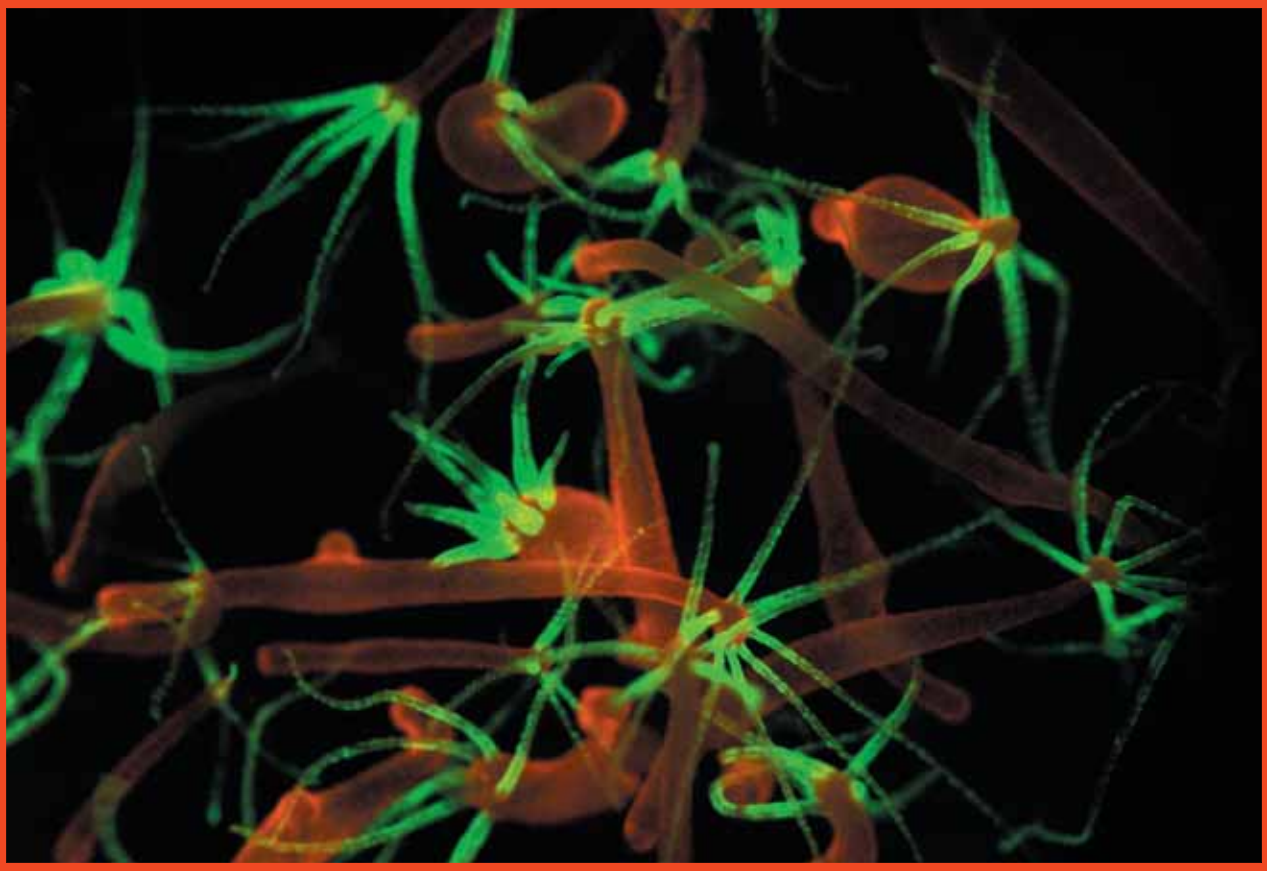
Cell News

Newsletter of the German Society for Cell Biology
Volume 38, 3/2012



Upcoming meetings:

– Physics of Cancer
– Molecular concepts in epithelial function
– Joint International Meeting DGZ & GfE

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Newsletter of the German Society for Cell Biology

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Cover image: *Hydra* polyps expressing a GFP-tagged protein. Experimental studies in Cnidaria provide insight into the evolution and the ecology of development. Photo credit: Javier Andrés López Quintero.

International meetings: Numbers take control

The German Society for Cell Biology hosted two meetings in September, the "International Meeting on Actin Dynamics" and the "Young Scientist Meeting", which addressed the fascinating cell biology of embryonic development. Both meetings had outstanding international speakers and outlined the basics as well as the most recent and exciting novelties in the fields of cytoskeletal research and developmental biology. The meetings had strong contributions from younger researchers, whose poster abstracts were selected as oral presentations and had very exciting poster sessions with animated discussions. Detailed meeting reports are in this issue of Cell News.

As a common trend in cytoskeletal research as well as in the field of developmental biology, it became obvious that after a decade, where we have discovered novel proteins and complexes and made many very interesting observations upon cellular dynamics, researchers now started to quantify cell biological processes in our aim to understand the underlying principles. Biophysical measurement, cellular mechanics and mathematical modelling are becoming and more and more important. Cell biology thereby rapidly develops into a multidisciplinary field and those of us who are involved in student teaching should integrate these novel demands into the educational programs.

Young scientist award

The German Society for Cell Biology would like to become more attractive for young scientists and would like to integrate them as early as possible into our scientific community. The DGZ therefore will strengthen the support for young and enthusiastic scientists. As a first measure the DGZ has implemented a novel award for graduate students and younger post-docs the "Young scientist award of the German Society for Cell Biology". Two of these prizes, which comprise a prize money of 1500 € each, will be given to the prize winners in a ceremony at the Annual Meeting. Younger DGZ members can apply for this prizes by sending in a published manuscript and a CV. A more detailed announcement is in this issue of Cell News.

DGZ board member rotation

The DGZ routinely restructures its advisory board in order to integrate new scientists with different perspectives. We hereby would like to thank the retiring advisory board members Silvia Erhardt (Heidelberg), Anne Spang (Basel) and Zuzana Storchova (Martinsried) for their support and we are proud to announce that Britta Qualmann (Jena) and Zeynep Ökten (München) recently agreed to join the advisory board. We hope to complete the new advisory board within the next weeks and the novel board members will be introduced in the next issue of Cell News.

Eugen Kerkhoff

Young Scientist Award of the DGZ

The German Society for Cell Biology offers **two** "Young Scientist Awards" for Ph.D. students and young postdocs (within 3 years after graduating).

Each award comprises a prize money of **EUR 1500**.

Candidates are invited to apply for the "Young Scientist Award" by themselves. DGZ membership is required.

Applications have to consist of a cover letter, a CV and PDF-files of publications that document the work of the applicant.

Applications will be reviewed by an independent commission of the DGZ. The award ceremony takes place at the next annual meeting – the "Joint International Meeting of the DGZ and the German Society for Developmental Biology (GfE) – which will be held on March 20-23, 2013 in Heidelberg.

Applications should be sent by e-mail (and in parallel one hard copy by mail) to the DGZ office:

Deutsche Gesellschaft für Zellbiologie e.V. (DGZ)
Sekretariat, z.H. Frau Reichel-Klingmann
c/o Deutsches Krebsforschungszentrum
Im Neuenheimer Feld 280
D-69120 Heidelberg
E-mail: dgz@dkfz.de

Deadline for applications:
January 15, 2013

Physics of Cancer Symposium

Leipzig, November 1-3, 2012

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 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 this Physics of Cancer 2012 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.

Scientific Programme

Thursday, November 1

13:00 - 13:15 **Opening of the Symposium**
Rector of the University of Leipzig
Beate A. Schücking

Session I:
Biomechanics of Cell Adhesion and Gene Expression

13:15 – 13:45 **Do tumor cells are about physics?**
Josef A. Käs

13:45 – 14:15 **Cell shape and rigidity control by actomyosin contractility**
Gijsje Koenderink

14:15 – 14:45 **Force-dependent and -independent integrin regulation of ROS-production**
Staffan Johansson

14:45 – 15:15 **Coffee Break/Discussion**

15:15 – 15:45 **Lamin-A levels limit 3D-migration but protect against migration-induced apoptosis**
Dennis E. Discher

15:45 – 16:15 **Significance of the mechanical properties of the cell nucleus in cell migration and transit through narrow constrictions**
Jan Lammerding

16:15 – 16:45 **Surface changes on dying tumor cells instruct the immune system**
Martin Herrmann

16:45 – 17:15 **Reprogramming cellular mechanosensing by hyaluronic acid and its receptors**
Paul Janmey

17:15 – 18:00 + 3 contributed talks selected from the abstracts

19:00 **Poster Session**
with discussions, snacks and fingerfood
– in front of ecture hall –

FUTURE MEETINGS

Friday, November 2

Session II:
Cell Migration and Forces I

08:30 – 09:00 **The role of mechano-sensing and matrix geometry in cancer invasion**
Erik Sahai

09:00 – 09:30 **Novel materials and systems at the interface between the inorganic, organic and biological world**
Joachim A. Spatz

09:30 – 10:00 **Mechanical regulation of cell contraction**
David Fletcher

10:00 – 10:30 **Coffee Break/Discussion**

10:30 – 11:00 **Biomechanical properties of cancer cells determine their aggressiveness**
Claudia T. Mierke

11:00 – 11:30 **Self-organization of the actin cytoskeleton: Physical mechanisms and signaling pathways**
Alexander Bershadsky

11:30 – 12:00 **Mechanical Regulation of Adhesive Bonds**
David Boettiger

12:00 – 12:30 + 2 contributed talks selected from the abstracts

12:30 – 14:30 **Lunch**

Session III:
Cell Migration and Forces II

14:30 – 15:00 **Identification of pathways in metastatic tumor cells that regulate cortical actin polymerization and motility in vivo**
John S. Condeelis

15:00 – 15:30 **Modeling surface tension and viscoelasticity in cell aggregates and tissues**
Lisa Manning

15:30 – 16:30 + 4 contributed talks selected from the abstracts

16:30 – 17:00 **Coffee Break/Discussion**

17:00 – 17:30 **Boron Clusters in Cancer Therapy**
Evamarie Hey-Hawkins

17:30 – 18:00 **Beyond conventional limits to cancer: Where can a physical sciences perspective fit in?**
Larry Nagahara

19:00 Get Together for the invited Speakers

Saturday, November 3

Session IV:
Membrane mechanics, cytoskeletal dynamics and tumor progression

8:00 – 08:30 **Modeling surface tension and viscoelasticity in cell aggregates and tissues**
Florian Rehfeldt

08:30 – 09:00 **Mechanics of contractile actomyosin bundles**
Philippe Marcq

09:00 – 09:30 **Forcing transformation**
Valerie M. Weaver

09:30 – 10:00 **Nanomechanical signature of breast cancer**
Roderick Lim

10:00 – 10:30 **Coffee Break/Discussion**

10:30 – 11:00 **The keratin desmosome connection: crucial player in tissue integrity and malignancy**
Thomas A. Magin

11:00 – 11:30 **Regulation of Cell Adhesion by the Actin Cytoskeleton**
Margaret Gardel

11:30 – 12:00 **Cell Motility and Cytoskeleton Assembly**
Julie Plastino

12:00 – 12:30 **Ruthenium II polypyridyl complexes as carriers for DNA delivery**
Avinash S. Kumbhar

12:30 – 13:00 **Role of substrate stiffness on the spreading and motility of cellular aggregates**
Francoise Brochard-Wyart

13:00 – 13:15 **The End**

Molecular concepts in epithelial differentiation, pathogenesis and repair

November 7th – 10th, 2012, Leipzig

International Meeting of the German Society for Cell Biology

Meeting site: Fraunhofer Institute for Cell Therapy and Immunology, Perlickstraße 1, 04103 Leipzig

Local Organizers: Prof. Thomas M. Magin, Prof. Mechthild Hatzfeld

Scientific Programme

Wednesday, November 7

12:00 – 14:00	Welcome and lunch
14:00-18:00	**Epithelial morphogenesis and regeneration** Chair: V. Botchkarev COST session
14:00-14:30	**Dermal CSL signaling in control of skin homeostasis and field cancerization: more than Notch?** Paolo Dotto (Lausanne)
14:30-15:00	**Live imaging of wound repair and inflammation** Paul Martin (Bristol)
15:00-15:30	**Cytoskeletal regulators and skin inflammation** Cord Brakebusch (Kopenhagen)
15:30-16:00	**Novel functions of Nrf transcription factors in skin homeostasis and disease** Sabine Werner (Zürich)
16:00-16:30	Coffee break
16:30-17:00	**p63 transcription factor and regulation of higher-order chromatin remodeling in epidermal keratinocytes** Vladimir Botchkarev (Bradford)
17:00-18:00	**short talks to be selected from poster abstracts** N.N.
18:00- 21:00	**Poster session and buffet dinner**

Thursday, November 8

8:30-12:30	**Cell biology and biophysics of the cytoskeleton** Chair: P. Coulombe COST session
8:30-9:00	**Mechanics of the Cytoskeleton** Josef Käs (Leipzig)
9:00-9:30	**Spatially and temporally coordinated process of cells: from molecular to cellular scale** Joachim Spatz (Stuttgart)
9:30-10:00	**Analyzing intracellular force transduction using novel biosensors** Carsten Grasshof (Martinsried)
10:00-10:30	Coffee break
10:30-11:00	**Cytoskeleton in motion: the dynamics of keratin intermediate filaments in epithelia** Rudolf Leube (Aachen)
11:00-11:30	**Interrelationships between keratins, stress, and inflammation in skin epithelia** Pierre Coulombe (Baltimore)
11:30- 12:00	**A role of keratins in cell adhesion and tissue homeostasis** Thomas Magin (Leipzig)
12:00-12:30	**short talks to be selected** N.N.
12:30-14:00	**Lunch and posters**

FUTURE MEETINGS

13:30-17:00 **Visit to BMW Factory**

18.00-20:00 **Skin barrier, inflammation and immunity**
Chair: Tsukita

18:00-18:30 **Skin barrier dysfunction and cutaneous sensitization**
Masa Amagai (Tokio)

18:30-19:00 **Role of Membrane Protein Shedding in Inflammation and Cancer**
Stefan Rose-John (Kiel)

19:00-19:30 **NF-κB in the regulation of epithelial homeostasis and inflammation.**
Manolis Pasparakis (Köln)

19:30-20:00 **Modulation of cellular functions by artificial extracellular matrices as biomaterial coatings**
Jan Simon (Leipzig)

Buffet dinner and poster session

Friday, November 9

8:30-13:00 **Matrix adhesion and migration**
Chair: M. Inagaki
COST session

8:30-9:00 **Regulation of membrane traffic by integrin signaling**
Reinhard Fässler (Martinsried)

9:00-9:30 **Integration at junctions: cadherin adhesion, signaling and the actin cytoskeleton**
Alpha Yap (Brisbane)

9:30-10:00 **Rho GTPases: signalling in cell adhesion and migration**
Ann Ridley (London)

10:00-10:30 **Post-transcriptional control of tumor cell migration and EMT**
Stefan Hüttelmaier (Halle)

10:30-11:00 Coffee break

11:00-11:30 **Pathophysiological roles of intermediate filaments and intermediate filament phosphorylation**
Masaki Inagaki, (Nagoya)

11:30-12:00 **Cell polarity regulators in mammalian tumor formation and progression**
Sandra Iden (Köln)

12:00 – 14:00 **Lunch and posters**

14:00 – 17:00 **Tour of Nicolaikirche and Johann S. Bach (organ)**

17:00-20:00 **Adhesion receptors, cell contact and growth control**
Chair: C. Niessen
COST session

17:00-17:30 **Coupling Desmosomal Adhesion to Epidermal Morphogenesis**
Kathleen Green (Chicago)

