CONTENT

Newsletter of the German Society for Cell Biology

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Cover image: Live zebrafish embryo (17 h post fertilization) ubiquitously expressing histone-GFP. Recorded using light sheet microscopy. The perpendicular illumination scheme of light sheet microscopy is evident from the strong shadow that is cast along the x-direction by the developing tail. The image is a maximum intensity projection of a 3D volume with inverted intensity gray-values.
Burkhard Höckendorf (Centre for Organismal Studies (COS) , University of Heidelberg).

Combining forces: DGZ/GfE joint meeting in Heidelberg 2013

The annual meeting of the German Society for Cell Biology in 2013 will be a joint meeting with the German Society for Developmental Biology (GfE). Organized by Harald Hermann (DGZ) and Jochen Wittbrodt (GfE), the societies have set up an outstanding international meeting, which will be held in March 2013 in Heidelberg. Both societies represent key topics of modern life sciences and the perfect synergy of cell and developmental biology makes it difficult to separate the two disciplines. In this line the joint meeting was a logical consequence and we are very proud that we have realized it.

Heidelberg, as one of the world´s major life science centres was chosen as meeting location. The contributions of the Heidelberg research community very much add to the scientific excellence of the meeting. Invited international speakers such as Robert A. Weinberg, who will give the Carl Zeiss Lecture on his dedicated work on molecular cancer cell biology, and many other national and international leaders will present a snap shot on our current knowledge of cellular processes and functions.

We especially encourage younger scientist, students and postdocs to attend the meeting. In two poster sessions we will provide a forum for young scientists to present and discuss their research and to integrate into the community. The excellence of the scientific programme and the efforts it took both societies to set it up should be reflected in a high attendance. Therefore we hope to see you all in March in Heidelberg. It is your attendance which finally will make it "the best meeting" ever.

Eugen Kerkhoff

DGZ Member Meeting 2013

We are inviting all members to attend our next member meeting that will take place on

Thursday, March 21, 2013, 12:30 - 13:30

at the International Joint Meeting (36th DGZ annual meeting) in Heidelberg,
Conference Venue: Universität Heidelberg, Hörsaalzentrum Chemie + Bioquant, Im Neuenheimer Feld 252

Agenda:
1. Confirmation of the minutes of the last year's DGZ member meeting 2011
2. The president's annual report
3. Financial report
4. The auditors' report
5. Approval of the executive board
6. Annual membership fee
7. Change of the DGZ bylaws (for a possible cooperation with the GfE Society for Developmental Biology)
8. „Other"

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**

09:00 – 12:00 **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)

09:00 – 12:00 **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)

09:00 – 12:00 **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)

09:00 – 12:00 **Symposium S4: Epigenetics**
Chair: Sylvia Erhardt (Heidelberg)
Invited Speakers:
- M. Cristina Cardoso (Darmstadt)
- Sandra B. Hake (München)
- Dirk Schübeler (Basel, Switzerland)

12:00 **Lunch**

12:30 – 13:30 **DGZ Member Meeting**

13:30 – 16:30 **Symposia 5 – 8**

13:30 – 16:30 **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)

13:30 – 16:30 **Symposium S6: Cell Metabolism**
Chair: Eckhard Lammert (Düsseldorf)
Invited Speakers:
- William Martin (Düsseldorf)
- Nils-Göran Larsson (Köln)
- Pierre Maechler (Geneva, Switzerland)

JOINT INTERN. MEETING 2013

The continuation from Thursday, March 21

13:30 – 16:30 **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)

13:30 – 16:30 **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**

09:00 – 12:00 **Symposium S9: Primary Cilia & Signaling**
Chair: Achim Gossler (Hannover)

Invited Speakers:
- Hiroshi Hamada (Osaka)
- Heiko Lickert (München)
- Heymut Omran (Münster)

09:00 – 12:00 **Symposium S10: Biomechanics of Cells**
Chair: Jochen Guck (Dresden)

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

09:00 – 12:00 **Symposium S11: Cortical Development**
Chair: Orly Reiner (Rehovot, Israel)

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

09:00 – 12:00 **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)

09:00 – 12:00 **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 **Lunch**

12:00 – 15:00 **Poster Session 2**

12:30 – 13:30 **GfE Member Meeting**

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**

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**

General Information

Organizer:
The German Society of Cell Biology
www.zellbiologie.de

Legal Organizer (PCO):
MCI Deutschland GmbH
Markgrafenstr. 56
10117 Berlin, Germany
Phone: +49(0)30 / 204 59 27
Fax: +49(0)30 / 204 59 50
E-mail: zellbiologie@mci-group.com

Conference Venue
Universität Heidelberg
Hörsaalzentrum Chemie + Bioquant
Im Neuenheimer Feld 252
69120 Heidelberg, Germany

Conference Dates
Beginning of the conference: March 20, 2013
End of the conference: March 23, 2013

Social Events
Welcome Reception: Wednesday, March 20, 2013, 7.00 p.m
Get Together: Friday, March 22, 2013, 8.30 p.m.

Important Dates and Deadlines
Online registration open: October 1, 2012
Abstract submission open: October 1, 2012
Abstract submission closing: January 31, 2013
Last day for early bird rate registration: February 15, 2013
Registration closing: March 10, 2013

Registration

Registration: **www.celldevelopment2013.de**

Registration fee includes conference participation, welcome reception and the conference material.

Registrations Fees	until Feb 15, 2013	from Feb 16, 2013
Pre-Registration		
Member DGZ/GfE	EUR 175,00	EUR 205,00
Non-Member	EUR 225,00	EUR 275,00
Students (Member DGZ/GfE)	EUR 95,00	EUR 105,00
Students	EUR 125,00	EUR 165,00
Invited Speaker/Chair	free	free
Day tickets (price per day)		
Member DGZ/GfE		EUR 95,00
Non-Member		EUR 95,00
Students (Member DGZ/GfE)		EUR 40,00
Students		EUR 50,00

Talk & Question Time: DFG Funding Opportunities for all Career Stages

The Deutsche Forschungsgemeinschaft (DFG) funds top-level research in all branches of science and the humanities. We support individuals, individual projects and research consortia. We foster (international) scientific cooperation and are committed to promoting young researchers. The DFG is science-driven: researchers choose the topics of their projects and can submit their proposals at any time. The DFG funding programmes have constantly been adapted to the changing research environment in Germany and provide funding opportunities for all career stages.

Peer reviewers evaluate all proposals submitted.The final assessment will be carried out by the review boards (Fachkollegien). The members of the Fachkollegien are elected by researchers in Germany in their individual subject areas every four years.

Funding decisions are taken by committees made up of researchers and government representatives. With an annual budget of over 2.5 billion Euros, the DFG is Germany´s largest organisation funding basic research.

At the Joint International Meeting of DGZ and GfE (Wednesday, March 20, 2013), we want to take the opportunity to provide more insight into the DFG as a highly diversified funding organism. During this event, information will be given by Astrid Klingen and Dorette Breitkreuz (DFG head office, Bonn), but also by members of the review boards which represent the subject areas of cell and developmental biology. We aim at giving a brief overview of the most widely used funding programmes. Additionally, there will be ample time for your questions but also the opportunity to engage in a discussion with the members of the Fachkollegium representing your research area and with the members of the DFG head office looking after your proposals and your grants. This event aims at giving practical information how to make the best use of the DFG funding programmes and how to increase your chance of getting funded.

We look forward to meeting you on Wednesday, March 20, 2013 !

Dorette Breitkreuz, DFG Bonn
Astrid Klingen, DFG Bonn
Members of the DFG Fachkollegium
„Grundlagen der Biologie und Medizin“

The Special Symposium is organized by Young Scientists

The scientific part of the meeting on Wednesday 20th of March will open with a two-hour session of platform presentations, which will be selected from the abstracts sent in for the three topics of the *Plenary Sessions* and for *General Subjects*.

A committee of young scientists will select the speakers for this session. The four members are Post-Docs and PhD students (see image below) working in the field of stem cells, nuclear biology and developmental biology, respectively. Below you will also find short CVs and their affiliations. This is the first time we include students/young scientists into the shaping of the programme. However, we intend to continue this way to integrate the intentions of younger scientists more directly into the planning of the programme in the future.

The session will of course be chaired by these four committee members, and we are looking forward to an exciting session and surely a highlight of the meeting.

Harald Herrmann and Jochen Wittbrodt

From left to right:
Agata Olszak,
Michael Eichenlaub,
Teresa Rigo Watermeier,
Marcel Tiebe

Agata Olszak

2000-2005	Biotechnology at the University of Poznan, Poland
2004	Socrates-Erasmus student at the University of Ghent in Belgium
2006-2010	PhD thesis at the Max-Planck Institute in Freiburg in the laboratory of Patrick Heun. By induction of neocentromere formation I showed that heterochromatin boundaries are the preferential sites of CenH3 accumulation and thereby are facilitating the new centromere assembly.

Currently I am working in the laboratory of Peter Lichter (Division Molecular Genetics, DKFZ), focusing on the novel mechanism of genomic instability called chromothripsis, where single chromosomes are shattered into multiple pieces and then stitched together by repair process.

Michael Eichenlaub

COS - Centre for Organismal Studies,
Im Neuenheimer Feld 230, 69120 Heidelberg,
E-mail: michael.eichenlaub@cos.uni-heidelberg.de

2009-2012	PhD student at COS Heidelberg with Jochen Wittbrodt
2006-2008	Research Associate at BASF Plant Science GmbH
2005-2006	Diploma thesis at EMBL Heidelberg with Eileen Furlong
2001-2005	Engineering degree in Biotechnology, University of Applied Sciences Mannheim

Research interests: Genetics and genomics, evolution of transcriptional regulation and cis-regulatory elements

Teresa Rigo Watermeier

PhD student, Department of Stem Cells and Cancer,
German Cancer Research Center (DKFZ)
Heidelberg, Germany

Teresa Rigo Watermeier studied Biology at the Karlsruhe Institute for Technology (KIT) from 2005 to 2010. In July 2010 she received her diploma for her work on „Significance and sustainment of non-canonical Wnt-proteins in the cytoskeleton modulation during convergent extension movements". Since October 2010 she is a PhD student in the Division of Stem Cells and Cancer, headed by Andreas Trumpp, at the DKFZ. The subject of her thesis is renal cell carcinoma.

Marcel Tiebe

DKFZ – German Cancer Research Center,
Im Neuenheimer Feld 580, 69120 Heidelberg,
E-mail: m.tiebe@dkfz.de

2005-2008	B.Sc, Heidelberg, Germany "Molecular Cell Biology"
2008-2010	M.Sc, Heidelberg, Germany "Molecular Biosciences"
2010-	PhD student in the Lab of Aurelio Teleman, DKFZ, Heidelberg

Research interests: Signaling in Growth and Metabolism, Control of transcriptional regulation, Epigenetics, Molecular Biology, Genetics

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

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.

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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:

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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

The Potential of Single Cells Within Multi-Cellular Organisms. What do Fish Models Have to Offer?

Lázaro Centanin

Summary

At the very beginning of our own history, each and every one of us was just a single cell –a zygote. That only cell massively divided, its progeny differentiated and here we are after all, stereotypic multicellular animals, mature organisms (reasonably) gifted for a number of tasks. Amazingly, even after reaching our final size we still host a plethora of individual cells capable of doing remarkable things –the so-called stem cells. Stem cells have the unique ability to generate both differentiated cells and also cells identical to the mother, maintaining the stem cell pool to be used once and again. In mammals, adult stem cells have been well studied in the skin, blood, intestine, epithelia and even brain (1-5). In all these cases, they produce post-mitotic cells that are integrated into the functional adult tissue. Since stem cells constitute a never-ending source for new differentiated cells of several types, they have always been a big hope concerning clinical approaches to treat human diseases.

