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General Information

Conference Venue

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

Biocity Leipzig – Leipzig University

Center for Biotechnology
and Biomedicine (BBZ)
Deutscher Platz 5
04103 Leipzig, Germany
ground floor

Antje Ferrier, BBZ (2019)

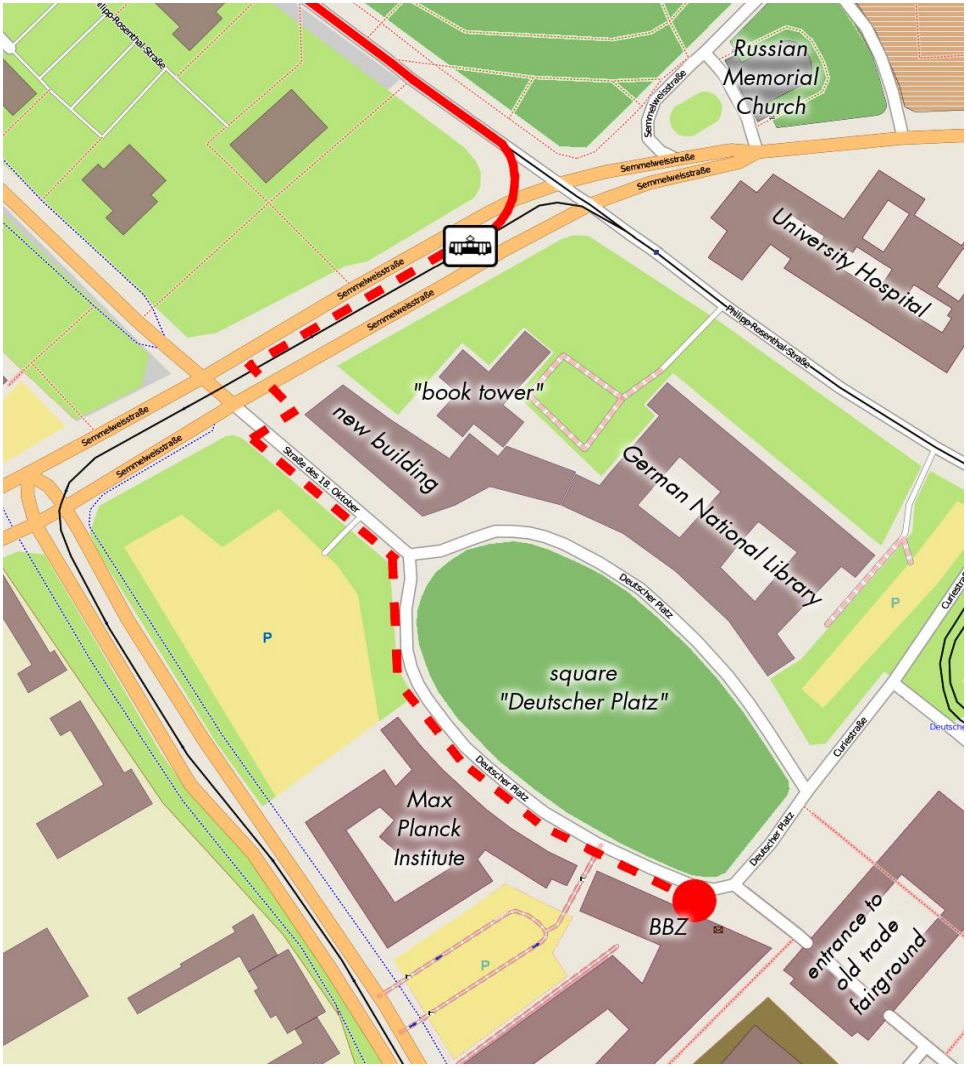
Young Scientist Awards

The three best posters will be chosen by the organizers of "Physics of Cancer" after the Poster Session on Wednesday, September 25, 2019.

They will award

- **500 EUR for best poster**
- **250 EUR each for second and third best poster!**

The Young Scientist Award is kindly funded by the **German Society for Cell Biology (DGZ)**.



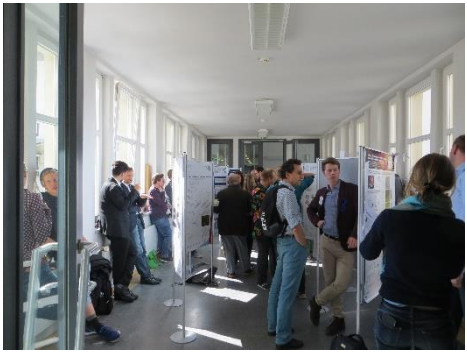
Map: *Detailed view of the area around the square "Deutscher Platz". The solid red line depicts the track of tram line 16 coming from the main train station or "Augustusplatz" (not shown in this map) to your target stop called "Deutsche Nationalbibliothek" (German National Library). The dashed red line depicts the walk from the tram stop to the conference location (BBZ). (Map source: OpenStreetMap)*

Presentations

Scientific presentations will be held either orally, i.e. talk or by poster.

Talk sessions will take place at the **lecture hall of BBZ on ground floor**.

- Contributed talks are allocated 15 min (including discussion).
- Invited talks are scheduled 20 min plus 10 min discussion.



Poster Session

The poster session will be on

Wednesday, September 25th, 2019
17:30 – 20:00
at BBZ foyer (near lecture hall).

During this session, a buffet will be provided for all to join. Poster boards will be marked with numbers according to the scientific program. Push pins for mounting will be provided. Please remove your poster until Thursday, end of scientific sessions.

In Case of Questions...

… or any queries, 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).

A G E N D A

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

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

Session 1: Cell mechanics

13:15 – 13:45 **Cell and tissue mechanics in solid tumors: Hype or progress?**
JOSEF KÄS (Leipzig University, Germany)

13:45 – 14:15 **From molecular interactions to intermediate filament mechanics**
SARAH KÖSTER (Georg-August University Göttingen, Germany)

14:15 – 14:45 **Cell mechanics and cancer dissemination**
JOCHEN GUCK (TU Dresden & MPI for Physics of Light, Erlangen, Germany)

14:45 – 15:00 **Mechanobiological control of Circular Dorsal Ruffle dynamics**
HANS-GÜNTHER DÖBEREINER (University of Bremen, Germany)

15:00 – 15:30 Coffee break

15:30 – 16:00 **3D shape transitions of active contractile sheets**
ANNE BERNHEIM (Ben Gurion University, Israel)

16:00 – 16:30 **Viscous dissipation in soft substrates affects focal adhesion formation, cell morphology, and motility**
PAUL JANMEY (University of Pennsylvania, USA)

16:30 – 17:00 **Viscoelastic properties of cell cortices – implication for cellular adhesion**
ANDREAS JANSHOFF (Georg-August University Göttingen, Germany)

17:00 – 17:15 **Tumor heterogeneity – a possible mechanical origin**
TOBIAS BÜSCHER (Forschungszentrum Jülich GmbH)

Wednesday, September 25, 2019

Poster Session with buffet dinner / Young Scientist Awards

The poster session is mainly to take place at the BBZ entrance area.

17:30 – 20:00

1 **Interaction of neuronal cells with electrode materials**
ALICE ABEND (Leipzig University, Germany)

2 **Can breast cancer cells be distinguished from blood cells by mechanical parameters? A label-free CTC detection approach**
BAHRIYE AKTAS (University Hospital Leipzig, Germany)

3 **Monitoring cancer cell cycle progression within quiescence-inducing 3D matrices**
SADRA BAKHSHANDEH (Max Planck Institute of Colloids and Interfaces, Germany)

4 **Contractile forces of tumor spheroids**
DAVID BÖHRINGER (FAU Erlangen-Nuremberg, Germany)

5 **Tumor heterogeneity – a possible mechanical origin**
TOBIAS BÜSCHER (Forschungszentrum Jülich GmbH, Germany)

6 **Entropy production, entropy generation, and fokker-planck equations for cancer cell growth**
SALVATORE CAPOTOSTO (Midwestern State University, USA)

7 **Mechanobiological control of Circular Dorsal Ruffle dynamics**
HANS-GÜNTHER DÖBEREINER (University of Bremen, Germany)

8 **Mechanics of actin-keratin composite networks**
IMAN ELBALASY (Leipzig University, Germany)

9 **Actin remodeling and intermediate filaments contribution during cancer cell migration in physical confinement**
CARLOTTA FICORELLA (Leipzig University, Germany)

10 **Using microstructured hydrogels to analyse mechanical forces of cancer cells while altering the microenvironment**
CHRISTINE FRANKE (University of Canterbury, Christchurch, New Zealand)

11 **Impact of oscillatory shear motion on cancer cell fate: Can we influence proliferation?**
MARLIES GLATZ (King´s College London, GB)

12 **Elongated cells fluidize malignant tissues**
STEFFEN GROSSER (Leipzig University, Germany)

13 **Invasion, migration and force generation of primary epithelial and mesenchymal breast cancer cells**
NADINE CLAUDIA GRUMMEL (FAU Erlangen-Nuremberg, Germany)

14 **Reptation dynamics in semiflexible polymer networks**
TINA HÄNDLER (Leipzig University, Germany)

15 **The role of stickiness in the rheology of semiflexible polymers**
KAMRAN HOSSEINI (TU Dresden, Germany)

16 **Mechnosensitivity as a driver of a non-equilibrium phase transition in model epithelium**
MAXIME HUBERT (FAU Erlangen-Nuremberg, Germany)

17 **Development of microtentacles in suspended cells upon weakening of the actin cortex**
LUCINA KAINKA (Saarland University & Leibniz Institut for New Materials, Germany)

18 **Strategies for Individual and Collective Cell Migration by Heterogeneous Cell Populations during Cancer Metastasis**
PARAG KATIRA (San Diego State University, USA)

19 **Collective motion promotes multi-step drug resistance evolution in dense cellular populations**
JONA KAYSER (University of California, Berkeley, USA)

20 **The integrin beta4-keratin link impairs mechanosensing by protecting the nucleus form mechanical loading**
JENNY Z. KECHAGIA (Institute for Bioengineering of Catalonia (IBEC), Spain)

21 **Active folding of epithelial shells**
DIANA KHOROMSKAIA (The Francis Crick Institute, GB)

22 **Cell morpho-rheological properties in microcirculation**
MARTIN KRÄTER (Max Planck Institute for the Science of Light & Max-Planck-Zentrum für Physik und Medizin)

23 **Roadmap to local tumour growth: Insights from cervical cancer**
HANS KUBITSCHKE (Leipzig University, Germany)

24 **Kinetics of cell jamming**
JÜRGEN LIPPOLDT (Leipzig University, Germany)

25 **Cooperativity between multiple types of receptor-ligand bonds in membrane adhesion**
LONG LI (FAU Erlangen-Nuremberg, Germany)

26 **Cell shape during cellular fate transitions**
WOLFRAM PÖNISCH (University of Cambridge, GB)

27 **Cell size pleomorphism drives aberrant clone dispersal in proliferating epithelia**
SUBRAMANIAN P. RAMANATHAN (Stowers Institute for Medical Research, USA)

28 **Modeling co-evolution of mechanically heterogeneous cell populations**
GUDUR ASHRITH REDDY (San Diego State University, USA)

29 **Multiscale modeling of tumor development**
JAKOB ROSENBAUER (Forschungszentrum Jülich GmbH, Germany)

30 **The Physics of Carcinomas: A multi-scale analysis on primary tumor tissues**
FRANK SAUER (Leipzig University, Germany)

31 **Systematic altering of semiflexible biolpolymer networks via tunable cross-linking**
JANA SIEVERS (Leibniz Institute of Polymer Research Dresden & Max Planck Institute of Colloids and Interfaces, Germany)

32 **MITF-mediated changes of tumour architecture, tensile stress and in extracellular matrix (ECM) control intratumour heterogeneity in melanoma models**
LOREDANA SPOERRI (University of Queensland, Brisbane, Australia)

33 **MD Modeling of YAP Mechanosensing in Cancer Progression**
TOM STADTMÜLLER (University of Groningen, The Netherlands)

34 **Flush and trap: microfluidic chips allow single cell analysis of breast cancer cell cycle progression**
HUBERT M. TAIEB (Max Planck Institute of Colloids and Interfaces, Potsdam, Germany)

35 **Vinculin regulates lamellipodium protrusion velocity**
INGO THIEVESSEN (FAU Erlangen-Nuremberg, Germany)

36 **Classification of breast cancer and peripheral blood mononuclear cells by machine learning mechanical parameters**
DIMITRIJ TSCHODU (Leipzig University, Germany)

37 **Better, faster, stronger: a new era of measuring cell mechanics and why we should care about strain rates**
MARTA URBANSKA (TU Dresden, Germany)

Session 2: Cancer cells and tumors in mechanical confinement

09:00 – 09:30 **Mechanical heterogeneity in tissues promote rigidity and control cellular invasion**
DAPENG BI (Northeastern University, USA)

09:30 – 10:00 **Continuum theory of tissue dynamics**
FRANK JÜLICHER (MPI for Physics of Complex Systems Dresden, Germany)

10:00 – 10:30 **3D microenvironment stiffness regulates tumor spheroid growth and mechanics via p21 and ROCK**
ANNA TAUBENBERGER (TU Dresden, Germany)

10:30 – 11:00 ***Coffee break***

11:00 – 11:30 **3D motion in cancer cells in confined space**
TIMO BETZ (University of Münster, Germany)

11:30 – 12:00 **Extracellular matrix stiffness and transforming growth factor-ß modulates pancreatic stromal cells' cytoskeletal remodeling**
ANDREAS STYLIANOU (University of Cyprus, Cyprus)

12:00 – 12:30 **The role of tissue biophysics in organ selectivity in metastasis**
KANDICE TANNER (National Cancer Institute, USA)

12:30 – 13:30 Lunch buffet

Session 3: Tumor – stroma interaction

13:30 – 14:00 **Adhesion regulated mechanotransduction in cancer**
JOHANNA IVASKA (University of Turku, Finland)

14:00 – 14:30 **Oxygen in cancer and neovascularization**
SHARON GERECHT (Johns Hopkins University, USA)

14:30 – 15:00 **Organic and inorganic ECM components as synergistic regulators of cancer mechanosignaling**
CLAUDIA FISCHBACH-TESCHL (Cornell University, USA)

15:00 – 15:30 **Fusogenic liposomes as general pass key for RNA-based approaches against cancer**
RUDOLF MERKEL (Forschungszentrum Jülich GmbH, Germany)

Session 4: Cellular mechanosensing

08:45 – 09:15 **Adhesion G protein-coupled receptors – Metabotropic force sensors that shape development and mechanosensation**
TOBIAS LANGENHAN (Leipzig University, Germany)

