INSTITUTE OF MOLECULAR BIOTECHNOLOGY

OF THE AUSTRIAN ACADEMY OF SCIENCES

VIENNA BIOCENTER

2006

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IMBA
Institute of Molecular Biotechnology
of the Austrian Academy of Sciences

CONTENTS

JOSEF PENNINGER
Managing Director/Science

In Alice's adventures in wonderland, Alice asks the Cheshire Cat: "Would you tell me, please, which way I ought to go from here?" "That depends a good deal on where you want to get to," said the Cat. "I don't much care where … as long as I get somewhere", added Alice as an explanation. "Oh, you're sure to do that," said the Cat, "if you walk long enough." We have had a landmark year. We busied ourselves with moving and populating our new institute, the new Life Sciences Center Vienna of the Austrian Academy of Sciences.

Let me thank everybody who has helped ensure that the new institute exists: All members of the Austrian Academy of Sciences who, even in rough waves, believed in IMBA; Andreas Barner and his colleagues at Boehringer Ingelheim, without whose support this could not have been done; all our colleagues at the Campus Vienna Biocenter who took us in, giving up their own lab space and helped us along the way; the architectural team lead by Boris Podrecca and all the workers and companies who designed and built our new institute; the City of Vienna and the Austrian government for funding this new endeavor; and the Austrian Chancellor Wolfgang Schuessel who has always supported us and who graced us with his visit at the official opening of the new Life Sciences Center Vienna. We had a great opening party. Most importantly, I have to thank and acknowledge all members of IMBA and our close partners, the IMP and Gregor Mendel Institute, who put untold hours of work and their life's energy into the creation of something new.

What delights me most of all is that we not only have a new building but people truly use the new facilities. We have already hosted multiple international meetings with great success which also gave us an opportunity to present IMBA to the research community. Together with Dialog Gentechnik and in collaboration with the DNA learning center at Cold Spring Harbor, we initiated the Vienna Open Lab for kids - and everybody else - interested in molecular biology. The Vienna Open Lab is located in our new building, is professionally run, and has taken flight within a few months. Many shared services such as proteomics, electron microscopy, histology, the media kitchen, sequencing, the Drosophila laboratories, and in the near future the animal house have also taken root in our new building. The whole campus is bound to benefit from it. Our students and postdocs moved into great new laboratory space where working is indeed fun – the table soccer and ping pong tables might of course also contribute. In addition, I am pleased to announce that two young faculty members have joined IMBA in 2006: Leonie Ringrose who works on Polycomb gene regulation, and Kazufumi Mochizuki who investigates genome stability and RNAi pathways in Tetrahymena.

What pleases me in particular is that the science of our faculty members has started to shine in spectacular ways. It is one thing to build a nice home, but it is an entirely different accomplishment to bring alive the concrete and bricks of a building. Excellence in research is based on great and unique minds. The excellence of an institution is to provide these scientists with an academic and financial environment where they can succeed. This is the vision and goal of IMBA.

In his keynote address at our official opening ceremony, the former President of the Austrian Academy of Sciences, Werner Welzig, who initiated IMBA, talked about the fairytale Hänsel and Gretel as a metaphor for our first years. In his spirit, I also want to ask the fairies to grant IMBA, its partner institutes, and all their current and future members three wishes: to give us enough funding to continue to make a splash in science; to permeate the architectural spirit of the new building into a spirit of cooperation, mutual respect, and community - it is not only the results that count but most importantly the way of getting there. And finally, that all current and future members enjoy and succeed doing science so that IMBA can happily live on ever after.

There is still a long way ahead of us. But we have achieved major accomplishments within a very short time. IMBA has developed better than I ever hoped for in my restless dreams. Many people deserve the credit and I am indeed proud to work with such exceptional people and that I have been given the opportunity to head this institution.

MICHAEL KREBS
Director/Finance and Administration

The completion of our new laboratory and office building has definitely been the most prominent milestone in the still young history of our institute. After years of restrictions and improvisation, all IMBA employees can now benefit from a state-of-the-art laboratory and office infrastructure built within a very communicative and inspiring environment.

The new infrastructure has led to significant improvements for all researchers and most of our scientific and administrative services at the IMP-IMBA Research Center. Space has more than doubled compared to last year, which means an enormous progress in the working conditions for all our staff. Moreover, we have been able to consolidate all research and service activities in mass spectrometry for IMBA, IMP and the Max F. Perutz Laboratories at the IMBA building after a long period of interim solutions. Last but not least, the expansion of the cafeteria with its larger variety of international dishes has created an attractive lunch and meeting place for all members of the Campus Vienna Biocenter.

2006 has been a very exciting year of transition and improvement but also a year of consolidation. The slowdown in institutional growth has been an important strategic move to allow the IMBA organisation to digest the dynamic growth of previous years and to focus resources and management attention on the set up of our new infrastructure. In the medium-term, the IMBA management remains fully committed to seek for and pursue opportunities to further expand our research activities.

With an annual budget of almost € 12 million the number of staff has reached a total of 126 at the end of November, an 8% increase compared with last year. The 2006 budget growth has been mostly subject to our increasing efforts in commercializing our scientific know-how through collaboration with industry partners such as Boehringer Ingelheim and the US biotech company Genentech. We are very proud that such renowned companies have decided to join forces with us in the search for new treatments in human medicine. The new Center for Molecular and Cellular Nanostructure Vienna (CMCN) and the Vienna Drosophila RNAi Center (VDRC), both joint initiatives of IMBA and our partner institute, the Research Institute of Molecular Pathology (IMP), have started their operations recently. We thank the City of Vienna for their generous financial support of the CMCN and wish the heads of both Centers, Thomas Marlovits and Krystyna Keleman, all the best for the future of these very promising and exciting new research ventures.

I would like to thank all researchers for their cooperation and patience and all employees in scientific services and administration for their high service commitment during this difficult and challenging transition period. Special thanks go to Alex Chlup and his team, Werner Kubina and the IT service group and all others involved in setting up and running our new facilities for their tremendous efforts and persistence in turning this place into a fantastic new home for researchers at IMBA and all our partner institutes. We also thank the Austrian government, the Austrian Academy of Sciences, the City of Vienna and all national and international project sponsors for their substantial financial support to position IMBA as a Center of Excellence for molecular biology research in Europe.

IMBA and Its Surroundings

The Institute of Molecular Biotechnology (IMBA) is located in Vienna, the capital of Austria. IMBA was founded in 1999 by the Austrian Academy of Sciences in cooperation with Boehringer Ingelheim, an international pharmaceutical company with its headquarters in Germany. IMBA operates in close collaboration with the Research Institute of Molecular Pathology (IMP), Boehringer's basic research center in Vienna. The two institutes are located next to each other and share large parts of their infrastructure. The collaboration is known under the name of "IMP-IMBA Research Center".

The Campus Vienna Biocenter

IMBA is situated at the "Campus Vienna Biocenter" (VBC), a rapidly growing biotechnology hub located halfway between Vienna's international airport and the city center. Apart from IMBA and its partner institute IMP, the VBC is also home to the Max F. Perutz Laboratories (University and Medical University of Vienna), the Gregor Mendel Institute (GMI) of the Austrian Academy of Sciences, a University of Applied Sciences, several biotech companies, a PR agency, a non-profit scientific society and the Vienna Open Lab.

More than 1000 people from 40 different nations currently work at the Campus VBC. Campus members enjoy a scientifically and socially stimulating environment and take advantage of shared facilities such as the Max Perutz Library. A number of events, including seminars and lectures, are open to all.

Vienna – a City of many Facets

For those whose interests stretch beyond science, Vienna also has a lot to offer. Home to about 1.6 million people, the city is the political and cultural center of the country and its gateway to the east. Once the heart of the largest European empire, Vienna draws on a rich cultural heritage which is reflected in splendid buildings and unique art collections. But Vienna is a city of many facets. Modern architecture, splendid galleries and stylish shops are as much a part of everyday life as the famous concert halls, the big museums and the nostalgic little streets. As any European capital, Vienna also offers a vibrant nightlife, with a rich selection of restaurants, cozy bars, and trendy clubs.

Apart from Vienna's focus on art and culture, it also has a long-standing tradition in science. Founded in 1365, the University of Vienna is the oldest university in the German-speaking world and the largest in Austria. With a student population of more than 100,000, Vienna offers not only the academic but also the cultural and social infrastructure that comes with student life.

And if your brain needs to be refreshed, there is always the call of nature. A day away from the lab may take you skiing to the nearby Alps, windsurfing at Lake Neusiedl or watching rare birds in the Seewinkel. Even within the borders of Vienna you can enjoy a hike through dense woods, go canoeing in a National Park, climb impressive limestone cliffs or stroll through rolling vineyards. In fact, more than 50% of Vienna's surface area is covered by vegetation.




Your Career at IMBA

IMBA offers exciting positions at all levels of your research training and career. If you consider joining IMBA, you will find first class research and state-of-the-art scientific services. As a member of one of the scientific groups, you will be part of a young, international team, using English as a working language. The atmosphere at IMBA is stimulating and focused, and a certain pioneering spirit can be felt among its staff. The brand-new state-of-the-art laboratory and office building was officially opened in May and is now the inspiring home to more than 120 scientists and administrative staff.

Graduate students join the IMBA through the Vienna Biocenter International PhD Program, run jointly with the Max F. Perutz Laboratories, the Institute of Molecular Pathology (IMP) and the Gregor Mendel Institute (GMI). A call for applications goes out twice a year, with contracts typically lasting 3-4 years.

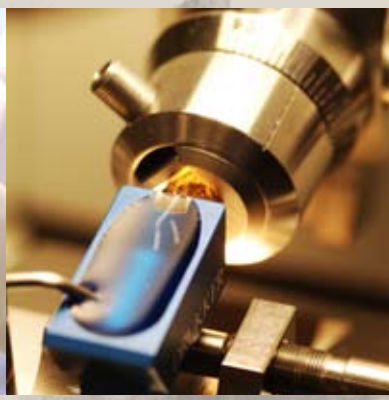
IMBA's research groups are well funded to support a number of pre- and postdoctoral positions. A substantial travel budget allows scientists to take part in meetings, conferences and courses. IMBA and the IMP organize a couple of conferences, workshops and symposia every year. An intensive seminar program brings internationally renowned scientists to the institute on a regular basis.

If you come to work at IMBA, you'll obviously come in the first place for the science. We do, however, appreciate your private needs and try to make relocation as smooth as possible. For newcomers, there are several in-house apartments to bridge the time until they have found a place of their own. Our administrative staff is helpful in finding housing, and our personnel department will take care of your legal requirements including visas, registration, health insurance and family matters. For parents with young children, two day-care facilities are available in the immediate neighborhood: a municipal kindergarten offers admission from baby-age, and a privately run nursery is also just around the corner. For school-age children, Vienna offers a large range of different types of schooling, from public to private, German- or foreign language-speaking, traditional or with more experimental concepts.

Many of our new employees are accompanied by spouses who are themselves looking for a qualified position in line with their training. IMBA is certainly aware of this fact and can, in some cases, help with securing a job. We also support your efforts to learn German and sponsor language courses run by one of Vienna's best language schools as well as team sports.

More information about career opportunities at IMBA is available at:
www.imba.oeaw.ac.at



JÜRGEN KNOBLICH

Asymmetric Cell Division and Proliferation Control in *Drosophila* Neural Stem Cells

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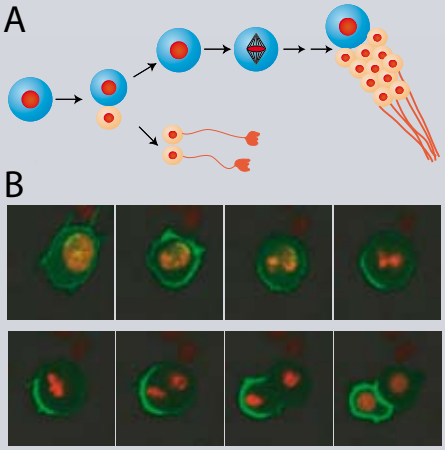

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[7] until August, [8] until December, [9] since February,
[10] since April, [11] since July, [12] since September

Stem cells are capable of generating two different kinds of progeny: On one hand, they give rise to differentiating cells which exit the cell cycle and replace cells in the target tissue. On the other hand, they undergo self-renewal and generate other stem cells which continue to proliferate. How one cell can generate two daughter cells of such dramatically different properties and how defects in this asymmetry can contribute to tumor formation, are the questions we are trying to resolve.

The model system we use is the Drosophila brain. During development, thousands of neurons present in the adult fly brain arise from stem cell-like precursors called neuroblasts. Neuroblasts undergo repeated rounds of asymmetric cell division during which they form a large and a smaller daughter cell (Figure 1A). While the small daughter cell divides only once more into two differentiating neurons, the large cell continues to proliferate in a stem cell-like manner. For this, it has to grow continuously to make up for the "loss" of cytoplasm during mitosis. Why are the two daughter cells so different in their cell growth and proliferation properties ?

Stem Cell Tumors in *Drosophila*

The answer is that neuroblasts are capable of segregating key regulatory proteins into only one of the two daughter cells during mitosis (Figure 1B). One of them is the tumor suppressor Brat (Brain tumor). We found Brat by mass-spectoscopy in a search for proteins regulating fly brain development. Brat is a member of a conserved protein family that is characterized by a similar domain structure (Figure 2A). In neuroblasts, Brat is uniformly distributed in the cytoplasm during interphase. During mitosis, however, it concentrates at the plasma membrane and localizes into a crescent overlying one of the two spindle poles, so that it is inherited by only one of the two daughter cells. When Brat is missing, cell growth and proliferation are no longer restricted to only one cell. Now, both cells proliferate leading to an exponential, tumor-like expansion of the neuroblast pool. As a consequence, brains grow to an enormous size (Figure 2B). Ultimately, the developing brain tumors fill out the whole body cavity and kill the fly. Very similar tumors are seen in mutants that affect the asymmetric segregation of Brat, presumably because in these mutants Brat concentration is too low in both daughter cells to inhibit proliferation. How Brat inhibits proliferation and growth and whether its function is conserved in vertebrates, are questions we are currently trying to answer.

Mechanisms of Asymmetric Cell Division

How does Brat get into one of the two daughter cells ? Brat localization requires a conserved protein kinase called aPKC. Before mitosis, aPKC localizes to the

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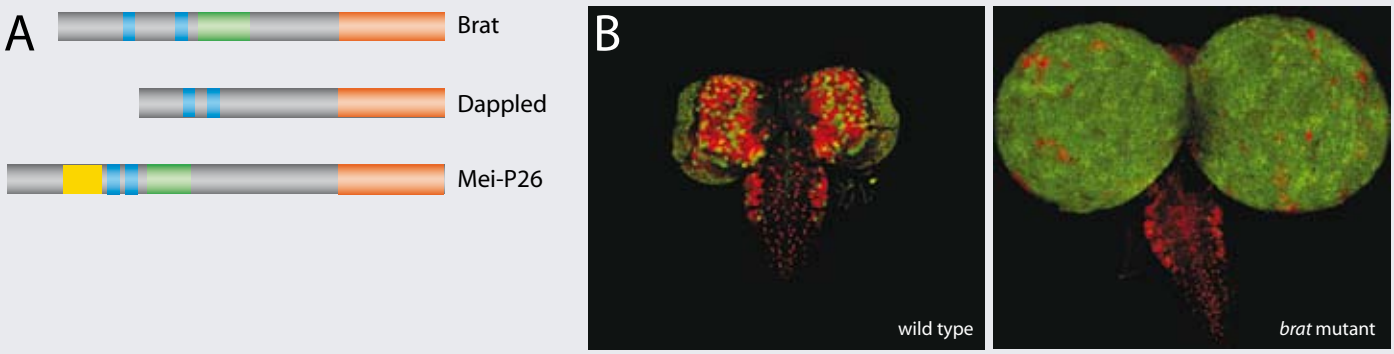

Figure 1: *How cells divide asymmetrically. A. Drosophila neuroblasts divide asymmetrically in a stem cell-like fashion. B. Live imaging of asymmetric cell division. Stills from a movie (available on our website) of asymmetric cell division in the Drosophila peripheral nervous system. Histone-RFP (red, to visualize chromatin) and Pon-GFP (green, to visualize asymmetric protein segregation) are recorded.*

Figure 2: *Stem cell derived tumor formation in Drosophila. A. The Brat protein family. NHL domains are red, Coiled coil motifs green, B-boxes (Zn-finger like motifs) blue and Ring fingers yellow. B. Larval brain from a wild type (top) and brat mutant animal. Neuroblasts are green, differentiating neurons are red. brat brains show a dramatic overproliferation of neuroblasts.*

Figure 3: *Spindle orientation in Drosophila neuroblasts. During interphase, an area of the cell cortex (red) forms a microtubule attachment site. In this area, the Mud protein associates with astral microtubules, which pull one of the two centrosomes to rotate the mitotic spindle. Correct spindle orientation ensures asymmetric segregation of Brat in a wild type (left) but not mud mutant (right) neuroblast.*

side opposite to where Brat will accumulate. During mitosis, it phosphorylates a cytoskeletal protein called Lgl (Lethal (2) giant larvae). Lgl is present all around the cell cortex and is necessary for Brat to localize to the plasma membrane. Phosphorylation by aPKC, however, inactivates Lgl on one side of the cell and restricts its activity to the opposite side. This is why Brat becomes asymmetrically localized during mitosis. Currently, we do not know how Lgl acts in recruiting proteins to the plasma membrane. We have carried out genome-wide RNAi screens for genes involved in asymmetric cell division and the players we expect to identify might hold the answer to this important question.

