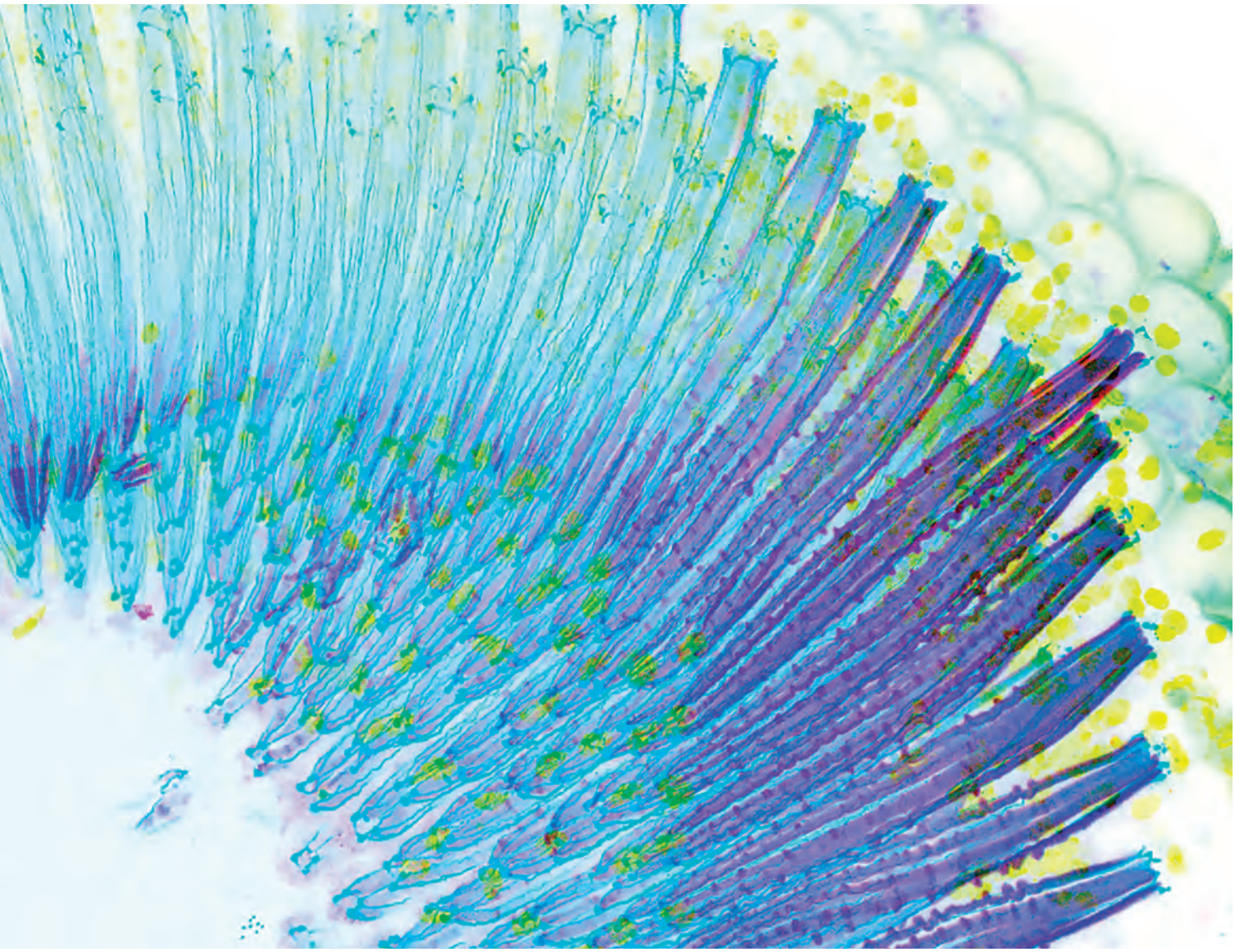
RESEARCH INSTITUTE OF MOLECULAR PATHOLOGY

VIENNA BIOCENTER

2014



Boehringer Ingelheim

IMP
Research Institute of Molecular Pathology

CONTENTS

INTRODUCTION

JAN-MICHAEL PETERS Managing Director/ Science

HARALD ISEMANN Managing Director/ Finance and Administration

Science is changing the world, all the time, and in the last decades faster than ever. When the IMP opened its doors, now more than a quarter of a century ago, it aspired to become one of the driving forces in this process. The IMP aimed for nothing less than helping to uncover fundamental principles of life, motivated primarily by scientific curiosity, but realizing that it is today's basic research in biology which will lay the foundation for better medicine in the future. Since then the IMP has indeed contributed to our understanding of how "life works". This is remarkable, given that the IMP is tiny by comparison to other research organizations, and given that it is located far away from the centers where today's prevailing life science disciplines, molecular biology, biochemistry, structural biology, genetics, immunology and neurobiology, were invented.

Research at the IMP has never just been "me too", but is driven by the desire for real novelty. The first key molecules of epigenetic regulation, methyl-DNA binding proteins and histone modifying enzymes, important principles of the metastatic epithelial-mesenchymal transition, cohesin and separase as key regulators of chromosome structure and segregation, the mechanisms by which the fruitless gene determines sexual behavior, the decisive role of the transcription factor Pax5 in determining B-cell differentiation, the existence of arginine phosphorylation and the enzymes that create and remove this modification, methods that enable the genome-wide identification of enhancers or the organism-wide visualization of neuronal activity, these were all discovered or invented at the IMP, and in many cases only here. It is fair to say that without the IMP, biology textbooks would not be the same.

The reasons that have enabled these achievements have often been described and praised: the generous funding by our sponsor Boehringer Ingelheim, the exceptional quality of our core scientific services, the internationality of our PhD Programme, the ability of the IMP to attract some of the most talented young scientists from all over the world, the complete freedom and independence of our group leaders in their research, the relatively high turn-over rate among all scientists, including faculty members, and - last but not least - the unusual commitment of all staff members to making the IMP a great success and a wonderful place to work. We are very grateful to Boehringer Ingelheim and the shareholder families for making the existence of an institute with such unique assets possible, to the national and international funding agencies who support us in this endeavor. And of course we want to pay a special tribute to the IMP's founding director Max Birnstiel on whose vision all of these principles are based. We are very sad that Max passed away this year, unexpectedly and too early. We encourage you to read more about Max and how he opened the IMP on the following pages, and in obituaries written by Jeff Schatz (Cell 160:11-12, January 15, 2015) and by Adrian Bird and Michael Grunstein (PNAS 112:302-3, January 13, 2015).

If you will read how Max decided to become the first IMP director, in a place that was hardly known for modern life science research at the time, with a total staff of only 90 employees at the beginning, but fearlessly willing to compete with the best and biggest biology centers of the world, you may be reminded of Asterix the Gaul who in a tiny remote village resisted the legendary Roman army. But Max had the wise intuition that - unlike Asterix and his villagers - the IMP might not be able to succeed and survive just on its own. Max therefore added one more key ingredient to his magic potion that would allow the tiny IMP to survive in a global scientific world among giants like MIT or Harvard: the idea for the Vienna Biocenter (VBC). Max made his acceptance conditional on the commitment of the University of Vienna to move its molecular biology departments directly next to the IMP. This led to the foundation of what is now known as Max F. Perutz Laboratories (MFPL) and initiated the formation of a life science campus whose size and success even Max could not have predicted at the time. Together with MFPL professor Alexander von

Gabain, Max founded InterCell (now Valneva), which later led to the set up of Affiris by Walter Schmidt who was a postdoc in Max´s lab at the IMP. On the academic side, Boehringer Ingelheim and the IMP entered a collaboration with the Austrian Academy of Sciences, an agreement which initiated the foundation of IMBA and GMI. In order to keep pace with the rapidly advancing technologies required for modern biomedical research a Campus Science Support Facility CSF, which now perfectly complements our internal services was established a couple of years ago with generous support from the Austrian Science Ministry and the City of Vienna. At the IMP we are both proud and grateful: proud that the IMP initiated these developments, and grateful to our colleagues at the Vienna Biocenter for sharing and so enthusiastically supporting our vision to do life science research at its very best on this campus.

Can we now lay back and rest assured that the IMP and the Vienna Biocenter have a safe place in the world of life science? By no means at all. It is inherent to the scientific process that it changes all the time, as a result of the knowledge that it creates itself. With this, also the IMP is constantly changing and might do so even more in the future. In 2014, Simon Rumpel left the IMP to take on a professor position at the University of Mainz in Germany. We would like to thank Simon for being a wonderful colleague and for being one of the pioneers of circuit neuroscience at the IMP, and wish him all the best for the future. Other faculty members are also planning their next career steps, so the recruitment of new scientists is currently a top priority for the IMP. Alex Stark who joined the IMP six years ago and is meanwhile widely recognized and highly respected for his work on genomics and gene regulation has been promoted to a Senior Scientist at the IMP. With his visionary commitment to scientific excellence he will help shape the IMP´s path in the years to come.

Inside the IMP, our facility management and workshop teams proved once more their "anything is possible – let's do it" attitude and built a room shielded from the magnetic field of the Earth, one of a few of its kind on the planet. Inside this magic room, David Keays and his group will now be able to perform experiments that simply were not possible before. At the whole-institute level the IMP has even more ambitious aims and completed the planning phase for a new building, scheduled to be constructed from spring 2015 until the end of 2016. This beautiful new lab-building will provide the modern, state-of-the-art but flexible infrastructure that will be needed for innovative life science research in many years to come.

But not only scientific knowledge, technologies and infrastructure are constantly changing, so are also modern societies and what they expect from the next generations of scientists. To prepare these as well as possible for their future, at the IMP and beyond, academic training coordinator Inês Crisostomo launched for the first time in 2014 two "prime your PhD" courses. These three-week events "were tough", many participants said, "but extremely useful". Inês also launched the "Ambassador Programme" in which senior or freshly graduated members of the VBC PhD Programme visit their home university to spread the word about how exciting doing a PhD at the VBC can be. Together with the VBC Summer School, which was initiated five years ago by David Keays, the Ambassador Programme is an initiative to increase the international visibility of the IMP and the VBC further, a necessity in times where more and more programmes and places compete for the best students and postdocs in a global science community. The VBC Summer School has again been a huge success, in 2014 with more than 1,000 applications from all over the world. In the future, we expect that it will become even more important that the IMP and the VBC not only perform world-class research, but also ensure that the rest of the world knows about this, to be able to compete internationally for the best young scientists. We are, therefore, glad that in summer 2014 we were able to recruit Stefan Bernhardt who together with Heidemarie Hurtl will work in the Public Relations office of the IMP.

Last but not least, 2014 has of course not only been a year of making plans for the future, but where science has been in full swing at the IMP, in form of exciting experiments and discoveries in the research labs, in form of lively discussions and lectures in the cafeteria and the lecture hall, in form of more than 80 high-profile publications, and leading to international recognition of IMP scientists by numerous granting and prize awarding committees. Manuel Zimmer received the prestigious Global Brain Research Award of the Simons Foundation and Alex Stark was listed among the "Highly Cited Researchers 2014" by Thomson Reuters, to name just two of these.

We would like to thank all IMP members and our colleagues at the VBC for this success and hope you will enjoy reading more about the exciting science at the IMP on the following pages.

Jan-Michael Peters and Harald Isemann

OBITUARY PROF. MAX BIRNSTIEL

Max Birnstiel, the IMP's first Director, died on 15 November 2014 at the age of 81. With his passing, the IMP and the entire Vienna Biocenter lost their most influential figure and a role model for those who followed him. He will be sorely missed and our condolences go to his wife and family.

It is impossible to overstate the difficulty of establishing an institute, especially in a country that – in those days – was not well known as a centre for research in the life sciences. For the new venture to succeed, it was essential to recruit top-class scientists from the very start but who would commit their future to somewhere so lacking in modern biological research? Fortunately, Max Birnstiel was prepared to take on the challenge and was able to persuade five world-leading scientists to join him in Vienna.

Max negotiated with potential recruits from a position of great strength. Interested in biology from an early age, he studied physical chemistry at the ETH in Zurich, reasoning that quantitative methods would be key to solving important biological problems. He retained this belief throughout his life, as shown by his foresight in equipping the IMP with core facilities that are still the envy of its competitors.

After a doctorate at the ETH and a postdoc at CalTech, Max moved to the new MRC Epigenetics Research Group in Edinburgh, where he stayed for nearly a decade. His familiarity with physical methods enabled him to become the first person to purify eukaryotic genes (for ribosomal RNA) to homogeneity, long before the advent of cloning procedures, and together with Hugh Wallace he showed that the ribosomal RNA genes of the frog *Xenopus laevis* were arranged in tandem repeats in the nucleolus organizer, thereby revealing the nucleolus as the site of ribosomal RNA production.

Max returned to Zurich as Director of the Institute of Molecular Biology, where over the following 16 years he made a number of groundbreaking discoveries. His group isolated vertebrate histone genes and transfer RNA genes and did more than any other to advance our understanding of how the 3' ends of histone messenger RNA (mRNA) are formed. His characterization of the regulatory regions (promoters) of eukaryotic genes attracted considerable attention and led to numerous awards.

By the mid-1980s, when he was invited to set up the IMP, Max was firmly established as a pioneer in the field of molecular biology, someone whose mere presence at an institute could be seen as a guarantee of success. Someone able to pilot the IMP through its difficult early period, assembling a Scientific Advisory Board of eminent scientists from throughout the world and encouraging researchers of the calibre of Adrian Bird, Meinrad Busslinger, Kim Nasmyth, Erwin Wagner and the late Hartmut Beug to join him.

Even with such a stellar cast, Max knew the IMP could not exist for long on its own. His scientific standing stood him in good stead in negotiations with local politicians and with other academic institutions and he was able to persuade the University of Vienna to move its own molecular biology departments (now the Max F Perutz Laboratories) to an adjacent site. In time, more institutes and spin-off companies set up stall on the campus, leading to the creation of the Vienna Biocenter, which currently hosts about 1,400 staff and 700 students.

Although Max oversaw the development of "his" institute with justified pride, he was not content merely to manage the IMP. During the decade he spent in Vienna he maintained a productive research group, extending his work on the 3' processing of histone mRNA and focusing also on improving gene delivery systems and on developing new approaches for cancer vaccines. Max's own work contributed to the IMP's worldwide reputation and by his retirement in 1996 the IMP could be considered one of the top institutes in the field.

As expected, Max remained scientifically active after his retirement. He was the driving force behind the founding of Intercell (now Valneva), the first biotech company located at the Vienna Biocenter, and subsequently served as Chair of the Scientific Advisory Board of Affiris. He retained a keen interest in the IMP's research and was always willing to discuss ideas and visions with his many scientific friends.
In a brief article it is impossible to do justice to Max's many and varied achievements. However, it is fair to say that he almost single-handedly changed the face of biological research in Austria, creating an institute in his own image and one that within a few years he helped to reach the very forefront of his field. He will indeed be sorely missed.

"In no time, Max had recruited five first-rate young scientists as group leaders who were to shape the IMP during its crucial starting phase and beyond." ... " By creating a set of core facilities, Max gave the young IMP an edge over its competitors and quickly propelled it into the top league of biomedical research centers."

Gottfried (Jeff) Schatz
Cell 160, January 15, 2015

Max L. Birnstiel 1933-2014

… Max would have been proud of the following publications in 2014 …

Schwickert, T.A., Tagoh, H., Gültekin, S., Dakic, A., Axelsson, E., Minnich, M., Ebert, A., Werner, B., Roth, M., Dickins, R.A., Zuber, J., Jaritz, M., and Busslinger, M. (2014). Stage-specific control of early B cell development by the transcription factor Ikaros. Nat. Immunol. 15, 283-293,

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MEINRAD BUSSLINGER

Transcriptional control of B cell immunity

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Acquired immunity to foreign pathogens depends on the differentiation of B and T lymphocytes from hematopoietic stem cells, which is controlled by a multitude of transcription factors. We study the process by which transcription factors regulate the commitment of early hematopoietic progenitors to the B-lymphoid lineage, and control their subsequent differentiation to mature B lymphocytes and plasma cells.

B cell development

A fundamental question in hematopoiesis is how stem cells and early progenitors become committed to a single developmental pathway and then differentiate into mature cell types of the selected lineage. The entry of lymphoid progenitors into the B-cell lineage depends on several transcription factors, including E2A, EBF1 and Pax5. E2A and EBF1 function as B-cell specification factors, and Pax5 as the B-cell commitment factor that restricts the development potential of hematopoietic progenitor cells to the B-cell pathway. We recently demonstrated that the transcription factor Ikaros stringently controls signaling from the pre-B cell receptor, which functions as an important checkpoint in early B cell development. B cell immunity critically depends on mature B cells. As the early-acting transcription factors are also expressed in mature B cells, we are currently studying their molecular functions in controlling B-cell immune responses to foreign antigens (see Figure). Whereas the identity of mature B cells strictly depends on Pax5, the transcriptional regulator Blimp1 controls terminal differentiation to plasma cells, which secrete high-affinity antibodies to neutralize foreign pathogens. We are investigating the molecular functions of these and novel transcription factors in B cell immunity by using mouse transgenic, cell biological and genome-wide molecular approaches.

