International Meeting of the German Society for Cell Biology

3rd Annual Symposium

Physics of Cancer

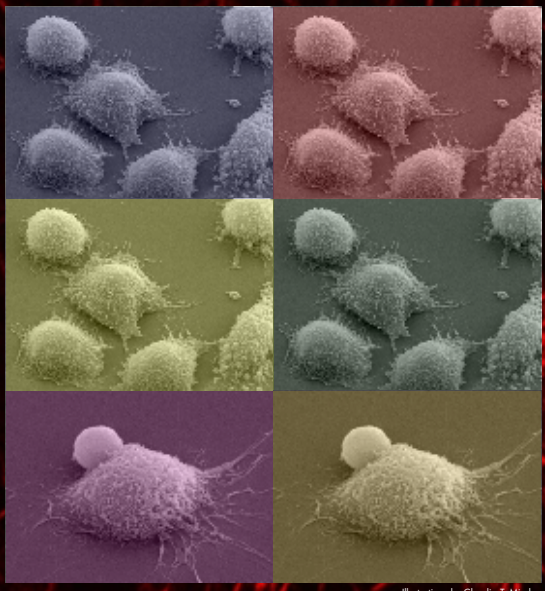
Leipzig, Germany
November 1–3, 2012

PoC

Program

Invited Speakers:

Alexander Bershadsky (Israel)
David Boettiger (USA)
Françoise Brochard-Wyart (France)
John A. Condeelis (USA)
Dennis E. Discher (USA)
Daniel A. Fletcher (USA)
Margaret Gardel (USA)
Martin Herrmann (Germany)
Evamarie Hey-Hawkins (Germany)
Paul Janmey (USA)
Staffan Johansson (Sweden)
Josef A. Käs (Germany)
Gijsje Koenderink (Netherlands)
Avinash S. Kumbhar (India)
Jan Lammerding (USA)
Roderick Lim (Switzerland)
M. Lisa Manning (USA)
Thomas M. Magin (Germany)
Philippe Marcq (France)
Claudia T. Mierke (Germany)
Larry A. Nagahara (USA)
Julie Plastino (France)
Florian Rehfeldt (Germany)
Erik Sahai (UK)
Joachim P. Spatz (Germany)
Valerie M. Weaver (USA)



Illustrations by Claudia T. Mierke.

Organizing Committee:

Claudia T. Mierke (Leipzig)
Josef A. Käs (Leipzig)
Sarah Köster (Göttingen)
Harald Herrmann (Heidelberg)

General Information

Dear participants,

welcome to the *3rd annual "Physics of Cancer" symposium* held at the *University of Leipzig*. This fall, we look forward to a meeting again assembling scientists worldwide pioneering in the investigation of the physical mechanisms underlying cancer progression.

The scientific program consists of invited talks as well as contributed talks and posters. This booklet contains the schedule and abstracts for the three conference days. For more information, please visit our conference website:

www.uni-leipzig.de/poc/2012

Imprint

Responsible for content: PROF. DR. DR. CLAUDIA T. MIERKE

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Aim of the Conference

The analysis of physical properties of cells undergoing malignant transformation is a highly important and an emerging field in current cancer research, cellular biophysics, and cell biology. Recent findings in this novel research field "physics of cancer" revealed that biomechanical properties of cancer cells promote tumor growth, cell motility, and metastasis formation within the human body. In the focus of the studies are certain observations regarding biomechanical properties: First, the actin cortex of cancer cells is pronouncedly softer and hence supports elevated tumor growth and enhanced cancer cell division. Second, although the actin cortex softens, the cancer cells can still resist high pressures exerted from the microenvironment which enables the primary tumor to break-through the tumor boundaries and invade into the surrounding connective tissue extracellular matrix. In return, components of the cytoskeleton are pronounced which results in an overall stiffening of the primary tumor. Third, the ability to transmit and generate contractile forces of cancer cells increases their aggressive potential to invade into the connective tissue microenvironment, promote tumor progression and metastasis formation.

Finally, these novel insights have an impact on the understanding of how and why certain cancer cells get the ability to invade into the human body and form metastases at targeted sites. Thus, we are convinced that the *"Physics of Cancer" symposium* in Leipzig will provide state-of-the-art research technologies, high-class knowledge and fruitful discussions. In addition, these novel insights into physical interactions between cancer cells, the primary tumor, and the microenvironment may help to answer some "old" questions in the progression of cancer disease and may subsequently lead to novel approaches for development and improvement of cancer diagnostics and therapies.

Organizing Committee

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General Information

Conference Location

The *"Physics of Cancer" symposium* will take place at the *University of Leipzig*, more precisely at the building of the *Center for Biotechnology and Biomedicine (BBZ)*.

University of Leipzig
Center for Biotechnology and Biomedicine (BBZ)
Deutscher Platz 5
04103 Leipzig, Germany

The easiest way to get from the city center or the main train station of Leipzig to the BBZ is to use tram line 16. You have to travel in direction "Lößnig" until you arrive at stop "Deutscher Platz". Form here it is just a 5 minute's walk to the BBZ building which lies opposite to *German National Library* and next to the *Max Planck Institute*.
On your way back, you have to travel with tram line 16 in the opposite direction called "Messegelände". For detailed information, please have a look at the interactive map on our website.

Presentations

Scientific presentations will be held either orally or by poster.

Talk sessions will be in the large auditory (ground floor, SR 1.1 to 1.3) of the BBZ. The room is equipped with a data projector with VGA input. Contributed talks are allocated 15 min (including discussion), whereas invited talks are allocated 25 min plus 5 min discussion.

The poster session will be on Thursday, November 1st, 2012 at 19:00 in the foyer of the BBZ. During this session snacks and fingerfood will be provided for all. Authors are asked to mount their posters between 12:00 and 15:00 on that day. Poster boards will be marked with the number according to the scientific program. The material necessary to mount the poster (pins or "Poster Strips") will be provided.

13:00 – 13:15 *Welcome*
BEATE A. SCHÜCKING (Rector of the University of Leipzig)

Session I: Biomechanics of Cell Adhesion and Gene Expression

13:15 – 13:45 **Do tumor cells care about physics?**
JOSEF A. KÄS (University of Leipzig, Germany)

13:45 – 14:15 **Active cell shape control by contractile actin-myosin networks**
GIJSJE KOENDERINK (FOM Institute AMOLF, The Netherlands)

14:15 – 14:45 **Force-dependent and -independent integrin regulation of ROS-production**
STAFFAN JOHANSSON (Uppsala University, Sweden)

14:45 – 15:15 *Coffee break*

15:15 – 15:45 **Extracellular matrix models and the cytoskeleton**
FLORIAN REHFELDT (Georg August University of Göttingen, Germany)

15:45 – 16:15 **Significance of the mechanical properties of the cell nucleus in cell migration and transit through narrow constrictions**
JAN LAMMERDING (Cornell University, USA)

16:15 – 16:45 **The keratin desmosome connection: Crucial player in tissue integrity and malignancy**
THOMAS M. MAGIN (University of Leipzig, Germany)

16:45 – 17:15 **Reprogramming cellular mechanosensing by hyaluronic acid and its receptors**
PAUL JANMEY (University of Pennsylvania, USA)

17:15 – 17:30 **Higher ordered actin bundle assembly induced by counterions and crowding agents**
JÖRG SCHNAUSS (University of Leipzig, Germany)

17:30 – 17:45 **Quantification of live keratin network dynamics**
MARCIN MOCH (RWTH Aachen University, Germany)

17:45 – 18:00 **Keratins are major determinants of migration and invasion by influencing adhesion and cell stiffness**
KRISTIN SELTMANN (University of Leipzig, Germany)

Poster Session

19:00

1 **Native root extract of *Linum usitatissimum* induces cytoskeletal remodeling in the breast cancer cell line MCF-7**
NADJA ENGEL (University of Rostock, Germany)

2 **The role of cellular adhesion for compartmentalization and its impact on tumor spreading**
STEVE PAWLIZAK (University of Leipzig, Germany)

3 **Binding of hyaluronan to sulfated glycosaminoglycans in CD44**
MARIA SCHÖNBERG (University of Leipzig, Germany)

4 **Quantitative characterization of biomaterials and their interaction with living cells by AFM**
TORSTEN MÜLLER (JPK Instruments AG, Germany)

5 **3D topology of tumor cell colonies on 2D substrates**
JANINA LANGE (University of Erlangen-Nuremberg, Germany)

6 **Blood platelets- a model system for understanding cellular mechanics**
AISHWARYA PAKNIKAR (Georg August University of Göttingen, Germany)

7 **Modulation of cell adhesion by non-covalently attached ligands**
ANDREAS MÜLLER (University of Leipzig, Germany)

8 **Circular ruffle dynamics on fibroblast cells**
ERIK BERNITT (University of Bremen, Germany)

9 **Cell adhesion on different materials in the presence or the absence of fetal bovine serum**
MARTINA VERDANOVA (Charles University Prague, Czech Republic)

10 **Blood platelets as a model system for cell substrate interactions**
RABEA SANDMANN (Georg August University of Göttingen, Germany)

11 **Inherently slow and weak forward forces of neuronal growth cones measured by a drift-stabilized atomic force microscope**
THOMAS FUHS (University of Leipzig, Germany)

12 **Mechanics of collagen gels – what cells feel**
JULIAN STEINWACHS (University Erlangen-Nuremberg, Germany)

13 **The evolution of collagen mechanics in response to large amplitude loading**
STEFAN MÜNSTER (University Erlangen-Nuremberg, Germany)

14 **The nanomechanical signature of breast cancer**
MARIJA PLODINEC (University of Basel, Switzerland)

15 **β1 integrins restrict the growth of foci and spheroids**
RAJESH GUPTA (Uppsala University, Sweden)

16 **Sensitive control of active gel contraction**
FELIX KEBER (TU Munich, Germany)

17 **Virtual probing of cells with microscopic imaging and computational modeling**
EVGENY GLADILIN (German Cancer Research Center, Heidelberg, Germany)

18 **Biomechanical studies on human primary cervix cells**
ANATOL FRITSCH (University of Leipzig, Germany)

Session II: Cell Migration and Forces I

08:30 – 09:00 **The role of mechano-sensing and matrix geometry in cancer invasion**
ERIK SAHAI (London Research Institute, UK)

09:00 – 09:30 **Spatially and temporally coordinated processes of cells at molecular to cellular scales**
JOACHIM P. SPATZ (Max Planck Institute for Intelligent Systems, Germany)

09:30 – 10:00 **Mechanical regulation of tumor reversion**
DANIEL A. FLETCHER (University of California, Berkeley, USA)

10:00 – 10:30 *Coffee break*

10:30 – 11:00 **Biomechanical properties of cancer cells determine their aggressiveness**
CLAUDIA T. MIERKE (University of Leipzig, Germany)

11:00 – 11:30 **Self-organization of the actin cytoskeleton: Physical mechanisms and signaling pathways**
ALEXANDER BERSHADSKY (Weizmann Institute of Science, Israel)

11:30 – 12:00 **Mechanical regulation of adhesive bonds**
DAVID BOETTIGER (University of Pennsylvania, USA)

12:00 – 12:15 **The percolation transition of transportation networks as a universal gauge for tumor vascularization**
HANS-GÜNTHER DÖBEREINER (University of Bremen, Germany)

12:15 – 12:30 **Forces in cellular growth and division**
JÖRN HARTUNG (Max Planck Institute for Dynamics and Self-Organisation, Göttingen, Germany)

12:30 – 14:30 *Lunch break*

Session III: Cell Migration and Forces II

14:30 – 15:00 **Coordination of locomotory and invasive protrusions during migration and dissemination of tumor cells in breast tumors**
JOHN S. CONDEELIS (Albert Einstein College of Medicine, USA)

15:00 – 15:30 **Predictive mechanical models for dynamic tissue remodeling**
M. LISA MANNING (Syracuse University, USA)

15:30 – 15:45 **Assembly of cytoplasmic intermediate filament proteins**
NORBERT MÜCKE (German Cancer Research Center, Germany)

15:45 – 16:00 ***In vivo* imaging of lysyl oxidase by fluorine-18 labeled substrate-based radiotracers**
MANUELA KUCHAR (Helmholtz-Zentrum Dresden-Rossendorf, Germany)

16:00 – 16:15 **Temperature-dependent assembly properties of keratin 8/18**
INES MARTIN (Ulm University, Germany)

16:15 – 16:30 **Optical breast tissue pre-screening for the identification of cancer risk and presence of malignancies**
LOTHAR LILGE (University of Toronto, Canada)

16:30 – 17:00 *Coffee break*

17:00 – 17:30 **Boron clusters in cancer therapy**
EVAMARIE HEY-HAWKINS (University of Leipzig, Germany)

17:30 – 18:00 **Beyond conventional limits to cancer: Where can a physical sciences perspective fit in?**
LARRY A. NAGAHARA (National Cancer Institute, USA)

19:00 *Get together for invited speakers*

Session IV: Membrane Mechanics, Cytoskeletal Dynamics, and Tumor Progression

08:00 – 08:30 **Lamin-A levels limit 3D-migration but protect against migration-induced apoptosis**
DENNIS E. DISCHER (University of Pennsylvania, USA)

08:30 – 09:00 **Mechanosensitivity and motility of cellular aggregates**
FRANÇOISE BROCHARD-WYART (Institute Curie, France)

09:00 – 09:30 **Extrinsic and intrinsic force regulation of tumor progression**
VALERIE M. WEAVER (University of California, San Francisco, USA)

09:30 – 10:00 **The nanomechanical signature of breast cancer**
RODERICK Y. H. LIM (University of Basel, Switzerland)

10:00 – 10:15 **Nonlinear fibrin mechanics and its alterations by platelets**
LOUISE JAWERTH (Harvard University, USA)

10:15 – 10:45 *Coffee break*

10:45 – 11:15 **Surface changes on dying tumor cells instruct the immune system**
MARTIN HERRMANN (University Hospital Erlangen, Germany)

11:15 – 11:45 **Regulation of focal adhesion maturation by the actin cytoskeleton**
MARGARET GARDEL (University of Chicago, USA)

11:45 – 12:15 **Cell motility and cytoskeleton assembly**
JULIE PLASTINO (Institute Curie, France)

12:15 – 12:45 **Ruthenium(II) polypyridyl complexes as carriers for DNA delivery**
AVINASH S. KUMBHAR (University of Pune, India)

12:45 – 13:15 **Mechanics of contractile actomyosin bundles**
PHILIPPE MARCQ (Institute Curie, France)

13:15 – 13:30 *Prospective end*

Session I: Biomechanics of Cell Adhesion and Gene Expression

Invited Talk Thu 13:15

Do tumor cells care about physics? — JOSEF A. KÄS, ANATOL FRITSCH, TOBIAS KIESSLING, DAVID NNETU, STEVE PAWLIZAK, ROLAND STANGE, FRANZISKA WETZEL, MAREIKE ZINK — University of Leipzig, Faculty of Physics and Earth Sciences, Institute of Experimental Physics I, Soft Matter Physics Division, Linnéstr. 5, 04103 Leipzig, Germany

With an increasing knowledge in tumor biology an overwhelming complexity becomes obvious which roots in the diversity of tumors and their heterogeneous molecular composition. Nevertheless in all solid tumors malignant neoplasia, i.e. uncontrolled growth, invasion of adjacent tissues, and metastasis, occurs. Recent results indicate that all three pathomechanisms require changes in the active and passive cellular biomechanics. Malignant transformation causes cell softening for small deformations which correlates with an increased rate of proliferation and faster cell migration. The tumor cell's ability to strain harden permits tumor growth against a rigid tissue environment. A highly mechanosensitive, enhanced cell contractility is a prerequisite that tumor cells can cross its tumor boundaries and that these cells can migrate through the extracellular matrix. Initial tumor growth is limited to the developmental compartments from which the tumor cells originate. The observation that compartmentalized cell growth is not merely found during development but throughout tumor progression does not only radically redefine how tumors have to be resected, it also has critical impact on how a tumor progresses and what the target cells must be when screening for new cytostatics. It is the cells that can cross compartment boundaries and thus are not restricted to local tumor growth that have to be fought by chemotherapy. Therefore, passive and active biomechanical behavior of tumor cells, cell jamming, cell demixing and surface tension-like cell boundary effects are investigated as key factors to stabilize or overcome compartment boundaries. Insights into changes of these properties during tumor progression may lead to selective treatments. Such drugs would not cure by killing cancer cells, but slow down tumor progression with only mild side effects and thus may be an option for older and frail patients.