The recently reported possibility to reprogram post-mitotic cells into induced pluripotent stem cells (iPS) (6) has deeply changed the field of stem cell research. The realistic promise behind induced reprograming is to generate patient-specific iPS, perform genetic modifications *in vitro*, differentiate them into a specific cell type, tissue and/or organ and transplant them back to the patient. Initial experiments have raised an understandable enthusiasm for both, engineering reprogramed cells (7, 8) and developing ESCs into cell types and even organs *in vitro* (9, 10). In that respect, it is interesting to see how all the progress achieved during the last four decades in understanding how embryos and organs are built and which are the signaling pathways involved in the process -namely developmental biology- is being re-examined and applied to this promising field.

Naturally, all the knowledge acquired on how stem cells can be isolated and differentiated *in vitro* has to be accompanied by a deep understanding on how stem cells perform *in vivo* and in their natural niche. Since a couple of decades, teleost fish like zebrafish (*Danio rerio*) or medaka (*Oryzias latipes*) have emerged to constitute an impressive vertebrate model among developmental biologists (11, 12). The fast, external embryonic development and full transparency, complemented by the microinjection of dyes and morpholinos have facilitated the observation of morphogenetic processes happening in real time (13). Remarkably, after embryogenesis is completed fish continue growing life-long due to the presence of genuine stem cells distributed in the different organs of their body. For years, the lack of proper genetic tools to do long-term lineage analysis has discourage researchers for using teleost fish to study stem cells at post-embryonic stages. The hype of adult stem cell research in other vertebrate models, the highly regenerative capacity of fish and new molecular resources developed in zebrafish and medaka is now supporting the use of adult teleosts for post-embryonic stem cell research. My plan here is to stress the main points that make fish a great system for the study of adult stem cells.

Permanent Growth by Active Stem Cells in Adult Fish.

In our adult, mature body adult stem cells generate daily tens of thousand of new cells that are incorporated into the blood, the skin, and the intestine among other tissues and organs. Even though we periodically produce that huge amount of cells, we are not bigger than yesterday or the day before mainly because we also loose an enormous number of cells in those tissues as well. The main function for adult stem cells in mammals is therefore to maintain homeostasis, i.e. to generate again what we constantly lose.

Contrary to what happens in most animals, fish growth is not restricted to embryonic and larval stages, but rather continues during the entire life. In medaka, sexual maturation occurs around 6-7 weeks after hatchling. Females of that age already produce fertilized eggs that hang from their belly, as shown in **Figure 1**. After reaching adulthood, fish can live under lab conditions up to two years growing permanently and still producing viable offspring (**Figure 1**). The impressive, life-long post-embryonic growth happening in fish occurs by addition of new cells into an already complete body

plan –namely, an early juvenile. The fry that hatches out of the chorion when embryonic development is finished can swim, eat, and contains most of the functional organs of an adult fish. The challenge is then to provide post-mitotic cells of different types to every tissue in the body in a coordinated manner, at a pace given by the metabolic state of the organism, to allow allometric proportions of the body during growth –during life.

Since fish grow by incorporation of newly generated cells, they must have active stem cells in every tissue/organ. In fact, a pulse of BrdU at juvenile and adult stages labels several mitotically active zones all along the fish body, from the caudal fin to different regions in the brain -see as an example (14, 15). Fish constitute therefore an ideal model for post-embryonic stem cells studies: every single cell type of the body is produced at all times during life by a given stem cell. Additionally, the constant increase in size occurring in fish creates extra-room for incorporating the new generated cells with no need of loosing older cells. This constitutes a big difference on how homeostasis is maintained in fish compared to higher vertebrates. Adult stem cells in mammals are mainly involved in generating what was lost, and therefore their present lineage is restricted to cells produced in the near past -depending on the renewal rate of the tissue. In fish however, the total amount of post-mitotic cells generated by a given stem cell during the entire life can co-exist in an adult. That allows the examination of the entire history of cell divisions that a stem cell went through.

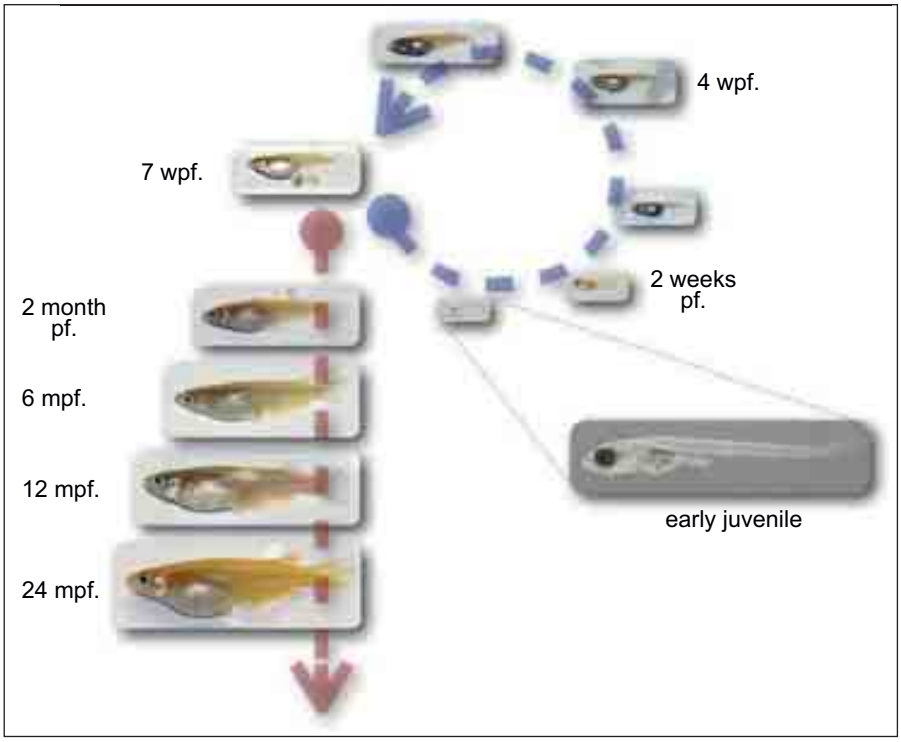

Figure 1. Permanent Post-Embryonic Growth in Fish. When embryonic development is completed, medaka juveniles hatch-out of the chorion and are capable of independent swimming and eating. Medaka reaches sexual maturation in around 6-7 weeks after hatching, as indicated by the production of viable embryos that hang from the belly of female fish. They continue growing by addition of new cells in each organ, and keep sexual activity virtually until they died -up to 20 months later.

The Order of Cell Addition Helps Defining Lineages *in vivo*.

In addition to the global and permanent activity of adult stem cells, some organs display a particular feature regarding the spatial distribution of cells added at different time points. The neural retina (NR) is part of the central nervous system and constitutes an extreme example of the temporal and spatial inter dependence of cell incorporation. After embryonic development is complete, the central retina consists of seven types of neurons and glia stereotypically distributed in three nuclear layers (**Figure 2A**). The retinal stem cells (RSC), which will generate life-long the seven cell types of the NR, are located in the cilliary marginal zone (CMZ), a proliferative domain at the periphery of the retina. The growth of the retina happens in a counter-intuitive way: RSCs move outwards as they generate neurons that stay in the place at which they were generated (16-19). In a way, it is reminiscent of the order of concentric rings observed in a perpendicular section of an old tree. Just as inner rings of the tree were formed long time ago and outer rings more recently, neurons in the center of the fish retina were generated at embryonic stages, while neurons at the periphery are way younger and were incorporated at adult stages (**Figure 2B**).

The spatio/temporal organization of the growing retina was shown in Xenopus decades ago, using radioactive thymidine to label neurons generated at different time points (16, 17). The use of thymidine analogous like BrdU or IdU showed with great detail that the fish retina displays the same temporal organization, in which neurons born at different times map to different stereotypic regions and do not mix with each other. Neurons generated close in time will map to neighbor positions, and the more age difference between two cells, the more distant they will be (**Figure 2B**). The high spatio/temporal order of cell distribution in the fish retina can be seen as calendar, in which the position of a neuron *tells* us the time at which it was generated. Such a scenario in which all the

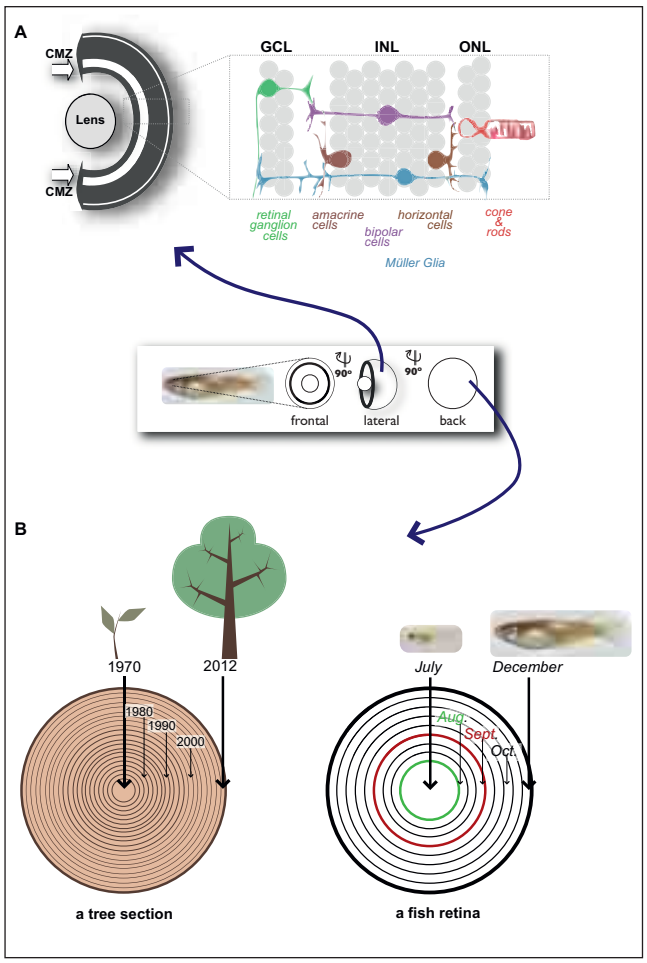

Figure 2. Exquisite Spatio/Temporal Organization of the Fish Retina. A, the vertebrate retina is composed of seven main cell types stereotypically distributed in three nuclear layers: retinal ganglion cells in the GCL, photoreceptors (cones & rods) in the ONL, and amacrine, bipolar, horizontal and Müller Glia cells in the INL. The fish retina contains in addition a peripheral domain, the CMZ, hosting the RSCs (white arrows). **B**, neurons generated at different times occupy different places in the adult fish retina (right), resembling the spatio/temporal organization of a tree section (left). Pulses of IdU (green) and BrdU (red) given at different times (August and September, respectively) of the fish life will label distinct groups of neurons that do not mix with each other. *Ab*: GCL, ganglion cell layer; ONL, outer nuclear layer; INL, inner nuclear layer; CMZ, ciliary marginal zone; RSCs, retinal stem cells.

cells generated during life are distributed in a spatio/temporal stereotypical manner significantly facilitates lineage analysis of stem cells.

Clonal Analysis and Chimera Generation I. A Mechanical Approach.

The most conventional way to generate a fish chimera is through mechanical transplantation of cells at early embryogenesis, from one blastula of a given genotype (the *donor*) into a second blastula of a different genotype (the *host*). If we use transgenic, EGFP expressing blastula cells as donors and use a *wild-type*, non EGFP expressing blastula as host, then every EGFP$^+$ cell in the growing chimera will belong to the lineage of the transplanted cells (**Figure 3A**). By reducing the initial amount of transplanted cells, lineage relations become even clearer. In fact, transplantation of individual labeled cells demonstrated the common origin for hematopoietic and endothelial lineages in the zebrafish gastrula (20).

