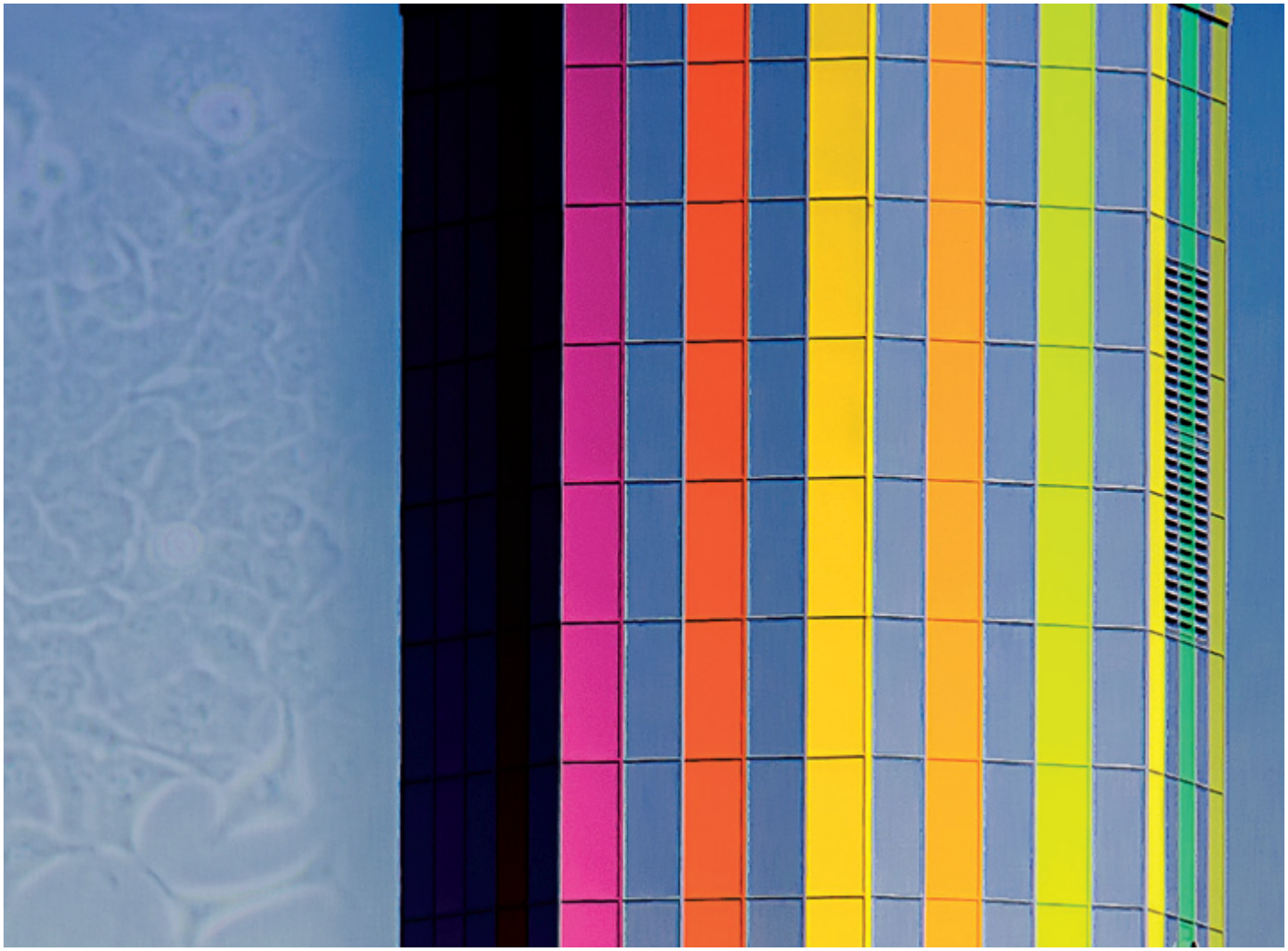


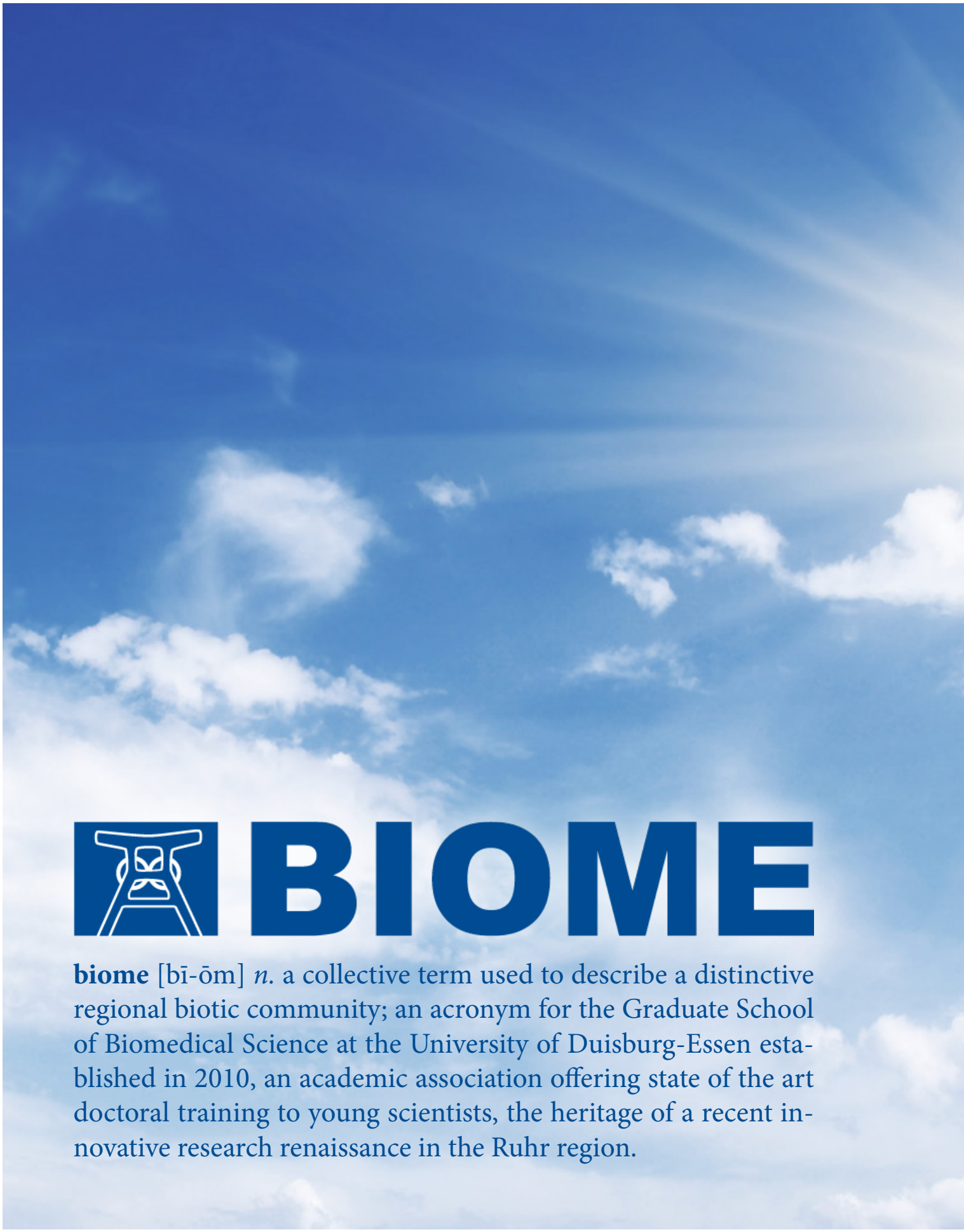
UNIVERSITÄT
DUISBURG
ESSEN

Open-Minded

BIOME

Graduate School of Biomedical Science

Continuity: 2012-2013



BIOME

biome [bī-ōm] *n.* a collective term used to describe a distinctive regional biotic community; an acronym for the Graduate School of Biomedical Science at the University of Duisburg-Essen established in 2010, an academic association offering state of the art doctoral training to young scientists, the heritage of a recent innovative research renaissance in the Ruhr region.