Spatial regulation of V(D)J recombination

The development of B cells and $\alpha\beta$ T cells depends on functional rearrangement of the *Igh* and *Igk*, or *Tcrb* and *Tcra* antigen receptor loci, respectively. All four loci are large in size (0.7 to 3 megabases), have a complex structure, and undergo reversible contraction by long-range looping in rearranging lymphocytes. Locus contraction is thus a general mechanism that juxtaposes distantly located V genes of the large V gene cluster next to D or J segments in the 3' proximal domain, which facilitates synapse formation and V-(D)J recombination. We previously demonstrated the crucial role of Pax5 in the control of *Igh* locus contraction, and identified Pax5-activated intergenic repeats (PAIRs) in the distal V_H gene cluster as potential regulatory elements involved in this process. By genetic inactivation in cultured pro-B cells and mice, we are currently investigating the role of *cis*-regulatory elements (such as the PAIRs) and novel *trans*-acting factors in the control of long-range looping at the *Igh* locus.

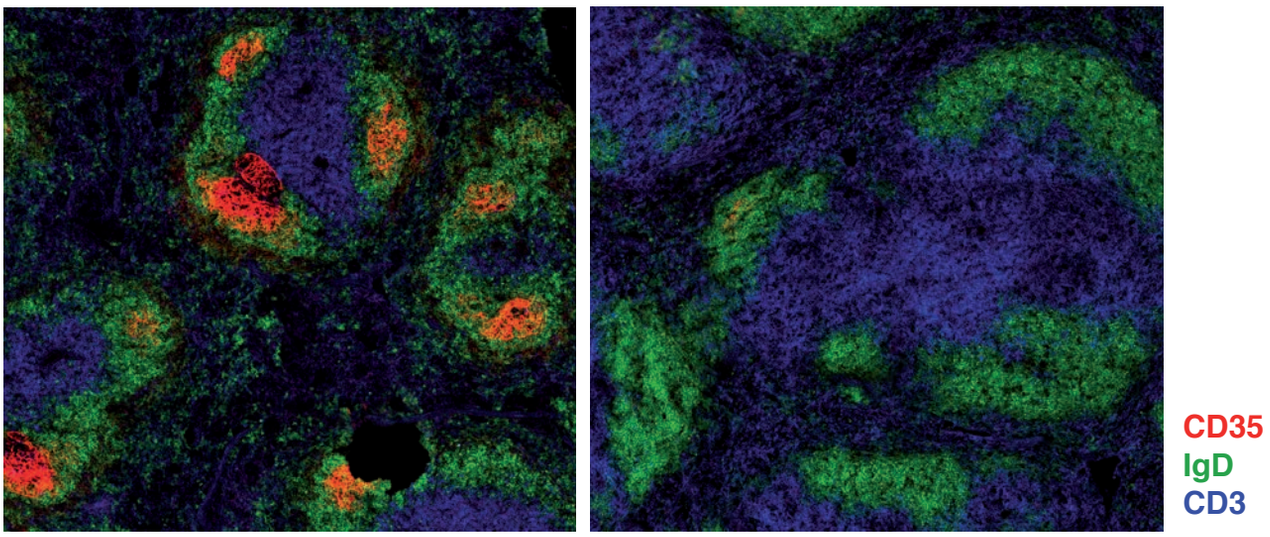

FIGURE: **Critical role of Pax5 in B cell immunity**. Mice expressing or lacking *Pax5* in mature B cells were immunized with the antigen NP-KLH. Immunostaining of spleen sections from control mice (left) revealed $CD35^+$ follicular dendritic cells (red), mature IgD^+ B cells (green), and $CD3^+$ T cells (blue). In the absence of Pax5 (right), germinal centers with follicular dendritic cells were, however, not formed in experimental mice.

Further reading:

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TIM CLAUSEN

Molecular basis of protein quality control

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Our group is interested in understanding the molecular mechanisms that underlie the quality control of cellular proteins preventing their misfolding and aggregation. In addition to characterizing the respective protease and chaperone machines, we address the molecular basics of stress response pathways. To this end we use an integrative approach combining methods from structural biology, protein biochemistry and molecular cell biology.

Muscle development and function rely on the correct assembly of contractile units known as sarcomeres. Their main components, i.e. thin (actin) and thick (myosin) filaments, are organized in a precisely arranged, quasi-crystalline protein framework that mediates muscle contraction. Although the overall architecture of the sarcomere has been studied in detail, little is known about its complicated assembly process. In particular, the mechanism of myosin incorporation into thick filaments is poorly understood.

It has been shown that the folding of myosin involves the assistance of certain molecular chaperones. Chaperones are specialized helper proteins that bring their client proteins into the correct fold and keep them in good shape. The myosin-specific chaperone UNC-45 has been known to play a key role in muscle formation, but its exact function has remained elusive.

To address the underlying principle of how myosin filaments are assembled in muscle cells, my group performs a detailed biochemical and structural analysis of the UNC-45 protein from the nematode worm *C. elegans*. Interestingly, our recent structural data revealed that UNC-45 can polymerize into a linear protein chain. As a result, multiple binding sites for the myosin units as well as the co-working chaperones are periodically arranged along the UNC-45 chain. Indeed, this multi-chaperone complex precisely mimics an industrial assembly line (Figure). Consistent with in vitro data, the observed UNC-45 chain also occurs in living cells and is critical for coupling myosin folding with myofilament formation.

The newly discovered mechanism decisively alters the current view of how muscle filaments are formed and, subsequently, kept in shape. The UNC-45 chaperone is a novel type of filament assembly factor that provides a molecular scaffold for specific chaperones to work at regularly spaced positions on captured client proteins. It will be interesting to see whether this "patterned folding" mechanism is critical for the assembly of other protein filaments, and to what extent this mechanism is connected with protein folding diseases. Aberrant UNC-45 function is associated with severe muscle defects, resulting in skeletal and cardiac myopathies. Thus, our data may help to develop strategies for the treatment of diseases connected with myosin folding and assembly defects.

FIGURE: Our work demonstrates that UNC-45 establishes a multi-chaperone complex that allows the folding of myosin in a defined array along the thick filament. The cartoon illustrates the "patterned folding" principle of how UNC-45 composes a protein assembly line that places the chaperone mechanics Hsp70 and Hsp90 (highlighted) at regularly spaced positions to work on the series of motor domains protruding from the myosin filament.

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LUISA COCHELLA

Spatiotemporal specificity of miRNA biogenesis and function

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How many cell types form our bodies and how many neuron types exist in our brains? What makes them different and how do they all derive from a single totipotent cell at the beginning of multicellular life? Changes in gene expression produce diverse cell types, each with its own gene expression profile and functional properties. How do different gene regulatory mechanisms contribute to generating cell-type complexities during development and evolution?

As a single-cell zygote divides and its daughters continue to do so, the patterns of gene expression in each cell are altered due to intrinsic and external cues. These changes in gene expression have been primarily studied at the transcriptional level, with a number of transcription factors and chromatin-associated proteins being implicated in driving many of the changes required for development. However, the role of post-transcriptional regulation in this process is much less understood. We are currently studying how transcriptional and post-transcriptional mechanisms integrate into gene regulatory networks that define different cell types during development. We are also interested in how the different mechanisms of gene regulation have contributed to the evolution of cell-type complexity.

With the discovery of microRNAs- short RNAs that can act as specific repressors of gene expression at the post-transcriptional level- we have a very good entry point to understand the impact of post-transcriptional regulation of gene expression on development and evolution. To do so, we use as a model system the nematode *Caenorhabditis elegans*, which is widely known because of the availability of extremely powerful genetic tools for its study. Additionally, *C. elegans* offers an invariant body plan in which the lineage history and identity of each of its ~950 cells, as well as the function of every cell are known to a great extent. Moreover, a growing group of *Caenorhabditis sp.* as well as other outgroups have had their genomes fully sequenced and are also tractable with genetic approaches, making these species useful for comparative studies. Together, this makes "the worms" ideally suited model organisms to investigate our questions of interest.

Combining genetic approaches, next generation sequencing and *in vivo* strategies that enable us to follow miRNA expression and function with single-cell resolution, we are currently investigating the roles of miRNAs in providing specific cell types with their respective functional properties. We found that many miRNAs are themselves expressed with very high spatiotemporal specificity. An extreme case is a miRNA that is made and acts in just one of the 302 neurons that make up the *C. elegans* nervous system. This allows us to generate hypotheses about the roles of these miRNAs in cell-type specification, helps to understand how their expression is regulated, and how this class of regulators is integrated into the cascade of events that unfolds from the totipotent one-cell zygote.

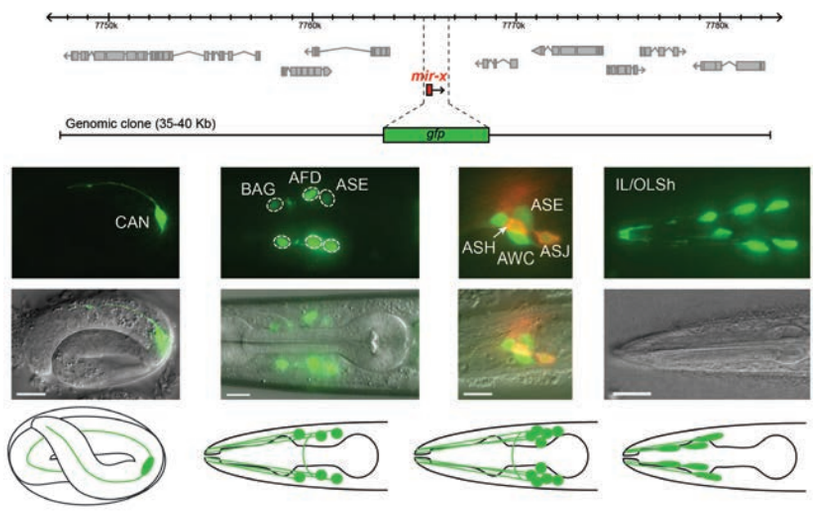

FIGURE: **Top**. Schematic diagram of the reporter system used to monitor miRNA expression *in vivo*, which is based on recombineering into large genomic clones and transformation into *C. elegans*. **Middle**. Representative images (GFP or Nomarski) of four miRNA reporters expressed in specific subsets of neurons or glial cells at different stages of development. The identity of each cell can be unambiguously determined and is shown. Scale bars = 10 µm. **Bottom**. Schematic diagram of the observed expression patterns, ranging from a single neuron to multiple pairs of cells.

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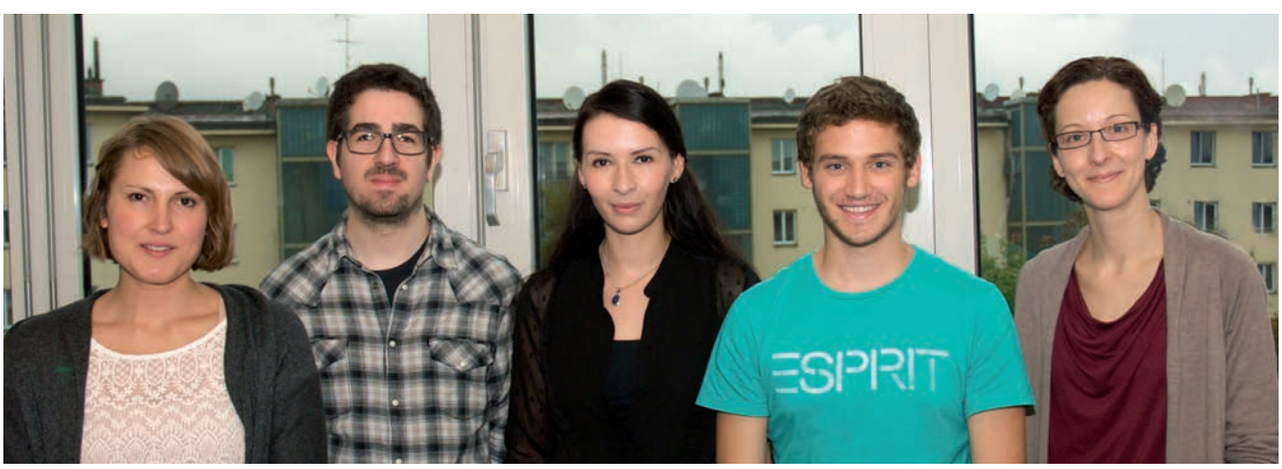

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[1] starting November , [2] until December

WULF HAUBENSAK
Circuit mechanics of emotions

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Emotions tag those aspects of life that are important and guide behaviors crucial for survival: fear keeps us away from danger; reward-related emotions help to seize opportunities. How are emotions wired in the brain? Using molecular genetics, pharmacogenetics, optogenetics, electrophysiology, fMRI and behavioral analysis, we explore the circuit mechanics of basic emotional behavior in mice. Our research yields information about the neural basis of a biomedically important part of our mental self and the neural circuit design of brain functions in general.

Deconstructing the functional circuitry of the brain

Fear and reward are basic biomedically important emotions that can be addressed reliably in animal model systems. Fear and reward states are assembled from distributed patterns of neural activity, encompassing many interconnected circuits, each contributing different features (such as cognitive awareness, motor behavior responses and learning). To deconstruct this distributed functional network at the circuit level [1], we follow a two-step strategy. First, we combine – in collaboration with Andreas Hess (CSF) and Katja Bühler (VRVis) - optogenetic manipulations with high-resolution fMRI and computational neuroanatomy to delineate a brain-wide network of hot spots for fear and reward, and their structural and functional connectivity. Second, within these hubs we develop genetic strategies that tag circuits recruited during fear- and reward-specific behavioral tasks.

Behavioral decisions and learning in fear/reward networks

These combined efforts revealed a bi-stable neural switch in the extended amygdala [2] that integrates stress signals from thalamic sources and top-down inputs from higher cortical association areas. We found that the switch is part of a larger cortical and subcortical network. Within this network, a corticolimbic feedback loop integrates cortical interoceptive awareness and determines the experience of emotional events. A minimal extended amygdala-midbrain learning circuit writes these experiences into synaptic memory by dopaminergic feedback. We believe that these circuit motives reflect evolutionary constraints for efficient emotional response selection, decision error reduction, and behavioral flexibility in the face of threats and rewards.

Circuit-level psychopharmacology

While molecular and cellular drug effects have been worked out in great detail at the molecular and cellular level, the circuit mechanics by which this translates into behavioral changes are largely unknown. To gain a foothold into this problem, we set up a behavioral-histological pipeline for brain-wide screening of drug target circuits. Interestingly, these experiments revealed several interconnected forebrain regions as major targets of benzodiazepine anxiolytics. Our results indicate that benzodiazepines interfere with stress signals in this network, thus providing a circuit-mechanism-based explanation for their psychological effect.

Collectively, our research will resolve principles of neural circuit organization of clinically relevant brain functions [3] and provide a mechanistic framework for the psychological effects of psychotherapeutic drugs.

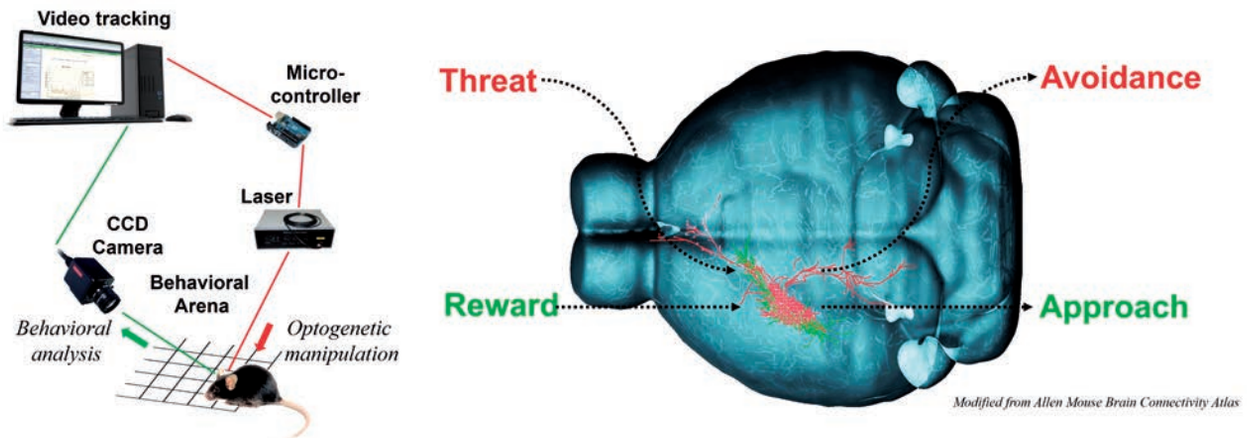

FIGURE: Exploration of emotional processing in the forebrain: Fear/reward behaviors are gated through extended amygdala circuits.

Further reading:

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K. Deisseroth, "Circuit dynamics of adaptive and maladaptive behaviour.," Nature, vol. 505, no. 7483, pp. 309–17, Jan. 2014.

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DAVID KEAYS

Neuronal Migration and Magnetoreception

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The Keays lab is interested in answering two intriguing questions: (1) How do neurons migrate in the developing brain? (2) How do animals sense the Earth's magnetic field? In tackling these questions we are driven by a reductionist approach that aims to unravel Nature's wonder by persistent attention to detail.

How do neurons migrate in the developing brain?