17:30-18:00 **Functions of plakophilin 1 in cell adhesion and growth control**
Mechthild Hatzfeld (Halle)

18:00-18:30 **How to form a barrier: regulation of intercellular junctions in the skin**
Carien Niessen (Köln)

18:30-19:00 Coffee break

19:00-19:30 **Regulation of cadherin cell-cell adhesion and actin dynamics: An evolutionary perspective**
James Nelson (Stanford)

19:30-20:00 **Role of Tight Junction Claudins in Biological Systems**
Sachiko Tsukita (Osaka)

20:00 **Buffet dinner and poster session**

Saturday, November 10

9:00-12:00 **Cell and molecule-based therapies and perspectives**
Chair: L. Bruckner-Tudermann

9:00-9:30 **Towards a gene therapy for epidermolysis bullosa**
Michele DeLuca (Modena)

9:30-10:00 **Fibroblast-based gene therapy**
Leena Bruckner-Tuderman (Freiburg)

FUTURE MEETINGS

10:00-10:30	**Desmosomes, protein kinase C and epidermal wound healing** David Garrod (Manchester)
10:30-11:00	Coffee break
11:00-11:30	**Exploring the Therapeutic Potential of Induced Pluripotent Stem (iPS) Cells for Inherited Skin Blistering Diseases"** Dennis Roop (Denver)
11:30-12:00	**Towards gene therapy of epidermal disease** Alain Hovnanian (Paris)
12:00-12:30	**genetic analysis of cancer susceptibility: from mouse models to humans** Allan Balmain (San Francisco)
	Lunch and departure

Support
DFG, FCI, TRM Leipzig, , BBZ Leipzig, EU (COST)

Registration and General Information: MCI Deutschland GmbH, E-mail: molcedpare@mci-group.com
Detailed scientific program, further information and registration: http://www.molcedpare.de

Joint International Meeting of the German Society for Cell Biology (DGZ) and the German Society for Development Biology (GfE)

March 20 - 23, 2013, Heidelberg

Organized by Harald Herrmann (DGZ) and Jochen Wittbrodt (GfE)

Scientific Programme

Wednesday, March 20

08:00 – 20:00 Registration

09:00 – 10:30 **Talk & Question Time: DFG Funding Opportunities for all Career Stages**
Dr. Dorette Breitkreuz, German Research Foundation (DFG), Programme Director, Life Sciences 2
Dr. Astrid Klingen, German Research Foundation (DFG), Programme Officer, Life Sciences 2
Review Board Members of the German Research Foundation (DFG)

11:00 – 13:00 **Student Symposium**: The Abstract Highlights

14:00 Introduction – Welcome

14:15 – 16:15 **Plenary Session PS1: Cell Polarity**
Chair: Jiri Friml (Gent, Belgium)

Invited Speakers:
- Carl-Philipp Heisenberg (Klosterneuburg, Austria)
- Erez Raz (Münster)
- Jochen Rink (Dresden)
- Marja Timmermans (Cold Spring Harbor, USA)

16:30 – 17:30 **DGZ Awards**
- Walther Flemming Medal
- Binder Innovation Prize
- Werner Risau Prize

17:30 – 18:30 **Carl Zeiss Lecture**
Robert A. Weinberg (Cambridge, USA)

18:30 – 19:00 **Campos-Ortega-Lecture**
will be selected in December by the GfE Board

19:00 **Welcome Reception – Posters for Display**

Thursday, March 21

09:00 – 12:00 **Symposia 1 – 4**

Symposium S1: The Nuclear Envelope: Barrier & Transport Functions
Chair: Jörg Großhans (Göttingen)

Invited Speakers:
- Vivian Budnik (Worcester, USA)
- Amnon Harel (Haifa, Israel)
- Ulrike Kutay (Zürich, Switzerland)

Symposium S2: Non-coding RNA in Development and Disease
Chair: Sven Diederichs (Heidelberg)

Invited Speakers:
- Stefan Hüttelmaier (Halle)
- Judy Lieberman (Boston, USA)
- Nikolaus Rajewsky (Berlin)

Symposium S3: Ubiquitin-related Proteins
Chair: Frauke Melchior (Heidelberg)

Invited Speakers:
- Stefan Jentsch (Martinsried)
- Madelon M. Maurice (Utrecht, The Netherlands)
- Richard D. Vierstra (Madison, USA)

Symposium S4: Epigenetics
Chair: Sylvia Erhardt (Heidelberg)

Invited Speakers:
– M. Cristina Cardoso (Darmstadt)
– Sandra B. Hake (München)
– Dirk Schübeler (Basel, Switzerland)

13:30 – 16:30 **Symposia 5 – 8**

Symposium S5: Centrosomes
Chairs: Ralph Gräf (Potsdam) and Oliver Gruss (Heidelberg)

Invited Speakers:
– Monica Bettencourt Dias (Oeiras, Portugal)
– Andrew Fry (Leicester, UK)
– Ingrid Hoffmann (Heidelberg)

Symposium S6: Cell Metabolism
Chair: Eckhard Lammert (Düsseldorf)

Invited Speakers:
– William Martin (Düsseldorf)
– Nils-Göran Larsson (Köln)
– Pierre Maechler (Geneva, Switzerland)

Symposium S7: Vesicular Transport
Chair: Karin Schumacher (Heidelberg)

Invited Speakers:
– Peter Robin Hiesinger (Dallas, USA)
– Juan Ramón Martínez Morales (Sevilla, Spain)
– Anne Spang (Basel, Switzerland)

Symposium S8: Evolution of Morphogenesis
Chairs: Steffen Lemke (Heidelberg) and Alexis Maizel (Heidelberg)

Invited Speakers:
– Patrick Lemaire (Montpellier, France)
– Nicholas Gompel (Marseille, France)
– Miltos Tsiantis (Oxford, UK)

17:00 – 18:00 **Distinguished Lecturer**
Maria Leptin (Heidelberg)

18:00 – 21:00 **Poster Session 1**

Friday, March 22

09:00 – 12:00 **Symposia 9 – 13**

Symposium S9: Primary Cilia & Signaling
Chair: Achim Gossler (Hannover)

Invited Speakers:
– Heiko Lickert (München)
– Heymut Omran (Münster)
– John Wallingford (Austin, USA)

Symposium S10: Biomechanics of Cells
Chair: Jochen Guck (Dresden)

Invited Speakers:
– Eric M. Darling (Providence, USA)
– Sirio Dupont (Padua, Italy)
– Franziska Lautenschläger (Paris, France)

Symposium S11: Cortical Development
Chair: Orly Reiner (Rehovot, Israel)

Invited Speakers:
– Michael Frotscher (Hamburg)
– Wieland B. Huttner (Dresden)
– Joseph LoTurco (Storrs, USA)

Symposium S12: Advanced Microscopic Methods
Chair: Paul Walther (Ulm)

Invited Speakers:
– Ernst H.K. Stelzer (Frankfurt)
– Shigeki Watanabe (Salt Lake City, USA)
– Sonja Welsch (Einhoven, The Netherlands)

Symposium S13: Lateral Gene Transfer & Evolution of Symbiosis
Chair: Thomas Bosch (Kiel)

Invited Speakers:
– Tal Dagan (Düsseldorf)
– Angela E. Douglas (Ithaca, USA)
– Giles Oldroyd (Norwich, UK)

12:00 – 15:00 **Poster Session 2**

15:00 -18:00 **Plenary Session PS2: The Nucleus and the Genome**
Chair: Peter Lichter (Heidelberg)

Invited Speakers:
– Andrew Belmont (Urbana, USA)
– Ana Pombo (London, UK)
– Karsten Rippe (Heidelberg)
– Bas van Steensel (Amsterdam, The Netherlands)

18:15 – 19:00 **Young Scientist Awards**

19:00 – 19:45 **Frontiers in Science Lecture**
Reinhard Jahn (Göttingen)

20:30 **Get Together at Heidelberg Castle**

Saturday, March 23

08:30 – 09:30 **Matthias Schleiden Lecture**
Thomas Cremer (Martinsried)

09:30 **The Open Symposium: Quantitative Biology – Where do we stand?**

Ueli Aebi (Basel, Switzerland)
Roland Eils (Heidelberg)
Josef Käs (Leipzig): Do cells care about physics?
Yitzhak Rabin (Ramat-Gan, Israel)
Kai Simons (Dresden)

09:30 – 12:30 **Plenary Session PS3: Stem Cells**
Chair: Andreas Trumpp (Heidelberg)

Invited Speakers:
- Oliver Brüstle (Bonn)
- Bruce Edgar (Heidelberg)
- Marieke Essers (Heidelberg)
- Timm Schröder (Neuherberg)

12:30 **Closing Ceremony**

Travel grants for young DGZ members

Young researchers and students with no or only half-time positions are eligible to apply for a DGZ travel grant for participation in the DGZ annual meeting. Prerequisites are active participation at the meeting with a poster or oral presentation and DGZ membership.
Grants will be giro transferred to the account given by the applicant.

Deutsche Bahn AG brings you fast, comfortably and conveniently to the 36th Annual Meeting of the German Society for Cell Biology. Enjoy pleasant and relaxed travelling with special service. Travel per rail at a special rate from a DB-station of your choice to Heidelberg and return. The fare for a round trip to Heidelberg is a fixed price from all stations within Germany: **EUR 99,00** (2nd class). The exclusive offer is valid on all DB trains including the ICE. Changes and reimbursement before 1st day of validity EUR 15, from 1st day of validity excluded.
The tickets are valid between March, 18th and 25th, 2013. You can book your ticket from October 1, 2012 on by calling the hotline + 49 1805 - 31 11 53 (Telephone costs are 14 ct/min from Deutsche Telekom's network) from Monday to Saturday. Please use the reference "DGZ"

Please refer to the following points in your application:

1. Personal data (name, title, address, date of birth)
2. Grade of education (subject of study, subject of theses, supervisors)
3. Title and co-authors of your presentation at the DGZ annual meeting
4. Information about your income
5. Your bank account data for reimbursement

Please send your application by e-mail to the DGZ Office (Attn. Mrs. Reichel-Klingmann): dgz@dkfz.de

Deadline for applications: **January 31, 2013**

Please do not send joint applications, only personal applications will be considered.

Applications received after the deadline cannot be considered anymore.

Cell and Developmental Biology merge Concepts

Harald Herrmann

As you may already have seen in this issue the announcement for the "Joint International Meeting" of the German Society for Cell Biology and the Society for Developmental Biology (GfE), I want to continue on this issue. If you have not seen it, please go to page 8 to have a look at the programme. Ten years back, we had a joint meeting of the two societies organized by Thomas Magin and Michael Hoch in Bonn, March 2003. The meeting was indeed busy and I had the impression that it was exceptionally good and actually wonder now, why we did not have it again earlier. When I became President of the DGZ in 2010, I immediately contacted Elisabeth Knust, then President of the GfE, in order to ask if she would want to have another joint meeting of the two societies. However, I had to learn that their Annual Meeting for 2011 was already planned as an international joint meeting with the Japanese Society of Developmental Biologists. As a result, Elisabeth Knust agreed to organize the Annual Meeting of the DGZ in Dresden in 2012. And furthermore, she encouraged me to contact the President-elect of the GfE, Jochen Wittbrodt, in order to organize the next meeting of the GfE in a more open, international mode together with the DGZ. This went extremely well: In spring this year, the boards and advisory boards of the DGZ and the GfE met in Heidelberg to construct the layout of such an international conference with the aim to generate a strong integrated programme providing the frontiers of our science, hence highlighting how close a cell and a developmental approach mostly is, be it in stem cell biology or in the generation of cellular and consequently organismal polarity, for instance.

In order to provide readers with the "new scope" to be expected at the meeting, we invited several members of the GfE to write about their views how organismal biology proceeds and these articles will be published in *Cell News*. Naturally, as we want to inform the members of the GfE about these activities, we decided to provide them with the next three issues of *Cell News*, to be published before the conference begins. In this issue, Sebastian Fraune and Thomas Bosch (Christian-Albrecht-University Kiel) and Damien Devos (Centre for Organismal Studies Heidelberg, COS) have written exciting articles as you will see. At the meeting, Thomas Bosch will be chairing the symposium "Lateral Gene Transfer & Evolution of Symbiosis".

In line with concepts how cells make tissues, organs and organisms, the conference: *"Molecular concepts in epithelial differentiation, pathogenesis and repair"* to be held in Leipzig (November 7 – 10), is an example how modern life sciences have generated a merger of cell and developmental biology, biochemistry and biophysics (see p. 5). Likewise, the third conference of "Physics of Cancer", will also take place in Leipzig (November 1 – 3). I want to draw your attention to this meeting, because biophysics is becoming more and more a part of cell and developmental biologists' concepts, and it is a great move that scientists from both communities see the necessity and advantage to join forces. No wonder, also the ASCB is heavily campaigning now to draw biophysics into cell biology. Moreover, as I am personally engaged as a co-organizer joining forces with Josef Käs (Leipzig), Claudia Mierke (Leipzig) and Sarah Köster (Göttingen), and since I attended both previous meetings, I can ensure you that the format of the meeting is ideal for both young and established scientists to attend and to discuss their work. Moreover, also those who consider to go more into the direction of biophysics, come and join: You will find time to talk to leaders in the field. As a "starter" for the meeting, Florian Rehfeldt (Universität Göttingen) has written an article on "Mechanics Matters for Life". In Leipzig, he will give a talk entitled "Modeling surface tension and viscoelasticity in cell aggregates and tissues". Please, have a look at the programme on p. 3. The list of speakers is "breathtaking".

Last but not least, this issue contains two meeting reports documenting DGZ activities of September this year. The Young Scientist Meeting "Cell Biology shapes the Embryo" truly exemplified how close cell biology and developmental biology have come (see article by Jörg Grosshans and Doris Wedlich on p. 32). Also the second meeting on "Actin Dynamics" had a rather wide scope, from the characterization of motor proteins to aberrant neuron behaviour (see article by Anika Steffen and Markos Schulte on p. 34). No question that the investigation of transgenic mice occupies a centre stage in the research on the various actin systems, and here of course we are in the middle of developmental processes of whole organisms.

Walther Flemming Medal 2013

The German Society for Cell Biology offers a research award named after Walther Flemming, one of the pioneers of cell biological research. In 1875 he provided us with a detailed description of processes during cell division, which he named mitosis.

The Walther Flemming Medal is awarded annually for outstanding scientific merits from all fields of cell biological research. Eligible are researchers up to an age of 38 years. The award consists of the medal itself and a prize money of **EUR 4000** and is partly sponsored by the *European Journal of Cell Biology*.

Applications have to consist of a cover letter, a CV and a list of publications. The subject of the application should relate to one distinct field of research. In addition, a short summary of the work and a compelling description of the importance of the work for cell biology should be presented.

Both individual applications and nominations are accepted. Applications will be reviewed by an independent commission of the DGZ. The award ceremony takes place at the next annual meeting – the "Joint International Meeting of the DGZ and the German Society for Developmental Biology (GfE) – which will be held on March 20-23, 2013 in Heidelberg.

Please send your application by e-mail
(and in parallel one hard copy by mail) to the DGZ office:

Deutsche Gesellschaft für Zellbiologie e.V. (DGZ)
Sekretariat, z.H. Frau Reichel-Klingmann
c/o Deutsches Krebsforschungszentrum
Im Neuenheimer Feld 280
D-69120 Heidelberg
E-mail: dgz@dkfz.de

Deadline for applications:
January 15, 2013

Werner Risau Prize 2013

Werner Risau throughout his scientific career always had a strong interest in promoting young scientist. He enjoyed teaching and it was easy to pick things up from him, as Werner Risau had the rare gift to boil things down to the essentials and explain complicated concepts or hypothesis with simple words.
Consequently, the Prize Committee decided that The Werner-Risau Prize of the German Society for Cell Biology (DGZ) will be awarded for outstanding studies in endothelial cell biology to young scientists within the first 5 years after obtaining their PhD or MD (except in cases of maternal leave). The Werner Risau Prize will be awarded for an article already published or in press, and consists of a personal diploma and a financial contribution of **EUR 4000**. No other restrictions apply!