Retinal progenitors in fish migrate individually during early development to populate the optic vesicle (21), which constitutes indeed a clone-generating event. If a transplanted EGFP$^+$ cell happens to migrate into the optic vesicle, then its entire progeny will be labeled and clonal assignment happens rather unambiguously. This principle of clone generation is easily testable by multicolor transplantation using blastula cells from various donors, each labeled a different fluorescent proteins. Within the host, individual migration of labeled and non-labeled retinal progenitors results later in a retina having cells of different colors intermingled all along the tissue (**Figure 3B**).

The Wimbledon transgenic fish constitutes an ideal source of labeled cells for long-term lineage analysis in medaka (22). Since Wimbledon fish expresses EGFP in every cell and during the entire life of the fish, transplantation of Wimbledon cells into an unlabeled host allows lineage studies even at adult stages and irrespective of the terminal, post-mitotic fate of the labeled cells. We have already used this strategy to demonstrate the occurrence of *bona fide* neural stem cells in the retina of medaka(22). Following blastula transplantation, most of the EGFP$^+$ transplanted cells adopt post-mitotic fates during embryonic development. However, in some cases an EGFP$^+$ cell is integrated in the peripheral CMZ of an embryo, and when those fish are grown the entire lineage of that cell can be assessed thanks to the temporal organization of the retina and the permanent label of the Wimbledon cells. The question we focused on referred to the potency of the retinal stem cells in the neural retina (NR-RSCs). If all seven cell types of the neural retina are generated constantly during life, then i) are there specific NR-RSCs committed for each different cell type? or, ii) is there just one NR-RSC common for the seven cell types?". In other words, are NR-RSCs multipotent or alternatively, restricted in fate? Our analysis on several hundred clones demonstrated that every NR-RSCs examined was indeed multipotent, always generating all types of retinal neurons and glia(22). Altogether, clonal relations in medaka during retinal growth turned-out somehow counter-intuitive: two neighboring photoreceptors (two cells of the very same type located next to each other) are less related in lineage than two different cell types lying in independent layers. Clonality seems to actually operate

maintaining functional units (the axis photoreceptor-*horizontal*-bipolar-*amacrine*-RGCs) rather than differentiated cell types of the same kind.

Clonal Analysis and Chimera Generation II. A Molecular Approach.

Some main caveats of transplantation studies are i) the chances that the mechanical manipulation of the transplanted cells affect their natural behavior, ii) the risk of triggering a regenerative response when grafting the cells in the donor and iii) in blastula transplantations the donor cells are label from the very beginning and go through early phases of development, potentially confusing the read out for most of the post-embryonic organs. Inducible recombination methods, classically ^{ERT2}CRE/LoxP or ^{PR}FLP/FRT, allow labeling of specific populations of cells within an organism at a desire time point and without the need of mechanical manipulations like microinjection or transplantations. Typically, two LoxP sequences flank a STOP cassette that seats between a promoter of choice and a reporter protein (**Figure 4A**, left). As long as the STOP cassette is there, there is no expression of the reporter. Expression of the CRE recombinase in a specific type of cells will catalyze the recombination of the two LoxP and the removal of the STOP cassette, allowing the expression of the reporter protein.

A limitation of the classical LoxP system regarding lineage analysis is that two different cells going through independent recombination processes end up expressing the very same reporter (**Figure 4A**, left). Therefore, there is no way to know whether two, three or twelve given cells expressing the reporter protein share a common progenitor or not. The development the Brainbow system in mouse(23) solved that issue, allowing a combinatorial and therefore unambiguous labeling of cells. Brainbow systems contain multiple fluorescent proteins (FP's) flanked by identical (BBW 2.0 and 2.1) (**Figure 4A**, right) or slightly modified (BBW 1.0 and 1.1) Lox sites. Upon addition of CRE, two neighbor cells that went through independent recombination events will most likely express a different combination of FP's (**Figure 4A**, right). *Brainbow* constitutes therefore a non-invasive system to unambiguously label single cells within an intact mature multicellular organism.

The beauty of the Brainbow system to do single-cell labeling and lineage analysis was already exploited using embryonic and post-embryonic stem cell paradigms in mouse (24, 25). These first reports involving unambiguous single cell labeling and permanent tracking of its progeny have certainly revealed unexpected behaviors when compared to what was assumed based on observations at the population-level. Focusing on *Lgr5*+ intestinal stem cells, Snippert and colleagues changed the classical view on how stem cells perform. They showed that instead of having individual stem cells dividing asymmetrically to generate an identical stem cell and a differentiated cell (or a partially differentiated, transient amplifying cell in this case), stem cells divided rather symmetrically most of the times (25). While some of them generated two amplifying cells, some others divided into two intestinal stem cells, maintaining constant the *Lgr5*+ stem cell number in the crypt. In this way, although at the level of the population *Lgr5*+ stem cells are generating both differentiated and post-mitotic

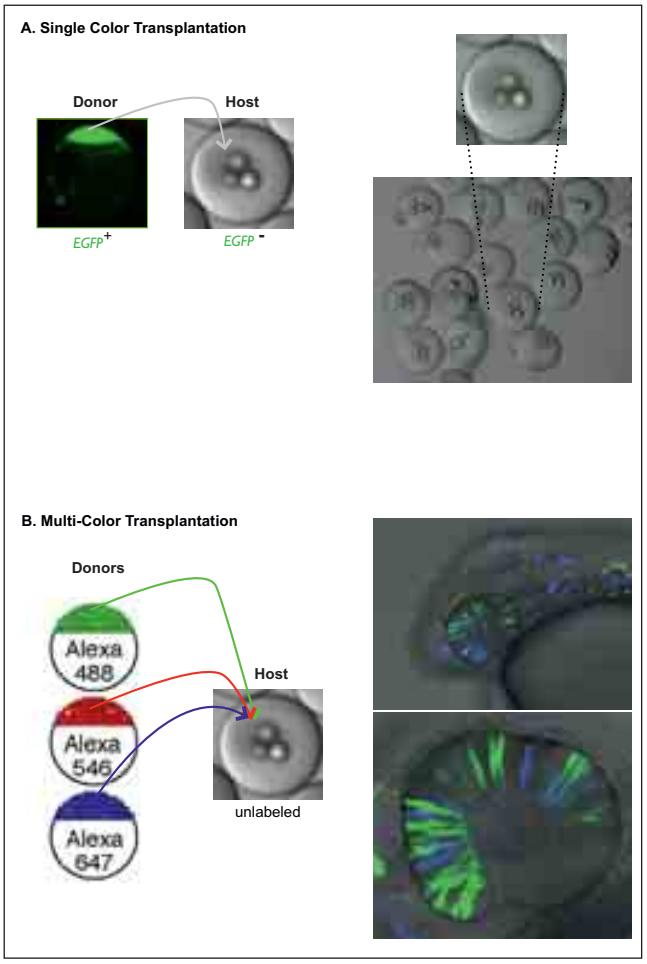

Figure 3. Clone Generation by Transplantations at Blastula Stage. A, transplantation of labeled cells into an unlabeled blastula allows lineage analysis during embryogenesis. Note the small proportion of fluorescent transplanted cells at the tip of the host *wild type* blastulas. **B**, combining cells from multiple donors labeled by different fluorophores facilitates clonal analysis generated by individual transplanted cells in certain organs, like the fish retina.

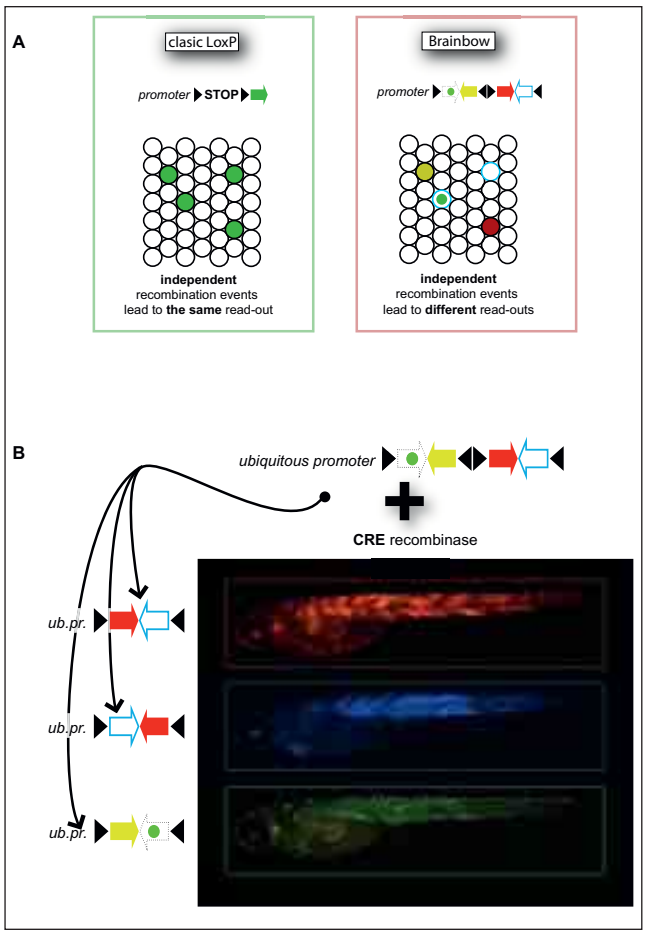

Figure 4. Clonal Labeling by Stochastic Expression of Fluorescent Proteins. A, a classical LoxP reporter construct (*promoter*::LoxP-STOP-LoxP-Reporter) produces an identical reporter expression in cells that went through independent events of recombination (left). Even cells that do not share a clonal origin are labeled with the same FP, the only possible read-out of recombination. Alternatively, the Brainbow system (right) combines several FP's separated by multiple LoxP sites. The stochastic recombination of any two of these LoxP sites results in the expression of 1 out fo 4 possible read-outs. Additional copies of the Brainbow cassette exponentially expands the possible combinatorial FP's expression. **B**, Transgenic juveniles containing a Brainbow cassette under a ubiquitous promoter express the different FP's upon CRE recombinase expression.

cells, each one of the individual *Lgr5+* cells in the population is doing either one or the other cell type in each division(25).

Due to its external and transparent development, teleost fish represent an ideal model to exploit the Brainbow system. Indeed, initial approaches for imaging Brainbow cassettes during embryogenesis (26) raised an understandable enthusiasm. Furthermore, a transgenic zebrafish expressing a Brainbow cassette specifically in cardiomyocites was used to characterize the morphogenesis of the adult heart(27). By labeling individual cells in different colors the authors reported that the entire adult cortical muscle was generated from just eight cardiomyocites that expanded clonally(27). The generation of fish lines expressing Brainbow cassettes in a broader (ideally ubiquitous) expression domain will certainly expand the possibilities for lineage analysis of post-embryonic stem cells in a permanent growing animal model.

Perspectives

I have already stated that the vast knowledge acquired on how stem cells can be isolated and differentiated *in vitro* needs to be complemented by understanding how stem cells perform *in vivo* and in their natural niche. My personal impression is that there is still an enormous gap to fill, regarding: a) how *individual* -and not entire populations of- stem cells behave in their intact environment, and b) how different stem cells in the body are coordinated to sustain allometric growth. To answer these questions it is required to analyze the growth of a population/ a tissue/ an organ with a single cell resolution. In my lab, we have set up a number of transgenic fish containing ubiquitously expressed Brainbow cassettes(23) (**Figure 4B**) and different expression domains for the CRE recombinase. The availability of these tools constitutes a pre-requisite for quantitative biology approaches, like i) how many cells are involve in maintaining an entire organ at different life periods? ii) how similar is the contribution of different stem cells in a given tissue? iii) how is coordination among stem cells in diverse organs orchestrated to maintain body proportions during post-embryonic growth?