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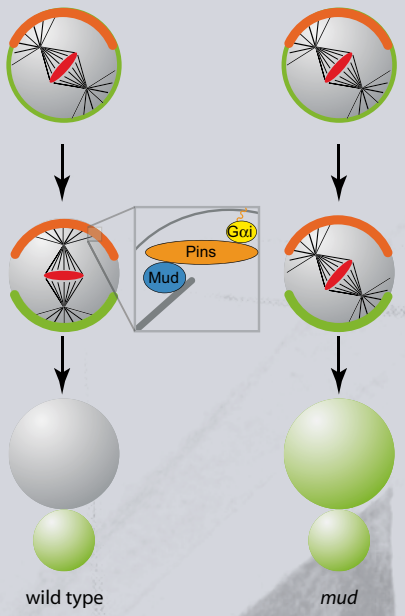

Spindle Orientation

The asymmetric localization of Brat has to be coordinated with the orientation of the mitotic spindle so that Brat will segregate into only one of the two daughter cells. Mitotic spindles are oriented by astral microtubules emanating from the centrosome to the cell cortex (Figure 3). It is thought that a microtubule attachment site at the cortex is critical for pulling one of the two centrosomes to orient the mitotic spindle. In Drosophila neuroblasts, spindle orientation requires aPKC, but Lgl is not a critical factor. Instead, aPKC (and its binding partners Par-6 and Par-3) recruits two adaptor proteins called Inscuteable and Pins and the heterotrimeric G-protein a-subunit Gai. These proteins are required for spindle orientation but do not bind microtubules so that the nature of the cortical site is unknown. We have recently found that the coiled-coil protein Mud is an additional member of the Inscuteable/Pins/Gai complex. Mud colocalizes with Pins and Gai and is required for the correct orientation of the mitotic spindle. Mud is the Drosophila homolog of NuMA, a well characterized microtubule binding protein in vertebrates. Indeed, Mud can bind microtubules and enhance their stability and therefore seems to be the site for cortical microtubule attachment that orients the mitotic spindle in neuroblasts.

THOMAS MARLOVITS

Design and Function of Molecular Machines

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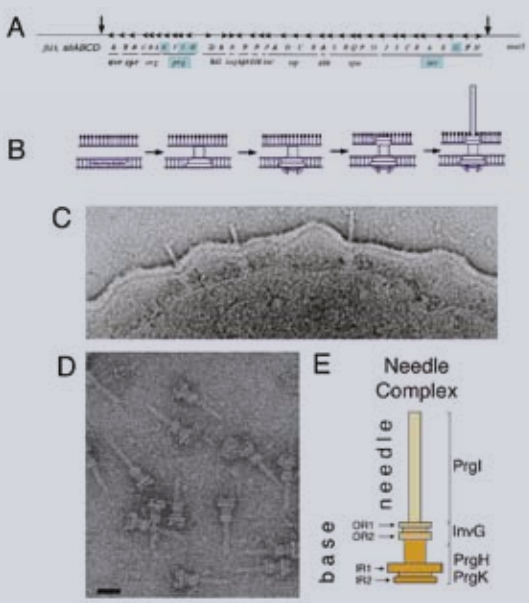

What keeps cells and organisms alive are specific functions performed by highly organized macromolecular assemblies. Our research is motivated to understand the fundamental design and function of such macromolecular complexes. In particular, we are interested in systems that are involved in protein transport and signaling. At the center of our research, our laboratory takes an integrated approach and combines tools for structural and molecular biology, biochemistry and biophysics. In particular, we use three-dimensional electron cryomicroscopy and image processing as a platform to link high-resolution structural biology with cell biology in order to obtain for the first time a mechanistic view of macromolecular machines from an atomic to cellular level.

Host-Pathogen-Interaction

Gram negative pathogens, like *Salmonella, Yersinia,* or *Shigella,* use the type III secretion system (TTSS) to initiate infection in eukaryotic cells. The TTSS is a complex macromolecular system that serves as a structural platform to make physical contact between cells and mediates the unidirectional transport of bacterial toxins (effector proteins) into eukaryotic cells. These systems are essential for a successful infection resulting in well-known clinical symptoms ranging from mild headaches and diarrhea to even life-threatening diseases, such as typhoid fever or bubonic plaque. Comprised of more than twenty proteins, TTSSs assemble into large "molecular nanomachines" composed of a set of soluble as well as membrane proteins. All of the structural components as well as other proteins involved in assembly and function are encoded on specific pathogenicity islands (Fig 1A). Recently, genetic and biochemical analysis revealed that assembly of the TTSS is a step-wise process during which stable intermediate substructures are formed (Figure 1B).

The Molecular Design

The most prominent substructure of the TTSS is known as the "needle complex", a cylindrical, needle-shaped and membrane-embedded organelle protruding from the bacterial envelope (Figure 1CD). The needle complex is believed to serve as a conduit for the safe transport of virulence factors from the bacterial cytoplasm through a number of natural barriers into eukaryotic cells. In *Salmonella typhimurium,* which serves as our model for bacterial delivery systems**,** this complex is formed by multiple copies of only five proteins: PrgH, PrgK, and InvG make up the membrane associated base-structure, PrgJ, the inner rod, and PrgI, the needle filament extending into the extracellular environment (Figure 1E and 2D). In order to investigate the molecular mechanism of type III secretion, we first set out to determine structural components of the TTSS. We were challenged by the mega-dalton size of the complex, its natural composition (membrane and soluble proteins), and the limited availability. Nevertheless, we were able to

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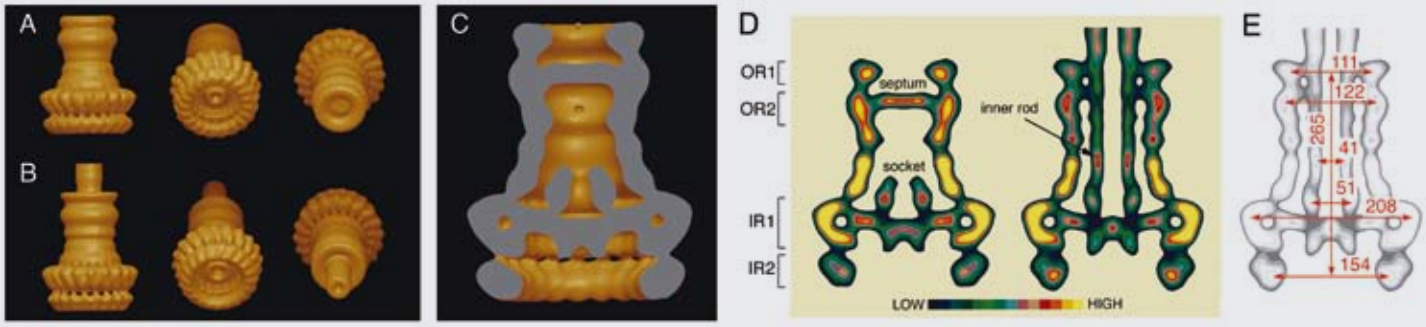

Figure 1: *The type III secretion system (A) The type III secretion system is located on the bacterial chromosome but encoded on a specific pathogenicity island. Structural proteins of the needle complex are indicated in blue color. (B) Formation of stable intermediate substructures during assembly. (C) Electron micrograph of osmotically shocked S. typhimurium showing the needle complex embedded in the bacterial envelope and released after detergent treatment (D) bar: 100 nm. (E) Schematic representation of the Salmonella needle complex and its components. PrgH, PrgK, and InvG make up the membrane embedded base structure, whereas PrgI forms the helical filament protruding into the extracellular environment. The inner rod (see Figure 2D) anchors the filament into the base.*

Figure 2: *The structure of the base and the needle complex Surface renderings of the base (A) and the needle complex (B) show that their overall shape is quite similar. However, tilted views indicate that during the assembly, individual domains must undergo large structural rearrangements. (C) The inside of the base reveals an internal structure (socket), which serves as a docking site for the inner rod. (D) Contoured, longitudinal sections show the overall protein density distribution present in the base and the needle complex. (E) Key dimensions are given in Angstroms.*

purify sufficient amounts of the entire 'needle complex' and its precursor, the 'base', by a combination of detergent extraction, and size separation by velocity gradient centrifugation. Our biochemical analysis using quantitative amino acid analysis showed that the membrane associated base proteins are present in equimolar amounts (PrgH:PrgK:InvG = 1:1:1). On a structural level, this suggests that the three proteins are likely to share the same rotational symmetry of the cylindrically-shaped base. We were intrigued, however, to discover that the membrane-anchored base can adopt different sizes. A detailed structural analysis by three-dimensional electron cryomicroscopy and single-particle analysis finally revealed that several rotational symmetries or oligomeric states are present in the population of the 'needle complex' and the 'base'. Whether all of these complexes have a physiological role remains an open question.

In addition, our analysis identified a new structural component, the inner rod, which is located in the center of the needle complex (Figure 2). It (1) extends the secretion path from the base into the needle filament, and (2) serves also as an anchor to stably connect the needle filament into the base. During assembly, the inner rod and the needle filament are added as new structural components to the base. As a consequence, it must undergo large conformational rearrangements, which demonstrates the flexible but also stable property of the base. Functionally, this dynamic behavior is a crucial event during the assembly process, which reprograms the secretion machine such that it becomes competent for the secretion of virulence factors only after the growth of the needle filament is completed.

Although the design of the TTSS appears to be conceptually simple, structural characterization of the needle complex is at an early stage, leaving many questions unanswered: What nucleates the assembly of the TTSS? How dynamic is the entire assembly process? How does the export machinery interface with the needle complex and what determines the substrate specificity for protein secretion? We have just begun to address such questions, and we hope that by understanding the molecular mechanism of TTSS-mediated protein transport we may provide the basis for the development of novel therapeutic strategies to either inhibit its activity or modify the system for a targeted drug delivery.

JAVIER MARTINEZ
Mechanisms of RNA Silencing in Human Cells

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It will not be easy, for those of us working on RNA silencing, to forget the year 2006. The Nobel Prize has been awarded to Andrew Fire and Craig Mello for their pioneering work on the ability of double-stranded RNA to degrade, and therefore, silence the expression of genes with a complementary sequence. Our laboratory contributes to the RNA interference (RNAi) field by identifying a novel, human RNA-kinase that phosphorylates short interfering RNAs (siRNAs) upon transfection into cells. The phosphorylation event is crucial for the assembly of siRNAs into RISC, the RNA-Induced Silencing Complex. The field of microRNAs (miRNAs), small RNAs that regulate a large portion of the genome by binding to the 3'-UTR of target mRNAs, has continued to flourish in 2006, with major advances in terms of processing mechanisms, target mRNA identification and functions. We have recently reported that the processing of a ~23-24 nt miRNA from a ~70 nt precursor (pre-miRNA) can be regulated in a tissue-specific manner. Our laboratory is now attempting to purify the protein responsible for such regulation. In addition, we are searching for miRNAs involved in cancer and, in particular, in the process of metastasis.

Identification of hClp1 as a Novel Human RNA-kinase that Phosphorylates siRNAs and 3' Exons during tRNA Splicing

For its incorporation into the RNA-Induced Silencing Complex (RISC) in order to mediate efficient RNAi, the guide strand of an siRNA duplex needs to display a phosphate group at the 5' end (Figure 1A). However, transfection of human cells with non-phosphorylated siRNAs also leads to potent gene silencing due to the presence of an endogenous siRNA-kinase activity. So far, the identity of this kinase has remained elusive. Monitoring siRNA phosphorylation, we applied a classical chromatographic approach that resulted in the identification of the protein hClp1 (human Clp1) as the siRNA-kinase. hClp1 has previously been described as a component of both tRNA splicing and mRNA 3' end formation machineries. We revealed hClp1 as the RNA-kinase activity that acts during human tRNA splicing, where it phosphorylates the 5' end of the 3' exon allowing subsequent ligation of both exon halves (Figure 1B). Future studies will be aimed at investigating the function of hClp1 in other RNA metabolic pathways, such as mRNA 3' end formation.

Post-transcriptional Regulation of miRNA Expression: Who Controls the Controllers?

miRNAs are a large family of small (~22-nt), non-coding RNAs that bind to complementary sequences in the 3'-untranslated region (3'-UTR) of mRNAs, and mediate translational repression or mRNA cleavage. miRNAs are transcribed as mono- or polycistronic primary transcripts (pri-miRNAs) that are cleaved

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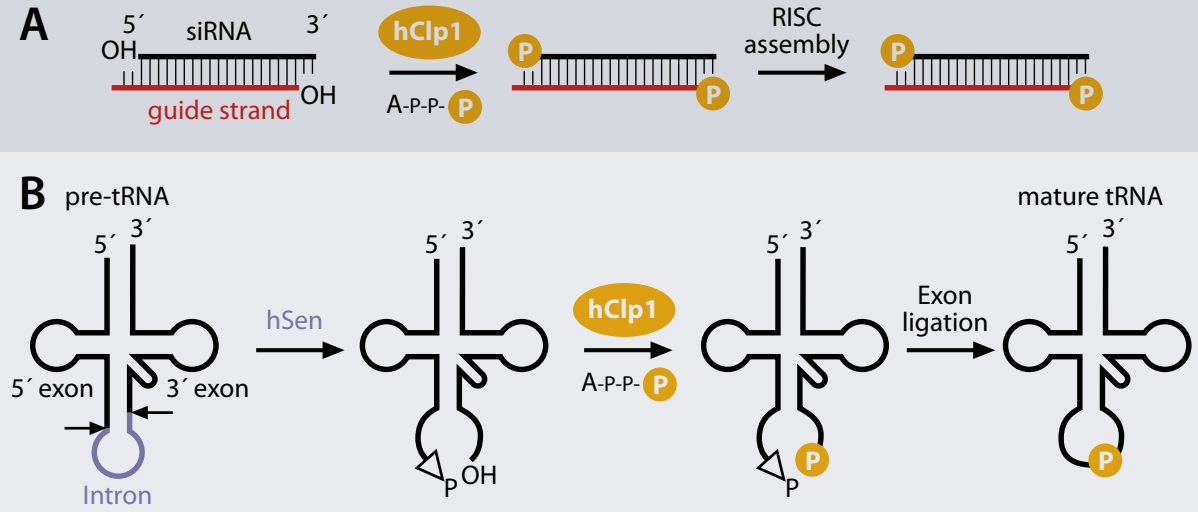

Figure 1: *The function of hClp1 in RNAi and tRNA splicing. A) hClp1 phosphorylates siRNAs bearing 5' hydroxy groups using ATP, a requirement for assembly of the guide strand onto RISC. B) The human Sen endonuclease (hSen) complex recognizes and cleaves at the 5' and 3' splice sites to remove the intron from pre-tRNAs. The endonucleolytic cleavage results in 2', 3' cyclic phosphate and 5' hydroxyl termini, at the 5' and 3' splice site, respectively. hClp1 is the RNA-kinase activity that phosphorylates the 5' end of the 3' exon using ATP for the subsequent ligation of both exons.*

Figure 2: *Searching for the inhibitor that impairs maturation of pre-miR138 in HeLa cells. A) Purification scheme. Highlighted is the purification step depicted in Figure 2B. B) Heparin chromatography. The lane "Buffer" refers to a pre-miRNA processing reaction containing recombinant Dicer and buffer instead of fractions from the column.*

Figure 3: *Metastatic potential of miRNAs. Murine lungs after the injection of cells overexpressing a scrambled siRNA duplex (left) or a candidate, metastasis-specific miRNA (right).*

into ~70-nt precursor hairpins (pre-miRNAs) by the nuclear RNase III-like enzyme Drosha. Subsequently, pre-miRNAs are exported to the cytoplasm, where they are processed by another RNase III-like enzyme, Dicer, into ~22-nt duplexes, followed by assembly into RISC. Many mammalian miRNAs are tissue- and/or developmental stage-specifically expressed, and it is currently believed that miRNA expression is controlled at the promoter level. However, we have recently found that miRNA expression can also be regulated after transcription, at the level of pre-miRNA processing. In particular, miR-138 is spatially restricted to distinct cell types in the brain, while its precursor, pre-miR-138-2, is ubiquitously expressed. We hypothesized the existence of a tissue-specific inhibitor that could impair pre-miRNA processing in those tissues where the mature miR-138 is not detected. We are pursuing the identification of such an inhibitor. Starting from HeLa cytoplasmic extracts and monitoring inhibition of Dicer-mediated pre-miR-138 processing, we have developed a purification protocol (Figure 2A). A Heparin chromatography is shown (Figure 2B), where the inhibiting activity results in the accumulation of ~70 nt pre-miR-138 and the disappearance of the mature, ~23-24 nt miR-138. We will perform mass spectrometry analysis to identify proteins present in the most purified fraction, and RNAi-knock-downs to validate candidate genes.

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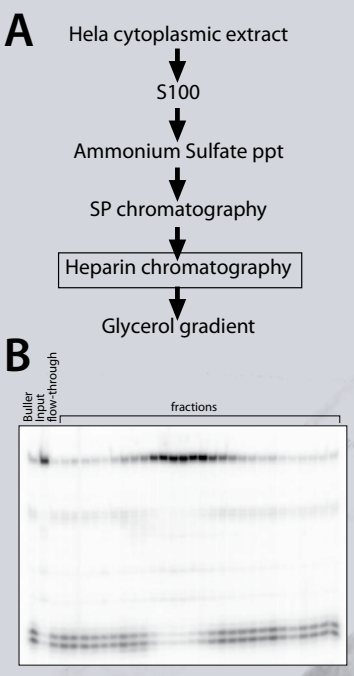

Deciphering the Role of miRNAs in Metastasis

We have recently started a new project with the goal of identifying and functionally characterizing miRNAs involved in metastasis. In cooperation with Exiqon A/S, Denmark, we perform miRNA-chip screens comparing non-metastatic with metastatic cells and tumor samples with non-tumorigenic tissue. Our goal is to uncover miRNAs that promote or interfere with the process of metastasis and identify the regulated targets and pathways. Preliminary results show an enhanced metastatic potential of tumorigenic cells overexpressing miRNAs that were identified in the microarray screen (Figure 3).

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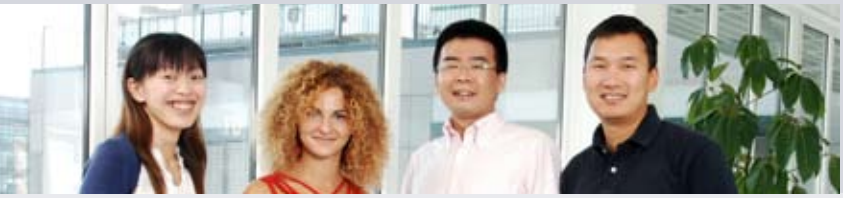

KAZUFUMI MOCHIZUKI

RNA-directed DNA Elimination in *Tetrahymena*

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The onion has more than 12 times as much genome as a human has. Does this mean the onion is more complicated and more intelligent than we are? Perhaps yes, but this presumably means an onion has more "junk" DNA than a human has. If some DNA are useless, why doesn't an onion discard them? Actually, several creatures do discard such DNAs during their development. Our group is attempting to find out how one such intelligent creature, Tetrahymena, dumps useless DNA.