Applicants are requested to send a cover letter together with their CV and one copy of the article (electronially plus one hardcopy) to the

Werner Risau-Preiskomitee
c/o Prof. Dr. rer. nat. Rupert Hallmann
Westfälische-Wilhelms-Universität Münster
Waldeyerstr. 15
D-48161 Münster, Germany
email: hallmanr@uni-muenster.de

Deadline for applications:
January 15, 2013

Binder Innovation Prize 2013

The Binder Innovation Prize is founded by BINDER GmbH in Tuttlingen and awarded by the German Society for Cell Biology (DGZ). It is endowed with **EUR 4000** and was awarded the first time in 1998. The award is given for outstanding cell biological research with a focus on cell culture or the use of cell cultures.

Candidates may apply for the prize themselves. DGZ membership is desired but not required.

Applications have to consist of a cover letter, CV and a research profile.

Applications will be reviewed by an independent commission of the DGZ. The award ceremony takes place at the DGZ annual meeting – the "Joint International Meeting of the German Society for Cell Biology (DGZ) and the German Society for Developmental Biology (GfE) – which will be held on March 20-23, 2013 in Heidelberg.

Please send your application by e-mail (and in parallel one hard copy by mail) to the DGZ office:

Deutsche Gesellschaft für Zellbiologie e.V. (DGZ)
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Im Neuenheimer Feld 280
D-69120 Heidelberg
E-mail: dgz@dkfz.de

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January 15, 2013

Host-symbiont interactions: why Cnidaria matter

Sebastian Fraune and Thomas C.G. Bosch

Abstract

Animals, ranging from basal metazoans to primates, are engaged in symbiotic relationships with complex microbial ecosystems. These resident microbes influence fitness and thus ecologically-important traits of their hosts, ultimately forming a metaorganism consisting of a multicellular host and a community of associated microorganisms. The evolutionary dynamics within such a metaorganism and the involved molecular interactions are rather complex and often difficult to investigate experimentally. Untangling the complex interactions requires simple animal models with only a few specific symbiotic partners. Here we show that organisms at the base of the evolutionary scale such as the Cnidaria may be key to dissecting the fundamental principles that underlie all host-microbe interactions.

Introduction

In 1877, Karl Möbius, Professor of Zoology at Kiel University, coined the term "biocenosis" for a community of living beings belonging to different species and associated by way of inter-species interdependence. In one of the first studies, later to become a classic, to be conducted in the emerging science of ecology, Möbius was seeking to determine why some oyster beds in the Atlantic were becoming exhausted, while the oyster beds in the British river estuaries and the Schleswig-Holstein oyster beds were very rich (Möbius, 1877). He related this phenomenon to the other species present, rather than to the oysters in the beds themselves. Möbius thus was the first to recognise that an ecological system must be taken as a whole and coined the term "biocenosis" for a living community. About a hundred years later it became obvious that not only ecological systems but also complex "environmental" diseases can only be understood if the relationships between the interacting infectious agents present at a given time in a given territory are recognized. By analogy with "biocenosis", the understanding of a disease as a complex dynamic phenomenon was conceptualized with the word "pathocenosis" (Grmek, 1969).

Today we realize that all epithelia in animals are colonized by microbial communities; and that, therefore, any multicellular organism must be considered a meta-organism comprised of the macroscopic host and synergistic interdependence with bacteria, archaea, fungi, and numerous other microbial and eukaryotic species. The «metaorganism» concept (Bosch & McFall-Ngai, 2011) considers the dynamic communities of bacteria on epithelial surfaces as an integral part of the functionality of the respective organism itself. Today there is also an increasing appreciation that microbes are an essential part of the animal phenotype influencing fitness and thus ecologically-important traits of their hosts (O'Hara & Shanahan, 2006, McFall-Ngai, 2007, Fraune & Bosch, 2010). Disease onset is seen as a complex set of interactions among a variety of associated partners that affect the fitness of the collective holobiont (Rosenstiel et al, 2009). Discovering that individuals are not solitary, homogenous entities but consist of complex communities of many species that likely evolved during a billion years of coexistence led to the hologenome theory of evolution (Rosenberg et al, 2007, Zilber-Rosenberg & Rosenberg, 2008, Rosenberg et al, 2009) which considers the holobiont with its hologenome as the unit of selection in evolution. Thus, modern symbiosis research has become an emerging cross-disciplinary field focused on understanding the general principles by which these complex host-microbe communities function and evolve. What is the complexity in species number and structural organization of these associations? What is the physiological role of temporal differences of associated microbiota during life cycles? Which selective forces drive the evolution of these interactions, i.e. how do the associated organisms influence each other's fitness? Which forces shape the colonizing microbial composition? Finally, what are the consequences of the associations on molecular pathways and the reactive genomes? Here we show that for addressing these questions and untangling the complex interactions that influence the host's health and development, members of the ancient animal phylum Cnidaria may serve as simple but highly informative models.

The cnidarian holobiont

Cnidarian are not only among the earliest known phyletic lineages known to contain stem cells **(Fig. 1 A)** but also possess most of the gene families found in bilaterians and have retained many ancestral genes that have been lost in *Drosophila* and *C. elegans* (Kortschak et al., 2003; Miller et al., 2005; Technau et al., 2005; Putnam et al., 2007; Hemmrich et al., 2012). Similar to other animals, Cnidaria are complex holobionts consisting of the animal and its associated endogenous microbiota. Inter-species interactions in several Cnidaria species **(Fig. 1 A-D)** between symbiotic algae and host cells have been the subject of research since decades since they not only provide insights into the basic "tool kit" necessary to esta-

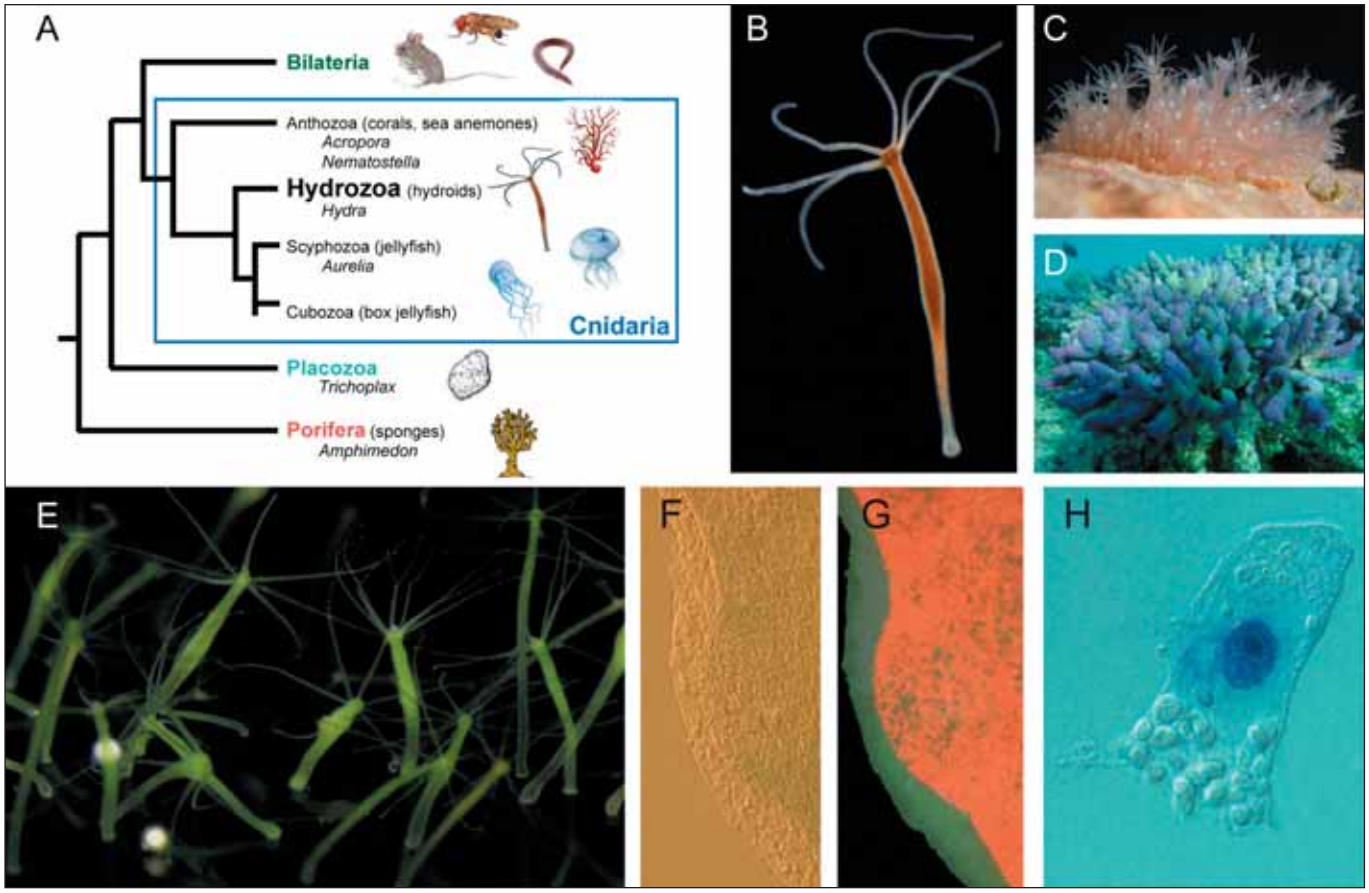

Figure 1: Cnidaria are a sister group of all Bilateria. A: Phylogeny of basal metazoan animals. B: *Hydra oligactis* (taken from Fraune &Bosch, 2007). C: *Hydractinia milleri* (printed with permission from Gary McDonald). D: Blue coral (taken from http://www.jcu.edu.au/cgc/CoralGenomicsHP.html). E: *Hydra viridis* with Chlorella symbionts. F: Phase-contrast micrograph of *Hydra viridis*. G: Flourescence microscopy of the same area shown in F. Chlorella algae appear red, Hydra tissue green. H: Phase contrast micrograph of a single mazerated endodermal epithelial cell containing symbiotic algae in the basal part below the nucleus (stained blue) (F-H taken from Habetha et al 2003).

blish symbiotic interactions, but are also of relevance in understanding the resulting evolutionary selection processes (e.g. (Muscatine & Lenhoff, 1963; Pool, 1979; Thorington & Margulis, 1981; O'Brien, 1982);for review see Bosch, 2012a). In the meantime it is becoming evident that in Cnidaria such as green *Hydra viridis* **(Fig. 1 E-H)** or many coral species, a long term persistence of mutualistic associations is prevalent not only in two-party interactions of polyp and symbiotic algae, but also in more complex systems comprising three or more associates including bacteria and viruses (Bosch, 2012a, 2012b). Thus, beside photosynthetic algae **(Figure 1G, H)**, bacteria are another important component of the cnidarian holobiont. In Hydra, the 36 identified bacterial phylotypes represent three different bacterial divisions and are dominated by Proteobacteria and Bacteroidetes (Fraune & Bosch, 2007, 2010). Disturbance or shifts in any of these partners can compromise the health of the whole animal (Fraune et al, 2009). Loss of symbiotic algae from coral tissues, for example, can lead to coral bleaching and death. Since healthy individuals of the same coral species from different location are colonized by similar bacterial communities (Rohwer et al, 2002) but diseased or bleached corals contain changed bacterial communities that differ greatly from healthy ones (Ritchie, 2006, Rosenberg et al, 2007), it seems that similar to complex "environmental" diseases in human, understanding diseases within corals requires an in-depth knowledge of the basic biology of each holobiont member.

The host actively shapes the colonizing microbiota

For decades a number of *Hydra* species have been cultivated under standard conditions at constant temperature and identical food. It came as a complete surprise, therefore, that examining the microbiota in different *Hydra* species kept in the laboratory for more than 20 years under controlled conditions revealed an epithelium colonized by a complex

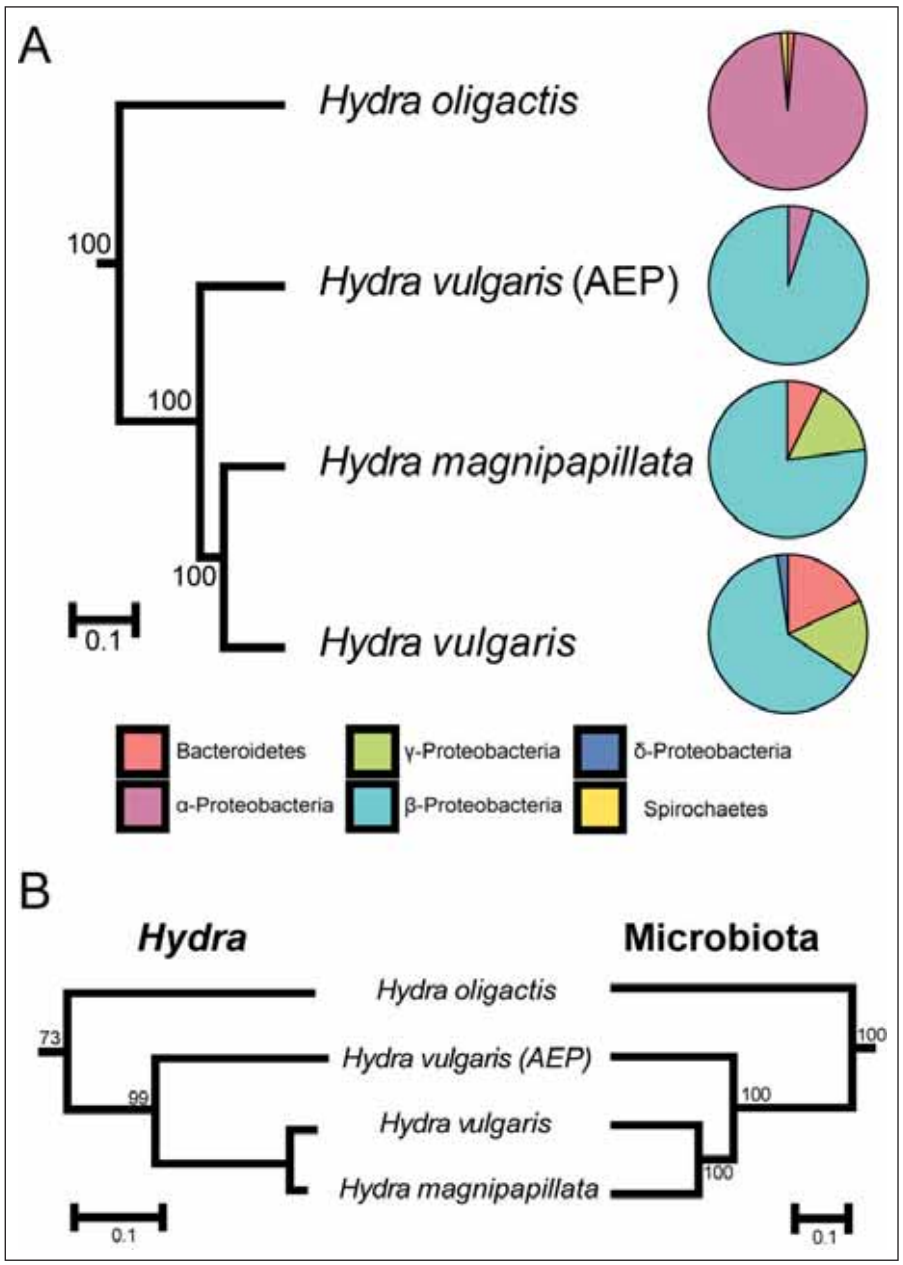

Figure 2: Hydra polyps are colonized by species specific microbiota. A: Bacterial communities identified from four different Hydra species. B: Comparison of the phylogenetic tree from Hydra and the environmental cluster tree of the corresponding microbiota.

community of microbes, and that individuals from different species differed greatly in their microbiota. Even more astonishing was the finding that individuals living in the wild were colonized by a group of microbes that is similar to that in polyps grown in the lab, pointing to the maintenance of specific microbial communities over long periods of time. Bacteria in *Hydra* are specific for any given species **(Fig.2 A)** (Fraune & Bosch, 2007, Fraune et al, 2010). Closely related Hydra species as *Hydra vulgaris* and *Hydra magnipapillata* are associated with a very similar microbial community. In contrast, *Hydra oligactis*, the most basal *Hydra* species analysed so far (Hemmrich et al, 2007), is associated with the most distinct microbial community compared to the other Hydra species. In line with this, comparing the phylogenetic tree of the Hydra species with the according cluster tree of associated bacterial communities reveals a high degree of congruency **(Fig.2B)**. This strongly indicates that distinct selective pressures are imposed on and within the *Hydra* epithelium. The forces that shape the colonizing microbial composition are the focus of much current investigation (Bevins & Salzman, 2011).

