] P. Paiè *et al.*: Selective plane illumination microscopy on a chip, Lab Chip 16, 1556-1560 ((2016))

Prospective End: 17:30

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