Invited Talk Thu 13:45

Active cell shape control by contractile actin-myosin networks — GIJSJE KOENDERINK — FOM Institute AMOLF, Science Park 104, 1098 XG Amsterdam, The Netherlands

Cells need to constantly change their shape to perform vital functions, such as growth, division, and movement. Dysregulation of cell shape can have severe consequences such as cancer. An important contributor to cell shape changes is the actin cortex that lies underneath the cell membrane. This polymeric cortex has the remarkable ability to drive shape changes by means of myosin motors that actively generate contractile forces. Single-molecule studies have provided detailed insights into the mechanisms of force production by individual motor molecule. However, a mechanistic understanding of collective self-assembly of myosin motors and actin filaments into force-generating arrays is still lacking.
I will discuss our recent studies of the mechanisms by which myosin motors collectively organize actin filaments into contractile structures using simplified model systems devoid of biochemical regulation. Using fluorescence microscopy, we were able to resolve how myosin motors contract actin networks. In principle, motors exert both tensile and compressive forces in networks of randomly oriented actin filaments. However, actin filaments buckle under compression, which breaks the symmetry and leads to contraction. By systematically tuning the network crosslink density (using fascin), we were able to show that motors contract actin networks only above a sharp threshold in crosslink density. We discovered that right at this threshold, the motors rupture the network into clusters that exhibit a broad distribution of sizes, as expected in filamentous networks near a percolation threshold.
I will end with an outlook about our recent work on membrane deformation by contractile actin-myosin networks.

Invited Talk Thu 14:15

Force-dependent and -independent integrin regulation of ROS-production — STAFFAN JOHANSSON — Department of Medical Biochemistry and Microbiology, The Biomedical Center, Uppsala University, Box 582, SE-751 23, Uppsala, Sweden

We have analyzed the role of the integrin subunit β1 in three-dimensional (3D) cell cultures using integrin β1 null mouse cells (MEFβ1-/- and GD25) and their β1 integrin-expressing counterparts. GD25 and GD25β1 cells proliferated with similar kinetics in sub-confluent 2D cultures, but GD25 cells formed foci with 5-fold higher frequency than GD25β1 cells. During 3D growth as spheroids, GD25 continuously increased in size for >30 days while the growth of GD25β1 spheroids ceased after 14 days. Similarly, MEFβ1-/- cells formed foci and grew as spheroids, while the β1 integrin-expressing MEF did not. The expression levels of cell cycle markers were similar between GD25β1 and GD25 spheroids. Apoptotic cells accumulated earlier in GD25 spheroids; however, cell death increased with spheroid volume in both spheroid types. In both cell systems, the presence of β1 integrins resulted in higher levels of both active myosin light chain and inactive myosin light chain phosphatase, and in a more compact spheroid structure. The results reveal that regulation of 3D growth in spheroids and foci is dependent on the β1 subfamily of integrins, and suggest that myosin-based contraction in combination with cell death limits the growth of β1-expressing spheroids.

We also compared integrin signals induced by mechanical force with signals generated during cell attachment in GD25β1 and the non-transformed human fibroblasts BJ hTERT. The phosphorylation of several intracellular signaling mediators was strongly elevated after cell attachment to fibronectin and vitronectin for 30 minutes, while the main response during cyclic stretching of the cells was the phosphorylation of ERK1/2. Several of the integrin signals generated during the early phase of cell attachment and spreading occurred independently of intracellular contractile force acting on the adhesion sites since they were unaffected by inhibition of ROCK or myosin II.

The importance of reactive oxygen species (ROS) for the integrin-induced signaling pathways during attachment and cyclic stretching was investigated. Rotenone, a specific inhibitor of complex I in the mitochondrial respiratory chain, abolished the activation of AKT during adhesion. Rotenone also prevented adhesion-induced ERK1/2 phosphorylation in the BJ hTERT cells but had the opposite effect in GD25β1 cells. Rotenone did not markedly influence signals induced by cyclic stretching of the cells. On the other hand, scavenging of extracellular ROS did not significantly influence the adhesion-derived signaling in the cell lines, but in GD25β1 it led to a selective and pronounced enhancement of stretch-induced ERK1/2 phosphorylation. The results point to a role of NOX-generated ROS in the regulation of ERK1/2 during stretching of GD25β1 cells. Thus, different types of integrin stimulation (ligand-binding and mechanical force) may generate ROS from different sources.

Invited Talk Thu 15:15

Extracellular matrix models and the cytoskeleton — FLORIAN REHFELDT — 3rd Institute of Physics – Biophysics, Georg August University Göttingen, Germany

It is nowadays well appreciated that mechanical properties of microenvironments of cells are as important as their biochemical composition. An especially striking experiment of this mechano-sensitivity demonstrated that the Young's modulus E of the substrate can even direct the lineage differentiation of human mesenchymal stem cells (hMSCs).

To elucidate the complex interplay of physical and biochemical mechanisms of cellular mechano-sensing and force transduction, mechanically well-defined extracellular matrix (ECM) models are essential. While elastic substrates made of poly-acrylamide (PA) are widely in use, they have the potential drawback that the precursors are cytotoxic.

Here, a novel biomimetic ECM model based on hyaluronic acid (HA) was successfully established that exhibits a widely tuneable and well-defined elasticity E, enables 2D and 3D cell culture and enables us to mimic a variety of distinct *in vivo* microenvironments.

Invited Talk Thu 15:45

Significance of the mechanical properties of the cell nucleus in cell migration and transit through narrow constrictions — JAN LAMMERDING — Cornell University, Weill Institute for Cell and Molecular Biology, Department of Biomedical Engineering, 235 Weill Hall, Ithaca, NY 14853-7202, USA

Metastasis is responsible for the majority of cancer deaths and presents one of the primary challenges in the fight against cancer. During metastatic progression, cancer cells migrate through dense tissues and extracellular matrices with typical pore sizes of only a few micrometers; constrictions encountered during intra- and extravasation and the perfusion through small capillaries present similar challenges. Since the nucleus occupies a large fraction of the cell volume and is (normally) significantly stiffer than the surrounding cytoplasm, we hypothesized that the nucleus presents a substantial physical obstacle when cells pass through constrictions smaller than the size of the nucleus. Increased nuclear deformability, caused by changes in the expression of nuclear envelope proteins such as lamins or altered chromatin organization, could then facilitate passage of cancer cells through narrow spaces or pores, thereby promoting invasion and metastasis. To test whether altered nuclear envelope composition and deformability could enhance cellular passage through narrow constrictions, we created a panel of cell lines in which we systematically modified nuclear envelope composition by overexpression or knockdown of specific nuclear envelope. The effect on nuclear mechanics was confirmed by observing nuclear deformations under applied substrate strain or by atomic force microscopy. To determine the minimal physical pore size through which cells can successfully traverse, we fabricated microfluidic devices with precisely engineered constrictions ranging from 2 to 15 µm in size and then perfused cells through these channels or induced the cells to migrate along a chemotactic gradient across the channels. These studies were complemented with transwell migration assays and with experiments in which cells were monitored during migration in 3-dimensional collagen scaffolds with variable pore sizes in the absence and presence of matrix metalloprotease inhibitors. We found that cells that lack the nuclear envelope proteins lamins A and C have softer, more deformable nuclei and were able to traverse narrow constrictions significantly faster in the perfusion studies than cells expressing normal levels of lamins A and C. Conversely, ectopic expression of lamin A resulted in significantly slower passage through narrow constrictions and in the migration assays. Similar results were observed in the presence of cytoskeletal disrupting drugs, indicating that nuclear deformability is a rate-limiting factor in the passage of cells through narrow constrictions. In the migration studies, we similarly found that cells lacking lamins A/C had increased migration efficiency through narrow pores, while cells with increased lamin A/C levels were impaired in their migration. Importantly, the observed differences were more severe for smaller pore sizes than for larger pores, indicating that deformation of the nucleus rather than general defects in cell migration was responsible for these effects. In conclusion, our results indicate that the normally large and stiff nucleus can pose a substantial obstacle for the passage of cells through narrow constrictions, and that modifications in nuclear envelope composition that alter nuclear stiffness can modulate the ability of cells to transit pores smaller than the size of the nucleus.

Invited Talk Thu 16:15

The keratin desmosome connection: Crucial player in tissue integrity and malignancy — THOMAS M. MAGIN — Division of Cell and Developmental Biology, Institute of Biology and Translational Center for Regenerative Medicine, University of Leipzig, 04103 Leipzig, Germany

Stable cell-cell interactions are crucial for the maintenance of cell shape and the coherence of epithelial sheets. Transient disruption of cell interactions, changes in cell shape and cell rigidity are hallmarks of epithelial-mesenchymal transition, a process that may underlie tumor metastasis. While the role of the actin-adherens junction complex for maintenance of intercellular adhesion and cell rigidity is widely accepted, the respective contribution of the keratin intermediate filament- (IF) desmosome complex has been largely ignored, owing to the unique properties of keratins. We have recently established transgenic mouse and corresponding keratinocyte cell lines that lack the entire keratin protein family or re-express a single keratin pair. We find that keratinocytes lacking all keratins show decreased intercellular cell adhesion, reduced stability of epithelial sheets upon mechanical stress, elevated cell migration and invasion. Reduced stability of desmosomes in the absence of keratins is mediated by elevated desmoplakin phosphorylation through PKCα. Re-expression of the single keratin pair K5/14 or blocking of PKCα activity rescued the phenotype. In contrast to prediction, we find that keratins but not actin, are major contributors of cell rigidity, based on optical stretcher data. These findings uncover a major role of keratins in supporting intercellular adhesion and epithelial cell mechanics. Our data suggest that the keratin cytoskele-

ton may represent a barrier against transformation and metastasis through multiple protein interactions and shaping cell rigidity.

Invited Talk Thu 16:45

Reprogramming cellular mechanosensing by hyaluronic acid and its receptors — PAUL JANMEY — Institute for Medicine and Engineering, University of Pennsylvania, USA

Changes in tissue and organ stiffness occur during development and are frequently symptoms of disease. Many cell types respond to the stiffness of substrates and neighboring cells *in vitro*, and *in vivo* cells engage their extracellular matrix (ECM) by multiple mechanosensitive adhesion complexes and other surface receptors that potentially modify the mechanical signals transduced at the cell/ECM interface. Hyaluronic acid (also called hyaluronan or HA), a soft polymeric glycosaminoglycan matrix component prominent in embryonic tissue and upregulated during wound healing, cancer, and other pathologic states, augments or overrides mechanical signaling by some classes of integrins to produce a cellular phenotype otherwise observed only on very rigid substrates. Most normal primary cell types cannot use HA as an adhesive anchor without simultaneous linkage to an integrin ligand, but many cancer cell types adhere directly to HA-containing matrices. The effects of HA, mediated by its receptors CD44 and CD168 interact specifically with signals initiated by matrix proteins such as fibronectin that bind β3 integrins. Because HA production is tightly regulated during development and injury and frequently upregulated in disease, interaction of signaling between HA receptors and specific integrins might be an important element in mechanical control of development and homeostasis.

Contributed Talk Thu 17:15

Higher ordered actin bundle assembly induced by counterions and crowding agents — JÖRG SCHNAUSS[1], FLORIAN HUBER[1,2], DAN STREHLE[1], MARTIN GLASER[1], JOSEF A. KÄS[1] — [1]University of Leipzig, Faculty of Physics and Earth Sciences, Institute of Experimental Physics I, Soft Matter Physics, Linnéstr. 5, 04103 Leipzig, Germany — [2]FOM Institute for Atomic and Molecular Physics (AMOLF), Science Park 113, 1098 XG Amsterdam, The Netherlands

Various cellular functions depend on the properties of cytoskeletal actin structures. These structures range from loosely networks to densely packed bundles and can form clusters in higher-level assemblies like asters and nematic phases.
Aster formation was usually attributed to dissipative processes, e.g. actin and its associated motor-protein (myosin). We show non-dissipative bundle arrangements in aster-like structures independent of other proteins.
Ordering occurs due to either a high divalent counterion concentration or crowding agents. These processes are well-known to form single actin bundles without any crosslinkers. In our case, we did not only observe bundle formation but also the development of tertiary structures. Emerging structures depend on the concentration of actin and bundling agents accordingly. To observe the transition from an unordered to an ordered state, we use an oil-layer to control evaporation of actin droplets precisely [1]. Moreover, we developed further experimental systems to study the formation of actin networks by entropic forces.
Experiments revealed a general tendency of homogeneous F-actin solutions to aggregate into regular actin bundle networks connected by aster-like centers. Preordering of filaments already induces drastic changes in the network's architecture. Due to the independency of other proteins, this effect emphasizes that structure formations on higher levels can be controlled by self-assembly arguments and hence energy minimization.

[1] F. HUBER, D. STREHLE, J. KÄS: *Counterion-induced formation of regular actin bundle networks*, Soft Matter 8 (4): 931–936 (2012)

Contributed Talk Thu 17:30

Quantification of live keratin network dynamics — MARCIN MOCH[1], GERLIND HERBERICH[2], TILL AACH[2], REINHARD WINDOFFER[1], RUDOLF LEUBE[1] — [1]RWTH Aachen University, Institute of Molecular and Cellular Anatomy, 52074 Aachen, Germany — [2]RWTH Aachen University, Institute of Imaging and Computer Vision, 52056 Aachen, Germany

Keratin intermediate filaments are major components of the epithelial cytoskeleton, which protects epithelial cells against different forms of stress. In cell culture most of

the keratin network is in motion and subject to continuous assembly and disassembly. On the other hand, certain parts of the network are static and rather stable, notably in regions around the nucleus and in desmosome- and hemidesmosome-anchored filaments. The situation becomes even more complex when cells respond in a non-uniform manner to different growth factors and drugs. At present tools are lacking to quantitatively describe local keratin dynamics.

In this study we present combined experimental/computational approaches to measure keratin network motility and turnover rates in cultured cells. To this end, keratin filaments were tagged with enhanced green fluorescent protein. Stable A431 vulva carcinoma-derived cell clones were then analysed by confocal time-lapse fluorescence microscopy under highly standardized conditions. The resulting fluorescence micrograph series were further subjected to computational image analyses. Based on a maximum-a-posteriori motion estimation algorithm motion vector fields were generated to determine local speed and direction of keratin fluorescence. Taking relative fluorescence intensities into account we were then able to identify sources and sinks within the imaged cells. We found that keratin assembly occurred primarily in the cell periphery, whereas disassembly was localized to the nucleus. For statistical analyses and comparison of different culture conditions, the data were stratified onto an idealized round cell. This revealed a synchronized inward-directed flux of 165 nm/min from the cell periphery toward the nucleus 24-35 h after seeding, and a flux of 108 nm/min 48-58 h after seeding.