09:15 – 09:45 **EMT – induced cell mechanical changes enhance mitotic rounding strength**
ELISABETH FISCHER - FRIEDRICH (TU Dresden, Germany)

09:45 – 10:00 **MITF – mediated changes of tumour architecture, tensile stress and in extracellular matrix (ECM) control intratumour heterogeneity in melanoma models**
LOREDANA SPOERRI (The University of Queensland, Brisbane, Australia)

10:00 – 10:30 **Nuclear rupture at high curvature and high rates leads to defects in DNA repair to affect cell cycle, differentiation, and genome variation**
DENNIS DISCHER (University of Pennsylvania, USA)

10:30 – 11:00 ***Coffee break***

Session 5: Translational research

11:00 – 11:30 **Human tissue culture**
SONJA KALLENDRUSCH (Leipzig University, Germany)

11:30 – 12:00 **Biophysical properties of tumors in vivo**
INGOLF SACK (Charité Berlin, Germany)

12:00 – 12:15 **Collective motion promotes multi-step drug resistance evolution in dense cellular populations**
JONA KAYSER (University of California, Berkeley, USA)

12:15 – 13:30 ***Lunch break***

Session 6: Cancer cell migration

13:30 – 14:00 **Dissecting cell migration and mechanics by systematic gene editing approaches**
KLEMENS ROTTNER (Technical University Braunschweig, Germany)

14:00 – 14:30 **Mechanobiology of epithelial migration, growth and folding**
XAVIER TREPAT (IBEC, Barcelona, Spain)

14:30 – 15:00 **Collective cell migration and viscoelasticity**
IVANA PAJIC - LIJAKOVIC (University of Belgrade, Serbia)

15:00 – 15:15 **Strategies for individual and collective cell migration by heterogeneous cell populations during cancer metastasis**
PARAG KATIRA (San Diego State University, San Diego, USA)

15:15 – 15:45 ***Coffee break***

15:45 – 16:15 **Confinement induces DNA damage causes increased matrix degradation and invasiveness in duct carcinoma in situ breast cancer cells**
GUILHERME NADER (Institut Curié, France)

16:15 – 16:45 **Integrated optofluidic devices for cancer cell analysis and imaging**
NIR GOV (Weizmann Institute of Science, Israel)

16:45 – 17:15 **Vimentin provides the mechanical resilience required for amoeboid migration and protection of the nucleus**
FRANZISKA LAUTENSCHLÄGER (Saarland University, Germany)

17:30 ***Prospective end***

From 18:00 to open end: Join the final party at „Ratstonne“ in Moritzbastei Leipzig with buffet and live music!

Opening Talk Wed 13:15

Cell and tissue mechanics in solid tumors: Hype or progress?

Josef Käs – Leipzig University, Faculty of Physics and Earth Science, Linnéstr. 5, 04103 Leipzig, Germany

Since 20 years mechanical aspects have had a central role in the Physics of Cancer.

Despite that, it has currently no translational impact.

Does mechanics keep its promise?

Session 1: Cell Mechanics

Invited Talk Wed 13:45

From molecular interactions to intermediate filament mechanics

Sarah Koester - Georg August University Göttingen, Institute for X-Ray Physics, Friedrich-Hund-Platz 1, 37077 Göttingen, Germany

Intermediate filaments (IFs) represent one of the three filament networks in eukaryotic cells and as such are majorly involved in defining the mechanical properties of the cell. Two aspects make these filaments particularly interesting from a cell physics point of view: they show an interesting behaviour at high strains and they are expressed in a cell type specific manner. The latter point is particularly interesting in biological processes like the epithelial-to-mesenchymal-transition (EMT), i.e. during cancer metastasis, wound healing or development. When stationary cells transform into motile cell, they need to alter their mechanical properties, possibly driven by differential expression of IFs. Our single filament studies using optical tweezers in combination with analytical and numerical descriptions unravel the molecular origins of the force-strain behavior of IFs and provide evidence of how cell may tune their properties in order to adapt to specific requirements.

Invited Talk Wed 14:15

Cell mechanics and cancer dissemination

Jochen Guck - TU Dresden, Biotec, Tatzberg 47/49, 01307 Dresden, Germany & Max Planck Institute for the Science of Light, Staudtstraße 2, 91058 Erlangen, Germany

It is generally accepted that the mechanical properties of cancer cells are related to their ability to disseminate through the body. While the connection seems obvious, this simplistic view has to be diversified to take into account the time-dependence of cell mechanical properties in light of the mechanical challenges encountered during the different stage of the metastatic cascade. At a minimum, the journey has to be divided into two parts where cells are advected passively through the vasculature and microcirculation and where they actively migrate through tissues. I will present our latest research results related to these two aspects. Overall, the emerging view is that the mechanical properties of cancer cells constitute a possible therapeutic target to interfere with metastasis as the most fatal aspect of the disease.

Contributed Talk Wed 14:45

Mechanobiological control of Circular Dorsal Ruffle dynamics

Julia Lange[1], Erik Bernitt[1,2], Nir Gov[2], Arik Yochelis[3], Malte Ohmstede[1], Merthe Schwachenwald[1], Hans-Günther Döbereiner[1]

[1] Institut für Biophysik, Universität Bremen, Otto-Hahn-Allee 1, 28359 Bremen, Germany

[2] Department of Chemical Physics, Weizmann Institute of Science, Herzl St 234, Rehovot 76100, Israel

[3] Department of Solar Energy and Environmental Physics, Ben-Gurion University of the Negev, 849900 Midreshet Ben-Gurion, Israel.

Dynamic structures of polymerized actin play a crucial role in cellular processes. These include different kinds of actin waves in a multitude of cell types, like Dictyostelium, neutrophiles, macrophages, and fibroblasts. These actin waves are remodeling the cytoskeleton, and are instrumental for cell protrusion and migration, as well as the uptake of extracellular fluids, but their specific functions are still debated. One type of them are circular dorsal

ruffles (CDRs), actin-based ring-like membrane undulations on the dorsal cell side of fibroblasts, which emerge after growth factor stimulation, followed by a collapse after 5 to 20 minutes while forming endocytotic vesicles. [1] Because of the prompt uptake of extracellular fluids through this process, it is evident that it is used by cancer cells to gain nutrients for propagation. This process can be used as a tool to infiltrate engineered cytotoxic exosomes into cells in order to medicate cancer. A large number of macromolecules were shown to be localized in CDRs and to be crucial for CDR formation. However, to date, the detailed signaling pathway and the underlying mechanism of CDR formation including their molecular main players remain unknown. Different studies on CDRs described them as actin waves in an excitable system [2] or as wavefronts in a bistable regime [3] between two stable states of actin. However, other studies focused on the interaction between actin polymerization and the cell membrane via the interplay of curved membrane protein complexes. We investigate the mechanism underlying CDR formation. For this study, the morphology of cells is an essential effector for the dynamics of actin waves. Their complexity and dynamical remodeling pose a challenge to the comparability of data. Therefore, in this work, fibroblasts are shaped into well-defined morphologies by seeding them on disk-like adhesion patterns made of fibronectin. [1] This enables to identify long-range interactions between different CDRs combined with the influence of stochastic perturbations and thus uncovers the important role of the membrane tension in CDR dynamics. In combination with microfluidics, the response of the actin wave machinery to biochemical interference with drugs that target different parts of the actin machinery is investigated. The system allows systematical measurements of CDR velocities, periodicities and lifetimes that are performed to carry out a before/after comparison of the treated cells for examining the influence of actin, PIP3 and N-WASP. We observe a dependence of CDR velocities, periodicities and lifetimes on the total amount of actin underlining a direct regulating role of actin in CDR formation and propagation. Our data provide experimentally characterized cellular states and transitions between them in dependence on the total actin concentration. Hence, this leads to a direct measurement of trajectories in a phase space with similar characteristics like the phase diagram of wavefronts in a bistable regime of a model system. Furthermore, it is found that the actin nucleator N-WASP plays a fundamental role in CDR formation but not in CDR propagation. Numerical solutions of wavefronts in a bistable regime of a model system on an annulus domain resemble experimentally gained data, like the dependence of wavefront velocities on the total amount of actin and number of concurrently occurring wavefronts, as well as further uncover a dependence of the stimulation threshold for propagating wavefronts on the total actin concentration. The results underline the hypothesis that CDRs can be considered wavefronts between two (bi-)stable states of actin. Conceptually, we provide a detailed quantitative picture of functional dependences along trajectories in phase space.

Reference:

[1] Erik Bernitt, Cheng Gee Koh, Nir Gov, Hans-Günther Döbereiner: Dynamics of actin waves on patterned substrates: a quantitative analysis of circular dorsal ruffles, PloS one 10, 1, e0115857 (2015)

[2] Erik Bernitt, Hans-Günther Döbereiner: Spatiotemporal Patterns of Noise-Driven Confined Actin Waves in Living Cells, Physical Review Letters 118, 4, 048102 (2017)

[3] Erik Bernitt, Hans-Günther Döbereiner, Nir S Gov, Arik Yochelis: Fronts and waves of actin polymerization in a bistability-based mechanism of circular dorsal ruffles, Nature Communications 8, 15863 (2017)

Invited Talk Wed 15:30

3D shape transitions of active contractile sheets

ANNE BERNHEIM - Bernheim Lab, Chemical Engineering Department, Ben-Gurion University of the Negev, Yitzhack I. Rager Blvd, 84105, Be'er Sheva Israel

Shape transitions in developing organisms can be driven by active stresses, notably, active contractility generated by myosin motors. The mechanisms generating tissue folding are typically studied in epithelia. There, the interaction between cells is also coupled to an elastic substrate, presenting a major difficulty for studying contraction induced folding. Here we study the contraction and buckling of active, initially homogeneous, thin elastic actomyosin networks isolated from bounding surfaces. The network behaves as a poroelastic material, where a flow of fluid is generated during contraction. Contraction starts at the system boundaries, proceeds into the bulk, and

eventually leads to spontaneous buckling of the sheet at the periphery. The buckling instability resulted from system self-organization and from the spontaneous emergence of density gradients driven by the active contractility. Our system offers a well-controlled way to study mechanically induced, spontaneous shape transitions in active matter (Ideses Nat. Comm. 2018).

Invited Talk Wed 16:00

Viscous dissipation in soft substrates affects focal adhesion formation, cell morphology, and motility

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

Hydrogels made from polyacrylamide or other cross-linked flexible polymers are increasingly used to study the response of cells to substrate stiffness. These gels are also purely and linearly elastic, which simplifies computation of cell traction forces. Real tissues, however, are often viscoelastic solids, and have loss moduli that are 10 to 20% of their elastic moduli at time scales of seconds, at which cells respond to physical signals. We have recently synthesized soft viscoelastic solids in which the elastic and viscous moduli can be independently tuned to produce gels with viscoelastic properties that more closely resemble those of soft tissues. Studies of multiple cell types, including fibroblasts, mesenchymal stem cells, and a number of different cancer cell lines show that the cellular response to viscous dissipation within the substrate is an important aspect of cellular mechanoresponse, for which the signaling pathways are only beginning to be identified.

Invited Talk Wed 16:30

Viscoelastic properties of cell cortices - implications for cellular adhesion

ANDREAS JANSHOFF— Institute of Physical Chemistry, University of Göttingen, Germany

Cellular mechanics and adhesion are two related properties that need to be balanced in order to permit cells to migrate on suitably functionalized substrates dieplaying a compatible surface chemistry. Therefore, organisms that cope with varying environmental surface cues require an adaptive strategy to survive under different conditions. We found that the model organism Dictyostelium discoideum faces the challenge of coping with hightly variable chemistry in the search of food. Employing AFM-based single cell force spectroscopy we could show that experimental force curves upon retraction of cells from the surface exhibit two regimes. The first part up to the maximum adhesion force can be described in terms of a continuum model that permits to relate the mechanical properties of cells to their capability to adhere onto a wide variety of substrates, while the second regime of the curve beyond the critical rupture force is governed by stochastic unbinding of individual binding partners and bond clusters extending the life time of the bonded state. .This versatile adhesion mechanism, which works on almost all surface chemistries, allows the cells to adapt to a large variety of natural surfaces and conditions.

In order to relate the viscoelastic properties found for living cells to the mechanics of the cellular cortex we devised a top-down and bottom-up strategy to measure the viscoelasticity of isolated cortices. Our findings go hand in hand with a theoretical model to unify the different geometries encountered in experiments.

Contributed Talk Wed 17:00

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

TOBIAS BÜSCHER, NIRMALENDU GANAI, GERHARD GOMPPER, JENS ELGETI - Forschungszentrum Jülich GmbH, Germany

[1] Basan et al., Phys. Biol. 8, 026014 (2011
[2] Podewitz et al., EPL 109, 58005 (2016)
[3] Podewitz et al., New J. Physics 18, 083020 (2016)
[4] Ganai et al., New J. Physics, 21, 063017 (2019)

Tumor heterogeneity, the observation that tumors consist of many different populations of cells, is inconsistent with a simple mechanical picture of growth and competition. The simplest mechanical model of growth assumes a linear coupling between growth and pressure – the homeostatic pressure approach. This approach predicts that in a competition between different tissues for space the one with the highest homeostatic pressure wins [1,2,3]. However, if always the stronger tissue outcompetes the weaker one, only one cell type should be observable. Furthermore, the homeostatic pressure approach predicts a critical radius, below which micro-tumors get eliminated

by Laplace pressure and above which they grow indefinitely. However, microscopic tumors are widely observed. Using particle based computer simulations we show how stable coexistence between such a microscopic tumor and the host can arise, even when the tumor has a lower homeostatic pressure [4]. Small adhesion between them leads to an enhanced growth rate at the interface, which in turn stabilizes coexistence. Interestingly, even when the adhesion is increased, coexistence can still be found, given the right adhesive properties of tumor and host.Starting from there, we employ a dynamic setup in which cells can mutate and change their mechanical properties dynamically. Given a tradeoff between a change in growth strength and adhesion, we find a mechanical explanation how intra-tumor heterogeneity between many subpopulations may arise.