In addition, teleost fish have an impressive capacity to regenerate most organs of their body (see a clear review of brain regeneration in zebrafish by Volker Kroehne and Michael Brand, in the *Cell News* Volume **38, 1**/2012). Ablation of a significant portion of the posterior fin, as an example, results in the formation of a blastema that will regenerate the amputated portion within days (28). An interesting phenomenon occurring during blastema formation in different species, is that each individual lineage of the amputated tissue (fins in fish, limbs in newts) is generated by cells that belonged to that same lineage before the ablation (new bones are generated from old bones, new skin is generated from old skin) (29, 30). Little is known, however, about the clonal contribution of individual stem cells to this lineage-maintaining repair process. The very same questions appear once and again, and the very same tools seem appropriate to addressing them i) how many cells are required to do the job? ii) what fraction of a given population of stem cells has the capacity to respond to external challenges as mechanical injuries?

In summary, stem cells are involved in both the permanent growth of every organ in the fish as well as in the inducible regenerative

responses of certain tissues. The magnitude of different cell types continuously generated throughout life makes teleost fish an attractive model for stem cell research. The accessibility for *in vivo* imaging of certain tissues and organs, on the one hand, and the growing collection of genetic tools to label individual post-embryonic stem cells, on the other, opens the realistic possibility of following entire lineages not just in their natural environment, but also in real time.

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Lázaro Centanin studied Biology in Buenos Aires, Argentina. After a first approach to genetic model organisms at Benny Shilo's Lab, in the Weizmann Institute, Israel, he moved back to Buenos Aires for his Ph.D. He joined Pablo Wappner's Lab at he Leloir Institute, and studied the transcriptional response to hypoxia in *Drosophila melanogaster*. Particularly, he was interested in which molecules mediated the external environmental cues and the physiological responses happening in the fly. He joined for his PostDoc Jochen Wittbrodt's Lab, first at EMBL and later at COS Heidelberg, where he focused on the study on stem cells in the retina of teleost fish. Since 2012 he has a Junior Group at COS studying post-embryonic stem cells in medaka in diverse tissues, during normal growth and regeneration.

Evolution of fly gastrulation

Steffen Lemke

Introduction

Morphological differences between two species are shaped by diverging developmental trajectories: ultimately, the adult form of an organism rests on sequential changes in shape and behavior of cells and tissues. On the level of the cell, morphogenesis is modulated by the cytoskeleton, actin, and non-muscle myosin; on the genetic level, it is controlled by developmental patterning genes such as transcription factors or signaling pathways. To explore the cellular and genetic bases of morphological evolution, we study and compare cell behavior, developmental patterning and how they are linked in different organisms. The experimental framework for such a study needs to comprise comparable yet morphologically diverse species, each of which are accessible to molecular/genetic manipulation, and it ideally contains a reference species in which the essential connections between developmental patterning and the generation of form are known.

A framework for comparative morphogenetic studies

In our lab, we are using gastrulation in the insect order Diptera ("true" flies) as a genetically tractable model to study the evolution of form (Figure 1). Gastrulation is the first set of morphologically dynamic events during animal embryonic development, and often it is directly influenced by preceding genetic patterning. Gastrulation in flies is morphologically sufficiently complex to serve as a reasonable model for the generation and evolution of form. Gastrulation can be readily compared between our reference (*Drosophila melanogaster*) and other flies, because, on the one hand, gastrulation in all flies follows a similar set of morphogenetic transformations. On the other hand, gastrulation has diverged sufficiently between flies to be able to explore the evolution of morphogenetic differences. The insect order is estimated to allows for comparisons on various evolutionary scales ranging from the population level, sub-family and family level, and up to higher taxa comparisons of species that diverged more than 250 million years ago. Over the last years, we and others have established lab cultures and molecular genetic tools for basic gain- and loss-of-function approaches in multiple fly species at key positions in the phylogenetic tree (Lemke and Schmidt-Ott, 2009; Lemke et al., 2011; Lemke et al., 2008; Rafiqi et al., 2011; Rafiqi et al., 2008). The insect order now provides a functional framework for evolutionary studies, within which our lab currently focuses on the origin of specific gastrulation differences between the fruit fly *Drosophila melanogaster*, the hover fly *Episyrphus balteatus*, the scuttle fly *Megaselia abdita*, and the midge *Chironomus riparius*.

Gastrulation in flies

Up until gastrulation, fly development is syncytial, i.e., the zygote nucleus divides without cell division (Anderson, 1966; Anderson, 1972). In Drosophila, the first thirteen mitotic cycles occur in globally synchronized waves (Foe and Alberts, 1983; Krzic et al., 2012; Tomer et al., 2012), which give rise to an embryo with about 6000 nuclei assembled in a single layer at the cortex, plus a group of about 30 germ line cells, which, at the posterior pole, lie on top of the syncytial blastoderm. During cellularization, the peripheral nuclei are encapsulated by plasma membrane, and following Leptin's definition (Leptin, 2005), gastrulation starts with the completion of ventral cellularization. From now on, cells divide with local synchrony in distinct clusters termed "mitotic domains", which are controlled by the cdc25 homologue *string* and have been mapped with near single-cell resolution for the first postblastoderm nuclear division cycle (Edgar and O'Farrell, 1989; Edgar and O'Farrell, 1990; Foe, 1989). The mesoderm primordium invaginates along a longitudinal fold on the ventral side of the blastoderm embryo. The endoderm, made up of two spatially separated primordia, invaginates at the anterior and posterior ends of this ventral furrow. Additionally, transient folds are generated with a lateral cephalic furrow in the anterior third and two dorsal transversal folds behind the cephalic furrow. Superimposed on invagination and folding of the germband, the germband increases 2.5-fold in length along the anterior-to-posterior axis. During this extension, the dorsal-most blastoderm cells flatten into a single thin extraembryonic epithelium, the amnioserosa, which then folds up between extending germband and head. Until internalization of the endoderm, gastrulation in Drosophila takes about 2.5 to 3 hours (Campos-Ortega and Hartenstein, 1997; Costa et al., 1993; Lye and Sanson, 2011). In its most general aspects, gastrulation in flies appears very conserved and similar to Drosophila. However, specific aspects like the mode of mesoderm invagination or dorsal sealing of the embryo during the course of gastrulation, are less conserved and have undergone evolutionary changes during the radiation of flies (Anderson, 1966; Schmidt-Ott et al., 2010).

Apical cell constriction and furrow formation

Mesoderm invagination in Drosophila provides a textbook example of mechanics and

molecular mechanisms that coordinate cell behavior and tissue morphogenesis. Mesoderm internalization is initiated by a pulsed constriction of the apical cell surfaces in a band of about 18 cells wide and 60 cells long on the ventral side of the embryo (Martin et al., 2009; Sweeton et al., 1991; Turner and Mahowald, 1977). Under control of the transcription factor Twist, a ratchet-like, actin-myosin based mechanism stabilizes the cell shape in between constriction pulses (Martin et al., 2009; Martin et al., 2010), the nuclei of the initially columnar ventral cells drop basally, and the cells assume a wedge-shaped morphology. The change in overall cell morphology bends the ventral epithelium, which forms a shallow furrow along the ventral midline. This furrow then contracts rapidly into an invagination as cells inside the furrow shorten by about 50% along their apical-basal axes (Kam et al., 1991; Sweeton et al., 1991; Turner and Mahowald, 1977). During formation and invagination of the ventral furrow, the cells of the presumptive mesoderm do not divide (Foe, 1989). Following invagination, the mesodermal cells loose their epithelial character, start to divide and adhere to the neuroectoderm to form a mesenchymal layer of mesoderm cells (Leptin and Grunewald, 1990; McMahon et al., 2008; Murray and Saint, 2007). It has been suggested that mesoderm morphogenesis in Drosophila has been an adaptation to an extremely rapid mode of embryogenesis. Mesoderm invagination without tube formation has been reported for dipterans in the nematoceran suborder, including gnats and mosquitoes (Carvalho et al., 1999; Goltsev et al., 2007; Raminani and Cupp, 1975). Mesoderm invagination in Chironomus riparius also invaginates without tube formation and thereby offers a system to explore – in comparison with the network known in Drosophila – how a program for high coordination and accuracy of cell movements could have evolved.

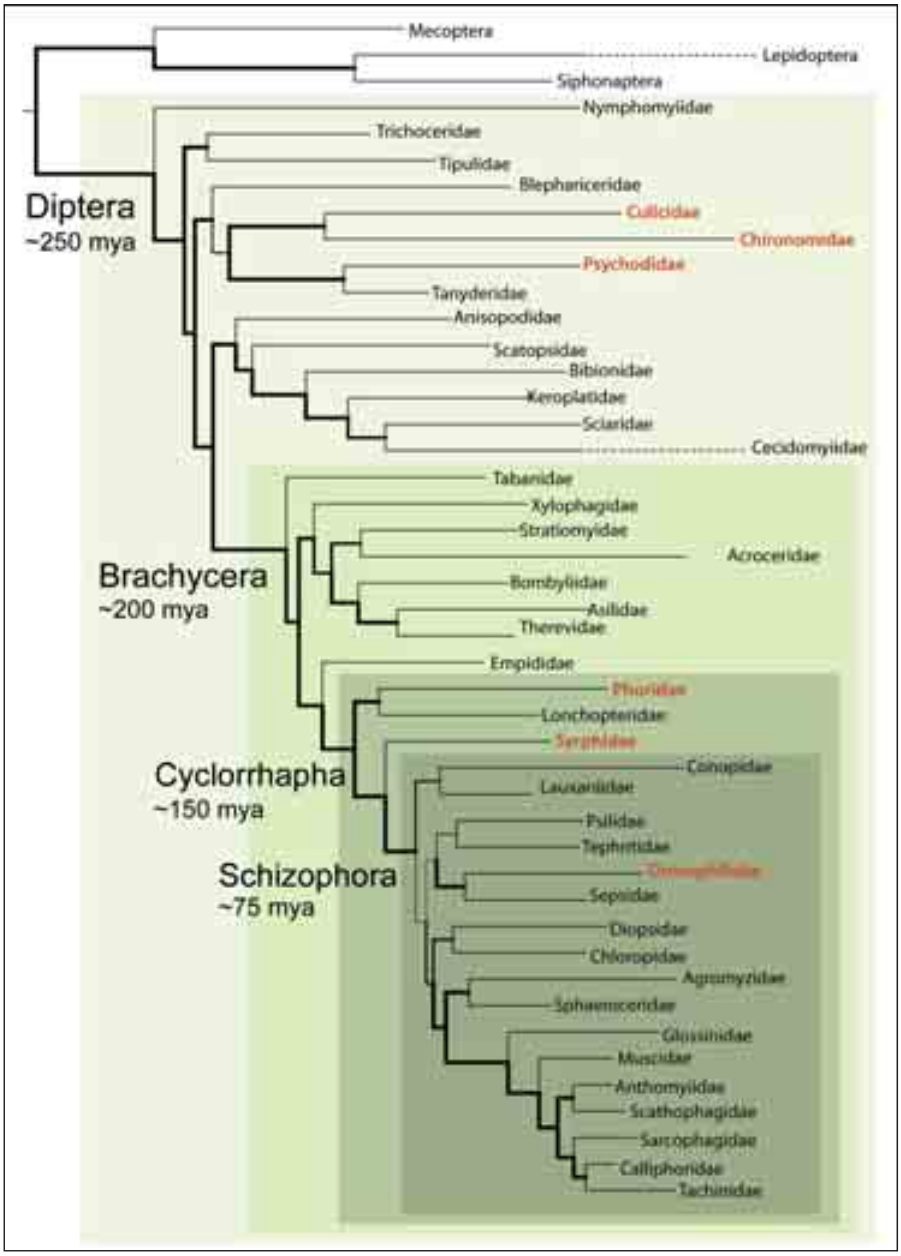

Figure 1. Phylogeny of Diptera based on molecular and morphological data (14 nuclear genes, full mitochondrial genomes, and 371 morphological features). Thick branches show >90% posterior probability in Bayesian analysis. Major taxonomic groups are indicated with estimated age (mya: million years ago) in shaded boxes. Selected families at critical positions in the phylogeny with lab cultures and molecular tools established are in red (Culicidae: *Anopheles gambiae*, *Culex fuscipes*, *Aedes aegypti*; Chironomidae: *Chironomus riparius*; Psychodidae: *Clogmia albipunctata*; Phoridea: *Megaselia abdita*; Syrphidae: *Episyrphus balteatus*; Drosophilidae: *Drosophila melanogaster*). (Adapted from Wiegmann et al., 2011).