Finally, we applied this work flow to a direct comparison of cells cultured in the presence and absence of epidermal growth factor and found that motility and turnover were significantly increased immediately after growth factor addition. This effect was inhibited by epidermal growth factor receptor antibodies and corresponded well with turnover measurements using fluorescence recovery after photobleaching (FRAP) analyses.

Taken together, the newly developed tools allow us to detect changes in the dynamic properties of the keratin cytoskeleton with high temporal and spatial resolution and will therefore be useful to study the influence of regulatory pathways controlling different epithelial properties.

Contributed Talk Thu 17:45

Keratins are major determinants of migration and invasion by influencing adhesion and cell stiffness — Kristin Seltmann[1], Anatol Fritsch[2], Josef A. Käs[2], Thomas M. Magin[1] — [1]University of Leipzig, TRM Leipzig & Institute of Biology, Division of Cell and Developmental Biology, Philipp-Rosenthal-Straße 55, 04103 Leipzig, Germany — [2]University of Leipzig, Division of Soft Matter Physics, Department of Physics, Linnéstr. 5, 04103 Leipzig, Germany

The keratin cytoskeleton is crucial for cell-matrix adhesion and migration in several epithelia including the epidermis. Cell motility is an essential process in the skin, where it participates in skin development, wound healing, inflammation and malignant progression. Despite extensive studies, the role of keratins in adhesion, migration and invasion is only partially understood.

Here, we address this issue in keratinocytes in which all keratins are depleted by genome engineering. Unexpectedly, such keratinocytes maintain many characteristics of normal counterparts. The absence of the entire keratin cytoskeleton, however, leads to loss of plectin from the hemidesmosomes. To investigate the functional consequences, migration and adhesion assays were performed. These revealed that in the absence of keratins, keratinocytes adhere much faster to ECM substrates and migrate ~2 times faster compared to wildtype cells. Re-expression of the single keratin pair K5 and K14 fully reversed the above phenotype. Moreover, invasion behaviour was also increased correlating with higher cell deformability in keratin-free cells. Our data uncover a novel role of keratins in the maintenance of hemidesmosomes upstream of plectin and thereby influencing adhesion, migration and invasion with implications for epidermal homeostasis and pathogenesis. This study supports the view that downregulation of keratins observed during epithelial-mesenchymal transition directly contributes to the migratory and invasive behavior of tumor cells.

Poster Session

Poster 1 Thu 19:00

Native root extract of *Linum usitatissimum* induces cytoskeletal remodeling in the breast cancer cell line MCF-7 — Nadja Engel[1], Sophie Bauer[2], Barbara Nebe[1] — [1]University of Rostock, Medical Research Center, Department of Cell Biology, Schillingallee 69, 18057 Rostock, Germany — [2]TU Dresden, Biotechnology Center, Department of Molecular Bioengineering, Tatzberg 47/49, 01307 Dresden, Germany

Breast cancer cells differ in many aspects from their healthy counterparts. Our research focuses on natural products with anti-tumor activity which addresses cytoskeletal and adhesion-related proteins, cancer metabolism or migration processes of breast cancer cells. Here we report of the cytoskeletal alterations of MCF-7 breast cancer cells after treatment with either the single phytoestrogen genistein (G) or a mixture of phytoestrogens within the native root extract of Linum usitatissimum (L). By means of the newly developed software FilaQuant for actin filament recognition [1,2], we are able to quantify the actin organization via mathematical image processing of the confocal microscopic exposures. The automatic processed images represent the actin filament formation in conformance to the confocal microscopic observations and show obviously, that the average filament length after treatment with genistein (100 µM) or the flax extract (50 µg/ml) is significantly higher. Furthermore, the influences on α- and β-tubulin expression as well as the formation of focal adhesions under exposure of G and L were studied.

[1] C. Matschegewski, S. Staehlke, H. Birkholz, R. Lange, U. Beck, K. Engel, B. J. Nebe: *Automatic Actin Filament Quantification of Osteoblasts and Their Morphometric Analysis on Microtextured Silicon-Titanium Arrays*, Materials 5: 1176–1195 (2012)

[2] H. Birkholz: *Extracting the Ridge Set as a Graph for Quantification of Actin Filament Images obtained by Confocal Laser Scanning Microscopy*, Journal of Electronic Imaging 21(2): 021110 (2012)

Poster 2 Thu 19:00

The role of cellular adhesion for compartmentalization and its impact on tumor spreading — Steve Pawlizak, Anatol Fritsch, Mareike Zink, Josef A. Käs — University of Leipzig, Faculty of Physics and Earth Sciences, Institute of Experimental Physics I, Soft Matter Physics Division, Linnéstraße 5, 04103 Leipzig, Germany

Compartmentalization is a fundamental process of cellular organization that occurs in particular during embryonic development. A simple model system demonstrating compartmentalization involves mixing together two different populations of suspended cells. After a certain time, this mixture will eventually segregate into two phases, whereas mixtures of the same cell type will not. The *differential adhesion hypothesis* by Malcolm S. Steinberg (1960s) explains this organization behavior by differences in surface tension and adhesiveness of the interacting cells [1]. To understand to which extent the same physical principles affect tumor growth and spreading between compartments [2], we investigate cellular mechanical properties and interactions of various cell types, such as healthy and cancerous breast cell lines of different malignancy as well as primary cells from human cervix carcinoma. To this end, a set of techniques is applied: The *Optical Stretcher* is used for whole cell rheology. Cell-cell-adhesion forces are directly measured with a modified *atomic force microscope*. 3D segregation experiments are employed with a newly developed setup for long-term observation of *droplet cultures*. The combination of these techniques will help to clarify the role of cellular adhesion for compartmentalization and tumor spreading.

[1] R. A. Foty, M. S. Steinberg: *The differential adhesion hypothesis: a direct evaluation*, Dev. Biol. 278 (1): 255–263 (2005)

[2] A. Fritsch, M. Höckel, T. Kiessling, K. D. Nnetu, F. Wetzel, M. Zink, J. A. Käs: *Are biomechanical changes necessary for tumour progression?*, Nature Physics 6 (10): 730–732 (2010)

Poster 3 Thu 19:00

Binding of hyaluronan to sulfated glycosaminoglycans in CD44 — Maria Schönberg[1,2], Ulrike Obeck[2], Jürg Flemmig[1,2], Jürgen Arnhold[1,2] — [1]University of Leipzig, Translational Centre for Regenerative Medicine (TRM) Leipzig, Philipp-Rosenthal-Straße 55, 04103 Leipzig, Germany — [2]University of Leipzig, Institute of Medical Physics and Biophysics, Härtelstraße 16-18, 04107 Leipzig, Germany

Sulfation of glycosaminoglycans (GAGs) of components of extracellular matrix and cell surface is an important regulatory mechanism in inflammatory immune response and carcinogenic processes. All sulfotransferases use 3´-phosphoadenosine 5´-phosphosulfate (PAPS) as a common sulfate donor that is produced by PAPS synthase. In order to detect the sulfation level of monocytes/macrophages we established a CD44-hyaluronan binding assay based on flow cytometry. Monocytes were isolated from human peripheral blood of healthy volunteers. Macrophages were cultivated from monocytes at 37 °C in the presence of 100 U/ml granulocyte-macrophage colony-stimulating factor (GM-CSF). CD44 is a cell-surface receptor that binds via heparan sulfate side chains hyaluronan, a glycosaminoglycan that is released from cells at inflammatory sites. Using flow cytometry approaches, the expression of CD44 was followed by antibodies against CD44, while the ability of CD44 to bind hyaluronan was assessed with FITC-labelled hyaluronan. TNFα increased the expression of CD44 on macrophages, but shows no significant alterations of CD44 expression in monocytes. In macrophages, TNFα increased the hyaluronan binding on cell-surface, but in monocytes TNFα has no significant influence concerning hyaluronan binding. The inhibitor of PAPS synthase chlorate diminished the binding of hyaluronan in a concentration-dependent manner in both TNFα stimulated and non-stimulated cells. This assay is a convenient tool to investigate effect on sulfation after the treatment with anti-inflammatory and anti-carcinogenic agents.

Poster 4 Thu 19:00

Quantitative characterization of biomaterials and their interaction with living cells by AFM — Torsten Müller, Carmen Pettersson, Tanja Neumann — JPK Instruments AG, Bouchestr. 12, 12435 Berlin, Germany

Introduction: Topography, roughness and mechanical properties of biomaterials are crucial parameters influencing cell adhesion/motility, morphology and mechanics as well as the development of stem/progenitor cells [1,2,3,4]. Atomic force microscopy (AFM) is a powerful tool not only to study the morphology in terms of high resolution imaging and roughness measurements, but also to map mechanical and adhesive properties. Combining these remarkable abilities with advanced optical microscopy allows for extensive characterization of biomaterials.
Methods: AFM is based on a flexible cantilever stylus that is scanned over the sample. The probe-sample interaction induced deflection of the cantilever is finally converted into sample topography and interaction force. The sensitivity of the detection system and the accuracy of piezo actuators with capacitive sensors allow for resolving structures of less than 1 nm and forces on the pN scale. Different imaging modes can resolve structures of biomaterials in physiological conditions without the Abbe diffraction limit. In force spectroscopy mode, interaction forces between the (modified) cantilever and any substrate can be investigated. Using Single Cell Force Spectroscopy (SCFS), cell-substrate or cell-cell interactions can be measured down to single protein unbinding. The cantilever can also serve as nano-indentation tool to analyse mechanical properties like the Young's modulus of biomaterials or cells.
Results: Using AFM imaging, the nanostructure of biomaterials like aligned collagen matrices have been resolved as well as cell alignment on such structures [4,5]. SCFS quantified the adhesion force and the contribution of different components, e.g. from the extra cellular matrix of living cells to implant materials as from cochlear implants [6]. Force-indentation measurements on cells using colloidal probes showed a significant effect of micro-patterned substrates on cellular elasticity [2].
Discussion & Conclusions: AFM is a multipurpose technology which is much more than simple imaging. Interaction forces from single molecule unbinding to cell adhesion and analysis of surface and mechanical properties of biomaterials and cells make AFM to a key technology in biomaterial research. Nano-mechanical analysis of cells increasingly gains in importance in different fields in cell biology like cancer research [7] and developmental biology [8]. We present a strategy to comprehensively characterize biomaterials as well as

their interaction with cells and influence on cell behavior.

[1] Elter *et al.*, Eur Biophys J 40 (3): 317–27 (2011)

[2] McPhee *et al.*, Med Biol Comput 48 (10): 1043–53 (2010)

[3] Engler *et al.*, Cell 126 (4): 677–89 (2006)

[4] Kirmse *et al.*, J Cell Sci 124 (11): 1857–66 (2010)

[5] Cisneros *et al.*, Small 3 (6): 956–63 (2007)

[6] Aliuos *et al.*, Biomed Tech 55: 66–8 (2010)

[7] Cross *et al.*, Nat Nanotech 2 (12): 780–83 (2007)

[8] Krieg *et al.*, Nat Cell Biol 10 (4): 429–36 (2008)

Poster 5 Thu 19:00

3D topology of tumor cell colonies on 2D substrates — JANINA LANGE[1], CLAUS METZNER[1], JULIAN STEINWACHS[1], PAMELA STRISSEL[2], BEN FABRY[1] — [1]University of Erlangen-Nuremberg, Department of Physics, Biophysics Group, Henkestraße 91, 91052 Erlangen, Germany — [2]University of Erlangen-Nuremberg, Department of Obstetrics and Gynaecology, Universitätsstraße 21-23, 91054 Erlangen, Germany

Studies of collective cell migration on a 2D substrate have recently shown to be governed by force transmission through cell-matrix and cell-cell adhesions [1]. In these studies, confluent cell monolayers are constrained by PDMS-masks. After mask removal, cells at the colony edge begin to migrate outward, thereby increasing tensile cell-matrix and cell-cell forces that direct the migratory behavior of cells in the colony. Alternatively, the time evolution in the shape (2D-projection) of cell colonies formed from single cells has been studied [2]. A comparative analysis of 30 cell lines, including cancer cells, showed only negligible differences in the roughness of the colony outline. The 2D shape of the cell colony is therefore insensitive to differences in the cell-cell versus cell-matrix adhesion properties.
In our study, we reasoned that dividing cells disturb the cell layer and lead to a re-distribution of the local tension pattern; daughter cells can re-attach onto the substrate, or can pile up to form 3-dimensional cell clusters, depending more upon the cell-cell versus cell-matrix adhesion properties. Indeed, current theoretical models claim to predict 3D cell colony shapes from an energy minimization strategy between cell-matrix adhesion and cell-cell cohesion, and also consider cell-cell contact inhibition of proliferation, and apoptosis upon loss of cell-matrix contact [3]. However, active and persistent cell migration on a 2D substrate, which releases mechanical tension, is generally neglected in these models, as are chemical gradients and intercellular signaling.
In our investigations, we tested the described model predictions in a combined migration and tumor growth assay. We compared weakly adhesive C33a cervix carcinoma cells, and highly adhesive HT1080 fibrosarcoma cells. Cells were grown to a confluent monolayer with a circular shape (diameter 4 mm) using a PDMS mask. Moreover, cells were marked with 1µm fibronectin-coated fluorescent beads. After mask removal, cells were continuously observed with phase contrast and fluorescent microscopy. The 3D shape of the cell colony was measured with confocal microscopy.
Highly adhesive HT1080 fibrosarcoma cells showed pronounced directed migration away from the cell colony. The 2D projection of the colony shape remained perfectly circular, with a rapid increase of the colony diameter. At the same time, a complex 3D topology emerged, with hills and valleys showing a roughness of up to 100 µm in height. In contrast, weakly adhesive C33a cervix carcinoma cells showed a minimal increase in colony diameter even after 7 days of culture, with only a small increase in the roughness of the 2D shape outline by the emergence of finger-like protrusions. Cells piled up nearly evenly to a height of 60 µm, with little fluctuations in the 3D topology. These findings are in agreement with simple theoretical models that neglect signaling and active migration, and only consider adhesion/cohesion, growth, and apoptosis. We conclude that the 3D topology of cell colonies, in contrast to the shape of their 2D projections, is highly sensitive to cell-cell cohesion relative to cell-matrix adhesion, and may therefore provide a robust and simple readout to assay the phenotype of tumor cells.