Contents

Daniel Hoffmann, Dean of Biology

Message from the Dean of Biology

If you want to harvest honey, build a beehive. This is exactly the recipe behind BIOME. Actually, BIOME now consists of several hives, with PhD students buzzing to and fro in considerable numbers, bringing in new data from their fields of research, and jointly producing sweet new knowledge. And here the analogy ends. In BIOME, every worker has the chance to become a queen, and the PhD supervisors do not have to fear sharing the fate of drones (hopefully). Today, BIOME is stronger and more attractive than ever, thanks to the efforts of many people making this grand collaboration possible.

With further growth, new challenges will emerge, but I am optimistic that we can master these together.

I wish BIOME all the best so that we may reap sweet science for many years to come.

Daniel Hoffmann
Dean of Biology

Jan Buer, Dean of Medicine

Message from the Dean of Medicine

The times when scientists conducted research in ivory towers are hopefully long gone. Networking and interdisciplinary collaboration are more important today than ever. The fact that this is firmly established in the minds of our young scientists is due in no small part to the BIOME graduate school, where multidisciplinary biomedical research is combined with teaching in an exemplary manner. BIOME has offered highly qualified scientific training both to graduates of Medicine and Biology for four years now. BIOME can perform this function especially well because its very purpose is interdisciplinary collaboration. Networking is affected less than ever by national borders. This is evidenced by the increasing frequency of international events, for instance the meeting BIOME held last year jointly with the graduate school of Radboud University in Nijmegen, The Netherlands. The personal contacts established by young researchers at this and other events will stand them in good stead for a lifetime. More and more young researchers realise that this is the right approach: since BIOME was founded, the number of participating doctoral candidates has grown continuously. When we started in 2010 there were 80 participating graduate students. That number has now more than doubled to over 230 present and first-generation alumni doctoral members. Of the current doctoral candidates 85% have undergraduate degrees in life sciences. We are gratified by the strong external support provided to BIOME since its founding by the Medical Foundation of the Essen University Hospital (Stiftung Universitätsmedizin Essen) and the Essen Cultural Foundation (Kulturstiftung Essen), and look forward to equally enthusiastic support in the years ahead.

Jan Buer
Dean of Medicine

Universitätsklinikum Essen

Graduate School of Biomedical Science (BIOME)

2012-2013: Continuity of the BIOME story

A short while ago, a colleague charmingly described BIOME as being "*salonfähig*", implying that our acronym for the Graduate School of Biomedical Science has become an accepted buzz word for a concept of doctoral training within academic circles at the University of Duisburg-Essen. We reflect upon this and look back on the last four years since our establishment in 2010 with a sense of shared pride and achievement. Our school has remained young and dynamic, flexible enough to expand its structures to incorporate new ideas, ventures and partners, yet has proven solid enough to be recognised now widely as a set standard of quality in biomedical doctoral education. Proof of this was granted in February 2014: the Faculty of Biology's PhD Commission officially acceded that full participation in one of BIOME's programmes for three years meets with the recently introduced 18-point accreditation requirement in its entirety for the conferral of a doctoral degree in Biology.

2012 was a year of active growth for our school with the successful launch of three new cores, namely the German Research Foundation (DFG) funded research training group 1739 on Radiation Sciences in April, the more clinically-biased core on Transplantation Medicine in May, and a Ruhr-regional collaboration on Computational Biomedicine in October. In the same year, we welcomed the first candidate to opt for BIOME's MD/PhD programme, created especially for medical students wishing to deepen their research knowledge extensively enough to be able to obtain a PhD degree.

2013 started no less energetically with the first clinical grand rounds, a voluntary three-day translational opportunity aimed at allowing PhDs to experience life on the wards with the goal of forging greater understanding between young biomedical researchers and their clinical colleagues. Simultaneously, ELAN (*Essener Ausbildungsprogramm „Labor und Wissenschaft" für*

den aerztlichen Nachwuchs) was initiated, a prestigious doctoral programme for outstanding medical students, one of just three such programmes in the whole of Germany, funded by the Else Kröner Fresenius Foundation. Our graduate school and ELAN are closely linked: full participation in one of BIOME's cores for one year is an inherent component of ELAN. Furthermore, the year saw the full-term end of the nine-year DFG research training group 1045 on the "Modulation of Host Cell Functions for the Treatment of Viral and Bacterial Infections", a Rhine-Ruhr network which has been sufficiently enduring to warrant further DFG support in the form of the new research training group 1949 on the "Immune Response in Infectious Diseases – Regulation between Innate and Adaptive Immunity" starting in April 2014. Both these RTGs, referred to as "Host-Pathogen Interaction" and "Innate and Adaptive Immunity" by BIOME, include the doctoral members of the Transregio Collaborative Research Centre (TRR 60) on the "Mutual Interaction of Viruses with Cells of the Immune System: from Fundamental Research to Immunotherapy and Vaccination", an international, German-Chinese research cooperation based in Essen between universities in Duisburg-Essen, Bochum, Wuhan and Shanghai which was established in 2009 and is currently in its second period of funding.

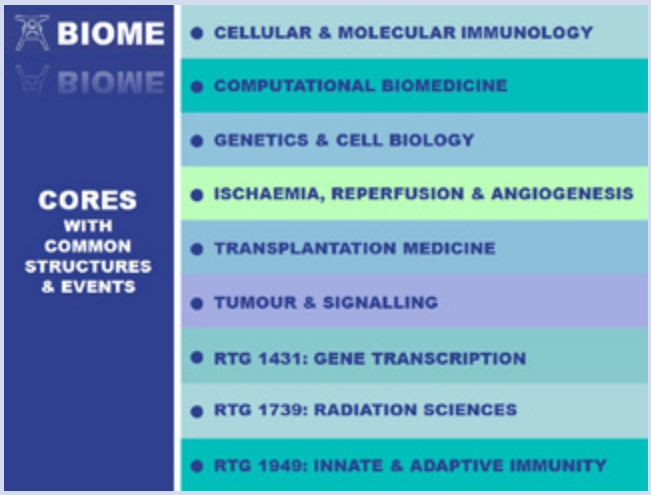
Within the last two years we have also seen the successful graduation of the first generation of BIOME doctorates to be awarded their PhD or MD degrees, around 120 young researchers in all, who have since moved on to post-doctoral positions in academia, medicine or the industry.

Pleasing headway has been made in strengthening our partnerships with other research centres and universities within Europe, a mutual collaborative exchange network winning ever more enthusiastic support. From the humble beginnings of our first IRUN Symposium on Immune Recognition of Pathogens and Tumours hosted by the University of Duisburg-Essen in October 2011 with four institutions from three countries, we now have a European proposal currently pending panel decision with around 40 researchers at 30 institutions in 18 countries. Further details of our European activities can be found in the section of this report on European Engagement.