The seat of human consciousness lies in the cerebral cortex: a remarkable structure consisting of 23 billion neurons, precisely layered, organized, and connected. To build a human brain, three developmental processes must occur in synchrony: the generation, migration, and differentiation of neurons. Neuronal migration begins at the proliferative ventricular zone and ends at the cortical plate. It is a perilous cellular journey guided by extracellular guidance cues and driven by a dynamic cytoskeleton. Impairments in migration have been linked to a host of neurodevelopmental diseases. One example is lissencephaly, a disease characterized by a "smooth brain", epilepsy, and mental retardation. We have shown that mutations in the alpha tubulin gene *TUBA1A* cause lissencephaly in humans and neuronal migration abnormalities in mice (Keays et al 2007). More recently we showed that mutations in the beta tubulin gene *TUBB5* reduce the size of the human brain and perturb both migration and neurogenic division (Breuss et al 2012). The Keays lab is using the mouse as a model system to gain insight into the role of different tubulin genes, how they cause disease, and the molecular mechanisms underlying the migration of neurons. To complement these murine studies we are employing next-generation sequencing and, in collaboration with a network of clinical colleagues, sequencing the exomes of patients with sporadic neuronal migration disorders. These genetic studies have already revealed a number of new disease-causing genes which are currently being investigated with human cerebral organoids (Lancaster et al, 2013).

How do animals detect magnetic fields?

Magnetoreception is an extraordinary sensory ability employed by a diverse array of species to aid their migration and navigation. The ability of bees, newts, lobsters, turtles, trout, bats, and robins to detect the Earth's magnetic field is well known, but we know very little about how they do this. One idea, known as the magnetite theory of magnetoreception, predicts that mechanosensitive ion channels coupled to an intracellular compass made of magnetite (Fe_3O_4) transduce local magnetic information into a neuronal impulse. We are investigating this hypothesis using the rock pigeon *Columbia livia* as a model. Our goal is to identify the cells, molecules and neuronal circuits required for magnetoreception. Recent functional data have implicated the inner ear in magnetosensation (*Wu and Dickman 2012*). Employing histological and subcellular techniques, we identified a population of sensory hair cells that contain a single iron-rich organelle in the pigeon's inner ear (Lauwers et al, 2013). This organelle, the "cuticulosome", is located beneath the stereocilia and is embedded in the actin-rich cuticular plate (See Figure). What does this structure do? Is it involved in magnetosensation? We are investigating its function using molecular, physiological, and behavioral techniques. In the future we hope to co-opt the molecules Nature employs for magnetosensation to create novel "magnetogenetic" tools permitting the activation of defined neuronal populations *in vivo* in the mouse.

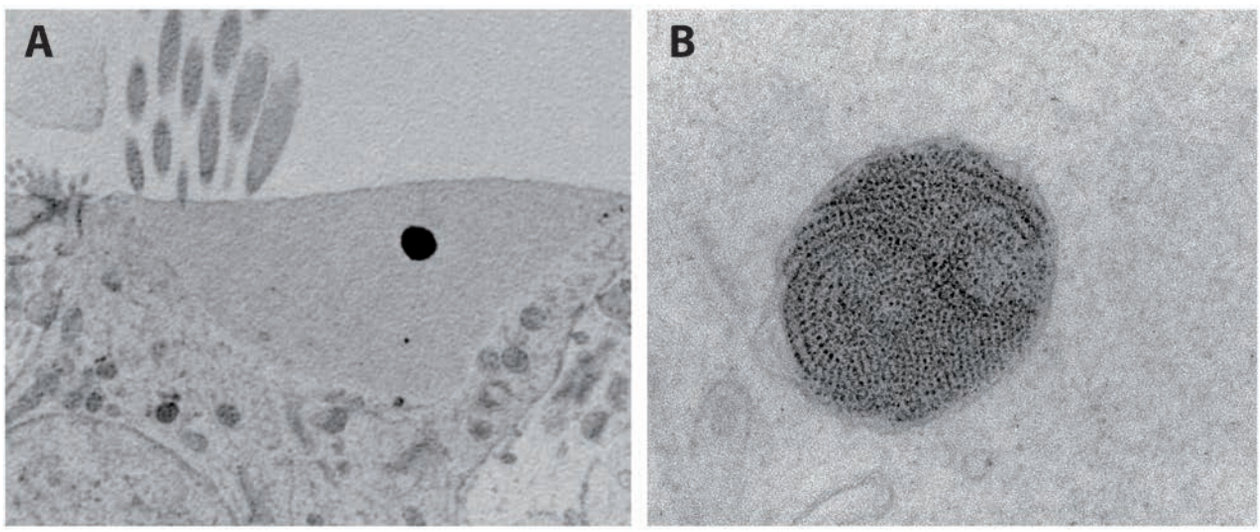

FIGURE: The electron micrograph shows a hair cell from the inner ear of pigeons. (**A**) An electron-dense sphere is seen embedded in the actin rich cuticular plate. This organelle, the "cuticulosome", is rich in iron and may play a role in magnetosensation. (**B**) A high resolution image of a cuticulosome.

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THOMAS MARLOVITS

Molecular Machines

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Membrane-associated processes are a fundamental characteristic of all living cells because they ensure that cells are able to effectively communicate with, and adapt to, their environment. Our laboratory is interested in understanding the molecular mechanism underlying such processes. Specifically, we focus on machineries capable of translocating bacterial toxins into eukaryotic cells.

Microbial Pathogenesis

Gram-negative pathogens such *Yersinia, Shigella, Pseudomonas, enteropathogenic/enterohemorrhagic E. coli* (*EPEC/EHEC*) and *Salmonella* are causative agents for many diseases in animals and humans. They range from mild to deadly outcomes, and often originate as food-borne diseases. A crucial element of their pathogenicity are bacterial toxins ('effectors'), which are delivered via the type III secretion system (a large membrane embedded machinery) from the bacterium to its host cell. As a consequence, translocated effector proteins have the remarkable capacity to modulate various host-cell pathways, including endocytic trafficking, gene expression, programmed cell death, or cytoskeleton dynamics that induce membrane ruffling and subsequently render the host accessible to bacterial infection.

Unfolded protein transport across membranes?

Safe and directional transport of effector proteins across membranes is the hallmark function of all type III secretion. Our recent structural analysis (Schraidt & Marlovits, Science 2010) of the injectisome, the most prominent cylindrical structure of the type III secretion system, revealed a potential secretion path through the central part of the membrane-embedded complex. However, the inner diameter of this path is too small to accommodate a fully folded effector protein, suggesting that either the injectisome must undergo large conformational changes during transport, or effector proteins need to be unfolded.

To investigate type III secretion of human pathogens, we focused on (1) determining the secretion path of injectisomes, (2) understanding the mechanism of transport, and (3) visualizing protein transport *in situ*. We discovered that substrates are inserted into the secretion path, a polar fashion (N-terminal regions first), and are transported in an unfolded state. To determine whether such behavior is in fact observed *in situ*, we analyzed protein transport across membranes in a near-native state by cryo-electron tomography. For the first time we were able to visualize pathogenic type III secretion systems from *Salmonella* in action and - more generally - protein transport across several membranes.

By understanding the molecular mechanism of TTSS-mediated protein transport, we hope to provide a basis for the development of novel therapeutic strategies that will either inhibit its activity or modify the system for targeted drug delivery.

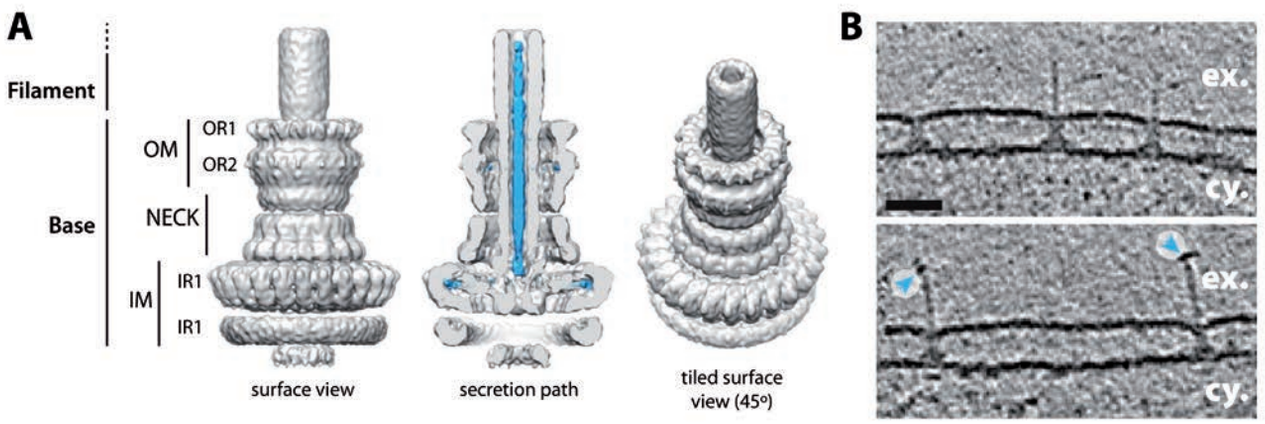

FIGURE: (A) Structure of the membrane-embedded (grey) and substrate-trapped (blue) injectisome resolved by cryo-electron microscopy and single particle analysis (B) *In situ* visualization of substrate-free and substrate-trapped injectisomes by cryo-electron tomography

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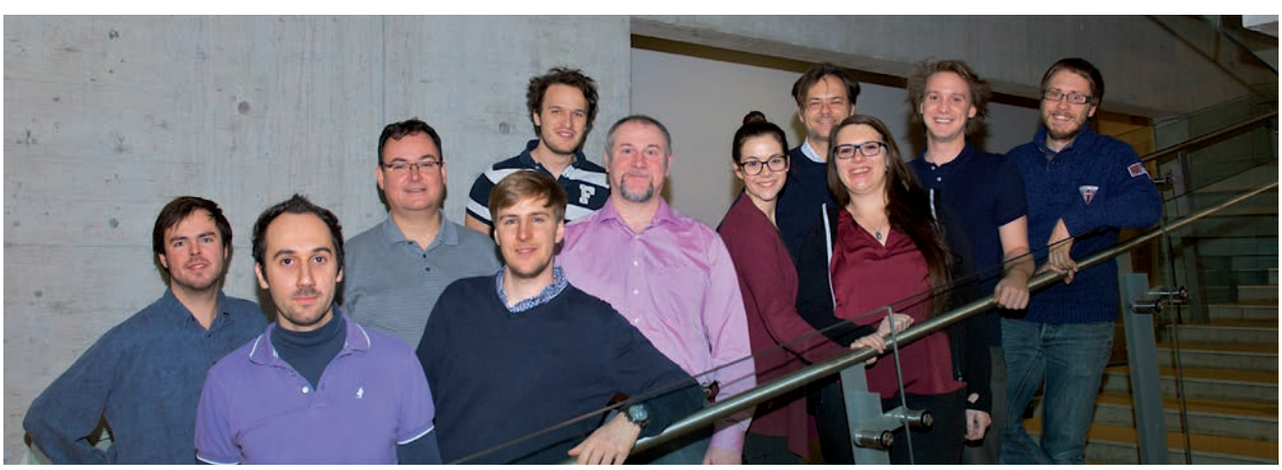

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RUSHAD PAVRI

Antibody diversification during the immune response

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Antibodies form the basis of all long-term serum immunity. The process by which antibody-producing B cells generate the vast repertoire of antibodies required to combat the wide range of pathogenic challenges faced by the immune system is known as antibody diversification. Understanding the detailed molecular mechanisms underlying this unique phenomenon is the core focus of our group.

Research description:

Antibody diversification occurs at the immunoglobulin (Ig) loci in B cells and consists of two processes: somatic hypermutation (SHM) which modulates the antigen-binding properties of the antibody by introducing mutations, and class switch recombination (CSR) which generates the various antibody isotypes via a complex pathway of mutation, repair and recombination (Figure). Mutations are triggered by activation-induced deaminase (AID), which coverts cytosines to uracils on single-stranded DNA. AID can also mutate other genes which result in oncogenic chromosomal translocations and lymphoid malignancies (Figure). Thus, antibody diversification is an inherently genotoxic process that requires tight regulation to minimize such genome instability.

Transcriptional regulation of antibody diversification

Transcription is essential for CSR and SHM, and AID itself acts co-transcriptionally. Thus, one of our core interests is to understand the role of transcription and co-transcriptional processes during CSR and SHM. We and others have shown that stalling or pausing of transcriptional complexes is important for AID targeting during antibody diversification, and that this mode of AID recruitment also explains features of AID-mediated mutagenesis on a genome-wide basis in B cells. In particular, we think the staling factor Spt5 is involved in AID targeting. On the basis of our findings, we have proposed a model for AID targeting via Spt5 and Pol II stalling, wherein AID is preferentially targeted to regions of Pol II stalling via direct interaction with Spt5. To further characterize its role, we generated a conditional Spt5 knockout mouse which we are currently characterizing. These studies are revealing new insights into the role of transcription in AID-mediated events and also regarding gene-regulatory mechanisms in general.

Identification and characterization of novel factors in CSR and SHM

We previously conducted shRNA screens to identify new cofactors involved in CSR. This yielded entirely new insights into the regulation of CSR, notably the role of cell cycle regulation, DNA replication and RNA processing, which we are currently characterizing. In addition, we are developing new assays to quantitatively test for SHM in B cells, which will allow us to identify novel regulators of this process using various means, such as RNAi and Crispr/Cas9-mediated technologies.

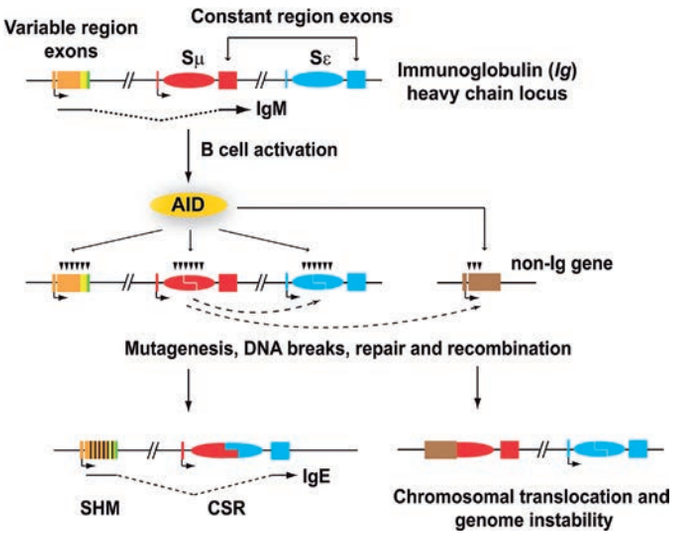

FIGURE: Antibody diversification at the Ig heavy chain locus. B cell activation triggers AID expression, which generates mutations (arrowheads) at specific regions. These lesions are processed via various DNA repair pathways resulting in SHM and CSR. Mutations at non-Ig genes results in reciprocal translocations between these genes and the Ig locus, leading to genome instability and tumorigenesis.

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JAN-MICHAEL PETERS

Mitosis and chromosome biology

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Although the importance of the human genome is widely recognized and its sequence can now be determined quite easily, we do not know how DNA is folded in chromosomes, and how exactly chromosomes are segregated during cell division. Our long-term goals are to understand these processes at the molecular level.

Proper chromosome segregation depends on physical connections between duplicated DNA molecules. A widely known fact is that this sister chromatid cohesion is mediated by a protein complex known cohesin, but how cohesin establishes cohesion is poorly understood. We discovered that cohesin's ability to mediate cohesion depends on a protein named sororin, which is recruited to cohesin once it becomes acetylated in the S-phase. Sororin then stabilizes the binding of cohesin to DNA by inhibiting the cohesion-associated protein Wapl, which can otherwise release cohesin again from DNA.

Cohesin complexes are also believed to be responsible for arranging chromatin fibers into higher-order structures, but we do not know how important this function is for determining chromosome architecture. Using conditional mutagenesis in the mouse, we found that depletion of Wapl stably locks cohesin on DNA, leads to clustering of cohesin in axial chromosomal structures, and causes chromatin condensation in interphase chromosomes. These findings reveal that the stability of cohesin-DNA interactions is an important determinant of chromatin structure, and indicate that Wapl may regulate this function.

In mitosis, sister chromatids are separated from each other once all chromosomes have been bi-oriented on the spindle. This step is initiated by a 1.5-MDa ubiquitin ligase complex known as the anaphase-promoting complex/cyclosome (APC/C). The degradation of APC/C substrates activates a pathway which leads to the complete removal of cohesin from chromosomes, and thereby triggers sister chromatid separation. As precocious activation of the APC/C would abrogate cell division, APC/C is tightly controlled by both co-activator and inhibitory proteins. We are using a combination of biochemical and structural approaches to understand how these proteins function.

Although mitosis has been studied for more than a century, our molecular understanding of this complicated process is far from complete. From 2004 to 2009 the MitoCheck consortium, funded by the European Union, developed and applied genomic and proteomic approaches to study mitosis (*www.mitocheck.org*). In a second project known as MitoSys (2010 to 2015), we are developing quantitative assays for mitosis and are collaborating with artists to generate a public exhibition and a movie about research on mitosis (*www.mitosys.org*).