How does the host control the microbiota in the context of specific developmental or environmental conditions?

In the same way that microbial communities are expected to change in different parts of a body, they are also dynamic in time. For a first understanding of the temporal dynamics in *Hydra*-microbe interactions we investigated the establishment of the microbiota during oogenesis and embryogenesis. Early embryonic stages in *Hydra* **(Fig. 3 A)** are colonized by a limited number of microbes (Fraune et al, 2010). During embryogenesis the number of bacterial colonizers changes in number and composition. For example, *Curvibacter*-related Betaproteobacteria are present only in late developmental stages while they appear to be absent in the early embryo. Thus, early developmental stages have a microbiota that is clearly distinct from later developmental stages. Interestingly, the differential colonization is reflected in differences in antimicrobial activity. *Hydra* embryos are protected by a maternally produced antimicrobial peptide (AMP) of the periculin peptide family, which controls the establishment of the microbiota during embryogenesis. Beginning with the gastrula stage, *Hydra* embryos express a set of periculin peptides (periculin 2a and 2b), which replaces the maternal produced pe-

riculin peptides 1a and 1b. This shift in the expression within the periculin peptide family represents a shift from maternal to zygotic protection of the embryo (Fraune et al, 2011). In adult *Hydra* polyps, additional AMPs including Hydramacin (Bosch et al, 2009) and Arminin (Augustin et al, 2009) contribute to the host-derived control of bacterial colonization.

Antimicrobial Peptides - key factors for host-bacteria co-evolution

Antimicrobial peptides (AMPs) are known as prominent effector molecules which get often secreted after external stimuli **(Figure 3 B, C)**. Do they have, in addition to their killing activity against pathogens, key regulatory functions in host-microbe homeostasis as the driving force that leads to changes in microbiota composition? To investigate whether the ectotopic expression of an AMP may affect the number and composition of the colonizing microbiota at the ectodermal epithelial surface, we generated transgenic *Hydra* expressing periculin1a in ectoderm epithelial cells (Fraune et al, 2010) **(Figure 3 D-F)**. Comparing the bacterial load of these transgenic polyps with that of wild-type control polyps revealed not only a significantly lower bacterial load in transgenic polyps overexpressing Periculin1a but also, unexpectedly, drastic changes in the bacterial community structure. Analyzing the identity of the colonizing bacteria showed that the dominant β-Proteobacteria decreased in number, whereas α-Proteobacteria were more prevalent. Thus, overexpression of Periculin causes not only a decrease in the number of associated bacteria but also a changed bacterial composition. With the transgenic polyps overexpressing periculin we apparently have created a new holobiont that is different from all investigated *Hydra* species **(Fig. 3 F)**. From these results we assume that specific associations between hosts and bacteria are a result of bacterial adaptation to different repertoires on AMPs

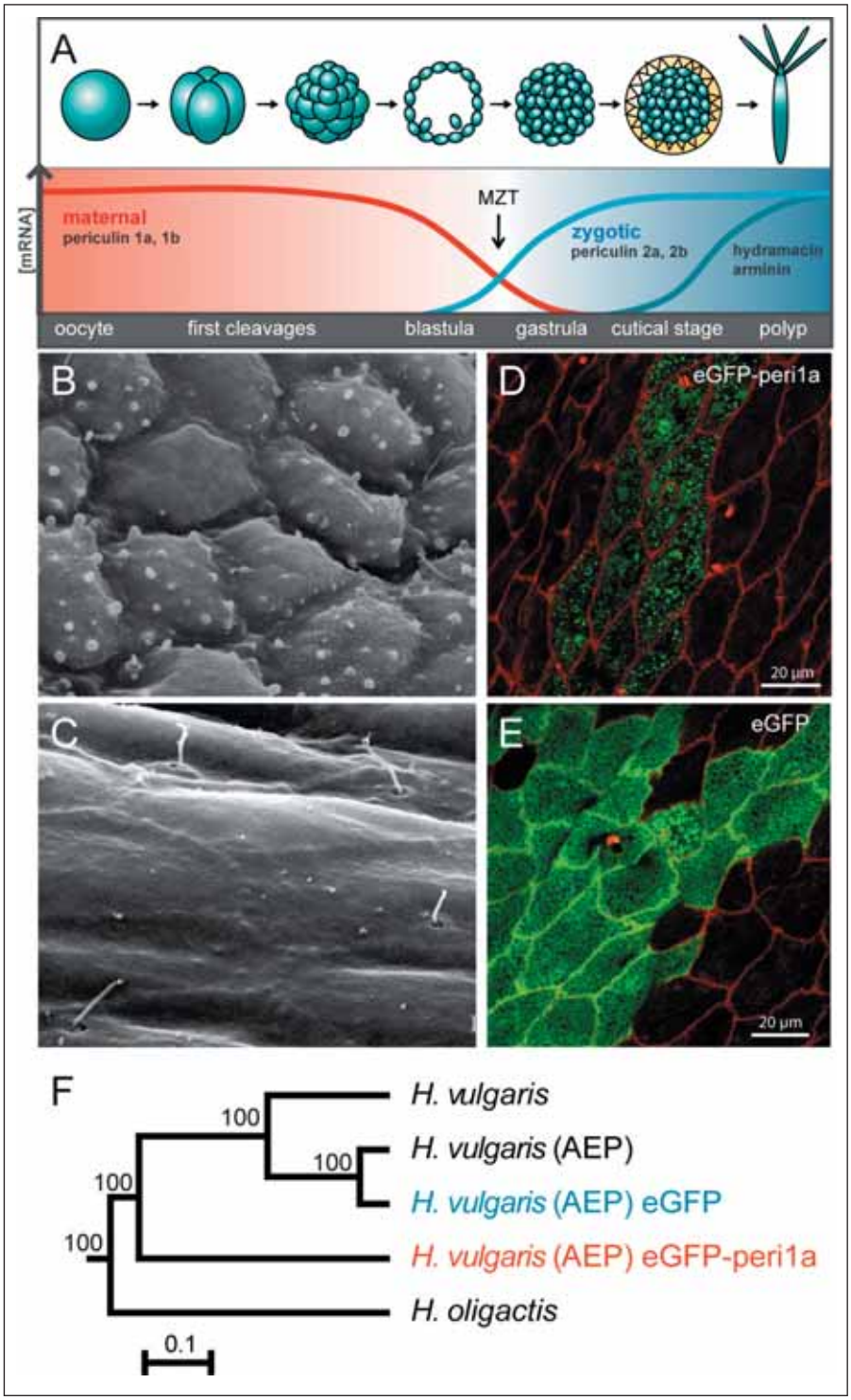

Figure 3: Antimicrobial peptides (AMPs) in Hydra. A: AMPs produced during ontogeny in the basal metazoan Hydra (modified from Fraune et al 2011). B: REM showing the ectodermal epithelium in polyps exposed to *Pseudomonas aeruginosa*. Note the increase of secretory vesicles at the surface of the epithelium. C: REM showing the ectodermal epithelium in control polyps (C and D modified from Bosch et al. 2009). D: Confocal micrographs of transgenic ectodermal cells of a transgenic *Hydra vulgaris* EGFP:periculin1a polyp (notice peptide localization in vesicles) and E: *Hydra vulgaris* EGFP control polyp (notice EGFP localization in the cytoplasm). F: Phylogenetic tree based on bacterial communities associated with Hydra. Periculin1a overexpression leads to changes in the composition of the associated microbiota compared to controls.

in different host species. Evolutionary changes in the AMP repertoire of host species, therefore, are expected to lead to changes in the composition of the associated bacterial community. Future efforts will be directed towards analyzing the performance of this new phenotype under different environmental conditions. Interestingly, patients with Crohn's disease often have strongly reduced α-defensin expression and drastically altered endogeneous microbiota (Wehkamp et al, 2005). Moreover, mice expressing human alpha-defensin-5 (DEFA5) and mice lacking an enzyme required for the processing of mouse alpha-defensins show significant changes in intestinal microbiota composition (Salzman et al, 2010). These findings support the view that epithelial-derived AMP may represent an important regulatory mechanism shaping the composition of epithelial microbiota.

What are the microbes for?

The intimacy of the interaction between host and microbiota, as well as the high evolutionary pressure to maintain a specific microbiota, points to the significance of the interkingdom association and implies that hosts deprived of their microbiota should be at a disadvantage. To investigate the effect of absence of microbiota in *Hydra* we have produced gnotobiotic *Hydra* polyps that are devoid of any bacteria. While morphologically no differences could be observed to control polyps, we are currently finding evidence that *Hydra* lacking bacteria suffer from fungal infections unknown in normally cultured polyps (Franzenburg, Fraune & Bosch, unpublished). Thus, do beneficial microbes associated with *Hydra* produce anti-fungal compounds? Future efforts are directed towards isolating the active substances from these bacteria that eventually may lead to the development of novel antimycotics.

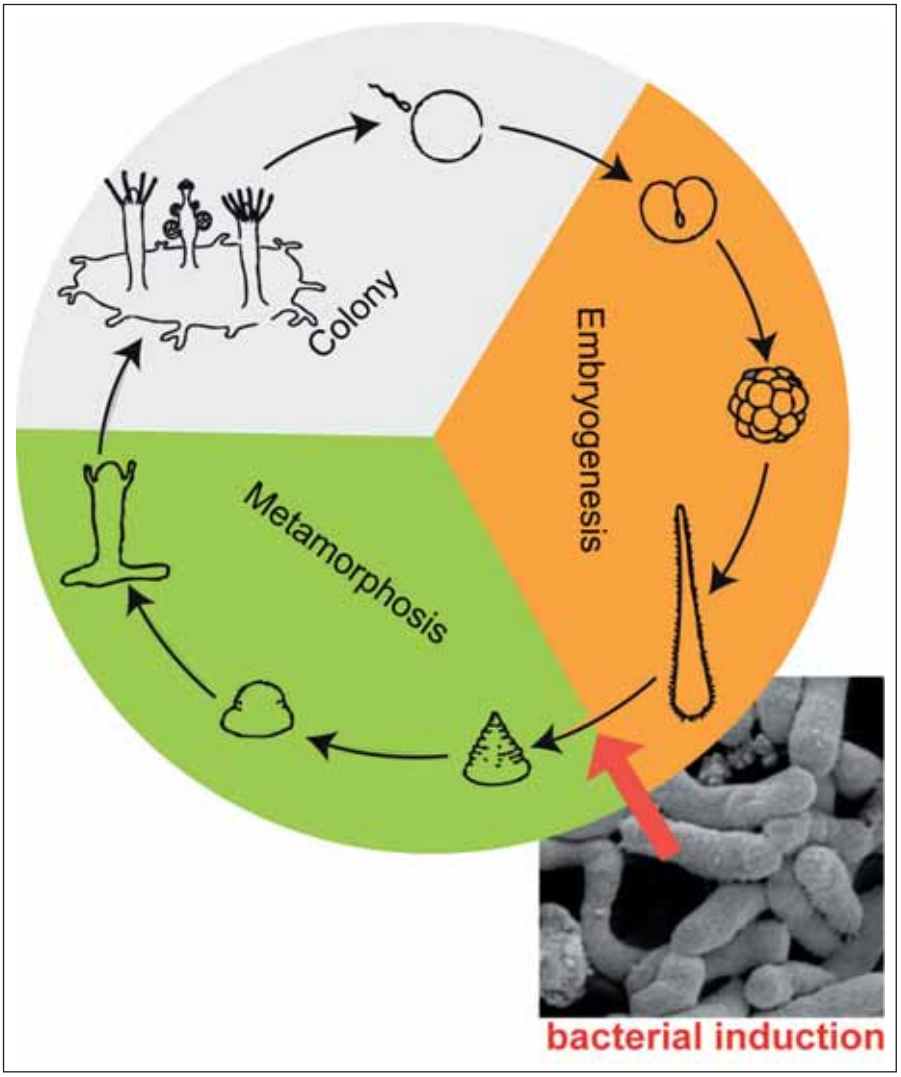

Figure 4: Life cycle of *Hydractinia echinata* (modified from Berking, 1991). Note that metamorphosis is depending on the presence of an external signal provided by the environmental bacteria *Alteromonas espejiana*.

Microbes also provide signals for multiple developmental steps. One of the most pervasive examples of microbial impact in animal development is in the induction of settlement and metamorphosis of many marine invertebrate larvae (Hadfield, 2011). This transition is an absolute requirement for completion of the animal's life cycle, and is dependend upon induction by exogenous morphogenetic cues, many of which are produced by bacteria associated with a particular environmental surface. *Hydractinia*, for example, **(Fig. 1 C)** a marine colonial Cnidaria frequently found in the North Sea, commonly covers shells inhabited by hermit crabs. Fertile colonies, male and female, produce eggs and sperm, respectively, and within less than three days the fertilized egg develops into a mature planula larva **(Fig. 4)**. "Mature" larva means a larva that is able to metamorphose into a polyp, but under sterile laboratory conditions it will never do. It will rather die as it is unable to take up food (Leitz & Wagner, 1993; Walther et al, 1996; Frank et al, 2001). To continue its development, it needs an external trigger that

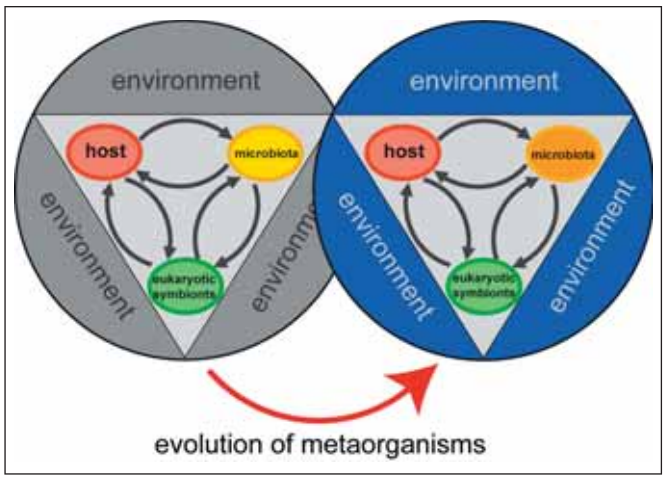

Figure 5: The metaorganism under changing environmental conditions

appears to be provided in the natural habitat by certain sedentary bacteria of the genus *Alteromonas* **(Figure 4)**. A lipophilic substance produced by these bacteria is thought to act as this trigger (Leitz & Wagner, 1993). The mechanisms by which *Hydractinia* sense bacteria-derived environmental cues to form colonies and to reproduce may provide crucial insights into the genetic and developmental foundations of life cycles, but little is known about their natural history or biochemistry. Observations in a number of other invertebrates and vertebrates strongly support the view that microbes should be considered partners in animal development. Bacterial contributions are indispensable, for example, in shaping the immune system and development of organs such as the vertebrate intestine or the squid light organ (reviewed in Fraune & Bosch, 2010). Animal development has traditionally been viewed as an autonomous process directed by the genome. It seems that we have to rethink development at least in part, as an orchestration of both animal-encoded ontogeny and inter-kingdom communication.