An interesting intramural development which is so new that it has yet to unfold its potential is the Collaboration Network for Biomedical Scientists (CoLab Biomed), a social network site, a collaboration tool and an e-learning and knowledge management application designed to meet the needs of biomedical scientists at the University of Duisburg-Essen. It is a joint project of the Centre for Medical Biotechnology (ZMB) and BIOME, offering users both an on-line profile and a password-protected area for the swift and safe transfer of data. CoLab Biomed went live in December 2013.

The BIOME Concept – A Brief Revision

The main aims of our graduate school are to incorporate the vast majority of PhD or MD graduates conducting research in the biomedical field into integrated lecture programmes with thesis-related themes given by experienced researchers followed directly by seminars where graduates are able to present their own latest findings; to offer them close and extended interaction with visiting keynote speakers through regular meet-the-expert forums and annual retreats; and to expose them to opportunities for career-oriented networking. To this end, we have created a strong interdisciplinary research and training graduate school, a joint cooperation between the Faculty of Medicine (University Hospital Essen) and the Faculty of Biology (University of Duisburg-Essen, Campus Essen).



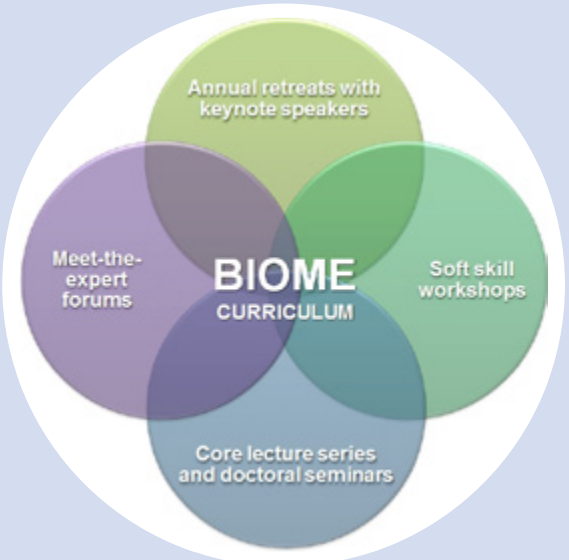
Although we are delighted at all the accomplishments generated within and external to our graduate school during the last four years, we nevertheless have not become complacent. The highly-motivated BIOME team is still brimming with exciting new impetus, the fruits of which we are looking forward to covering in our next report in two years' time.

Ulf Dittmer
BIOME Chair

Delia Cosgrove
General Coordinator

Sven Brandau
BIOME Chair

Regular workshops for the targeted training of career-related soft skills are an extended part of the BIOME programme. Topics include scientific writing, presentations, good scientific practice, acquisition of funding etc. To date, these seminars have been provided by sister organisations within the university such as Werkstatt Wissenschaftskarriere (a broad-based doctoral forum), the West German Tumour Centre (WTZ) and MediMent (a mentoring programme).

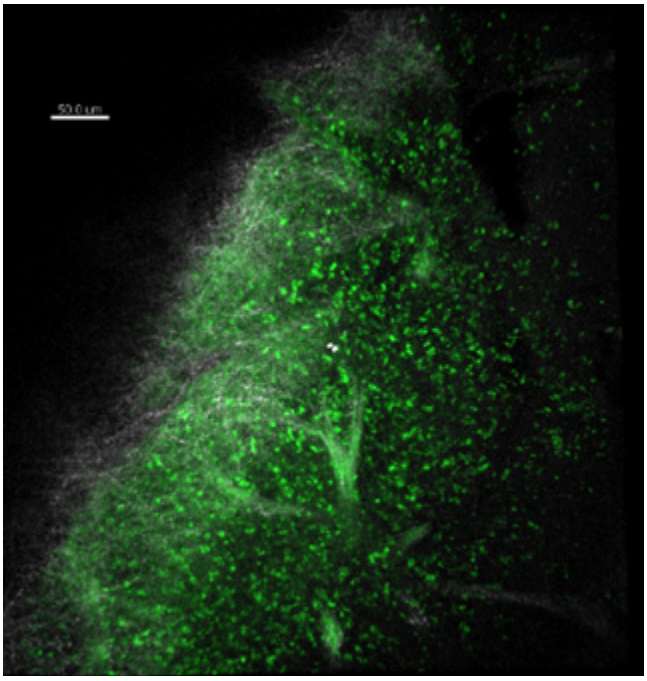


BIOME Research Themes

Cellular and Molecular Immunology

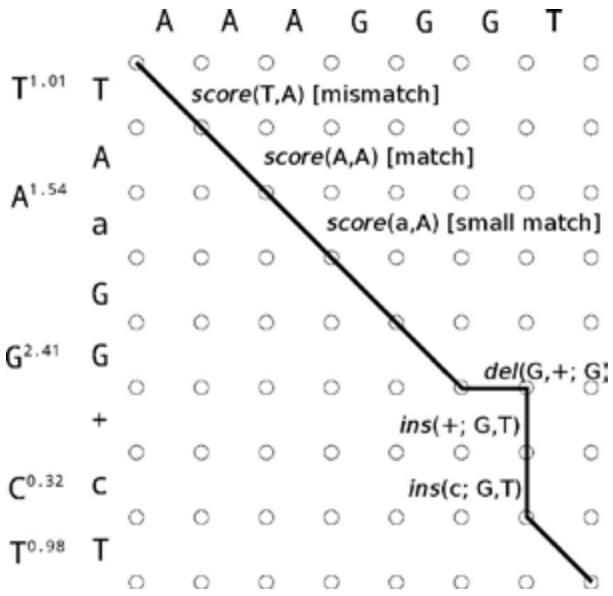
The core Cellular and Molecular Immunology has proven itself to be one of the most popular biomedical research themes at our university with an average of close to 30 graduate members at any given time. Some graduates work in clinical departments while others perform their studies at institutes of the Faculty of Medicine. We are very happy to see that, consequently, the research topics of those graduates cover a wide range of projects combining clinical, translational and experimental immunology in this core. Examples of such graduate projects include the analysis of immune cells in kidney transplantation and multiple sclerosis (clinical), projects on cancer immunotherapy (translational), or the development of an artificial human haematopoietic stem cell niche *in vitro* (experimental). While many projects analyse various aspects of T cell biology, we also host projects on myeloid cells, NK cells, B cells and haematopoietic stem cells.

The lectures are held on a fortnightly basis and, within the three-year curriculum, are hosted jointly with the core Tumour and Signalling for two years followed by a specialisation year of autonomous topics, with each core holding separate graduate seminars after each talk.



Computational Biomedicine

The BIOME core Computational Biomedicine aims at helping PhD students to obtain a comprehensive overview of computational techniques in biomedicine, and to expose their own work to the suggestions and critical questions of their peers and experienced scientists.