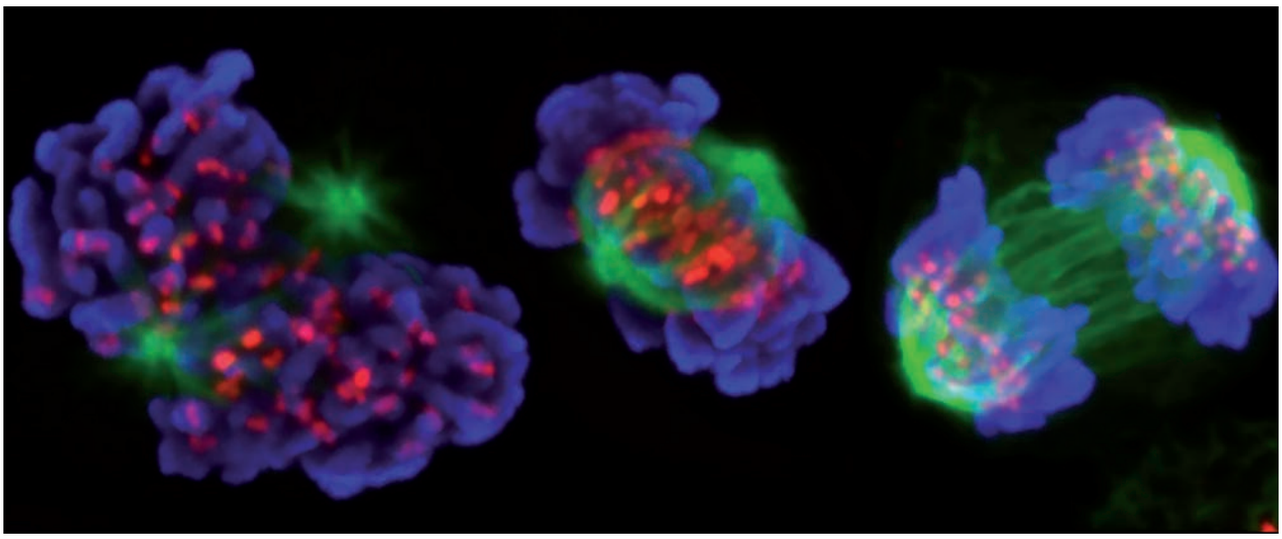

FIGURE: Human cells (HeLa) in prometaphase (left), metaphase (middle) and anaphase (right) stained for histone H3 phosphorylated on serine 10 (blue), a centromere protein (red) and alpha-tubulin (green). Courtesy of Rene Ladurner.

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SIMON RUMPEL
Auditory perception and memory

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Neuronal circuits of the neocortex mediate higher-order cognitive functions in mammals, including humans. We are using sounds as well controllable stimuli to understand how the external world is represented in the neocortex and how these representations are transformed into long-term memories. This is fundamental in understanding the mind: memories of past experiences shape our personalities and influence our current perception of the world.

Memories about relevant experiences are essential for successful adaptation of behavior in a changing environment. A current model of memory formation proposes plastic adaptations in neuronal connections (synapses) caused by relevant experiences. Yet, how such changes in synaptic connectivity lead to the formation of a memory trace remains elusive. How is the processing of external stimuli altered after the formation of a memory? How are we able to continuously store novel memories in a given neuronal circuit without corrupting previously stored memories? In order to understand the mechanisms by which the auditory cortex mediates processing of sounds and is involved in the formation of memories, we are currently applying *in vivo* imaging techniques in mice.

Two-photon laser scanning microscopy in transgenic animals expressing green fluorescent protein in just a small subset of cells permits the same neurons, and even the same individual synapses, to be revisited day after day. This is truly remarkable because we estimate that the brain comprises about 10 trillion (10^{13}) synapses. We find that neocortical circuits are highly dynamic: remodeling occurs by the formation/elimination of synaptic connections as well as adaptations in the strength of existing connections. In addition, we observe that memory formation induced by classical conditioning of a sound stimulus is correlated with a transient increase in spine formation that leaves a long-lasting trace in the network.

In vivo imaging not only permits analysis of synaptic connections, but also monitoring of neuronal activity in hundreds of neurons simultaneously. Increases in calcium levels triggered by neuronal activity can be detected as changes in fluorescence of calcium indicators. We are investigating activity patterns elicited by various sounds in neuronal populations of the auditory cortex in order to learn about the principles how sounds are encoded and recognized in the brain. We are currently investigating the circuit mechanisms that lead to the generation of new sound representations by combining behavioral training paradigms cued by sounds and chronic calcium imaging.

Jointly, these approaches pave the way to address the storage of information in living neuronal networks: a field of research that has been almost exclusively the domain of theoretical neuroscientists thus far.

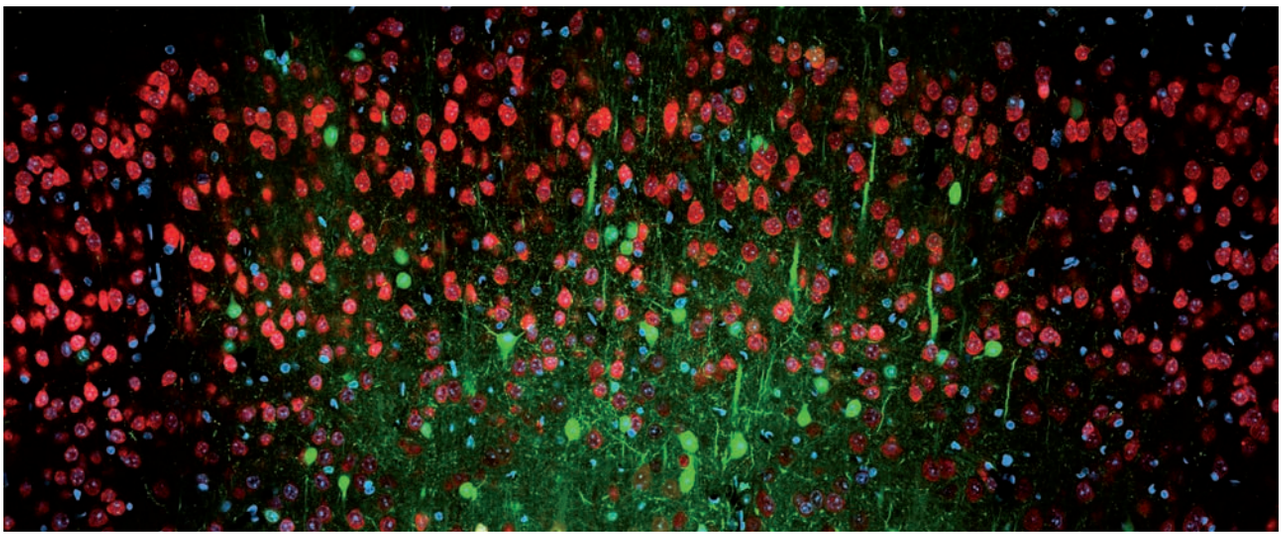

FIGURE: Coronal section of the mouse auditory cortex transduced with an AAV-vector mediating the expression of a green fluorescent protein. Neurons are labeled in red; cell nuclei in blue.

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ALEXANDER STARK

Towards understanding gene regulation

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The development and function of all multicellular organisms is achieved through cell type-specific patterns of gene expression. Specialized genomic regions termed enhancers encode such patterns in their DNA sequences, which bind transcription factors in different combinations. Our group studies the architecture and function of enhancers and transcription factors by combining systematic genome-wide experiments and computational analyses.

All multicellular organisms, including humans, consist of various cell types with diverse morphologies and functions. These cell types acquire their unique properties by expressing different sets of genes. The cell type- and tissue-specific gene expression patterns are encoded in the DNA sequences of regulatory regions known as enhancers. One of the most important and fascinating questions in biology is to learn how to locate enhancers in the genomes of animals and the human being, and to interpret their sequences.

Enhancers contain short DNA motifs that are recognized by transcription factors (TFs). Combinations of bound TFs define where and when the enhancers are active. Disruptions of enhancer function, for example by sequence mutations, have been implicated in several diseases, including cancer. Yet, the functional consequences of sequence changes are generally unknown. Similarly, as enhancers often lie at a significant distance from the genes they regulate, it is difficult to locate them in large genomes. The goal of our group is to learn how regulatory sequences are organized and how they function, in order to ultimately be able to predict enhancer activities from their DNA sequences. Similarly, we are interested in understanding how TFs work together to activate enhancers. To this end we employ high-throughput methods that allow genome-wide readouts in combination with computational analyses.

To identify enhancers in large genomes based on their function, we developed a direct and quantitative method for testing millions of candidate DNA fragments simultaneously (STARR-seq or self-transcribing active regulatory region sequencing; Arnold et al. 2013), and applied it to various systems including hormone signalling (Shlyueva et al. 2014). In addition, we systematically characterized the *in vivo* activity of ~8000 enhancer candidates in *D.melanogaster* embryos throughout embryonic development (Kvon et al. 2014). Computational analyses of the enhancers' sequences allowed us to identify functionally important DNA motifs (Figure 1). We are also studying the cellular machinery that can "read" the regulatory information encoded in enhancers and activate or repress their functions. For this purpose we are systematically testing the majority of *Drosophila* TFs and co-factors for their ability to activate transcription individually and in different contexts *in vitro*.

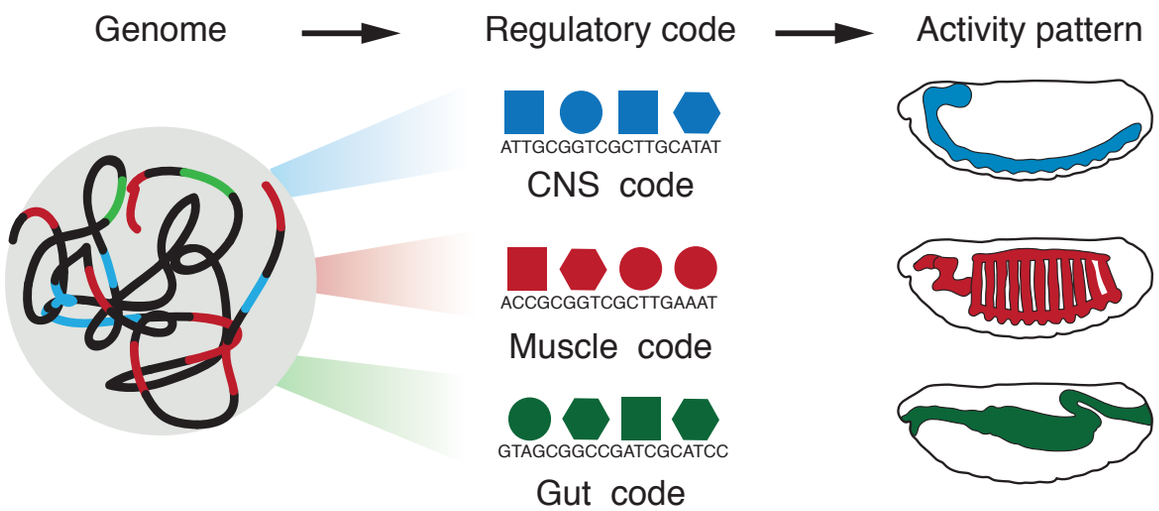

FIGURE: The genome contains genes and the information regarding the genes' cell type-specific expression, which jointly define the development of an entire organism. By looking at the activities of thousands of DNA fragments *in vitro* and *in vivo*, we are deriving general rules about enhancer sequences ('regulatory codes').

Further reading:

Kvon EZ, Kazmar T, Stampfel G, Yáñez-Cuna JO, Pagani M, Schernhuber K, Dickson BJ, Stark A. Genome-scale functional characterization of Drosophila developmental enhancers in vivo. Nature, 2014. Aug 7;512(7512):91-5. Pubmed 24896182.

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ANDREW STRAW

Neural circuits for vision

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To establish a mechanistic understanding of neuronal circuit function and the computational purpose of behavior, we study visually guided locomotion of the fruit fly.

The questions we address are as follows: 1) What are the identity and functions of neurons and molecules required for specific behaviors? This is *neural circuit mapping*. 2) What individual sub-behaviors does an animal use and how do these sub-behaviors interact? We define, rigorously quantify, and model these sub-behaviors and their interactions using concepts of control theory, Bayesian inference, and cognitive science. This is *systems behavior*. 3) We wish to connect these levels of understanding into a mapping that lets us traverse from neuronal implementation to the computational task and behavioral context in a rigorous way. Ultimately, we aim to link physiology with computation.

We utilize and develop cutting-edge techniques from several disciplines. For example, we are known for building state-of-the-art virtual reality systems (see *http://flyvr.org/*), combining optogenetics, thermogenetics and computer vision (see *http://flymad.strawlab.org/*) We have collaborated with other scientists to develop novel physiological preparations and are now engaged in several large-scale data analyses and machine learning, based on data from our lab and those of others.

We focus on the visual behaviors of the fly *Drosophila* because of this animal's suitability for our purposes, but our work is relevant for the behavior of all animals. Vision allows the fruit fly Drosophila, with its tiny brain, to stabilize flight, approach objects, and remember specific locations in space. The neuro-crystalline structures of the optic lobes suggest that early stages of visual processing occur in parallel before converging onto a relatively small number of neurons that project to the central brain and are thus able to influence behavior. For example, in one recent project we exploited the fly molecular toolbox to demonstrate the necessity of an intact motion processing pathway (specifically T4 and T5 cells) for flies to approach objects under several conditions. With biologically plausible models inspired by this result, we suggested the simplifying hypothesis that behavioral responses to both objects and background motion may arise from processing in the same neurons and without an explicit representation of object position. In general, we seek to extend these findings to create a systematic understanding of the basic principles of vision in natural behavior not only in flies, but in other species as well.

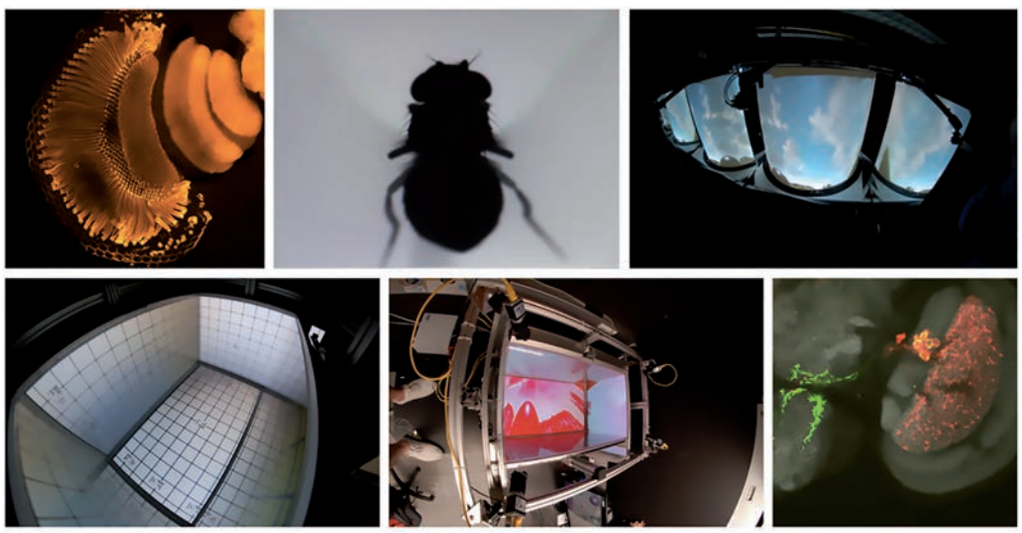

FIGURE: From left to right: (top row) Visual system of *Drosophila*, tethered flight experiments, virtual reality free-flight arena, (bottom row) small VR cube, VR cube with tracking cameras and visual stimuli, synaptic inputs (red) and outputs (green) of *Drosophila* HS and VS cells.

Further reading

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ALIPASHA VAZIRI

Dynamics of coupled biological systems: Methods and Phenomena

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How do the dynamics of coupled biological systems confined by their structure lead to function? While we investigate this question in different systems and at different scales, a major goal is to understand how sensory inputs are represented across brain hierarchies, and how their processing generates innate and learnt motor output. To answer these questions, we focus on the development of optical technologies for high-speed, single cell-specific and brain-wide modulation and functional imaging of neuronal circuits.

The Vaziri lab is focused on the intersection between physics, neuroscience and information theory. We are interested in understanding how the information processing capabilities of the brain emerge from the dynamic interaction of neuronal networks. Our ultimate aim is to discover the computational algorithms underlying object recognition, generalization, learning, and decision-making. Addressing these questions has been hampered by a paucity of appropriate tools and methods that permit parallel and specific spatiotemporal application of excitation patterns to neuronal populations while capturing the dynamic activity of the entire network at high spatial and temporal resolution.

Taking a multidisciplinary and reverse engineering approach, we develop and apply new techniques to address the above questions. Over the last few years we have developed two new high-speed calcium imaging techniques that, for the first time, enable the investigator to capture the dynamics of the neuronal network at single-cell resolution *in vivo* and in whole brains, at tens of Hertz for small model organism such as the nematode *C. elegans* or zebrafish larva. This provides the opportunity to capture the flow of information from the primary sensory neurons across different stages of representation, to their processing and interaction with internal brain states for generating behavior in real time.