The holobiont in a constantly changing environment

The association between host and microbes is strongly effected by the environment. To determine the impact of different environmental conditions on the bacterial community in *Hydra*, we cultured polyps, which were taken from the wild, for two months under standard laboratory conditions. Thereafter, we analysed the associated bacteria in comparison to the bacteria from polyps taken directly from the wild. Culturing of polyps from the wild under laboratory conditions involves a change in culture temperature, culture medium and food source. These changes have significant effects on the composition of the bacterial community. For example, while one bacterial phylotype belonging to the α-Proteobacteria could be identified as the most dominant species in long term culture, in polyps from the wild and two month after the shift to the laboratory this bacterium was present only in relative low abundance (Fraune & Bosch, 2007). Other bacterial species completely disappeared from the tissue due to the change in culturing conditions. Thus, Hydra is not only associated with species specific bacteria but also responds to changes in the environment with changes in the bacterial community. In sum, the holobiont appears to be a dynamic system being characterized by functional redundancy and fast adaptations to altered environmental conditions.

Based on the holobiont concept, Rosenberg and colleagues in 2007 proposed that corals are able to adapt rapidly to changing environmental conditions by altering their associated microbiota **(Figure 5)** (Rosenberg et al., 2007). Depending on the variety of different niches provided by the host, which can change with developmental stage, diet or other environmental factors, a more or less diverse microbial community can be established within a given host species. Since this, for example, may provide corals with resistance against certain pathogens enabling them to adapt much faster to novel environmental conditions than by mutation and selection, host-microbe interactions may be considered as significant drivers of animal evolution and diversification. This hypothesis is supported by at least three observations: (i) corals are associated with diverse microbiota (Rohwer et al, 2002, Bourne et al, 2008); (ii) the associated microbiota change in response to environmental stress (Ritchie & Smith, 1995, Pantos et al, 2003) or seasons (Koren & Rosenberg, 2006); and (iii) corals are able to develop resistance against pathogens although they lack adaptive immune response (Reshef et al, 2006).

Concluding remarks

The beneficial microbiota is a complex and multifunction ecosystem that is essential to the development, protection, and overall health of its host. Thus, the microbiota appears to function as an extra organ, to which the host has outsourced numerous crucial metabolic, nutritional, and protective functions. Studies from Cnidaria to primates indicate that the host's role far outweighs other environmental factors in molding the composition of the microbiota. Antimicrobial peptides appear to be key factors for host-bacteria co-evolution and the driving force that leads to changes in microbiota composition. Finally, and maybe most important, the dynamic relationship between symbiotic microorganisms and environmental conditions results in the selection of the most advantageous holobiont. In corals, changing

their microbial partners may allow them to adapt to changing environmental conditions much more rapidly than via mutation and selection (Fig. 5).

Taken together, studying host-microbe interactions in basal metazoans is a challenging and exciting field of symbiosis research. Cnidaria not only offer valuable models for exploring the basis of interkingdom-communication and the role of bacterial signaling in animal development. Findings derived from the in vivo context of the Cnidaria models may also provide one of the simplest possible systems to address questions of how a stable host-microbe community is established and remains in balance over time. The uncovered basic molecular machinery can be transliterated to more complex organisms, providing conceptual insights into the complexity of host-microbe interactions. Symbiosis research in Cnidaria, therefore, is an emerging field in which scientists from many disciplines can make fundamental discoveries and rapidly advance scientific understanding of a strictly microbe-dependent life style and its evolutionary consequences while combining laboratory and field studies.

Acknowledgments

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(i) Are there identifiable core microbiota associated with a given host species?
(ii) How is the microbiota selected, and how did they evolve within and between hosts?
(iii) Which influences have associated microbes on the development of host organisms?

Microbiology's platypus

Damien P Devos

Introduction

The eukaryotic cell differs from bacteria and archaeal cells by many features and the question as to the origin of those features and, by transition, of the eukaryotic cell itself, is one of the most fundamental and fascinating in Biology (Box 1). For many years, eukaryotic origin has been investigated by the top-down approach that consists in starting from all the features or genes found in eukaryotes and tracking back the common ones in order to infer those that are likely to have been present in the first eukaryotic cells. This approach has revealed many such putative eukaryotic ancestral features (Koonin *Cell* 2010). However, much remains to be done and the identity of the first eukaryotic cell still remains to be deciphered. The opposite approach starts from bacterial features that are, or appear, to be related to the eukaryotic ones in order to study their emergence and characteristics in the eukaryotic cell. Because it is slowly filling the gap between pro- and eukaryotes, this bottom-up approach is beginning to show promises. In our laboratory, we study the bacteria *Gemmata obscuriglobus* from the poorly described bacterial superphylum Planctomycetes-Verrucomicrobia-Chlamydiae (PVC). This bacteria is fascinating in itself for its many characteristics that are normally not found in bacteria (Table). This includes the production of sterol, a process ususally defined as typically eukaryotic, or the presence of ester linked lipids usually found only in archaea. In addition to their intrinsic interest, those features and those bacteria might give us clues to the origin of the eukaryotes as their ancestors might have been related (Reynaud & Devos *Proceedings. Biological Sciences / The Royal Society* 2011). Thus, we study those bacteria in order to understand eukaryogenesis. We use a combination of computational, molecular biology, and electron-microscopy to first, decipher the peculiar biology of the Planctomycetes and second, to understand their contribution to eukaryotic origin. Computationally, we use structure to push the limits of sequence homology detection. Amongst other tools, we use protein architecture correlation to detect potential relationship between distantly related proteins (Santarella-Mellwig *et al. PLoS Biol.* 2010).

Feature	Specific to	Found in
Complex membrane organization	Eu	Pl, Ve
Condensed DNA	Eu	Pl
Division by budding	Eu	Pl
Membrane coats	Eu	Pl
Sterol	Eu	Pl, Ch
Peptidoglycan loss	Eu, Ar	Pl, Ch
Proteic cell wall	Eu	Pl
Ester & Ether lipids	Ar	Pl
FtsZ loss	Eu, Ar	Pl, Ch
Tubulin	Eu	Ve
C1 transfer	Ar	Pl
Endocytosis	Eu	Pl

Table: *Superphylum features*. The PVC superphylum of bacteria display features found in eukaryotes (Eu) and archaea (Ar). Planctomycetes (Pl), Verrucomicrobia (Ve), Chlamydiae (Ch).

Box 1: Eukaryotic and archaeal origin.

The origin of the eukaryotes is one of the most important and longuest standing mystery in Biology. Eukaryotes possess numerous specific features that can be traced back to the last eukaryotic common ancestor, but the timing and mechanisms of their appearance are unclear. Understanding the origin of the ancestral lineage leading to this ancestor is a key issue, because it profoundly affects our understanding of fundamental aspects of eukaryote cell biology. It is increasingly accepted that eukaryotes and archaea have shared a common ancestor. However, the precise nature of the archaeal-eukaryotic relationship remains uncertain since phylogenomic and other types of evolutionary reconstructions that aimed at elucidating the nature of this ancestry have yielded conflicting results (Gribaldo *et al. Nat Rev Micro* 2010). It is thus not clear if eukaryotes have evolved from an already formed archaeon or if this common ancestor was an intermediary organism from which both diverged.

The Planctomycetes-Verrucomicrobia-Chlamydiae superphylum

The PVC superphylum is an assemblage of bacterial phyla which is consistently recovered as a monophyletic group with different data and phylogeny estimation methods (Wagner & Horn *Curr Opin Biotechnol* 2006; Pol *et al. Nature* 2007; Hou *et al. Biol. Direct* 2008; Pilhofer *et al. J Bacteriol* 2008; Kamneva, Liberles, & Ward *Genome Biol Evol* 2010). It includes the Planctomycetes (Fuerst & Sagulenko *Nat. Rev. Microbiol* 2011),

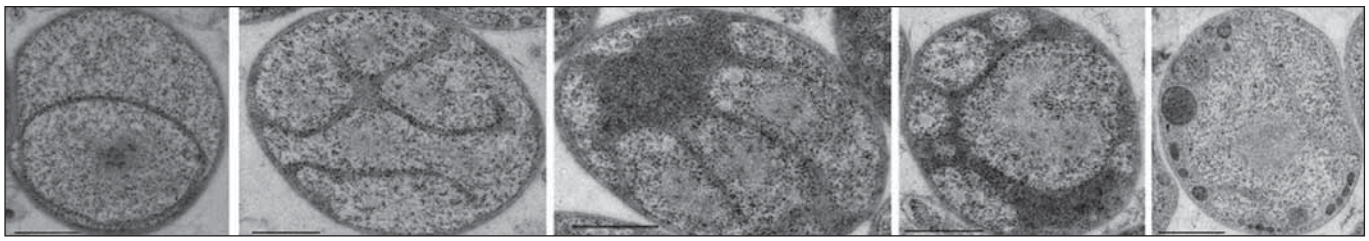

Figure 1: The *G. obscuriglobus* membrane morphology is variable. Electron micrographs of whole sectioned *G. obscuriglobus* cells representative of the morphologies observed. The inner membrane invaginates extensively towards the interior of the cell to form a network of sheets within the cytoplasm. Scale bar: 500 nm. Adapted from (Santarella-Mellwig et al. PLoS Biol. 2010).

the Verrucomicrobia, the Chlamydiae, the Poribacteria, the Lentisphaerae, and the OP3 candidate phyla which contain no cultured relatives, along with several other groups. PVC members exhibit distinctive cellular properties, widespread environmental distribution, unique physiologies, and unusual associations with eukaryotic hosts. These microorganisms are a largely unexplored group that represents an excellent example of the value of studying bacteria other than 'classical' models such as *Escherichia coli*. The recent discovery of some planctomycetes and verrucomicrobia within the human microbiome raises intriguing questions about their contributions to health and disease (Ley *et al*. Science 2008; Andersson *et al*. *PLoS ONE* 2008).

A range of characters that were previously either considered absent or rare amongst the bacteria, but which are common or ubiquitous in archaea or eukaryotes, were recently identified within some PVC members (Table). These include, for example, the presence of complex internal membrane organization and condensed DNA (Devos & Reynaud *Science* 2010; Reynaud & Devos *Proceedings. Biological Sciences / The Royal Society* 2011). PVC members are not the only bacteria to display archaeal- or eukaryotic-like features. However, compared with other bacterial features and disregarding those that are due to horizontal gene transfer, the PVC trait is often the one that is most 'similar' to the corresponding eukaryotic or archaeal ones. For example, the endomembrane vesicles found in Rhodobacter are mostly protein dominated (vs mainly membranous) (Murat, Byrne, & Komeili *Cold Spring Harbor Perspectives in Biology* 2010). In addition, the PVC superphylum is the only one combining so many of these features in related species. As such, their analysis might reveal some clues concerning eukaryotic origin.

The planctomycete Gemmata obscuriglobus

We study a poorly characterized bacterial gender of the Planctomycetes phylum, *Gemmata obscuriglobus*. Planctomycetes are major players in the global nitrogen and carbon cycles and are uniquely capable of anaerobic ammonium oxidation (a globally important nitrogen transformation). Within that phylum, the bacteria of the gender *Gemmata* are particularly interesting due to their complex intracellular membranous organization that is sustained by proteins showing similarity to the eukaryotic equivalent ones and their capability to internalize fully folded proteins in a process reminiscent of eukaryotic endocytosis (Fuerst & Sagulenko *Nat. Rev. Microbiol* 2011).

Cell plan complex but not different

Bacterial cell organization has proven to be surprisingly complex but PCV members are nevertheless exceptional in displaying diverse and extensive intracellular membranes organization (although they are not the only ones, e.g. magnetotactic or photosynthetic bacteria (Komeili *et al*. *Science* 2006; Pinevich *Endocytobiosis and Cell Research* 1997)). We and other have shown that membrane organization in *G. obscuriglobus* is complex, variable and dynamic (Fig. 1) (Santarella-Mellwig *et al*. *PLoS Biol*. 2010; Lee, Webb, & Fuerst *BMC Cell Biol* 2009), a feature shared with the Verrucomicrobia (Lee *et al*. *BMC Microbiology* 2009). In particular, the inner membrane (IM) of *G. obscuriglobus* sends invaginations inside the cytoplasm and vesicles-like structures are observed in the periplasm of some cells.

However, how the membranes are organized in three-dimensions (3D) is not known for any of the PVC bacteria. We have thus investigated the 3D organization of the membrane in multiple *G. obscuriglobus* cells and reconstructed the full volume of a few cells where we followed the entire internal membranes organization (Fig 2). A full three dimensional reconstruction reveals that the *G. obscuriglobus* cells have a cell plan that is not radically different from that of a typical Gram-negative bacterium. The organization is topologically compatible with an extension of the periplasmic space by invagination of the bacterial inner membrane (IM) towards the cell's interior. The space inside the invaginations is continuous with the periplasm, the space between the IM and the outer membrane (OM) is devoid of ribosomes, as in other bacteria. The main difference is that the *Gemmata* IM invaginates extensively towards the interior of the cell to form a network of sheets within the cytoplasm (Fig. 1 & 2). This is supported by the fact that ri-

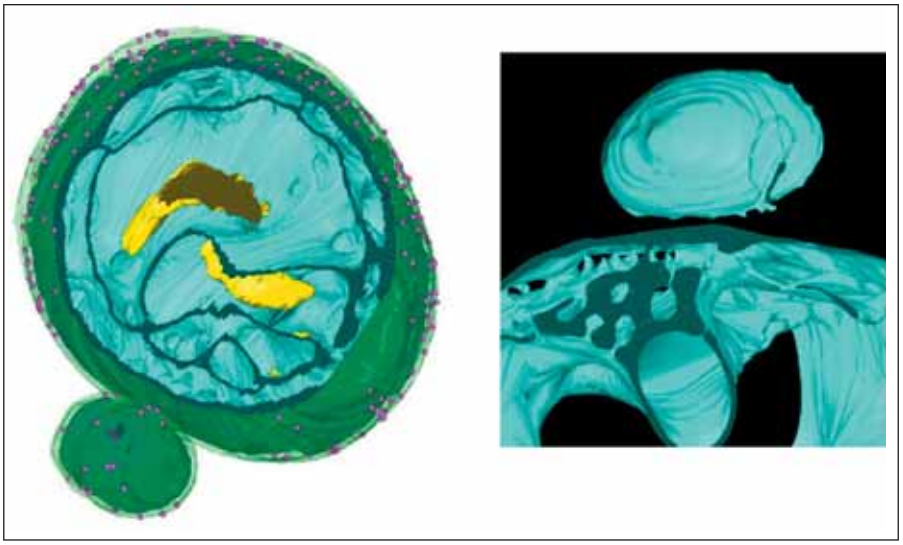

Figure 2: Three-dimensional reconstruction of bacteria with a complex endomembrane system. Left: The OM is in green, the IM in cyan, the DNA in yellow and OM invaginations are in pink. View through the full volume is represented, notice that the cell is budding. Right: Membrane organization around the bud neck. 3D model of the membrane organization in the proximity of the budding neck. Only the internal membranes are represented in the false color image. Adapted from (Santarella-Mellwig *et al.*, Submitted).

bosomes align on the IM and its invaginations in the *G. obscuriglobus* cell as they do along the IM of better-studied bacteria such as *Escherichia coli*, and by genomic analysis that indicates the presence of an asymmetric bilayer outer membrane in Planctomycetes and Verrucomicrobia (Speth, Teeseling, & Jetten *Front. Microbio.* 2012). Our three-dimensional reconstructions reveal that the bacterial cells are not 'compartmentalized' nor 'nucleated' and show that this species does not represent a challenge to our bacterial cell definition, but just an extension of it (Santarella-Mellwig *et al. Submitted*).