Poster Session /
Young Scientist Awards

(17:30, at Foyer outside lecture hall in BBZ)

Poster Session

Poster 1

Interaction of neuronal cells with electrode materials

Alice Abend, Chelsie Steele, Mareike Zink— Leipzig University, Peter Debye Institute for Soft Matter Physics, Junior Research Group Biotechnology and Biomedicine, Linéstraße 5, 04103 Leipzig, Germany

The interaction of cells with artificial biomaterials in terms of adhesion, proliferation and many other biological functions are crucial for biomaterial performance and their application in vivo and in vitro. In fact, stimulation of neuronal cells with neuroelectrodes is already employed for medical treatment of different diseases (e.g. epilepsy and Parkinson's disease) as well as for in vitro measurements with multielectrode arrays in lab-on-a-chip designs [1]. We investigate the neuronal cells' adhesion dynamics, bioactivity as well as network formation on custom-made electrode materials. The human glioblastoma cell line U87-MG, as well as the human neuroblastoma cell line SH-SY5Y, are used in the experiments as glia-like and neuronal-like cells, respectively. The employed electrode materials are gold (Au), indium tin oxide (ITO), titanium nitride with and without nanocolumnar surface patterning (TiN nano, TiN) and the photoresist SU-8.

[1] M. Eichler, HG. Jahnke, D. Krinke, A. Müller, S. Schmidt, R. Azendorf, AA. Robitzki: A novel 96-well multielectrode array based impedimetric monitoring platform for comparative drug efficacy analysis on 2D and 3D brain tumor cultures, Biosensors and Bioelectronics (67, 582-589) (2015)

Poster 2

Can breast cancer cells be distinguished from blood cells by mechanical parameters? A label-free CTC detection approach

Ivonne Nel[1], Erik W Morawetz[2], Josef A Käs[2], Bahriye Aktas[1]

[1] University of Leipzig, Medical Center, Dept. of Gynaecology, Leipzig, Germany

[2] Soft Matter Physics Division, Peter-Debye-Institute Leipzig, Leipzig, Germany

Background: 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, 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.
Methods: One approach might be CTC detection based on mechanical properties such as deformability and stiffness. In an optical rheometer, cells are deformed non-invasively by a dual beam trap. Thus, the softness of a single cell can be measured while phase contrast and fluorescent images can be obtained. For proof of premise we used peripheral blood mononuclear cells (PBMC) isolated from a healthy donor. To mimic CTC samples, PBMCs were spiked with human GFP-expressing MDA-MB 231 cells as a model for breast cancer cells. For translational experiments a blood sample was collected from a breast cancer patient at primary diagnoses. Hematopoietic cells were depleted using CD45. The cell suspensions were applied to the optical stretcher and rheological parameters were measured. Phase contrast images of potentially interesting cells were analyzed manually to eliminate dead cells and to identify possible CTC candidates.
Results: Distinct cellular profiles could be obtained from hematopoetic cells and breast cancer cells, respectively. Relative deformation was significantly different between both cell types. Furthermore, 10:1 mixtures of PBMC and MDA-MB 231 cells could be sorted into subpopulations of significantly different cellular stiffness. Analysis of the patient sample revealed that relative deformation curves of viable CTC candidates were clearly very different from healthy PBMC. CTC candidates were much softer compared to PBMC.
Conclusion: Together with morphology and cell size, the deformation pattern indicated that at least 2 candidates appeared to be true CTCs. Further experiments for usability testing of the optical stretcher in order to detect CTCs in the peripheral blood of breast cancer patients are currently ongoing.

Poster 3

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

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Outgrowth of tumor cells disseminated to secondary organs might not occur instantly, with recurrences ranging from years to decades, suggesting that a number of these cells might go into a state of dormancy. It has long been accepted that soluble biochemical signals might orchestrate such events; nonetheless, increasing evidence also points towards the role of biophysical cues. In this regard, the physicochemical properties of the extracellular matrix (ECM), as the context-provider of the metastatic niche, have been shown to deeply affect cancer cell proliferation. Classical 3D biomaterials meant to replicate such interactions, such as Matrigel, collagen or native ECMs, are often poorly defined and/or do not allow the decoupling of adhesion and mechanical properties.

In contrast, the biocompatibility and inertness of alginate-based biomaterials allow for specific and modular functionalization of 3D cultures. Norbornene-modified alginate in particular, was crosslinked with dithiothreitol and functionalized with the thiol-coupled cell adhesion peptide RGD via UV-mediated thiol-ene chemistry, resulting in covalent and non-degradable hydrogels with tunable mechanical properties. To visualize and quantify the cell cycle state in real time, the human breast cancer cell line MDA-MB-231 was genetically modified with fluorescence ubiquitination cell cycle indicator-2 (FUCCI-2) through lentiviral transduction, displaying the G1 phase in red (mCherry) and S/G2/M phase in green (mVenus), while cells in the G0 phase remain colorless.

Unlike in Matrigel, cells encapsulated within alginate hydrogels were restricted in migration and proliferation with no detectable metabolic activity, resembling a quiescent state. Monitoring single-cell cycle progression over a period of 5 days within physically confined non-degradable 3D matrices of varying stiffness and w/o RGD, pointed towards a significantly higher percentage of surviving cells with initial cell cycle state G0/G1 vs. S/G2/M. Current work involves morphological characterization of the surviving cells by means of FIB/SEM and TEM, coupled with their phenotypic and molecular profiling.

Poster 4

Contractile forces of tumor spheroids

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We developed a technique to measure the contractile forces that tumor spheroids exert on 3D collagen matrices. Traditionally, traction force microscopy computes contractile forces from the matrix deformations surrounding adherent cells. For non-linear matrices such as collagen networks, the computational algorithm requires regularization and is currently possible only with time-consuming finite-element simulations. In the case of tumor spheroids, however, their spherical geometry can be exploited to greatly simplify the problem. In particular, we find a scale-invariant relationship between spheroid radius and matrix deformation amplitude that allows us to derive a look-up table of spheroid contractility as a function of the radially decaying matrix deformations. For spheroids with low contractility, matrix deformations decay with increasing distance to the spheroid center according to a power law with an exponent of −2, as ex-

pected for a linear elastic material. With increasing contractile forces, however, the deformations close to the spheroid decay more slowly, with an power law exponent of -0.2 near the spheroid surface, indicating long-range force transmission due to the stiffening of collagen fibers. Far from the spheroid surface, however, the deformations again decay with radius according to an exponent of -2. This holds true also for non-spherical tumoroids and histoids so that deviations from spherical geometry do not pose a problem for our method.

With this method, we investigate primary breast cancer tumor spheroids derived from patient biopsies and observe forces that are substantially greater compared to forces of breast cancer cell lines. We observe a constant contractility per surface area, indicating that mostly cells at the outer surface contribute to collective forces. Furthermore, we observe periodic force fluctuations in primary luminal B tumor spheroids, indicating collective synchronization of traction generation across the entire spheroid.

Poster 5

Tumor Heterogeneity – a possible mechanical origin

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Tumor heterogeneity, the observation that tumors consist of many different populations of cells, is inconsistent with a simple mechanical picture of growth and competition. The simplest mechanical model of growth assumes a linear coupling between growth and pressure – the homeostatic pressure approach. This approach predicts that in a competition between different tissues for space the one with the highest homeostatic pressure wins [1,2,3]. However, if always the stronger tissue outcompetes the weaker one, only one cell type should be observable. Furthermore, the homeostatic pressure approach predicts a critical radius, below which micro-tumors get eliminated by Laplace pressure and above which they grow indefinitely. However, microscopic tumors are widely observed. Using particle based computer simulations we show how stable coexistence between such a microscopic tumor and the host can arise, even when the tumor has a lower homeostatic pressure [4]. Small adhesion between them leads to an enhanced growth rate at the interface, which in turn stabilizes coexistence. Interestingly, even when the adhesion is increased, coexistence can still be found, given the right adhesive properties of tumor and host.Starting from there, we employ a dynamic setup in which cells can mutate and change their mechanical properties dynamically. Given a tradeoff between a change in growth strength and adhesion, we find a mechanical explanation how intra-tumor heterogeneity between many subpopulations may arise.

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Poster 6

Entropy production, entropy generation, and fokker-planck equations for cancer cell growth

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It is rather difficult to understand biological systems from a physics point of view, and understanding systems such as cancer is even more challenging. There are many factors affecting the dynamics of a cancer cell, and they can be understood approximately. We can apply the principles of non-equilibrium statistical mechanics and thermodynamics to have a greater understanding of such systems. Very much like other systems, living systems also transform energy and matter during metabolism, and according to the First Law of Thermodynamics, this could be described as a capacity to transform energy in a controlled way. The properties of cancer cells are different from regular cells. Cancer is a name used for a set of malignant cells that lost control over normal growth. Cancer can be described as an open, complex, dynamic, and self-organizing system. Cancer is considered as a non-linear dynamic system, which can be explained to a good degree using techniques from non-equilibrium statistical mechanics and thermodynamics. We will also look at such a system through its entropy due to to the interaction with the environment and within the system itself. Here, we have studied the entropy generation versus

the entropy production approach, and have calculated the entropy of growth of cancer cells using Fokker-Planck equations.

Poster 7

Mechanobiological control of Circular Dorsal Ruffle dynamics

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Dynamic structures of polymerized actin play a crucial role in cellular processes. These include different kinds of actin waves in a multitude of cell types, like Dictyostelium, neutrophiles, macrophages, and fibroblasts. These actin waves are remodeling the cytoskeleton, and are instrumental for cell protrusion and migration, as well as the uptake of extracellular fluids, but their specific functions are still debated. One type of them are circular dorsal ruffles (CDRs), actin-based ring-like membrane undulations on the dorsal cell side of fibroblasts, which emerge after growth factor stimulation, followed by a collapse after 5 to 20 minutes while forming endocytotic vesicles. [1] Because of the prompt uptake of extracellular fluids through this process, it is evident that it is used by cancer cells to gain nutrients for propagation. This process can be used as a tool to infiltrate engineered cytotoxic exosomes into cells in order to medicate cancer. A large number of macromolecules were shown to be localized in CDRs and to be crucial for CDR formation. However, to date, the detailed signaling pathway and the underlying mechanism of CDR formation including their molecular main players remain unknown. Different studies on CDRs described them as actin waves in an excitable system [2] or as wavefronts in a bistable regime [3] between two stable states of actin. However, other studies focused on the interaction between actin polymerization and the cell membrane via the interplay of curved membrane protein complexes. We investigate the mechanism underlying CDR formation. For this study, the morphology of cells is an essential effector for the dynamics of actin waves. Their complexity and dynamical remodeling pose a challenge to the comparability of data. Therefore, in this work, fibroblasts are shaped into well-defined morphologies by seeding them on disk-like adhesion patterns made of fibronectin. [1] This enables to identify long-range interactions between different CDRs combined with the influence of stochastic perturbations and thus uncovers the important role of the membrane tension in CDR dynamics. In combination with microfluidics, the response of the actin wave machinery to biochemical interference with drugs that target different parts of the actin machinery is investigated. The system allows systematical measurements of CDR velocities, periodicities and lifetimes that are performed to carry out a before/after comparison of the treated cells for examining the influence of actin, PIP3 and N-WASP. We observe a dependence of CDR velocities, periodicities and lifetimes on the total amount of actin underlining a direct regulating role of actin in CDR formation and propagation. Our data provide experimentally characterized cellular states and transitions between them in dependence on the total actin concentration. Hence, this leads to a direct measurement of trajectories in a phase space with similar characteristics like the phase diagram of wavefronts in a bistable regime of a model system. Furthermore, it is found that the actin nucleator N-WASP plays a fundamental role in CDR formation but not in CDR propagation. Numerical solutions of wavefronts in a bistable regime of a model system on an annulus domain resemble experimentally gained data, like the dependence of wavefront velocities on the total amount of actin and number of concurrently occurring wavefronts, as well as further uncover a dependence of the stimulation threshold for propagating wavefronts on the total actin concentration. The results underline the hypothesis that CDRs can be considered wavefronts between two (bi-)stable states of actin. Conceptually, we provide a detailed quantitative picture of functional dependences along trajectories in phase space.

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Poster 8

Mechanics of Actin-Keratin composite networks

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How does the interplay between the individual mechanical components of the cytoskeleton give rise to the complex mechanical behaviors of living cell? It is extremely difficult to address this question due to the great complexity and dynamic nature of the cytoskeleton. In vitro reconstitution of cytoskeletal protein networks is a powerful approach to circumvent this problem. Previous studies have largely focused on reconstituting single cytoskeletal elements rather than composite systems. However the cytoskeleton is a unified system in which all components engaged in complex cross-talk and it cannot be treated as a collection of individual parts
Here we investigate, for the first time, the bulk mechanical properties of in vitro reconstituted composite networks comprised of F-actin (Act) and simple epithelial keratin (K8/K18) with varying actin:keratin ratios. We create all networks with comparable theoretical mesh sizes which is an important factor affects directly the networks mechanics, as described in [1]. We complement our rheological measurements with architectural characterization using confocal microscopy.
By systematically varying the relative ratios of actin and keratin, we find that the linear viscoelastic behavior of all composites is between that of pure actin and keratin networks in correlation with the ratio of each protein in the composite. This indicates the formation of well-integrated mixed composite networks. In the non-linear regime, addition of keratin induces strain stiffening to the non-strain stiffened actin networks even in actin-dominated composite networks. Confocal microscopy shows that, in selected assembly buffer, K8/K18 form huge dense networks with homogeneous morphology in a matter of seconds while actin forms isotropic entangled networks. In composites, actin changes the architecture of keratin networks by preventing or reducing its collapse depending on actin and keratin contents.

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Poster 9

Actin remodeling and intermediate filaments contribution during cancer cell migration in physical confinement

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The extra-cellular microenvironment has a fundamental role in tumor growth and progression, and strongly affects the migration strategies adopted by single cancer cells during metastatic invasion. In this study, we focus on the ability of mesenchymal and epithelial breast carcinoma cells to migrate through quasi-three-dimensional narrowing microstructures upon chemoattractant stimulation. We address the question of how the dynamical restructuring of the filamentous actin cytoskeleton modulates cell migration through narrowing micro-constrictions. Our findings show that both epithelial and invasive cells have the ability of easily disassemble and reorganize their cytoskeleton, in order to achieve migration through the constriction openings. Additionally, we investigate possible correlations between the migration behavior in the microstructures and the expression of vimentin and keratin intermediate filaments in our cancer cell lines.

Poster 10

Using microstructured hydrogels to analyse mechanical forces of cancer cells while altering the microenvironment

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Cells are able to sense forces and mechanical properties of the microenvironment and use mechanotransduction to translate them into biochemical signals. Furthermore cells are able to apply forces for cell migration or as a reaction on a changing microenvironment. These reaction are depending on the origin of the cell and the properties of the microenvironment like stiffness, shape and the presence of extracellular matrix proteins. In order to measure the cellular response to these changes in properties of the microenvironment we develop a 3D polymeric grid to measure lateral forces on the nanoscale by analysing the displacement of the grids side walls.