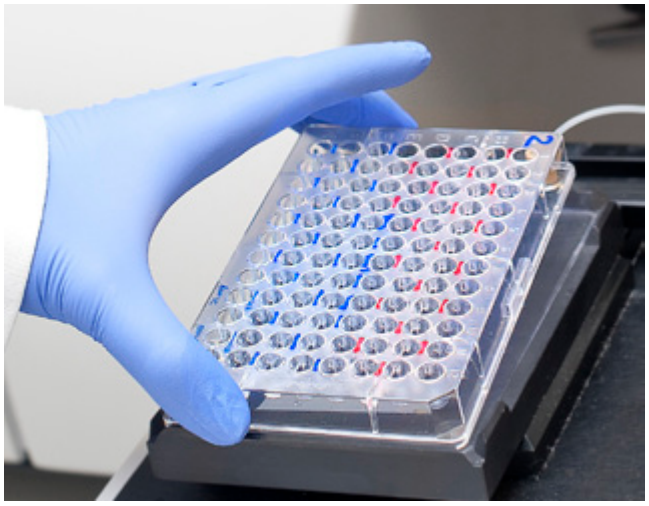
The core was founded in 2012 by four bioinformatics groups from University of Duisburg-Essen, University Hospital Essen, Ruhr University Bochum and the Technical University Dortmund. All are members of the larger regional academic network known as the University Alliance Metropolis Ruhr (UAMR). In 2013, the first full year of the core, a seminar programme was established with talks by PhD students from these bioinformatics groups, but also with national and international speakers, and included presentations by the core leaders. This scientific programme is flanked by soft skills courses offered to the students, e.g. a course on Scientific Writing. The programme has so far attracted 12 PhD students who participate regularly in the seminar talks at the University Campus Essen. For internal communication, an e-mail distribution list and a moodle course have been set up that are both used frequently.

Genetics and Cell Biology

The BIOME core Genetics and Cell Biology, established in 2010 by two scientific coordinators from the University Campus Essen and two coordinators from the University Hospital Essen, can look back on two very successful and exciting years of scientific teaching and interaction.

Since the beginning of this BIOME core 38 students have been enrolled, 16 of which are currently members of the programme. 18 students have already completed their three years of membership. Most of them have already successfully defended their PhD theses.

The 16 currently enrolled PhD graduates belong to the Faculties of Biology and Medicine and are working on projects either at the University Campus Essen or at the University Hospital Essen. This core focuses on basic and clinically-oriented research in the fields of molecular and cell biology and genetics. In this context, state-of-the-art technologies and knowledge of the most recent developments in these fields are discussed in monthly seminars with a keynote lecture followed by



an oral student presentation, leaving room for plenty of stimulating discussions about the participants' projects and usage of methods with their peers. Last but not least, this scientific foundation is supplemented by the offer of soft skill seminars adding value to the training of the graduates towards becoming successful and independent scientists.

Ischaemia, Reperfusion and Angiogenesis

Depriving an organ of its blood supply is a critical factor in the clinical outcome of myocardial infarction, stroke, organ transplantation and various kinds of shock. In this context, ischaemia-reperfusion injury (due to insufficient perfusion and/or due to reperfusion of a previously ischaemic tissue) plays a decisive role and is a fundamental topic to two of the declared core themes of the University Hospital Essen, the cardiovascular system and transplantation.

The course introduces young scientists to the mechanisms and consequences of cell and tissue injury during ischaemia-reperfusion of various organs including heart, brain, intestine, liver, kidney and muscle. Furthermore, the fortnightly lectures focus on the regenerating processes following ischaemia-reperfusion injury such as angiogenesis, and the protective/therapeutic measures such as pre- and post-conditioning and pharmacological treatment. In addition to this, the graduates on the course have the opportunity to present and discuss the results of their own experimental work, thus enhancing/strengthening their presentation skills and the development of their own scientific projects. The current research topics within the core cover a wide range of projects combining clinical, translational and experimental studies, e.g. rehabilitation of upper limb ataxia in patients with cerebellar degeneration (clinical), projects on artificial oxygen carrier for intravenous application (translational), or the analysis of Vitamin C as a substrate for the respiratory chain (experimental).

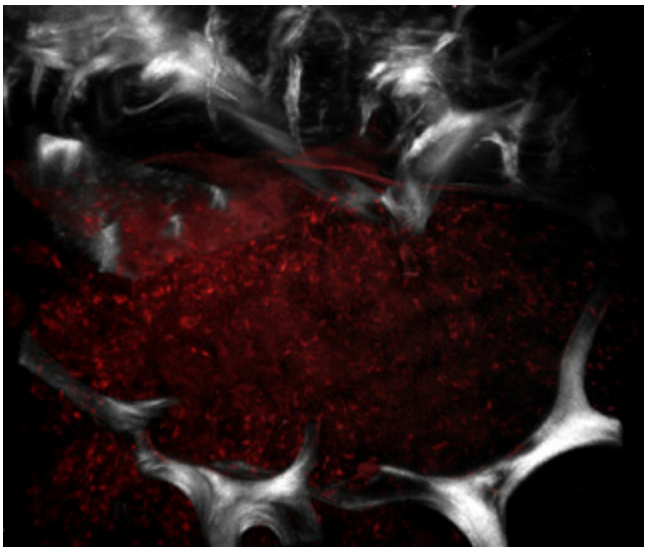
In November 2012 and 2013 the annual retreat was organised as a joint meeting with the Xanten Workshop "Cell and Tissue Damage: Mechanism, Protection and Treatment" where the graduates had the chance to present their latest findings to a critical and experienced audience. It is planned to repeat this excellent three-day workshop in November 2014.

Transplantation Medicine

While the core Transplantation Medicine is specifically aimed at meeting the needs of MD graduates for a structured research programme, PhD graduates are also most welcome to sign up for this core for an 18-month period. Thereafter, these doctorates (i.e. PhD or MD/PhD candidates) may join one of BIOME's other cores for a further 1.5 years in order to meet the full three-year participation requirements.

To improve organ transplantation and to overcome shortages of organ donation and limitations in patient and graft survival after transplantation it is our aim to strengthen the research endeavour "Basic Science in Transplantation Medicine". In a close cooperation between surgeons, physicians and basic scientists, the main research topics are (i) organ protection and organ regeneration, (ii) inflammation and (iii) immunity in transplantation. Our lectures focus on clinical aspects of transplantation and basic knowledge, e.g., on preservation injury, tubular injury induced by immunosuppressive medication, monocyte/macrophage-mediated organ- and recipient inflammation, natural killer cell functions after transplantation, tolerogenic dendritic cells, genetic modification of stem cells, induction of T cell tolerance, modification of T lymphocyte functions due to CNS-immune system interaction, and risk assessment and monitoring in kidney transplantation. Following the lectures of advanced scientists, the MD/PhD students present and discuss their own results.

The core started in 2012 with eight MD and three PhD graduates. In addition, it has since been joined by junior doctors and bachelor/master students interested in transplantation. It is greatly interdisciplinary and has become more and more international. As a rather small core, it benefits very much from lively discussions and exchange. The participants of our core work in the field of anatomy, biochemistry, bone marrow transplantation, gastroenterology, immunology, nephrology, ophthalmology, otorhinolaryngology, paediatrics, psychology and transfusion medicine. Currently, we have members from Germany, China, Brazil and Greece.



Tumour and Signalling

The course introduces young scientists (PhD and/or MD graduates) to the cell and molecular biology of tumourigenesis and medical oncology. The fortnightly lectures of the three-year course focus on signalling in tumours, intracellular signalling as well as the communication within the tissue environment. The course does not recapitulate textbook knowledge but gives insight into aberrant signalling and communication pathways during tumourigenesis and metastasis. Special emphasis is placed on new therapeutic concepts interfering with tumour-specific signalling. The course imparts knowledge on modern laboratory tools such as cell imaging, array technologies, proteomics and flow cytometry. Furthermore, the aim is to convey knowledge about up-to-date *in vivo* cancer models utilising transgenic mouse technology. The lectures are accompanied by literature seminars to train members in the critical discussion of recent papers of interest, or seminars where graduates present their own results, thus furthering the extension of their presentation skills and the development of their own scientific projects. In addition, scientific guests are regularly invited to share their expertise with the doctorates within the framework of these lectures and seminars. The molecular and cell biological signature of the most important tumour entities are presented and correlated to clinical aspects. To achieve translational research, members are given the chance to participate in defined clinical grand rounds. This core currently has 26 registered graduates.