[1] SERRA-PICAMAL *et al.*, Nat Phys 8: 628–634 (2012)

[2] BRÙ *et al.*, Biophys J 85(5): 2948–2961 (2003)

[3] GALLE *et al.*, Biophys J 88 (1): 62–75 (2005)

Poster 6 Thu 19:00

Blood platelets- a model system for understanding cellular mechanics — AISHWARYA PAKNIKAR, SARAH SCHWARZ G. HENRIQUES, RABEA SANDMANN, SARAH KÖSTER — Georg August University

of Göttingen, Institute for X-Ray Physics/ CRC Nano-Spectroscopy and X-Ray Imaging, Research Group 'Nanoscale Imaging of Cellular Dynamics', Friedrich-Hund-Platz 1, 37077, Göttingen, Germany

Platelets or thrombocytes are the smallest cells (2-5 µm in diameter; discoid shape) in the human body, which play a key role in the formation of blood clots in response to bleeding. When activated during a bleeding event, they rapidly rearrange their actin-myosin cytoskeleton to generate forces resulting in contraction and change in shape. This activation is a highly dynamic, non-equilibrium process and although it is known to be driven by biochemical interactions and cellular forces, the underlying mechanical principles are still poorly understood. In our recent work, 2D traction force fields generated by single platelets during contraction were measured on soft polyacrylamide (PAA) substrates (elasticity ~4 kPa), and the average total force of a single platelet was found to be ~34 nN [1]. Experimental evidence also indicated that myosin contributes majorly to the total force generation and the platelet cytoskeletal reorganization is dependent on the stiffness of the substrate. These findings have led to several open questions. Firstly, the extent of contribution of other, myosin-independent forces to the total measured forces is still unclear. We are seeking an answer to this important question by using a chemical inhibitor of myosin, blebbistatin, and recording the platelet force fields with the help of traction force microscopy (TFM). To this end, we have designed an efficient microflow setup that allows the locally and spatially defined application of blebbistatin to the platelets adhered to PAA substrates during an ongoing TFM recording. From these experiments, we hope to learn about the contribution of myosin-independent forces such as actin depolymerization forces and/or passive, elastic forces, to the previously measured total forces. Secondly, a quantitative analysis of the mechanical response of the platelets to different substrate stiffnesses is still elusive. We are doing these analyses by measuring the total forces of single platelets as a function of substrate elasticity using the TFM technique. It is possible to vary the substrate elasticities by adjusting the monomer to crosslinker ratio for the PAA polymer. From this, we will gain insights into some aspects of the mechanosensing property of platelets. Our experimental findings aim to build a mechanical model for platelet activation. Such a model will add to our knowledge on the general principles governing cellular force generation and cell mechanics which play an important role in cancer research.

[1] S. Schwarz Henriques, R. Sandmann, A. Strate, S. Köster: *Force field evolution during human blood platelet activation*, Journal of Cell Science 125(16): 3914–3920 (2012)

Poster 7 Thu 19:00

Modulation of cell adhesion by non-covalently attached ligands — Andreas Müller[1], Christina Müller[1], Rayk Hassert[2], Annette Beck-Sickinger[2], Tilo Pompe[1] — [1]Universität Leipzig, Institute of Biochemistry, Biophysical Chemistry, Johannisallee 21/23, 04103 Leipzig, Germany — [2]Universität Leipzig, Institute of Biochemistry, Biochemistry and Bioorganic Chemistry, Brüderstraße 34, 04103 Leipzig, Germany

The adhesion of cells influences cell fate as extracellular mechanical and physicochemical signals can trigger cell differentiation, proliferation or even apoptosis. In this context it is crucial to focus on cell adhesion to well-defined substrates as the strength of cell adhesion and the activation of biochemical signals depend on substrate characteristics such as stiffness and the coupling of extracellular adhesion ligands. We concentrate on non-covalently bound ligands, as this is an underestimated aspect in cell adhesion with respect to frequently mobile adhesion ligands on cell culture substrates and implant materials.

We fabricated thin film coatings of maleic acid copolymers on top of polyacrylamide hydrogels to tune ligand affinity by changing the fraction of polar groups on the surface (i.e. variable hydrophobicity) in combination with the modulation of substrate stiffness. Time-resolved cell traction force microscopy was used to investigate behavior of human umbilical vein endothelial cells during the initial stages (up to 2h) of the adhesion process.

We address the time dependence of biophysical cell signals (cell traction, strain energy and contractile moment) in dependence on ligand affinity and substrate stiffness using fibronectin ligands. Furthermore, pull-down assays are performed to reveal the biochemical activation of key signaling proteins in intracellular mechanotransduction, including FAK, Rac1, Cdc42, RhoA.

In addition, synthetic peptide ligands with an RGD-sequence were designed and used in cell experiments in

order to shed further light on the mechanisms of non-covalent ligand-substrate anchorage on cell behavior. The usage of small peptide ligands with a gradually altered ligand-substrate affinity will provide a better mechanistic understanding of cell adhesion and ligand reorganization phenomena.
In summary, the combined biophysical and biochemical analysis of the impact of substrate stiffness and ligand affinity in cell adhesion will elucidate the pivotal role of mechanotransduction in cell adhesion and development. It will further point to novel aspects for designs of materials scaffolds in tissue engineering and regenerative medicine.

Poster 8 Thu 19:00

Circular ruffle dynamics on fibroblast cells — Erik Bernitt[1,2], Julia Strübig[1], Malte Ohmstede[1,2], Pritpal Singh[3], Cheng-Gee Koh[2,3], Hans-Günther Döbereiner[1,2] — [1]University of Bremen, Institute for Biophysics, Döbereiner Lab, Otto-Hahn-Allee, Bremen, Germany — [2]National University of Singapore, Mechanobiology Institute, 5A Engineering Drive 1, Singapore, Singapore — [3]Nanyang Technological University, School of Biological Sciences, 50 Nanyang Avenue, Singapore, Singapore

Circular Dorsal Ruffles (CDRs) are ring-like actin-based structures that, in contrast to peripheral ruffles, form at the dorsal side of cells. The biological function of CDRs is still under discussion. CDRs might play a role in endocytotic uptake and cytoskeletal rearrangements. CDRs are a phenomenon that is known to occur, e.g., on fibroblast cells upon growth factor stimulation. Fibroblast cells that over-express POPX2 however show spontaneous dorsal ruffling. The serine/threonine phosphatase POPX2 is over-expressed in various tumor-derived cell lines such as HeLa, MKN28 and MCF-7. It has been linked to invasive migration behavior.
Even though the phenomenon of dorsal ruffling is well-known for decades, the underlying mechanisms leading to formation and propagation of these coherent solitary waves are not well understood and it is only recently that models have been published describing CDRs as being based on diffusion reaction processes in the cytosol and at the membrane.
We present data of actin waves on NIH 3T3 fibroblast cells showing that these actin waves lead to different types of ruffle morphology, ranging from flat soliton waves of high wavelengths to barrel-like structures composed of lamellipodia-like walls. The later typically collapses after a few minutes under formation of one or more endocytotic vesicles. We analyze and discuss the dynamics of these waves with regard to the proposed models for explanation of CDRs.

Poster 9 Thu 19:00

Cell adhesion on different materials in the presence or the absence of fetal bovine serum — Martina Verdanova[1,2,3], Antonin Broz[1,2], Martin Kalbac[3], Alexander Kromka[4], Marie Kalbacova[1,5] — [1]Institute of Inherited Metabolic Disorders, 1st Faculty of Medicine, Charles University Prague, Ke Karlovu 2, 128 08 Prague 2, Czech Republic — [2]Faculty of Science, Charles University in Prague, Albertov 6, 128 43 Prague 2, Czech Republic — [3]J. Heyrovsky Institute of Physical Chemistry of the ASCR, v. v. i., Dolejškova 2155/3, 182 23 Prague 8, Czech Republic — [4]Institute of Physics of the ASCR, v.v.i., Cukrovarnická 10, 16200 Prague 6, Czech Republic — [5]Biomedical Centre, Faculty of Medicine in Pilsen, Charles University, Czech Republic

In this work we compare cell adhesion on nanocrystalline diamond (NCD) and graphene with standard tissue culture substrates - polystyrene or glass. Both graphene and NCD were already tested for their biocompatibility with affirmative results. These carbon-based materials could be used with advantage in biomedicine thanks to their unique chemical and mechanical properties. It is also possible to modify their surface e.g. by oxygen or hydrogen treatment using chemical or plasma methods. That results in different material wettability which will affect the cell adhesion.
Before the usage of these materials for biomedical applications the understanding of their basic interactions with cells should be clarified. The physical properties of these materials – mechanical toughness and electrical conductivity - predetermine them to be used as surface coatings in implantology as well as for biosensors development.
In this study we investigated the short term adhesion (2h) of the human osteosarcoma cell line (SAOS-2) to these materials. The substrate surface treatment together with presence or absence of fetal bovine serum (FBS) were observed as the main determinants of the cell adhesion. FBS and its single components (fibronectin, vitronectin) play very important role in the process of cell adhesion. These proteins adsorb to the surface

before the cells attachment and thus create the substrate surface environment. Cell number, cell size and formation and function of focal adhesions (FAs) were monitored. FAs are complexes of tens of proteins (e.g. vinculin, talin, paxillin, pFAK, actin – proteins studied in this work) located in the cell membrane and its proximity ensure a transduction of information from the extracellular space. Vinculin functions as a transducer of mechanical force from integrin receptors to the cytoskeleton, whereas pFAK mediates signalization from integrins to cell nucleus about cell surrounding and plays a role in cell migration.

We observed some interesting common adhesion patterns on all substrates (NCD, graphene, polystyrene and glass). We detected only minimal vinculin-based focal adhesions in the FBS absence after 2h of incubation in contrast to the FBS presence. Cells adhering to substrate without FBS had larger cell area and star-like shape in comparison with cells cultivated in medium with 15% FBS which were more rounded and had vinculin based FAs. We also found out that 1% FBS is sufficient for sustaining this pattern of cell adhesion. We observed that signal of pFAK copies the signal of vinculin, thus cells cultivated in the absence of FBS did not have active pFAK. The cells adhering only to fibronectin had FAs over the entire surface in contrast to vitronectin surface where cell adhesions were mainly on the cell edge and larger localized in clusters.

On graphene the early cell adhesion is significantly compromised by the presence of FBS in the medium. Double the number of cells adhered on sample without FBS than on samples with FBS. The cells adhering without the FBS in medium were larger according to the general trend. The role of surface treatment was insignificant.

Cell adhesion on NCD shows some similarities and also some differences compared to the graphene or other studied surfaces. Cells adhere on NCD willingly but again the presence of FBS slows down the adhesion significantly. This is indicated by significantly higher numbers of larger cells on sample without FBS in medium after 2h of cultivation. The surface termination made by plasma treatment in oxygen or hydrogen influences cell adhesion without the FBS in the growth medium. More cells adhere on hydrophilic oxygenated sample.

It is apparent that primary cell adhesion is strongly influenced by FBS. In the absence of FBS and single proteins contained in it, the contact between cell and surface could be carried out by non-specific bonds and it is likely that following signalization in cell and thus cell response differs from standard situation with the FBS presence.

Poster 10 Thu 19:00

Blood platelets as a model system for cell substrate interactions — Rabea Sandmann[1], Sarah Schwarz G. Henriques[1], Hansjörg Schwertz[2], Florian Rehfeldt[3], Sarah Köster[1] — [1]Georg August University of Göttingen, Institute for X-Ray Physics & CRC Physics, Friedrich-Hund-Platz 1, 37077 Göttingen, Germany — [2]University of Utah, Division of Vascular Surgery, 15 North 2030 East Bldg. 533, Rm. 4225 Salt Lake City, UT 84112 USA — [3]Georg August University of Göttingen, Third Institute of Physics, Friedrich-Hund-Platz 1, 37077 Göttingen, Germany

Blood platelets are among the smallest cells in the human body. Nevertheless they can exert strong forces [1] believed to help in blood clot contraction. In their natural environment platelets usually encounter structured surfaces (wounds). These wounds display a microstructure, which arises when the endothelial lining of a blood vessel is damaged, and a nanostructure provided by the proteins that lie underneath the endothelial lining.

Our studies aim at investigating the influence of substrate topography on platelet behavior on the single cell level. On substrates with 1.1 µm large holes which are either (i) coated with fibrin(ogen) (a binding protein for platelets) or (ii) chemically blocked (in both cases the interspaces are coated with fibrin(ogen)), platelets behave quite similar by avoiding the holes at their periphery and bending around the holes. We conclude that both spanning over the holes and bending inside the holes, costs more energy than bending around the holes. As the spreading area on both substrate types is nearly equal, we conclude that platelet shape is determined by an interplay between intrinsic spreading area and membrane energy minimization. Varying the hole size we observe that the interaction between platelets and fibrin(ogen) changes on substrates with chemically blocked holes. On substrates with 0.5 µm large holes platelets occasionally pull on the fibrin(ogen) layer and distort it uniformly by pulling it towards their center. In contrast, on substrates with 1.1 µm large holes the cells pull along one axis towards their center.

A second interesting topic of our research is mimicking

the process of platelet production in a microfluidic chamber.
These studies will give us further inside into the processes of wound closure and platelet production and thus are also of great medical importance.

[1] S. Schwarz Henriques, R. Sandmann, A. Strate, S. Köster: *Force field evolution during human blood platelet activation*, Journal of Cell Science 125(16): 3914–3920 (2012)

Poster 11 Thu 19:00

Inherently slow and weak forward forces of neuronal growth cones measured by a drift-stabilized atomic force microscope — Thomas Fuhs[1,2], Iris Vonderhaid[1], Lydia Reuter[1], Thomas Claudepierre[3], Josef A. Käs[1] — [1]University of Leipzig, Faculty of Physics and Earth Sciences, Linnéstr. 5, 04103 Leipzig, Germany — [2]University of Leipzig, Paul-Flechsig-Institut für Hirnforschung, Jahnallee 59 04109 Leipzig, Germany — [3]Klinik und Poliklinik für Augenheilkunde, Universitätsklinikum Leipzig, Liebigstr. 10-14, 04103 Leipzig, Germany

Previous results have shown that glial cells provide a soft environment for the neurons of the mammalian central nervous system. This raises the question whether neurons are confined to the CNS and cannot wander off into more rigid tissues, such as brain capillary walls. We investigated the mechanical properties and force generation of extending mouse retinal ganglion cells and NG108-15 growth cones using different AFM based methods. For the first time, to our knowledge, we were able to measure the forward pushing forces at the leading edge of outgrowing neuronal growth cones with our drift-stabilized AFM. Our results demonstrate that these growth cones have neither the required stability nor the ability to produce forces necessary to penetrate tissues that are at least an order of magnitude stiffer.

Poster 12 Thu 19:00

Mechanics of collagen gels – what cells feel — Julian Steinwachs, Claus Metzner, Stefan Münster, Nadine Lang, Ben Fabry — University Erlangen-Nuremberg, LPMT, Biophsics Group, Henkestraße 91, Erlangen, Germany

During wound healing, immune response or cancer metastasis, cells migrate through connective tissue. Biopolymer networks, in particular collagen gels reconstituted from purified animal collagen, mimic to some extend the chemical and morphological properties of connective tissue and are therefore frequently used to study cell migration in a three-dimensional environment. The mechanical properties of reconstituted collagen gels are governed by non-affine deformation of the collagen fibrils, such as buckling and tautening, resulting in strain stiffening under shear and a strong lateral contraction under stretch at the macroscopic scale. It is currently unknown how these properties translate to the microscopic scale and the geometry of a migrating cell. To explore this question, we develop a non-linear elastic material model for collagen gels based on observations from confocal microscopy that fibrils can evade mechanical stress using their internal degrees of freedom. This non-affine behavior results in a non-linear force length relationship of fibril segments. Because the fibrils deform in an affine way beyond the scale of the cross-link distance, forces from individual fibril segments can be spatially averaged over finite volume elements. The resulting model replicates the macroscopic behavior (strain stiffening and lateral contraction) for strains up to 35%. We show that tautening of fibrils results in a strong material stiffening against expanding forces that can arise, for example, when the diameter of a migrating cell is larger than the network pore diameter. As a consequence, the gel acts as a steric hindrance. The cells can overcome steric hindrance with the help of matrix adhesion at the front end and the generation of contractile (pulling) forces. However, strain stiffening against contractile forces is less pronounced. Our findings may explain why many metastatic cancer cell lines are unable to migrate in dense collagen gels. In addition, using our material model we can calculate the 3D cell forces from collagen deformations measured around migrating cells. We show that migrating cells assume a polarized spindle-shaped morphology that allows them to generate highly localized contractile forces at the cell poles.