By using nanoengineering methods it is possible to fabricate a silicon mould to obtain microstructured and protein patterned polyacrylamide gels. To achieve a 5 µm deep structured silicon mould, optical lithography is used to pattern photoresist which serves as a mask for inductively coupled plasma etching. To combine structuring of silicon with a protein patterning a lift-off process is used. Therefore the surface is passivated with PLL-g-PEG polymeric brushes. By stripping off the photoresist PLL-g-PEG is removed exclusively in areas covered with photoresist. The resulting open surface spots can be functionalised with a protein backfill of collagen. The polymerisation of polyacrylamide under the processed silicon mould allows a precise and effective transfer of structures and protein patterns to the hydrogels.

Cancer cells of the ovarian cancer cell line SKOV3 can be cultured on these polyacrylamide gels, and will just attach to protein covered areas in the lower parts of the structures. The soft characteristics of the gels will enable the cells to deform the side walls. The amount of displacement can be measured under the microscope, and because of the known defined material properties, allow to calculate the force the cell applied. This method will not just show how cells can apply forces to a microenvironment they are not adhered to, but also measures lateral cellular forces in 3D without embedding the whole cell into a matrix of polymers like it is done for classical traction force measurements.

By varying the size of the protein patterns and structures of the polyacrylamide gel the number of cells in one protein covered area can be controlled from single cells, two cells to multiple cell aggregates. Additionally a reduced space exerts a passive pressure on the cells. The influence of substrate stiffness on cells can be investigated by adjusting the stiffness of the polyacrylamide gels, which can be easily tuned by the concentrations of acrylamide and the cross linker bis-acrylamide. Even the effect of extracellular matrix proteins like collagen and fibronectin on cellular forces can be determined.
This experimental setup will enable force measurements of cells in 3D and allows to investigate the influence of size, shape and protein covering on cellular responses independently.

Poster 11

Impact of oscillatory shear motion on cancer cell fate: Can we influence proliferation?

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Despite significant progress, cancer is still the second common cause of death worldwide after cardiovascular diseases.[1] One of the difficulties in treating cancer and developing new therapeutic approaches is the complexity and heterogeneity of tumours; they are considered to be a diversified conglomerate, where cancer cells act and react with their surrounding multicellular system of non-malignant cells.[2-5]

Mechanical and structural cues can influence multiple cancer hallmarks and disease progression.[6] For the most part, mechanical stress in cells is caused by tissue deformation (stretch and compression). Shear strain, however, is a mechanical deformation cells don't normally encounter.
Therefore, we investigated the impact of low-frequency oscillatory shear strain on cancer cells. Multicellular tumour spheroids were embedded into a matrix, bovine collagen type 1, and exposed to a 3h shaking treatment once every 24h. Image acquisition documented the changes/effects on growth and migration behaviour. Proteomic studies via LC-MS/MS were performed on the intermediate and high acceleration cases.The effect of oscillatory shear waves at 120h on the embedded spheroid was analysed and plotted against the measured acceleration. The effect of oscillatory shear waves at 120h on the embedded spheroid was analysed and plotted against the monitored acceleration. Low acceleration (30-40mG) showed both an increase and decrease of mother core growth due to shaking. Higher accelerations, in contrast, show a more defined outcome towards mother core growth reduction. High acceleration (>100mG) showed a 20% reduction of mother core over time in comparison to the non-shaken group. Thus, an increased acceleration triggers a higher reduction in tumour spheroid growth. Differential analysis of proteomic data showed that high acceleration impacts mitotic checkpoints whereas intermediate acceleration impacts cellular communication proteins compared with control groups.
In conclusion we tested the potential impact of oscillator shear strain on a breast cancer cell line. The results show an interference with cancer cell proliferation in a 3D environment. This opens up new opportunities for further research into shear stress as a mechanism for non- invasive cancer therapy.

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Poster 12

Elongated Cells Fluidize Malignant Tissues

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Multicellular spheroids are an active multi-particle system that serve as a tumour model. These spheroids posess fluid properties such as wetting, droplet fusion etc. But what is the microscopic base of this apparent fluidity, and are cells in them moving like particles in a liquid, or are they stuck or jammed like grains of sand in a pile?
We show that cell spheroids are densely packed at volume fractions near 100% well above jamming densities. Nonetheless, cells in a malignant sample are motile by elongating and squeezing through between other cells. A healthy sample by contrast shows cells in stable, jammed positions. We have developed a 3D segmentation with single-cell resolution and find more elongated cells in the malignant spheroid. Cell spheroids can thus switch between fluid-like and solid-like behaviour. Our findings give cell shapes and cell pleomorphism a new role in defining the state of matter of tumours.

Poster 13

Invasion, migration and force generation of primary epithelial and mesenchymal breast cancer cells

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For cancer cells, the ability to leave the primary tumor and form distant metastases is a crucial part of malignancy. To migrate, cancer cells must overcome cell-cell-contacts, break through tissue boundaries, polarize, and exert forces to the surrounding matrix. These processes are known to depend sensitively on cross-talk with other cells and the extracellular matrix, but many details are still elusive. Here, we analyse the behaviour of pure and mixed fractions of breast epithelial and mesenchymal cells (single cells and spheroids) from breast cancer patients (Luminal B or triple negative), non-cancer patients, and breast cancer cell lines (HTB20, HTB26, MDA-MB-231) as regards 2D migration, force generation, and 3D invasion behaviour in collagen gels. In general, single cells migrate less persistent and are slower in 3D collagen gels compared to 2D collagen-coated plastic. However, differences in migration speed and directionality among the various cell lines, primary tumor and non-tumor cells are uncorrelated between 2D and 3D conditions. Therefore, migration behaviour under 2D conditions are not predictive for invasion behaviour under 3D conditions. Importantly, we find that spheroids from primary mesenchymal tumor cells contract a 3D collagen gel considerably (5-fold) stronger than spheroids from tumor cell lines, whereas spheroids from primary epithelial tumor cells show only weak contractile activity. Epithelial tumor cells do not migrate from the spheroid into the surrounding collagen matrix, whereas mesenchymal tumor cells from different patients show a large range of invasive behaviour. However, the degree of invasiveness as measured by the spreading distance is not correlated with spheroid contractility. Total contractility of mixed mesenchymal/epithelial spheroids containing Luminal B primary tumor cells decreases linearly with increasing fraction of epithelial tumor cells. By contrast, contractility of mixed triple negative primary tumor spheroids show a maximum contractility at a mixing ratio of approximately 50%. Taken together, our data establish pronounced differences in the cross-talk between mesenchymal and epithelial breast cells in different breast cancer subtypes.

Poster 14

Reptation dynamics 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 entangled and crosslinked semiflexible polymer network. 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 latest predictions about the dynamics of single filaments inside entangled solutions vs. crosslinked networks.

Poster 15

EMT-induced cell mechanical changes enhance mitotic rounding strength

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To undergo mitosis successfully, animal cells need to acquire a round shape to provide space for the mitotic spindle. This mitotic rounding relies on mechanical deformation of surrounding tissue and is driven by forces emanating from actomyosin contractility. Cancer cells are able to maintain successful mitosis in mechanically challenging environments such as the increasingly crowded environment of a growing tumor, thus, suggesting an enhanced ability of mitotic rounding in cancer. Here, we show that epithelial mesenchymal transition (EMT), a hallmark of cancer progression and metastasis, gives rise to a cell-cycle dependent cell-mechanical switch and enhanced mitotic rounding strength in breast epithelial cells. Furthermore, we show that this cell-mechanical change correlates with a strong EMT-induced change in the activity of Rho GTPases RhoA and Rac1. Accordingly, we identify Rac1 as a cell-cycle dependent regulator of actin cortex mechanics. Our findings hint at a new role of EMT in successful mitotic rounding and division in mechanically confined environments such as a growing tumor.

Poster 16

Mechanosensitivity as a driver of a non-equilibrium phase transition in model epithelium

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The mechanosensitivity of cells is at the core of many biophysical processes [1], spanning from morphogenesis [2,3] to immunity [4] and cancer proliferation [5]. Yet, its role in the collective behavior of the constitutive cells and the whole tissue remains a heavily debated subject. Here we show that mechanosensitivity affects the tissue homeostatic steady state and its large-scale self-organization. Specifically, seeding MDCK-cell colonies on substrates with increasing rigidity induces a phase transition from tubular to squamous tissue as well as a dramatic change in the cell-density distributions. The homeostatic density in both structures is radically different, while surprisingly the projected two-dimensional organization remains unique. After recovering the same effects in theoretical modelling, we show that these results unequivocally relate the cellular properties and the macroscopic lengths scales in tissues mechanoresponse, an effect that could be important for understanding the pathology of living systems.

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Poster 17

Reptation dynamics in semiflexible polymer networks

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Circulating Tumor Cells (CTCs) pose a significant threat due to their role in metastasis. It has been proposed that CTCs are able to escape the blood stream and reattach to the tissue by the formation of so-called microtentacles (McTNs) [1].

McTNs are microtubule based membrane protrusions with a diameter of less than 1 μm and a length of tens of μm [2].
In CTCs the balance of the outward growing microtubule and the contractive forces of the actin cortex is disrupted [3] enabling microtubules to form these kind of protrusions. Using cytoskeletal drugs such as Latrunculin A and Y27632, which are targeting the actin cortex integrity and its contractility, we induce McTNs even in non-cancerous RPE1 cells. We investigate the presence of microtubule, actin and vimentin, which is supposed to stabilize microtubule within the McTNs [4].

We establish a statistic over the number and lengths of McTNs depending on different drug concentrations applied. Further experiments on the dynamics of McTNs, especially during retraction after drug wash-out, give a better insight in the role of individual cytoskeletal elements.
Understanding the mechanisms of the formation of McTNs may help the development of new cancer therapies targeting CTCs in the microvasculature.

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Poster 18

Strategies for Individual and Collective Cell Migration by Heterogeneous Cell Populations during Cancer Metastasis

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Analyzing cancer from a mechanics perspective leads to several paradoxical questions of interest, both from a cell proliferation and tumor growth perspective as well as cell migration and metastasis perspective. Here I will focus on two such questions regarding cell migration and metastasis – 1) Most cells in vitro undergo durotaxis – migration up a substrate/matrix stiffness gradient. However, during metastasis, cancer cells migrate out and away from the stiffer stroma/connective tissue around a tumor and into the surrounding softer regions. What allows for this negative durotactic behavior of metastatic cancer cells? 2) Metastatic sites are more likely to form when clusters of cancer cells disseminate to the secondary sites rather than individual cells. However, in a lot of cases, migratory cancer cells show at least a partial epithelial to mesenchymal transformation with a decrease in inter-cellular adhesion. How can these weakly bound cells still migrate together in a cluster to successfully colonize distant metastatic sites? Using experimental and computational approaches, we find that heterogeneity in the mechanical/biochemical phenotypes of a tumor cell population might hold the answer to both these questions.

Poster 19

Collective motion promotes multi-step drug resistance evolution in dense cellular populations

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One of the most pressing challenges in modern cancer treatment is the evolution of drug resistance. As cancer

cell populations proliferate, they can rapidly acquire mutations in their genome, some of which may render their carriers resistant to one or even multiple drugs. Recent work has yielded substantial progress in our understanding of the molecular mechanisms of resistance, revealing that many drug resistance mutations are associated with an inherent fitness cost prior to the onset of treatment. Current models of tumor expansion suggest that, consequently, these slower-growing resistant subclones should be rapidly outcompeted by faster-growing susceptible cells via purifying selection and purged from the population. However, this prediction is in stark contrast to the observed prevalence of drug resistance in the clinic.
Here, using a microbial model system of neoplastic growth, I show that the collective motion inherent to dense cellular populations, including solid tumors, can drastically boost drug resistance evolution. In addition, I present new results advocating for an intricate interplay between such an emergent mechano-cooperation and multistep adaptation: The prolonged lifetimes of slower-growing resistant lineages substantially increases their potential to acquire subsequent compensatory mutations which alleviate the cost of resistance. This "evolutionary rescue" allows resistant lineages to escape purifying selection indefinitely and, consequently, may lead to treatment failure. Introducing a genetically tailored system of fluorescently trackable "synthetic mutations", tunable in rate and effect, allows us for the first time to quantitatively study evolutionary rescue dynamics from the single-cell scale to the population level. The uncovered mechanisms lay the foundation for a new conceptual framework of intratumoral evolutionary dynamic as an emergent phenomenon, which might crucially inform novel treatment strategies, such as adaptive therapy.

Poster 20

The integrin beta4-keratin link impairs mechanosensing by protecting the nucleus form mechanical loading

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There is ample evidence on the importance of matrix rigidity and composition in triggering cellular responses during morphogenesis and disease progression. However, how these two factors jointly influence cell behavior and gene expression remains unclear. During invasive dissemination of breast cancer cells, for instance, the composition of the extracellular matrix (ECM) changes from a laminin rich basement membrane (BM) to a collagen and fibronectin rich environment with altered mechanical properties. To understand the mechanisms involved in these physiological scenarios, we plated the cells on gels of varying stiffnesses (0.5-30kPa) and coated them with different ECM proteins (laminin-111, collagen 1 and Fibronectin). We found that cells seeded on laminin exerted lower traction forces and exhibited compromised mechanosensitivity as shown by reduced YAP nuclear translocation, and smaller focal adhesions (FAs). Blocking integrin $\beta 4$, a laminin-specific integrin, led to changes in the organization of the keratin network and its interaction with the actin cytoskeleton, and increased nuclear YAP ratios. By perturbing the interaction between integrin $\beta 4$ and keratins and stretching cells, we show that the link between laminin, integrin $\beta 4$, and the keratin cytoskeleton shields the nucleus from mechanical loading, thereby reducing YAP nuclear localization. Overall, we propose a novel mechanism, by which ECM composition can influence gene expression, by protecting the nucleus from mechanical loading.

Poster 21

Active folding of epithelial shells

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The folding of epithelial cell sheets into various complex shapes underlies processes such as embryogenesis, the proliferation of cancerous tissue, and the growth of in vitro organoids. Such out-of-plane deformations can result from differential forces generated at the cell level, but the

overall deformation depends on the geometry and topology of the tissue. We study in a continuum framework how an initially spherical closed epithelial shell folds under active tensions and bending moments.

Poster 22

Cell morpho-rheological properties in microcirculation

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Following tumor cell dissemination, cells need to circulate through the blood stream, where they are exposed to multiple forces, including tactile squeezing through the capillary networks. Here, we asked whether the cells morpho-rheological phenotype need to be appropriately adapted to effectively squeeze through the capillaries. In 2007, Schrepfer, et al. reported that the lung barrier is a major hurdle for intravenous mesenchymal stromal cell (MSC) transplantation. They suggested that the entrapment of MSCs in the lung is correlated to cell sizes larger than the diameter of pulmonary capillaries [1]. However, the cells mechanical phenotype was not considered to play a role in microcirculation.