RTG 1045: Host Pathogen Interaction

The research training group on the "Modulation of host cell functions to treat viral and bacterial infections" in the Rhine-Ruhr area of Germany was established in 2004 for young scientists, offering them an excellent opportunity to further their fundamental education in the science of immunology and infection. A high competence in the fields of infections, immunomodulation and signal transduction was set up by a number of departments at the Universities of Bochum, Düsseldorf and Duisburg-Essen. New strategies were developed for the intervention of acute or chronic infections in which the focus of therapy was not the pathogen itself but rather the function of host cells or cells of the immune system. The different working groups of the graduate course were located at ten different institutes, providing about 30 participants per funding period – including scholarship holders, associated members and graduates from the Transregional Collaborative Research Centre (TRR 60) – with a sound academic education on the subjects of the graduate course. Lectures were held on a fortnightly basis with graduate presentations after each talk. International guest scientists were invited regularly to give keynote lectures on their field of expertise. The DFG supported this course with close to € 5 million for a nine-year period. The research training group expired in June 2013. In the course of two funding periods, about 70 doctoral students achieved their PhDs, and are now pursuing successful careers in science or research and development.

List of keynote speakers (selection)

- Wolfram Brune (Hamburg)
- Oliver Fackler (Heidelberg)
- Xin-Hua Feng (Houston / USA)
- Kim Hasenkrug (Hamilton / USA)
- Kuan-Teh Jeang † (Bethesda /USA)
- Massimo Levrero (Rome / Italy)
- Judy Lieberman (Boston / USA)
- Michaela Müller-Trutwin (Paris / France)
- Lara Myers (Hamilton / USA)
- Jacob Piehler (Osnabrück)
- Thomas Pietschmann (Hannover)
- Hanspeter Pircher (Freiburg)
- Liisa Selin (Worcester / USA)
- Stefan Stevanović (Tübingen)
- Robert Thimme (Freiburg)
- Zoe Waibler (Langen)

6th Annual Meeting RTG 1045 in Wermelskirchen / Bergisches Land
6 – 8 September 2010

7th Annual Meeting RTG 1045 in Balve / Sauerland
19 – 21 September 2011

8th Annual Meeting RTG 1045 in Sundern / Sauerland
9 – 11 September 2013

Research Training Group 1431: Gene Transcription

The goal of the DFG-funded graduate research training programme RTG 1431 "Transcription, chromatin structure and DNA repair in development and differentiation" is to understand aspects of chromatin-based regulation in diverse cellular processes that govern expression of the genetic information during development and differentiation, faithful inheritance of the genome during cell division and maintenance of genomic stability during proliferation through sophisticated checkpoint and DNA repair mechanisms.

Over 30 graduates have been trained since the RTG 1431 was established in 2006. Currently, 14 scholarship holders from both the medical and biology faculties profit from the diverse training opportunities and education that include regular seminars of the graduates and lectures by senior researchers to convey a broad spectrum of scientific knowledge and technical approaches. This is complemented by courses to promote presentation and software skills.

The active research within RTG 1431 of the past two years is reflected in a series of publications of our graduates on DNA damage checkpoint robustness, T-cell signalling and melanoma growth, genetic alterations underlying Hodgekin lymphoma, chromatin methylation in chromosome segregation, subcellular compartmentalisation of oxygen sensing, tau aggregate clearance and transcription in archeae just to name a few.

Research Training Group 1739: Radiation Sciences

The research programme of the research training group RTG 1739 aims to achieve a better mechanistic understanding of key molecules that determine the cellular response to ionising radiation and thus radiation sensitivity with the goal of providing a scientific basis for novel approaches of effective response modulation. A major aim is to generate a profound understanding of the complex cellular and molecular processes that determine the cellular responses to ionising radiation and the interaction of ionising radiation with drug therapy. Eleven excellent scientific projects covering cutting-edge topics in radiation biology and experimental radiation oncology form the basis of a multidisciplinary education in the field. Project-oriented laboratory training is complemented with training in general and specific methods of radiation biology and related fields and lectures in radiation oncology and radiology. Furthermore, method days are offered focusing on different aspects or techniques, e.g. a one day excursion to the 7-Teslar MRT at the Erwin L. Hahn Institute. Since the start of the RTG 1739 in April 2012, international contacts have been built up by the growing number of graduates during stays abroad to learn new techniques, or by the successful recruiting of RISE students. Furthermore, over the last two years a number of internationally high-ranking scientists have held talks in the syllabus of the RTG 1739 and given insights into new findings in radiation research as well as their personal experiences/careers.

Annually, retreats take place where graduates and invited guest speakers present their work and have time to build up scientific and social contacts to researchers from all over the world. Furthermore, in 2012, the RTG 1739 had the great opportunity of nominating UDE's guest professorship – the "Scientist in Residence". Alan Ashworth, a world leader in breast cancer research and personalised cancer medicine, was nominated and honoured in a one day symposium at Zeche Zollverein and a public lecture.

A total of 10 clinical and scientific working groups from the Faculties of Medicine and Biology are involved in the programme of the RTG 1739 providing a comprehensive multi-disciplinary training in basic, translational, and clinical research aspects in radiation sciences. To date, 3 MD students have already finished their syllabus in the RTG 1739. However, the number of participants is still growing: 15 PhD students and 4 MD students are part of the research training group at the moment. The central goal of the RTG - to educate the graduates to become independent scientists that are optimally prepared for a future scientific career in the areas of radiation biology/radiation oncology and biomedical sciences - is funded by the DFG for the initial 4.5 year period with € 3.8 million.

Research Training Group 1949: Innate and Adaptive Immunity

Infectious diseases are worldwide among the ten leading causes of mortality. Despite intensive research efforts effective therapies or prophylactic vaccines are available only for a limited number of pathogens. A detailed understanding of the pathomechanisms of infectious diseases is most important for the development of future therapeutic interventions. Traditionally, the host response to pathogens is divided into the innate and the adaptive immune response.

To date, research with a specific focus on the interaction between innate and adaptive immunity is still underrepresented. The scientific goal of the research training group (RTG) on "Immune Response in Infectious Diseases – Regulation between Innate and Adaptive Immunity" is to fill this gap by bringing together highly qualified researchers working on different aspects of the immune response in various infectious diseases or in vaccine development against pathogens. The mutual scientific question is: How is the adaptive immune response against pathogens modulated by the innate immune response, and how does the adaptive immune response influence innate immunity? The educational goal of the RTG is the training of excellent young researchers in infection and immunity. To support this effort, the RTG provides and coordinates a structured one-year programme for MD students, and a regular three-year PhD or MD/PhD programme for young scientists from both the natural sciences and medicine. Located in the Rhine-Ruhr area, this RTG links the knowledge of distinguished scientists at the Universities of Bochum, Duisburg-Essen and Düsseldorf. This training will ensure long-term progress in this important research field in the Rhine-Ruhr area and provide the PhD students with fundamental education in the science of infection and immunity. The course starts in April 2014.