Poster 13 Thu 19:00

The evolution of collagen mechanics in response to large amplitude loading — Stefan Münster[1,2,3], Louise Jawerth[4], David Weitz[2,4], Ben Fabry[1] — [1]University Erlangen-Nuremberg, Department of Physics, Erlangen, Germany — [2]Harvard University, School of Engineering and Applied Sciences, Cam-

bridge, MA, USA — [3]Max-Planck-Institute for the Science of Light, Erlangen, Germany — [4]Harvard University, Department of Physics, Cambridge, MA, USA

The migration of cancer cells through the dense, fibrillar meshwork of the extracellular matrix (ECM) is a crucial step during metastasis. The major challenge cells face during this process is to overcome the mechanical resistance posed by the three-dimensional network of ECM fibers. Therefore, the migration of cancer cells depends on their ability to generate forces as well as the mechanical properties of their environment.

To understand this process, reconstituted networks of type I collagen are routinely used as a 3D cell culture environment for migration studies. These fiber networks possess intriguing, complex mechanical properties: they exhibit non-linear strain-stiffening, a stiffness that increases with increasing strain, and they are also viscoelastic. Viscoelasticity leads to stress relaxation through dissipative processes that usually originate from structural alterations in the material. Such alterations are expected to influence the mechanical response of a material particularly at high stresses, for instance, as they occur when collagen networks are strained into the non-linear regime. Surprisingly, most studies characterize only the low strain behavior of these ECM equivalents and assume they remain unchanged. However, whether or not the mechanical response of collagen type I networks is influenced by exposure to large strains has never been investigated.

Here, we show that repeated large strain loading of collagen networks progressively changes their mechanical properties. Specifically, in the absence of covalent crosslinks, the non-linear mechanical response of a collagen network gradually shifts to higher strains while the linear modulus successively decreases. We demonstrate the generality of this behavior by comparing it to the response of another prominent ECM matrix, fibrin. Using confocal microscopy, we present direct evidence that this behavior does not arise from material rupture; instead, it results from an interplay between the lengthening of individual fibers under tension and their buckling when they are compressed, leading to a persistent increase of their rest lengths. Moreover, we show that covalent crosslinking of collagen or fibrin networks inhibits the shift of the material response, suggesting that the molecular origin of the fiber lengthening may be slip of monomers within the fibers.

Our results suggest that covalent crosslinking might play an important role in controlling how fibers of these ECM networks can sustain tension. As a consequence, uncrosslinked fibers may not be able to support enough tension for cells to migrate. By contrast, crosslinked fibers may not relax their internal tension as much, thereby, supporting traction forces, which would facilitate cell migration. Indeed, recent results have implicated covalent crosslinking in tumor progression [1]. Hence, not only the stiffening of the ECM caused by the crosslinking, but also the inhibition of fiber lengthening might play an important role for the increased ability of cancer cells to invade the surrounding ECM.

[1] K. R. Levental *et al.*: *Matrix Crosslinking Forces Tumor Progression by Enhancing Integrin Signaling*, Cell 139(5): 891–906 (2009)

Poster 14 Thu 19:00

The nanomechanical signature of breast cancer — Marija Plodinec[1], Marko Loparic[1], Christophe A. Monnier[1], Ellen C. Obermann[2], Rosanna Zanetti-Dallenbach[3], Philipp Oertle[1], Janne T. Hyotyla[1], Ueli Aebi[4], Mohamed Bentires-Alj[5], Cora-Ann Schoenenberger[1,4], Roderick Y.H. Lim[1] — [1]Biozentrum and the Swiss Nanoscience Institute, University Of Basel, 4056 Basel, Switzerland — [2]Institute of Pathology, University Hospital Basel, 4031 Basel, Switzerland — [3]Department of Gynecology and Gynecological Oncology, University Hospital Basel, University of Basel, 4031 Basel, Switzerland — [4]Maurice E. Mueller Institute for Structural Biology, Biozentrum, University of Basel, 4056 Basel, Switzerland — [5]Mechanisms of cancer, Friedrich Miescher Institute for Biomedical Research, 4058 Basel, Switzerland

Breast cancer is the second most common cancer in women worldwide with more than 425'000 fatalities in 2010 alone. Yet, after decades-long investigations, comprehensive understanding of the disease is missing and advances in treatment are limited. Today, it is increasingly being recognized that a key to the problem lies in the physicality of the tumor tissue environment and how biomechanics plays a key role in cancer cell migration, invasion and metastasis [1,2]. This sets the stage for our work where we have applied the nanoscale sensitivity and unprecedented spatial resolution of indentation-type atomic force microscopy (IT-AFM) [3,4] to comprehensively investigate the stiffness properties of unadulterated breast biopsies from human patients [5]. Here, a most striking finding is that normal

glandular tissue, benign lesions and malignant tumors exhibit qualitatively unique and reproducible biomechanical signatures across different patients. In exploiting these nanomechanical stiffness characteristics as potential diagnostic markers, our results gave a near-100% correlation with conventional histopathology of the same biopsies in double-blind experiments. Because the molecular and environmental etiology of patient biopsies is extremely variable, we further validated our findings in MMTV-PyMT transgenic mice (i.e., a widely accepted model for human breast cancer), which effectively confirmed our human biopsy measurements [5]. In particular, we could resolve malignant cells that exhibited a soft phenotype surrounded by stiffer stroma. When compared to histological analysis, our data indicate that cancer cell compliance is associated with hypoxia, which has been speculated to promote aggressiveness and invasion [6]. Indeed, we could detect the invasive soft phenotype in lung metastasis for the first time. Importantly, our work reconciles major long-standing differences that have polarized the cancer field wherein tumor-level measurements indicate to increased stiffness (i.e., in accordance with conventional wisdom) [7] while single isolated cancer cells are soft [8]. Finally bridging the length scale divide by IT-AFM highlights how such stiffness signatures can be used as novel biomarkers in clinical applications with diagnostic and prognostic potential.

[1] D. Wirtz *et al.*: *The physics of cancer: the role of physical interactions and mechanical forces in metastasis*, Nature Reviews Cancer 11 (7): 512–522 (2011)

[2] A. Fritsch *et al.*: *Are biomechanical changes necessary for tumour progression?*, Nature Physics 6 (10): 730–732 (2010)

[3] M. Stolz *et al.*: *Early detection of aging cartilage and osteoarthritis in mice and patient samples using atomic force microscopy*, Nature Nanotechnology 4 (3): 186–192 (2009)

[4] M. Plodinec *et al.*: *The nanomechanical properties of rat fibroblasts are modulated by interfering with the vimentin intermediate filament system*, J Struct Biology 174 (3): 476–84 (2011)

[5] M. Plodinec *et al.*: *The Nanomechanical Signature of Breast Cancer*, Nature Nanotechnology, in press (2012)

[6] J. T. Erler *et al.*: *Lysyl oxidase is essential for hypoxia-induced metastasis*, Nature 440 (7088): 1222–1226 (2006)

[7] M. J. Paszek *et al.*: *Tensional homeostasis and the malignant phenotype*, Cancer Cell 8 (3): 241–254 (2005)

[8] S. E. Cross *et al.*: *Nanomechanical analysis of cells from cancer patients*, Nature Nanotechnology 2 (12): 780–3 (2007)

Poster 15 Thu 19:00

β1 integrins restrict the growth of foci and spheroids — Rajesh Gupta, Staffan Johansson — Department of Medical Biochemistry and Microbiology, The Biomedical Center, Uppsala University, Box 582, SE-751 23, Uppsala, Sweden

Members of the integrin family are main regulators of extracellular matrix (ECM) assembly and transmitters of signals from the ECM to cells. We have analyzed the role of integrin subunit β1 in two-dimensional (2D) and three-dimensional (3D) cell cultures using integrin β1 null cells (MEFβ1-/- and GD25) and their β1 integrin-expressing counterparts. GD25 and GD25β1 cells proliferated with similar kinetics in sub-confluent 2D cultures, whereas GD25 cells attained higher cell numbers in confluent culture and formed foci with 5-fold higher frequency than GD25β1 cells. Fibronectin fibrils were abundant throughout the GD25β1 colonies but strictly limited to the multilayered area (focus) of GD25 colonies. During 3D growth as spheroids, GD25 continuously increased in size for >30 days while the growth of GD25β1 spheroids ceased after 14 days. Similarly, MEFβ1-/- cells formed foci and grew as spheroids, while the β1 integrin-expressing MEF did not. Expression levels of the cell cycle markers Ki67, PCNA, and histone H3-pSer10 were similar between GD25 and GD25β1 spheroids. Apoptotic cells increased with spheroid volumes in both spheroid types, but accumulated earlier and to higher numbers in GD25. In both cell systems, the presence of β1 integrins resulted in higher levels of active myosin light chain and inactive myosin light chain phosphatase, and a more compact spheroid structure.

In conclusion, our results reveal that regulation of 3D growth in spheroids and foci is dependent on the β1 subfamily of integrins, and suggest that myosin-based

spheroid contraction in combination with cell death limits the growth of β1-expressing spheroids.

Poster 16 Thu 19:00

Sensitive control of active gel contraction — Felix Keber, Katharina Henneberg, Simone Koehler, Kurt Schmoller, Andreas Bausch — TU Munich, Institute of Molecular and Cellular Biophysics, Physik-Department, Zellbiophysik, E27, James-Franck-Straße 1, 85748 Garching, Germany

Cellular processes, such as endocytose, migration or division, are organized by the cytoskeleton. To fulfill these various tasks, the cytoskeleton is a highly dynamic structure which makes use of a special building principle: its actin filaments are connected by different crosslink proteins and myosin motors apply contractive forces on them, creating an active gel. The properties of this gel depend on the interplay between crosslink strength and motor force. Three major regimes emerge: static network, macroscopic contraction and local contraction. The state of the gel is not only determined by the ratio between crosslinker and motor protein, but is also influenced by environmental conditions, such as salt concentration or pH.
We study the transition between the regimes of the active actin gel *in vitro* by altering the crosslinking activity. For all studied crosslinkers, small variations of the pH of only 0.1 already cause contraction. The calcium dependent binding affinity of alpha-actinin can also be used to control the properties of reconstituted networks.

Poster 17 Thu 19:00

Virtual probing of cells with microscopic imaging and computational modeling — Evgeny Gladilin[1], Paula Gonzalez[2], Roland Eils[1,2] — [1]German Cancer Research Center, Heidelberg, Germany — [2]BioQuant, University Heidelberg, Germany

Mechanical forces play an important role in many basic biological phenomena on different spatial-temporal scales: from tissues and single cells to sub-cellular structures. The ability of cells to appropriately sense, transmit and respond to mechanical forces is essential for the normal function of the entire organism. A number of severe diseases, including cancer, is known to be related to altered material properties of the cellular matter. Due to a number of natural and technical reasons, investigation of material properties of cellular structures in living cells remains a challenging task. Conventional experimental techniques do not allow non-destructive probing of intracellular sub-regions in living cells, especially if they are not enclosed by membranes, i.e. cellular/nuclear interior. In order to enable probing of mechanical properties inside of living cells, we develop an image- and model-based framework which is based on fitting a numerical model of cellular mechanics onto experimental time series of microscopic images by minimizing dissimilarity between experimentally assessed and computationally simulated images. Here, we demonstrate application of this framework to virtual probing of cellular/nuclear matter on the basis of image data from different experimental modalities, including uniaxial, planar, 3D medium stretchers.

Poster 18 Thu 19:00

Biomechanical studies on human primary cervix cells — Anatol Fritsch[1], Steve Pawlizak[1], Michael Höckel[2], Josef A. Käs[1] — [1]University of Leipzig, Faculty of Physics and Earth Sciences, Institute of Experimental Physics I, Soft Matter Physics Division, Linnéstraße 5, 04103 Leipzig, Germany — [2]University of Leipzig, University Hospital, Department of Obstetrics and Gynecology, Liebigstraße 20a, 04103 Leipzig, Germany

In cooperation with the university hospital of Leipzig, we were able to develop a robust protocol for the cultivation of primary cervix epithelial cells from human patients both normal and tumorous tissue. With this cell-system at hand, we were able to systematically probe biomechanical parameters using the Optical Stretcher. For the first time, we have access to a statistically relevant amount of data for normal and tumorous cells from the same patient. Our data confirms previous studies on cell lines as tumorous cells are more deformable than their normal counterparts.

Session II: Cell Migration and Forces I

Invited Talk Fri 08:30

The role of mechanosensing and matrix geometry in cancer invasion — ERIK SAHAI — London Reasearch Institute, 44 Lincoln's Inn Fields, London, WC2A 3LY, UK

The acquisition of invasive behaviour enables the tumour cells to move into either the surrounding tissue or the vasculature and thereby spread to other parts of the body. To study cell motility in tumours we perform intravital multi-photon confocal imaging of tumours in anaesthetised mice. Cell migration depends on the complex interplay of actin polymerisation, deformation of the plasma membrane, actomyosin contractility, and cell-matrix adhesion. Recent work has revealed that cancer cells can use different migratory strategies, particularly when challenged with complex three-dimensional matrices *in vivo*. Further the mode of cell migration determines the sensitivity of invading cancer cells to interventions that target either regulators of actin polymerisation or actomyosin contractility. This presents a particular problem when attempting to extrapolate findings from simple *in vitro* experiments to the complex matrix environments that surround tumours. To address this we have developed an agent based-finite element model of cell motility within different ECM topologies. This enables the optimal migration strategy and response to anti-invasive agents in different matrix geometries to be predicted. We then test these predictions by intravital imaging of melanoma.

Invited Talk Fri 09:00

Spatially and temporally coordinated processes of cells at molecular to cellular scales — JOACHIM P. SPATZ — Max Planck Institute for Intelligent Systems, Dept. New Materials and Biosystems — University of Heidelberg, Dept. Biophysical Chemistry

Our approach to engineer cellular environments is based on self-organizing spatial positioning of single signaling molecules attached to synthetic extracellular matrices, which offers the highest spatial resolution with respect to the position of single signaling molecules. This approach allows tuning tissue with respect to its most relevant properties, i.e. viscoelasticity, peptide composition, nanotopography and spatial nanopatterning of signaling molecule. Such materials are defined as "nano-digital materials" since they enable the counting of individual signaling molecules, separated by a biologically inert background. Within these materials, the regulation of cellular responses is based on a biologically inert background which does not initiate any cell activation, which is then patterned with specific signaling molecules such as peptide ligands in well defined nanoscopic geometries. This approach is very powerful, since it enables the testing of cellular responses to individual, specific signaling molecules and their spatial ordering. Detailed consideration is also given to the fact that protein clusters such as those found at focal adhesion sites represent, to a large extent, hierarchically-organized cooperativity among various proteins. We found that integrin clusters have a functional packing density which is defined by an integrin-integrin spacing of approximately 68 nanometers. Such critical spacing values vary as matter of transmembrane receptor choice of interest. We have also developed methods which allow the light initiated activation of adhesion processes by switching the chemical composition of the extracellular matrix. This enabled us to identify the frequency of leader cell formation in collective cell migration as a matter of initial cell cluster pattern size and geometry. Moreover, "nano-digital supports" such as those described herein are clearly capable of involvement in such dynamic cellular processes as protein ordering at the cell's periphery which in turn leads to programming cell responses.