MSCs can be used as a model system, since the generation of organ-like 3D mesenspheres allows the expansion of softer and smaller cells compared to classically cultured MSCs on 2D surfaces; measured by real-time deformability cytometry and atomic force microscopy. We found that mesensphere-derived cells can effectively pass the pulmonary network in vitro, using a microfluidic microcirculation mimetic and in vivo, by transplanting MSCs intravenously to NOD/SCID mice. These findings were also validated by remodeling the physical phenotype of 2D cultured MSCs using a subsequent 3D culture systems. Thus, the adaptation of the morpho-rheological properties of cells is essential to overcome capillary entrapment. Our findings highlight the physical phenotype of cells as a promising therapeutic target, regarding the improvement of circulation under pathological and physiological conditions.

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Poster 23

Roadmap to local tumour growth: Insights from cervical cancer

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Wide tumour excision is currently the standard approach to surgical treatment of solid cancers including carcinomas of the lower genital tract. This strategy is based on the premise that tumours exhibit isotropic growth potential.

We reviewed and analysed local tumour spreading patterns in 518 patients with cancer of the uterine cervix who underwent surgical tumour resection. Based on data obtained from pathological examination of the surgical specimen, we applied computational modelling techniques to simulate local tumour spread in order to identify parameters influencing preferred infiltration patterns and used area-proportional Euler diagrams to detect and confirm ordered patterns of tumour spread.
Some anatomical structures, e.g. tissues of the urinary bladder, were significantly more likely to be infiltrated

than other structures, e.g. the ureter and the rectum. Computational models assuming isotropic growth could not explain these infiltration patterns. Introducing ontogenetic distance of a tissue relative to the uterine cervix as a parameter led to accurate predictions of the clinically observed infiltration likelihoods. The clinical data indicates that successive infiltration likelihoods of ontogenetically distant tissues are nearly perfect subsets of ontogenetically closer 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.

Poster 24

Kinetics of cell jamming

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The transition between fluid-like cell motion in mesenchymal tissue and a jammed or glassy behaviour in epithelial tissue suggest the existence of underlying general rules for these complex biological processes. The driving forces behind this transition are in discussion at the moment, with different candidates being the cell number density [1], the cell shape [2] and protein driven aging [3]. It is not established, yet, what importance the local, caging, structure has compared to global, collective, parameters.

We observe layers of epithelial-like MCF-10A cells with a stained nucleus, allowing us to track the cells and analyse the individual kinetics. A Voronoi tessellation around these tracks is used to estimate the local structural features and rearrangement events. Thereby, we can describe the local fluidity of a cell layer and look for the onset of cellular jamming. The random forests method is used to estimate the importance of structural parameters regarding the dynamics of the system. A moderately high density is required for epithelial-like MCF-10A cells to jam. The system shows a pronounced aging effect. Within the confluent layer, the cell shapes in the immediate neighbourhood of the cell in question exhibits higher influence on the dynamics of this cell, than the local density.

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Poster 25

Cooperativity between multiple types of receptor-ligand bonds in membrane adhesion

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In biological system, receptor-ligand bonds rarely work alone and often simultaneously help cells sense their surrounding environments together with other kinds of receptor-ligand bonds. However, the effect of multiple types of receptor-ligand bonds on formation dynamics of adhesion domain is still elusive. We combine the first theoretical model and effective Monte Carlo simulations to investigate the fluctuating membrane adhesion to a rigid substrate via both the short and long type receptor-ligand bonds. Both our stochastic model and effective Monte Carlo simulations find that there are significant cooperative effects of multiple types of bonds on nucleation dynamics of adhesion domain. Specially, the phase diagram of adhesion state of short type bonds even can be transformed from unstable adhesion state to stable adhesion state after adding the long type bonds. We further examine the distinct positive and negative cooperativity among these two types of bonds in membrane adhesion in terms of bonds' physical and geometric properties. These results not only shed light on the biophysical mechanism of cooperativity between multiple types of bonds in membrane adhesion and but also are interested to the study of multiple types of adhesion molecules-based biomedical engineering.

Poster 26

Cell shape during cellular fate transitions

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The development of an organism is characterized by a series of cellular fate transitions where cells become increasingly specialized. For many animal cells, fate transitions are accompanied by shape changes and there are strong indications of coupling between cell shape and fate.

Here, we present a pipeline to quantify and analyse cell shapes as cells undergo fate transitions. We will present how the morphological features of the cell can be quantified and analysed with the help of dimensional reduction methods. To identify clusters of cells and classify cells based on those clusters, we use a variety of algorithms, particularly those coming from the fields of data mining and machine learning. We then apply our analysis pipeline to investigate the coupling between cell shape and fate during exit from naïve pluripotency in mouse embryonic stem cells. We find that cells can be classified into two distinguishable clusters, closely associated with their state: While naïve cells display spherical shapes, cells undergo spreading during pluripotency exiting. The shape changes correlate with the expression of pluripotency markers.
After defining the distinct cellular shape clusters corresponding to specific states, we now study how the morphological features of a cell change during fate transitions. To this aim, we investigate cell trajectories of morphological features in a low-dimensional space. By integrating morphometric analysis into studies of cell fate changes, we aim to better understand the crosstalk between cellular fate and shape changes.

Poster 27

Cell size pleomorphism drives aberrant clone dispersal in proliferating epithelia

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As epithelial tissues develop, groups of cells related by descent tend to associate in clonal populations rather than dispersing within the cell layer. While frequently assumed to be a result of differential adhesion, precise mechanisms controlling clonal cohesiveness remain unknown. Here we employ computational simulations to modulate epithelial cell size in silico and show that junctions between small cells frequently collapse, resulting in clone cell dispersal amongst larger neighbors. Consistent with similar dynamics in vivo, we further demonstrate that mosaic disruption of Drosophila Tor generates small cells and results in aberrant clone dispersal in developing wing disc epithelia. We propose a geometric basis for this phenomenon, supported in part by the observation that soap foam cells exhibit similar size-dependent junctional rearrangements. Combined, these results establish a link between cell size pleomorphism and the control of epithelial cell packing, with potential implications for understanding tumor cell dispersal in human disease.

Poster 28

Modeling co-evolution of mechanically heterogeneous cell populations

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Biological tissues are commonly heterogeneous with many different cellular phenotypes populating them. This heterogeneity can be witnessed in the different biomechanical properties of cells such as differences in cell stiffness, cell-cell adhesion and cell contractility. These differences in cell mechanotype can manifest themselves as

varying rates of proliferation, migration and apoptosis. Here we simulate the coevolution of co-cultures of mechanically different cells to understand how heterogeneity in the cellular mechanotype influences cell-cell interactions and overall tissue dynamics. The key features of our simulations are the incorporation of mechanosensitive cell death and division rates, and fate dependent changes in cell mechanotype to accurately capture the effects of these on tissue function and dynamics. When the simulations are run without cell death and division, the simulated fate of the tissue aligns with the predictions of the SPV model and the differential adhesion hypothesis in terms of the extent of mixing or de-mixing and self-organization of the different cell types. However, the introduction of cell death and division into the model provides contrasting results such that there is – 1) fluidization of previously jammed epithelial tissue, 2) de-mixing of epithelial and mesenchymal-like cells even though the overall tissue is fluid, and 3) mixing of cells types with different adhesion. These results show that mechanosensitive cell proliferation and death play a significant and not yet completely quantified role in driving tissue dynamics and structure.

Poster 29

Multiscale Modeling of Tumor Development

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The temporal and spatial resolution in the microscopy of tissues has increased significantly within the last years, revealing new mechanisms that are acting on cell as well as on tissue level. Hence, yielding new insights into the dynamics of tissue development and the role of the single cell within it. A thorough theoretical description of the connection of single cell processes to macroscopic tissue reorganizations is still lacking. Especially in tumor development single cells play a key role in the advance of tumor properties. We introduce a scale-bridging method that is able to model tissue development up to the centimeter scale with micrometer resolution of single cells. Through parallelization it enables the efficient use of HPC systems, therefore facilitating detailed simulations on a large scale. We developed a generalized tumor model that respects adhesion driven cell migration, cell-to-cell signaling and mutation driven tumor heterogeneity. We scan the response of the tumor development and composition in dependence of different treatment plans using chemotherapy as well as radiation therapy. We then investigate how the presence of tumor stem cells changes tumor evolution, composition and treatment response. Here the occurrence of individual cells impacts the behavior of the macroscopic tissue. With this model, we enable in silico medicine to deepen the theoretical understanding of the interplay of tissue and single cells and therefore moving towards to computational personalized medicine.

Poster 30

The Physics of Carcinomas: A multi-scale analysis on primary tumor tissues

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Cancer is a heterogeneous disease that is very hard to outline. Besides a multitude of localized ways of initiation

and patterns of growth, in most cases, the ultimately fatal properties of a neoplasm is its ability to systemically metastasize. The steps along this metastatic cascade take place at multiple scales. In cooperation with the University Hospital Leipzig, we are realizing a full-scale biophysical analysis on primary tumor tissue samples, f.e. resectates from mammary or cervical carcinomas. By using a broad spectrum of techniques and covering a range from macroscopic bulk properties down to single cell features we are aiming at a interdisciplinary tumor characterization to contribute to a better understanding of the systemic nature of the disease cancer.

Poster 31

A biphasic three-dimensional mineralized in vitro hydrogel model for the study of breast cancer cell invasion into bone

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About 70% of patients with advanced breast cancer (BC) develop bone metastasis. So far, it is only possible to treat symptoms but not significantly enhance survival, making bone metastasis the leading cause of death in these patients. The bone is a highly organized and complex organ that with its mineralized bone extracellular matrix has a unique composition and structure compared to the extracellular matrix (ECM) in other metastatic organs. However, very little is known about how the unique bone microenvironment and in particular the inorganic component – the bone mineral (hydroxyapatite), influences BC cell adhesion and migration into the bone. While there is a lot of knowledge about the later osteolytic stage of bone metastasis, much less is known about the initial cancer cell colonialization and here in most studies the contribution of the bone ECM and particularly the role of the mineral is often disregarded. Here, we developed and characterized a biphasic three-dimensional in vitro hydrogel model that consists of a bulk hydrogel containing the BC cells casted on top of a mineralized macroporous hydrogel (cryogel) representing the bone niche. The hydrogel networks are based on the synthetic polymer poly(ethylene glycol) and the natural glycosaminoglycan heparin. The biphasic system was designed to allow the systematic variation of different ECM parameters in a highly defined manner in order to dissect relevant microenvironmental mechanisms that influence BC cell invasion into the bone. One key aspect of this model is the defined mineralization of the cryogel via a solution-based method to study the effect of mineral on BC cell invasion. Detailed X-ray analysis was performed to precisely characterize the type of mineral and crystal size, which were found to be comparable to human bone. We in particularly show that the presence of a mineral phase in our hydrogel system varies the migration response of BC cell, as compared to unmineralized controls. Due to the underlying highly modular hydrogel system, we can further mimic and modulate other biochemical and biophysical aspects of the natural ECM in our biphasic scaffold. These are the tuning of mechanical properties, the customized administration of cytokines and chemokines via the cytokine affine heparin component, the cell-based degradability via incorporation of matrix metalloproteinase-cleavable sequences, and the presentation of cell adhesion ligands via functionalization of the hydrogel matrix with short peptide sequences (e.g. RGD). Using our biphasic hydrogel-assisted model, we exemplarily show the influence of selected biophysical and biochemical cues on the migration behavior of BC cells (mono-culture) and in addition the impact of other cells, such as human mesenchymal stem cells (co-culture). Summarizing, our results demonstrate the utility of the presented in vitro system to investigate cell-matrix and heterotypic cell-cell communications in BC migration to bone.

Poster 32

MITF-mediated changes of tumour architecture, tensile stress and in extracellular matrix (ECM) control intratumour heterogeneity in melanoma models

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Differential tumour cell behaviour caused by environmental conditions, termed dynamic heterogeneity, is a prime source for drug resistance, and understanding its underlying mechanisms is crucial to design effective therapies. Due to their dynamic nature and three-dimensionality, tumours and tumour models are challenging systems to study spatio-temporal phenomena. The FUCCI cell cycle sensor allowed us to assess individual cycling cells within their endogenous multicellular environment. Whole measurements of the three-dimensional structures of samples required single-plane illumination microscopy to achieve sufficient penetration depths, while being minimally invasive. Using these techniques, we have demonstrated dynamic heterogeneity in melanoma xenograft tumours and melanoma spheroids. This heterogeneity was characterised by the presence of clusters of proliferating cells and clusters of G1-arrested cells in the same tumour/spheroid. The location of the quiescent zones suggested oxygen/nutrient deprivation as the cause of cell cycle arrest, and the G1-arrested cells reversed to cycling when cultured under normoxia in 2D culture. Here we demonstrate that this heterogeneity is consistently decreased in vivo and in vitro by MITF, a transcription factor strongly associated with melanoma development, progression and therapy response. While this phenomenon was not associated with a reduced hypoxic core, we show that high MITF expression allows proliferation under hypoxia. Importantly, modulation of MITF expression leads to changes of spheroid architecture, tensile stress and in extracellular matrix (ECM) and cell-ECM adhesion and crosstalk proteins. Currently undergoing atomic force microscopy measurements of spheroids will reveal whether these changes are accompanied by stiffness modulation of cells, ECM or both. In addition, we are in the process of incorporating fluorescent stress beads into spheroids to assess forces that cells undergo at different locations within these structures. Furthermore, inhibition of the Rho/ROCK signalling pathway mimics the morphology and cell cycle effects of high MITF expression. These findings support a novel role of MITF in controlling intratumour melanoma heterogeneity through changes in cell-ECM crosstalk and mechanotransduction.

Poster 33

MD Modeling of YAP Mechanosensing in Cancer Progression

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The Yes-Associated Protein (YAP) is a transcriptional regulator that acts as mechanosensor and mechanotransducer. It controls cell proliferation and survival, but also confers oncogenic properties. As such, it is of vital importance in homeostasis, development and wound healing, but also in tumor proliferation, motility and invasiveness of various cancers. YAP activity is regulated by a complex network of biochemical cell signaling pathways, usually in the form of phosphorylation cascades. YAP also integrates a multitude of mechanical signals to determine its activity. Those signals originate from the cell's contact points with neighboring cells and the extracellular matrix (ECM). Conversely, YAP can drive remodeling of the ECM. In cancer, the finely balanced network of biochemical and mechanical cues that controls YAP activity is dysregulated, leading to excessive transcription of YAP target genes.