BIOME Symposia 2012-2013

Cellular & Molecular Immunology together with Tumour & Signalling

The first BIOME awards for the best doctoral poster and talk were presented during the joint annual retreat of two cores of the graduate school at Akademie Klausenhof, Hamminkeln, 12-13 November 2012. Judith Hönes received the prize for the best poster presentation while Stefanie Rost received the best lecture prize. Invited speakers included Sebastian Wesselborg (Heinrich Heine University Düsseldorf), Matthias Gunzer (University of Duisburg-Essen), Christoph Plass (German Cancer Research Center, Heidelberg) and Gerty Schreibelt (Radboud University Nijmegen). An extramural highlight of this event was the guided tour of the Derik Baegert Society's current scholarship holders' exhibition of contemporary German/Dutch art and the studios of artists in residence at Ringenberg Castle, Hamminkeln. The two-day retreat was kindly sponsored by the Kulturstiftung Essen.

The following year, the same cores held a local retreat in Essen's city centre on 15 November 2013. The meeting was organised by the doctorates for the doctorates, a concept that was enthusiastically embraced by the organising team consisting of Jolanthe Baingo, Tina Danielzik and Christina Heeke, with Stefanie Haller offering technical support on locus. At the close of the retreat, the new BIOME scientific coordinator, Laura Steenpass, held an introductory lecture on her research, drawing attention to it being the international centennial Angelman, Prader-Willi and Chromosome 15q Duplication syndrome day (15q11-q13 Day).

Genetics and Cell Biology

After the prosperous first annual retreat in May 2011 with the RTG 1431, the annual meeting in November 2012 was an academic highlight as well. The venue of the Unperfekthaus in the city of Essen provided an excellent background for this event. The students Philipp Kirchner, Tanja Vieregge and Christian Reiter arranged a well-organised programme of talks, incorporating keynote lectures held by renowned scientists as invited speakers. Together with the student presentations and a stimulating poster session, the talks from Nathan Brady (DKFZ Heidelberg) and Martin Hasselmann (University of Cologne) made the annual retreat of 2012 a full success.

The intention of the students organising the annual retreat in December 2013 was to keep up this high level of scientific discussion and interaction of the years before. Since 18 students had completed the programme in 2012 and only a few new members had enrolled on the programme since then, Julia Westermeier, Jonas Seiler and Antje Zickler, the 2013 retreat organisers, again selected the familiar atmosphere of the Unperfekthaus in Essen as the venue for the retreat for the second time. They managed to engage four well-known scientists, Erez Raz (University of Münster), Simon Alberti (MPI Dresden), Andrea Musacchio (MPI Dortmund) and Jürgen Scheller (University of Düsseldorf), to present their scientific work within this rather small circle of students and principal investigators. Presentations and posters about the students' projects made this scientific meeting perfect.

In July 2014 the annual retreat will be organised together with the RTG 1431. Again, we expect a stimulating meeting discussing the most recent developments in the students' projects within the fields of cell migration, cell division, regulation, transcription and epigenetics as well as ageing, cancer and stem cells.

18th and 19th Xanten Workshops on "Cell and Tissue Damage: Mechanisms, Protection and Treatment"

Since 2011 the annual workshop in Xanten is organised as a joint meeting with the BIOME core "Ischaemia, Reperfusion and Angiogenesis". It always starts on the Thursday before the first day of Advent, therefore in 2012 it took place from 29 November to 01 December and in 2013 from 28–30 November at Hotel van Bebber, Xanten.

As at the previous annual meeting in 2011, presentations were given by the graduates and invited guest speakers. The latter reported on, e.g. "Preconditioning of brain slices with a *Gynostemma pentaphyllum* extract to decrease hypoxia induced damages" (Lorenz Schild, Magdeburg), "Response prediction in the multimodal therapy of locally advanced oesophageal cancer" (Daniel Vallböhmer, Düsseldorf), "Citrulline infusion rescues intestinal microcirculation and NO production during chronic endotoxemia" (Ernst van Faassen, Leiden), and "Arginine metabolism in the reperfused heart: functional relevance" (Klaus-Dieter Schüter, Gießen). Besides some selected plenary talks (20 minutes), the main part of this workshop consists of short lectures (7 minutes) followed by extensive discussion of the lecture contents.

The sessions of this workshop are highly interdisciplinary, including varying topics such as inflammation, regeneration, animal stress physiology, as well as applied clinical aspects (e.g., ischaemia/reperfusion injury, trauma/haemorrhagic shock, artificial oxygen carrier, and tissue protection).

The workshop enabled lively discussion not only through lectures and talks, but also during the communal evenings as well as on the guided tour through the archaeological park in Xanten which was visited as a cultural programme. The event was a great success and a rewarding experience for all participants. For this reason, both young scientists as well as experienced researchers are invited to participate actively, not least in order to provide an intensive, mutual scientific exchange and to offer medical and graduate students to present their latest findings to a critical and experienced audience.

The date for the 20th Workshop in Xanten has already been fixed for 27–29 November 2014.

Transplantation Medicine

In 2012, the retreat took place in Xanten, together with the core "Ischaemia, Reperfusion and Angiogenesis". It consisted of lectures and poster presentations. The combined retreat of two cores had the advantage that the graduates could learn to think outside the box. In the following year, we organised a retreat together with the ELAN students and also invited senior clinical researchers who reported on their experience in combining clinical and research activity. We describe the combined ELAN/BIOME retreat in greater detail in the ELAN part of this report.

Computational Biomedicine

A mini-symposium on Microscopy and Image Analysis was held by the core for Computational Biomedicine at the Ruhr University Bochum on 7 December 2012. Speakers included Axel Mosig, Klaus Gerwert (both Ruhr University Bochum), Tim Nattkemper (University of Bielefeld) and Matthias Gunzer (University of Duisburg-Essen). During the mid-afternoon coffee break there was a poster session. The meeting closed convivially with a group visit to Bochum's Christmas market.

ELAN/Transplantation Medicine Retreat 2013

ELAN and the core for Transplantation Medicine held a day-long joint meeting at Robert-Koch-Haus on Essen's medical campus on 9 November 2013. While most of the day's presentations came from the students of both groups, an interesting expert discussion round on how clinical care and experimental research can best complement each other was held at the middle of the day's proceedings.

Research Training Group 1431: Gene Transcription

Our annual meetings provide the opportunity for additional scientific exchange. In 2012, the conference "Chromatin and Epigenetics" was organised in Essen in cooperation with the German Genetics Society (GfG) with high-ranking international speakers from Germany, UK, Sweden, the Netherland, Denmark and France. As a highlight, one of our members, Bernhard Horsthemke, was honoured with the Max-Delbrück-Lecture by the GfG. The meeting was thus a great success and served as a showcase for chromatin research at the University Duisburg-Essen that has firmly established Essen's place in "the epigenetic landscape". In 2013, the graduates organised a cosier retreat at Beverland Hotel in Münsterland. It was, however, no less interesting with eight external speakers and student presentations offering two days of extensive discussion and scientific exchange among the graduates and guests.

In the coming two years, we will continue with additional training units including career development seminars. In July 2014, we will convene with the BIOME core "Genetics and Cell Biology" for a shared annual retreat to foster exchange between the two groups in the remotely situated Wolfsburg in Mülheim-an-der-Ruhr. In addition, we are already looking forward to another international meeting in Essen with the topic "Chromatin Regulation in Cell Fate" in 2015 that is being organised by the RTG 1431 and will conclude the programme.