Tissue development and topology

The Drosophila amnioserosa provides a developmental model to study origin, maturation, differentiation and function of a well-defined epithelium. The flexile epithelium is generated during gastrulation to seal the dorsal portion of the embryo but later does not contribute to the formation of the embryo proper. At the blastoderm stage, the amnioserosa anlage expresses the homeodomain transcription factor Zerknüllt (Zen) and consists of a narrow dorsal band of about 5 cells wide and 40 cells long. Midway through germband extension, this set of cells changes the morphology as the cells shrink in height by a factor of four, and increase their apical surface area by a factor of six (Pope and Harris, 2008). As a result, the initially columnar epithelium turns into thin sheet of squamous cells that do not divide and remain continuous with the neighboring embryonic epithelium (Campos-Ortega and Hartenstein, 1997; Costa et al., 1993; Turner and Mahowald, 1977). This sheet spreads onto the lateral sides, and by the end of germband extension, most of the extraembryonic tissue is folded up and in between the ventral and the dorsal halves of the germ band. After gastrulation, the amnioserosa is required for germband retraction and dorsal closure, during which it is resorbed by the yolk while ectoderm closes the embryo dorsally (Kiehart et al., 2000; Lamka and Lipshitz, 1999). In contrast to Drosophila, gastrulation in most other flies and insects is accompanied by formation of two distinct extraembryonic epithelia (amnion and serosa). The specialized and faster development in Drosophila may be due to adaptation to a generally humid environment and fast decaying food sources. The more ancestral mode of extraembryonic development has been described for serosa and dorsal amnion in the lower cyclorrhaphan flies *Episyrphus balteatus* and *Megaselia abdita* (Rafiqi et al., 2008), where, like Drosophila, these two tissues originate from a dorsal anlage. However, unlike Drosophila, the serosa completely separates and detaches from the embryo proper. Until the middle of germband extension, extraembryonic development proceeds very similar to Drosophila. Then, in contrast to Drosophila, the future serosa starts to expand and fold over the embryo proper. This fold is torn by the expanding serosa, which then detaches from the embryo, expands further and fuses on the ventral side to eventually enclose the embryo. Concurrently, the amnion fuses underneath the serosa and closes the embryo dorsally. The comparison of extraembryonic development in E*pisyrphus balteatus*, *Megaselia abdita*, and Drosophila provides a model system to explore the genetic setup of tissue separation versus tissue integrity.

Exploring cell and tissue distortion in context of the entire embryo

During fly gastrulation cells divide, the me-

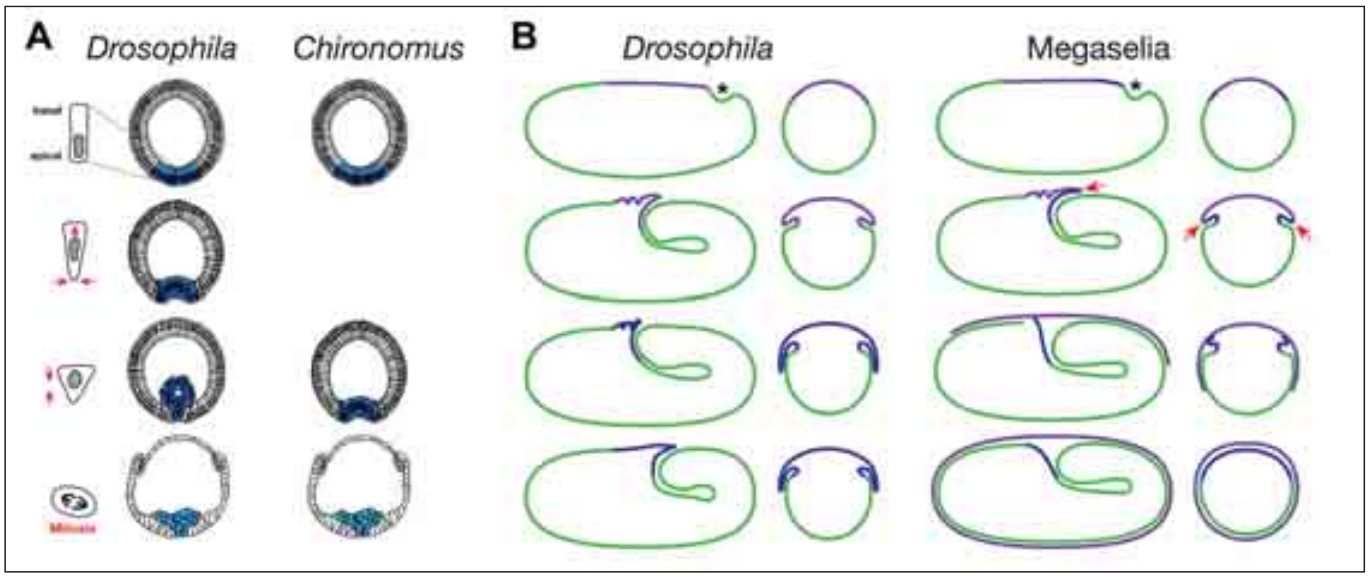

Figure 2. Differences in fly gastrulation. (A) Mesoderm internalization in Drosophila and Chironomus. Shown are cross section views, dorsal is up. Changes in shape and behavior of a representative mesoderm cell during furrow formation in Drosophila are indicated on the left. The invaginating mesoderm is marked in blue, coinciding with expression of the transcription factor Twist (modified after Leptin, 2005). (B) Schematic representation of extraembryonic development in Drosophila and the lower cyclorrhaphan fly Megaselia. Embryonic tissue (green), as well as *zen* expressing (purple) and non *zen*-expressing extraembryonic tissues (blue) are indicated. In each of the panels, a lateral section is to the left and a cross section to the right. The proctodeal invagination in flies (asterisk) and tearing of the serosa at the amniosersal fold in the intermediate type (red arrows) are indicated (modified after Rafiqi et al., 2008).

soderm invaginates, the germband extends, and an extraembryonic epithelium is formed almost all at the same time. This means that local cell rearrangements and epithelial distortions contribute to a global morphogenetic process, within which local changes can overlap and influence each other. A systematic understanding of specific differences in fly gastrulation therefore requires an analysis that encompasses the organism as a whole while still being at a spatial and temporal resolution that allows to follow individual cells and cell behavior. Recent advances in fluorescent light sheet microscopy have started to provide a unique opportunity to approach embryonic morphogenesis on the scale of the entire organism (*in toto*) and at the spatiotemporal resolution of individually moving cells inside of the embryo. Specifically, light sheet microscopes offer three critical technical advantages that had been required for high resolution *in toto* live imaging of embryonic development: high speed and high resolution image acquisition at low photo toxicity (Huisken and Stainier, 2009). To visualize cell movements during live imaging, cell positions are approximated with nuclear position that is typically marked by a histone fused to a fluorescent protein. Current implementations of light sheet microscopes have demonstrated that the spatiotemporal resolution is sufficient for computer routines to automatically extract cell position, division, and migratory tracks, which can be digitalized and stored in a four-dimensional digital atlas of embryonic development (4D digital embryo, i.e., 3D plus time; Keller and Stelzer, 2008; Keller et al., 2010; Krzic et al., 2012; Tomer et al., 2012). Thus, complex cellular movements can be decomposed, parameterized, and readily compared between individual wildtype embryos, between wildtype and mutant embryos, and, presumably, between embryos of different species. In this sense, the functional dissection of gastrulation in a selected set of fly species combined with an extended live imaging approach may become the stepping stone to unravel genetic changes that triggered morphological evolution.

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Research interests
Morphogenesis, evolution, development, embryonic patterning, cell biology, microscopy.

Friend or foe? The interplay between RNA turnover and quality control and RNA silencing in Plants

Alexis Maizel

Introduction

Eukaryotic organisms must ensure faithful expression of their own genetic programs. This requires first, to regulate the half-life of mRNA in order to control protein abundance (RNA turnover) and second, to ensure quality control mechanisms that eliminate defective mRNA and dampened the production of potentially toxic proteins (RNA quality control; RQC).

In parallel to ensuring the proper expression of their genome, eukaryotes must protect themselves against parasitic and pathogenic organisms (viruses, bacteria), which can introduce and express their genetic information. To resist the deleterious effects of these invaders, host organisms have developed protection programs that act at both preventive and combative levels. One of these programs is post-transcriptional gene silencing (PTGS) or RNA silencing. It consists of transforming part of the invader RNA into small RNA molecules that can fight back by directing the degradation of the non-self invader RNA. In addition to defend against exogenous invaders, many eukaryotic organisms have adapted RNA silencing to regulate the expression of protein coding genes at the post-transcriptional level (e.g. micro RNA).

Cooperatively, RNA decay and PTGS pathways ensure cell survival by neutralizing defective or invading RNA, while allowing correct self RNA to remain intact. Although these pathways rely on different mechanisms, they share common substrates (RNAs) and final goal (destruction). The question arises then of how these pathways co-exist.

In the following sections I will review our knowledge on the interplay between RNA decay and RNA silencing focusing on recent advances obtained in the model plant *Arabidopsis thaliana*. I will first briefly present the main routes and enzymes responsible for RNA surveillance decay and RNA silencing. I will then present the evidences for a tight interwinding of the two processes and finish by discussing whether RNA decay and RNA silencing compete or collaborate.