One approach relies on "sculpting" the excitation volumes in biological samples using non-linear optics while the other relies on light-field imaging, a tomography-type approach for simultaneous readout of neuronal activity in 3D. Using these techniques, we recently performed brain-wide functional imaging of entire nervous systems at single-cell resolution. Further, we performed intrinsically simultaneous volumetric calcium imaging in the entire brain of larval zebrafish during sensory stimulation. We are able to track the activity of 5000 neurons distributed throughout the brain at a volume rate of 20 Hz. The simplicity of this technique and the possibility of its integration into conventional microscopes make it an attractive tool for high-speed volumetric functional imaging. These tools, combined with high-speed optogenetic control of neuronal circuits, advanced statistical tools and mathematical modeling, will be crucial together with the anatomical wiring maps for establishing dynamic maps of neuronal circuits and ultimately generative models of brain network dynamics.

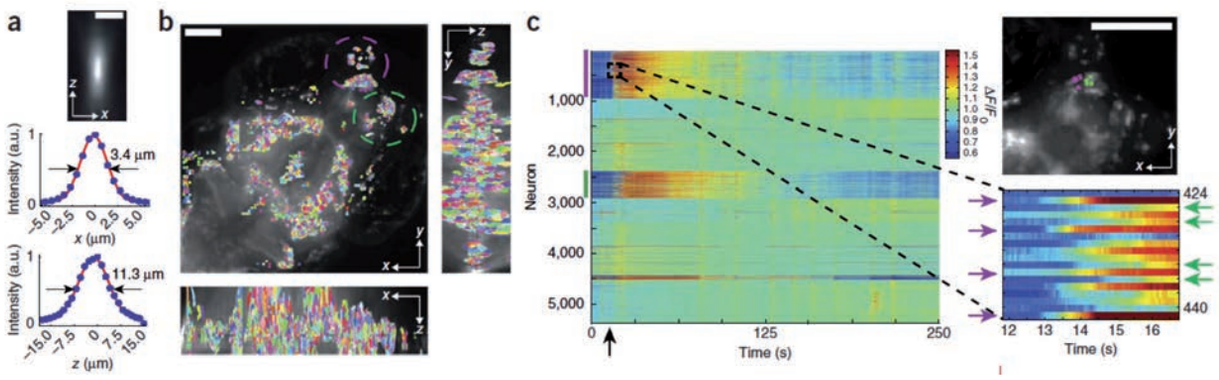

FIGURE: High-speed whole-brain calcium imaging in larval zebrafish via light-field deconvolution microscopy. (a) Maximum-intensity projection (MIP) of a light-field deconvolved volume, (b) Extracted $Ca2^{+}$ intensity signal (ΔF/F 0) of GCaMP5 fluorescence using spatial filters shown in a. Each row shows a time-series heat map. Color bars denote encircled regions in b, which include the olfactory epithelium, olfactory bulb and telencephalon. The arrow at 15 s denotes the addition of an aversive odor. A close-up of the dashed box is shown (right, lower panel);

Further reading:

Prevedel, R., et al., Simultaneous whole-animal 3D imaging of neuronal activity using light-field microscopy. Nature Methods, 2014. 11(7): p. 727-730.

Schrodel, T., et al., Brain-wide 3D imaging of neuronal activity in Caenorhabditis elegans with sculpted light. Nature Methods, 2013. 10(10): p. 1013-1020.

Andrasfalvy, B., et al., Two-photon Single Cell Optogenetic Control of Neuronal Activity by Sculpted Light. PNAS, 2010. 107.

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STEFAN WESTERMANN

Kinetochores and the Microtubule Cytoskeleton

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Originating from a single fertilized egg, an adult human body contains about 100 trillion cells. How do cells achieve the segregation of their genomes during cell division with extremely high precision? We are studying the conserved molecular machinery that drives chromosome segregation, focusing on the kinetochore, which is a large protein complex that connects chromosomes to the microtubules of the mitotic spindle.

Towards biochemical reconstitution of the chromosome segregation machinery

The kinetochore is a macromolecular machine that assembles from a set of conserved multi-protein complexes. We use budding yeast as a simple model organism to study the assembly, function, and regulation of kinetochores. For this purpose we reconstituted a number of kinetochore complexes by co-expressing multiple subunits in bacteria or insect cells, and studied their biochemical properties. This analysis has already yielded some important insights: the Dam1 complex, a specialized microtubule-binding component of the budding yeast kinetochore (see Figure) oligomerizes to form a ring around microtubules *in vitro*. This ring slides along the microtubule lattice and remains attached to the plus-end even during microtubule disassembly. These properties make the Dam1 ring a very efficient force coupler at the kinetochore. A challenge for the future is to understand how the Dam1 ring is connected to the rest of the kinetochore, visualize the structure of the fully assembled interface, and analyze how it is regulated, for example by mitotic kinases. Our investigations into kinetochore assembly have led to the identification of a conserved receptor molecule for the microtubule-binding Ndc80 complex. We have solved the crystal structure of the interface between Ndc80 and the histone-fold protein Cnn1, and are further investigating how the cell employs different Ndc80 receptors to promote chromosome segregation.

Single-molecule analysis of microtubule-associated proteins and motors

A defining feature of kinetochores is their ability to interact with microtubule plus-ends through multiple rounds of polymerization and depolymerization. How does the kinetochore achieve this remarkable task? What features allow it to follow a polymerizing microtubule end, but also stay connected during disassembly? To analyze this process we reconstituted dynamic microtubules *in vitro* and visualized the interaction of individual kinetochore components using total internal reflection fluorescence (TIRF) microscopy. This technique allows the observation of individual kinetochore complexes and microtubule-binding proteins with single-molecule sensitivity to reveal their mode of interaction with dynamic plus-ends. We recently started to investigate motor proteins involved in kinetochore transport. We hope not only to provide a mechanistic understanding of this process, but also to explore more generally the types of features that allow translocation of molecules along microtubules.

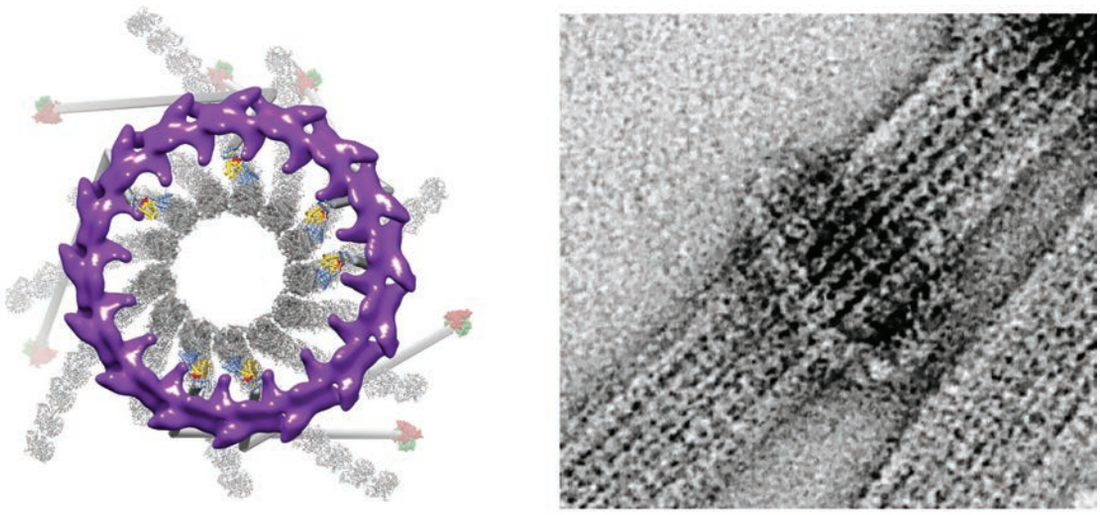

FIGURE: Left panel: Model of the Dam1-Ndc80 interface. A Dam1 ring (purple) seen in "end-on view", associating with six Ndc80 complexes (grey). The microtubule-binding CH domains of the Ndc80 complex are shown in yellow and blue. Right panel: negative stain electron micrograph of a Dam1 ring bound to a microtubule.

Further reading:

Peter Hornung, Paulina Troc, Francesca Malvezzi, Michael Maier, Zuzana Demianova, Tomasz Zimniak, Gabriele Litos, Fabienne Lampert, Alexander Schleiffer, Matthias Brunner, Karl Mechtler, Franz Herzog, Thomas C. Marlovits and Stefan Westermann (2014). A cooperative mechanism drives budding yeast kinetochore assembly downstream of CENP-A. Journal of Cell Biology, Aug 18; 206(4) 509–524

Francesca Malvezzi, Gabriele Litos, Alexander Schleiffer, Alexander Heuck, Tim Clausen and Stefan Westermann (2013). A structural basis for kinetochore recruitment of the Ndc80 complex via two distinct centromere receptors, EMBO J., Feb 6;32(3):409-23

Alexander Schleiffer, Michael Maier, Gabriele Litos, Peter Hornung, Karl Mechtler and Stefan Westermann (2012). CENP-T proteins are conserved centromere receptors of the Ndc80 complex, Nature Cell Biology 14, 604-613

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[5] Master student until September, [6] joint appointment with Karl Mechtler

MANUEL ZIMMER

Neuronal network dynamics of perception and behavior

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How do networks of neurons operate as a single brain to produce sensations, thoughts, and behavior? At our lab we study this question using the nematode *C. elegans*, which is equipped with a small and anatomically well-defined nervous system. Specifically, we combine genetics, quantitative behavioral analysis, functional imaging, and theoretical modeling to elucidate the neural circuits that control locomotion and chemosensory behaviors.

Network dynamics and stimulus-evoked activity determine motor states

Even in the absence of environmental stimuli, brains are found to exhibit diverse activities across neuronal networks and different brain regions. Modern concepts in neuroscience challenge the traditional view of linear feed-forward sensory to motor flow, and instead state that intrinsic dynamics are at least as important as sensory processing of the outside world. To test this hypothesis, we recently developed a new platform for whole-brain imaging of neuronal activity (Figure). This approach enables us to capture the activity of nearly all neurons in the worm's brain in real time and at single cell resolution, while it parses sensory information. Imaging of unstimulated worms revealed that a large proportion of neurons exhibit spontaneous activity dynamics, which can be described as oscillations between attractor-like states. These correspond to groups of synchronously active interneurons and motor neurons, which reliably encode transitions in motor output; i.e. transitions between forward- and backward-directed locomotion. These behaviors have been reported to occur spontaneously as well as in a stimulus-regulated fashion. Next, we tested the effect of sensory stimulation and found that network attractors (i.e. activity patterns) are robust. However, the probabilities by which the network transits from one attractor state to another were changed in a way that reflects stimulus-evoked behaviors in freely moving animals. These data show that a large part of the worm's brain is involved in generating coordinated network activity reflecting behavioral output. Sensory circuits recruit these dynamics by controlling network state transitions. This work provides evidence that brain dynamics are a prerequisite, and not a cause, of stimulus-evoked activity to control subsequent behaviors.

Head-body coordination determines foraging strategy

In animal movement, a common trade-off exists between stereotypy and flexibility: efficient locomotion requires coherent coordination of body parts while other behaviors such as explorative search rely on deviations in gait and posture. We identified a head-body control system that counterbalances these needs during long distance travel and exploratory behavior. Upon chemosensory stimulation, animals reciprocally down-regulate regular undulatory crawling and up-regulate head-sweeping patterns. Using genetics and functional imaging of neural activity, we identified a peptidergic pre-motor circuit that controls head-body coupling. We show that head-body coupling is a graded response to environmental changes, and that the implicated neural circuits are required for determining the direction of locomotion during oxygen chemotaxis. This work shows how the nervous system combines elementary motion patterns to generate controlled complexity, which enables animals to execute appropriate decisions during navigation.

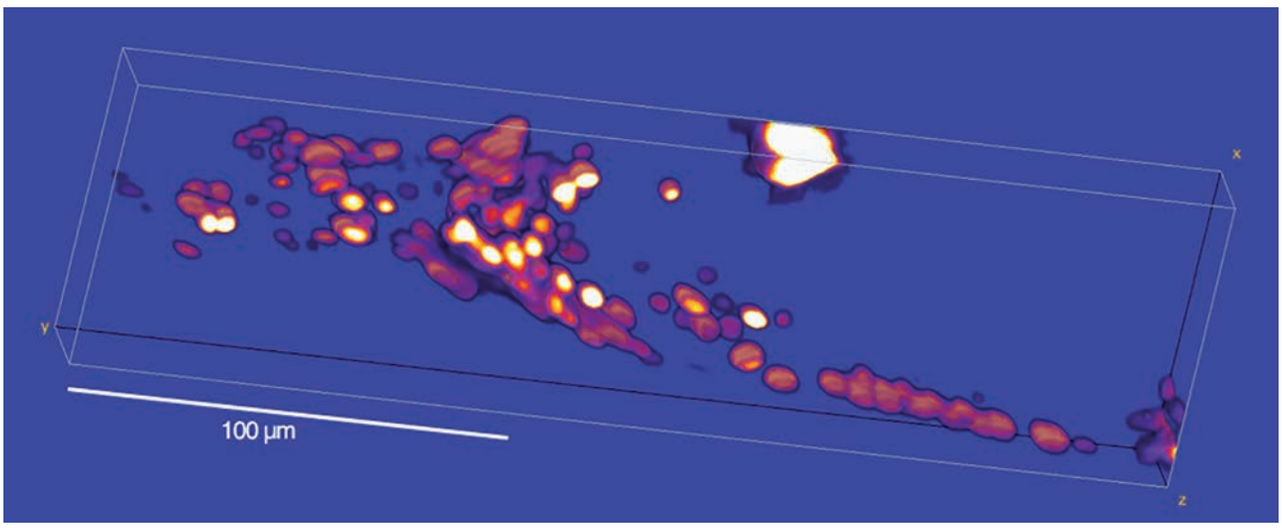

FIGURE: Volumetric calcium imaging using nucleus-localized Ca^{2+}-sensor NLS-GCaMP5K. The worm is aligned with its anterior-posterior body axis along the y-axis from left to right.

Further reading:

Schrödel, T., Prevedel, R., Aumayr, K., Zimmer, M., Vaziri, A. (2013). Brain-wide 3D imaging of neuronal activity in Caenorhabditis elegans with sculpted light. Nat Methods. 10(10):1013-20

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Yapici, N., Zimmer, M., Domingos, AI. (2014). Cellular and molecular basis of decision-making. EMBO Rep. 15(10):1023-35

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JOHANNES ZUBER

Finding and probing cancer dependencies

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In addition to rapid advances in cancer genome analysis, recently developed functional genetic tools have opened new avenues for identifying effective cancer therapies. Our lab combines genetically engineered cancer models and multiplexed functional genetic screens to systematically identify cancer-specific dependencies (so-called "non-oncogene addictions"), and study their function and therapeutic potential prior to drug development.

Genetic tools for target discovery and validation

The vast complexity and heterogeneity of human cancer genomes complicate the search for targeted therapies. Despite their diversity at the DNA level, driver mutations converge at the functional level to dysregulate a limited number of cellular processes which, besides promoting malignant growth, result in cancer-specific dependencies. While some of the most promising cancer therapies exploit such "non-oncogene addictions", their targets cannot be inferred from genomic data, but need to be identified through functional studies. Our lab develops and employs genetically engineered cancer models and multiplexed shRNAmir and CRISPR/Cas9 screening to systematically identify non-oncogene addictions in defined cancer contexts, and study their mechanistic role in a physiologically relevant setting.

Mechanisms and targets in aberrant cell fate programs

A major focus of our lab is the exploration of mechanisms and candidate targets promoting aberrant cell fate programs in leukemia. Both genetic studies and some targeted therapies have shown that terminal differentiation can be restored even in genetically complex cancers. However, the precise mechanisms underlying aberrant cell fate decisions remain poorly understood. To investigate these mechanisms and related therapeutic targets, we have established a series of Tet-conditional leukemia models involving self-renewal-associated driver alleles, and are probing candidate genes derived from their analysis in functional genetic screens.

Systematic analysis of chromatin dependencies in leukemia

A complementary project employs a chromatin-focused shRNA library constructed in the optimized miR-E backbone to systematically study chromatin dependencies. In a pioneering screen we identified the epigenetic reader BRD4 as a promising target in myeloid leukemia. While BET bromodomain inhibitors have meanwhile shown promise in clinical trials, the mechanistic basis underlying sensitivity and resistance to BRD4 suppression remains elusive. This is a challenge commonly associated with non-oncogene addiction targets, which we are addressing in follow-up studies. After successful pilot screens we are now expanding our approach to comparatively study chromatin dependencies in diverse leukemia subtypes. We seek to establish functional genetic dependency profiles that will, analogous to expression profiling a decade ago, provide a new layer of cancer classification with direct translational implications.