Research Training Group 1739: Radiation Sciences

In May 2012 the RTG 1739 was launched and the first retreat took place at Hotel Schloss Schnellenberg in Attendorn. As this was its kick-off meeting with all participants of the RTG 1739, time was taken to introduce the 11 new graduates as well as project leaders and to introduce the participating groups and research projects. During the two day meeting, the principal investigators presented the work plans for the PhD projects in scientific talks whereas the PhD students focused on new methods. The event was complemented by two external speakers: Nils Cordes from Dresden presented the importance of the 3D context for the development of novel concepts in radiation biology and Wilfried Budach (Düsseldorf) gave insights into current research trends in radiation oncology. The outstanding weather and the lovely surroundings were enjoyed during a hiking tour and the meals, whereas the evenings were used for socialising and skittle competitions. The RTG 1739 used the wonderful days for scientific exchange and gathering for a group.

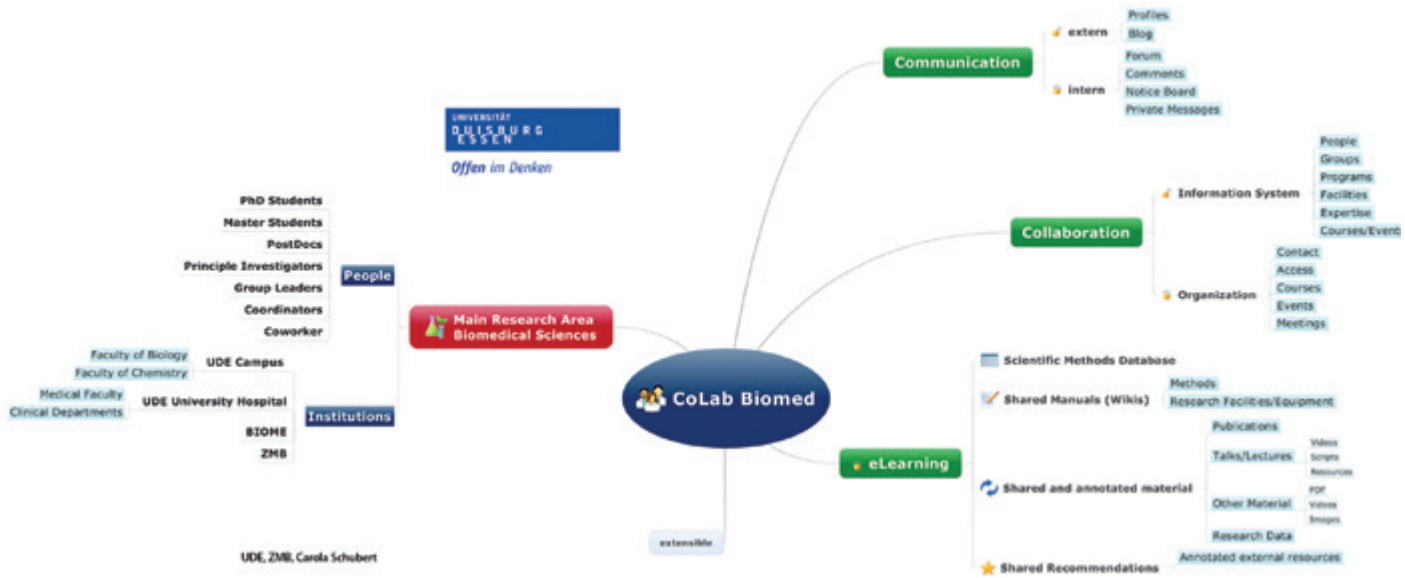
After one year of work the second annual get together was organised in July 2013. On the occasion of a two-and-a-half day meeting at Schloss Raesfeld, the graduates presented the progress of their research projects. The invited speakers from Oxford were impressed by the research results obtained during the first year and the levels of presentation of the progress reports. With their years of experience Peter Wardman (Oxford, UK), Ruth Muschel (Oxford, UK) and Gillies McKenna (Oxford, UK) used their talks to highlight their views on the past, present and future in radiation oncology and biology. Social time was used to enjoy the weather during a guided walk through the neighbouring "Renaissance Tiergarten" and to forge contacts with the invited guest speakers. All participants took the opportunity to strengthen scientific exchange and enjoyed scholarly debates in a beautiful environment.

Collaboration Network for Biomedical Scientists

At the University of Duisburg-Essen (UDE) more than 80 groups perform research in the university's main research area of biomedical sciences. The groups and scientists are affiliated to different faculties (Biology, Medicine and Chemistry), scientific centres, several BMBF or DFG research projects, and DFG research training groups as well as to the university's biomedical graduate school BIOME, and thus are distributed at several locations on the main campus and at the university hospital.

The Collaboration Network for Biomedical Scientists (CoLab Biomed), available as a beta version since December 2013, provides a virtual research environment (VRE) or virtual collaboratory designed to help biomedical scientists at the UDE to collaborate. It is technically based on the open source content management system and code framework Drupal whose modular expandability allows the building of a unique system tailored to specific requirements and whose main focus lays on Web 2.0 and social network technology. The integrated tools and services of CoLab Biomed focus on the support of mainly young scientists (Master and PhD students) providing them with easy access to both an established, widely-specialised research community and to the available research infrastructure. Members can decide voluntarily to either become a visible part of the research community themselves and communicate about their research interests and work in the open via an on-line profile or research blog or to participate only internally. As an important part of the Colab Biomed intranet, researchers can share records of scientific methods thereby accumulating a common knowledge base over time. Moreover, the platform enables them to also share and provide further valuable resources starting with relevant information in time through to various materials that are either recommended by an expert colleague or are reusable (e.g. plasmids) and therefore contributes towards saving time and money. Besides the additionally integrated efficient web-based administration tools (e.g. on-line booking, course and event management), CoLab Biomed serves as a PhD e-learning platform based on established Web 2.0 functionalities that enable a lively collaborating learning community.

Although CoLab Biomed, a joint project of the Centre for Medical Biotechnology (ZMB) and BIOME, is still in its launching phase, its website already provides a comprehensive overview of and insight into the interconnected, multi-faceted, modern and highly-specialised biomedical research being performed at the University of Duisburg-Essen.



European Engagement

The following two past press releases in this section reveal BIOME's and its partners' ongoing drive to unite their research efforts within Europe. The latest achievement of this network has been the recent submission of a final-phase European grant application which has very much sprung its initial IRUN framework, generating immense interest and excitement amongst the scientific community and now enjoying the solid backing of around 40 researchers at nearly 30 institutions in 18 countries.

Should the proposal be successful in the last instance, it will start with a kick-off meeting with members from Austria, Belgium, Croatia, France, Germany, Greece, Hungary, Ireland, Israel, Italy, Netherlands, Poland, Portugal, Romania, Spain, Sweden, Switzerland and the United Kingdom. The network also has collaborative partners in USA. We are all hoping for the best.

Bios for IRUN:
European Collaboration on Immune Integrity – University of Münster

From 27-28 April 2012 European biomedical researchers held an IRUN strategy meeting in Münster, Germany. The two-day event, hosted by Stephan Ludwig, Vice Rector of the University of Münster and an internationally recognised influenza virologist, also included fellow founding partners of this research initiative from the Radboud Institute for Molecular Life Sciences (RIMLS), Radboud University Nijmegen and the Graduate School of Biomedical Science (BIOME), University of Duisburg-Essen. Not only was international consensus reached on the clear structure, themes and goals of the forthcoming scientific symposium on immune integrity which is to be held in Nijmegen in June 2013, but also the groundwork for a joint research proposal at the European Union level was decisively laid.

After initially exploring each university's innovative research landscape and doctoral training programmes, participants at this meeting were better able to understand their partners' aims and the challenges currently facing them. This led to deeper insight into finding ways of how best to proceed with the establishment of a mutual collaboration. "We want to breathe life into the IRUN network with common approaches to research in specialised, well-defined areas," said Stephan Ludwig, who was very pleased with the outcome of the talks.