Invited Talk Fri 09:30

Mechanical regulation of tumor reversion — DANIEL A. FLETCHER — Bioengineering & Biophysics, UC Berkeley — Physical Biosciences, Lawrence Berkeley National Laboratory

Tumors are characterized by disorganized growth of normally organized tissue. During mammary morphogenesis, normal epithelial cells form highly organized and growth-arrested structures known as acini, while tumorigenic mammary epithelial cells form disorganized structures without lumens. Exposure of pharmacological agents to tumorigenic cells have been shown to rescue

the formation of normal acini, but the role of stresses and strains on tumor reversion has not been explored. We investigated the effect of external forces on tumor reversion by compressing mammary epithelial cells embedded in a three-dimensional laminin-rich extracellular matrix. Individual epithelial cells were tracked over multiple days as they formed multi-cellular acini. We found that compression applied to mammary epithelial cells during acini formation led to 'phenotypic reversion' of the tumorgenic cells, leading to formation of organized acini rather than the disorganized acini observed without compression. This mechanically-induced reversion occurred without the use of exogenous pharmacological agents previously shown to be required, indicating a key role for mechanics in tumorigenesis.

Invited Talk Fri 10:30

Biomechanical properties of cancer cells determine their aggressiveness — CLAUDIA T. MIERKE — University of Leipzig, Faculty of Physics and Earth Sciences, Institute of Experimental Physics I, Linnéstr. 5, 04103 Leipzig, Germany

Cell invasion through the extracellular matrix (ECM) of connective tissue is an important biomechanical process, which plays a prominent role in tumor progression. The malignancy of tumors depends mainly on the capacity of cancer cells to migrate and metastasize. A prerequisite for metastasis is the invasion of cancer cells through connective tissue to targeted organs. Cellular stiffness and cytoskeletal remodeling dynamics have been proposed to affect the invasiveness of cancer cells. Here, this study investigated whether highly-invasive cancer cells are able to invade into dense 3D-ECMs with an average pore-size of 1.3 µm or 3.0 µm when phagocytized beads (2.7 and 4.5 µm diameter) increased their cellular stiffness and reduced their cytoskeletal remodeling dynamics compared to weakly-invasive cancer cells. The phagocytized beads decreased the invasiveness of the α5β1high cancer cells into 3D-ECMs, whereas the invasiveness of the α5β1low cancer cells was not affected. The effect of phagocytized beads on the highly-invasive α5β1high cells was abolished by knock-down of the α5 integrin subunit and addition of an anti-α5 integrin blocking antibody. Furthermore, the reduction of contractile forces using MLCK and ROCK inhibitors abolished the effect of phagocytized beads on the invasiveness of α5β1high cells. Additionally, the cellular stiffness of α5β1high cells was increased after bead phagocytosis, whereas the bead phagocytosis did not alter the stiffness of α5β1low cells. Taken together, the α5β1 integrin-dependent invasiveness was reduced after bead phagocytosis by altered biomechanical properties, suggesting that α5β1high cells needs an appropriate intermediate cellular stiffness to overcome the steric hindrance of 3D-ECMs, whereas the α5β1low cells were not affected by phagocytized beads.

Invited Talk Fri 11:00

Self-organization of the actin cytoskeleton: Physical mechanisms and signaling pathways — ALEXANDER D. BERSHADSKY[1,2], YEE HAN TEE[2], TOM SHEMESH[1], ALEXANDRA LICHTENSTEIN[1], MASHA PRAGER-KHOUTORSKY[1], VISALATCHI THIAGARAJAN[2], RAMASWAMY KRISHNAN[3], BENJAMIN GEIGER[1], MICHAEL M. KOZLOV[4] — [1]Weizmann Institute of Science, Rehovot, Israel — [2]Mechanobiology Institute, National University of Singapore, Singapore — [3]Harvard School of Public Health, Harvard University, Boston, MA, USA — [4]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

The critical stage of cell morphogenesis is a transition from a radially symmetrical to polarized organization. In fibroblast-like cells, polarized morphology is associated with a development of an array of parallel actomyosin cables (stress fibers) with focal adhesions (FAs) at their ends. The cytoskeletal and signaling mechanisms underlying this process are poorly understood. Here, we demonstrate that fibroblast polarization and formation of stress fiber arrays depends on FA mechanosensitivity, and does not occur on compliant substrates. To gain insight into control mechanisms regulating these processes we used a siRNA screening approach. siRNA-mediated knockdowns of 85 known human protein tyrosine kinases (PTKs) revealed distinct alterations in the cell polarization response and diverse changes in the cell traction force generation and FA formation. Remarkably, changes in rigidity-dependent traction force development, or FA mechanosensing, were consistently accompanied by abnormalities in the cell polarization response. Thus, different stages of cell polarization are regulated via multiple, PTK-dependent molecular checkpoints that control cell contractility and FA-mediated mechanosensing. We further studied in detail the actin cytoskeleton self-organization in fibroblasts confinined within circular adhesive islands

(1,600-1,800 sq microns). The process begins with formation of a radially symmetrical actin cytoskeleton, consisting of radial (R)-fibers growing from peripheral focal adhesions, and numerous transverse (T)-fibers emerging from the lamellipodium-lamellum boundary and moving centripetally along the R-fibers. The R-fibers were enriched in alpha-actinin, relatively poor in myosin II and apparently non-contractile. The T-fibers were enriched in myosin-IIA and demonstrated shortening during the centripetal motion. Formation of R-, but not T-fibers can be suppressed by formin inhibitor SMIFH2. The radial organization of the actin fibers was transient and was followed by a chiral rotation of the entire system of R- and T-fibers in the counter-clockwise direction ("cytoplasmic swirl"). Subsequently, the stable array of parallel stress fibers, containing both alpha-actinin and myosin IIA assembled. We present a model for the dynamic redistribution of T- and R-fibers, assuming that contraction of myosin IIA-containing T-fibers generates stresses, which result in a centripetal motion of these fibers, as well as force dependent growth of the R-fibers from the focal adhesions. The orientation of R-fibers, the motion of T-fibers, and the forces acting on the FAs are coupled together. Using numerical simulations we demonstrate that noise in the system can cause a spontaneous symmetry breaking, resulting in swirling motion. The chirality of swirling is explained as a consequence of helical symmetry of actin filaments in the radial fibers.

Invited Talk Fri 11:30

Mechanical regulation of adhesive bonds — DAVID BOETTIGER — University of Pennsylvania School of Medicine, 211B Johnson Pavilion, 3610 Hamilton Walk, Philadelphia, PA 19104, USA

The pathologist recognizes cancer as a change in cell structure and in the morphological relationship of cells in tissues. The molecular biologist recognizes signaling pathways that are modified or deregulated in cancer. The connection between the two requires both the approaches of molecular biology to identify components and Physics to understand the driving forces and structures that modify the chemical reactions within the cell. This report focuses on adhesive bonds that form between cell surface integrin adhesion receptors and surface-bound ligands. In addition to their adhesive function, adhesive bonds can influence intracellular biochemistry from metabolism to development to pathologies like cancer my modulating intracellular signals. Both the adhesive and the signaling functions are proportional to the number of adhesive bonds. Adhesive bonds can be controlled by both biochemical and mechanical factors. The mechanics is based on the formation of catch bonds in which tension increases bond stability and hence provides a control of the number of adhesive bonds. The objective here is to translate these ideas into intact cells. First, we used a chemical cross-linking method that can distinguish two forms of $\alpha5\beta1$ integrin-fibronectin adhesive bonds (tensioned and relaxed). Relaxed bonds could be converted to tensioned bonds by the application of force. This controlled not only the conformation of the integrin but also bond stability and signaling ability. Since this regulates the bound form, it will modulate the dissociation rate. Second, to measure the kinetics of adhesive bond formation and dissociation the total adhesive bonds were measured as a function of time in a cell spreading model. The data showed a 100,000-fold decrease in the on-rate due to the reduced diffusion and a 700-fold decrease in the off-rate. The reduction on the off-rate follows the prediction that tension would stabilize the bonds and hence reduce the off-rate. Finally, we have used the AFM to investigate the initial binding step. The analysis showed three modes that depended on the contact force. At low contact force there were no adhesive bonds. At high contact forces the increase in adhesive bonds with time was linear. At intermediate forces there was a delay and then a jump to forces representing up to several 100 bonds suggesting the assembly of a focal complex with very little adhesive stability and a rapid conversion to strong adhesion. This implies that even the initial attachment event appear to require a force activation.

Contributed Talk Fri 12:00

The percolation transition of transportation networks as a universal gauge for tumor vascularization — HANS-GÜNTHER DÖBEREINER[1,2], ADRIAN FESSEL[1,2], CHRISTINA OETTMEIER[1,2], ERIK BERNITT[1,2], NILS C. GAUTHIER[2] — [1]Universität Bremen, Institut für Biophysik, Bremen, Germany — [2]National University of Singapore, Mechanobiology Institut Singapore, Singapore

Percolation in transportation networks, i.e., the formation of a large connected structure from disconnected pieces, can be described by a single topological parameter characterizing local connectivity. Details, like

the system size or specific material parameters, do not enter the description of this topological phase transition. The universality of percolation may be used as a general gauge in the analysis of transportation networks. Recently, this has been applied to network formation of the slime mold Physarum Polycephalum and modeling of vascularization of endothelial cells [1].
Further, this should be applicable to vasculogenic mimicry and alternative strategies of vascularization in tumors. Some malignant tissues derive their blood vessels not by angiogenesis, i.e., remodeling of existing vessels, but rather by de-novo vascularization like embryos. Since topologically, percolation is independent from detailed mechanisms and even space dimensions, i.e., 2D versus 3D growth, it may serve as a reference point in space and time when comparing the dynamics of network formation in tumors of varying size and shape. Since restricting blood supply by hindering vessel percolation is paramount for suppressing tumor growth, this may foster development of anti-angiogenic therapy.

[1] A. Fessel, C. Oettmeier, E. Bernitt, N.C.L. Gauthier, H.-G. Döbereiner: *Physarum polycephalum percolation as a paradigm for topological phase transitions in transportation networks*, Phys. Rev. Lett. 109: 078103 (2012)

Contributed Talk Fri 12:15

Forces in cellular growth and division — Jörn Hartung, Hedvika Toncrova, Stephan Herminghaus, Oskar Hallatschek — Max Planck Institute for Dynamics and Self-Organisation, Bunsenstraße 10, Göttingen, Germany

Ensembles of cells, e.g. tissues, exert forces on their environment during growth and proliferation [1]. A tumor for instance has to be able to grow under external pressure, since it is confined by surrounding tissue and has to push it away to make room for new tumor cells [2]. A profound knowledge of pressure build-up due to expanding ensembles of cells can provide fruitful information, for instance about the mechanical stress, which is exerted on the confining environment and its feedback on growth properties of cells. Therefore, we construct microfluidic devices made of PDMS, which enable us to entrap cells, e.g. yeast and bacteria, observe their growth and proliferation, and measure the mechanical stress exerted on the surroundings *in vitro*.
As an example we show that *Saccharomyces cerevisiae* (baker's yeast) can build up a maximal pressure of about 0.8 MPa. After this there is no further deformation of the device walls detectable. This value is a lower bound for the homeostatic pressure at which division rate and apoptosis rate of the cells are equal.

[1] M. Basan, T. Risler, J.-F. Joanny, X. Sastre-Garau, J. Prost: *Homeostatic competition drives tumor growth and metastasis nucleation*, HFSP Journal 3 (4): 265–272 (2009)

[2] F. Montel, M. Delarue, J. Elgeti, D. Vignjevic, G. Cappello, J. Prost: *Isotropic stress reduces cell proliferation in tumor spheroids*, New Journal of Physics 14 (2012)

Session III: Cell Migration and Forces II

Invited Talk Fri 14:30

Coordination of locomotory and invasive protrusions during migration and dissemination of tumor cells in breast tumors — John S. Condeelis — Albert Einstein College of Medicine, Michael F. Price Center, 1301 Morris Park Avenue, Bronx, NY 10461, USA

Multi-photon intravital imaging of single tumor cells in breast tumors has revealed the requirement for the coordination of locomotion and invasion in breast tumors and the microenvironments *in vivo* in which the coordination occurs. One of these microenvironments is adjacent to blood vessels where macrophage-tumor cell pairing and streaming migration occur and this requires paracrine signaling and chemotaxis. Multi-photon intravital imaging was used with expression profiling to reveal the genes expressed by tumor cells during migration and intravasation (the Invasion Signature).
The motility pathways identified in the Invasion Signature converge on the RhoC/Cofilin/Mena pathway identifying it as a master regulator of chemotaxis,

invasion and dissemination of breast tumor cells *in vivo*. Using markers derived from imaging and the RhoC/Cofilin/Mena pathway, prognostic markers have been developed. These are TMEM, MenaINV/Mena 11a, and MenaCalc, markers of macrophage-tumor cell paracrine signaling, and cofilin x P-cofilin, a marker of activation of the Cofilin/Mena pathway in tumor cells. These four markers have been used successfully to predict metastatic risk in human invasive ductal carcinomas of the breast as shown in large clinical studies.
To understand why the RhoC/Cofilin/Mena pathway determines metastatic risk, FRET biosensors and multiphoton imaging have been used *in vivo* leading to the following conclusions for breast tumors which will be discussed:
1. Tumor cell movement during streaming and intravasation involves coordination of locomotory protrusions (pseudopods) and invasive protrusions (invadopods).
2. Both protrusions involve actin polymerization at the front of each protrusion.
3. Chemotaxis to EGF determines cell direction and comigration with macrophages in streams– macrophages are a source of EGF.
4. ECM degradation occurs during linear migration on collagen fibers at the cell front.
5. Cofilin activation is sufficient to determine the site of actin polymerization, protrusion and cell direction.
6. Mena activity regulates the sensitivity of the EGFR to EGF and supports streaming migration with macrophages.
7. RhoC/LIM and Arg kinase activities regulate the geometry and localization of cofilin activity.
8. Mena regulates the amount of cofilin activity during locomotion and this affects tumor cell plasticity.

Invited Talk Fri 15:00

Predictive mechanical models for dynamic tissue remodeling — M. Lisa Manning — Syracuse University, Department of Physics, Syracuse, NY 13244, USA

Organogenesis during development and metastasis during cancer progression both rely on programmed cell shape changes and rearrangements between cell-cell contacts. How can we develop quantitative, predictive mechanical models for these tissue processes? While simple "shape equilibrium" models make useful and verifiable predictions about the mechanically stable shapes of cells in tissues, new extensions are required if we want them to make predictions about dynamics. In contrast, "active matter" models are inherently dynamic, but have difficultly accounting for cell geometry and properties at tissue interfaces. I will discuss our recent work to (a) extend "shape equilibrium" models to explain cell dynamics in the zebrafish organ of asymmetry (Kupffer's vesicle) and in epithelial layers, and (b) add geometric constraints to "active matter" models so they behave more realistically at tissue interfaces. These results suggest new avenues for experiments in developmental organogenesis and advance a method for estimating rates of cell diffusion or migration in confluent tissues that might be relevant for metastasizing tumor cells.