Bacterial membrane coat proteins

We have previously proposed the protocoatomer hypothesis (Box 2) that states that membrane coat (MC) proteins have been critical to eukaryotic endomembrane system origin (Devos *et al. PLoS Biol.* 2004). Using sequence information only, proteins having the MC architecture are found exclusively in eukaryotic proteins. However, structure is more conserved than sequence during evolution because structure has to be maintained to conserve function while amino-acids can change relatively more easily. We thus turned to structure to search for proteins related to the eukaryotic MCs. We performed a structure-based screen on all available genomes, searching for proteins containing a β-propeller or a stacked pairs of alpha-helices (SPAH) domain. Because the sequence and structural divergences are so pronounced even between eukaryotic MCs, and since we aimed at maximizing the sensitivity of detection, we used one of the most sensitive tools with a permissive cut-off and were very lax in our detection of fold type and considered β-propeller and SPAH domains at a very broad level. We identified all known and various unknown eukaryotic MCs. We were unable to identify any such protein in archaea and in bacteria, with the exception of members of the PVC superphylum and Bacteroidetes where we identified up to 15 such sequences in some genomes (Santarella-Mellwig *et al. PLoS Biol.* 2010). There is no doubt that the identified bacterial proteins have the MC architecture given our evaluations at the sequence and structural levels. However, as with the eukaryotic MCs, variability is observed within the predicted structural features of the bacterial MCs both within and in between species. The bacterial MCs are structurally as similar to the eu-

Box 2: The protocoatomer hypothesis.

A key role in the protein complexes which shape membranes in the eukaryotic cell is played by membrane coat (MC) proteins. MCs includes coated vesicles components, such as the clathrin heavy chain, COPI α and β' subunits, and COPII Sec31, but also components of the nuclear pore comlex, such as Nup85 and Nup133. A common origin to all MCs was originally inferred from the detection of shared structural features in some of them suggesting a related origin for all these protein complexes and thus for all compartments in which they are involved in the eukaryotic cell (Devos *et al. PLoS Biol.* 2004). The protocoatomer hypothesis thus states that "a simple coating module containing minimal copies of the two conserved folds (the β-propeller and the SPAH domain) evolved in protoeukaryotes as a mechanism to bend membranes into sharply curved sheets and invaginated tubules" (Devos *et al. PLoS Biol.* 2004). The major evolutionary innovation that this mechanism represented, which allowed among other possibilities, the elaboration of internal subcompartments, endocytosis, phagocytosis and endosymbiosis, ensured the success of those organisms possessing it. Duplication and divergences then allowed for specialization, with the partitioning of different functions into separate, interconnected compartments, each with their own specialized set of coating modules. Thus, the protocoatomer hypothesis predicts that the acquisition of MC proteins was a turning point in the origin of the eukaryotes.

karyotic ones as the eukaryotic MCs are to one another (Devos *BioEssays* 2012)., i.e. the differences between bacterial and eukaryotic MCs are not bigger than in between the eukaryotic MCs. Unlike them however, most of the bacterial MCs show significant sequence similarity to each other, suggesting a reduced evolutionary pressure to diverge after duplication or recent duplication events. Given the uneven distribution of MC proteins in members of the PVC superphylum, it is likely that their common ancestor already possessed a few copies of those proteins, which have been retained and duplicated in some lineages, while lost in some others during divergence of the species (Santarella-Mellwig *et al*. *PLoS Biol*. 2010). The presence of such proteins in Bacteroidetes might not be so surprising given the recent call to unify them with the PVC superphylum (Yutin *et al*. *PLoS ONE* 2012).

Because of its peculiar internal membrane organization, we focused on the planctomycete *Gemmata obscuriglobus*. We thus raised antibodies against one of the *G. obscuriglobus* MCs, namely GobsU_11075 to reveal its localization in the bacterial cell by cryo-electron-microscopy (Fig. 3). We found that the majority of the GobsU_11075 protein is located in the periplasm of the *G. obscuriglobus* cells. In addition, a significant proportion, between one third and one half of the proteins was found in close proximity to a bent membrane (Santarella-Mellwig *et al*. *PLoS Biol*. 2010). Thus, members of the Planctomycetes have proteins that have structural features similar to the one of the eukaryotic proteins involved in eukaryotic endomembrane system and that are most likely involved in the maintenance or organization their endomembrane system.

In addition, we have shown that *G. obscuriglobus* cells are able to internalize proteins from the external milieu and collect them into their periplasm, where they are associated with vesicles. As in eukaryote endocytosis, this process is energy-dependent, appears to be receptor-mediated and the internalized proteins are subjected to intracellular proteolytic degradation. The MC protein GobsU_11075 was also found in tight association with the membranes of the internalization vesicle (Lonhienne *et al*. *Proc. Natl. Acad. Sci. U.S.A.* 2010). Thus in addition to the similarity of architecture, the bacterial MCs (or at least GobsU_11075) appear to have a function similar to the eukaryotic ones. Taken together, those results suggest that PVC members might have lain on the path of eukaryotic endomembrane system origin (Santarella-Mellwig *et al*. *PLoS Biol*. 2010).

Evolutionary relationship: Microbiology's platypus

In conclusion, PVC members display features that are usually not found in bacteria but more commonly associated to eukaryotes or archaea. The presence of the those characteristics in a diffuse pattern throughout members of the PVC superphylum suggests that their ancestor, the Last PVC Common Ancestor (LPCA) had most of these features and some were subsequently lost during divergence of the phyla. Additional sampling of the PVC superphylum will undoubtedly refine our perception of the LPCA and its characteristics.

Evaluating the evolutionary relationship of these particular bacterial features is a difficult task owing to 1) our lack of knowledge of the molecular mechanism for most of the features and 2) the dominant lack of sequence similarity between PVC proteins and their non-bacterial counterparts. The paucity of sequence information raises the possibility that any similarities observed may be the result of misinterpretation or, at best, convergence. On the other hand, the lack of sequence similarity does not necessarily imply a lack of homology, as demonstrated by the bacterial and eukaryotic cytoskeleton proteins, MreB/Actin and FtsZ/Tubulin (Gitai *Curr Opin Cell Biol* 2007). In fact, despite the lack of sequence similarity, some PVC traits seem to be intermediate between bacterial and non-bacterial ones (Devos & Reynaud *Science* 2010). In addition, aspects of several features can be interpreted as signs of homology followed by divergence of the coding sequences. For example, tertiary structure and

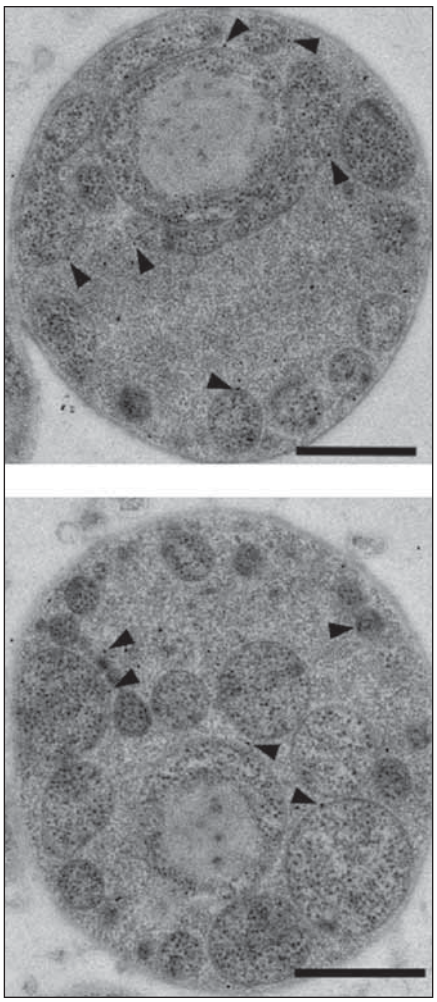

Figure 3: Bacterial MCs localization in Gemmata obscuriglobus. Electron micrographs of GobsU_11075-immuno-labelled *G. obscuriglobus* cells. Gold particles associated to membranes are indicated by arrowheads. The paryphoplasm can be distinguished from the cytoplasm by the lack of ribosomes and the presence of 15 nm gold particle-labelled antibodies. Scale bars: 500 nm. Adapted from (Santarella-Mellwig *et al*. *PLoS Biol*. 2010).

function similarities link the bacterial and eukaryotic MC proteins (Santarella-Mellwig *et al*. *PLoS Biol*. 2010; Lonhienne *et al*. *Proc. Natl. Acad. Sci. U.S.A.* 2010), as predicted by the protocoatomer hypothesis (Devos *et al*. *PLoS Biol*. 2004). Lateral gene transfer has been ruled out as the likely origin of some of those features (Budd and Devos, *Submitted*).

Reviewing the various eukaryotic or archaeal characteristics found in the PVC members (Table), we have suggested a new hypothesis for the origin of the archaea and eukaryotes where the Last Archaeal and Eukaryotic Common Ancestor (LAECA) was a sister group of the LPCA. Their common ancestor would have served as a 'cauldron' for the evolution of eukaryotic and archaeal features. Similar to the platypus that exhibits a combination of characteristics that are a legacy of the common ancestor shared between birds, reptiles and mammals, the archaeal and eukaryotic features found in PVC members might reflect a common ancestor between the LPCA and the LAECA. Thus the bacterial PVC superphylum might be microbiology's equivalent of the platypus. In this LPCA-based scenario, the features found in the LPCA are ancestral to the eukaryotic and archaeal ones, and also to the current PVC ones. The features found in current PVC members are then derived from the LPCA ones and are not ancestral to the eukaryotic or archaeal features. The current PCV features share a sisterhood relationship with the current eukaryotic or archaeal ones, having diverged from the same ancestor. But one is not ancestral to the other, e.g. PVC features are not ancestral to the eukaryotic ones. Think about the platypus, its milk-feeding apparatus is not the ancestor of our breast-feeding one, but both are derived from a common ancestor, although the platypus one might have conserved ancestral features.

Conclusions

The PVC superphylum exemplifies the power of the bottom-up approach for deciphering the origin of the eukaryotes. PVC members present particular features that are likely to have been present in their common ancestor and are usually associated with eukaryotes, archaea or both. This led us to suggest an evolutionary scenario entitled 'the cauldron hypothesis' where the PVC ancestor was related to the archaeal and eukaryotic ancestor. Although division into three domains of life remains the norm (Woese, Kandler, & Wheelis *Proc. Natl. Acad. Sci. U.S.A* 1990), the PVC superphylum may reflect continuity between the three domains, blurring their distinction.

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Mechanics Matters for Life

Florian Rehfeldt

Introduction

In two years (2014) we will celebrate the 100th anniversary of Ross Granville Harrison's seminal paper "The Reaction of Embryonic Cells to Solid Structures" that for the first time demonstrated successful *in vitro* tissue culture (1). In this century we saw great progress and success of *in vitro* cell culture and arrived at a stage where we have a plethora of different cell culture systems ranging from simple two dimensional polystyrene plastic dishes to sophisticated three dimensional structures allowing to fine tune the environment for the needs of different cell types. The impact of parameters like temperature, ionic concentration, pH, CO2 and O2 concentration, as well as biochemical drugs has been studied extensively in the last decades and is understood in great detail. Considering the human body, we do find a wide variety of specialized tissue and organs that are characterized extensively by their morphology and biochemical composition, however, these micro-environments also differ in their mechanical properties, i.e. their Young's elastic modulus *E* that characterizes how much force is needed for a certain deformation (e.g. compression) and has units of [Pa].

Physiological Range of Elasticity

In the same way that we talk about a physiological salt concentration or pH value, there is also a range of physiologically relevant elastic Young's moduli of living tissue (see Fig. 1) that starts from a zero Young's modulus of blood (which has no elasticity but is a viscous fluid) over neurons that are very soft cells (E_C ~ 0.1 -1 kPa), further to an intermediate stiffness exhibited by relaxed muscle fibers (E_C ~ 10 kPa), then osteoids, collagen densifications that make up the pre-mineralized part of bones (E_C ~ 30-50 kPa) (2).

Mechano-Sensitivity of Cells

Cells can sense the mechanical properties of their environment, the same way we would measure material properties in the lab, by applying a force and seeing how much the surrounding is deformed. The cellular muscles applying these contractile forces are acto-myosin stress fibers composed of actin filaments and non-muscle myosin II (NMM II) mini filaments (see Fig. 1). While it is obvious that muscle cells are able to produce contractile forces, Harris et al. showed already in 1981 that other cell types (fibroblasts, liver parenchyma cells, pigmented retina cells) also produce contractile forces when they are adhering on an elastic silicon rubber substrate (4).Today we know that even neuronal cells can exert forces on their surroundings and that force generation and transduction happen in virtually all cell types.

After the paper by Harris et al. it took another decade until Pelham and Wang clearly showed significant differences in cell and focal adhesion morphology between soft and stiff substrates (5). This was the beginning of a systematic study of mechanical cell-matrix interactions using elastic hydrogels (6).

One of the most striking reports on mechano-sensitivity was published in 2006 by Engler et al. showing that human mesenchymal stem cells (hMSCs) grown in identical media conditions on elastic polyacrylamide (PA) substrates differentiated within a week towards different lineages directed by the Young's modulus of the substrate (7).

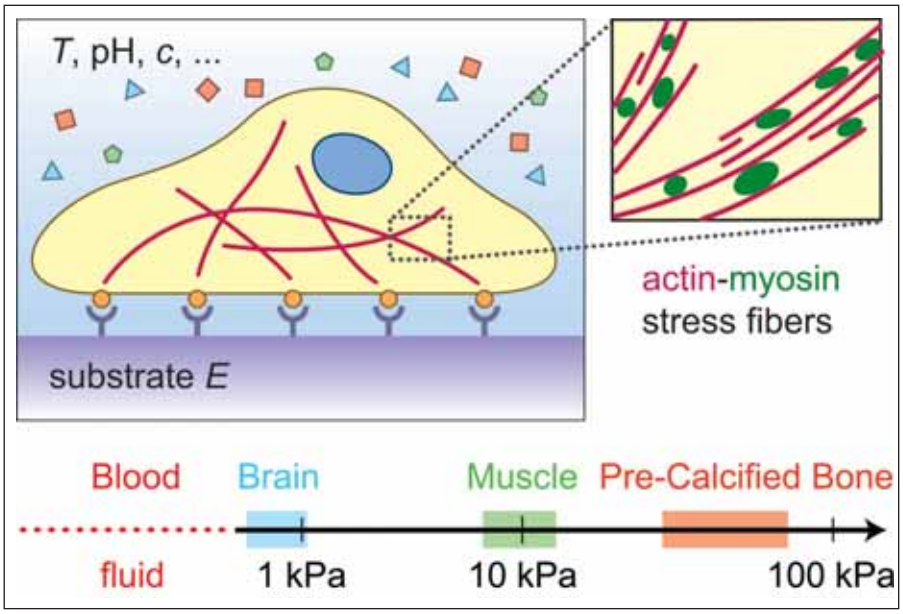

Figure 1: Sketch of a cell adhering on a two-dimensional substrate via focal adhesions. Acto-myosin stress fibers span the cell and produce contractile forces. Physiological range of elasticity in the human body (2, 3).