During sexual reproduction, *Tetrahymena*, a ciliated protozoan, eliminates useless or even harmful DNAs from its nuclei, instead of continuing to silence such, as do other eukaryotes. But how do they precisely recognize "useful" and "useless" DNA? In recent years, we revealed that *Tetrahymena* uses small RNA of about 28 nucleotides to identify the useless DNA for elimination. This small RNA is produced by an RNAi-related mechanism and induces the formation of heterochromatin, a typical form of silenced chromatin. Thereafter, *Tetrahymena* eliminate the heterochromatins for "forever" gene silencing. Thus, the DNA elimination in *Tetrahymena* is a unique system to study two gene silencing mechanisms, RNAi and heterochromatin. Our study focuses on the molecular mechanisms linking the RNAi, heterochromatin and the DNA elimination. Links between RNAi and heterochromatin have also emerged in many other eukaryotes. Thus, this study should provide us with important insights not only into the DNA elimination in a curious microbe but also into how chromatin-level silencing is epigenetically directed by tiny RNAs in general eukaryotes.

Each interphase *Tetrahymena* cell (Figure 1) has a macronucleus (Mac) and a micronucleus (Mic). Mac is polyploid and is transcriptionally active, while Mic is diploid and is transcriptionally inert during the vegetative growth. Mic has the ability to undergo meiosis during the sexual process of conjugation and to form both new Mac and Mic for the next generation. After the new Mac forms, the old, parental Mac is destroyed. During development of the new Mac, massive DNA elimination occurs. About 15% of the Mic genome, called internal, eliminating sequences (IESs), is eliminated from the developing Mac. DNA elimination sites are healed by re-ligation of the flanking macronuclear-destined sequences (MDSs). IESs are range in size from ~0.5 to 20 kb in length and are mostly moderately repeated in Mic. Many IESs are probably derived from transposons or viruses. Thus, IES elimination could be evolved as a defense system against transposons invaded in the Mic genome by eliminating those potentially harmful DNAs.

No consensus sequences have been found in or around IESs that could explain how they are precisely recognized and are targeted for elimination. Recent studies revealed that an RNAi-related mechanism was involved in DNA elimination. Dcl1p, a Dicer family protein, and Twi1p (Figure 2), an Argonaute family protein, are required for DNA elimination. Both Dicer and Argonaute family proteins are

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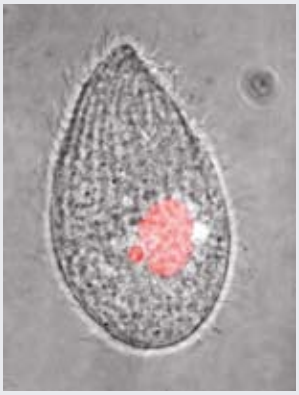

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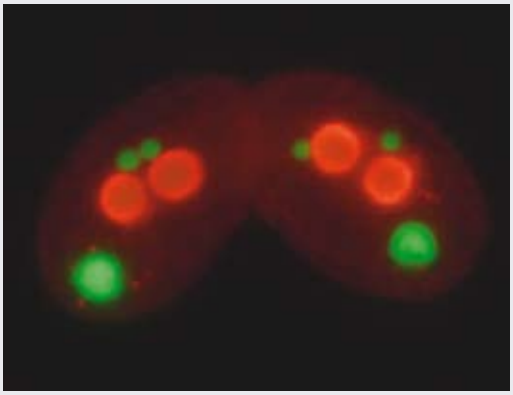

Figure 1: *Nuclear Dimorphism of Tetrahymena. Tetrahymena thermophila have two different nuclei (stained red), smaller micronucleus (Mic) and larger macronucleus (Mac), in a single cell.*

Figure 2: *Localization of Twi1p. Twi1p (stained red) and DNA (stained green) were localized in the new Mac development stage. Twi1p was observed only in new Macs.*

Figure 3: *DNA Elimination is Controlled by an RNAi-related Mechanism Left: Localization of the proteins involved in the genome rearrangement. Middle: Putative localization of scnRNA. Right: A model that explains how DNA elimination is epigenetically controlled by an RNAi-related mechanism. First, the entire Mic genome is transcribed bi-directionally in early conjugation by RNA polymerase II. These transcripts then form dsRNAs that are processed to scnRNAs by Dcl1p. The scnRNAs then accumulate in the cytoplasm and make a complex with Twi1p. Next, the scnRNA-Twi1p complex transfers to (old) Mac where we propose that those having a homologous Mac DNA sequence are degraded. As a result, only scnRNAs homologous to Mic-specific (IES) sequences remain in the old Mac. Finally, these scnRNAs move (in association with Twi1p) to the developing new Mac. There, the sequences homologous to the scnRNAs are identified as IESs and targeted for methylation of histone H3 Lys-9 and accumulation of Pdd1p. Finally, these marked sequences are eliminated.*

known to be involved in RNAi-related gene-silencing events in many eukaryotes. ~28nt siRNAs (named scnRNA) are specifically expressed during conjugation. Dcl1p is required for making scnRNA from the Mic transcripts. Twi1p is associated with scnRNAs and is required for their accumulation. The specificity of scnRNAs for Mic-limited sequences gradually increases during conjugation. Also, injection of *in vitro* synthesized dsRNAs homologous to MDSs induces ectopic elimination of the MDSs during conjugation.

Other evidences suggested that the DNA elimination was also related to heterochromatin formation. First, like the heterochromatin in other eukaryotes, methylated histone H3 on lysine-9 residue (H3K9me) is enriched on the eliminating IESs. Secondly, two chromodomain containing proteins, Pdd1p and Pdd3p, specifically bind to H3K9me and also accumulated on eliminating IESs. In other eukaryotes, the chromodomain protein HP1/Swi6 specifically interacts with H3K9me and is also enriched on heterochromatin. Genetic studies suggested that H3K9me and Pdd1p were required for the DNA elimination. Also, an RNAi-related mechanism is required for formation of heterochromatin-like state on IESs because disruption of *DCL1* or *TWI1* causes loss of H3K9me. Thus, RNAi, heterochromatin and DNA elimination are linked. From these studies, we proposed a model to explain how IESs, lacking any consensus sequences, are recognized during Mac development by using an RNAi-related mechanism (see Figure 3 for details).

Our long-term goal is to understand how RNAi induces heterochromatin and how heterochromatin induces DNA elimination. To understand these, we are trying to find out how the known "players" (scnRNA, Dcl1p, Twi1p, H3K9me and Pdd1p) communicate with each other so well as to identify more players involved in the genome rearrangement by biochemistry, genetics and molecular biology techniques.

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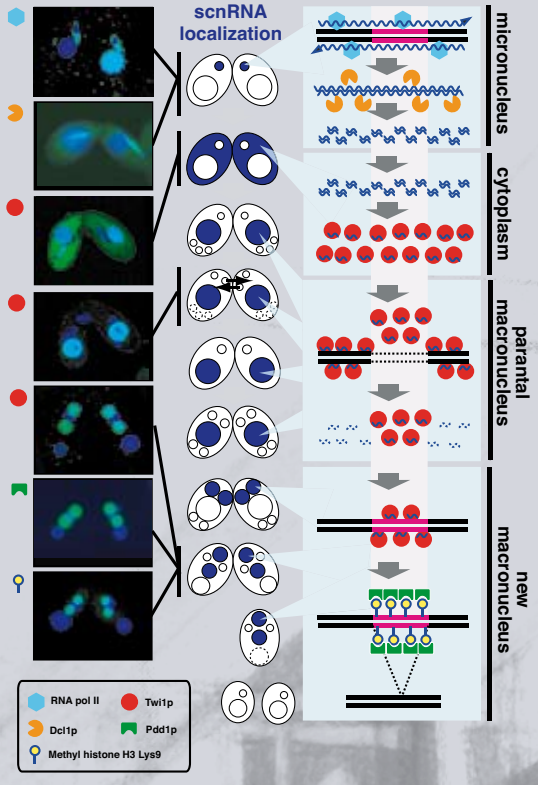

JOSEF PENNINGER

RANKL/RANK: Linking Bones, Immunity, and Cancer

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We have previously shown that RANKL and its receptor RANK control osteoclast differentiation and are essential for the development of a lactating mammary gland in pregnancy and lymph node organogenesis. Interestingly, RANKL plays a role in migration and tissue-specific metastatic behavior of cancer cells suggesting that RANKL is a "soil" factor for bone-specific metastases of epithelial tumors.

RANKL-RANK - the Master Regulators of Osteoclast Development

Millions of people worldwide are affected by bone-related disease such as osteoporosis, rheumatoid arthritis, and cancer metastases into bones. The TNF-family molecule RANKL (ligand-to-receptor activator of NFκB ligand) and its receptor RANK are key regulators of bone remodeling and essential for the development and activation of osteoclasts (Kong et al. Nature; Figure 1). RANKL expression on immune cells, e.g. activated T cells, can directly trigger osteoclastogenesis and explains why autoimmune diseases, cancers, leukemias, asthma, or periodontal disease result in systemic and local bone loss. In particular, RANKL appears to be the pathogenetic principle that causes bone and cartilage destruction in arthritis. Inhibition of RANKL function via the natural decoy receptor osteoprotegerin (OPG) prevents bone loss in postmenopausal osteoporosis, periodontitis-associated tooth loss (Teng et al. J. Clin. Inv.), and completely blocks crippling in a rat model of arthritis (Kong et al. Nature). RANKL also mediates T cell/dendritic cell communications and lymph node organogenesis. Moreover, RANK-L and RANK play essential roles in the formation of a lactating mammary gland in pregnancy (Fata et al. Cell; Figure 2). RANK signaling in osteoclasts and mammary cancer utilize similar activation pathways such as Gab2 (Wada et al. Nature Med.) Thus, this system provided an unexpected molecular paradigm that links bone morphogenesis, organization of lymphoid tissues, and mammary gland formation. This data also provided an evolutionary rationale for hormonal regulation and gender bias of osteoporosis.

Bone Metastases

Metastases are the main cause of cancer death. In particular, bone metastases are a frequent complication of many cancers that result in severe disease burden and pain. In 1893 it was proposed that local tissue environments actively participate in the propensity of certain cancers to metastasize to specific organs, and that the bone provides an especially fertile "soil". Since RANKL is the critical osteoclast differentiation factor highly expressed in the bone marrow and its receptor RANK is expressed on multiple tumor cells, which preferentially metastasize to bone, we speculated that RANKL might be one of the long sought after "soil" factors that facilitates metastasis to bone. Our results showed that RANKL triggers migration

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[6] EuroThymaide EU grant,
[7] EuGeneHeart EU grant

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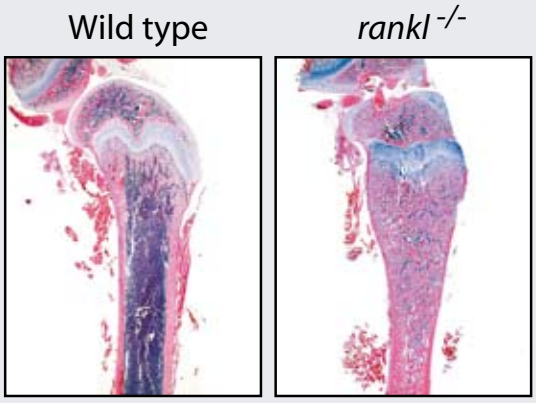

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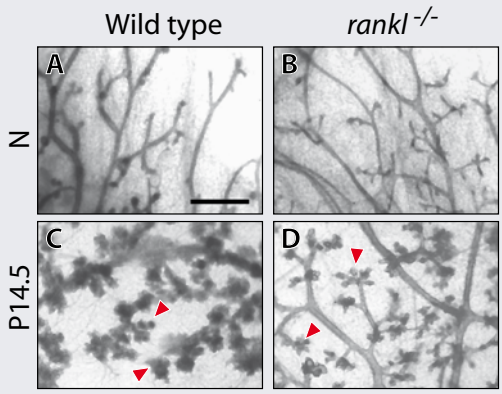

Figure 1: *Osteopetrosis and absence of osteoclasts in rankl$^{-/-}$ mice. The femur of rankl$^{-/-}$ mice is shortened and club-shaped and the shaft of the femur is filled with cartilage and bone. H. E. staining. Extensive analysis of bone showed that osteoclasts were completely absent in rankl$^{-/-}$ mice. A femur from a normal wild-type mouse is shown for comparison. (Kong et al. Nature).*

Figure 2: *Essential role of RANKL in the formation of lobulo-alveolar mammary structures in pregnancy. Whole-mount analyses of mammary tissue of (A) nulliparous wild-type females; (B) nulliparous rankl$^{-/-}$ females; (C) wild-type females at day 14.5 of pregnancy (P14.5); and (D) rankl$^{-/-}$ females at P14.5. Mammary gland ductal morphogenesis appears normal in nulliparous rankl$^{-/-}$ females (A,B). Alveoli in gestating wild-type females (arrowhead in C) have progressed to form lobular structures, whereas development is completely arrested at a rudimentary alveolar bud in rankl$^{-/-}$ females (arrowheads in D). The same can be seen in pregnant rankl$^{-/-}$ females. Scale bar: 0.5 mm. (Fata et al. Cell).*

Figure 3: *Inhibition of RANKL/RANK signaling results in reduced tumor metastasis in the bones. Macroscopic appearance of long bones on day 14 after injection of melanin-producing B16F10 melanoma cells into female recipients left untreated (tumor) or following in vivo treatment with the RANKL inhibitor OPG (Tumor/OPG). Arrows point at metastatic foci. Similar results, i.e. massive tumor burden in non-treated and markedly reduced melanin-producing tumors in OPG-treated mice, were observed in vertebrae, ribs, and skull.*

of multiple human tumor cells that express RANK. RANKL also triggers migration of primary breast epithelial cells and osteoclasts, i.e. RANKL-induced migration occurs in normal, non-transformed cells. In a model of melanoma metastasis, *in vivo* neutralization of RANKL by OPG results in complete protection from paralysis and a marked reduction in tumor burden in bones but not other organs (Figure 3). Thus, RANKL might be one of the long-sought-after "soil" factors for tissue-specific cancer metastases (Jones et al. Nature 2006).

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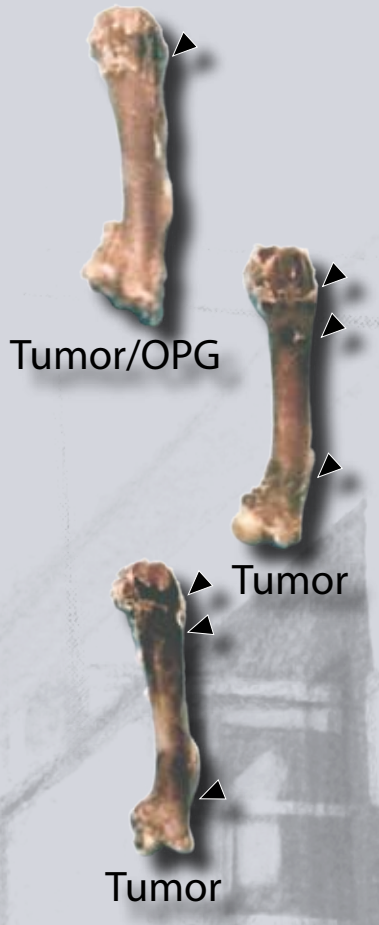

Future Direction

Our study introduced the concept that RANKL exhibits additional actions on cancer cells beyond its effects on osteoclasts. But what is the ultimate role of osteoclasts in bone metastases? All of the proposed paradigms are based on correlative localization studies and experiments with bisphosphonates that affect not only osteoclasts, but also apoptosis, proliferation, or migration. Genetic experiments to address this key question were not possible, since all mutant mice with disrupted osteoclasts have severely altered bone structures and/or additional pathways are affected. We have therefore generated RANK^{floxed} mice as a tool to selectively knock-out RANK in adult osteoclasts. One prediction is that the role of RANKL and RANK in cancer might extend beyond their function in osteoclasts and cell migration to growth of the primary cancer (Jones et al. Nature, 2006). Importantly, because of its role in both osteoclasts and tumor cells, independently confirmed by many laboratories, inhibition of RANKL-RANK interactions offers a promising therapeutic target for interfering with tumor metastasis in bone. Moreover, our newly developed RANK^{flox} mice will be a useful tool to further address the role of the RANKL-RANK system in other organs such as the link between UV-induced immunosuppression in the skin (Loser et al. Nature Med. 2007).

LEONIE RINGROSE

Epigenetic Regulation by the Polycomb and Trithorax Group Proteins

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How do different cell types remember their identities over many cell generations? Part of the answer lies in the Polycomb and Trithorax groups of proteins. We aim to understand this epigenetic regulatory system on both the molecular and the genomic levels, in terms of the design, function and evolution of its components.

The Polycomb (PcG) and Trithorax (TrxG) groups of proteins work antagonistically on the same target genes, to maintain the repressed (PcG) or active (TrxG) transcription states that were established earlier on by transiently acting transcription factors. In flies and vertebrates, the PcG and TrxG operate on several hundred developmentally important genes (Figure 1A), which they recognise through specialized DNA elements called PRE/TREs (Polycomb/Trithorax Response elements, Figure 1B). Our main aim is to understand the interaction between the PcG and TrxG proteins and PRE/TREs. To achieve this, we use an interdisciplinary combination of experimental biology, mathematical modelling and computational prediction.

1) What Makes a PRE/TRE?

PRE/TREs are fascinating pieces of DNA. Within only a few hundred base pairs, they contain information that enables them to remember and maintain the active or silenced transcriptional state of their associated genes over many cell generations. Until recently, a central and long-standing question in the field was: "Why do the handful of known Drosophila PRE/TREs have no apparent sequence homology, although they all have similar properties in transgenic assays?" To answer this question, we designed an algorithm that detects similarities in PRE/TREs without using linear alignment. Using this algorithm for genome-wide PRE/TRE prediction, we identified 167 candidate sequences (Figure 2A), many of which are bound and regulated by the Polycomb group of proteins *in vivo* (Figure 2B). This analysis demonstrates that functional PRE/TREs are complex combinatorial elements that can have many different designs, but we still do not know all the rules. We now aim to understand the design and function of different classes of PRE/TRE element, using *in vivo* assays in flies.

In a complementary project, we are using the recently released genome sequence and annotation for several other *Drosophila* species, in combination with *in vivo* experiments, to elucidate the principles governing the evolution of PREs. We find that PRE/TRE evolution is extraordinarily dynamic. The number, position and design of PRE/TREs changes rapidly in evolution and suggests that these regulatory elements may provide a rich source of potential phenotypic variation.