A prerequisite for YAP activity is translocation to the nucleus, where it acts as transcriptional co-activator to TEAD family transcription factors, driving the expression of proliferative and oncogenic genes. While the upstream signals controlling YAP activity are diverse, YAP inhibition is usually effected by preventing entry into the nucleus. One

of the regulatory mechanisms to prevent the nuclear translocation of YAP is by binding to 14-3-3 proteins, which is preceded by phosphorylation at S127.
Molecular Dynamics (MD) simulations are performed to study the conformational changes in YAP's disordered binding motifs induced by phosphorylation and how YAP binds to 14-3-3, TEAD and other proteins that are involved in the mechanotransduction mechanisms that lead to tumorigenesis.

Poster 34

Flush and trap: microfluidic chips allow single cell analysis of breast cancer cell cycle progression

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Disseminated cancer cells can be found in different organs than the primary tumor site and colonization of these can lead to a critical failure, causing the death of the patient. Breast cancer bone metastasis can occur ten years after tumor ablation. This suggest that cancer cells can undergo a dormancy phase. Among various physical cues, changes in osmotic pressure have been shown to have an impact on cell proliferation and differentiation. Moreover, gradients in osmotic pressure along capillaries in the bone marrow allow for transcapillary fluid flow and nutrient exchange.
In this work, we investigate the response of cells subjected to osmotic pressure changes in relation to cell cycle. To do so, we used microfluidic technology that allows to change and regulate parameters of the cell microenvironment at relevant length and time scales. We designed microfluidic chips containing 60 chambers with posts to trap single cells. Cells isolated within the chips were then subjected to different osmotic pressure and monitored overtime.

To monitor cell cycle state, the human breast cancer cell line MDA-MB-231 was genetically modified with fluorescence ubiquitination cell cycle indicator 2 (FUCCI-2) through lentiviral transduction. Cells in G1 phase exhibit mCherry fluorescence and cells in S/G2/M phases display mVenus fluorescence, while cells in the G0 phase are colorless. In addition, live-cell imaging of endogenous actin allowed cell volume quantification.
The kinetics of cell spreading, migration and proliferation did not exhibit significant differences between the FUCCI-2 modified and the unmodified cells. The design of the chambers in the microfluidic chip allowed successful isolation of single cells. The cell cycle state and migration were monitored over days. Osmotic shocks on trapped cells were followed and compression levels were quantified. Current ongoing work investigates the effect of osmotic pressure on cell cycle state as well as cell and nuclear volume.

Poster 35

Vinculin regulates lamellipodium protrusion velocity

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The protrusive behaviour of invasive cancer cells is critical for their metastatic capacity. Protrusion of the leading cell edge is driven by actin polymerization in the lamellipodium (LP), which generates a retrograde flow of F-actin. Coupling retrograde F-actin flow to the extracellular

matrix (ECM) through focal adhesions (FA) allows cells to generate adhesion force for plasmamembrane protrusion. The FA protein vinculin is aberrantly expressed in various cancer types. It promotes cytoskeleton-ECM coupling, but nonetheless restrains cell migration velocity, indicating that vinculin may decrease, rather than increase, LP net protrusion. To investigate how vinculin affects LP protrusion and actin polymerization in migrating cells, we characterized the effects of vinculin-depletion on LP protrusion dynamics of primary murine embryonic fibroblasts (MEF) and compared our experimental data with predictions from a one-dimensional model of LP protrusion, which incorporates key LP parameters including actin polymerization, F-actin density, flow velocity and friction at FA, membrane tension, and myosin mediated LP contractions. Vinculin reduced LP net protrusion by specifically reducing membrane velocity in the protrusion phase of the LP protrusion/contraction cycle. This demonstrates that vinculin, despite its role in strengthening cytoskeleton-ECM coupling at FA to promote LP protrusion, effectively regulates LP protrusion velocity. Based on model predictions we tested whether vinculin regulates LP protrusion through effects on actin polymerization and/or F-actin density. While vinculin regulated lamellipodial actin polymerization rate, it increased LP F-actin density, suggesting that vinculin may regulate LP protrusion through effects on F-actin structure. Consistent with this, the vinculin-binding, cancer-associated, actin polymerase vasodilator-stimulated phosphoprotein (VASP), showed an altered S157-phosphorylation and a more pronounced localization at the lamellipodium tip, but not in FA, in the absence of vinculin. Our data suggest a regulatory function of vinculin for LP protrusion in migrating cells through a mechanism that might involve vinculin dependent regulation of VASP.

Poster 36

Classification of breast cancer and peripheral blood mononuclear cells by machine learning mechanical parameters

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A significant fraction of patients develop apparent metastases even years after resection of primary breast tumors. This metastatic relapse might be a direct consequence of a hematogenous spread at early desease stages. During these stages segregated tumor cells might change their biomechanical properties such as deformability to propagate to the lymphatic system and the blood circulation. Recent detection techniques of these circulating tumor cells (CTCs) use cell size and fluorescent labeling of CTCs for separation. Using this evaluation as a benchmark, we aim to find a robust and reproduciable method for a more accurate detection of CTCs in blood.

Poster 37

Better, faster, stronger: a new era of measuring cell mechanics and why we should care about strain rates

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The mechanical phenotype of a cell is an inherent biophysical marker of its state and function, with potential value in clinical diagnostics, including monitoring of can-

cer progression. Several microfluidic-based methods developed in recent years have enabled single-cell mechanophenotyping at throughputs comparable to flow cytometery, thereby opening a new era of cell mechanical characterization. Here we present a highly standardized cross-laboratory study comparing three leading microfluidic-based approaches to measure cell mechanical phenotype: constriction-based deformability cytometry (cDC) [1], shear flow deformability cytometry (sDC) [2], and extensional flow deformability cytometry (xDC) [3]. We show that all three methods detect cell deformability changes induced by exposure to altered osmolarity. However, a dose-dependent deformability increase upon latrunculin B-induced actin disassembly was detected only with cDC and sDC, which suggests that when exposing cells to the high strain rate imposed by xDC, other cell components dominate the response. The direct comparison presented here serves to unify deformability cytometry methods and provides context for the interpretation of deformability measurements performed using different platforms.

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[2] Otto et al.: Real-time deformability cytometry: on-the-fly cell mechanical phenotyping, Nature Methods 12, 3, 199-202 (2015)

[3] Gossett et al.: Hydrodynamic stretching of single cells for large population mechanical phenotyping, PNAS 109, 20, 7630-7635 (2012)

Session 2: Cancer cells and tumors in mechanical confinement

Invited Talk Thu 09:00

Mechanical heterogeneity in tissues promotes rigidity and controls cellular invasion

DAPENG BI— Northeastern University, Dept. of Physics, College of Science, Theoretical Soft Matter and Biophysics Group, Dana Research Center 110 Forsyth St. Boston, MA 02115, USA

We study the influence of cell-level mechanical heterogeneity in epithelial tissues using a vertex-based model. Heterogeneity is introduced into the cell shape index p0 that tunes the stiffness at a single cell level. We find the addition of heterogeneity can always enhance the mechanical rigidity of the epithelial layer by increasing its shear modulus hence making it more rigid. We find an excellent scaling collapse of our data as function of a single scaling variable fr, which accounts for the overall fraction of rigid cells. We identify a universal threshold fr*=0.21 that demarcates fluid vs. solid tissues. We also find this rigidity onset is far below the contact percolation threshold of rigid cells. This gives rise to a separation of rigidity and contact percolations processes, that leads to distinct types of solid states. We also investigate the influence of heterogeneity on tumor invasion dynamics. There is an overall impedance of invasion as the tissue becomes more rigid. Invasion can also occur in an intermediate heterogeneous solid state that is characterized by significant spatial-temporal intermittency.

Invited Talk Thu 09:30

Continuum theory of tissue dynamics

FRANK JÜLICHER — Max-Planck-Institute for the Physics of Complex Systems, Nöthnitzer Straße 38, 01187 Dresden Germany

T. b. a.

Invited Talk Thu 10:00

3D microenvironment stiffness regulates tumor spheroid growth and mechanics via p21 and ROCK

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Mechanical properties of cancer cells and their microenvironment contribute to breast cancer progression. While mechanosensing has been extensively studied using two-dimensional (2D) substrates, much less is known about it in a physiologically more relevant 3D context. Here we demonstrate that breast cancer tumor spheroids, growing in 3D polyethylene glycol-heparin hydrogels, are sensitive to their environment stiffness. During tumor spheroid growth, compressive stresses of up to 2 kPa built up, as quantitated using elastic polymer beads as stress sensors. Atomic force microscopy (AFM) revealed that tumor spheroid stiffness increased with hydrogel stiffness. Also, constituent cell stiffness increased in a ROCK- and F-actin-dependent manner. Increased hydrogel stiffness correlated with attenuated tumor spheroid growth, a higher proportion of cells in G0/G1 phase and elevated levels of the cyclin-dependent kinase inhibitor p21. Drug-mediated ROCK inhibition reversed not only cell stiffening upon culture in stiff hydrogels but also increased tumor spheroid growth. Taken together, we reveal here a mechanism by which the growth of a tumor spheroid can be regulated via cytoskeleton rearrangements in response to its mechanoenvironment. Thus, our findings contribute to a better understanding of how cancer cells react to compressive stress when growing under confinement in stiff environments and provide the basis for a more in-depth exploration of the underlying mechanosensory response.

Invited Talk Thu 11:00

3D motion of cancer cells in confined space

TIMO BETZ— University of Münster, Institute of Cell Biology, ZMBE, Von-Esmarch-Straße 56, 48149 Münster, Germany

Metastasis and invasion along-side, precise development, tissue rearrangement and wound healing are key biological processes that depend on collective cell migration. Thanks to a focused research effort in the past decades our understanding has made enormous advances in the description of collective cell migration. However, we are only slowly starting to assemble quantitative models that allow us to understand and predict the different migration phenotypes, and their relationship to different material states. Currently, it is well established that such different migratory phenotypes depend on several external, physical as well as internal, molecular parameters. This knowledge is based on recent groundbreaking studies on 2D epithelial tissue dynamics showing switch like behavior in motility phenotypes that is often paraphrased by physical phase transition, from solid-like to fluid or to gas-like.

We study the collective migration inside 3D cancer spheroids, and find that tuning collagen concentration leads to massive migration changes ranging from jammed over fluid like to burst like outgrowth. The bursting phenotype can be explained by a up-regulation of cellular contractility leading to a homeostatic pressure increase until a critical value of the surface tension is reached, where the outer layer ruptures and the cells within the spheroid are rapidly pressed out of the model tumor.

Invited Talk Thu 11:30

Extracellular matrix stiffness and transforming growth factor-β modulates pancreatic stromal cells' cytoskeletal remodeling

ANDREAS STYLIANOU, TRIANTAFYLLOS STYLIANOPOULOS - Cancer Biophysics Laboratory Department of Mechanical and Manufacturing Engineering, University of Cyprus, P.O. Box 20537 Nicosia 1678, Cyprus

The tumor microenvironment consists of the stomal cells, including fibroblasts (FBs) and cancer associated fibroblasts (CAFs), the extracellular matrix (ECM) and a myriad of soluble factors whose importance in cancer progression and metastasis is indisputable. In many solid tumor types, including pancreatic tumors, the complex interplay between stromal cells and the other tumor microenvironment components leads to a desmoplastic reaction. Desmoplasia, is a cancer-specific type of fibrosis, characterized by the presence of CAFs and overproduction of ECM proteins, such as collagen type I, the major fibrous protein of the ECM. Desmoplasia stiffens the tumor tissue, and as a result, it increases the compressive mechanical forces in the interior of the tumor and hinders treatment. ECM stiffening, transforming growth factor beta (TGF-β) and FBs/CAFs are thought to play a crucial role in this tumor desmoplastic reaction, although the involved mechanisms are unknown. We investigated the effect of collagen stiffness and TGF-β on pancreatic FBs and CAFs, particularly on specific cytoskeleton properties and gene expression involved in tumour invasion. Our results demonstrate that CAFs present specific myofibroblast-like characteristics (i.e., alpha-smooth muscle actin (α-SMA) expression, cell elongation, and lamellipodia formation) and are softer than FBs. Concerning TGF-β, we found that TGF-β treatment increases cell stiffness in terms of Young's modulus of both FBs and CAFs and increases CAF's elongation, cell spreading, lamellipodia formation and spheroid invasion. Gene expression analysis shows that these morphodynamic characteristics are mediated by Rac, RhoA and ROCK expression in CAFs treated with TGF-β. Furthermore, our studies have demonstrated that collagen stiffness makes stomal cells stiffer and to express higher levels of α-SMA. Although stress fibres in FBs become more oriented on stiff substrates, CAFs have oriented stress fibres regardless of substrate stiffness. Subsequently, we demonstrated that cells' invasion has a differential response to stiffness, which was associated with regulation of RhoA and ROCK-1 mRNA expression. Our findings elucidate on the effects of ECM stiffening and TGF-β on stomal cells' behavior and stiffness providing new insights into the mechanisms involved.

Invited Talk Thu 12:00

The role of tissue biophysics in organ selectivity in metastasis

KANDICE TANNER – Laboratory of Cell Biology, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892-4256, USA

In the event of metastastic disease, emergence of a lesion can occur at varying intervals from diagnosis and in some cases following successful treatment of the primary tumor. Is there a difference in strategy to facilitate outgrowth? Why is there a difference in latency? Genetic factors that drive metastatic progression have been identified, such as those involved in cell adhesion, signaling, extravasation and metabolism. However, organ specific biophysical cues may be a potent contributor to the establishment of these secondary lesions. Here I discuss using optical tweezer based active microrheology to measure the mechanical cues that may influence disseminated tumor cells in different organ microenvironments. I further discuss in vitro and in vivo preclinical models such as 3D culture systems and zebrafish in efforts of understanding the role of the biophysical properties of the stromal architecture on the earliest stage of organ colonization.

Session 3: Tumor-stroma interaction

Invited Talk Thu 13:30

Adhesion regulated mechanotransduction in cancer

JOHANNA IVASKA - Turku Bioscience, University of Turku, Finland

Tissue homeostasis is dependent on the spatially controlled localization of specific cell types and the correct composition of the extracellular stroma. Integrin mediated adhesions, in conjunction with the actin cytoskeleton, allow cells to sense the stiffness of the surrounding extracellular matrix (ECM). Conversely, cells exert acto-myosin and integrin dependent forces to remodel and organize the surrounding ECM. In cancer, stiffening of the tumor stroma is an instrumental contributor to tumor progression. Tissue stiffness acts as a migration cue in durotaxis and supports cell proliferation in cancerous tissue. I will describe our recent findings on the interrelationship between cancer cell mediated ECM remodelling and ECM induced mechanochemical signals regulating transcription of growth promoting pathways in cancer cells. I will also discuss our recent observations related to how adhesion maturation and increasing tissue stiffness regulate cell migration in a cell type dependent manner.