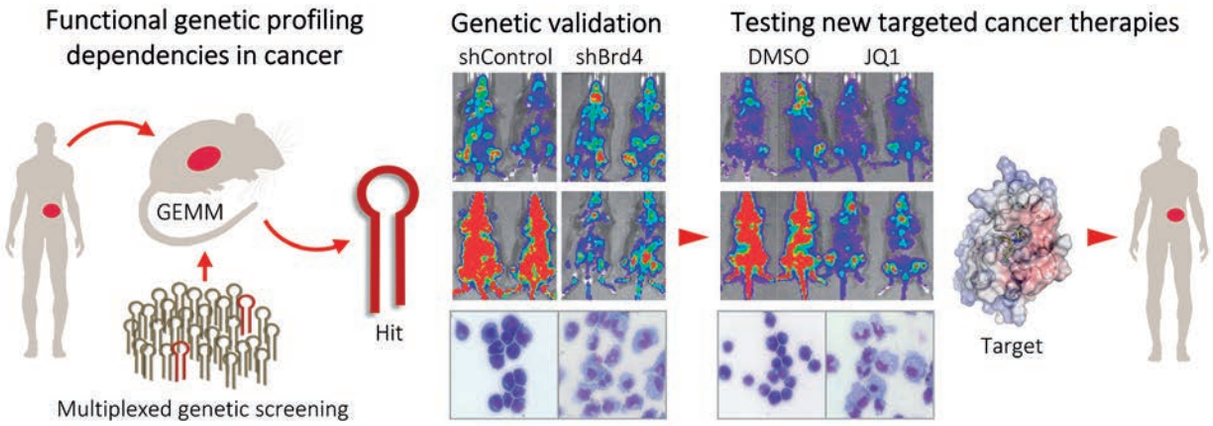

FIGURE: **Functional genetic exploration of candidate cancer targets**. Mutations commonly found in human cancer drive genetically engineered cancer mouse models (GEMM), which we use to systematically study cancer dependencies through functional genetic screening. Identified non-oncogene addiction targets, such as Brd4, can be investigated in vivo using Tet-regulatable RNAi, which serves as a powerful tool for probing their effects and mechanistic role prior to drug development.

Further reading:

Fellmann et al. (2013). An optimized microRNA backbone for effective single-copy RNAi. Cell Reports 5, 1704–1713.

Zuber & Shi et al. (2011). RNAi screen identifies Brd4 as a therapeutic target in acute myeloid leukaemia. Nature 478, 524-528.

Zuber & McJunkin et al. (2011). Toolkit for evaluating genes required for proliferation and survival using tetracycline-regulated RNAi. Nature Biotechnology 29, 79-83.

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BIOOPTICS FACILITY

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The services offered by the BioOptics Facility to researchers at IMP, IMBA and GMI encompass analytical flow cytometry and cell sorting, as well as a large variety of microscopy techniques, image processing and analysis.

Flow Cytometry

We provide instrumentation, education and expertise for all flow cytometry requiring experiments, and offer high-speed cell sorting, as well as advanced and general flow cytometry analysis. Users are given guidance and support with the planning of experiments, they are trained in the use of hardware and software for all of the three available state-of-the-art flow cytometers, as well as in data analysis. Three cell sorters are operated by the staff of the facility. Four cell populations can be sorted simultaneously in bulk, or single cell sorting can be performed.

Microscopy

The BioOptics Facility currently manages more than twenty microcopy systems, including wide-field microscopy, confocal laser scanning microscopy (CLSM), two-photon (2P) microscopy, total internal reflection (TIRF) microscopy, structured illumination microscopy (SIM) techniques and automated slide scanning. Most of the systems are motorized - thus providing automation for higher throughput - and are suitable for fixed samples as well as live cell experiments. The facility provides assisted use and training on instrumentation and consultation concerning all microscopy-related subjects, including project planning, staining, microscope selection, etc. Additionally intense basic as well as advanced practical microscopy courses are organized including hands-on sessions as well as lectures by internal and external faculty.

Image Processing and Analysis

Five state-of-the-art computer workstations are available at the BioOptics Facility, operating most of the common commercial image processing and visualization software. A server solution with a Web-based interface has been set up to enable deconvolution of microscopy images. The server permits efficient, multi-user, parallel, batch deconvolution that can easily be started from the individual scientist's computer. Users are trained in the use of specific software, depending on their demands or are trained in an annual course on image processing and analysis with lectures and hands-on sessions by the BioOptics staff. Customized classification and measuring algorithms are developed at the facility for advanced image analysis and automated object recognition.

For more information please visit http://cores.imp.ac.at/biooptics/

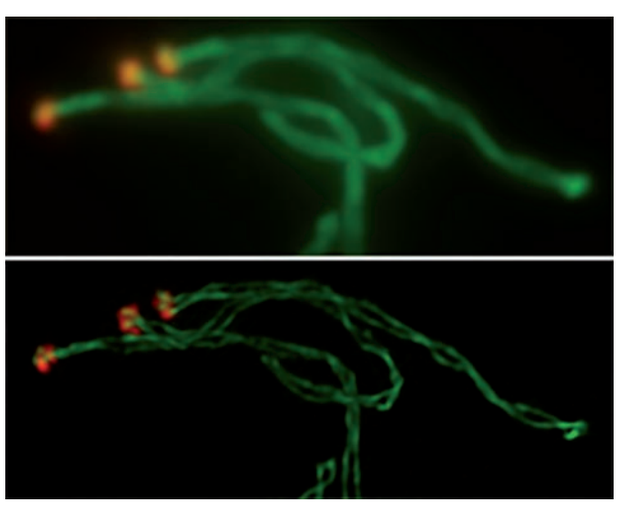

FIGURE: Chromosome spreads of pachytene oocytes in widefield (upper image) and structured illumination (lower image) microscopy. green: synaptonemal complex; red: centromeres. Sample from Mariana C.C. Silva, Peters Lab

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BIOINFORMATICS

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The Bioinformatics unit assists research groups in molecular-biology-related fields by providing sequence analysis services, scientific data mining, software infrastructure, and training in bioinformatics.

Sequence analysis

One of the principal areas of expertise at IMP-IMBA Bioinformatics is sequence analysis. Typical tasks include functional and structural characterization of proteins and genomic regions using methods such as pattern matching, complexity analysis, and homology searches. As conclusions in bioinformatics are achieved by synthesizing the results of multiple algorithms, we maintain and develop a set of specialized software tools to support this type of meta-analysis. Web access is provided for widely used scientific applications related to protein motif analysis (in-house development), similarity searching (BLAST, PSI-BLAST, FASTA), whole-genome viewing (GBrowse, UCSC browser), and various sequence manipulation and exploration tasks (EMBOSS).

Large-scale data analysis

Additional demands arise from the investigation of large functional genomics or high-throughput biological datasets. Assistance is provided in experimental design and subsequent analysis of next-generation sequencing, microarray, and mass-spectrometry-based proteomics experiments. The current main focus is on data analysis of small RNA-Seq, mRNA-Seq and haploid ES cell screens. We also engage in custom software and database development, and design computational and mathematical solutions that can cope with higher loads and memory requirements. Local instances of integrated model organism databases (Wormbase) and genome annotation portals permit visualization and analysis of in-house data with dedicated resources and additional privacy. User-driven data exploration is supported by the Ingenuity Pathway Analysis System. For scientists interested in computational biology, we offer hands-on training courses on basic principles and limitations of sequence analysis and data integration.

For heterogeneous computational tasks, we maintain a high-performance computing cluster (HPC) in which dedicated software is adapted to run in a batch and parallel computing environment. To enable researchers to use our server environment in an optimal way, we also provide training in Bash and Unix command line tools specific to the IMP/IMBA infrastructure.

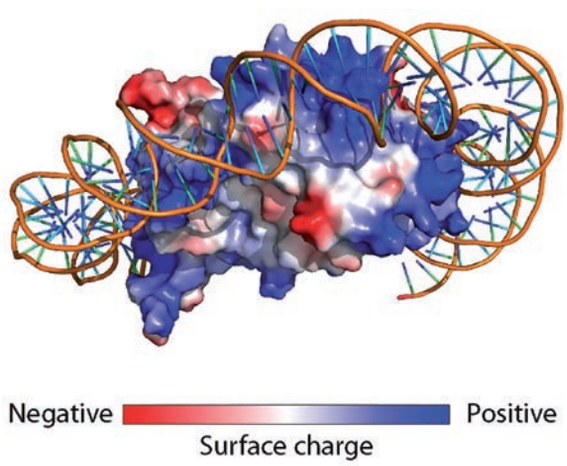

FIGURE: Hypothetical model of the non-canonical histone fold proteins CENP-T/W/S/X enclosed by a 73bp DNA fragment. The model is based on crystal structures of the CENP-T/W/S/X heterotetramer (PDB: 3VH5) superimposed on one half of the nucleosome core particle (only the DNA fragment is shown, PDB: 1KX5). The CENP-T/W/S/X heterotetramer is plotted as electrostatic surface potentials, illustrating the high density of positively charged surface residues (blue) that form the putative DNA interface.

PROTEIN CHEMISTRY

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[1]part time

At the Mechtler laboratory we identify, quantify and further characterize proteins with mass spectrometry. We also develop novel methods required by the research groups at IMP-IMBA for addressing their biological questions.

The sweet side of proteins…

Glycosylation is an abundant - yet functionally not very well characterized - post-translational modification of proteins with both high structural complexity and diversity. As a consequence, the exact structure of glycoproteins is difficult to analyze. Amongst many important topics, research in the Penninger group is also directed towards the elucidation of mechanisms in the immune response. Proteins of the immune system and plasma membrane proteins are frequently and extensively glycosylated. In order to successfully assess the proteome-wide abundance of N-glycosylations sites in neutrophils and to map glycosylated residues on the respective proteins, we had to design a novel method. The workflow combines a novel in-house developed software with an analytical strategy, highly optimized for the analysis of glycoproteins.

…and their social properties.

Proteins almost never act alone. Instead, proteins assemble into proteins complexes of defined stoichiometries and structure, fulfilling biological functions. Some of these complexes are very large molecular machines such as the ribosome. We apply different targeted proteomics approaches to quantify the stoichiometry of protein complexes. In collaboration with the Westermann group, we employ these methods to study the cell cycle-dependent changes in the composition of the kinetochore. Usually, proteomics is not used for directly studying structure; however, in cases were other techniques fail to deliver a model of protein complexes at atomic resolution, mass spectrometry might deliver structural information at a low resolution. Proteomic approaches do so by converting proximity of specific amino acids present in the three-dimensional structure into chemical links. These cross-links can be detected by mass spectrometry, allowing to construct low resolution models of the complex from which they originate. We recently adapted, optimized and down-scaled available protocols and started to apply them to biological questions addressed by several biological groups at IMP-IMBA.

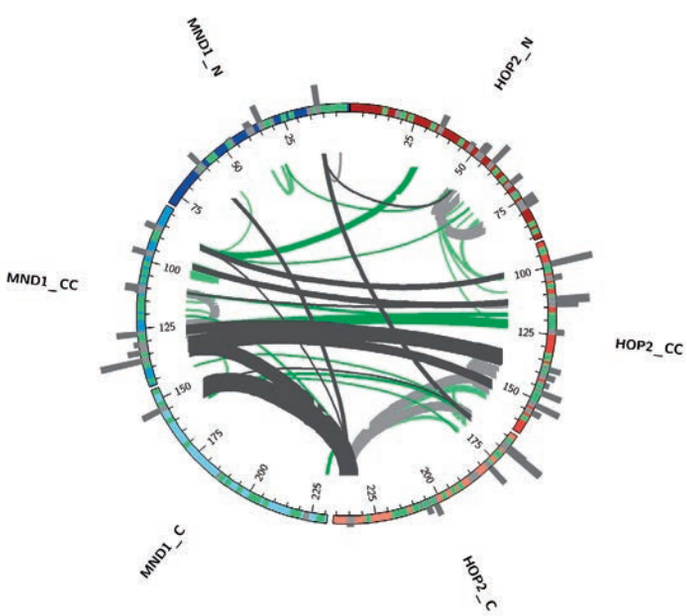
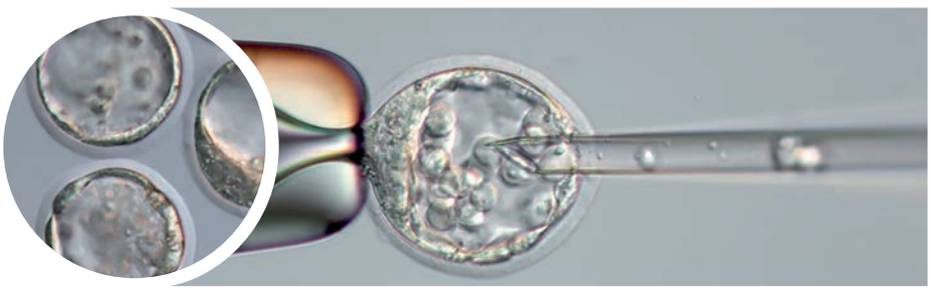


FIGURE: Circos Plot of crosslinks within the 3 domains of HOP2 (red) and MND1 (blue). The grey bars pointing outwards represent monolink abundance derived from amine-reactive linker.



COMPARATIVE MEDICINE

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TRANSGENIC SERVICE

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Comparative Medicine

Scientific work at the IMP and IMBA depends to a high degree on the use of model organisms. IMP and IMBA acknowledge and accept responsibility for the care and use of those animals according to the highest ethical standards. The institute ensures that all employees dealing with the animals understand their individual and collective responsibilities for compliance with Austrian laboratory animal law as well as all relevant regulations and rules concerning laboratory animal husbandries. In accordance with this institutional policy the animal house group - trained and highly qualified animal attandants - provides husbandry of animals and services for the various research groups.

HUSBANDRY:

The largest area of the animal house is the mouse section, which comprises 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, commonly used standard strains are routinely bred in-house.

COMPARATIVE MEDICINE SERVICES:

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

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

Transgenic Service

The Transgenic Service Department was set up in the beginning of 1998 to cope with the increasing demand for mouse studies and generation of transgenic mice. The Transgenic Service Department is shared by the IMP and IMBA.

The main tasks of this service unit are the injection of ES cells into blastocysts [also tetraploid] and 8-cell, and DNA into the pronucleus of fertilized mouse eggs. The service also provides for the transfer of 'clean' embryos into our Animal House, freezing of embryos for the preservation of specified mouse strains, and teaching basic embryological techniques to the staff of IMP and IMBA.

Many different ES cell clones and DNA/BAC constructs are being injected every year. The activities of the department are supervised by an Animal User Committee, which meets on a regular basis to set priorities and coordinate tasks. Currently it is chaired by Meinrad Busslinger.

MOLECULAR BIOLOGY SERVICE

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TEAM MEDIAKITCHEN:
Christa Detz-Jaderny, Gabriele Botto, Ulrike Windholz, Jens Schaich

The unit offers a wide variety of standard services to all scientists at IMP/IMBA and GMI. These include Sanger Sequencing, a "Speed Congenics Service", the preparation of competent cells of various E. coli strains, production of monoclonal antibodies and a routine mycoplasma testing service for tissue culture cells to mention the most important ones. In addition, we provide instrumentation and expertise for lab automation and high-throughput methods.

In the past year, expression of recombinant proteins became a rapidly growing task for our facility. We produce a wide range of proteins ranging from enzymes to cytokines providing our researchers with low cost, high quality material for their research.

Besides the use of E. coli, we have developed and established protocols for eukaryotic expression systems (Komagataella pastoris). This system helped us to overcome the common problems especially encountered expressing cytokines in prokaryotic systems, e.g. production of inclusion bodies. It not only allows fast and easy purification of proteins from supernatant, we also observe a far higher biological activity of these proteins compared to the material produced in E. coli. Currently, our current batch size lies in the range of 100 mg.

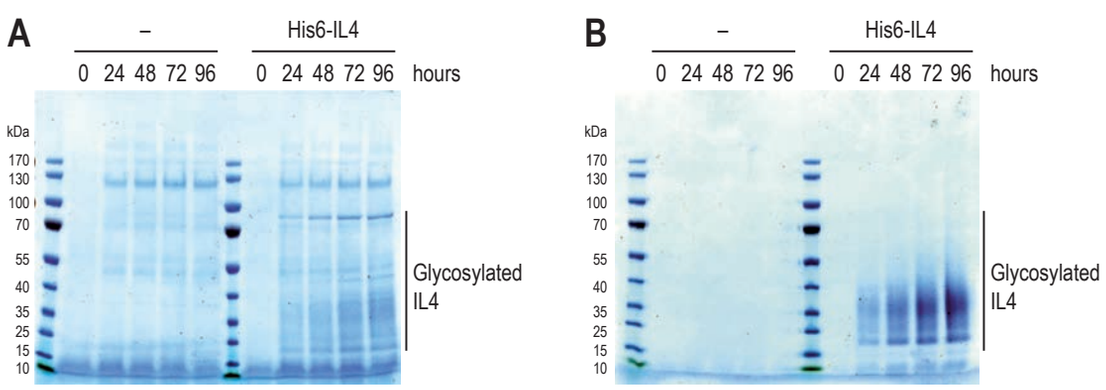


FIGURE: Example of a cytokine produced in K. Pastoris Panel A shows the protein composition of wildtype (-) and murine Il4 (His6-Il4) expressing cells; Panel B the protein eluted from a Ni-NTA column after binding and washing of the respective supernatants. (SDS gel stained with Coomassie brilliant blue). Biological Activity was measured by E. Wiedemann, Pavri group.

LIBRARIAN: Karlo Pavlovic

MAX PERUTZ LIBRARY

library@imp.ac.at

The Max Perutz Library is a specialized reference library located at the Vienna Biocenter (VBC). Its mission is to develop and maintain collections and services that support research at the IMP, IMBA and GMI.