RNA turnover and quality control

Expression of protein coding genes follows a complex suite of coordinately regulated processes, which include pre-mRNA synthesis, capping, polyadenylation, splicing, mRNA transport across the nuclear pore complex, mRNA translation and, ultimately, mRNA turnover. Throughout these maturation processes, mRNA shuttle between dynamic protein complexes, which, divulge the history of the RNA and influence its subsequent fate (*1*, *2*). To make a functional protein, mRNA must proceed through all of these processes error-free. However, cells routinely make mistakes. Some mistakes are genetically encoded mutations, and others occur because metabolism can be intrinsically inefficient or inaccurate. Once dysfunctional RNA are pro-

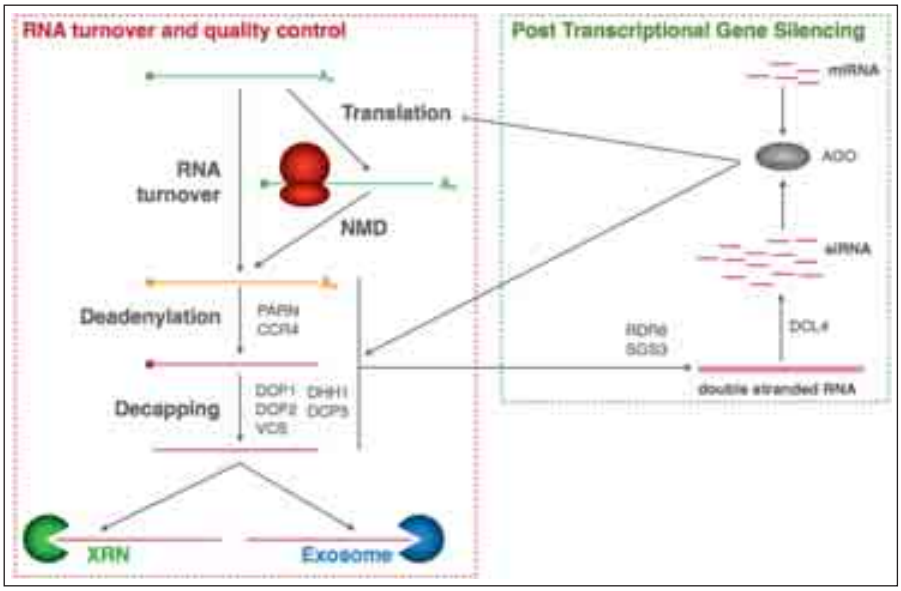

Figure 1: Model for the relationships between RNA processing and RNA Silencing in plants. Exonucleolytic mRNA decay can be initiated by deadenylation, followed by 3' → 5' degradation by the exosome, or decapping, followed by 3' → 5' degradation by the XRN family of exoribonucleases. RNA silencing is induced by double stranded RNA converted in siRNAs by DCL4 or by miRNA. Si/miRNA-loaded AGO can induce translational suppression or trigger endonucleolytic cleavage of mRNA. This generates uncapped and unpolyadenylated RNA products, which can either be substrates for RDR6 and secondary siRNA biogenesis to reinforce RNA silencing, or substrates for the exonucleolytic RNA decay pathways.

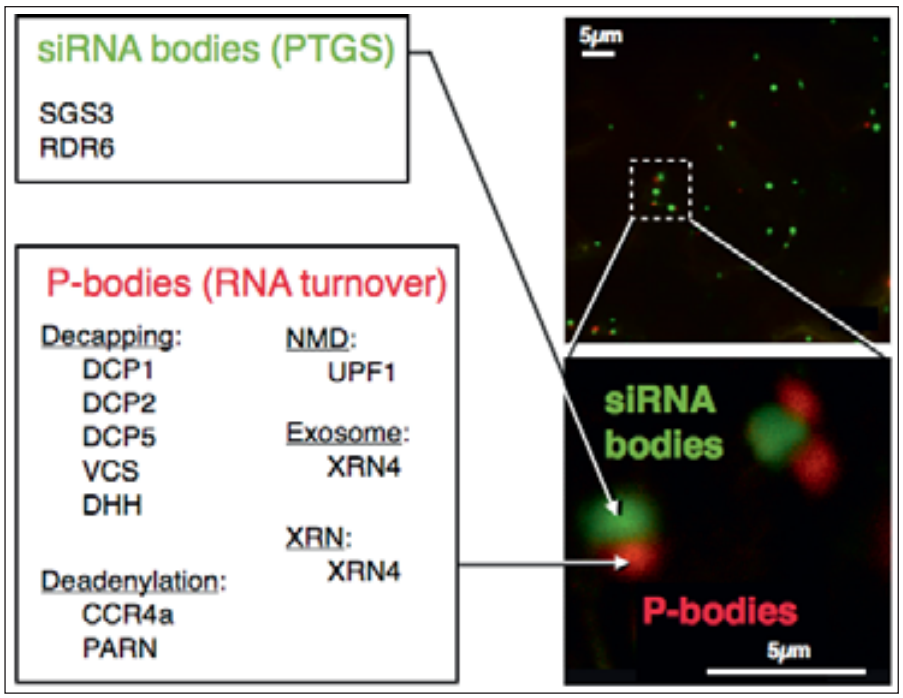

Figure 2: Spatial relationships between cytoplasmic RNA processing and RNA Silencing in plants. Confocal images of tobacco leaf cells expressing transiently a SGS3-GFP fusion (green) and DCP1-RFP (red). SGS3-GFP marks siRNA bodies whereas DCP1-RFP marks P-bodies. The boxes list the additional components detected in these two bodies.

duced, cellular mechanisms must discriminate these RNA from functional RNA to ensure that the production of deleterious proteins are kept in check, while enabling functional mRNAs to produce proteins. Eukaryotic cells accomplish this by employing diverse RQC proteins that associate and mark mRNA as defective (2). These RQC proteins, together with mRNA-associated proteins that facilitate downstream maturation reactions and chemical modifications that protect RNA from degradation, influence whether a mRNA will exit the maturation course prematurely and be degraded or will successfully mature and be translated.

Two modifications, the 5'-cap and the 3'-polyA tail, and their associated proteins, distinguish a normal mRNA from an aberrant mRNA. The 5'-cap and 3'-polyA tails are added shortly after the start of transcription or upon transcription termination, respectively, and protect mRNA from exoribonucleases, ensuring mRNA stability and facilitating translation. However, if these marks (and as a result their associated proteins) do not get deposited or if they are removed by RQC, their absence has drastic consequences on the stability of the mRNA and represents an initial step in transcript degradation (3).

The removal of the 3'-polyA tail (deadenylation) is catalyzed by the conserved 3'-to-5' poly (A) specific ribonuclease PARN as well as by the conserved carbon catabolite repressor protein 4 (CCR4) complex (4-7). The removal of the cap structure is catalyzed by a set of conserved decapping proteins (DCP). In Arabidopsis thaliana, DCP1, DCP2 (TDT), DCP5, VARICOSE (VCS) and possibly DEA(D/H)-box RNA helicase 1 (DHH1) constitute the decapping complex (8-11). DCP2 removes the cap, whereas the other proteins likely contribute to mRNA recognition or stimulate decapping. Decapping and deadenylation are a prerequisite for a RNA to be degraded by 5'-to-3' XRN exoribonucleases and the multimeric 3'-to-5' exoribonuclease exosome complex, respectively. Arabidopsis expresses three XRN proteins, the nuclear XRN2 and XRN3 and the cytoplasmic XRN4 (12), whereas biochemical and molecular characterization of the Arabidopsis exosome core complex revealed the exosome subunits RRP4, RRP41, RRP42, RRP44, RRP45 (CER7), RRP46, CSL4 and MTR3 (13).

Nonsense-mediated decay (NMD) is a well-characterized RQC pathway involved in the genome-wide suppression of dysfunctional mRNAs containing premature termination codons (PTC-mRNAs) and involves both decapping and deadenylation. Messenger RNAs with PTCs create a substantial problem for cells because they have the potential to be translated into potentially deleterious truncated proteins. In plants, PTC recognition relies on the distance between a stop codon and downstream introns, which are marked by the exon junction complex proteins (EJC) after splicing, or uses 3' UTR length and context as a guide (14, 15). It is generally accepted that an early pioneer round of translation is responsible whereby a ribosome scans the transcripts for PTC, indicating that translation and NMD are linked. In all eukaryotes, the NMD pathway involves recruitment of the core NMD proteins UPF1, UPF2 and UPF3, to PTC-containing RNA transcripts. Once bound, the UPFs promote either DCP-mediated decapping or PARN-mediated deadenylation (16-18), or endonucleolytic cleavage of the transcript near the PTC (in Drosophila) (19). The resulting aberrant RNA products, which lack either a 5'-cap or a 3'-polyA tail, are subjected to XRN or exosome degradation, respectively (20).

Unspliced or mis-spliced transcripts are also subjected to RNA decay. In plants, it has been shown that unspliced pre-mRNAs accumulate in the nucleoli of Arabidopsis, together with components of the NMD (21). How these aberrant RNAs are recognized is not known.

Post-transcriptional RNA silencing

The gene silencing pathways of plants are crucial to regulating endogenous gene expression and protecting plants from transposons and viruses. RNA-mediated gene silencing has three basic steps: (i) production of double- stranded RNA (dsRNA), (ii) dicing of dsRNA by Dicer-like (DCL) enzymes to generate small interfering RNA (siRNA) or microRNA (miRNA), ~21–24 nt in length, and (iii) siRNA- or miRNA- directed execution of gene silencing by a member of the Argonaute (AGO) family. Post-transcriptionally, AGO proteins can direct mRNA cleavage and/or translational repression. The dsRNA can result from the transcription of an inverted repeat locus (e.g. miRNA precursors or RNAi constructs) or through the conversion of a single-stranded RNA template by a RNA-dependent RNA polymerase. Once triggered, PTGS destroys RNA molecules based on sequence homology without discriminating between self and non-self RNA or between correct and defective RNA.

Genetic interplay between RNA decay and RNA silencing

As more is learnt about the mechanisms of RNA decay and RNA silencing, it is becoming increasingly apparent that spatial and functional overlaps exist between them. Initial studies of transgene silencing in plants noted a correlation between high expression levels and the induction of silencing (*22*). It was proposed that gene silencing would be induced following a "quantitative aberration" in gene expression (*22*). While this model held true in most cases, a report showing that equivalent transcription rates could exist in both silenced and expressing plants, meant that refinements to the model were needed (*23*). It was proposed that specific RNA molecules may have qualitative aberrations that lead to the induction of RNA silencing (*23*), perhaps by acting as a template for an RDR and leading to the synthesis of dsRNA. Under high rates of transcription, these aberrant RNA molecules would be more likely to accumulate as a result of transcriptional errors, and would therefore become increasingly likely to trigger the RNA silencing cascade. This "threshold model" accounts for both qualitative and quantitative aspects of gene expression, and posits that excessive transcription can lead to an accumulation of aberrant transcripts. These abnormal transcripts would in turn increase the likelihood of being recognized by an RDR and ultimately trigger RNA silencing.

Several lines of evidence point to dysfunctional RNA as the initial trigger of PTGS. First, mutations in an RNA splicing factor or several proteins acting in mRNA 3' end formation result in enhanced RNA silencing of a transgene (*24*, *25*). Second, it has been shown that a transgene cleaved by a miRNA (and resulting in production of a aberrant RNA) enters PTGS (*26-30*). Finally, mutations in Arabidopsis XRNs, in particular cytoplasmic XRN4, enhance PTGS, suggesting that in the absence of XRN-mediated degradation, dysfunctional RNAs may be redirected to the PTGS pathway (*31-33*). These data could be reconciled in a model where dysfunctional cellular mRNAs are diverted from translation or PTGS and degraded by the XRNs and the exosome (*34*). This model posits that if targeting of dysfunctional RNAs to the RNA decay pathway was impaired, then its ability to enter the PTGS pathway would be enhanced, and that RNA turnover and PTGS either compete or act antagonistically on their RNA substrates. Interestingly, recent evidences indicate that compromising the function of enzymes involved in NMD (UPF_1, UPF_3), decapping (DCP2, VCS) and deadenylation (PARN, CCR4) result in increased efficiency of RNA silencing of transgenes and some endogenous transcripts (*35*, *36*) and our unpublished observations.

Spatial connections between RNA decay and RNA silencing

If RNA quality control and RNA silencing are interacting, then these pathways must be spatially connected to allow an exchange of RNA substrates.

At the cellular level, numerous proteins implicated in RNA decay (DCP1, DCP2, DCP5, VCS, XRN4, UPF1) are concentrated in cytoplasmic foci called P-bodies (processing bodies) (*8*, *11*, *37*, *38*). By contrast, the exonucleases XRN2 and XRN3 and the NMD factors UPF2 and UPF3 are observed in the nucleus (*12*, *36*, *39*). Accumulation in cytoplasmic foci was reported for PARN (*5*), but the nature of the foci and whether they constitute P-bodies is unknown.