Contributed Talk Fri 15:30

Assembly of cytoplasmic intermediate filament proteins — Norbert Mücke[1], Stefan Winheim[1], Jörg Langowski[1], Harald Herrmann[2] — [1]German Cancer Research Center, Biophysics of Macromoleculs, Heidelberg, Germany — [2]German Cancer Research Center, Functional Architecture of the Cell, Heidelberg, Germany

Eukaryotic cells contain three cytoskeletal filament systems that exhibit very distinct assembly properties, supramolecular architectures, dynamic behavior and mechanical properties. Microtubules and microfilaments both assemble from globular subunits, are relatively stiff and are polar structures. Their ends exhibit very different association rates for annealing subunits. In contrast, the constituents of intermediate filaments (IFs) are fibrous proteins, they assemble into very flexible, non-polar structures and filament ends are functionally identical.
We have investigated the properties of three major cytoplasmic human intermediate filament proteins: vimentin, desmin and keratin 8/18. We studied their assembly- competent starter units in low ionic strength and high pH conditions by analytical ultracentrifugation. After raising the ionic strength or lowering the pH, we observed a nearly identical assembly behaviour for all three IF proteins. Within seconds, most of the soluble starter units associate into 60 nm long, full-width filaments, so-called unit-length filaments (ULFs). These ULFs assemble longitudinally into longer filaments. In addition, long filaments can fuse longitudinally with each other. We measured filament length distributions by stopping assembly after distinct time points; for the same mean lengths, the distribution histograms were compa-

rable. However, the three IF proteins assemble with entirely different speeds. Comparing the measured distribution plots with simulated data allowed us to describe the assembly process with a simple kinetic model for all three IFs if we take filament flexibility into account. One important prerequisite to describe our results is that we need to allow filaments to fuse end on. Most importantly, this end-on fusion of long filaments has been visualized directly by us using total internal reflection fluorescence microscopy with mixtures of filaments labelled by two different fluorophores. In a next step to characterize the three different IF systems, we compared the mechanical properties of the individual filaments using the persistence length as a measure for the flexibility. The persistence length for vimentin and desmin, as measured by atomic force microscopy and electron microscopy was about 1 µm, while that of keratin 8/18 was significantly lower with about 0.3µm.

Contributed Talk Fri 15:45

***In vivo* imaging of lysyl oxidase by fluorine-18 labelled substrate-based radiotracers** — Manuela Kuchar, Jens Lenk, Ralf Bergmann, Robert Wodtke, Birgit Mosch, Jörg Steinbach, Jens Pietzsch, Reik Löser — Helmholtz-Zentrum Dresden-Rossendorf, Bautzner Landstraße 400, Dresden, Germany

The ability of solid tumours to invade surrounding tissues and, in consequence, to metastasise to distant organs is mediated by bidirectional molecular interactions between tumour cells and the extracellular matrix [1,2]. Recently, the copper-dependent amine oxidase lysyl oxidase (LOX, EC 1.4.3.13) could be identified as one of the key players in these processes [3]. Therefore, the development of molecular probes that enable the imaging of this enzyme *in vivo* by positron emission tomography (PET) was in the focus of this study.

As the enzyme is catalysing the oxidative crosslinking of lysine side chains in collagen and other extracellular proteins, the design of radiotracers based on substrates seemed to be promising. Thus, the N-terminal telopeptide of the alpha1-chain of type I collagen containing the key sequence Asp-Glu-Lys-Ser [4] and peptides derived from this including a cyclic derivative were chosen to be functionalised with fluorine-18 at their N-termini. To achieve this, a method was developed that allows the site-selective ^{18}F-fluorobenzoylation of peptides [5]. The metabolic stability and biodistribution of these potential radiotracers was investigated in male wistar rats.

To estimate the potential of the different lysine-containing peptides for crosslinking with collagen *in vivo*, their interaction with bovine atelocollagen was investigated by surface plasmon resonance (SPR) experiments.

A panel of tumour cell lines was screened for expression of the enzyme. The presence of LOX could be confirmed for the human breast cancer cell-lines MDA-MB-231, MCF-7 and the melanoma cell line A375 by RT-PCR as well as western blots. Based on the human A375 cell line, an animal model was established consisting of nude mice bearing tumours derived from these cells. Expression of LOX in the developed tumours was proven by immunohistochemical methods and western blots.

The developed labelling method for site-selective radiolabelling of peptides allowed to obtain the 18F-fluorobenzoylated telopeptide in high radiochemical yields and purities. All peptides show good stability *in vivo* and even no metabolites could be detected for the cyclopeptide. The biodistribution studies indicate no organ enrichment and fast renal elimination. For the first time, the telopeptide-collagen interaction could be studied quantitatively, indicating dissociation constants in the high micromolar range.

Despite unfavourable pharmokinetics due to fast blood clearance, the compounds show the potential to reflect the LOX acticity *in vivo*, as concluded from PET imaging experiments with nude mice bearing A375 tumours.

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Contributed Talk Fri 16:00

Temperature-dependent assembly properties of keratin 8/18 — Ines Martin[1], Anke Leitner[1], Michael Beil[2], Harald Herrmann[3], Othmar Marti[1] — [1]Ulm University, Department of Experimental Physics, Albert-Einstein-Allee 11, 89081 Ulm — [2]Ulm University, Department of Internal Medicine I, Albert-Einstein-Allee 23, 89081 Ulm — [3]German Cancer Research Center (DKFZ), Im Neuenheimer Feld 280, 69120 Heidelberg

The keratin 8/18 dimer is a structural building block of intermediate filaments (IFs), which are basic constituents of the cytoskeleton in some epithelial cells. The understanding of the cytoskeleton is of crucial importance for the characterization of the movement of metastasizing cells.

The assembly process of keratin 8/18 can be described as a three-step process, which is highly sensitive to changes in temperature and which exhibits very interesting kinetics. We assembled keratin 8/18 *in vitro* at different temperatures (4°C, 21°C, 30°C, 37°C) for different time periods (10 s, 1 min, 5 min, 10 min, 20 min). The resulting filaments were diluted to a concentration suitable for the detection of single filaments and imaged by Transmission Electron Microscopy (TEM). The samples were negatively stained with uranyl acetate to enhance the contrast.

We observed long and smooth IFs, approximately 12 nm in diameter, no matter which temperature was used for assembly. However, we noted a strong dependence of the length distribution on temperature and assembly time. We analyzed these distributions by two distribution models commonly used in polymer chemistry: the Schulz-Zimm model and the "condensation-polymerization" model. We found that the Schulz-Zimm-model gives a slightly superior fit to the data. The data will allow us to eventually describe the dynamics of cytoskeletal structures in tissue-bound as well as in migrating cells.

Contributed Talk Fri 16:15

Optical breast tissue pre-screening for the identification of cancer risk and presence of malignancies — Lothar Lilge, Jane Walter, Kristina Blackmore, Julia Knight — University of Toronto, Department of Medical Biophysics and Department of Public Health, Ontario, Canada

While the tumour stem cell is only now gaining acceptance, it is long accepted that tumours do not arise spontaneously in healthy tissue. Initial genetics hits result in a change in large parts of the effected organ which will show higher mitotic figures throughout or higher cellularity and modifications to the stroma and scaffold. This is often referred to field modifications. These effected tissues also shield the growing aberrant cells from identification by the immune system. From a physics point these initial field modifications will reduced the endogenous contrast between the modified tissue and the tumour essentially independent of the detection technology to be employed, but it also provides a possibility to identify individual at risk of progressing towards the development of a malignancy in the next few years. The latter opens avenues for exogenous contrast free determination of the breast cancer risk. In bilateral organs, such as the female breast, the field modifications can also indicate the probability for the presence of a cancer, in particular if the initial genetic hits are temporal separated in the two breasts or affect the field modification differently.

In ongoing clinical research program the ability to quantify, the probabilities for women to develop breast cancer in the future or harbour breast cancer, via their bulk optical tissue properties is evaluated. Numerical light propagation models determined that 8 optodes, 2 sources and 6 detectors, can interrogate about 80% of the total breast tissue volume. Spectroscopic transmission measurements demonstrated that the optical properties correlate with established physical and demographic risk factors for identification of women at risk to develop breast cancer in the future and for the identification of women with confirmed malignancies. For example an AUC of 0.922 was determined to identify women with high mammographic density as well established physical risk factor for women in the breast cancer screening age. In a cohort of younger women a rate of optical breast tissue changes was determined after 6 visits suggesting the ability to determine rates for metabolic tissue aging through a women's life and hence their long term cancer risk according to the Pike model. In the long term one can thus identify women with high metabolic breast tissue aging early in live and offer targeted risk reduction intervention to this cohort. Current work focuses on the quantification of the tissue chromophores as surrogate for the contributions of the various tissue components.

Invited Talk Fri 17:00

Boron clusters in cancer therapy — René Frank[1], Solveig Boehnke[1], Verena Ahrens[2], Annette Beck-Sickinger[2], Sven Stadlbauer[1], Evamarie Hey-Hawkins[1] — [1]University of Leipzig, Institute of Inorganic Chemistry, Johannisallee 29, 04103 Leipzig, Germany — [2]University of Leipzig, Institute of Biochemistry, Brüderstraße 34, 04103 Leipzig, Germany

Therapy of malignant tumours is based on three strategies: surgery, irradiation and chemotherapy. An alternative method is boron neutron capture therapy (BNCT). The binary method of BNCT proposed by G. L. LOCHER in 1936 [1] is based on the accumulation of appropriate boron compounds in tumour cells and their subsequent activation by thermal neutrons. The fission products are the actual cytotoxin. Originally, BNCT was developed as an alternative to other methods for the treatment of deep-seated tumours. Nowadays, BNCT is employed in the treatment of head and neck cancer, metastatic liver cancer and cutane and intracerebral melanoma.

High and selective accumulation in tumour cells is an important requirement for a BNCT agent. Up to now, only BPA (L-para-boronophenylalanine), its fructose complex and BSH (sodium mercapto-closo-dodecaboronate) made it into clinical trials. In the past few years, promising approaches in the area of tumour targeting have been established, in which selectively acting hormones or antibodies are employed for the localisation and destruction of tumours. The combination of the pharmacologically active scaffolds of cancer pharmaceuticals with a tumour-specific ligand is envisioned to be used for the selective accumulation of the pharmaceutical in diseased cells and their elimination without harming the healthy tissue.

Our approach in increasing the tumour selectivity of BNCT agents is the use of conjugates of glycosides with carbaboranylphosphonates, which combine the boron-bearing part with a hydrophilic, less toxic and tumour-selective moiety, [2,3,4,5] as well as incorporation of carbaboranes into breast-tumour-selective neuropeptide Y [6,7]. Both strategies will be discussed.

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Invited Talk Fri 17:30

Beyond conventional limits to cancer: Where can a physical sciences perspective fit in? — Larry A. Nagahara — Office of Physical Sciences – Oncology, National Cancer Institute, Bethesda, MD 20892, USA

The National Cancer Institute (NCI) is exploring new and innovative approaches to better understand and control cancer. By partnering with scientists from various non-biology disciplines, NCI envisions novel approaches to help generate answers to some of the major questions and barriers in cancer research. Interfacing physical sciences (physics, chemistry, engineering, mathematics, etc.) with oncology has brought significant advancements from a technology perspective in the way we clinically diagnose and treat cancer. Besides technology, the physical sciences can bring orthogonal views that can both challenge and enlighten cancer research. One of NCI's recent programs, the Physical Sciences - Oncology Centers (PS-OC) Program, attempts to better understand the physical laws and principles that shape and govern the emergence and behavior of cancer. Researchers examine non-traditional approaches to cancer research by bringing a physical sciences perspective to explore four thematic areas, namely, the physical laws and principles of cancer; evolution and evolutionary theory of cancer; information coding, decoding, transfer and translation in cancer; and deconvoluting cancer's complexity. In this presentation, examples of blending physical sciences perspectives on

oncology will be presented to illustrate that fostering the development of innovative ideas and new fields of study could lead to a paradigm shift in the way we understand and ultimately and treat cancer.

Session IV: Membrane Mechanics, Cytoskeletal Dynamics, and Tumor Progression

Invited Talk Sat 08:00

Lamin-A levels limit 3D-migration but protect against migration-induced apoptosis — DENNIS E. DISCHER — Biophysical Eng'g. Lab., 129 Towne Bldg., University of Pennsylvania, Philadelphia, PA 19104-6315, USA

Cell migration through dense tissue and matrix generally requires the cell and its nucleus to contort and flow. A strong dependence of 3D-migration processes on the variably expressed nucleoskeletal protein lamin-A is revealed here across widely different cell types relevant to disease and regeneration. Crawling through tissue is modeled by motility through micro-pores, with small decreases in lamin-A producing large increases in net migration. Surprisingly, the largest effects occur when wildtype lamin-A is low relative to constitutive lamin-B's. Nuclear shape changes after micro-pore migration as well as nuclear response times in micropipette aspiration scale strongly with the lamin-A:B ratio across cell types, revealing lamin-A's role in nuclear plasticity and lamin-B's role in nuclear elasticity. Lamin-A also protects against apoptosis induced by micro-pore migration, with deeply deficient cells showing defects in stress-resistance. Xenografts provide *in vivo* insight and show moderately low lamin-A levels promote growth of the graft. The nuclear lamina thus acts as a physical impediment to motility and also promotes survival in withstanding the mechanical stresses of migration.

Invited Talk Sat 08:30

Mechanosensitivity and motility of cellular aggregates — FRANÇOISE BROCHARD-WYART, DAMIEN CUVELIER, STÉPHANE DOUEZAN, SYLVIE DUFOUR, JULIEN DUMOND, GREGORY BEAUNE, DAVID GONZALEZ-RODRIGUEZ, KARINE GUEVORKIAN — Institute Curie, Soft Interfaces Group, Paris, France

We first describe the biomechanics of multicellular aggregates, a model system for tissues and tumors. We first characterize the tissue mechanical properties (surface tension, elasticity, viscosity) by a new pipette aspiration technique. The aggregate exhibits a viscoelastic response but, unlike an inert fluid, we observe aggregate reinforcement with pressure, which for a narrow range of pressures results in pulsed contractions or "shivering". We interpret this reinforcement as a mechanosensitive active response of the acto-myosin cortex. Such an active behavior has previously been found to cause tissue pulsation during dorsal closure of Drosophila embryo.

We then describe the spreading of aggregates on decorated glass substrates, varying both intercellular and substrate adhesion. We find both partial and complete wetting regimes. For the dynamics, we find a universal spreading law at short time, analogous to that of a viscoelastic drop. At long time, we observe, for strong substrate adhesion, a precursor film spreading around the aggregate. Depending on aggregate cohesion, this precursor film can be a dense cellular monolayer ("liquid state") or consist of individual cells escaping from the aggregate body ("gas state"). The transition from "liquid" to "gas state" appears also to be present in the progression of a tumor from noninvasive to metastatic, known as the epithelial-mesenchymal transition.

Finally, we describe the effect of the substrate rigidity on the phase diagram of wetting. On soft gels decorated with fibronectin and strongly cohesive aggregates, we have observed a wetting transition induced by the substrate rigidity: on ultra soft gels, below an elastic modulus Ec the aggregates do not spread, whereas above Ec we observe a precursor film expending with a diffusive law. The diffusion coefficient D(E) present a maximum for E=Em. A maximum of mobility versus the substrate rigidity had also been observed for single cells. Near Em, we observe a new phenomenon: a cell monolayer expends outwards from the aggregate I

apparently under tension. In this tense monolayer, holes nucleate, and lead to a symmetry breaking as the entire aggregate starts to move in a similar fashion as a "giant" keratocyte.