Cytoskeletal Organization as a Morphological Marker

How mechanical cues are integrated into bio-chemical signaling pathways that ultimately regulate transcription in the nucleus is still one of the big open questions in mechano-biology. Recent advances studying DNA organization and chromosome territories together with reports on mechanical deformation of the nucleus foster speculations of a direct mechanical pathway from the extra-cellular environment to the nucleus and therefore differentiation (8). As the complex process of mechano-guided lineage specification takes several days up to weeks, the question arises if there are early markers that can help to elucidate the mechanism.

We plated hMSCs on PA substrates of varying stiffness and fluorescently stained F-actin and non-muscle myosin IIa to analyze the structure and organization of the stress fibers after the first 24 hours. Cells growing on soft 1kPa substrates were small, showed only little elongation (aspect ratio r = 1.7), and did not show any anisotropic structure of acto-myosin filaments (see Fig. 3). Figure 3 b,d shows that cells on the 11 kPa substrate, which has a rigidity comparable to that of relaxed muscle tissue (see Fig. 1), exhibit an elongated, spindle-like morphology (r = 3.3) and parallel stress fibers well aligned with the long axis of the cell. On the stiffest substrates (34 kPa, Fig. 3c,f), cells are more isotropic in their overall shape and their stress fiber organization (9, 10).

This demonstrates that while transcriptional up-regulation of lineage specific proteins takes several days, the cytoskeletal organization as quantified by the order parameter S already shows significant differences ($p<0.05$) after 24 hours of culture and is therefore an ideal early morphological marker of hMSC differentiation through matrix mechanics (9).

From 2D to 3D – Hyaluronic Acid Hydrogels

The vast majority of cell experiments is performed on 2D substrates as this ideally suits the need of standard microscopy and also ease-of-use in handling the cultures. In our body however, cells face a three dimensional environment and although many of them are quasi two dimensional as they are stratified (e.g. skin, blood vessel walls, etc.) the geometry differs from the standard culture dish as the cells are conformally embedded and mechanically connected throughout their whole membrane.

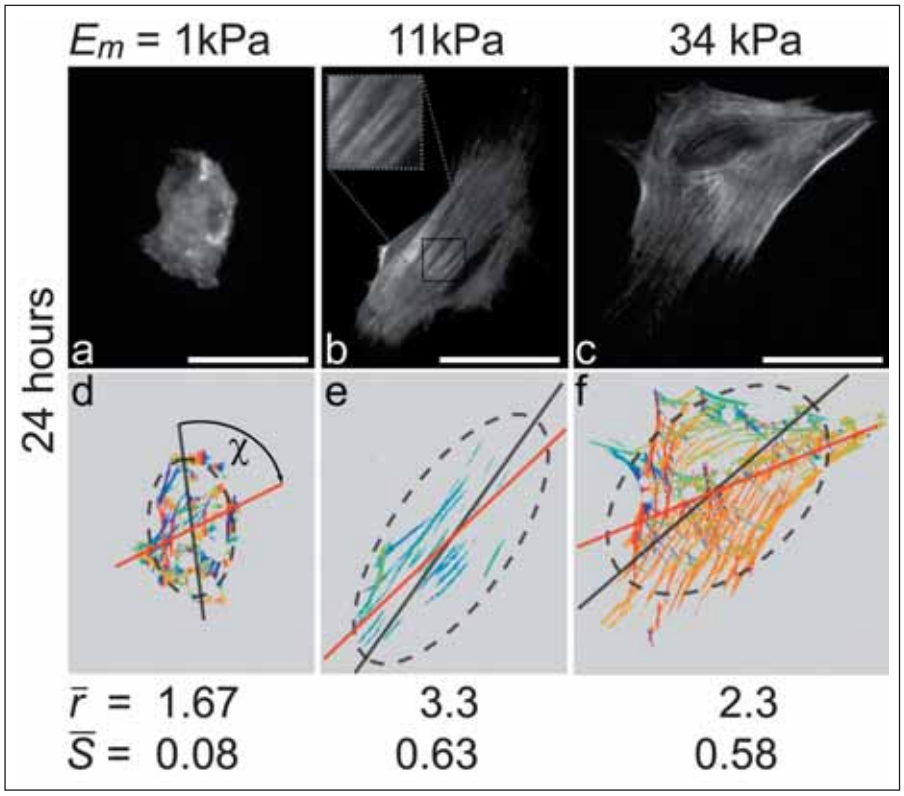

Figure 2: Acto-myosin stress-fibers in hMSCs on 2D substrates of different elasticities. (a,b,c) hMSCs immunostained for non-muscle myosin IIa 24 h after plating on elastic substrates with Young's moduli E_m of 1 (a), 11 (b) and 34 kPa (c). (d,e,f) Respective orientational plots, where the orientation of filaments is depicted with different colors. Scale bars represent 50 µm. (9)

Since PA gels and PDMS, the standard mechanically tunable substrates, do not allow for such a three dimensional environment, we came up with a biocompatible hydrogel system based on hyaluronic acid (HA), a linear polysaccharide abundant in our bodies. We chemically modified HA with thiol functionalities to facilitate cross-linking with PEG-diacrylate. By varying the HA concentration and cross-linker density we can finely tune the Young's elastic modulus E_m of the hydrogel within the physiological relevant range from 0.1 kPa to 150 kPa (3). With the biocompatible and non-cytotoxic HA hydrogel it is now possible to encapsulate cells in a 3D environment and it allows us to create stratified 3D environments that have distinct bio-chemical compositions and mechanical properties in the lower and upper hydrogel half spaces. This is especially interesting for mimicking the *in vivo* niche of certain micro-environments where cells face two different types of extracellular matrix on their basal and apical side, e.g. muscle satellite cells that reside between the muscle fiber and the basal lamina, and are difficult to culture *in vitro* (11).

Implications for Medicine

Understanding the complex mechano-sensing processes of cells to elucidate fundamental cell-matrix interactions is not only of great academic interest, but also has major implications for medical applications. There are currently many approaches to use hMSCs for therapeutic purposes, e.g. injecting mesenchymal stem cells to repair the muscle in an infarcted heart. Mechanical measurements by atomic force microscopy reveal that fibrotic tissue is stiffer than healthy myocardium (12). The results of Engler et al. (7) suggest that the introduced hMSCs are more likely to differentiate towards the osteogenic lineage due to the mechanical stimulus of the degenerated tissue than towards the myogenic lineage as desired. Indeed, this experiment was performed in rats, leading to calcifications in the infarcted hearts after stem cell injection which is counterproductive therapeutically (13). There is also a rapidly growing community investigating how mechanics and physics in general impacts cancer cells. This starts with experiments testing the efficacy of molecularly specific drugs, e.g. addition of an apoptosis inducing antibody against CD47 (B6H12) has little effect on the viability of human lung cancer derived epithelial cells (A549) on soft gels (E_m = 4 kPa), but is effective against cells spread on rigid glass substrates (14), opening the door for potential matrix-mechanics modulated therapies. But also the mechanical characterization of cancer cells and tumor environment seems very promising. Paszek et al. showed that tissue from breast tumors is stiffer than the healthy counterpart and could conclude that this correlates among other factors with a higher Rho-dependent cytoskeletal tension (15). Mechanical characterization of isolated cancer cells with an optical stretcher revealed that the optical deformability of cancer cells is significantly higher than that of healthy cells (16).

All these novel approaches to study mechanical cell-matrix interactions and biomechanics of cells will eventually lead to a better understanding of complex diseases and their potential therapeutic cure.

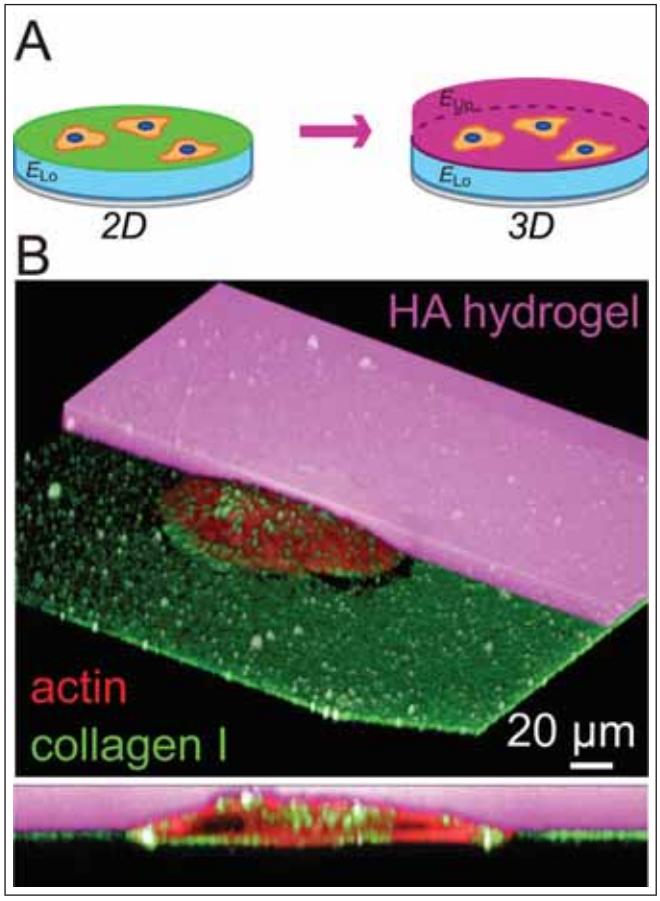

Figure 3: A) Cells are first plated on a hydrogel of elasticity E_{Lo}, then overlaid with a gel of Young's modulus E_{Up}. B) 3D reconstruction of a stack of confocal microscopy images of an hMSC (actin stained in red) on a collagen-I coated (green) hydrogel overlaid with a second hyaluronic acid hydrogel (purple) (3)

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Florian Rehfeldt, born in 1975 in Munich, Germany, studied Physics at the Technische Universität München (TUM) and received his PhD in Physics in 2005 for his work on "Novel Ultrathin Polymer Films as Biomimetic Interfaces" under the supervision of Motomu Tanaka and Erich Sackmann at the Institute for Biophysics E22. In 2006, he was awarded a Feodor-Lynen-fellowship of the Alexander-von-Humboldt foundation and moved to the University of Pennsylvania in Philadelphia to work with Dennis E. Discher on cell mechanics and the design of biomimetic *in vitro* culture systems with well-defined elasticity. Since 2008 he is at the Georg-August University in Göttingen, leading the Cell & Matrix Mechanics group within the Third Institute of Physics – Biophysics directed by Christoph F. Schmidt.

Report of the 13th Young Scientist Meeting "Cell Biology shapes the Embryo"

September 20-22, 2012, Jena

Jörg Großhans and Doris Wedlich

From September 20th to 22nd 45 doctoral students, postdocs and young group leaders met with 17 invited speakers at the 13th Young Scientist meeting in Jena. The organisers, Doris Wedlich (Karlsruhe) and Jörg Großhans (Göttingen) put together a programme about tissue formation and morphogenesis from a cellular as well as developmental point of view. The specific topics of the programme ranged from cellular aspects such as actin organisation, cell and tissue polarity, endocytosis, cell contacts, stem cells and proliferation, cell migration to tissue behaviour including collective movement, epithelia and epithilial organisation and cell ordering. All these topics were linked by their physiological function in morphogenesis and tissue formation.

The meeting was opened by two presentations about formation and organisation of tubular structures. Eyal Schejter (Rehovot, Israel) focused on the function of the actin nucleator Dia in polarisation and directed secretion in trachea of Drosophila and acinar cells in the pancreas of mice. He presented new data addressing the role of lipid composition in the plasma membrane and of the N-terminal region of Dia for cortical localisation of Dia. Whereas trachea are composed of many cells, the tubular organ of C. elegans - the excretory cell - is formed by a single cell. Michel Labouesse (Illkirch, France) presented his studies concerning the morphogenesis of this tubular cell, focusing on how an apical side is generated and on the genetic control of the process, finding similarities to genetic control of lymphatic vessel determination.

Cell migration in various animal model systems was the topic of several talks. Ray Keller (Charlottesville, VA, USA), one of the pioneers in addressing the role of forces in tissue movement and analysis of gastrulation movements, gave a lecture summarising classical experiments and insights about Xenopus gastrulation. This was very informative especially for the part of the audience with a more molecular education. Giorgio Scita (Milano, Italy) presented his latest studies on the role of Rab5 and the endosome in switching between mesenchymal and amoeboid types of tumor cell migration. Erez Raz (Münster) surprised by presenting new data about dead end, an RNA binding protein which together with miRNA-430 controls the transformation of zebrafish primordial germ cells into polarized cells at the onset of their migration. Despite the complexity of dead end's function, he identified downstream targets that can complement specific aspects of dead end's function.

Pernille Rorth (Singapore) focused on collective cell migration. Following a thorough introduction she discussed her studies of border cell migration in Drosophila oogenesis, where a group of cells migrates from the pole of the egg chamber to a destination site at the prospective oocycte. Although the group of cells contains specialised cells, such as the tip cells, this specialisation is reversible for a given cell and can be adopted by other cells during the course of migration. By detailed studies of the RTK signal transduction within the migrating cells, she found that signalling polarity within an individual cell is not important. What matters is the difference in signalling within the group. Insightful were also the data from experiments with a photoactivatable Rac. Activation of a single cell triggered this cell to become a leader cell that moves the group into the given direction. Jeremy Nance (New York, USA) reported about the internalization of primordial germ cells (PGC) during gastrulation in C. elegans. The movement of the surrounding endoderm drives PGCs inwards. This process depends on E-cadherin, which is present on PGCs but not on the endodermal cells pointing to a heterophilic adhesive interaction.

Mark Peifer (Chapel Hill, NC, USA) studies the origin of epithelial polarity and compartmentalisation in Drosophila embryos. In this system de novo formation of an epithelium can be studied, since the first part of embryonic development proceeds as a syncytium. Starting from the established relationship of Baz/Par3, aPK-C and Cadherin complex in an epithelium, he focused on an early step in development, cellularisation, analysing genetic determinants of apical Baz accumulation. The main finding was that Canoe/Afadin and its regulators Rob1 and the GEF Dizzy act upstream. Interestingly, loss of Canoe, Rop or Baz results in variable apical area sizes, which is quite invariant in normal embryos. These observations suggest additional functions of these proteins in ensuring an invariant apical area within an epithelium or a link of apical-lateral polarity and cell shape.

The evolution of cell-cell adhesion and epithelial polarity was outlined in the talk of James Nelson (Stanford, CA, USA). Based on studies of α-catenin that binds actin and β-catenin in the non-metazoan Dictyostelium that lacks cadherin homologs he concluded that the role of catenins in cell polarity predates the evolution of classical cadherins. Furthermore, comparing the stoichiometry of α-catenin complex formation with β-catenin and/or actin and in the metazoans C. elegans, zebrafish and mice he discussed the evolutionary change of the α-catenin molecule. With increasing complexity of morphogenetic processed additional α-catenin binding proteins bridging the cadherin/catenin adhesion complex to the actin cytoskeleton might have been evolved for better adaptation to the requirements in fine-tuning cell adhesion. The amounts of β-catenin required in different morphogenetic processes vary as shown by Rolf Kemler (Freiburg). Low levels of β-catenin are sufficient to sustain cell adhesion but fail in Wnt-signaling. He also reported a novel function of β-catenin in regulating the expression of the telomerase subunit Tert, which underlines a common crucial role of β-catenin in stemness and tumorigenesis.