In contrast to *Drosophila*, it is still unclear what makes a vertebrate PRE/TRE, although several hundred target genes of the PcG have been identified. We are

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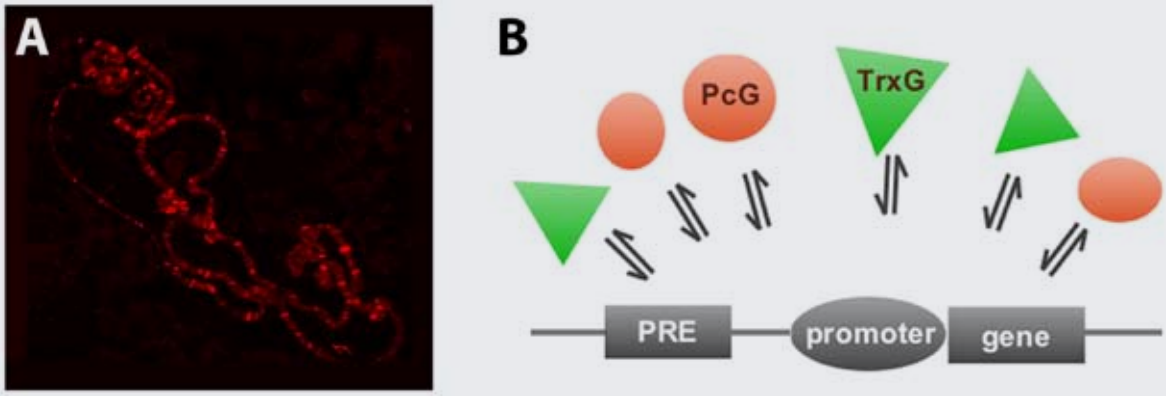

Figure 1: *A. Giant chromosomes from Drosophila larvae were stained with an antibody against the Polycomb protein, showing about 100 binding sites. B. The Polycomb and Trithorax group proteins recognise their targets via DNA elements called PREs.*

Figure 2: *A. Map of predicted PRE/TREs in the Drosophila melanogaster genome (vertical black lines on chromosome arms) agrees well with cytologically mapped sites of PcG and TrxG binding (grey boxes below the arms). B, C. Transgenic analysis of PREs, showing typical variegation of reporter gene activity in the eye. B. previously characterised PRE/TRE (bxd). C newly predicted PRE/TRE (vg).*

interested in understanding the DNA sequence requirements for vertebrate PRE/TREs. To this end, we aim to establish reporter assays in mouse cell culture, to dissect the function of candidate mouse PRE/TREs. Bioinformatic analysis will be used to unravel the underlying features of vertebrate PRE/TRE design.

2) How do Active and Silenced States Survive Mitosis?

Paradoxically, although the silenced and activated states perpetuated by the PcG and TrxG are stable over many cell generations, it is becoming clear that the proteins themselves associate with their targets as dynamic complexes, in constant flux between bound and free pools (Figure 1B). We recently combined *in vivo* assays and mathematical modelling to show that the Polycomb protein exchanges differently on individual loci in *Drosophila*. The challenge now is to obtain quantitative measurements of the kinetic processes involved, and to extend these observations to mitotically dividing cells. We aim to achieve this by studying the kinetic behaviour of PcG/TrxG proteins, and of the non-coding transcription that is associated with activation of target genes, during the cell cycle. We will use live imaging techniques for proteins and RNA in developing *Drosophila* embryos. This will be combined with mathematical modelling in order to integrate the results into a coherent quantitative model. In this way, we hope to understand how a system in constant flux can ensure both stability and flexibility.

3) How do PRE/TREs Change their States upon Developmental Transitions?

Mammalian PcG and TrxG proteins are intimately involved in maintaining stem cell identity, differentiated cell identity and cell proliferation. Aberrant expression of these proteins is associated with many types of cancer. We wish to use ChiP on chip analysis to identify changes in the binding profiles of mouse PcG and TrxG proteins upon differentiation of different types of stem cells to defined lineages. In parallel, we will look at the behaviour of the PcG and TrxG proteins themselves upon differentiation, in terms of their expression, modifications and subcellular localisations. The long-term aim will be to understand how the PcG and TrxG change their interactions with PRE/TREs upon changes in cell identity.

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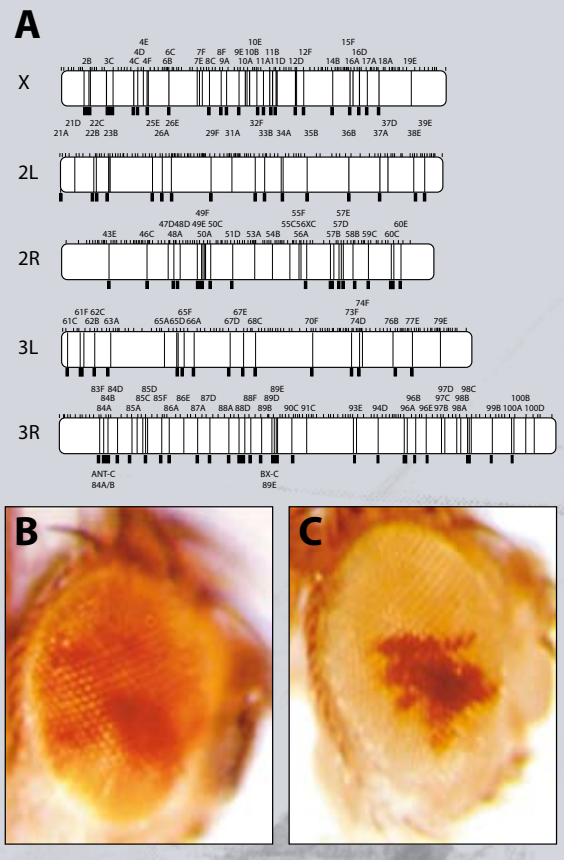

VIC SMALL

Mechanisms Underlying Cell Motility and Guidance

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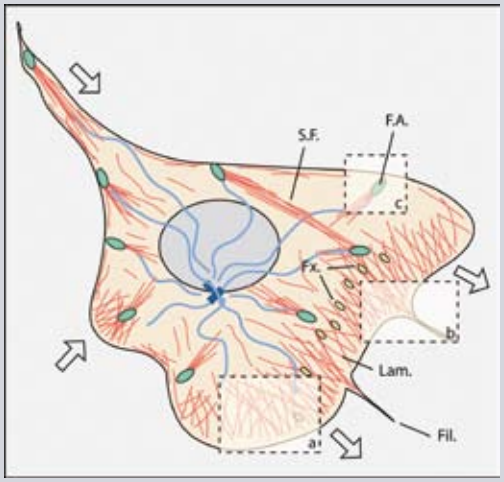

The migration of cells is essential to life, as a primary feature of developmental and repair processes. It also contributes to disease states, such as in the dissemination of malignant cells during metastasis. We address questions of how the process of cell motility is driven and controlled.

Guiding the Way with Microtubules

One area of our research programme addresses the question of how a cell polarises to move in a given direction. We now know that cell motility relies on the dynamic formation and reorganisation of actin filaments that form the "actin cytoskeleton". But in many cells, polarisation requires the "microtubule cytoskeleton" and our investigations are aimed at revealing how microtubules exert their influence on the turnover of the actin cytoskeleton to confer this polarisation. The dependence on microtubules for polarisation generally parallels the degree of anchorage of a cell with the substrate, namely with the extent of formation of "focal adhesions". Our recent work on fibroblasts has provided evidence for the involvement of microtubules in focal adhesion turnover. Thus, we have shown that the growing ends of microtubules specifically target focal adhesions and that multiple targeting events lead to focal adhesion disassembly, or their release from the substrate. Focal adhesion targeting by microtubules occurs also in rapidly moving cells, such as neutrophils, suggesting it has a more general role in cell guidance.

The idea that interactions of microtubules with the "cell cortex" are involved in morphogenetic processes has been substantiated in studies of diverse biological systems, from yeast to eukaryotes. A striking development in the field is the realization that microtubules accumulate at their growing tips a complex of protein components that appears to influence microtubule dynamics and mediate cortical interactions. Our current studies focus on characterizing the nature of the cross-talk between microtubules and the cell cortex and the mechanisms underlying the guidance of microtubules into cortical adhesion sites.

Pushing Forward

The first stage of cell movement involves the protrusion of a thin layer of cytoplasm, termed the lamellipodium, which is driven by the polymerisation of actin. The lamellipodium, together with integrated bundles, called filopodia, serve, in turn, to initiate adhesion with the substrate. Understanding the structural basis of motility requires knowledge of the organisation of the actin networks that make up the protrusive lamellipodia of migrating cells. Divided opinions about the mode of generation and assembly of actin filament networks in lamellipodia have however arisen through discrepancies in results obtained by different preparative

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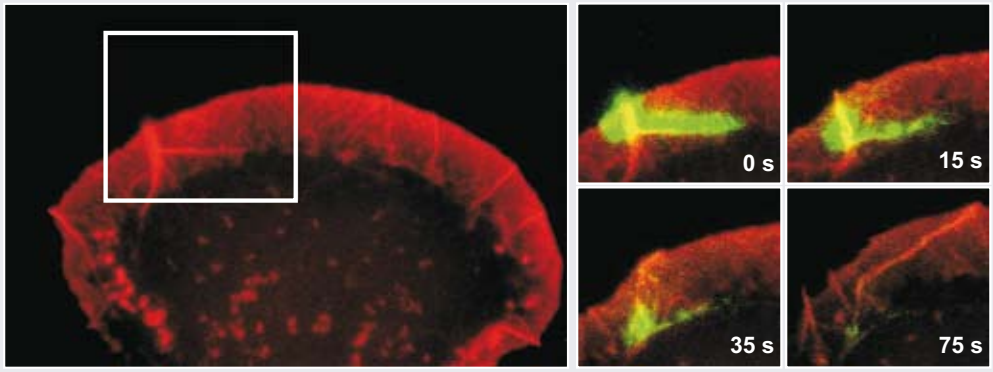

Figure 1: *Schematic illustration of a migrating cell, indicating the general organisation of the actin (red fibres) and microtubule (blue fibres) cytoskeletons. The actin cytoskeleton is indirectly coupled to the extra-cellular matrix through focal points of adhesion (green). Microtubules influence cell polarity by targeting adhesion sites to promote their turnover.*

Figure 2: *Rapid turnover of actin at the cell front, as demonstrated using photoactivatable-GFP-actin (PA-GFP-actin). Overview (left) shows a confocal image of a B16 melanoma cell transfected with RFP-actin (red) and PA-GFP-actin. Insets at right show video frames after activation of PA-GFP-actin with laser light at 405nm, in a selected region of the lamellipodium at the cell front. The rapid loss of label indicates that a major depolymerisation of actin occurs towards the base of the lamellipodium.*

Figure 3: *Border cell translocation is inhibited by the down regulation of known migration determinants by RNAi. Confocal images of Drosophila stage 10 egg chambers, stained for actin (phalloidin, red) and showing CD8GFP fluorescence (green) in the border cells. Note defective migration of border cells in which taiman and domeless are down-regulated.*

techniques used for electron microscopy. To help resolve current controversies, we have initiated the application of cryo-electron microscopy for investigations of cytoskeleton architecture. In parallel studies, we are developing techniques for the correlation of the motile activity of the living cell, in the light microscope, with the ultrastructure in the EM. Future aims include the characterization of actin reorganizations leading to adhesion formation and defining the organization of actin in mimetic models of actin driven motility.

Screening for Cell Motility Genes in *Drosophila*

Fertilisation in the *Drosophila* oocyte requires the migration of border cells through the egg chamber. In collaboration with the Dickson Lab, we have initiated an RNAi screen for genes required for the migration process. In the longer term, we aim to characterize the role of candidate genes in the motility of selected tissue cells involved in developmental and repair processes in *Drosophila*.

Additional information may be obtained from our website:
http://cellix.imba.oeaw.ac.at/Videotour/video_tour_1.html

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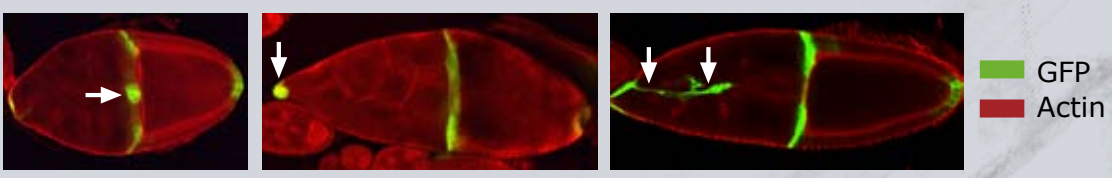
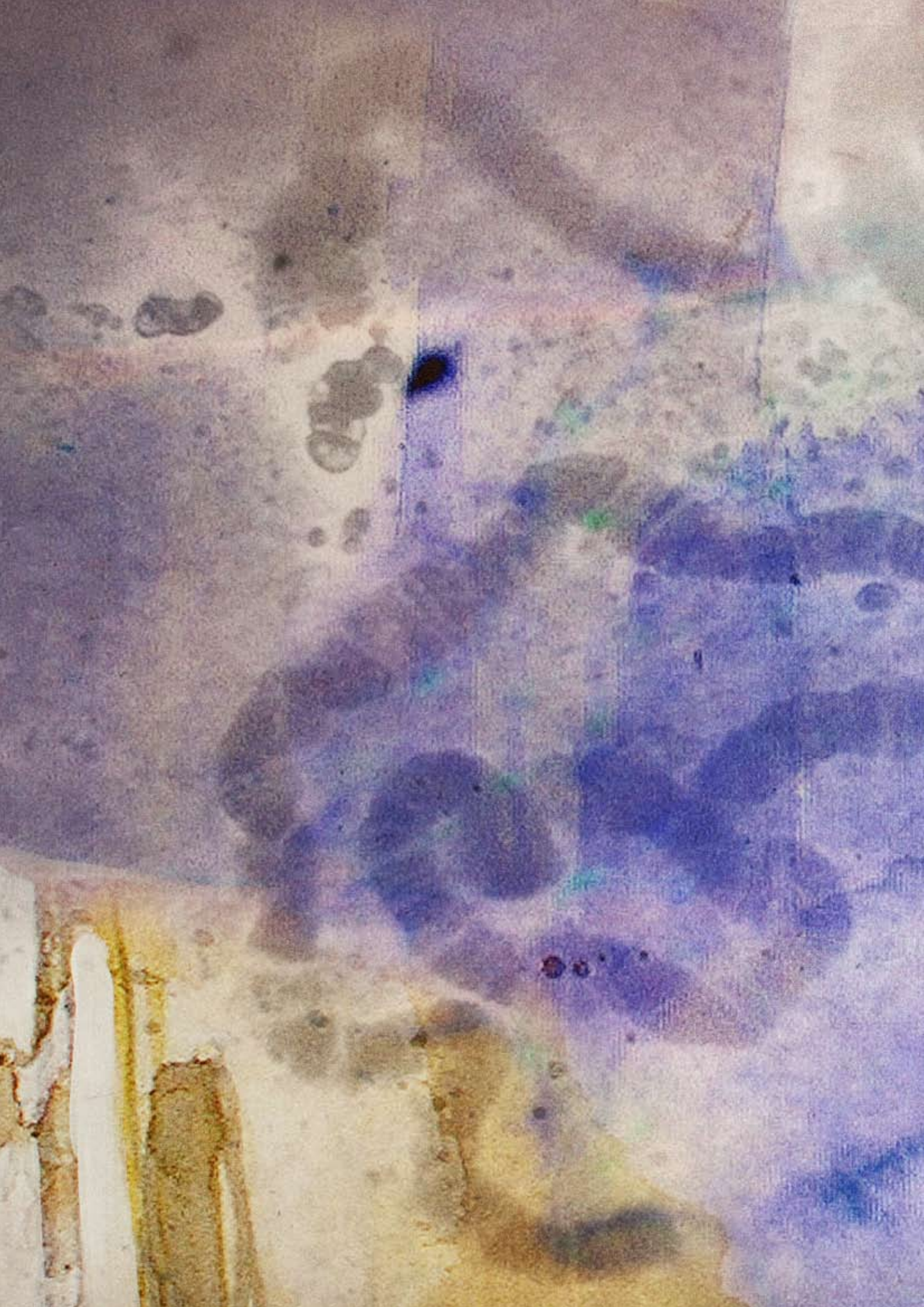
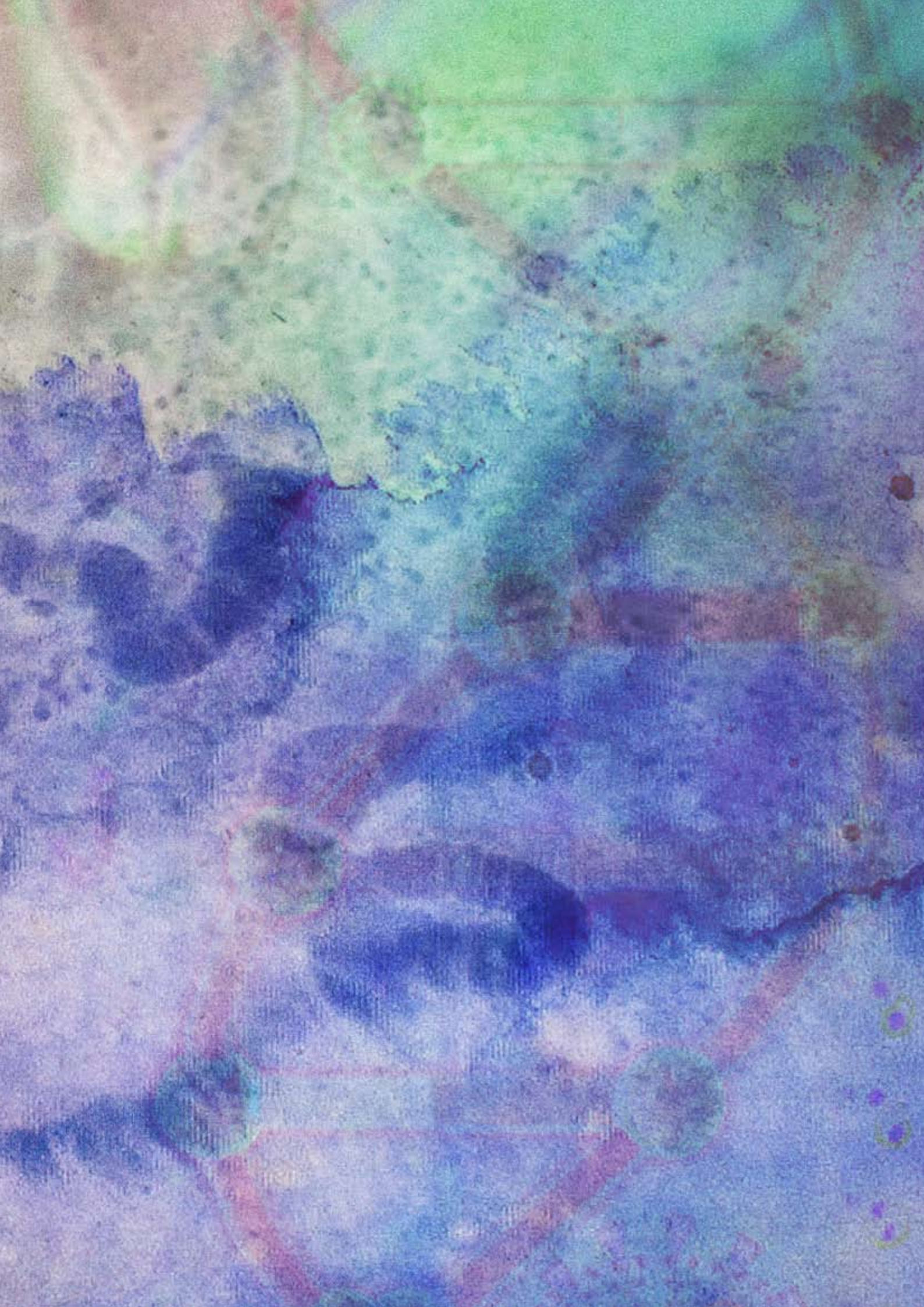


wild type *taiman* RNAi *domeless* RNAi





BIOOPTICS DEPARTMENT

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Peter Steinlein / Head of Facility

Karin Paiha / Microscopy and Image Analysis
Pawel Pasierbek / Microscopy
Martin Radolf / Micro arrays
Gabriele Stengl / Flow Cytometry
Sahra Derkits [1] / Diploma Student
Petra Dorninger [2] / Diploma Student

[1] *until July,*
[2] *February – July*

The services offered to the researchers at the IMP and IMBA by our department cover flow cytometry and cell sorting, a wide variety of microscopical techniques, image analysis and image processing as well as cDNA-micro-array production, hybridization and analysis.