Invited Talk Thu 14:00

Oxygen in cancer and neovascularization

SHARON GERECHT – Johns Hopkins University, Whiting School of Engineering, Dept. of Chemical & Biomolecular Engineering,, 3400 North Charles Street, Baltimore, MD 21218 Maryland Hall 221, USA

Oxygen acts as a potent upstream signaling molecule to control a plethora of cell functions and cell fates. In three-dimensional (3D) tissues, the oxygen concentration is not uniformly distributed, but rather a gradient that depends on distance from oxygen-carrying blood vessels. During tissue regeneration, development or uncontrolled growth (ie, tumor), restricted oxygen transport leads to severe hypoxic gradients. In these same tissues, the extracellular matrix (ECM) provides critical support for cell adhesion, proliferation, migration, and morphogenesis. Hydrogels provide a highly controlled 3D environment that is structurally and biomechanically similar to native ECM and can provide a rich biochemical landscape as well as biophysical cues to influence cell behavior. In this talk I will present our recent efforts to develop hydrogel matrices that activate hypoxic signaling pathways and to study how hypoxic signaling induce a myriad of cellular and systemic adaptations. Examples will include interface along stem cell differentiation, vascular assembly and sarcoma metastasis.

Invited Talk Thu 14:30

Organic and inorganic ECM components as synergistic regulators of cancer meachanosignaling

CLAUDIA FISCHBACH-TESCHL – Department of Biomedical Engineering, Cornell University, 157 Weill Hall, Ithaca, NY 14853, USA

T. b. a.

Invited Talk Thu 15:00

Fusogenic liposomes as general pass key for RNA-based approaches against cancer

RUDOLF MERKEL - Forschungszentrum Jülich GmbH, ICS-7, 52428 Jülich, Germany

During recent years, we have developed fusogenic lipid nanoparticles that can be used as carriers for a broad variety of molecular cargo [1]. Delivery into cells occurs via membrane fusion that is mediated by a fast and purely physical mechanism. Neither immune nor inflammatory responses are induced. Fusogenic potential can be tuned by lipid composition and environmental conditions [2]. In the context of cancer prevention and cure, we have demonstrated that fusogenic liposomes can deliver free radical scavengers as well as cytostatica into living cells. Beyond this, RNA (including siRNA and mRNA) can be delivered with highest efficiency and little detrimental effects as has been demonstrated on cultivated cells [3] and in developing zebrafish embryos. Thus, fusogenic liposomes open new possibilities for general cancer research. Finally, we present a new strategy to endow mRNA with cell-type specificity. With this strategy we aim at modification or destruction of specific cells in the organism.

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[2] Kolasinac R, Kleusch C, Braun T, Merkel R, Csiszar A.: Deciphering the functional composition of fusogenic liposomes, International Journal of Molecular Sciences, vol. 19, 346. DOI: 10.3390/ijms19020346 (2018)

[3] Hoffmann M, Hersch N, Merkel R, Csiszar A, Hoffmann B.: Changing the way of entrance: Highly efficient transfer of mRNA and siRNA via fusogenic nano-carriers, Journal of Biomedical Nanotechnology, vol. 15, 170-183. DOI: 10.1166/jbn.2019.2663 (2019).

Session 4: Cellular mechanosensing

Invited Talk Fri 08:45

Adhesion G protein-coupled receptors - Metabotropic force sensors that shape development and mechanosensation

TOBIAS LANGENHAN— Rudolf Schönheimer Institute of Biochemistry Division of General Biochemistry, Leipzig University, Germany

G protein coupled receptors (GPCR) have proven a treasure trove for modern pharmacological intervention of numerous human ailments. However, in stark contrast to classically targeted GPCRs, adhesion GPCRs habe been largely neglected by biologists, pharmacologists and clinician scientists for decades. Only recently their physiological and signaling properties are being unravelled and show exciting features including their roles in tissue architecture, signaling through tethered agonism and their unusual activation through mechanical cues. I will discuss the recent developments on adhesion GPCR signaling and introduce the receptor family as a topical area in neuroscience and cancer research.

Invited Talk Fri 09:15

Probing the physiology of physical transport inside cells and developing tissues

ELISABETH FISCHER-FRIEDRICH — Technical University Dresden, BIOTEC, Tatzberg 47/49, 01307 Dresden, Germany

To undergo mitosis successfully, animal cells need to acquire a round shape to provide space for the mitotic spindle. This mitotic rounding relies on mechanical deformation of surrounding tissue and is driven by forces emanating from actomyosin contractility. Cancer cells are

able to maintain successful mitosis in mechanically challenging environments such as the increasingly crowded environment of a growing tumor, thus, suggesting an enhanced ability of mitotic rounding in cancer. Here, we show that epithelial mesenchymal transition (EMT), a hallmark of cancer progression and metastasis, gives rise to a cell-cycle-dependent cell-mechanical switch that increases mitotic rounding strength in breast epithelial cells. We connect this cell-mechanical change to an EMT-induced rise in activity of Rac1 and downstream effectors. We thus unveil a new mechanism of enhanced mitotic cell rounding through EMT suggesting an EMT-associated improved ability for cell division in the confined environment of a tumor.

Contributed Talk Fri 09:45

MITF-mediated changes of tumour architecture, tensile stress and in extracellular matrix (ECM) control intratumour heterogeneity in melanoma models

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[4] The University of Queensland School of Biomedical Sciences, Brisbane, Australia

[5] Mater Research Institute, Brisbane, Australia

Differential tumour cell behaviour caused by environmental conditions, termed dynamic heterogeneity, is a prime source for drug resistance, and understanding its underlying mechanisms is crucial to design effective therapies. Due to their dynamic nature and three-dimensionality, tumours and tumour models are challenging systems to study spatio-temporal phenomena. The FUCCI cell cycle sensor allowed us to assess individual cycling cells within their endogenous multicellular environment. Whole measurements of the three-dimensional structures of samples required single-plane illumination microscopy to achieve sufficient penetration depths, while being minimally invasive. Using these techniques, we have demonstrated dynamic heterogeneity in melanoma xenograft tumours and melanoma spheroids. This heterogeneity was characterised by the presence of clusters of proliferating cells and clusters of G1-arrested cells in the same tumour/spheroid. The location of the quiescent zones suggested oxygen/nutrient deprivation as the cause of cell cycle arrest, and the G1-arrested cells reversed to cycling when cultured under normoxia in 2D culture. Here we demonstrate that this heterogeneity is consistently decreased in vivo and in vitro by MITF, a transcription factor strongly associated with melanoma development, progression and therapy response. While this phenomenon was not associated with a reduced hypoxic core, we show that high MITF expression allows proliferation under hypoxia. Importantly, modulation of MITF expression leads to changes of spheroid architecture, tensile stress and in extracellular matrix (ECM) and cell-ECM adhesion and crosstalk proteins. Currently undergoing atomic force microscopy measurements of spheroids will reveal whether these changes are accompanied by stiffness modulation of cells, ECM or both. In addition, we are in the process of incorporating fluorescent stress beads into spheroids to assess forces that cells undergo at different locations within these structures. Furthermore, inhibition of the Rho/ROCK signalling pathway mimics the morphology and cell cycle effects of high MITF expression. These findings support a novel role of MITF in controlling intratumour melanoma heterogeneity through changes in cell-ECM crosstalk and mechanotransduction.

Invited Talk Fri 10:00

Nuclear Rupture at high curvature and high rates leads to defects in DNA repair to affect cell cycle, differentiation, and genome variation

Dennis Discher - Molecular & Cell Biophysics Lab, Univ. Pennsylvania, Philadelphia, PA, USA

The nucleus links physically to cytoskeleton, adhesions, and extracellular matrix – all of which are subject to forces. We find nuclear rupture in tumors [1], embryonic organs [2], and various in vitro models results from high

nuclear curvature and leads to cytoplasmic mis-localization of multiple DNA repair factors and transcription factors. Curvature is imposed by an external probe [1], by migrating quickly (not slowly) through small constricting pores [3,4], or simply by cell attachment to either aligned collagen fibers or stiff matrix [1], and theory indicates heterogeneous nucleation for pore formation [5]. Mis-localization of nuclear factors is greatly enhanced by depleting lamin A, requires many hours for nuclear re-entry, and correlates with pan-nucleoplasmic foci of the DNA damage marker γH2AX and with electrophoretic breaks. Excess DNA damage is rescued in ruptured nuclei by co-overexpression of multiple DNA repair factors as well as by soft matrix or inhibition of actomyosin tension and oxidative processes – with combination treatments needed to rescue cell cycle suppression [4]. Increased contractility has the opposite effect, and stiff tumors with low lamin A indeed exhibit increased nuclear curvature, more frequent nuclear rupture, and excess DNA damage. Normal differentiation processes of myogenesis and ostoegenesis are also affected, but oppositely by migration through constricting pores, suggesting general effects on cell fates [6]. Mis-repair of DNA is further suggested by two cancer lines that, after constricted migration, exhibit greater genome variation [1,3].

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[2] S Cho, D Discher: Mechanosensing by the lamina protects against nuclear rupture, DNA damage, and cell cycle arrest, Dev Cell (2019)
[3] J Irianto, D Discher: DNA damage follows repair factor depletion and portends genome variation in cancer cells after pore migration, Curr Biol (2017)
[4] Y Xia, D Discher: Rescue of DNA damage after constricted migration reveals bimodal mechano-regulation of cell cycle, J Cell Biol (2019)
[5] D Deviri, D Discher DE, SA Safran: Scaling laws indicate distinct nucleation mechanisms of holes in the nuclear lamina, Nature Physics (2019)
[6] LR Smith: Constricted migration modulates stem cell differentiation, Mol Biol of the Cell (2019)

Session 5: Translational research

Invited Talk Fri 11:00

Human tissue culture

SONJA KALLENDRUSCH – University of Leipzig, Institute of Anatomy, Oststraße 25, 04317 Leipzig, Germany

Although early diagnosis and development of novel treatment strategies led to improved cancer prognosis, the burden for the patient still remains high without guaranteed achievement. Three-dimensional (3D) cell culture models permit the investigation of a more natural, but complex microenvironment, promising the investigation of different cellular compartments and their interactions. We use human tumor tissue to investigate its relevance to predict patient response and enhanced drug selection for clinical trials. These biological complex, but necessary models have already been shown significant advancements and need to be narrowly enrolled in cancer drug discovery and the field of tumorbiology in the future. In this talk the slice culture model is presented with its shortcomings and advantages, when handling this simple but complex 3D tumor model.

Invited Talk Fri 11:30

Biophysical properties of tumors in vivo

INGOLF SACK — Charité Berlin, Department of Radiology, Germany

Tumor growth is associated with extensive alterations of tissue structures resulting from a number of processes such as neovascularization, accumulation of cells and remodeling of the extracellular matrix. Furthermore, leaky tumor blood vessels and impaired lymphatic drainage lead to interstitial fluid accumulation and elevated hydrostatic pressure. The altered structure and fluid turnover is mirrored by significant changes in the effective shear modulus as can be measured in vivo by MRE. This talk reviews recent approaches to structure- and pressure-sensitive high resolution MRE and outlines potential clinical applications. It will be discussed how mechanics-based image

contrast provides insight into the underlying tissue structure in health and disease with emphasis on tumors.

Contributed Talk Fri 12:00

Collective motion promotes multi-step drug resistance evolution in dense cellular populations

JONA KAYSER, OSKAR HALLATSCHEK — University of California, Berkeley, Physics Department, Evolutionary Dynamics Group, University of California, Berkeley, USA

One of the most pressing challenges in modern cancer treatment is the evolution of drug resistance. As cancer cell populations proliferate, they can rapidly acquire mutations in their genome, some of which may render their carriers resistant to one or even multiple drugs. Recent work has yielded substantial progress in our understanding of the molecular mechanisms of resistance, revealing that many drug resistance mutations are associated with an inherent fitness cost prior to the onset of treatment. Current models of tumor expansion suggest that, consequently, these slower-growing resistant subclones should be rapidly outcompeted by faster-growing susceptible cells via purifying selection and purged from the population. However, this prediction is in stark contrast to the observed prevalence of drug resistance in the clinic.

Here, using a microbial model system of neoplastic growth, I show that the collective motion inherent to dense cellular populations, including solid tumors, can drastically boost drug resistance evolution. In addition, I present new results advocating for an intricate interplay between such an emergent mechano-cooperation and multi-step adaptation: The prolonged lifetimes of slower-growing resistant lineages substantially increases their potential to acquire subsequent compensatory mutations which alleviate the cost of resistance. This "evolutionary rescue" allows resistant lineages to escape purifying selection indefinitely and, consequently, may lead to treatment failure. Introducing a genetically tailored system of fluorescently trackable "synthetic mutations", tunable in rate and effect, allows us for the first time to quantitatively study evolutionary rescue dynamics from the single-cell scale to the population level. The uncovered mechanisms lay the foundation for a new conceptual framework of intratumoral evolutionary dynamic as an emergent phenomenon, which might crucially inform novel treatment strategies, such as adaptive therapy.

Session 6: Cancer cell migration

Invited Talk Fri 13:30

Dissecting cell migration and mechanics by systematic gene editing approaches

KLEMENS ROTTNER - Helmholtz Centre for Infection Research, Inhoffenstraße 7 38124 Braunschweig, Germany

The core interest of my lab is to dissect the signalling pathways and downstream molecular mechanisms driving the formation of actin-based cell edge protrusions. Noteworthy, the same pathways are utilized by diverse pathogens to induce their own uptake into cells.

In this talk, I will focus on signalling through Rac and related small GTPases such as Cdc42 and RhoG, and in particular concerning their relative impact on the regulation of WAVE Regulatory Complex (WRC), which is crucial for the generation of branched actin filament networks in lamellipodia and membrane ruffles. Starting from recently published work on the genetic removal of the Sra-1 and PIR121 subunits of WRC, which constitute direct interaction surfaces with Rac, we are now extending our efforts to characterize interaction nodes of various upstream GTPases with WRC and other Arp2/3 complex activators operating at the plasma membrane. For instance, novel results will be discussed, which were obtained from characterizing a cell line lacking both Sra-1/PIR121 and their upstream regulators Rac1/2/3. This line in combination with re-introduction of constitutively active WRCs allowed us to decipher potential additional inputs to WRC regulation, in a fashion separable from Rac-mediated WRC activation in spite of the latter remaining obligatory for WRC activation.