RDR6 and SGS3 accumulate in cytoplasmic siRNA bodies that are distinct from P-bodies (*40*, *41*). Upon stress-induced translational repression siRNA bodies become positive for stress-granule markers, aggregates of non-translated mRNPs, suggesting that siRNA bodies are sites where mRNAs stall during translation accumulate (*41*). Immunolocalization of RDR6 has revealed a nuclear and cytoplasmic localization (*42*). In the cytoplasm, RDR6 is located in foci reminiscent of the ones observed in tobacco leaves. In the nucleus, RDR6 is observed in the entire nucleus with the exception of the nucleolus, which is consistent with previous observations in Arabidopsis trichomes with a *35S::RDR6:GFP* transgene (*25*). Tobacco leaf infiltration and immunolocalization in Arabidopsis root cells have established DCL4 localization in the nucleus (*40*, *42*). Although distinct, P- and siRNA-bodies often are spatially associated and display concordant movement in the cytoplasm, indicating stable association between the two foci. The movement of the foci relies on the actin network (Maizel, unpublished).

Conclusion

The evidences listed here demonstrate a strong integration between RNA processing and RNA silencing pathways in plants, suggesting the following possible scenario: RNA turnover of dysfunctional RNAs serves as a first and highly specific layer of defense

against defective RNA. Indeed, when a defective transcript is recognized by this RNA degradation machinery, only this defective transcript is eliminated while the homologous normal transcripts remain unaffected (cis-acting effect). However under conditions promoting a build-up of aberrant RNAs in the cell, the capacity of the turnover pathway likely becomes saturated, resulting in the activation of the PTGS pathway. It is reasonable to assume that PTGS is more efficient than RNA turnover in degrading RNA because it involves the production of siRNAs that guide RNA cleavage and amplify silencing efficiency; however PTGS is less specific because siRNAs do not distinguish a defective transcript from a homologous normal transcript, and thus both types of transcripts are degraded (trans-acting effect). With PTGS acting in trans to degrade all homologous transcripts and RNA turnover degrading individual aberrant/labile transcripts in cis, the division of RNA substrates between these pathways is likely to have major consequences for the genome-wide regulation of gene expression.

While much is known about the RNA decay and RNA silencing pathways of plants, there is possibility of further overlap between the two pathways that remains to be uncovered. This area of investigation could provide more important discoveries into the mechanisms of small RNA-directed gene regulation in plants.

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Short bio: Alexis Maizel studied biology at the Ecole Normale Supérieure de Lyon (France) from 1995 to 1999 and earned his PhD in 2002 from the René Descartes University and Ecole Normale Supérieure in Paris (France). Maizel was awarded an EMBO and Marie Curie fellowships for a postdoctoral position in San Diego (Salk Institute, USA) and in Tübingen (Max Planck Institute for developmental Biology, Germany). His work there on the molecular evolution of flower formation was highlighted by the magazine Science as a highlight for the year 2005. In 2006 he was appointed as CNRS staff scientist at the Plant Science Institute in Gif-sur-Yvette (France). Since 2010 he is an independent group leader at the Center for Organismal Studies of the Heidelberg University.

Research interests: Arabidopsis development, root biology, RNA-mediated gene expression regulation, cell biology, microscopy.

Abstract: Controlled degradation of RNA is essential to the cell's survival. RNA decay ensures that error bearing RNAs are eliminated in a process called RNA quality control (RQC), and that protein abundance is properly regulated through RNA turnover. In parallel to this regulation, eukaryotes degrade endogenous and exogenous RNAs through post-transcriptional gene silencing (PTGS) depending on small interfering RNA (siRNA)-directed ARGONAUTE-mediated endonucleolytic RNA cleavage. Here, I review current knowledge of these pathways as they exist in plants. I highlight some overlaps that exist between the RNA silencing and RNA decay pathways, as evidenced by their shared RNA substrates and genetic requirements.

International Meeting of the German Society for Cell Biology: Physics of Cancer 2012

Claudia Tanja Mierke

For the third time, the International Symposium *Physics of Cancer* (POC-2012) took place in Leipzig from 1st to 3rd November. The *Physics of Cancer* meeting was established in 2010 in Leipzig by ***Josef Käs*** and ***Mareike Zink***. This time it was organized by ***Josef Käs***, ***Sarah Köster***, ***Harald Herrmann*** and myself, and it received strong support by the German Society for Cell Biology (DGZ).In this short time, the *Physics of Cancer* meetings have received a lot of recognition as is mirrored in the impressing list of speakers. Hence, a special focus for Physics of Cancer has been established in Leipzig, for discussion of unconventional and highly non-mainstream concepts of cancer-related research projects with internationally well-known researchers from many different disciplines. In this year, the POC-2012 meeting took place in the Biotechnological-Biomedical Center (BBZ) providing ample space to have the poster session next to the lecture hall in the great lobby hall of the BBZ.

1st November (Thursday)

Prior to meeting start, the seminar room was quickly filled with students, doctoral students, post-docs, principal investigators and professors interested in the novel view on cancer, the biophysical view. The organizers () were delighted to welcome the rector of the University of Leipzig, ***Beate Schücking***, to open the meeting and explain the importance of *Physics of Cancer* to the audience in her own words, as she was formerly working the field of oncology. The meeting then processed very informal and familiar with a clear focus on the discussion after the talks as well as in the coffee and lunch breaks. The response from the audience was great and even critical points were discussed in a very friendly atmosphere. During the whole meeting it was always possible to talk to the invited speakers and to get their suggestions or comments for ones own research projects as well as questions regarding special biophysical methods.

Figure 1: At the "Bildermuseum", Alexander Bershadsky and Jan Lammerding (by courtesy of Martin Herrmann).

In the first talk of the meeting, ***Josef Käs*** presented his recent results of cancer cells expressing Mena11a or Mena(INV) and their impact on cell invasiveness and biomechanical properties such as the softness of cancer cells measured with an optical stretcher device and an atomic force microscope. ***Gijsje Koenderink*** talked about myosin motors and why they always contract cortical actin networks and how actin crosslinkers such as fascin affect the network. ***Staffan Johansson*** reported on mechanical stretching of cells lacking the beta1 integrin subunit using silicone chambers. Additionally, he revealed the impact of reactive oxygen species to integrins and hence cell adhesion as analyzed by total internal reflection fluorescence microscopy.

After the coffee break, ***Florian Rehfeldt*** showed how the matrix elasticity dictates the cytoskeletal arrangement by tuning the mechanical and biochemical properties of hyaluronic acid hydrogels. ***Martin Herrmann*** presented us his immunological view on cancer by introducing the major effect of dead cells on tumor growth, as occurring after radiation. ***Thomas Magin*** talked about the importance of keratin filaments for desmosome formati-

on and reorganization and that keratins act as barrier against the loss of an epithelial cell character. ***Paul Janmey*** brought as back to the physical properties such as cellular stiffness and how cells sense and respond to internal and external stiffness by using the polydimethylsiloxane pillar method with tunable flexibility. He demonstrated that cells can displace fluorescent dots by applying a certain amount of force on adhesive substrates of known mechanical properties. After the three short contributed talks by ***Jörg Schnauss***, ***Marcin Moch*** and ***Kristin Seltmann***, which had been selected from the submitted abstracts, dinner and the poster session started in the lobby in front of the big seminar room (Figure 2).

2nd November (Friday)

Erik Sahai started the session talking about his results on 2D and 3D adhesion and motility systems as well as cell contractility by using two-photon confocal microscopy. In particular, he mentioned the role of blebbs in driving cell migration forward. ***Joachim Spatz*** took over and presented the effect of stress and the actin-regulatory protein zyxin on the maturation of focal adhesions using adhesive substrate dots of certain sizes in 2D and hydrogels with a certain pore-size in 3D. In addition, he showed that the integrin-type alpha5 beta1 or alphav beta3 impacts the transmission and generation of contractile forces and thus motility. Due to the hurricane Sandy in the USA, Daniel Fletcher was not able to attend the meeting. Therefore, ***Harald Herrmann*** jumped in to give a presentation on nuclear architecture focusing on how the various lamin variants may impact cell mechanics.

After the coffee break, I gave my presentation about the role of mechanical properties such as cellular stiffness and contractile forces on the alpha5 beta1 integrin facilitated invasion of cancer cells in the presence of absence of phagocytized beads. In the discussion with the audience, I received really good comments for an experiment helping to understand the effect of the beads on cell invasion by blocking matrix-degrading enzymes. Then, ***Alexander Bershadsky*** talked about rigid and compliant substrates and their impact on the formation of stress fibers and on gene expression of phosphotyrosine, kinases which might serve as mechano-sensors. ***David Boettiger*** spoke about adhesion receptors such as alpha5 beta1 integrins and how they are modified by their cellular context such as catch bonds. In particular he presented the spinning disc device for measuring adhesion forces by the rupture of the whole adherent cell. After the two short contributed talks by ***Hans-Günther Döbereiner*** and ***Jörn Hartung***, lunch and further discussions with all participants took place in the lobby of the BBZ in a familiar atmosphere.

In the third session, ***Jan Lammerding*** talked about the impact of the mechanical properties of the nucleus such as the deformability on cell motility. In detail, he mentioned that the stiffness of the nucleus is mainly determined by lamin A and appears to be altered during cancer progression. ***Lisa Manning*** presented how geometry and cell shape affects active matter models and explained crawling, surface tension and jamming of cells over one another. After the four short contributed talks by ***Norbert Mücke***, ***Manuela Kuchar***, ***Ines Martin*** and ***Lothar Lilge***, René Frank gave a presentation replacing ***Evamarie Hey-Hawkins***, who was ill. He spoke about how to treat malignant cancers by an alternative method, the boron-neutron capture therapy, which seems to be more highly selective for cancer cells. In the last talk of the session, ***Larry Nagahara*** gave a summary of the cancer research performed at the twelve Physical Science-Oncology Centers in the USA. In particular, he pointed out the importance of interdisciplinary collaborations, including the physical community, to fight cancer and highlighted the potential great impact on future cancer research. After his talk, the invited speakers visited the Museum of Modern Art in Leipzig (Figure 1) and on their way to the Auerbach`s Keller they enjoyed the beautiful old historic town of Leipzig (Figure 2).

3rd November (Saturday)

Philippe Marcq opened the session with a report about the contractility of actin stress fibers by pulling on a fiber. ***Francoise Brochard-***

Figure 2: Beautiful Leipzig at night (by courtesy of Martin Herrmann).

Figure 3: Dennis Discher lecturing on cellular mechanics (by courtesy of Martin Herrmann).

Wyart talked about the mechano-sensitivity of multicellular aggregates using a novel pipette aspiration technique and compared the aggregates of cells with foams. ***Valerie Weaver*** showed the bulkiness of the glycocalyx consisting of hyaluronic acid and mucins has an impact on integrin assembly, integrin-ligand interaction and the recruitment of adhesion plaque proteins. She finally suggested that the altered glycocalyx is a novel player in perturbed mechanical signaling and cancer progression. The next talk was given by ***Roderick Lim*** who mentioned and investigated the discrepancy of tumors, which stiffen during cancer progression and the observed softening of highly invasive cancer cells compared to non-invasive cancer cells analyzed on single cell level. He reported that biopsies from tumors can be force mapped within hours after collection by using atomic force microscopy. In particular, he showed that there are stiffness differences in the core of a tumor compared to the periphery, which is much stiffer.