Current Research Activities

During the past year, one focus of our department was the implementation of multiplexed bead-assays for the quantification of various analytes using a BioPlex System. Even though a wide variety of kits are commercially available, standard methods for the generation of bead assays for more "exotic" analytes have been established.

In order to comply with increased demand by our users, the micro-array service now provides complete service including amplification and labeling, hybridization, image analysis and simple statistical analysis. Besides the convenience for the users the main reason to do so is to increase the robustness, significance and reproducibility of the obtained results.

To achieve these goals, we have established standard protocols for all steps involved with a strong focus on quality control of every step and the use of an automated hybridization station. Optimization of these procedures also allowed a reduction in overall costs, making it possible to routinely perform at least three technical replicates per sample. Comparative analyses with other platforms including Affymetrix revealed a very high correlation of the results obtained

As the production of the cDNA-arrays has been optimized for semi-automated image analysis, this step can now also be performed with minimal human interaction. The data generated by the image analysis is then fed into a processing pipeline where normalization and initial statistical analysis has been automated using modules from the BioConductor package adapted to the experimental designs currently applied. In a collaboration with Arndt von Haeseler (CIBIV, University of Vienna), more elaborate statistical tools will be implemented.

The supply of available cDNAs has also significantly increased by the acquisition and processing of 100,000 mouse cDNA clones of high quality from the RIKEN institute. Currently, the cDNAs are spotted on a set of arrays, which will be the basis of the future standard set of arrays. Together with very specialized arrays resulting from SSH-derived cDNA-libraries, we aim to cover most of the mouse transcriptome in the near future.

ELECTRON MICROSCOPY

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Günter Resch / Head of Facility

Nicole Aichinger[1] / Technical Assistant

[1]*until November 2006*

The Electron Microscopy Facility, established in the course of this year, offers a wide variety of preparation techniques for visualisation of tissues, cells and purified molecules by transmission electron microscopy, as well as support with microscopy and data management. In addition to the routine equipment up and running, preparations to set up a cryo-capable high-end microscope in 2007 are in progress.

Along with the move into the Academy Laboratory Building at the beginning of 2006, the work to establish an Electron Microscopy Facility at the IMP-IMBA Research Center entered a new phase.

A major part of starting up the facility was setting up and testing a good deal of specialised preparation equipment, including ultramicrotomes, high vacuum evaporators, glow discharge units, a freeze substitution device, etc. Routines for performing diverse preparation techniques were established, including: chemical and physical fixation, conventional resin embedding, freeze substitution, ultrathin sectioning, production of support films, negative staining, rotary shadowing of sprayed molecules, and others. Most of these approaches are now routinely used by both IMP and IMBA researchers as well as within external collaborations. Depending on future developments and the focus of the demand from the institutes, more preparation procedures will be made available.

With the long awaited installation of the FEI Morgagni transmission electron microscope in July, the major equipment for service purposes was completed. This robust and easy to use 100 kV instrument is tailored for routine needs in the multiuser environment of a facility. For suitable documentation of large fields as well as high resolution imaging, it is equipped with a 11 megapixel CCD camera. Immediately following its installation, the microscope was heavily booked, reflecting a local demand for electron microscopy in both institutes.

To support users with data management, a web-based project-oriented database system named MIMAS was established. All electron micrographs including metadata can be stored on and accessed from this database on a user restricted basis. It is now running in an early version and continuously being developed into a more stable and versatile platform, in close collaboration with users to meet their needs.

In parallel with these daily activities, the EM Service is overseeing the pre-installation of the FEI TF30 Polara. This 300 kV transmission electron microscope, equipped with the most advanced imaging systems, was funded by a Vienna Spot of Excellence grant to the Marlovits, Peters, Small and EM Service groups. It is scheduled to be delivered to site at the end of 2006 and planned to commence operations in the course of 2007. Primarily, it will be used for cryo-electron microscopy of molecules and cells, electron tomography, as well as analytical applications.

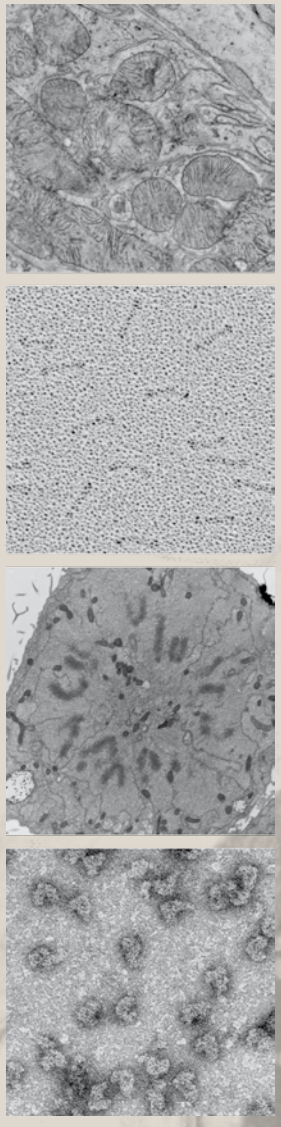

Figure 1: Techniques applied in the Electron Microscopy Service, from top to bottom : Ultrathin section of high pressure frozen and freeze substituted kidney tissue, glycerol sprayed and rotary shadowed α-actinin molecules, mitotic HeLa cell after flat embedding and sectioning (micrograph by Peter Lénárt), and negatively stained APC molecules.

BIOINFORMATICS SUPPORT

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Alexander Schleiffer / Head, Bioinformatics Support

Maria Novatchkova / Bioinformatics Support

The Bioinformatics Support unit is part of the Bioinformatics Research group of Frank Eisenhaber, and assists research groups in molecular biology-related fields, providing infrastructure, sequence-analytic services, support and education in bioinformatics.

The IMP-IMBA Bioinformatics support unit has its main expertise in the field of sequence-analysis. Typical tasks include the functional and structural characterization of proteins and genomic regions, using methods such as pattern matching, complexity analysis and homology searches.

Often problems arise from functional genomics or high-throughput biological datasets, for which we develop computational and mathematical solutions able to cope with the high load and memory requirements.

Software and Database Development

In order to efficiently handle recurring tasks, we also engage in custom software and database development. This year we have publicly released DOUTfinder, a software tool dedicated to the improved identification of known domains in protein sequences. True similarities to functionally described domains can easily be missed if they are reported as false negatives below recommended significance thresholds (see Figure 1). DOUTfinder is used to suggest biologically meaningful twilight zone domain similarities by providing a homology-backed procedure for filtering of relevant subthreshold hits.

Training

The IMP ANNOTATOR is an in-house facility providing a user-friendly web interface to integrate complex sequence-analytic tasks. We provide hands-on training courses on the use of the ANNOTATOR system, where participants learn the basis and limitations of sequence analysis.

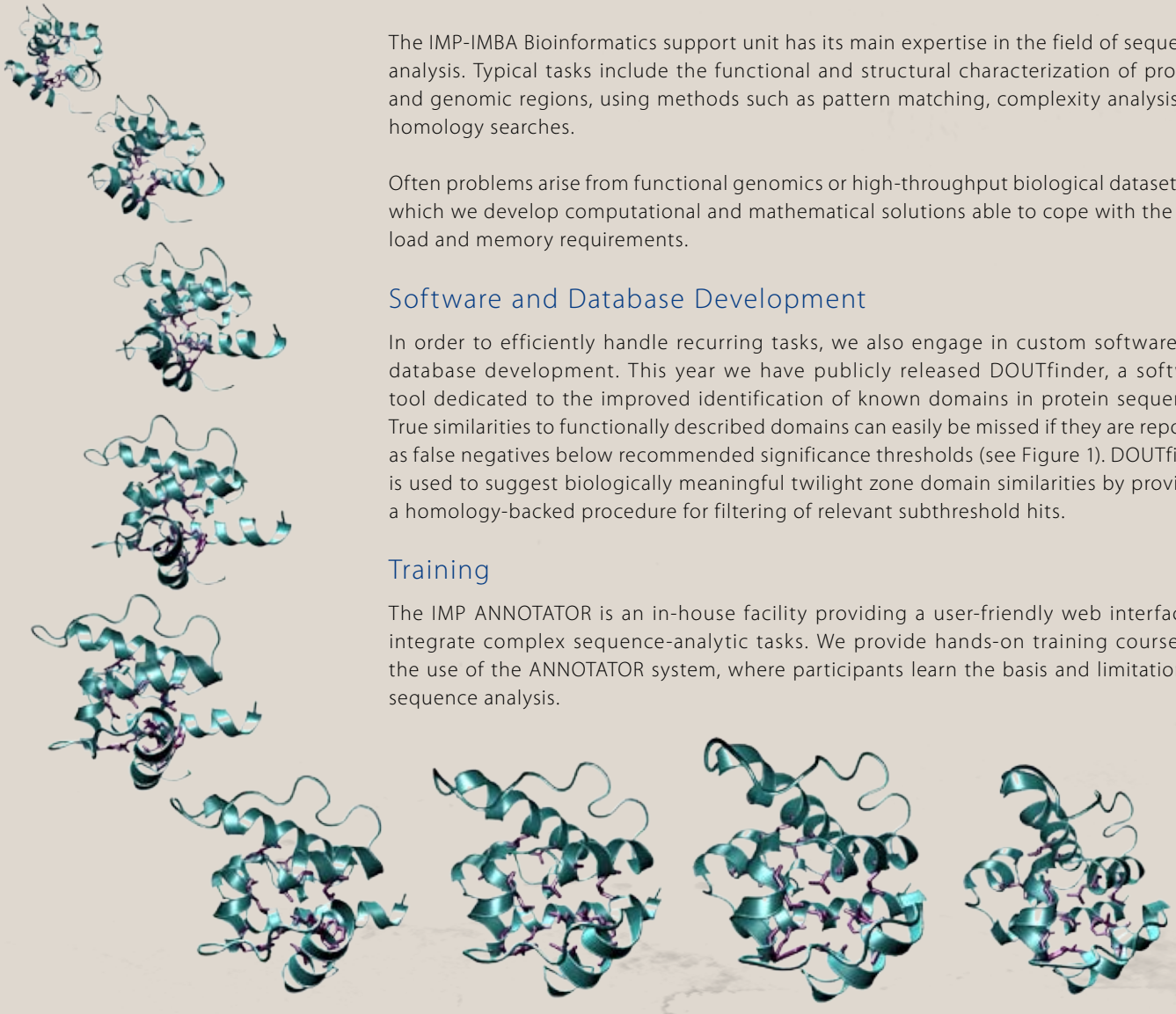

Figure 1: The tri-dimensional structure of a single CH domain (1H67) can serve as a model for understanding the organization of the N-terminal globular region in NuMA proteins. The similarity between the NuMA N-terminus and the CH domain is reported as a false negative and sub-significant hit in sequence similarity searches, but can be supported by DOUTfinder and structural similarities.

PROTEIN CHEMISTRY FACILITY

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The IMP-IMBA Protein Chemistry Facility performs a large variety of mass spectrometry experiments, including identification of proteins by peptide sequencing and characterization of post-translational modifications (PTMs), such as phosphorylation. In addition, we are developing new methods for the quantification of PTMs. Finally, our facility specializes in peptide synthesis and antibody purification.

Karl Mechtler / Head of Facility

Goran Mitulovic / Postdoc
Karin Grosstessner-Hain / PhD Student
Nedim Mujezinovic / PhD Student
Otto Hudecz / Technician
Richard Imre / Technician
Gabriela Krssakova / Technician
Mathias Madalinski / Technician
Michael Mazanek / Technician
Michael Schutzbier / Technician
Ines Steinmacher / Technician
Christoph Stingl / Technician

Improvement in Phosphorylation Analysis

Protein phosphorylation is the most important reversible post-translational modification. Thus, analysis of phosphorylated proteins and identification of the phosphorylation sites help us to understand their biological functions.

A. Analysis of protein complexes
We have developed a new offline chromatographic approach for the selective enrichment of phosphorylated peptides that is directly compatible with subsequent analysis by online nano electrospray ionization tandem mass spectrometry (ESI-MS/MS). Here, a titanium dioxide-packed pipette tip is used as a phosphopeptide trap for offline first dimension separation step in a two-dimensional chromatography system. This is followed by online nano reversed-phase high-performance liquid chromatography.

B. Enrichment of phosphopeptides from complex mixtures
Immobilized Metal-ion Affinity Chromatography (IMAC) was established for enrichment of phosphopeptides from complex mixtures. This technique, which is based on the affinity of negatively-charged phosphate groups for positively-charged metal ions (Fe^{3+}), immobilized on a chromatographic support.

C. Application of Different Fragmentation Techniques for the Analysis of Phosphopeptides using an Ion Trap - FTICR Mass Spectrometer
Electron capture dissociation (ECD) is a complementary technique for the fragmentation of peptides and proteins in mass spectrometry in addition to the commonly used collisionally activated dissociation (CAD). ECD has been shown to be applicable for the efficient sequencing of peptides and proteins, and has been proven especially valuable for mapping labile PTMs, such as phosphorylation sites.

The Christian Doppler Laboratory for Proteome Analysis. Together with Prof. Gustav Ammerer from the Max F. Perutz Laboratories we have established a project for the quantitative analysis of proteins based on mass spectrometry. Our goal is to study the composition of multi-protein complexes and their associated partners.

Peptide Synthesis and Antibody Purification. We synthesize about 350 peptides per year, including an increasing number of branched peptides containing acetylated, phosphorylated or methylated amino acid residues. We have developed procedures for affinity-purification of antibodies, including optimised elution under mild conditions.

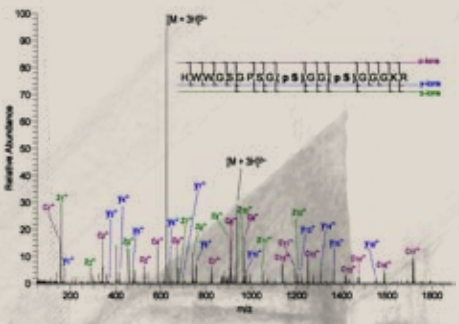

Figure 1: ECD product ion spectrum for the fragmentation of a triply-charged peptide $[M+3H]^{3+}$, at m/z = 625.2) reveals the positions of two phosphoserine residues.

HISTOLOGY DEPARTMENT

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Vukoslav Komnenovic / Head of Facility

Laura Göderle / Technician

The Histology Service Department offers state-of-the art sectioning, histology and immuno-histochemistry services to all IMBA and IMP scientists. In addition, we offer training and support for researchers in new technologies.

Histology Services

The histology services include the embedding of tissues, assistance with the sectioning of paraffin and cryo-preserved tissues, and preparation of slides for standard H&E stains, as well as specialized stainings such as PAS, Alcian blue, Cab, Gomeri, MayGruenwald-Giemsa and van Kossa stains for human, mouse, Xenopus and Drosophila studies. With these services, we are able to offer support to get quick results.

Sectioning of Paraffin and Frozen Tissues

In our group we have developed a high throughput method to cut paraffin and frozen tissues. Using this method, we could increase the quality and also the quantity of services.

Immunohistochemistry

The Histology Service Department also provides automated preparation and processing facilities for standardized immuno-histochemistry, in situ hybridization, FISH analysis, DNA microarray and tissues microarray applications. Various antibodies have been characterized for optimized in situ signaling studies. Standard antibodies such as apc, cd (several markers), l-ad, gfp, gfap, c-fos, c-jun, junB, fra1,2, jun-D, ki67, smad3, brdu, egf, egfr, H3K9me tri meth, H4K20me3 tri meth, cl. caspase3, caspase7, procatepsiK are available.
In addition, the Histology Service Department administrates legal regulatory affairs such as the record-keeping and documentation of experiments in accordance with the Austrian Histolaboratories guidelines (www.mta-labor.info).