Invited Talk Sat 09:00

Extrinsic and intrinsic force regulation of tumor progression — Valerie M. Weaver — University of California, Center for Bioengineering and Tissue Regeneration, 513 Parnassus Avenue, San Francisco, CA 94143-0456, USA

Tumors are characterized by profound changes in their mechanical properties and modifications in tissue level forces that include extracellular matrix (ECM) stiffening and interstitial compression. We and others showed that elevating cell tension or stiffening the ECM promotes malignant progression, and reducing interstitial pressure or ECM stiffness reduces tumor progression and aggression. We also found that oncogenic transformation increases Rho-Rock activity to enhance tumor cell contractility and that this elevated contractility drives ECM remodeling and stiffening to destabilize tissue organization and promote malignant transformation. Interestingly, we also noted that many oncogenes also significantly increase the expression of proteoglycans on the surface of tumor cells (the protein coating on the surface of cells termed the glycocalyx). Bioinformatics analysis revealed that tumors with an unusually bulky glycocalyx demonstrate high propensity to metastasize. Since molecules such as mucins and hyaluronic acid extend an order of magnitude further than typical cell surface receptors, we have been exploring whether these large molecules physically change the thickness and topography of cell-cell and cell-matrix interfaces to alter interactions between cell surfaces receptors and ligands on apposed cells or the extracellular matrix. In other words, we propose that large cancer-associated glycans and glycoproteins mechanically perturb the receptor-mediated flow of information from the microenvironment into cell signaling networks. This notion is supported by our computational model (Paszek et al., PLoS Comp Biol., 2009) which predicts that the physical properties of the glycocalyx is a key parameter that controls integrin adhesion receptor assembly to drive the assembly of focal adhesions. To experimentally explore this prediction we increased the glycocalyx either: by genetically manipulating nonmalignant epithelial cells to express oncogenes which up regulate bulky glycoproteins such as HA and mucins; by molecularly engineering cells to express large bulky glycoproteins such as muc-1 or by using a synthetic chemistry approach such as mucin glycol-mimetics to artificially modify the cell surface glycocalyx. Thse strategies consistently and significantly increased the height of the cellular glycocalyx as confirmed by scanning angle interference microscopy imaging (Paszek et al. Nature Methods 2012). Moreover, in all instances we observed that glycocalyx-mediated expansion of the cell-matrix interface slowed the rate of integrin binding to matrix-tethered ligands and promoted integrin clustering as well as the recruitment of adhesion plaque proteins and the assembly of mature focal adhesions. We noted that these integrin clusters typically formed adjacent to thick glycocalyx patches where the close proximity between the bulky glyco-proteins and integrins exerted reciprocal tension and compression due to their large differences in length (~200 nm versus 20 nm); as revealed by elevated compression forces measured using a unique glycocalyx FRET force sensor. Indeed, single cell force spectroscopy and fluorescence interference contrast microscopy confirmed that the cancer-associated mucin Muc1 must be compressed on the cell surface for integrins to efficiently engage matrix-tethered ligands. Since conformational activation of integrin receptors is induced by mechanical force, we tested whether Muc1 could induce integrin activation independent of actin- and myosin-mediated cell contractility. Remarkably, integrins were activated in a force-dependent manner in cells expressing Muc1 even if actomyosin contractility was inhibited. These results suggest that the increased expression of bulky glycoproteins that contribute to the glycocaylx observed in cancer cells may foster focal adhesion assembly and signaling to enhance tumor cell growth, survival and migration in a force-dependent manner. Consistently, we observed that that increased levels of Muc1 in breast epithelial cells or high HA levels in glioblastoma cells promote integrin clustering and enhanced growth factor signaling to increase their anchorage-independent growth and survival and to promote their invasion; hallmarks of invasive cancers. These findings identify an additional mechanism whereby a novel fundamental mechanism through which integrin adhesion and signaling is mechanically regulated by the cellular glycocalyx. We propose that an altered glycocalyx is a novel paradigm for perturbed mechanical signaling and cell behavior in cancer.

Invited Talk Sat 09:30

The nanomechanical signature of breast cancer — RODERICK Y. H. LIM — Biozentrum and The Swiss Nanoscience Institute, University of Basel, Switzerland

Tumor mechanobiology is an important yet unresolved aspect of cancer progression. How the mechanical properties of cells evolve from a healthy stage to malignancy and manifest themselves in tissues is poorly understood. Here, correlative stiffness maps obtained by indentation-type atomic force microscopy (IT-AFM) are used to identify distinct tumor stages of native human breast biopsies by resolving their local mechanical stiffness at the nanoscale. Healthy ductal epithelium and benign lesions are characterized by a uniform stiffness distribution. In comparison, primary cancer lesions owing to tissue heterogeneity exhibit a broad background stiffness distribution that is accompanied by a characteristic compliance representing cancer cells. Importantly, the stiffness profiles from each specific stage of tumor progression are validated in MMTV-PyMT transgenic mice. We remark further that hypoxia is apparent in areas of soft cancer phenotype that occur from early to late stages of tumor progression. Detecting the soft phenotype also in lung metastases suggests that the compliance of malignant cells in the primary cancer is correlated to aggressiveness and thus promotes migration and metastasis. Overall, our study unveils the clinical translational significance of nanomechanical signatures in the diagnosis of breast cancer.

Contributed Talk Sat 10:00

Nonlinear fibrin mechanics and its alterations by platelets — LOUISE JAWERTH[1], STEFAN MÜNSTER[2], DAVID WEITZ[1] — [1]Harvard University, Cambridge MA, USA — [2]University of Erlangen-Nuremberg, Erlangen, Germany

Stiff biopolymer networks, such as those in the extracellular matrix, are found throughout the body where they form the underlying structural scaffold of tissues, tendons and ligaments. The mechanical properties of these networks are of crucial importance to their proper function. Part of this function, is their interactions with cells that adhere to and remodel them. One prominent example of a stiff biopolymer which is significantly altered by cells are networks formed form the biopolymer fibrin. Fibrin networks form during blood coagulation where they serve as the structural meshwork which supports the cells and other proteins that together constitute a blood clot. During this process, these networks are significantly altered by the presence of platelets. In-vitro studies have shown that platelets have a profound effect on the mechanics of the fibrin network. Similar to other networks of stiff biopolymer such as collagen type I, fibrin networks in the absence of platelets show strain-stiffening: a stiffness that is constant at low strains and increases non-linearly with strain at high strains. The mechanism which underlies this transition in stiff biopolymer networks has remained elusive. In our study, we investigate the origin of strain-stiffening in fibrin gels and how this is influenced by platelets. Using confocal microscopy, we image the 3D network structure as it undergoes shear. With subsequent image analysis we find the deformation field of the network during this experiment. We analyze the individual fiber strain, non-affinity of fiber motion and find that the mechanics of the network are dictated largely by its structure. Specifically, at low strains the network utilizes soft bending modes to deform without stretching the individual fibers, while at high strains these modes are exhausted and the fibers must begin to become stretched. To understand how platelets change these properties, we polymerize fibrin gels together with activated platelets. We then image the structure of the network and measure its corresponding mechanical changes. We find that the low strain stiffness increases with increasing platelet concentration while the high strain stiffness remains unaltered. Platelets induce aster-like structures in the fibrin gel. The altered mechanical and structural properties are consistent with platelets reducing the number of available soft bending modes. To test whether this occurs through passive fiber nucleation or active gel contraction, we add platelets to pre-polymerized fibrin networks. We find that the structural changes induced by platelets can occur in pre-polymerized gels suggesting that the predominate mechanical change is a result of active platelet contraction and not passive fiber nucleation.

Invited Talk Sat 10:45

Surface changes on dying tumor cells instruct the immune system — LUIS MUNOZ, RICARDO CHAURIO, MARTIN HERRMANN — University Hospital Erlangen, Germany

In this abstract we use the following definitions: early apoptotic cells are cells that expose phosphatidylserine,

harbour fragmented chromatin and active caspases, and are still equipped with an intact plasma membrane. When the plasma membrane of these cells gets ion-permeable they are referred to as late apoptotic/secondary necrotic. Whereas early apoptotic cells are dying cells, primary and secondary necrotic cells are considered dead.

The phagocytosis of apoptotic cells is a fine-tuned process based on a highly complex interaction between dying cells and phagocytes. Favourably the phagocytic machinery finds and clears apoptotic cells before they progress to secondary necrosis. This helps to avoid inflammation and autoimmune diseases. Before and during the clearance process apoptotic cells (I) signal their demise to the environment and mark themselves for silent uptake, (II) maintain their membrane integrity as long as possible and (III) provide help for healing and/or repopulation of the tissue. To attract phagocytes to the site of cell death apoptotic cells secrete long ranging "find-me" signals and expose short ranging "eat-me" signals that initiate the engulfment. A well-established "eat-me" signal is the exposure of phosphatidylserine, which translocates from the inner to the outer leaflets of the cytoplasmic membranes early in the apoptotic process. Various phagocyte receptors (e.g. the vitronectin receptor [αvβ3 integrin], the β2-glycoprotein-I [β2-GPI] receptor, and the receptor-tyrosin kinase Mer) bind to phosphatidylserine via the corresponding bridging molecules (milk-fat-globule-EGF-factor 8 [MFG-E8], β2-GPI, and growth-arrest specific gene 6 [gas6]), respectively. The majority of the apoptotic cells are instantaneously phagocytosed without provoking inflammation. Those dying cells that escape early phosphatidylserine-dependent clearance may enter late stages of apoptosis characterised by cell shrinkage and plasma membrane loss due to extensive blebbing. Apoptosing cells reportedly retain their membrane integrity for a long time. The massive loss of plasma membrane is substituted by internal membranes, at least some of them are derived from endoplamic reticulum (ER) and are, therefore, equipped with immature ER-derived proteins. To avoid progression to secondary necrosis, a condition prone to challenge self-tolerance, second line surface signals which support clearance of late apoptotic cells are beneficial. Late apoptotic cells bind several non-phosphatidylserine-specific bridging molecules including C reactive protein (CRP), complement C1q, surfactant proteins A and D, mannose binding lectin. Most of these dying and dead cell ligands recognize (immature) carbohydrate moieties. However, the exact molecular nature of most targets on the apoptotic surfaces are still elusive. The analysis of alterations of the glycocalyx and the composition of plasma membranes of cells undergoing apoptosis have led to the identification of potential immune modulatory signals especially derived from late apoptotic cells.

Invited Talk Sat 11:15

Regulation of focal adhesion maturation by the actin cytoskeleton — MARGARET GARDEL — University of Chicago, Gordon Center for Integrative Science, GCIS E233, 929 E. 57th St, Chicago, IL 60637, USA

Myosin II motors drives changes in focal adhesion morphology and composition in a "maturation process" that is crucial for regulating adhesion dynamics and signaling that guide cell adhesion, migration and fate. However, the underlying mechanisms of maturation have been obscured by the intermingled effects of myosin II on lamellar actin architecture, dynamics and force transmission. Recent evidence from our laboratory challenges the prevailing notion that mechanical tension drives focal adhesion maturation. Instead, we find that adhesion size and composition depend instead on actin architecture and retrograde flow dynamics. Here, we show that focal adhesion growth rate and composition stay constant even when cellular tension is reduced by 75%. Instead we find that radial stress fibers that assemble at the adhesion plaque in an Dia1 and a-actinin fashion act as a template for the growth of adhesions and this architecture is required for adhesion compositional maturation. Thus, our work identifies a minimal myosin activity threshold necessary to drive lamellar actin retrograde flow is sufficient to permit focal adhesion maturation. Above this threshold, myosin-mediated actin organization and dynamics regulate adhesion maturation in a tension-insensitive fashion. Finally, we have found that cell environmental sensing arises predominately from myosin-II independent adhesions formed within the lamellipodia. These findings highlight the important roles of actin dynamics and organization in regulation of adhesion assembly and maturation. Moreover, these results call into question the extent to which myosin-II mediated tension plays a dominate role in regulating cell adhesion.

Invited Talk Sat 11:45

Cell motility and cytoskeleton assembly — JULIE PLASTINO — Institute Curie, Biomimetism of Cellular Movement Group, Paris, France

Many cell movements proceed via a crawling mechanism, where cytoskeleton assembly beneath the leading edge membrane pushes out the front of the cell to form a lamellipodia. The goal of our research is to study the interplay between membrane and cytoskeleton dynamics during motility. In a first part, we use a simple system of crawling cell motility, the Caenorhabditis elegans sperm cell, to probe the relationship between membrane tension and cytoskeleton dynamics, and find that increased tension enhances motility by increasing lamellipodia organization. We then turn to a simple model of cell motility *in vivo*, the ventral enclosure event of C. elegans embryogenesis, coupled with *in vitro* bead motility assays, to study how Ena/VASP proteins enhance lamellipodial protrusion. Based on results from this combined approach, we propose that VASP acts by retaining nascent filaments at the surface, thus potentially enhancing Arp2/3 complex activity, leading to an increase in actin network growth and motility. Overall these studies highlight how small alterations in the mechanical properties of the cell membrane or in cytoskeleton biochemistry have large effects on motility.

Invited Talk Sat 12:15

Ruthenium(II) polypyridyl complexes as carriers for DNA delivery — AVINASH S. KUMBHAR — Department of Chemistry, University of Pune, Pune-411007, India

The condensation of negatively charged DNA molecules into compact structures is a prerequisite for gene therapy of cancer. Several biomaterials have been studied as potential non–viral gene delivery vectors, these include multivalent cations, and organic polymers such as cationic lipids, peptides, polyamines, polysaccharides, spermidine and dendrimers, all condense DNA through electrostatic interaction. But metal based non-viral gene delivery vectors have not been explored fully. Therefore, a series of ruthenium(II) polypyridyl complexes of bipyridine functionalized molecular clip ligand having DNA condensation ability have been synthesized and characterized. These complexes self–associate in water by specific molecular recognition processes, to form polycationic aggregates. These aggregates containing electrostatic binders as well as intercalator ligands at micromolar doses rapidly condense free DNA into globular nanoparticles with varied sizes. The DNA condensation induced by these complexes has been investigated by electrophoretic mobility assay, dynamic light scattering and transmission electron microscopy. The cellular uptake of complex–DNA condensates and low cytotoxicity of these complexes satisfies the requirements of a gene delivery vector.

Invited Talk Sat 12:15

Mechanics of contractile actomyosin bundles — PHILLIPPE MARCQ — Institute Curie, Physical approach of biological problems group, Paris, France

Contractile actomyosin bundles are commonly observed in the cytoskeleton of metazoan cells. The spatial profile of the polarity of actin filaments they contain is either monotonic (graded) or periodic (alternating). We formulate the constitutive equations for a polar, active, elastic one-dimensional medium. An analysis of the resulting equations for the dynamics of polarity shows that active contractility is a necessary condition for the emergence of alternating polarity patterns [1]. Contractile actomyosin bundles retract when severed *in vivo* by laser ablation, or when isolated from the cell and micromanipulated *in vitro* in the presence of ATP. We identify the time scale for contraction as a viscoelastic time, where the viscosity is due to (internal) protein friction, and obtain an estimate of the order of 10 to 100 seconds, consistent with available experimental data. Our results are supported by an exactly solvable, hydrodynamic model of a retracting bundle as a three-dimensional, isotropic, active, viscoelastic cylinder [2].

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