After the short, contributed talk by ***Louise Jawerth*** and the coffee break, ***Martin Falcke*** gave a talk about detachment forces of cells and showed how cells apply pushing forces towards a bead. ***Margaret Gardel*** presented how the dynamic cytoskeletal reorganization underlies cell migration. In particular, she showed that high tension evoked by retrograde actin flow, but not necessarily by stress fibers, is important for the maturation of focal adhesions and hence the composition as well as the size of focal adhesions. The next talk was given by ***Julie Plastino*** about the impact of membrane tension on cell motility. In particular, a decrease in membrane tension reduced the formation of lamellopodia and hence decreased the motility of cells. This presentation was followed by ***Avinash Kumbhar*** who reported efficient gene transfer approaches into targeted cells by using Ru(II) polypyridyl complexes as rigid structures carrying DNA, which were easily phagocytized by (cancer) cells. The meeting was closed by a talk presented by ***Dennis Discher*** (Figure 3), who explained that certain tumor-types are stiffer by using tandem mass spectroscopy and correlated the tissue microelasticity with the content of lamin A/C (lamin B was constant). Finally, he concluded that tissue microstiffness affects lamin A and that lamin A regulates 3D migration sensitivity, when a nucleus is pulled through a barrier of extracellular matrix.

In summary, for me and maybe for all the other 111 participants of the *Physics of Cancer* meeting, it was the perfect composition of physical, medical, biochemical, chemical and cell biological talks and discussion breaks. As we were indeed impressed by the excellent response, we have just started to plan the next *Physics of Cancer* 2013 Meeting in Leipzig. We truly hope that the readers of this meeting report have been inspired and will present their data on the coming meeting.

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The meeting was supported by the German Researchh Foundation, (DFG, MI1211/7-1) and by the DGZ. Moreover, it was sponsored by BuildMoNa, Top level research areas: Multifunctional materials and processes from molecules to nanodevices and Molecular and cellular communication: biotechnology, bioinformatics and biomedicine in therapy and diagnosis, JPK instruments and the New Journal of Physics. Last but not least, the organizers would like to specially thank the Leipzig staff who tremendously helped with the organization. Without them the meeting would not have been possible.

Figure 4: In Auerbachs Keller, Josef Käs comments on the "Fassritt" as taking place in Goethe's "Faust" (by courtesy of Jan Lammerding).

Meeting report: Molecular concepts in epithelial differentiation, pathogenesis and repair

Thomas Magin

Understanding complex biological problems and translating them into applications requires intensive crosstalk between basic science disciplines including cell biology, biochemistry, genetics, biophysics and immunology with medicine. To meet this challenge and to foster collaborations among colleagues who represent this diversity, Profs. Thomas Magin (Leipzig) and Mechthild Hatzfeld (Halle), together with the German Society of Cell Biology, organized the first international meeting on „Molecular concepts in epithelial differentiation, pathogenesis and repair", which took place from Nov 7-10, 2012, in Leipzig. Despite being the first of its kind, the meeting, attracted 150 participants and 35 prominent speakers from countries across Europe, Australia, Japan and USA who enjoyed intensive discussions, great science and a very open, kind atmosphere.

Pierre Coulombe and Allan Balmain

Thomas Magin

Epithelia, in particular the epidermis, are uniquely suited to address fundamental questions in molecular biology and medicine, as genotype-phenotype correlations are manifest. This is exemplified by a large number of single gene and multifactorial disorders, the basis of which was discovered first in the epidermis. Many of these disorders relate to genetic defects in genes encoding cell adhesion and cytoskeletal proteins, growth factors, receptors and barrier proteins, but also to defects in the immune system, causing systemic disorders initiated in epithelia. P. Dotto (Lausanne and Boston) opened the meeting by highlighting the role of notch signalling in the crosstalk between dermal and epidermal compartments. He showed that defects in dermal Notch signalling contribute to "field cancerization", reporting that alterations in dermal Notch activity impacts on tumor formation in keratinocytes. S. Werner (Zürich) highlighted the importance of antioxidant defense mechanisms mediated by Nrf transcription factors for epidermal homeostasis and pointed out that expressing inappropriate amounts had severe consequences. C. Brakebusch reported on the role of Rho GTPases in regulating skin inflammation and cytoskeletal organization. The tight coordination of chromosomal organization, gene transcription and skin differentiation identified an important topic (V. Botchkarev (Bradford and Boston). Exciting insights into the role of Ca2+ -sensing during wound healing, a process requiring transient changes in adhesion, migration and cell migration, were reported by P. Martin (Bradford). A

number of short talks provided insights into cytoskeletal/adhesion crosstalk and membrane domains (K. grikscheit, Marburg; N. Kurle, Giessen; H. Paul Grikscheit, Frankfurt; S. Wickström (Köln). An emerging topic spearheaded by several colleagues related to biophysics and cell mechanics and their impact on cell fate, force sensing and tumor biology. There is no doubt that cytoskeletal and adhesion proteins sense force and not only react to it but affect cell behaviour including malignant transformation and metastasis (J. Käs, Leipzig; J. Spatz, Stuttgart; C. Grashof (Martinsried). Several colleagues illustrated new findings on the keratin cytoskeleton, demonstrating its dynamic behaviour, its involvement in the regulation of inflammatory processes and epithelial barrier maintenance and its importance for the cell adhesion and spatial control of Rho activity (R. Leube, Aachen; P. Coulombe, Baltimore; T. Magin, Leipzig; R. Keil, Halle; F. Loschke, Leipzig). The skin barrier depends on the complex interplay between protein-bound lipids, tight junctions and epidermal Langerhans cells. Barrier disturbance, misregulation of proteases, and NF-κB signalling can cause local and systemic inflammation. Contributions by M. Amagai (Tokio), M. Pasparakis (Köln) and S. Rose-John (Kiel) supported the emerging primary role of keratinocytes in inflammatory conditions. J. Simon (Leipzig) shed light on the potential of matrix engineering for tissue repair. The crosstalk sensed by integrin adapter proteins like kindlins and cadherins to the actin cytoskeleton, as well as the importance of receptor recycling were illustrated by R. Fässler (Martinsried) and A. Yap (Brisbane). A. Ridley (London) provided compelling evidence for Rho GTPases as targets to suppress tumor cell invasion and S. Hüttelmaier (Halle) reported on feedback loops between RNA-binding proteins, miRNas for EMT/MET processes. M. Inagaki (Nagoya) reported on a tour-de force to elucidate vimentin's multiple Ser phosphorylation sites. Knock-in mice unable to phosphorylate vimentin develop tissue-restricted defects resulting from impaired cell division. S. Iden (Köln) reported tumor-suppressive or –promoting functions for Par-3 depending on the tissue context. The multiple roles and interactions of IGF receptors, adherens junctions and desmosomal proteins in the control of epidermal growth and differentiation became apparent in talks by K. Green (Chicago), M. Hatzfeld (Halle) and C. Niessen (Köln). S. Tsukita (Osaka) reviewed the ever-growing family of claudins and their specific involvement in tissue-specific barriers and disorders and V. Braga (London) illustrated how the regulation of a complex network between cadherins and actin by Rho GTPases affects cell adhesion.

Kathy Green

Sabine Werner and Dennis Roop

How the knowledge of stem cell biology fostered the successful transition into the clinic was demonstrated by M. de Luca (Modena) who not only reported on a gene therapy trial with long-lasting success but also on the use of autologous keratinocytes for the therapy of corneal disorders. D. Garrod (Manchester) shared recent insights on PKC isoforms as potential targets to improve skin wound healing. D. Roop (Denver) illustrated the long path for iPS-based therapies of genetic disorders and shared a wealth of information supporting the role of Nrf transcription factors in skin barrier formation. A. Hovnanian (Paris) reviewed the role of proteases and their inhibitors in barrier function and illustrated their role as disease proteins in inflammatory disorders. A. Balmain (San Francisco) concluded a stimulating session by demonstrating the power of bioinformatic analysis in combination with large scale transcriptome profiling to elucidate the genetic basis of cancer susceptibility in various inbred strains of mice. The resulting gene networks hold great promises for understanding common regulatory mechanisms and may offer the basis for rational therapies.

Participants were thrilled not only by the excellent science but also by social events including a site visit of the Leipzig BMW factory and of St. Nicolai church with its famous organ, home to J. S. Bach. The meeting will take place again in November 2014 in a similar format. We are grateful for the support provided by the DFG, FCI, EU (COST), DGZ, TRM and BBZ.

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We thank Daniela Weber, TRM Leipzig, for providing the photographs.

Communication

Keiner denkt bei dem Wort genau und gerade das, was der andere denkt, und die noch so kleine Verschiedenheit zittert, wie ein Kreis im Wasser, durch die ganze Sprache fort. Alles Verstehen ist daher immer zugleich ein Nicht-Verstehen, alle Übereinstimmung in Gedanken und Gefühlen zugleich ein Auseinandergehen.

*Wilhelm von Humboldt**

As brought up in previous issues, scientific communication is changing tremendously fast these days. Regular research articles get shorter and the *Supplements* grow, sometimes to the extent of two or three conventional regular articles. Who ever reads this mass of data carefully? And, some of the journals do not even bother to provide print versions any more.

On a recent board meeting, the discussion came up – again – if we couldn't save money and reach more people by providing the newsletter only in the form of a portable document file (PDF). Either sent to the members by mail (however, we still do not have the email addresses of all members), or - as we do now already – provide the articles, or full issues, for download from our website.

The first newsletter that I received was that of spring 1980. It was loose pages, "hektographiert" - dict.cc: Sorry, no translations found (it is a kind of cheap way to copy). But they had, in addition to highlighting the next meeting, positions advertised. One of them redirected me to accept a Post-Doc position in Vienna instead of going - as intended - to the United States.

Ten years back, we started a more serious newsletter with information about the scientific activities of members instead of just reporting about prize winners of the DGZ. By now, you can find all of the newsletters from 2003 on online. This means, there are 33 issues available on the net providing far more than a 100 articles. The absolute number is of course less important, it is the content and the scope. Here you will find contributions from most of the scientists working in Germany in cell biology and related fields. Moreover, most of the authors found a very pleasant format to present both the latest findings in their field "in a nutshell" and to introduce the reader into what their specific expertise is. We hope that these articles helped and will help to connect scientist of our society. Moreover and may be even more important, the various groups have made themselves visible for students from all over Germany, and we wonder how many of them got attracted by these "research profiles" or "research news" to a new working place.

And it should also be mentioned that the design improved tremendously over the years, mostly because of the commitment of Heike Fischer, the art designer of our printing company. As a result, it is a joy to read in these issues, and I am sure most of our members keep them for some time. Surely, iPad and smartphones can be "App-erized" with all kinds of useful links, but who wants to read *Cell News*, the taz or *FAZ* on an iPad? We hear that *Twitter* and *Facebook* are tools in certain "spring movements", but how useful are these services for the scientific community? We will see. I heard the number of emails sent is going down, as the young people communicate differently, i.e. through social networks. Gladly, we experience that the young folks still come to attend seminars and meetings. Astonishingly, it is the principal investigators that are frequently missing in these days, even when top scientists are invited to give special lectures or when top-notch meetings are organized to bring the community together. Obviously, they are too busy for direct communication so that they do not attend, lay back and just listen and think. At least, as long as an attractive printed version of a journal, especially one that is for somehow "summing up", is present and waits on your table until there is time to relax and read, there is hope that scientific communication is more than a tip on a multi-touch display.

Harald Herrmann

A galery of representative cover images from the last 8 years.

* *Über die Verschiedenheit des menschlichen Sprachbaues und ihren Einfluß auf die geistige Entwicklung des Menschengeschlechts, Berlin 1836; zitiert nach Byung-Chul Han: Transparenzgesellschaft, Matthes & Seitz Berlin 2012.*

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