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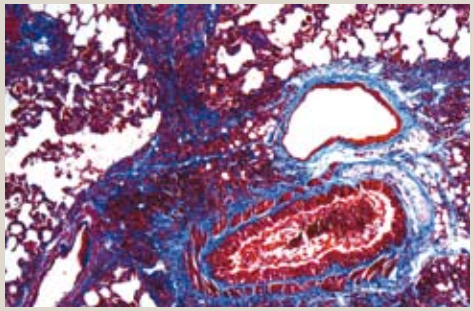

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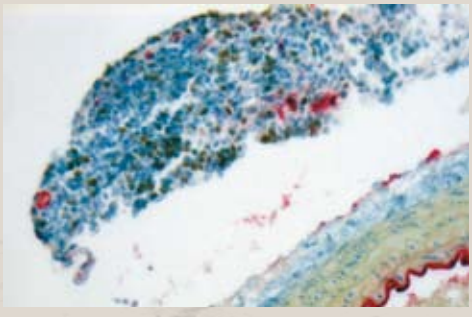

Figure 1: Trichrom blue staining. The picture shows 4 different signals, light blue for Lung fibrosis, red for Mast cells and Neutrophils, pink for Myeloiud cells and dark blue for the Nuclei.

Figure 2: Double Staining with Ki67 and von Willebrand Factor. Ki67 turnes out to be brown whereas vWF shows a red signal. The counter staining was done with Hematoxylin (blue).

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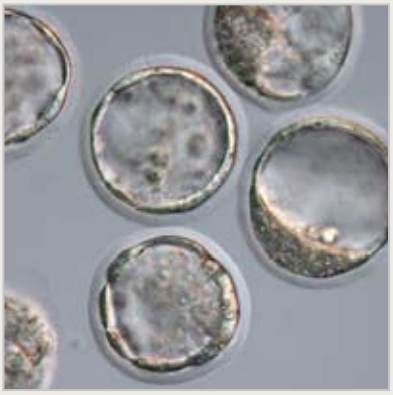

ANIMAL HOUSE

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MOUSE SERVICE

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The Animal House *group provides husbandry of animals and services for the various research groups at the IMP and IMBA.*

Husbandry

The husbandry is divided into two main areas containing the following species: mice and *Xenopus*. The larger area is the mouse section, where more than 10,000 mice are kept. These comprise breeding colonies, stock, and experimental animals including many transgenic and knock-out mouse lines. To provide a constant supply of mice for the various projects, 20 standard strains are routinely bred in-house.

Animal House Services

Veterinary services, such as monitoring of the facility's health-status (sentinel program etc.), experimental procedures in animals such as the collection of blood, implantation of tumor cells and administration of substances by iv, ip or sc injections. All procedures are performed to a high standard under appropriate anaesthetic regimes and in conjunction with the necessary project licenses.

Animal procurement, such as the ordering of mice from external breeding companies, and the organizing and handling of approximately 50 incoming and outgoing mouse shipments per year.

Administration of regulatory affairs in accordance with the Austrian laboratory animal law, which include record-keeping and updating of laboratory animal statistics, and specific documentation of laboratory animal experiments.

Animal House

Andreas Bichl / Head, Veterinarian
Erwin F. Wagner / Scientific Coordinator
Norma Howells / Consultant

The Mouse Service Department *was set up at the beginning of 1998 to cope with the increasing demand for mouse studies and generation of transgenics. The Mouse Service Department services are shared by the IMP and IMBA.*

The main duties of this service unit are the injection of ES cells into blastocysts (also tetraploid) and of DNA into the pronucleus of fertilized mouse eggs. This service also provides for the transfer of 'clean' embryos into our Animal House, the freezing of embryos for the preservation of specified mouse strains and the teaching of basic embryological techniques to the IMP and IMBA staff.
About 50 different ES cell clones and several DNA constructs are being injected per year. The activities of this department are overseen by an Animal User Committee, which meets bimonthly to set priorities and to coordinate the duties. At present, it is chaired by Erwin F. Wagner.

Mouse Service

Hans-Christian Theussl / Head of Facility
Jacek Wojciechowski / Technician

Figure 1: *Injection of embryonic stem cells into mouse blastocyst.*

Figure 2: *Mouse blastocysts.*

SERVICE DEPARTMENT

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Gotthold Schaffner / Scientist

Ivan Botto / Technician
Markus Hohl / Technician
Shahryar Tagybeeglu / Technician
Gabriele Botto / Technician Media Kitchen
Christa Detz-Jaderny / Technician Media Kitchen
Ulrike Windholz / Technician Media Kitchen
Franziska Stransky / Technician Fly Food Preparation
Anna Windholz / Technician Fly Food Preparation
Oliver Botto / Help Fly Food Preparation
Thomas Haydn / Help Fly Food Preparation

The Service Department offers a variety of high-quality and rapid services to IMP and IMBA scientists. The majority of our effort involves DNA sequencing, fly food production and preparation of various media and solutions.

Our Media Kitchen and Fly Food staff prepares substantial quantities of reagent quality solutions and media for cell culture, flies (approximately 1,200,000 bottles and tubes per year) and worms. We moved this year to the new IMBA building, where we have more space to create better and convenient working conditions for preparing fly food and all other products.
We also prepare many selected reagents such as DNA molecular-weight markers, enzymes, a variety of transformation-competent *E. coli* strains, and we maintain a stock of cloning vectors, sequencing primers and other cloning reagents.

Production of Antibodies

The production and isolation of many different monoclonal antibodies in hybridomas in collaboration with IMP group members, and organizing the antibody production in rabbits with an outside company requires a portion of our working time.

Sequencing and DNA Isolation

With the 16-capillery ABI 3100 Genetic Analyzer, and in particular, with the 48-capillary ABI 3730 DNA Analyzer, we sequenced approximately 38,000 samples in the first 10 months of this year. This demand increased in the last two months and we are expecting a further increase in the future not only due to the increased number of new customers, but also due to more new groups at IMBA and IMP.
We are primarily using the 3730 DNA Analyzer because of its sensitivity and its lower running costs. The average read-length is 700-900 bases for standard DNA samples with both Genetic Analyzers equipped either with 80-cm capillaries of ABI 3100 or 50-cm capillaries of ABI 3730.
A problem that is becoming significant is that DNA sample quality and, even more significantly, the concentration of DNA of samples corresponds to our skills in an inverse relationship and thus, the short "return time" (preparing the sample and getting results) leads additionally to increased trial-and-error and multiple-sample sequencing.
We are still using the same easy and fast clean-up protocol with Sephadex G50 superfine columns on a 96-well microtiter plate format, and we could eliminate, in most cases, the so-called "dye-blobs" in the sequencing reaction samples by further optimizing the Sephadex consistency and the centrifugation conditions.

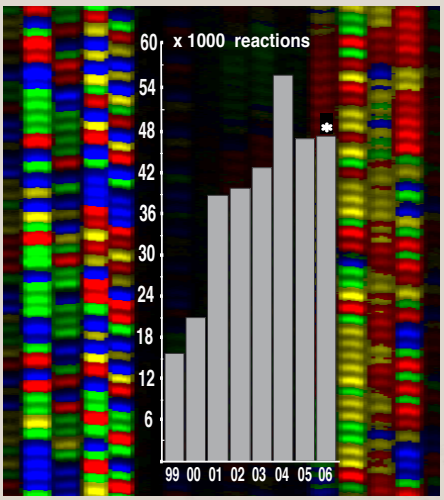
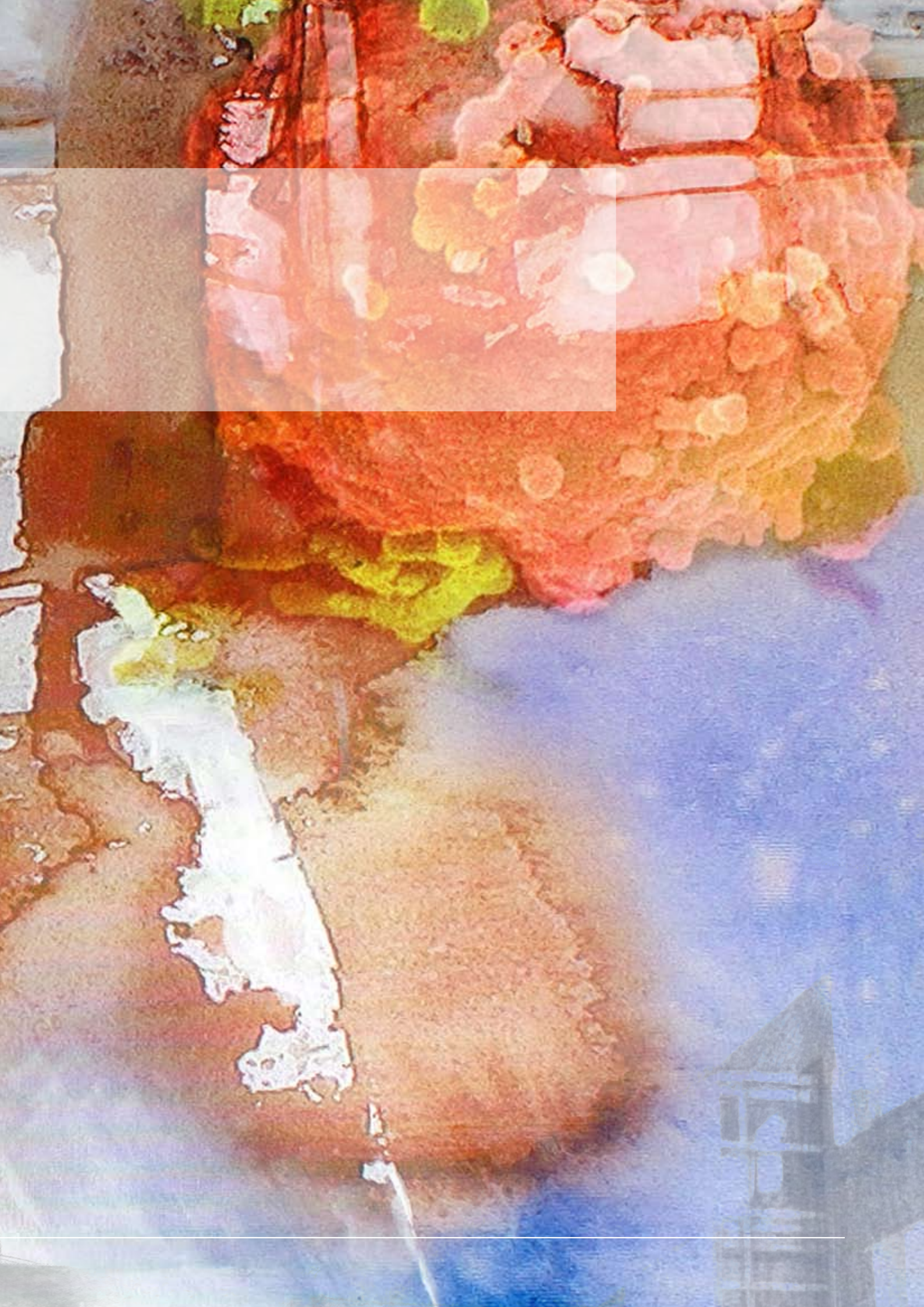


*Figure 1: A sequencing run on an ABI 377 PRISM and number of reactions analyzed on ABI 377 (1999 - 2001), on ABI 3100 (since 2001) and on ABI 3730 (since June 2004) done with dye deoxy terminators (v3.0 since 2001) in the years 1999 to 2006 (scale 0 to 60'000). *calculated from January 2006 to October 2006 data*



Publications

KNOBLICH

Betschinger, J., Mechtler, K., and Knoblich, J. A. (2006). Asymmetric segregation of the tumor suppressor brat regulates self-renewal in Drosophila neural stem cells. Cell. 124, 1241-53.

Bowman, S. K., Neumuller, R. A., Novatchkova, M., Du, Q., and Knoblich, J. A. (2006). The Drosophila NuMA Homolog Mud Regulates Spindle Orientation in Asymmetric Cell Division. Developmental Cell. 10, 731-42.

Emery, G. and Knoblich, J.A. (2006). Endosome dynamics during development. Curr Opin Cell Biol. 18, 407-15.

Gallagher, C. and Knoblich, J. A. (2006). The conserved C2 domain protein Lethal (2) giant discs regulates protein trafficking in Drosophila. Developmental Cell. 11, 641-53.

Hutterer, A., Berdnik, D., Wirtz-Peitz, F., Zigman, M., Schleiffer, A. and Knoblich, J. A. (2006). Mitotic activation of the kinase Aurora-A requires its binding partner Bora. Developmental Cell. 11, 147-57.

Knoblich, J. A. (2006). Cell biology. Sara splits the signal. Science. 314 (5802) 1094-6.

Vishnu, S., Hertenstein, A., Betschinger, J., Knoblich, J. A., Gert de Couet, H., and Fischbach, K. F. (2006). The adaptor protein X11Lalpha/Dmint1 interacts with the PDZ-binding domain of the cell recognition protein Rst in Drosophila. Developmental Biology. 289, 296-307

Wirtz-Peitz, F., and Knoblich, J. A. (2006). Lethal giant larvae take on a life of their own. Trends Cell Biol. 16, 234-41.

MARLOVITS

Marlovits, T. C., Kubori, T., Tejero, M.-L., Thomas, D., Unger, V. M., and Galan, J.E. (2006). Assembly of the inner Rod determines Needle Length in the Type III Secretion Injectisome. Nature. 441, 637-640.

MARTINEZ

Leuschner, P., Ameres, S., Kueng, S., and Martinez, J. (2006). Cleavage of the siRNA-passenger strand during RISC assembly in human cells. EMBO Rep. 7, 314-320.

Obernosterer, G., Leuschner, P. J.*, Alenius, M.* and Martinez, J. (2006). Post-transcriptional regulation of microRNA expression. RNA. 12 (7) 1161-7. (*equally contributing authors) Featured in "Leading Edge", Molecular Biology Select, Cell, 126.*

Obernosterer, G., Meister, G., Poy, M., and Kuras, A. (2006). The impact of small RNAs—Microsymposium on Small RNAs. EMBO Rep. (in press)

PENNINGER

Alnaeeli, M., Penninger, J. M., and Teng, Y.-T. (2006). Immune interactions with CD4+ T-cells promote the development of functional osteoclasts from murine CD11c+ dendritic cells. J. Immunol. 177, 3314-26.

Atfield, A. D., Liu, P., and Penninger, J. M. (2006). The biochemical mechanisms of T-cell anergy. Curr. Immunol. Rev. 2, 73-99.

Brown, D., Yu, B. D., Joza, N., Bénit, P., Meneses, J., Firpo, M., Rustin, P., Penninger, J. M., and Martin, G. R. (2006). Loss of Aif function causes cell death in the mouse embryo but the temporal progression of patterning is normal. Proc Natl Acad Sci USA. 103, 9918-23.

Cheng, H.-Y. M., Dziema, H., Papp, J., Mathur, D. P., Ralph, M. R., Penninger, J. M., and Obrietan, K. (2006). The molecular gatekeeper Dexras1 sculpts the photic responsiveness of the mammalian circadian clock. J. Neuroscience. (in press)

Cheung, E. C., Joza, N., Steenaart, N., McClellan, K. A., Neuspiel, M., McNamara, S., MacLaurin, J. G., Rippstein, P., Park, D. S., Shore, G. C., McBride, H. M., Penninger, J. M. and Slack, R. S. (2006). Dissociating the dual roles of apoptosis-inducing factor in maintaining mitochondrial structure and apoptosis. EMBO J. 25, 4061-73.

Danilczyk, U., and Penninger, J. M. (2006). Angiotensin-converting enzyme II in the Heart and the Kidney. Circ. Res. 98, 463-71.

Danilczyk, U., Sarao, R., Remy, C., Benabbas, C., Stange, G., Richter, A., Arya, S., Pospisilik, J. A., Camargo, S. M. R., Makrides, V., Verrey, F., Wagner, C. A., and Penninger , J. M. (2006). Essential role for Collectrin in renal amino acid transport. Nature. (advanced online publication Dec. 2006).

Feraud, O., Debili, N., Penninger, J. M., and Kroemer, G. (2006). Cavitation of embryoid bodies requires optimal oxidative phosphorylation and AIF. Cell Death Differ. online.

Fischer, L., Gukovskaya, A. S., Penninger, J. M., Mareninova, O. A., Friess, H., Gukovsky, L., and Pandol, S. J. (2006). Phosphatidylinositol 3-kinase facilitates bile acid-induced Ca2+ responses in pancreatic acinar cells. Am. J. Path. online.

Imai, Y., Kuba, K., and Penninger, J. M. (2006). The renin angiotensin system in acute respiratory distress syndrome. Drug Discovery Today 3, 225-229.

Imai, Y., Kuba, K., and Penninger, J. M. (2006). Angiotensin converting enzyme 2 (ACE2) in acute respiratory distress syndrome (ARDS). CMSL. (in press)

Jones, H. D., Nakashima, T., Sanchez, O., Kozieradzki, I., Komarova, S. V, Sarosi, I., Morony, S., Rubin, E., Sarao, R., Hojilla, C. V., Komnenovic, V., Kong, Y.-Y., Schreiber, M., Dixon, F. J., Sims, S. M., Khokha, R., Wada, T., and Penninger, J. M. (2006). Chemotactic regulation of cancer cell migration and bone metastasis by RANKL. Nature. 440, 692-6.

Kim, N. S., Kim, H. J., Koo, B. K., Kwon, M. C., Kim, Y. W., Cho, Y., Tokota, Y., Penninger, J. M., and Kong, Y. Y. (2006). Receptor activator of NF-B ligand regulates the proliferation of mammary epithelial cells via Id2. Mol. Cell Biol. 26, 1002-1013.

Kuba, K., Imai, Y., and Penninger, J. M. (2006). Angiotensin-converting enzyme 2 in lung diseases. Curr Opin Pharmacol. 6, 271-276. 2006.

Kuba, K., Imai, Y., Rao, S., Jiang, C., and Penninger, J. M. (2006). Lessons from SARS: control of acute lung failure by the SARS receptor ACE2. J. Mol. Med. 84, 814-820.

Kuba, K., Imai, Y., and Penninger, J. M. (2006). Angiotensin-converting enzyme 2 (ACE2)-mediated regulation of cardiovascular peptides and its application for treating disease. Experimental Medicine. 24, 71-77.

Kuba, K., Imai, Y., and Penninger, J. M. (2006). Angiotensin-converting enzyme 2 (ACE2)-mutant mice. Respiratory Molecular Medicine 10, 38-42.

Loser, K., Mehling, A., Loeser, S., Apelt, J., Kuhn, A., Grabbe, S., Schwarz, T., Penninger, J. M., and Beissert, S. (2006). Epidermal RANKL controls regulatory T cell numbers via activating dendritic cells. Nature Med. 12 (12) 1372-9.

Marty, R. R, Dirnhofer, S., Mauermann, N., Schweikert, S., Akira, S., Hunziker, L., Penninger, J. M., and Eriksson, U. (2006). MyD88 signaling controls autoimmune myocarditis induction. Circulation 113, 258-65.