The important role of cilia in defining left-right asymmetry and organ function (kidney, lung, liver) was introduced by Heiko Lickert (Neuherberg). His group identified pitchfork (PIFO), an important embryonic node gene in mouse. PIFO protein localizes at the basal body of cilia. Loss of PIFO results in cilia duplication leading to left-right asymmetry defects and heart failure.

During the last part of the meeting several speakers discussed the role of forces in epithelial formation, remodelling and repair. Yohans Bellaiche (Paris, France) showed how a combination of computational image analysis, genetics and theoretical modelling provides insight into the mechanisms of tissue behaviour. He developed an imaging system allowing the recording of the remodelling of the notum, part of the thorax in the Drosophila pupae over many hours. Image segmentation and computational analysis then provides then the trajectories, cell shapes and proliferation behaviour of several thousand cells in high temporal and spatial resolution. Furthermore, by inclusion of myosin labels during imaging, he analysed how planar polarity controlls force distribution and finally arrangement of the cells in the tissue. By a similar approach Buzz Baum (London, UK) first asked how bristles are regularly spaced within the notum. He found that the lateral inhibition mechanism not only depends on free diffusion of signalling molecules, but that the prospective bristle cells form basal protrusions that allow to establish direct contact with cells at a distance. In the second part of the presentation he focused on the question how the tissue reacts in case of overpopulation or, in other words, crowding conditions. By his experiments he could show that delamination and extrusion of cells from the tissue is the mechanism to adjust cell number to the available space and that the following apoptosis of the excess cells is only consequence.
The third talk using the Drosophila pupae was by Antonio Jacinto (Lisboa, Portugal), who studies tissue repair. Damage in Drosophila pupae can be locally induced by a strong laser beam. With the great experimental tractability of the pupal notum for imaging, it is possible to record the behaviour of the damaged tissue, especially the cells in the neighbourhood in high temporal and spatial resolution. Following the damage, a concentrical wave of myosin emerges flowing from a distance of multiple cell diameters towards the site of damage. By RNAi approaches he identified Dia and Rock as upstream regulators of the myosin wave. The initial trigger however involve Ca^{2+} influx, in that a TRPC stress activated ion channel might be opened in the cells around the site of damage.

Finally two talks from Benedicte Sanson (Cambridge, UK) and Jörg Großhans (Göttingen) dealt with cell rearrangement in the Drosophila embryo. Benedicte Sanson focused on directed cell rearrangement during gastrulation and establishment of straight compartment boundaries confining cells to their compartment, Jörg Großhans presented his studies of nuclear ordering in the syncytial embryo.

Young investigators and PhD students were given ample time to discuss their research projects with the invited experts in poster presentations. Twelve short talks from the registered participants spread between the presentations of the invited speakers were of high standard and triggered discussions with an involved audience that often had to be restricted due to time limitations but were continued during the breaks, poster sessions and the social programme. The meeting was enriched by a talk of Richard Ankerhold from Zeiss, who presented new instruments and developments, especially microscopy with light sheets (SPIM) and its advantages for imaging of tissues with a large axial extension and electron microsopy. As the intensive discussion after this presentation showed, these new instruments will be well received by the scientific community.

In summary, both aims of the "Young Investigator Meeting" were fulfilled: firstly to assemble cell and developmental biologists interested at the interface of their disciplines. This meeting with its intensive interactions and discussions may thus have served as a prelude for the joint meeting of the DGZ and GfE in March 2013 in Heidelberg. Secondly, to provide a framework for inspiring interactions of students with distinguished scientists discussing upcoming questions in the broad audience, in small groups at posters and not to forget over a glass of beer in the scenic guesthouse "Schwarzer Bär" and the hotel bar.

Actin 2.0

International Meeting on Actin Dynamics, Regensburg 2012

Anika Steffen and Markos Schulte

The beautiful town of Regensburg was chosen as the location for the second biennial actin dynamics meeting. In the middle of the historic scenery in the "Regensburger Kolpinghaus" round about 180 scientists from all over the world met to discuss about the current progress in actin research. This meeting was framed by keynote lectures of two intellectual fathers of actin research, Alan Hall and Thomas D. Pollard. Alan Hall, discoverer of Rho GTPase signaling to the actin cytoskeleton in the early Nineties (Nobes and Hall, 1995; Nobes et al., 1995; Ridley and Hall, 1992; Ridley et al., 1992), provided insights into Rho family downstream targets regulating epithelial junction formation. Surprisingly, he exclusively found kinases downstream of Rho and Cdc42, as for instance PRK2, a Rho-regulated kinase (Wallace et al., 2011) affecting cell junction formation. Upstream regulators, such as the RhoGAP myosin IXA, he presented to be involved in a distinct step during junction formation, which is the formation of actin "fingers" preceding contact initiation (Omelchenko and Hall, 2012). Thomas D. Pollard gave an impressive talk that substantially extended our textbook view on cytokinesis. He pointed out the importance to quantitatively assess concentrations of proteins, such that in vitro and in vivo studies on protein function can be precisely correlated (Vavylonis et al., 2008; Wu and Pollard, 2005). Lastly, he referred to the recent finding that the Arp2/3 complex harbours two binding sites for WASP-WCA, as uncovered by his and Michael Rosen's lab (Padrick et al., 2011; Ti et al., 2011). These multiple interactions are likely successive and potentiate Arp2/3 activation by WASP-WCA. This discovery tells us that actin branch formation is not a simple linear pathway, and encourages us all to revisit mechanistic details.

Figure 1: Poster session: Modelling session speaker Alex Mogilner finding his way to the next interesting poster.

In eight different sessions - nucleators, modelling, motor proteins, adhesion and contractile systems, trafficking, structure, cryoelectron microscopy, actin filament and Arp2/3 complex modulators- more than 40 established and young actin researchers gave a fascinating impression about their current work, and provided a current view on "what's hot" in the field. We also saw enthusiastic discussions at about 100 posters in the evenings, and although the organizers emphasized having liked to award all of the poster presenters due to their exceptional quality, Sonja Kühn (Dortmund, Germany) and Catherine Moreau (Heidelberg, Germany) were finally rewarded with a prize. From the short talk presenters, Christophe Le Clainche (Gif-sur-Yvette, France) was selected as prizewinner. He gave an exciting talk about a set-up he has developed to test for acto-myosin contractility and mechanosensitivity in vitro.

The nucleator session was set off by Shuh Narumiya, who gave a comprehensive view on mDia function. He found that mDia1/mDia3 double knockout mice are defective in coordinating leg movement, and he could narrow down aberrant neuron behaviour to a molecular defect in EphA-mediated neuron retraction. Actin nucleators are also mimicked by bacteria, exploiting the cytoskeleton of the host e.g. for intracellular propulsion. The temporal coordination of actin nucleation and elongation by bacterial and host

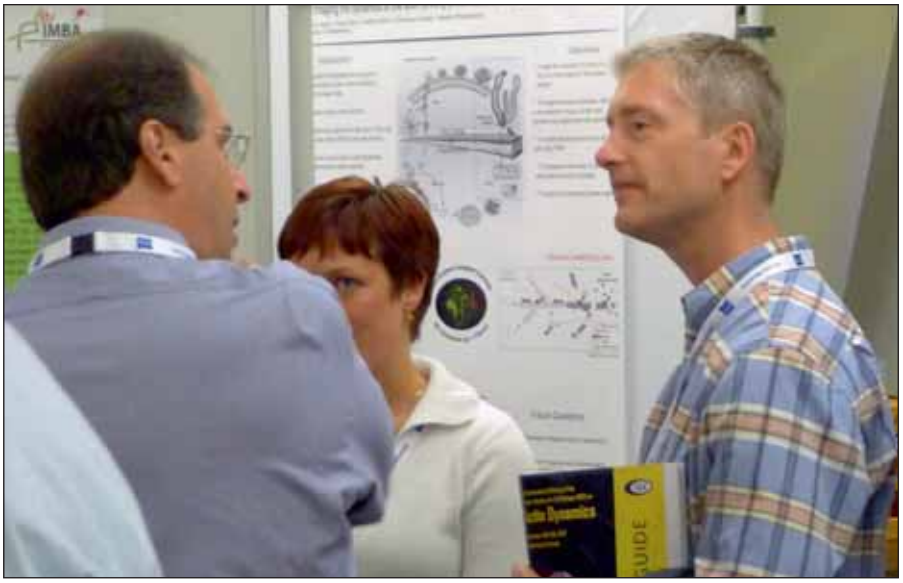

Figure 2: Poster session dicussions: Michael Rosen and Matt Welch (right).

proteins was presented in a stimulating talk by Matt Welch. While the Rickettsia species surface protein RickA activates the Arp2/3 complex early in infection, the more recently discovered Sca2 generates long and unbranched actin filaments at later infection stages (Haglund et al., 2010; Jeng et al., 2004), spotlighting how different nucleators can differentially contribute to complex physiological processes. New in vitro techniques as presented by Guillaume Romet-Lemonne and Christophe Le Clainche now allow testing for tension forces excerted by formins in a microfluidic chamber and recruitment hierarchies of contractile arrays on micropatterned glass surfaces, respectively.

Impressive work dealing with the harmonization of in vitro and in vivo data was shown by James Ervasti, who deepened our understanding of the function of different actin isoforms not only in in individual cells, but also in diseases such as deafness (Bunnell et al., 2011; Perrin et al., 2010). Again, addressing the relationship between protein function and physiological outcome, Elisabeth Ehler put forward the requirement of FHOD3 phosphorylation for its targeting to sarcomeres and maintaining myofibril integrity (Iskratsch et al., 2010). In her entertaining talk, she reminded the audience that if we run out of ideas on what to do with a given protein, all we have to do is a Y2H-screen - worked well for her!

Novel genetic tools allow manipulating the host genome in a way to express proteins of interest at more physiological levels and circumvent the problem of overexpression, as pointed out by many lecturers. Interestingly, Nick Brown could tackle this issue by combining molecular genetics and quantitative imaging. He gave an impressive talk on strategies employed in flies to analyse recruitment hierarchies and stoichiometries of various adhesion proteins engaged in integrin contacts (Delon and Brown, 2009). David Drubin compared the effects of overexpression of fluorescently-tagged proteins with genome-edited mammalian cells. In this approach, fluorescently-tagged proteins are expressed at endogenous levels, dramatically changing the outcome of results. In case of clathrin, endocytosis was observed to occur at much higher rates than deduced from overexpression studies, simply because excess ectopic protein inhibits proper functioning of the endocytic machinery (Doyon et al., 2011).

Besides genetic tools that were shown to aid future work in the field, novel imaging innovations, such as TIRF-SIM (Total Internal Reflection Fluorescence-Structured Illumination Microscopy) were also introduced. Using this method, Alexander Rohrbach showed

Figure 3: Keynote speaker Alan Hall informing himself about the work of future poster-prize winner Sonja Kühn.

fascinating new details on the dynamics of MreB filaments in bacteria.

Exciting structural insights into the functions of actin nucleation factors or cellular complexes such as adhesions were presented by Bob Robinson (Popp and Robinson, 2011), Niels Volkmann (Xu et al., 2012), Ohad Medalia (Bokstad et al., 2012) and Keiichi Namba (Fujii et al., 2010). Mathematical models on processes as complex as migration as presented e.g. by Alex Mogilner (Ofer et al., 2011) and David Odde (Chan and Odde, 2008) or on actin structures such as comet tails discussed by Richard Dickinson (Dickinson and Purich, 2006) are advanced enough now to be directly challenged by experiment. That canonical views present in all of our heads on how cell signalling works must be reconsidered was demonstrated in an impressive way by the thrilling presentation by Michael Rosen on supramolecular polymers formed simply by high concentrations of multivalent proteins (Li et al., 2012).

Lastly, actin filament and Arp2/3 complex modulators were revisited. John Hammer III. gave first insights on how CP activity on barbed ends is tuned by CARMIL action and how the latter might counteract the capping protein sequestering activity of V1 (Fujiwara et al., 2010). A novel player on the scene was introduced by Alexis Gautreau. He presented a novel acidic motif-containing protein termed Arpin that was concluded to act inhibitory on Arp2/3 complex function both in vitro and in vivo.

This year's actin dynamics meeting in Regensburg raised the bar. The lovely venue, perfect organization by Eugen Kerkhoff, Klemens Rottner and Theresia Stradal, supported by numerous helping hands and the professional venue team made this meeting a success. We all enjoyed the chance to discuss science during or after the meals offered directly at the venue, and last not least, the relaxing party. Keep the spirit! We are looking forward to Actin Dynamics 2014!

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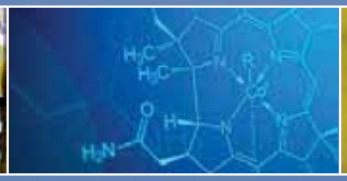


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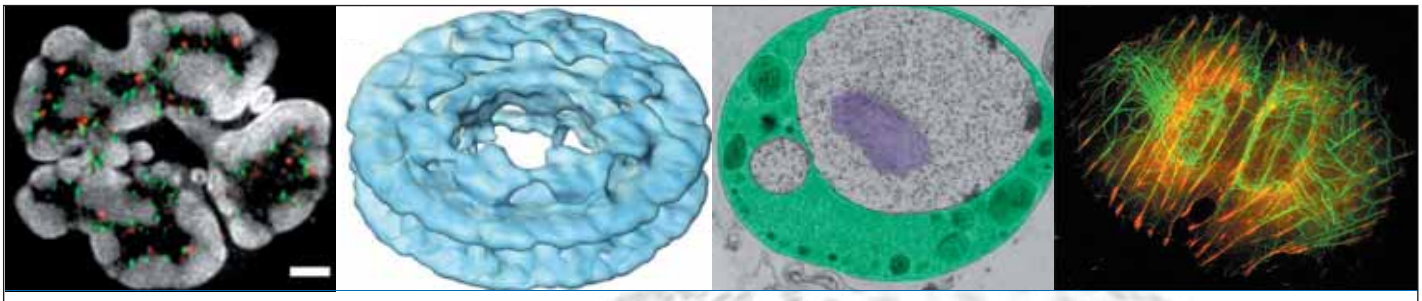

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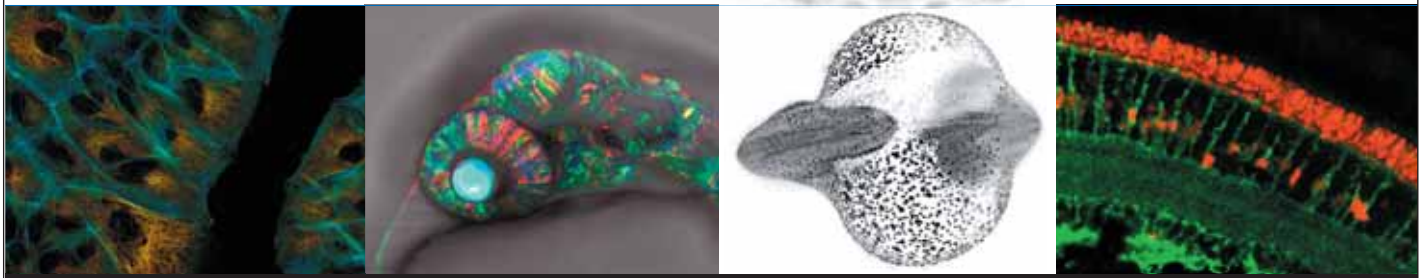

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