The main task of the library is to provide comprehensive scientific literature pertaining to the areas of research pursued at the institutes. The Max Perutz Library holds approximately 3000 titles in print. These are partly available in the library's premises itself, being labeled and shelved according to a specific classification system. A part of the titles are shelved in the group laboratories and offices. Increasingly, online books are being licensed in order to provide access for many readers simultaneously and from every workstation. Those several hundred individually selected online books along with the print books can be searched for systematically in the online catalog, where each title is described in respect of its availability and accessibility. The most heavily used kind of literature resource are the licensed online journals. Several bibliographic and full-text databases can be searched for relevant literature on a given topic. This also applies to literature on methods and protocols, including Springer Protocols, Current Protocols or the Journal of Visualized Experiments. A document delivery option is offered for the literature not held by the library, which is delivered within some hours for online content and one week for printed matter. Management as well as researchers are supported with bibliometric services.

Study environment

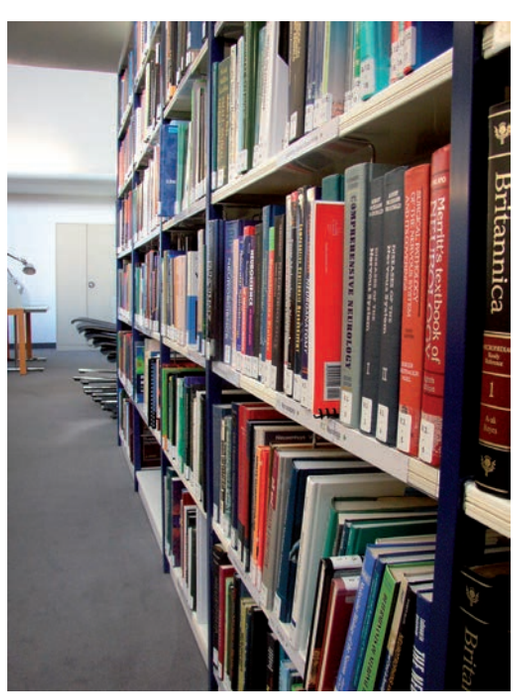
The reading room serves as a quiet and well-equipped place for reading, writing or just relaxing. Six study desks and a cozy lounge as well as two public computers, wireless LAN, a printer, a book scanner and a spiral binding machine are provided.

Teaching

The library offers special individually oriented training on literature search tools such as catalogs and bibliographic databases for all library users. This ranges from a comprehensive hands-on course on Pubmed searching, to a specific consultation concerning a single challenge in retrieving literature. Assistance is also provided for a variety of client- and web-based literature management tools, such as Endnote or Mendeley. The more, teaching is also provided during the VBC PhD Curriculum twice a year.

Users

The core user group consists of affiliates of the Research Institute of Molecular Pathology (IMP), the Institute of Molecular Biotechnology (IMBA), and the Gregor Mendel Institute of Molecular Plant Biology (GMI). External users from the Max F. Perutz Laboratories (MFPL), the FH Campus Vienna and other readers from the Vienna Biocenter (VBC) are welcome to visit the library premises.



Campus Science Support Facilities

The Campus Science Support Facilities GmbH (CSF) was established in 2011 at the Vienna Biocenter (VBC) to provide top scientific infrastructure operated and constantly further developed by highly qualified experts. The CSF supports IMP, IMBA and other institutions and companies situated on the VBC at the forefront of science. Besides scientific infrastructure, the CSF also offers social infrastructure such as the Child Care Center.

For more information visit the CSF website: www.csf.ac.at

Preclinical Phenotyping (pcPHENO)

The Preclinical Phenotyping Facility (pcPHENO) provides state of the art equipment and services to test mouse behavior, motor functions, physiology, and metabolism. Phenotypic screening is becoming an increasingly important step in the characterization of genetically modified mice, aiming to link molecular mechanisms to whole-body effects. After training under expert supervision, researchers can perform their experiments alone or make use of our services, ranging from the planning and performing of the experiments to final data analysis and interpretation.

Next Generation Sequencing (NGS)

The goal of the Next Generation Sequencing Facility (NGS) is to provide cutting edge next generation sequencing technology to its users. Next Generation Sequencing has become a key analysis method for biological research. The capacity to expand analysis from more or less defined genomic regions to genome wide studies has boosted the pace of research discovery and enabled researchers to obtain a global view on biological processes. Advice and guidance of sequencing projects are offered by our team that relies on years of experience with sequencing systems and sequencing data analysis. All common sequencing applications are supported and the development of novel methods and protocols encouraged.

Bioinformatics & Scientific Computing (BioComp)

The Bioinformatics & Scientific Computing Facility (BioComp) offers data analysis services and scientific software development for academic research groups and industrial research laboratories. Our wide range of services provides help to understand and exploit the large-scale data sets generated in modern biological and biomedical research. As a "knowledge hub" our facility also offers training, consultation and help-desk for all Vienna Biocenter (VBC) researchers in the fields of biostatistics, programming and bioinformatics.

Protein Technologies Facility (ProTech)

The mission of the Protein Technologies Facility (ProTech) is to help researchers at the Vienna Biocenter overcome two major experimental bottlenecks: protein production and purification. In addition we offer services upstream and downstream of these areas, including molecular cloning and protein characterization, and can provide expertise in most protein-related technologies. Our customers use the proteins and other reagents we generate for antibody generation, biochemical and cell biological assays, structural analysis, study of biomolecular interactions, CRISPR/Cas9 genome engineering experiments.

Electron Microscopy Facility (EM)

The EM Facility (EM) offers a large range of instruments, techniques and expertise to visualize the ultrastructure of biological samples - from molecules to cells & tissues. We have scanning (SEM) and transmission electron microscopes (TEM) and apply numerous techniques (from negative staining to cutting edge cryo-EM) to deliver quick sample screening and high resolution 2D or 3D imaging. Users chose whether they wish to get trained on how to use our equipment themselves or if they prefer us to do everything for them.

Vienna Drosophila Resource Center (VDRC)

The Vienna Drosophila Resource Center (VDRC), established in 2007, is a professionally organized bio-resource center of international significance. Our primary aim is to facilitate systematic analysis of gene function in Drosophila using in vivo transgenic technology. We maintain and distribute over 30,000 unique transgenic Drosophila stocks, including a genome-wide collection of RNAi lines, and to date have delivered more than 1,000,000 lines to over 2200 registered customers worldwide. We aim to further develop and expand our resources according to emerging technologies and community needs.

Plant Sciences (PlantS)

Many of the groundbreaking findings of molecular mechanisms of life were first described in plants. The Plant Sciences Facility (PlantS) provides 22 state-of-the-art plant growth chambers that allow precise control of environmental conditions. Our services include automated phenotyping for the objective, reproducible and high-throughput assessment of plant phenotypic traits and environmental simulation. Various plant stress conditions such as frost, drought and diverse light conditions can be realized. We help plant researchers to answer their most complicated questions.

Preclinical Imaging Facility (pcIMAG)

Preclinical Imaging Facility (pcIMAG) offers state of the art ultra-high-field magnetic resonance imaging on a 15.2 T Bruker magnet. We are continuously increasing our range of services to stay current with emerging applications relevant for biological systems. We are currently offering anatomical characterization of organ systems, axonal track tracing, quantitative perfusion measurement, angiography and proton magnetic resonance spectroscopy (1H MRS). Special focus is laid on top quality image analysis, data processing and 3D visualization. Our future outlook includes setting up combination of functional MRI (fMRI) and optogenetics.

Advanced Microscopy (advMICRO)

The Advanced Microscopy Facility (advMICRO) offers users access to a selection of cutting-edge optical microscopy and spectroscopy techniques, along with assistance in their implementation and data analysis. They also offer the development or customization of microscopes for applications where commercial solutions are not available.

Whether one is interested in measuring the dynamics of single molecules in live cells, the morphology and mechanical properties of entire embryos, or something in between – the Advanced Microscopy Facility has an expanding inventory of techniques at your disposal.

Histo Pathology (HP)

The HistoPathology Facility (HP) aims to combine expertise in histological techniques with scientific input from certified veterinary pathologist to provide customers with means for complete analysis of tissues. We offer top quality of standard services such as tissue processing, sectioning and most of the common histological stains for both paraffin and cryoblocks. In addition, customers can benefit from automatic immunostaining protocols, a continuously growing list of optimized antibodies and advanced pathological evaluations. Finally, our service includes consultation before and during the course of the experiment, interpretation of the results and pathology reporting.

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BIOOPTICS FACILITY

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SEMINAR SPEAKERS

JANUARY

09.01.14 Susan Gasser
Friedrich Miescher Institute for Biomedical Research
Probing roles for heterochromatin in development and genome stability in C elegans

14.01.14 Kathrin Plath
UCLA School of Medicine
Modeling the cell fate change of reprogramming and long-noncoding RNA function with X-inactivation

22.01.14 Pavan Ramdya
École Polytechnique Fédérale de Lausanne and UNIL
The organization of behavior in Drosophila: insights from robotics

23.01.14 Patrick Cramer
Gene Center Munich
Molecular systems biology of genome transcription

30.01.14 Keith Slotkin
The Ohio State University
The Regulation of Plant Transposable Elements - The Initiation of Epigenetic Silencing and How the Transposable Elements Fight Back

FEBRUARY

26.02.14 Matthias Kaschube
Frankfurt Institute for Advanced Studies
The role of lateral connections in shaping neural response properties in cortex

27.02.14 Jussi Taipale
Karolinska Institute
Genome-wide Analysis of Protein-DNA Interactions

MARCH

05.03.14 Brad Cairns
University of Utah
Chromatin Dynamics: Nucleosome movement, and germline-embyro epigenetics

06.03.14 Frank Kirchhoff
Institute of Molecular Virology, Ulm University Hospital
Reasons for the high virulence and effective spread of HIV-1

13.03.14 Craig Pikaard
Indiana University
Tales of repression: mechanisms of selective gene silencing and epigenetic inheritance

21.03.14 Jonathan Gale
University College London
Sensory hair cell death and survival in the inner ear: a Jekyll and Hyde story

26.03.14 Andrea Pauli
Harvard University
Toddler - a novel embryonic signal hidden in non-coding RNA

APRIL

02.04.14 Jennifer Lippincott-Schwartz
NIH
Navigating the cellular landscape with new optical probes, imaging strategies and technical innovations

03.04.14 Emmanuelle Charpentier
Helmholtz Center for Infection Research
CRISPR-Cas9: from bacterial adaptive immunity to RNA-programmable genome engineering

07.04.14 Leon Lagnado
University of Sussex
Synaptic mechanisms of adaptation and sensitisation in the retina

09.04.14 Melina Schuh
MRC Laboratory of Molecular Biology
New insights into aneuploidy in mammalian oocytes

10.04.14 Lynne Maquat
University of Rochester Medical Center
"Alu"strious Effects on Human RNA Metabolism

16.04.14 Denes Hnisz
Whitehead Institute for Biomedical Research
Roles for transcriptional super-enhancers in cell identity and disease

17.04.14 Dan Finley
Harvard Medical School
Regulation of proteasome activity by ubiquitin chain editing

24.04.14 Pierre Bruhns
Institut Pasteur
Roles of IgG receptors and myeloid cells in antibody-induced cancer immunotherapy

30.04.14 Duncan Smith
New York University
Eukaryotic DNA replication: the view from the lagging strand

MAY

06.05.14 Sebastian Maerkl
EPFL
Engineering gene regulatory networks in vitro and in vivo

07.05.14 Robert Johnston
Johns Hopkins University
Controlling stochastic gene expression in the Drosophila retina

07.05.14 Michel Nussenzweig
Rockefeller University
Affinity Maturation and Selection of B Cells

08.05.14 Nikolaus Rajewsky
MDC Berlin
Regulatory RNAs

14.05.14 Martin Rossel Larsen
University of Southern Denmark
Comprehensive quantitative proteomics and PTMomics applied to studying signal transduction pathways

14.05.14 Steffen Wolff
FMI
Amygdala interneuron subtypes control fear learning through disinhibition

15.05.14 Scott Keeney
Howard Hughes Medical Institute, Memorial Sloan-Kettering Cancer Center
A dangerous game: DNA breaks and meiotic chromosome dynamics

22.05.14 Iain Cheeseman
Whitehead Institute for Biomedical Research
Generating a Dynamic Kinetochore-Microtubule Interface

27.05.14 Andreas Diefenbach
University of Mainz Medical Centre
Transcriptional and epigenetic control of innate lymphoid cell fate decisions

JUNE

11.06.14 Gabriel Victora
Whitehead Institute of Biomedical Research
Dissecting antibody evolution by intravital microscopy

12.06.14 Marc Veldhoen
The Babraham Institute
The role of the AhR in epithelial immunology

13.06.14 Helmut Kessels
Netherlands Institute for Neuroscience
The effects of amyloid-beta on glutamatergic synapses

17.06.14 Ivan Oransky
Retraction Watch
Can We Still Trust Science?

24.06.14 Marlies Knipper
University of Tübingen
News about the molecular bases of Tinnitus and Hyperacusis

25.06.14 Mart Loog
University of Tartu
Multisite phosphorylation networks as signal processors for Cdk1

26.06.14 Teymuras Kurzchalia
MPI of Molecular Cell Biology and Genetics
Life without water: How worms survive desiccation

JULY

03.07.14 Tim Hughes
University of Toronto
C2H2 zinc fingers greatly expand the human regulatory lexicon

09.07.14 Lothar Schermelleh
University of Oxford
New insights into X chromosome inactivation by 3D superresolution microscopy

10.07.14 Nicolas Tonks
Cold Spring Harbor Laboratories
Drugging the undruggable: new approaches to exploiting the protein tyrosine phosphatase PTP1B as a therapeutic target

17.07.14 Iannis Aifantis
NYU Cancer Institute
Coming out of the shadows: epigenetic regulation and non-coding RNAs in acute leukemia

22.07.14 Catarina Vicente
The Node Community Manager
Joining the online conversation: how to use social media to communicate your science

22.07.14 Ilya Ruvinsky
University of Chicago
Conservation and divergence in evolution of gene regulation

23.07.14 Rob Klose
Oxford University
A new logic for polycomb domain formation

24.07.14 Robert Roeder
The Rockefeller University
Transcriptional Regulatory Mechanisms in Animal Cells

25.07.14 Jan Huisken
Max Planck Institute of Molecular Cell Biology and Genetics
Visualizing zebrafish development with high-speed light sheet microscopy

28.07.14 Gioacchino Natoli
Campus IFOM-IEO
A genomic regulatory framework for macrophage specification and function

31.07.14 Neil Hunter
HHMI, University of California, Davis
Regulation of Meiotic Prophase by Post-Translational Protein Modification

AUGUST

07.08.14 Jakob Fuhrmann
Scripps Research Institute
The chemical biology of protein arginine phosphorylation

26.08.14 Jörg Heierhorst
St. Vincents Institute of Medical Research
Essential functions of the Zinc-finger transcription factor ASCIZ in B cell development and lymphomagenesis

SEPTEMBER

03.09.14 Jeremy Shaw
University of Western Australia
Structural Studies of Iron Biomineralisation in Chiton Teeth

04.09.14 Tony Hyman
MPI of Molecular Biology and Genetics, Dresden
Liquid like compartments in cells: Implications for polarity and disease

09.09.14 Noboru Mizushima
Tokyo University
Physiological role and molecular mechanisms of autophagy

10.09.14 Paul Sternberg
California Institute of Technology
Molecular Circuitry for Sleep, Sex and Predation

18.09.14 David Julius
UCSF
TRP channels of the pain pathway: Connecting physiology to atomic structure

24.09.14 Nicole Föger
Austrian Agency for Research Integrity
Research integrity, questionable research practices and research misconduct – a narrow windy road?

25.09.14 Svante Pääbo
Max Planck Institute for Evolutionary Anthropology
Archaic Genomics

OCTOBER

08.10.14 Carlos Bustamante
University of California, Berkeley
Division of Labor and Coordination Among the Subunits of a Nearly Perfect Biological Machine

09.10.14 Jonathan Weissman
UCSF
Globally monitoring translation in space and time with ribosome profiling

16.10.14 Wendy Bickmore
MRC Human Genetics Unit
Gene regulation in the context of nuclear space

17.10.14 Stephen Nutt
The Walter and Eliza Hall Institute of Medical Research
Epigenetic and transcriptional control of lymphocyte differentiation

23.10.14 Andre Nussenzweig
NIH, Center for Cancer Research
Mechanisms that maintain genome stability

24.10.14 Sean Escola
Center for Theoretical Neuroscience, Columbia University
Sequence generating recurrent neural networks: a novel view of cortex, thalamus, and the basal ganglia

30.10.14 John T. Lis
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Probing Mechanisms of Transcription Regulation In Cells and Across Genomes

NOVEMBER

13.11.14 Herwig Baier
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Neural circuits for zebrafish behavior

18.11.14 Scott W. Emmons
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C. elegans Connectomics

20.11.14 James Hurley
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Structural Choreography of Cellular Self-Cannibalism

25.11.14 Pavel Nemec
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In search of the neural basis of magnetic orientation: cues from African mole rats and homing pigeons

27.11.14 Adele Marston
Wellcome Trust Centre for Cell Biology
Orienting chromosomes in mitosis and meiosis

DECEMBER

04.12.14 Takehiko Kobayashi
National Institute of Genetics
Stability of ribosomal RNA gene cluster and cellular senescence

09.12.14 Sophie Jarriault
IGBMC, Strasbourg
Control of cellular potential and identity: insights from natural direct reprogramming

11.12.14 Stirling Churchman
Genetics Department, Harvard Medical School
Global dynamics of nuclear and mitochondrial gene expression at nucleotide resolution

11.12.14 Manuel Mayr
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Proteomics and Lipidomics Combined for Cardiovascular Biomarker Discovery

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Opened in 1988 close to the city center, the IMP triggered the development of its neighbourhood into a teeming biotechnology hub. Today's "Vienna Biocenter" is also home to the Max F. Perutz Laboratories (MFPL; University and Medical University of Vienna), the Institute of Molecular Biotechnology (IMBA; Austrian Academy of Sciences) and the Gregor Mendel Institute of Molecular Plant Biology (GMI; Austrian Academy of Sciences), a University of Applied Sciences, several biotech companies, a non-profit scientific society and the Vienna Open Lab.