Maruyama, K., Takada, Y., Ray, N., Kishimoto, Y., Penninger, J. M., Yasuda, H., and Matsuo, K. (2006). Receptor activator of NF-kappaB ligand and osteoprotegerin regulate proinflammatory cytokine production in mice. J. Immunol. 177, 3799-805.

Nakashima T, and Penninger, J. M. (2006). Chemotactic regulation of cancer cell migration and bone metastases by RANKL. Experimental Medicine 24, 1777-80.

Oudit, G. Y., Herzenberg, A. M., Kassiri, Z., Wong, D., Reich, H., Khoka, R., Crackower, M. A., Backx, P. H., Penninger, J. M., and Scholey, J. W. (2006). Loss of angiotensin-converting enzyme-2 leads to the late development of angiotensin II- dependent glomeruloscerosis. Amer. J. Pathology 168, 1808-1820.

Rangachari, M., Mauermann, N., Marty, R., Dirnhofer, S., Kurrer, M. O., Komnenovic, V., Penninger, J. M. and Eriksson, U. (2006). T-bet negatively regulates autoimmune myocarditis by suppressing local production of interleukin 17. J. Exp. Med. 203, 2009-19.

Roy, A. A., Nunn, C., Ming, H., Zou, M.-X., Penninger, J., Kirshenbaum, L. A., Dixon, S. J., and Chidiac, P. (2006). Upregulation of endogenous RGS2 mediates cross-desensitization between Gs and Gq signaling in osteoblasts. J. Biol. Chem. 281 (43) 32684-93.

Sun, H., Kerfant, B.-G., Zhao, D., Trivievi, M. G., Oudit, G. Y., Penninger, J. M., and Backx, P. H. (2006). Insulin-Like Growth Factor-1 and PTEN Deletion Enhance Cardiac L-type Ca2+ Currents via Increased PI3Kalpha/PKB Signaling. Circulation Research, 98, 1390-7.

Valdes, G., Neves, L. A., Anton, L., Corthorn, J., Chacon, C., Germain, A. M., Merrill DC, Ferrario, C. M., Sarao, R., Penninger, J., and Brosnihan, K. B. (2006). Distribution of Angiotensin-(1-7) and ACE2 in Human Placentas of Normal and Pathological Pregnancies. Placenta 27, 200-7.

Vorbach, C., Capecchi, M., and Penninger, J. M. (2006)., Evolution of the mammary gland from the innate immune system? BioAssays. 28, 606-16.

Wada, T., Nakashima, T., Nishina, H., and Penninger, J. M. (2006). RANKL-RANK signaling in osteoclastogenesis and bone disease. Trends Mol. Med. 12, 17-25.

Yamamoto, Y., Udagawa, N., Matsuura, S., Nakamichi, Y., Horiuchi, H., Hosoya, A., Nakamura, M., Ozawa, H., Takaoka, K., Penninger, J. M., Noguchi, T., and Takahashi, N. (2006). Osteoblasts provide a suitable microenvironment for the action of receptor activator of NF-kappaB ligand. Endocrinology. 147, 3366-74.

Zhao, M., Song, B., Pu, J., Wada, T., Reid, B., Tai, G., Wang, F., Guo, A., Walczysko, P., Gu, Y., Sasaki, T., Suzuki, A., Forrester, J. V., Bourne, H. R., Devreotes, P. N., McCaig, C. D., and Penninger, J. M. (2006). Electrical signals control wound healing through phosphatidylinositol-3-OH kinase-gamma and PTEN. Nature 442, 457-60.

RINGROSE

Ringrose, L. (2006). Polycomb, Trithorax, and the decision to differentiate. BioEssays. 28, 330-4.

Ringrose, L, and Paro, R. (2006). Polycomb/Trithorax response elements and epigenetic memory of cell identity. Development. (in press)

SMALL

Caspani, E. M., Echevarria, D., Rottner, K. and Small, J. V. (2006). Live imaging of glioblastoma cells in brain tissue shows requirement of actin bundles for migration. Neuron Glia Biology, 2, 105-14.

Jenzora, A., Behrendt, B., Small, J. V., Wehland, J., Stradal, T. E. (2006). PREL1 provides a link from Ras signalling to the actin cytoskeleton via Ena/VASP proteins. FEBS Lett. 580 (12) 455-63.

Prast, J., Gimona, M. and Small, J. V. (2006). Immuniofluorescence microscopy of the cytoskeleton: combination with GFP tags. A Laboratory Handbook III (ed. J.E. Celis), Academic Press, Vol.1; 557-61.

Resch, G. P., Small, J. V., and Goldie, K. N. (2006). Electron Microscopy of Extracted Cytoskeletons: Negative Staining, Cryoelectron Microscopy and Correlation with Light Microscopy. In: Cell Biology - A Laboratory Handbook (J. E. Celis, ed.), 3rd edition, Elsevier Science.

Small, J. V. and Glotzer, G. (2006). Editorial overview; Cell structure and Dynamics. Curr. Opin. Cell Biol. 18, 1-3.

Steffen, A., Faix, J., Resch, G. P., Linkner, J., Wehland, J., Small, J. V., Rottner, K., Stradal, T. E. B. (2006). Filopodia formation in the absence of functional WAVE- and Arp2/3-complexes. Mol Biol Cell. 17 (6) 2581-91.

ELECTRON MICROSCOPY

Resch, G. P., Small, J. V., and Goldie, K. N. (2006). Electron Microscopy of Extracted Cytoskeletons: Negative Staining, Cryoelectron Microscopy and Correlation with Light Microscopy. In: Cell Biology - A Laboratory Handbook (J. E. Celis, ed.), 3rd edition, Elsevier Science.

Steffen, A., Faix, J., Resch, G. P., Linkner, J., Wehland, J., Small, J. V., Rottner, K., Stradal, T. E. B. (2006). Filopodia formation in the absence of functional WAVE- and Arp2/3-complexes. Mol Biol Cell. 17 (6) 2581-91.

BIOINFORMATICS SUPPORT

Bowman, S. K., Neumuller, R. A., Novatchkova, M., Du, Q., and Knoblich, J. A. (2006). The Drosophila NuMA Homolog Mud regulates spindle orientation in asymmetric cell division. Dev Cell 10, 731-42.

Hackl, H., Burkard, T. R., Sturn, A., Rubio, R., Schleiffer, A., Tian, S., Quackenbush, J., Eisenhaber, F., and Trajanoski, Z. (2005). Molecular processes during fat cell development revealed by gene expression profiling and functional annotation. Genome Biol. 6, R108.

Herzig, M., Savarese, F., Novatchkova, M., Semb, H., and Christofori, G. (2006). Tumor progression induced by the loss of E-cadherin independent of beta-catenin/Tcf-mediated Wnt signaling. Oncogene. online.

Hutterer, A., Berdnik, D., Wirtz-Peitz, F., Zigman, M., Schleiffer, A., and Knoblich, J. A. (2006). Mitotic activation of the kinase Aurora-A requires its binding partner Bora. Dev. Cell 11, 147-57.

Kueng, S., Hegemann, B., Peters, B. H., Lipp, J. J., Schleiffer, A., Mechtler, K. and Peters, J.-M. (2006). Wapl controls the dynamic association of cohesin with chromatin. Cell, 127 (5) 955-67.

Novatchkova, M., Schneider, G., Fritz, R., Eisenhaber, F., and Schleiffer, A. (2006). DOUTfinder--identification of distant domain outliers using subsignificant sequence similarity. Nucleic Acids Res 34, W214-218.

Watrin, E., Schleiffer, A., Tanaka, K., Eisenhaber, F., Nasmyth, K., and Peters, J.-M. (2006). Human Scc4 is required for cohesin binding to chromatin, sister-chromatid cohesion, and mitotic progression. Curr Biol 16, 863-874.

PROTEIN CHEMISTRY FACILITY

Betschinger, J., Mechtler, K., and Knoblich, J. A. (2006). Asymmetric segregation of the tumor suppressor brat regulates self-renewal in Drosophila neural stem cells. Cell. 124, 1241-53.

Fodor, B. D., Kubicek, S., Yonezawa, M., O'Sullivan, R. J., Sengupta, R., Perez-Burgos, L., Opravil, S., Mechtler, K., Schotta, G., Jenuwein, T. (2006). Jmjd2b antagonizes H3K9 trimethylation at pericentric heterochromatin in mammalian cells. Genes Dev. 20, 1557-62.

Ihling, C., Schmidt, A., Kalkhof, S., Schulz, D. M., Stingl, C., Mechtler, K., Haack, M., Beck-Sickinger, A. G., Cooper, D. M., Sinz, A. (2006). Isotope-labeled cross-linkers and fourier transform ion cyclotron resonance mass spectrometry for structural analysis of a protein/peptide complex. J Am Soc Mass Spectrom. 17 (8) 1100-13.

Kueng, S., Hegemann, B., Peter, B. H., Lipp, J. J., Schleiffer, A., Mechtler, K. and Peters, J.-M; (2006). Wapl controls the dynamic association of cohesin with chromatin. Cell. 127(5):955-67.

Mazanek, M., Mitulovic, G., Herzog, F., Stingl, C., Hutchins, J., Peters, J.-M., Mechtler, K. (2006). Titanium dioxide as a chemo-affinity solid phase in offline phosphopeptide chromatography prior to HPLC-MS/MS analysis. Nature Protocols. (in press)

Mitulovic G., Mechtler K. (2006). HPLC techniques for proteomics analysis. A short overview of latest developments. Brief. Funct. Genomic Proteomic. online.

Morandell, S., Stasyk, T., Grosstessner-Hain, K., Roitinger, E., Mechtler, K., Bonn, G. K., Huber, L. A. (2006). Phosphoproteomics strategies for the functional analysis of signal transduction. Proteomics. 6 (14) 4047-56.

Mujezinovic, N., Raidl, G., Hutchins, J. R., Peters, J.-M., Mechtler, K., Eisenhaber, F.* (2006). Cleaning of raw peptide MS/MS spectra: Improved protein identification following deconvolution of multiply charged peaks, isotope clusters, and removal of background noise. Proteomics. 6 (19) 5117-31. (*These authors jointly guided this work.)*

Petronczki, M., Matos, J., Mori, S., Gregan, J., Bogdanova, A., Schwickart, M., Mechtler, K., Shirahige, K., Zachariae, W., Nasmyth, K. (2006). Monopolar attachment of sister kinetochores at meiosis I requires casein kinase 1. Cell. 126 (6) 1049-64.

Riedel, C. G., Katis, V. L., Katou, Y., Mori, S., Itoh, T., Helmhart, W., Galova, M., Petronczki, M., Gregan, J., Cetin, B., Mudrak, I., Ogris, E., Mechtler, K., Pelletier, L., Buchholz, F., Shirahige, K., Nasmyth, K. (2006). Protein phosphatase 2A protects centromeric sister chromatid cohesion during meiosis I. Nature. 441 (7089) 53-61.

Schoeftner, S., Sengupta, A., Kubicek, S., Mechtler, K., Spahn, L., Koseki, J., Jenuwein, T. and Wutz, A. (2006). Recruitment of PRC1 function at the initiation of X inactivation independent of PRC2 and silencing. EMBO J. 25 (13) 3110-22.

Stingl, C., Ihling, C., Ammerer, G., Sinz, A., Mechtler, K. (2006). Application of different fragmentation techniques for the analysis of phosphopeptides using a hybrid linear ion trap-FTICR mass spectrometer. Biochim Biophys Acta. 1764 (2006) 1842-1852.

HISTOLOGY

Jones, D. H., Nakashima, T., Sanchez, O. H., Kozieradzki, I., Komarova, S. V., Sarosi, I., Morony, S., Rubin, E., Sarao, R., Hojilla, C. V., Komnenovic, V., Kong, Y. Y., Schreiber, M., Dixon, S. J., Sims, S. M., Khokha, R., Wada, T., Penninger, J. M. (2006). Regulation of cancer cell migration and bone metastasis by RANKL. Nature. 440 (7084) 692-6.

Rangachari, M., Mauermann, N., Marty, R. R., Dirnhofer, S., Kurrer, M. O., Komnenovic, V., Penninger, J. M., Eriksson, U. (2006). T-bet negatively regulates autoimmune myocarditis by suppressing local production of interleukin 17. J Exp Med. 203 (8) 2009-19.

MOUSE SERVICE

Haemmerle, G., Lass, A., Zimmermann, R., Gorkiewicz, G., Meyer, C., Rozman, J., Heldmaier, G., Maier, R., Theussl, C., Eder, S., Kratky, D., Wagner, E. F., Klingenspor, M., Hoefler, G., Zechner, R. (2006). Defective Lipolysis and Altered Energy Metabolism in Mice Lacking Adipose Triglyceride Lipase. Science. 312 (5774) 734-737.

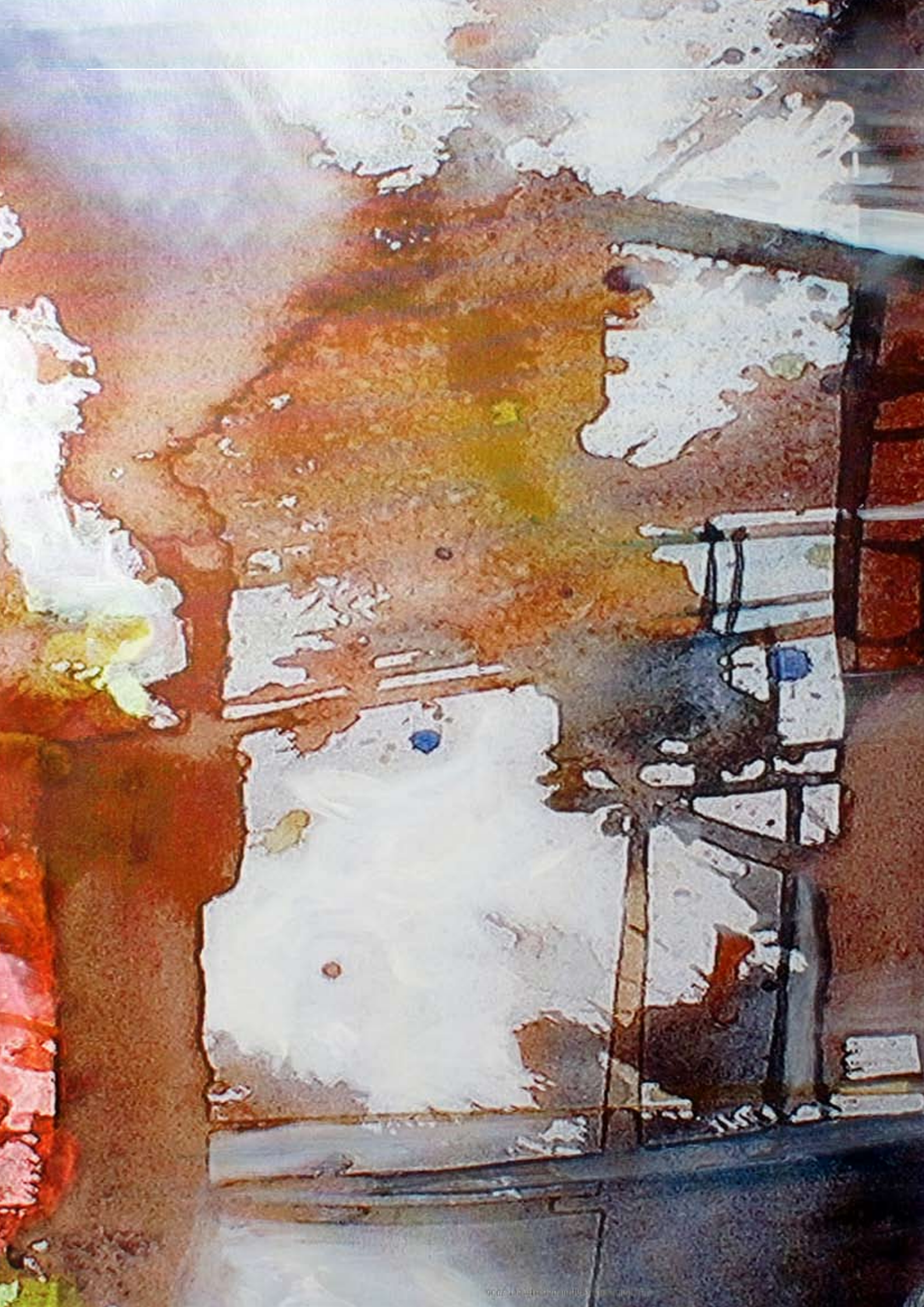
Awards

Andrea Hutterer

Annual Award of the Austrian Society for Biochemistry and Molecular Biology (September 2006)

Arabella Meixner

Prize for the Promotion of Science by the City of Vienna (September 2006)



Seminar Speakers

JANUARY

11 | 01 | 06 Andreas Hochwagen (MIT, Department of Biology)
19 | 01 | 06 Mauro Giacca (ICGEB Laboratories Trieste, Italy)
27 | 01 | 06 Conly Rieder (Wadsworth Center, Cellular Regulation, Albany, New York)

FEBRUARY

02 | 02 | 06 Henry Roehl (University of Sheffield)
09 | 02 | 06 Silke Sachse (Institute for Biology & Neurobiology, Free University, Berlin)
09 | 02 | 06 Richard Marais (The Institute of Cancer Research, London)
10 | 02 | 06 Yoichi Shinkai (Institute for Virus Research, Kyoto University)
16 | 02 | 06 David Van Vactor (Department of Cell Biology, Harvard Medical School, Boston)
28 | 02 | 06 Wolf-Dietrich Hardt (ETH Zurich, Institute of Microbiology)

MARCH

01 | 03 | 06 Andrea Sinz (University of Leipzig)
02 | 03 | 06 Matthias Wilmanns (EMBL Hamburg)
03 | 03 | 06 Morten Lindow (Bioinformatics Centre, University of Copenhagen)
09 | 03 | 06 Akira Shinohara (Institute for Protein Research, Osaka University)
10 | 03 | 06 Albert Heck (Department of Biomolecular Mass Spectrometry, Utrecht University)
16 | 03 | 06 Andrew McMahon (Harvard University)
21 | 03 | 06 Dave Jackson (Cold Spring Harbor Laboratory)
28 | 03 | 06 Jan van Deursen (Mayo Clinic College of Medicine)
30 | 03 | 06 Nenad Ban (Institute of Molecular Biology and Biophysics, Zürich)