Moreover, in complementary efforts to genetically target the Sra-1/PIR121-interactor Nap1, and its mostly hematopoietic counterpart Hem1, in migrating B16-F1 melanoma and fibroblast cells, we have found not only that Nap1 removal can cause a compensatory upregulation of Hem1, which occurs to differential extent in distinct cell lines, but also that Nap1/Hem1 double-null cell lines can be stimulated to form lamellipodia-like structures displaying specific but significant differences to canonical lamellipodia. A detailed characterization of these structures

will be provided, and resulting implications for their role in cell edge dynamics and mechanics discussed.

Invited Talk Fri 14:00

Cancer resection within morphogenetic fields

XAVIER TREPAT [1, 2]

[1] ICREA - Institute for Bioengineering of Catalonia (IBEC), Barcelona, Spain

[2] Barcelona Institute for Science and Technology (BIST), Barcelona, Spain

Biological processes such as morphogenesis, tissue regeneration, and cancer invasion are driven by collective migration, division, and folding of epithelial tissues. Each of these functions is tightly regulated by mechanochemical networks and ultimately driven by physical forces. I will present maps of cell-cell and cell-extracellular matrix (ECM) forces during cell migration and division in a variety of epithelial models, from the expanding MDCK cluster to the regenerating zebrafish epicardium. These maps revealed that migration and division in growing tissues are jointly regulated. I will also present direct measurements of epithelial traction, tension, and luminal pressure in three-dimensional epithelia of controlled size and shape. By examining epithelial tension over time-scales of hours and for nominal strains reaching 1000%, we establish a remarkable degree of tensional homeostasis mediated by superelastic behavior.

Invited Talk Fri 14:30

Coordination of tissue growth by cell mechanics

IVANA PAJIC – LIJAKOVIC, MILAN MILIVOJEVIC – Faculty of Technology and Metallurgy, Belgrade University, Karnegijeva 4, Belgrade, Serbia

A more comprehensive account of the main features of collective cell migration is necessary for the deeper understanding of biological processes such as embryogenesis, tumorigenesis and wound healing from a rheological point of view. A significant difference in cell stiffness between migrating and resting cell groups indicates that volume fraction of migrating cells and their distribution could influence long-time viscoelasticity of multicellular surfaces. This aspect of cell rearrangement could be treated by the analogy with physics in the form of two-phase blend consists of migrating and resting cell pseudo phases. Migrating cells could form three different types of configuration: (1) monolayer sheets (lamellar structure), (2) small clusters, and (3) and various combinations of these two types. Long-time viscoelasticity of multicellular surfaces caused by collective cell migration depends on: (1) the volume fraction and configuration of migrating cells and the rate of its change, (2) the viscoelasticity of migrating cell groups, and (3) the viscoelasticity of surrounding resting cells [1,2].

The key parameters that influence the viscoelasticity are the size, shape, and thickness of the biointerface between migrating cell groups and surrounding resting cells. The multi-scale nature of the biointerface dynamics represents the product of: (1) the local changes of the size and shape of migrating cell groups, (2) the local accumulation of resistance stress during movement through dense environment (internal effects), (3) the collision of the velocity fronts (external effects) [2]. The local changes in the size and shape of migrating cell groups induce additional energy dissipation. The accumulated stress could induce disordering of migrating cell groups, pronounced in their core regions, and consequently migrating-to-resting cell state transition. The collision of the velocity fronts caused by uncorrelated motility could lead to local stress generation and consequently to the formation of stagnant zones. This stress increase leads to increase of the volume fraction of resting cells. Uncorrelated motility is caused by intrinsic and extrinsic cellular processes [3]. Intrinsic processes are (1) gene expression differences, (2) cell signaling and (3) their inter-relations. Gene expression induces time delaying in cell response to a various mechanical and biochemical stimulus. This time delaying might be relevant for cell coupling because what cells acquire at the present time is the information of surrounding cells some time ago. These perturbations can induce that (1) cells in the same population respond to different signals and/or (2) cells behave differently in response to the same signals. Extrinsic processes depend on substrate mechanical properties and/or neighboring tissue forces. Cumulative effects of these mechanical and biochemical processes lead to local generation of normal and shear stresses which influence the configuration of migrating cells and the rate of its changes and on that base the

viscoelasticity of multicellular systems on various space and time scales.
Impact of the biointerface dynamics on viscoelasticity in the context of its size and thickness has been formulated based on mechanical coupling modes. Lower interface size corresponds to the lamellar structure of the pseudo-blend in which cells migrate within a few monolayer sheets. Higher interface size (for the same volume fraction of migrating cells) corresponds to cell migration within a large number of small migrating groups dispersed within the resting cell pseudo phase. The lamellar structure of the pseudo blend leads to parallel mode coupling between pseudo phases while the highly dispersed structure of pseudo blend leads to series mode coupling between pseudo phases. The biointerface can be sharp or finite. Finite biointerface could be more realistic in order to minimize generated shear stress within it. The magnitude of stress could be minimized by (1) decrease the speed of migrating cell groups, (2) increase the thickness of the biointerface, and (3) local circular single cell movement within the biointerface in order to decrease sliding and on that base to decrease the effective viscosity.

Results obtained in literature for various 2D and 3D multicellular systems point to necessity of additional rheological characterization of (1) the viscoelasticity of migrating cell groups, (2) viscoelasticity of surrounding resting cells and (3) viscoelasticity of the biointerface and their interrelations by proposing corresponding constitutive model equations [1-4]. Main questions arise. Can the migrating cell groups be treated as a viscoelastic liquid? Can the surface tension be used as an indicator of liquefied behavior or not. Amorphous viscoelastic solids such as polymer hydrogels and foams also have surface tension. What are the main characteristics of the viscoelastic liquid and viscoelastic solid in the context of system ability to relax? How to recognize the jamming state if appear? Does migrating-to-resting cell state transition can be treated as a jamming state transition? What could be the constitutive model for the jamming state? The main goal of this consideration is to offer some answers to these questions from a rheological standpoint. It is discussed on a simple model system such as cell aggregate rounding after uni-axial compression between parallel plates [3,4] based on the data from the literature.

[1] Pajic-Lijakovic I, Milivojevic M.: Viscoelasticity of multicellular surfaces, J Biomech, 60:1-8 (2017)

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[3] Pajic-Lijakovic I, Milivojevic M.: Successive relaxation cycles during long-time cell aggregate rounding after uniaxial compression, J Biol Phys, 43(2):197-209 (2017)

[4] Pajic-Lijakovic I, Milivojevic M.: Functional epithelium remodeling in response to applied stress under in vitro conditions, Appl Bionics and Biomech, doi.org/10.1155/2019/4892709 (2019)

Contributed Talk Fri 15:00

Strategies for Individual and Collective Cell Migration by Heterogeneous Cell Populations during Cancer Metastasis

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Analyzing cancer from a mechanics perspective leads to several paradoxical questions of interest, both from a cell proliferation and tumor growth perspective as well as cell migration and metastasis perspective. Here I will focus on two such questions regarding cell migration and metastasis – 1) Most cells in vitro undergo durotaxis – migration up a substrate/matrix stiffness gradient. However, during metastasis, cancer cells migrate out and away from the stiffer stroma/connective tissue around a tumor and into the surrounding softer regions. What allows for this negative durotactic behavior of metastatic cancer cells? 2) Metastatic sites are more likely to form when clusters of cancer cells disseminate to the secondary sites rather than individual cells. However, in a lot of cases, migratory cancer cells show at least a partial epithelial to mesenchymal transformation with a decrease in inter-cellular adhesion. How can these weakly bound cells still migrate together in a cluster to successfully colonize distant metastatic sites? Using experimental and computational ap-

proaches, we find that heterogeneity in the mechanical/biochemical phenotypes of a tumor cell population might hold the answer to both these questions.

Invited Talk Fri 15:45

Confinement induced DNA damage causes increased matrix degradation and invasiveness in ductal carcinoma in situ breast cancer cells

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During in vivo migratory events such as tissue morphogenesis, immune surveillance and cancer invasion, intracellular forces are transmitted across the cytoskeleton to the nucleus. Using as a model the development of tumor in the mammary duct of mice (intraductal xenograft of human tumor cells) Lodillinsky et al. (2016) showed that, in order to breach out of the mammary gland ducts, MCF10 ductal carcinoma in situ cells (MCF10.DCIS) degrade the basement membrane in a MT1-MMP-dependent manner, but what induced degradation remained unknown. Here, we observed that the nuclei of these cells are less deformed in early tumor stages (In situ) when compared to later stages (microinvasion). Microinvasion stages also displayed increased DNA damage. We previously showed that strong nuclear deformation can lead to nuclear envelope (NE) rupture events and DNA damage (Raab et al., 2016; Denais et al., 2016). We thus sought out to test whether the increased nuclear deformation and DNA damage observed in the DCIS model could contribute to trigger the invasive phenotype acquired by these cells to progress into infiltrating lesions, which ultimately results in the perforation of both the myoepithelium layer and the basement membrane, generating the invasive carcinoma. To apply a controlled deformation to cells and their nuclei we used confining slides containing a layer of micro-pillars of different heights. We observed that MCF10.DCIS cells harvested following strong (2µm) but not mild (10µm) confinement and then embedded in 3D collagen, exhibited highly dynamic actin protrusions and increased explored area. In agreement, strong confinement led to increased MMP-dependent collagen degradation activity. As expected, DCIS cells confined at 2µm but not 10µm exhibited frequent NE rupture events and increased DNA damage. Similarly to what we had observed for RPE1 cells, only cells displaying NE rupture displayed DNA damage, suggesting that DNA damage was a consequence of NE rupture induced by confinement. We then developed an on-chip duct assay to reproduce the confined growth observed in intraductal tumor xenografts. Strikingly, as cell density increased in this device, nuclei deformation, rupture and DNA damage increased, likely due to the strong migratory activity of the crowded cells, squeezing between themselves as they move in the confining duct. Doxorubicin-treated cells displayed increased 3D collagen degradation and invasion in the mammary duct device, suggesting that DNA damage could be the cause of the invasive phenotype observed both in vivo and in vitro. Since in both MCF10.DCIS and RPE1 cells DNA damage is associated to NE rupture, we next sought to identify a potential cytoplasmic factor that would gain access to the exposed nuclear DNA following the NE rupture events, causing DNA damage. TREX1 is the most abundant cytosolic exonuclease and it was shown to attack chromatin bridges that persisted in cytokinesis, following rupture of the NE that reformed around them (Maciejowski et al., 2015). Strikingly, both transient TREX1 depletion and stable CRISPR KO in MCF10.DCIS and RPE1 cells almost abolished DNA damage associated to NE rupture upon strong confinement and we obtained consistent results overexpressing wild type and dominant negative TREX1. Strong confinement in TREX1-depleted cells also abrogated collagen degradation and invasion in the on-chip duct assay. Consistently, overexpression of wild type TREX1 increased collagen degradation while its dominant negative inhibited it. Together these results show that confinement-induced collagen degradation and invasion in the on-chip duct in vitro assay are due to TREX1-dependent DNA damage following NE rupture. Strong confinement of 'normal' RPE1 cells also triggered a TREX1-dependent, DNA damage-associated phenotype and cell senescence, as evidenced by increased Beta-gal staining and cell cycle duration, p21 upregulation and lamin B1 downregulation. Here we use TREX1 depletion and overexpression to modulate the level of DNA damage associated to NE rupture following strong confinement and demonstrate a causal relationship between cell confinement and specific long term cellular phenotypes: senescence in RPE1 cells and collagen degradation and invasion in MCF10.DCIS cells. The mechanism of TREX1-dependent

DNA damage in confined cells with NE rupture could relate the observation of deformed nuclei and increased DNA damage (both in duct xenograft tumors in mice and in human breast tumors) to the development of an invasive phenotype and thus contribute to the initiation of certain types of breast cancers. We envisage that normal duct morphogenesis could require a balance of proliferation and matrix degradation and remodeling at the bud of the growing duct branches. We propose that TREX1-mediated DNA damage during mammary gland morphogenesis could constitute a safety mechanism to keep this balance by increasing matrix degradation and at the same time slowing down proliferation in case of overcrowding in the growing tissue. However, transformed duct cells which have escaped senescence programs could degrade the matrix without decreasing proliferation, ultimately leading to invasive carcinoma.

Invited Talk Fri 16:15

Physical model for cellular self-polarization and motility in one dimension: single cells and single-file chains

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We present a physical model for the self-polarization of a one-dimensional cell, where the two ends of the cell exert negative feedback on each other through the advection-diffusion of a cytoplasmic inhibitor of actin polymerization. We expose the full range of cell motility that the model describes: the process of symmetric cell elongation, symmetry breaking and onset of motility, and stick-slip persistent motion. These behaviors are compared to observations in experiments of cells moving on thin adhesive stripes.

We finally connect cells into linear clusters (single-file chains), where cells are connected by elastic springs, to compare to recent experiments exploring such systems. Our models are relevant to observations of cells moving singly and in cohorts through narrow spaces during cancer metastasis.

Invited Talk Fri 16:45

Vimentin provides the mechanical resilience required for amoeboid migration and protection of the nucleus

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The innate immune response depends upon the transmigration of dendritic cells to the lymph nodes. These cells migrate through constricted passages in the tissue in an amoeboid mode of migration. As bidirectional interplay between vimentin intermediate filaments and actomyosin-dependent contractile elements has been shown to regulate adhesion-dependent migration, we examined whether this type of interactions could be involved also in amoeboid migration. To this end, we analyzed the motility and mechanical properties of dendritic cells in the presence and absence of vimentin. Vimentin-deficient dendritic cells were impaired in their capacity to perform amoeboid migration in confined environments. Importantly, these results could also be recapitulated in in vivo mouse experiments. Amoeboid migration requires optimal mechanical resilience of the dendritic cells to be successful. We therefore analyzed mechanical properties of immune cells by shear flow-induced mechanical deformation and AFM and observed that vimentin was required for both long- and short-term stiffness of amoeboid dendritic cells. When the differential involvement of the two cytoskeletal systems was analyzed, we observed that it is not the vimentin IFs per se that provide the required stiffness for dendritic cells but the interaction between vimentin IFs and actin. Furthermore, loss of vimentin resulted in a significant increase in DNA double strand breakage and cell death in dendritic cells subjected to migratory compression. These findings demonstrate that vimentin controls the mechanical properties required for dendritic cell migration and supports the mechanical protection of genome integrity during nuclear positioning and compression in migrating dendritic cells.

Prospective end: 17:30

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