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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 120,000, Vienna offers not only the academic but also the cultural and social infrastructure that comes with student life.

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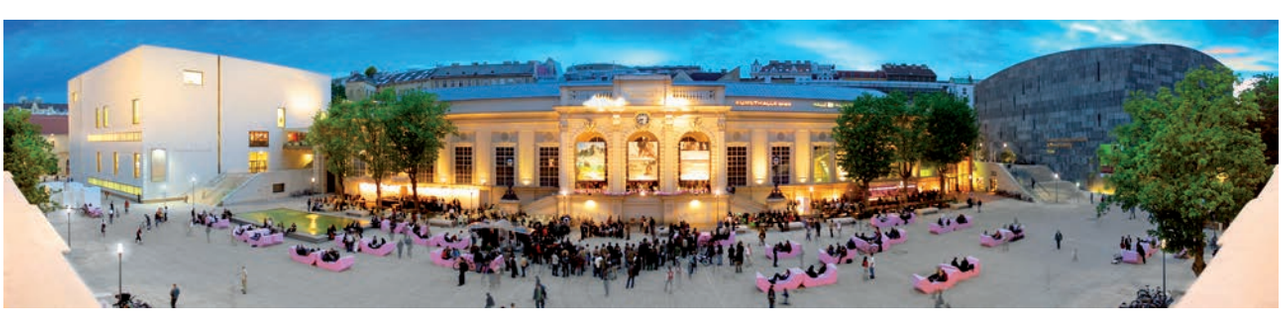


Attractive and family-friendly environment

IMP cares a lot about the quality of life of its staff. We offer competitive salaries with health and social benefits. The campus has its own kindergarten (with opening hours suited to the scientists' needs). You may also avail yourself of a number of social activities - such as weekly social hours, a ski trip, and various retreats - which help you to get acquainted with your colleagues.

We try to make relocation as smooth as possible. Several in-house apartments are available to bridge the time until a staff member has found a place of his/her own. Our administrative staff is helpful in finding housing, and our personnel department takes care of your legal requirements including visas, registration, health insurance, and family matters. For school-aged children Vienna offers different types of schooling ranging from public to private, German or foreign language based.
More information about career opportunities at IMP is available at: *http://www.imp.ac.at/students/*

Child Care Center (CCC)

Besides scientific infrastructure, the CSF is offering social infrastructure to the Vienna Biocenter, such as the Child Care Center. It is run by Wiener Kinderfreunde and hosts not only little researchers from the Vienna Biocenter but also young media kids from the Media Quarter Marx. First and foremost the head of our Child Care Center, Dagmar Mirek, and her highly motivated team provide a loving and caring atmosphere for the children. Besides that they offer extended opening hours and the possibility to attend a crèche from 3 month on. Also important for the international surrounding of the Vienna Biocenter are the English lessons with native speaker Betsy Higgins-Pösinger. The Child Care Center is a creative place for children where they undertake excursions into the countryside, visit kids theatre, grow vegetables, go ice skating and do everything else a child's heart desires.
For more information please visit our website (*www.csf.ac.at*) or contract Dagmar Mirek at +43 (0)1 798 56 10 or kdg.campus@speed.at.

YOUR CAREER AT THE IMP

The IMP focuses on providing a perfect environment for excellent science as well as education, which makes it the right place to develop your career. We offer an exciting setting for undergraduates, PhD students, postdocs, and principal investigators alike. All researchers have access to a superb infrastructure and generous funding, thus allowing for intellectual freedom.

The IMP is part of the Vienna Biocenter (VBC), and you will be part of a large scientific community. Most of our training offers are run jointly with the other research institutes at the VBC: Institute of Molecular Biotechnology (IMBA), the Gregor Mendel Institute of Molecular Plant Biology (GMI), and Max F. Perutz Laboratories (MFPL).

We have specific educational programmes for different career stages:

Undergraduate students – Vienna Biocenter Summer School

Every year the Vienna Biocenter Summer School provides a unique opportunity for approx. 25 international undergraduate students to experience cutting-edge scientific research for a period of two months. Our summer fellows are provided with a stipend, accommodation and a travel allowance. Throughout its five editions we have received over 3,000 applications from 97 nations, and have hosted 115 fellows.

"A great opportunity to learn new things, see how working in a leading European research institute looks like, meet new people from all over the world – altogether an amazing experience."
Testimonial from a student, member of the 2013 class

Every year we open a competitive call
(from December 1 – January 31). For more information visit our website: *www.vbcsummerschool.at*

Graduate students – Vienna Biocenter PhD Programme

As a PhD student at the IMP you can virtually do any experiment you can think of. Our goal is to train independent, critical and creative researchers. The VBC PhD Programme is focused on a 4-year research project. The research project is primed by an introductory course at the beginning of your studies and further complemented by courses, lectures, and seminars that run continuously on campus. The PhD students organize numerous networking activities, and the programme puts great emphasis on the career development of our students.

Most importantly, our faculty includes renowned scientists from all over the world, with outstanding publication records. They are all extremely committed to the training of young researchers. All PhD students benefit from the support extended by our scientific facilities, and are employed on a full-time contract.

The VBC PhD Programme is open for applications twice a year (September-November and March-April). We invite the best candidates for an interview and to visit the research institutions at the VBC for a few days. Check out our website for detailed information: *www.vbcphdprogramme.at*

Postdocs

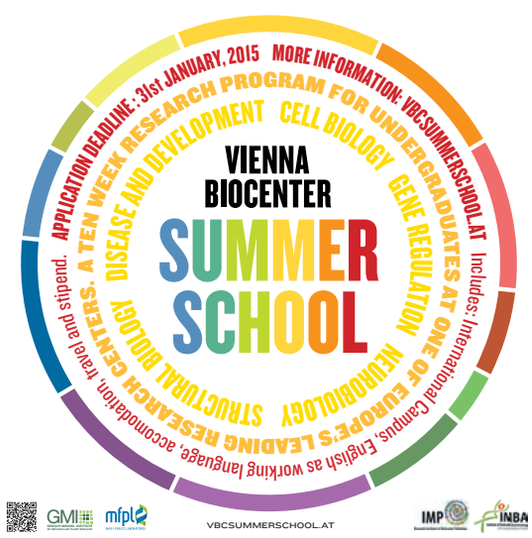
The IMP is the ideal scientific environment for postdocs to further develop as scientists. At the IMP postdocs find a supportive and mentoring faculty, have access to state-of-the-art research infrastructure, and are part of a lively scientific community.

The IMP postdocs are part of a larger network – the Vienna Area Postdoc Association – that organizes an annual retreat, career development initiatives, and a training programme, specifically designed to give you a competitive edge on the job market. Currently the programme includes courses in scientific writing, project management and leadership. All of the courses are facilitated by experienced and outstanding coaches.

Applications for postdoc positions at the IMP can be submitted directly to the relevant group leader. Funding is available from internal sources, however, postdoc applicants are strongly encouraged to apply for external fellowships to support their research.

No matter which stage of your career you are in, at the IMP you will always benefit from an **outstanding scientific infrastructure** Scientific success at the IMP results, to a significant extent, from a wide array of scientific service facilities. The variety and quality of these units is unmatched by most of the top international research institutes. Support is provided for a wide range of research approaches, including conventional and high-throughput sequencing, state-of-the-art mass spectrometry analysis, various microscopy and electron microscopy systems, and a bioinformatics unit. With very few exceptions, the scientist may access all of these facilities free of charge.

For further information on the facilities provided at the VBC, please refer to the pages 36-43 in this booklet.



SPOTLIGHTS

RNAISSANCE IN GUMPOLDSKIRCHEN

From the 15th to the 17th of January, forty specialists met in Gumpoldskirchen to discuss microRNAs and their potential role in treating human diseases. The meeting was jointly organised by IMP/IMBA faculty members and colleagues from the Boehringer Ingelheim Regional Center Vienna. It follows a tradition that started as an IMP-initiative 16 years ago and brings together researchers from basic and applied science in an informal setting for a fruitful exchange of ideas.

01/14

WINTER OUTING 2014

Over 250 colleagues from IMP, IMBA, GMI, and CSF took part in his year's ski-trip from the 27th until the 29th of March. As in previous years, Sporthotel Royer in Schladming, Styria was the destination. In the center of the Northern Alps, Schladming is not only famous for alpine skiing, it is also well known for the picturesque alpine scenery including the impressive Dachstein.

02/14

03/14

MAX BIRNSTIEL LECTURE HIGHLIGHT [05/03/2014]

Brad Cairns
University of Utah
Chromatin Dynamics: Nucleosome movement, and germline-embyro epigenetics
Host: Johannes Zuber

MAX BIRNSTIEL LECTURE HIGHLIGHT [02/04/2014]

Jennifer Lippincott-Schwartz
National Institute of Health (NIH)
Navigating the cellular landscape with new optical probes, imaging strategies and technical innovations
Host: Stefan Westermann

04/14

IMP-IMBA FACULTY RETREAT

On the 9th and 10th of May, the IMP and IMBA Group Leaders met in Zwettl, Lower Austria, for the annual Faculty Retreat. The two days were devoted to science, team building and the general exchange of ideas.

05/14

VBC PHD RETREAT

This year's VBC PhD retreat in June was held over three days in Zwettl, Lower Austria; 57 students from all four institutes attended. The talks focused on the often-neglected ethics of publishing in science and featured workshops, talks and stimulating discussions by and with Nicole Foeger (Austrian Agency for Research Integrity) and Ivan Oransky (Retraction Watch). In addition, nine students presented their current progress in a chalk talk format, and the remaining students showcased their work in poster sessions. Furthermore, one afternoon was dedicated to social activities, especially helping new students get to know each other.

06/14

MAX BIRNSTIEL LECTURE HIGHLIGHT [07/05/2014]

Michel Nussenzweig
Rockefeller University
Affinity Maturation and Selection of B Cells
Host: Martina Minnich and Meinrad Busslinger

IMP: RUNNERS-UP, DRAGON BOAT CUP 2014

In an exciting and extremely tight finish, the IMP team came second in the Vienna Dragon Boat Cup 2014 at the City Beach Club. Out of 24 teams from Austria and Germany, the increasingly inappropriately named IMPerfectos lost only to the semi-professional team of the "Vienna Dragons". Once again, the cheering crowd was able to witness a great display of team spirit and endurance, and everyone had a lot of fun.

IMP SUMMER EVENT – CATCH ME IF YOU CAN

On Wednesday 2 July, nine groups of fearless IMP employees searched Vienna's Prater area in the pouring rain to find hidden treasures and fulfill eccentric tasks. The IMP Summer Event took its toll: mosquito bites, wet feet and some ravaged undergrowth were rewarded by a most exciting and creative geo-caching afternoon and lots of team building along the way.

VIENNA BIOCENTER SUMMER SCHOOL

Once again the VBC Summer School, was hugely popular. Out of the nearly 2,000 inquiries from all over the world, 21 students were invited to join one of the labs at IMP, IMBA, GMI and MFPL for nine weeks. The whole programme is traditionally accompanied by a series of lectures, which give an opportunity for open discussions. There are also a number of social activities for the fellows to get to know each other. Each summer fellow can work on an independent research project under the close supervision of a graduate student. The results of each of their projects were presented during the Summer School Symposium held on August 28-29. Anna Sawicka (Vaziri Group), Philipp Dexheimer (Cochella Group), and Juan Iglesias Artola (Westermann Group) (IMP) were among the "best presentations award winners" this year.

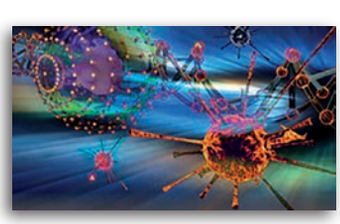
MAX BIRNSTIEL LECTURE HIGHLIGHT [10/09/2014]

Paul Sternberg
California Institute of Technology
Molecular Circuitry for Sleep, Sex and Predation
Host: Manuel Zimmer

07/14 08/14 09/14

LATE SUMMER PRACTICAL PROTEOMICS SEMINAR

In August, more than 170 scientists came to the IMP to attend a meeting centered on technology. The 8th Late Summer Practical Proteomics Seminar focused on quantitative techniques in mass spectrometry and the analysis of post-translational modifications. The practical workshops were intended to give an introduction to bio analytical methodologies. They covered a wide spectrum of topics ranging from phosphopeptide analysis with mass spectrometry to structural proteomics. The short courses were complemented by talks from international speakers, who presented their recent work and current developments in mass spectrometry-based proteomics.



THE VIENNA BIOCENTER AMATEUR DRAMATIC CLUB (VBC ADC)

presented Oscar Wilde's play, "The Importance of Being Earnest", on the 6th and 7th August in the Vienna Biocenter courtyard. Perfect weather in combination with a BBQ & Happy Hours made the performances wonderful evening open-air events with laughter and fun. This, the club's 14th production, was also taken "on tour" to IST Austria on August 5th.

IMP RECESS

From 1st of October until 3rd of October, IMP scientists met with members of the Scientific Advisory Board (SAB) to present their work and discuss their research. The SAB, consisting of internationally renowned scientists, was impressed by the scientific performance and high standards of the research presented during the recess. The IMP would like to thank all SAB members for their tremendous support. IMP SAB members: please refer to page 53.
This year's Added Dimensions Talk by José Alejandro Alvarez was on "Galapagos – Habitat and Inhabitants", most impressive images provided by nature, captured by a passionate photographer.

VBC PHD SYMPOSIUM – "COMPLEXITY OF LIFE"

Even though in the process of our research we aim to answer questions by reducing them to simple problems, this year's PhD symposium went big and focused on the complexity of life. More than 250 attendees from almost 20 different countries enjoyed talks from a broad array of international high profile speakers such as Mark Vidal (Dana-Farber Cancer Institute, Harvard), Uri Alon (Weizmann Institute of Science, Israel), David Baulcombe (University of Cambridge, UK) and Sean Carroll (Howard-Hughes Medial Institute/University of Wisconsin-Madison, USA). In addition, 13 international master students were awarded travel grants to visit the symposium and gave very positive feedback!

10/14

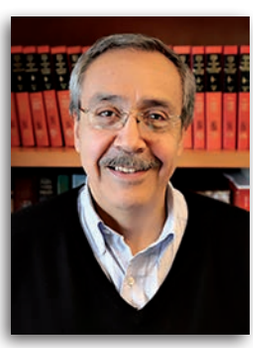
POSTDOC RETREAT

The postdoc retreat in september brought together 40 postdocs from all four institutes on the Campus VBC. In addition, the Research Center for Molecular Medicine (CeMM) and the Institute of Science and Technology (IST) Austria was represented.
The retreat with the topic "bones" took place in Prague and was organized by the Vienna Postdoc Organisation.

11/14

MAX BIRNSTIEL LECTURE HIGHLIGHT [08/10/2014]

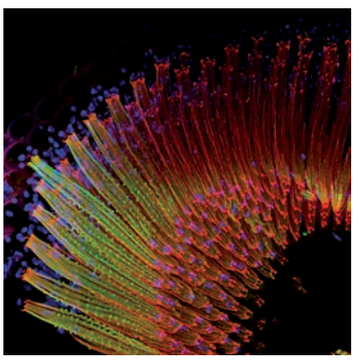
Carlos Bustamante
University of California, Berkeley
Division of Labor and Coordination Among the Subunits of a Nearly Perfect Biological Machine
Host: Alipasha Vaziri



12/14

CHARITY PUNCH EVENT

On 20th of November several service facilities from IMP and IMBA teamed up to organize the third "Charity Punsch Event". In front of a beautifully decorated stand in the VBC courtyard little snacks and steaming hot drinks with varying concentrations of ethanol, keeping the crowd warm, were served. The ship's bell, signaling extra donations, rang continuously – only interrupted by a harmonious performance of a brass quartette, spreading wintertime atmosphere. The money collected during the evening event (a record amount!) was donated to the charity "Kindertraum" (Children's Make-A-Wish Foundation).



Cover Illustration

The image represents fruit fly (*Drosophila melanogaster*) ommatidia
Karin Panser from the Research Institute of Molecular Pathology (IMP) in Vienna received the first prize in the international 'Huygens Image Contest' 2013, colouring inspired by the oeuvre of Max Weiler

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