APRIL

06 | 04 | 06 Pitter Huesgen (Department of Physiology and Plant Biochemistry, University of Konstanz)
13 | 04 | 06 Thomas L. Volkert (Whitehead Institute for Biomedical Research, Cambridge, USA)
20 | 04 | 06 Masaru Okabe (Genome Information Research Center, Osaka University)
27 | 04 | 06 Joel L. Sussman (Dept. of Structural Biology, Weizmann Institute of Science)

MAY

05 | 05 | 06 Anuhar Chaturvedi (Department of Hematology, Hannover Medical School)
10 | 05 | 06 Owen Sansom (Beatson Institute for Cancer Research, Glasgow)
11 | 05 | 06 Claude Desplan (New York University, Dept. of Biology)
12 | 05 | 06 James Langridge (Waters Corporation, Manchester, UK)
12 | 05 | 06 Matthias Wilm (EMBL, Heidelberg)
18 | 05 | 06 Juan Valcarcel (ICREA & Ctr de Regulacio Genomica, Barcelona)
19 | 05 | 06 Harold Varmus (Memorial Sloan-Kettering Cancer Center, New York)
24 | 05 | 06 Bill Hahn (Dana Farber Cancer Institute)
29 | 05 | 06 Montserrat Corominas-Guiu (Dept. of Genetics, University of Barcelona)

JUNE

01 | 06 | 06 Helen Blau (Baxter Laboratory in Genetic Pharmacology, Stanford University)
06 | 06 | 06 Andrea Vortkamp (Centre for Medical Biotechnology, University Duisburg-Essen)
06 | 06 | 06 Jean-Pierre David (Rheumazentrum, Berlin)
08 | 06 | 06 Fiona Watt (ICRF, London)
14 | 06 | 06 Jacques Neefjes (Division of Tumor Biology, The Netherlands Cancer Institute, Amsterdam)
16 | 06 | 06 Bernd Fritzsch (Dept of Biomed Sciences, Creighton University, Omaha)
21 | 06 | 06 Frank Uhlmann (Chromosome Segregation Laboratory, Cancer Research UK, London)
28 | 06 | 06 Erik Sahai (Tumour Cell Biology Laboratory, Cancer Research UK)
29 | 06 | 06 James Zheng (Dept. of Neuroscience and Cell Biology, University of Medicine and Dentistry, New Jersey)

JULY

03 | 07 | 06 Catherine Dulac (Howard Hughes Medical Institute, Harvard University)
04 | 07 | 06 Jody Haigh (Department for Molecular Biomedical Research, Ghent University)
06 | 07 | 06 Alexander Tarakhovsky (Laboratory of Lymphocyte Signaling, The Rockefeller University, New York)
13 | 07 | 06 Li Huei Tsai (Department of Brain and Cognitive Sciences, HHMI, Massachusetts)
14 | 07 | 06 Will Wood (Gulbenkian Institute and Institute of Molecular Medicine, Lisbon)
18 | 07 | 06 Reinhold G. Erben (University of Veterinary Medicine, Vienna)
20 | 07 | 06 Ulrich Hartl (Max Planck Institute for Biochemistry, Department of Cellular Biochemistry, Martinsried)

AUGUST

01 | 08 | 06 Goetz Laible (AgResearch, Hamilton, New Zealand)
04 | 08 | 06 Vigo Heissmeyer (GSF-Institute of Molecular Immunology, Munich)
17 | 08 | 06 Norbert Perrimon (Department of Genetics, HHMI/ Harvard Medical School, Boston)
18 | 08 | 06 Michel Pairet (Boehringer Ingelheim Germany)
22 | 08 | 06 Martin Kupiec (Dept. of Molecular Micro & Biotech, Tel Aviv University)

24 | 08 | 06 Paul Klenerman (Institute for Emergent Infections of Humans, University of Oxford)
31 | 08 | 06 Eckhard Mandelkow (Max-Planck-Unit for Structural Molecular Biology, Hamburg)

SEPTEMBER

12 | 09 | 06 David Drubin (University of California, Berkeley)
15 | 09 | 06 Thomas Steitz (Howard Hughes Medical Institute, Yale University)
15 | 09 | 06 Alex Bird (Max-Planck Institute of Molecular Cell Biology and Genetics)
18 | 09 | 06 Michaela Kress (Department of Physiology and Medical Physics, Innsbruck Medical University)
19 | 09 | 06 Thomas Winkler (Fiebiger Center for Molecular Medicine, Erlangen)
19 | 09 | 06 Ed Sturrock (University of Cape Town)
19 | 09 | 06 Rosemary J. Akhurst (Cancer Research Institute, University of California at San Francisco)
21 | 09 | 06 Gerhard Christofori (Institute of Biochemistry and Genetics, University of Basel)

OCTOBER

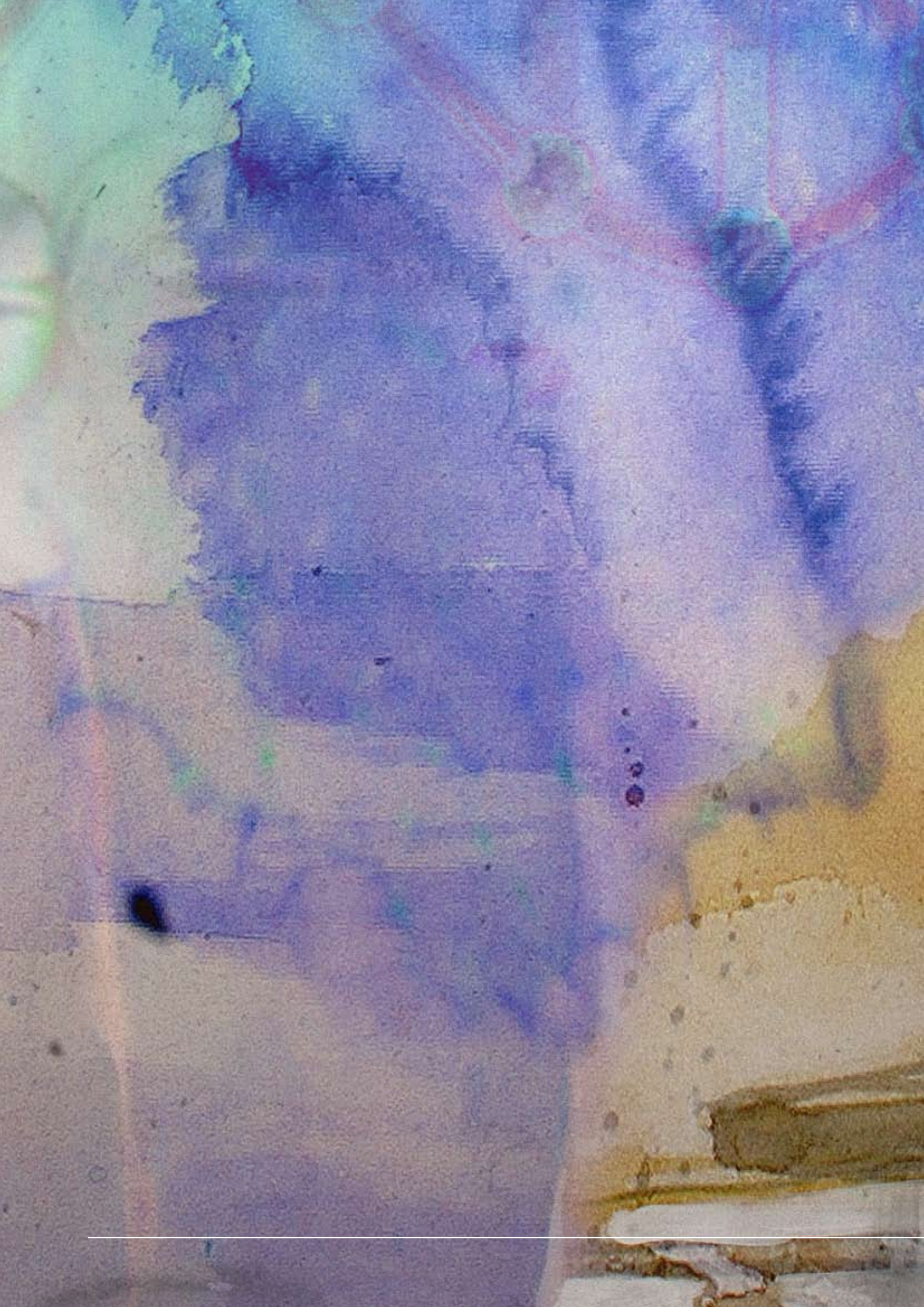
03 | 10 | 06 Ada Yonath (Weizmann Institute Rehovot, Israel)
11 | 10 | 06 Mark S. Anderson (UCSF Diabetes Center, San Francisco)
12 | 10 | 06 Winship Herr (Center for Integrative Genomics, University of Lausanne)
16 | 10 | 06 Yosef Rafaeli (National Jewish Medical and Research Center, Denver)
18 | 10 | 06 Michael Ehrmann (ZMB Uni, Duisburg-Essen)
25 | 10 | 06 Pamela J. Green (Delaware Biotechnology Institute, Newark)

NOVEMBER

06 | 11 | 06 Min Zhao (University of Aberdeen, Institute of Medical Sciences)
09 | 11 | 06 David Holden (Centre for Molecular Microbiology and Infection, Imperial College, London)
14 | 11 | 06 Witold Filipowicz (Friedrich Miescher Institute for Biomedical Research, Basel)
16 | 11 | 06 Albert Osterhaus (Institute of Virology, Erasmus MC, Rotterdam)
23 | 11 | 06 Bettina Warscheid (Medical Proteome-Center, Ruhr-University Bochum)
23 | 11 | 06 Frank Grosveld (Erasmus University Medical Center, Faculty of Medicine and Health Sciences, Rotterdam)
24 | 11 | 06 Thorsten Hoppe (ZMNH, University of Hamburg)
27 | 11 | 06 Andreas Trumpp (ISREC, Lausanne)
28 | 11 | 06 Katsuhiko Shirahige (Tokyo Institute of Technology)
28 | 11 | 06 Peter Lobie (Liggins Institute, Auckland)

DECEMBER

04 | 12 | 06 Jürgen Ruland (Technical University, Munich)
05 | 12 | 06 Gregory Jefferis (Dept. of Zoology, University of Cambridge)
07 | 12 | 06 Oleg Glebov (MRC Laboratory of Molecular Biology, Cambridge)
14 | 12 | 06 Holger Stark (MPI for Biophysical Chemistry, Goettingen)
14 | 12 | 06 Stefan Kaufmann (Max Planck Institute for Infection Biology, Berlin)



Spotlight on 2006

IMP IMBA Recess

Every year, IMBA scientists meet with members of the Scientific Advisory Board to present their work, discuss their research and look for advice and feedback from their peers. Three days in October are devoted to this strictly internal event. It is a time of extensive preparations and heightened activity. This year's Recess took place from October 4-6 at the premises of IMBA and IMP, taking advantage of IMBA's impressive winter garden for poster exhibitions and coffee breaks. The SAB members were unanimously impressed by the scientific performance and high standards of the research presented.

Symposium "Timing Age"

As in previous years, PhD students of IMBA, together with students of the Vienna Biocenter, organized a scientific symposium in fall. The meeting, which took place on November 2 and 3, was devoted to "aging". World class specialists explored the topic from various angles. Their contributions covered such diverse fields as cellular and molecular aging, systems biology, diseases and therapies, as well as the use of model organisms in the study of aging. The last sessions on both days focused on ethical implications of aging research, giving rise to interesting and lively discussions. The meeting was a big success, with close to 200 participants attending, many of them from abroad. This series will be continued in 2007 with a symposium on "Molecular Psychology".

PhD Student and Postdoc Retreat

Two new initiatives were started in the summer of 2006. The PhD Students of the Vienna Biocenter organized a retreat in Litschau (Lower Austria) and the Postdoctoral Fellows met at the Augustinian Abbey of Brno (Czech Republic). Both events lasted for two days and were highly interactive, with presentations and poster sessions as well as a healthy dose of sports and fun. Invited guest speakers added an extra dimension to the meetings. Both initiatives were received with enthusiasm by the participants and will now become regular annual events.

MicroSymposium on Small RNAs

On May 29 and 30, IMBA hosted the "Microsymposium on Small RNAs", organised by IMBA Group Leader Javier Martinez. The aim of the meeting was to link the key European investigators working in the field of RNA silencing. Keynote speaker Steve Cohen from the EMBL gave a comprehensive lecture, describing how microRNAs regulate genome expression. A series of short talks followed, addressing the molecular mechanisms driving RNA silencing, function of small RNAs in viruses, plants, *C. elegans*, zebrafish and humans, closed by lectures on new developments in the field of bioinformatics regarding the prediction of small RNAs and their targets in the genome. The meeting was very successful and will be made into an annual event at IMBA.

Opening of the "Life Sciences Center Vienna"

On May 23, IMBA's brand new home, the "Life Sciences Center Vienna", was opened with due ceremony. The impressive building of the Austrian Academy of Sciences also accommodates the Gregor Mendel Institute (GMI) and the Vienna Open Lab, a hands-on laboratory for the public. The day started out with a press conference, followed by extensive filming of the labs and interviews for the media. In the evening, the building was transformed by the work of light artists and took on a festive appearance. Hundreds of invited guests spilled into the lecture hall to witness the official opening ceremony. Among the speakers was Austrian Federal Chancellor Wolfgang Schüssel, who expressed his best wishes for the future of IMBA.
After the speeches, the guests were taken on guided tours of the new research building before joining the employees for a big party which lasted well into the next morning.

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Michael KREBS	*Director/Finance and Administration*

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Ursula KOSIR	*Executive Assistant*

Administrative Assistance

Denise KLOSS	*Assistant to the Admin. Director*

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Katharina JANDRASITS	*Technical Assistant*
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Sarra OVUIKE	*Technical Assistant*
Sabina SANEGRE SANS	*Technical Assistant*
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Nuray KILIC	*Laboratory Technician*
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Taoufik BAHMOU	*Chef*
Markus GIGLER	*Chef*
Helga MEHOFER	*Buffet*
Sabine SMALCL	*Buffet*
Farzana UDDIN	*Buffet*
Güler CICOS	*Kitchen Helper*
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Biology, Utrecht, NL

In order to maintain the highest standard of research, IMBA, together with the IMP, has installed a process of review and feedback: the Scientific Advisory Board (SAB), consisting of internationally recognized scientists. The Board meets yearly at IMBA, and, together with IMBA researchers, discusses the quality, significance, and main focus of research conducted at IMBA.

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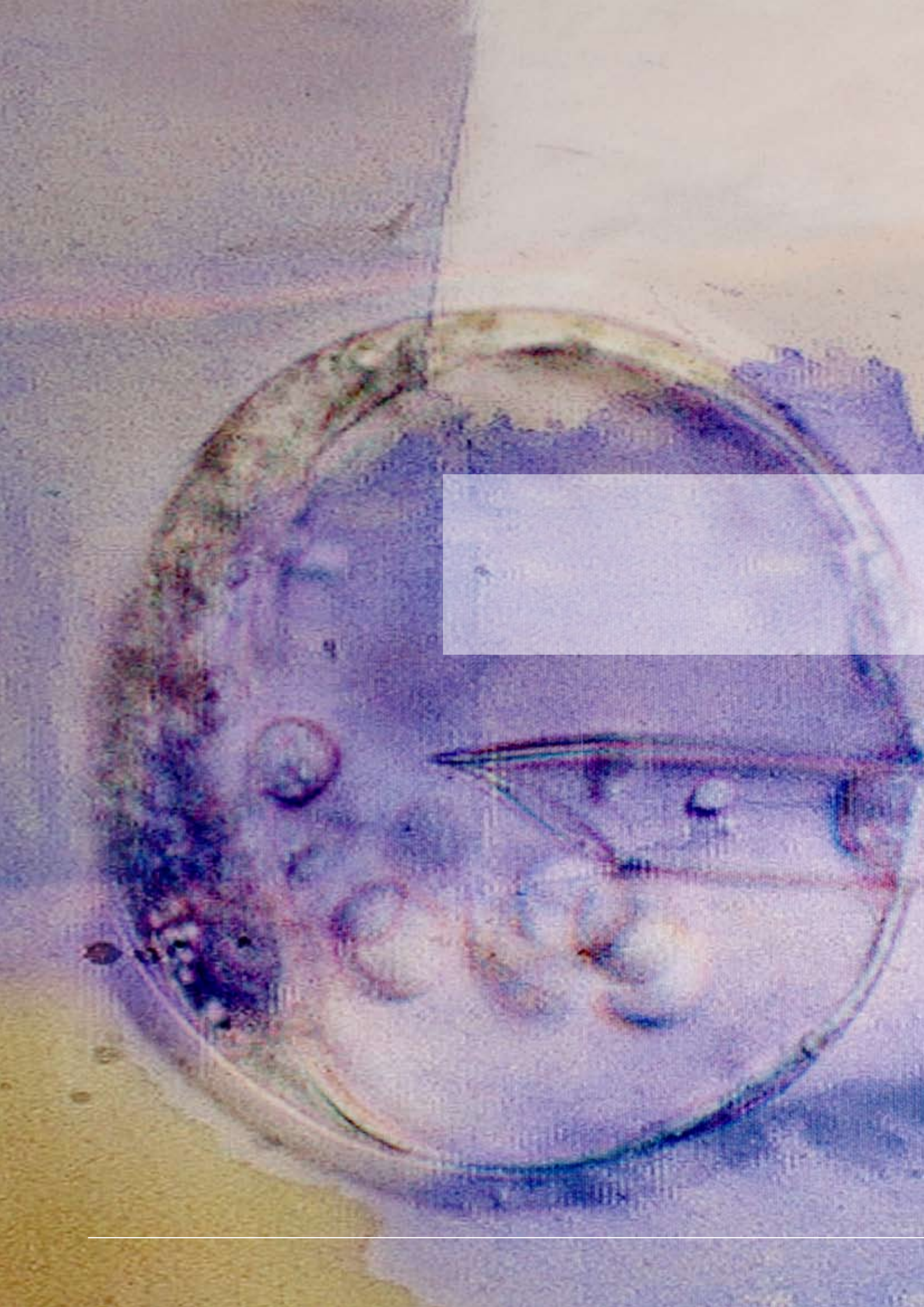

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U3
Rennweg
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St.Marx - Campus
Vienna Biocenter
S7
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Dr. Bohr-Gasse 3
Landstrasser Gürtel
A4 Ostautobahn / Airport
A23 Südostangente
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