The initiative stems from the successful IRUN Symposium on Immune Recognition of Pathogens and Tumours hosted by BIOME together with RIMLS in the Duisburg-Essen area in October last year. "We discovered that most IRUN partners have similar large research centres with fascinating thematic overlap and

Photo: WWU Press

parallel graduate structures," explained Delia Cosgrove, BIOME's general coordinator, "and we envisaged realising a closer exchange between them on both the principal investigator and doctorate levels." "It made sense to draw on IRUN as an advantageous basis for building a life science network," added Sven Brandau, co-chairman, BIOME.

Collaborating scientists at Nijmegen are in agreement. "Together we have paved out a path towards strengthening cross-border Dutch-German collaborations in infection, immunity and immune regulation. RIMLS is delighted to be able to host the next symposium on immune integrity in May 2013, a valuable step in furthering our European ambitions," stated Adrian Cohen, RIMLS's scientific manager.

To date, significant interest in this venture has also been expressed by colleagues at the University of Glasgow, Jagiellonian University in Krakow and the University of Barcelona. It is hoped, in time, to include further affiliated IRUN and European centres as well.

Release from April 2012, Delia Cosgrove.

Courtesy of RIMLS

European Workshop on Immune Integrity (IRUN)
Radboud University Nijmegen

As part of the IRUN biomedical strategy to promote our network's universities, graduate schools and medical centres in Europe, RIMLS organised an international workshop on Immune Integrity, a survival kit for PhD students. This interactive and hands-on workshop involved over 35 PhD students and more than 15 group leaders from 6 different countries.

The Immune Integrity workshop was held on Monday 27th and Tuesday 28th May 2013 and is the third in a series highlighting the growing nature of the network. Feedback was overwhelmingly positive: everyone really loved the interactive and hands-on concept of the workshop. The students wanted to know why they hadn't heard of this meeting before! The group photo clearly summarises the atmosphere.

The students and their principal investigators came from various universities within the International Research Universities Network (IRUN): the University of Münster (Germany), University of Duisburg-Essen (Germany), University of Barcelona (Spain), University of Glasgow (Scotland), Jagiellonian University Kraków (Poland) and of course Radboud University Nijmegen (The Netherlands). Christian Münz (University of Zürich, Switzerland) was a specially invited speaker for the workshop.

René Bindels, scientific director of the RIMLS opened the programme on Monday. The principal investigators introduced themselves and in small subgroups participated in roundtable discussions. In parallel, the PhD's participated in a speed-date session to see if there was a scientific match. In the afternoon, there was also a poster-slam where the PhDs could present their posters in small groups. At the end of the first day there was time for bowling and dinner. Day two gave the PhD students opportunity to get hands-on experience from a choice of workshops: multiphoton microscopy, flow cytometry and genomics. In parallel there was brainstorm session with the group leaders to discuss future collaborative projects and joint grant applications. During these two days, four invited speakers from the Universities of Barcelona, Glasgow, Kraków and Zurich gave inspiring lectures on their recent scientific research.

At the end of the meeting four poster prizes were awarded to: Ellen van den Bogaard, Lotte de Winde, Lorena Valverde Estrella, Maria Göbel.

The next meeting is being planned at another European location in 2014.

Release from May 2013, Adrian Cohen.

Selected BIOME Graduate Reports

Impact of 5-Aza-2`-deoxycytidine and epigallocatechin-3-gallate for induction of human regulatory T cells

Roman Tatura

Institute of Medical Microbiology
Group: Jan Kehrmann

Regulatory T (Treg) cells are crucial for establishing a peripheral immune tolerance. Functional defects of Treg cells or their low ratio to all T cells may cause or worsen autoimmune and other inflammatory diseases as inflammatory bowel disease, rheumatoid arthritis, type I diabetes, multiple sclerosis or graft-versus-host disease. By reason of their limited availability, the transfer of *in vitro* generated Treg cells from CD4+CD25- T cells could be an additional therapeutic option for these diseases. So far, no effective and reliable *in vitro* induction of human Treg cells exists.

Naïve T cells differentiate into specific T cell lineages including Th1, Th2, Th17 and Treg cells. Cells of each lineage are characterised by the expression of master transcription factors and leading cytokines, which are TBX21 and IFNγ for Th1, GATA3 and IL-4 for Th2, RORγT and IL-17 for Th17 and FOXP3 and IL-10 and TGFβ for Treg cells.

During differentiation, epigenetic changes have been shown to be important for the commitment of T cells to a lineage. Treg cells are unmethylated within the Treg specific demethylated region (TSDR) of FOXP3, which ensures stable FOXP3 expression, suppressive function and commitment to the Treg cell lineage.

The aim of this study was to analyse the potency of the two DNA methyltransferase (DNMT) inhibitors 5-Aza-2`-deoxycytidine (5-Aza-dC) and epigallocatechin-3-gallate (EGCG) for *in vitro* induction of functional Treg cells through generation of a specific methylation pattern within FOXP3-TSDR. We analysed FOXP3-TSDR methylation, Treg cell specific gene expression and the functional characteristics of induced cells. Furthermore, we studied the extent of expression of the master transcription factor genes and leading cytokines of the other T cell lineages in induced cells.

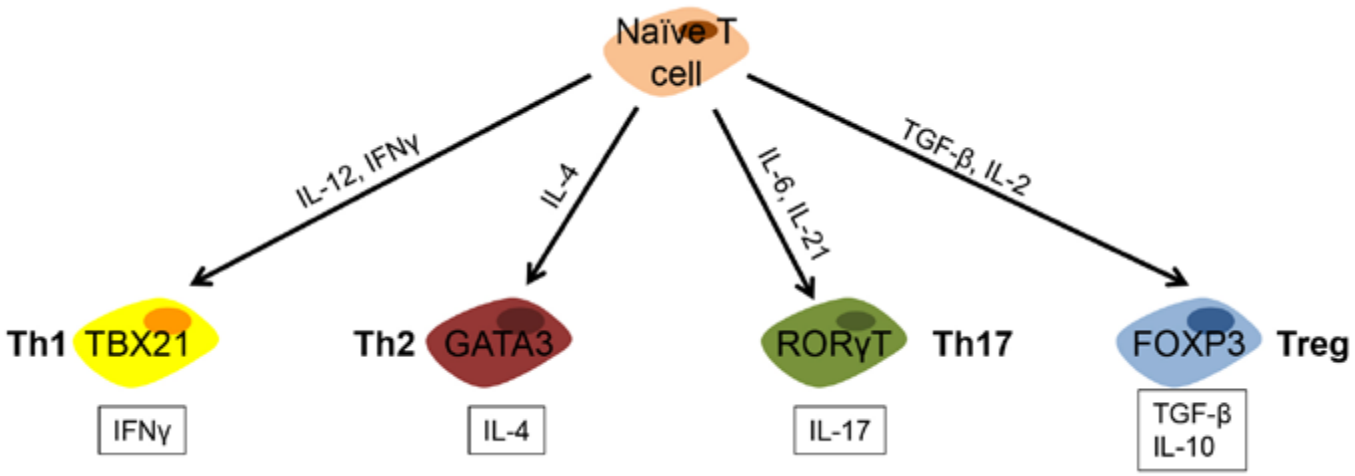


Figure 1: T cell differentiation from naïve T cells to Th1, Th2, Th17 and Treg cells. Expression of their major transcription factors and leading cytokines.

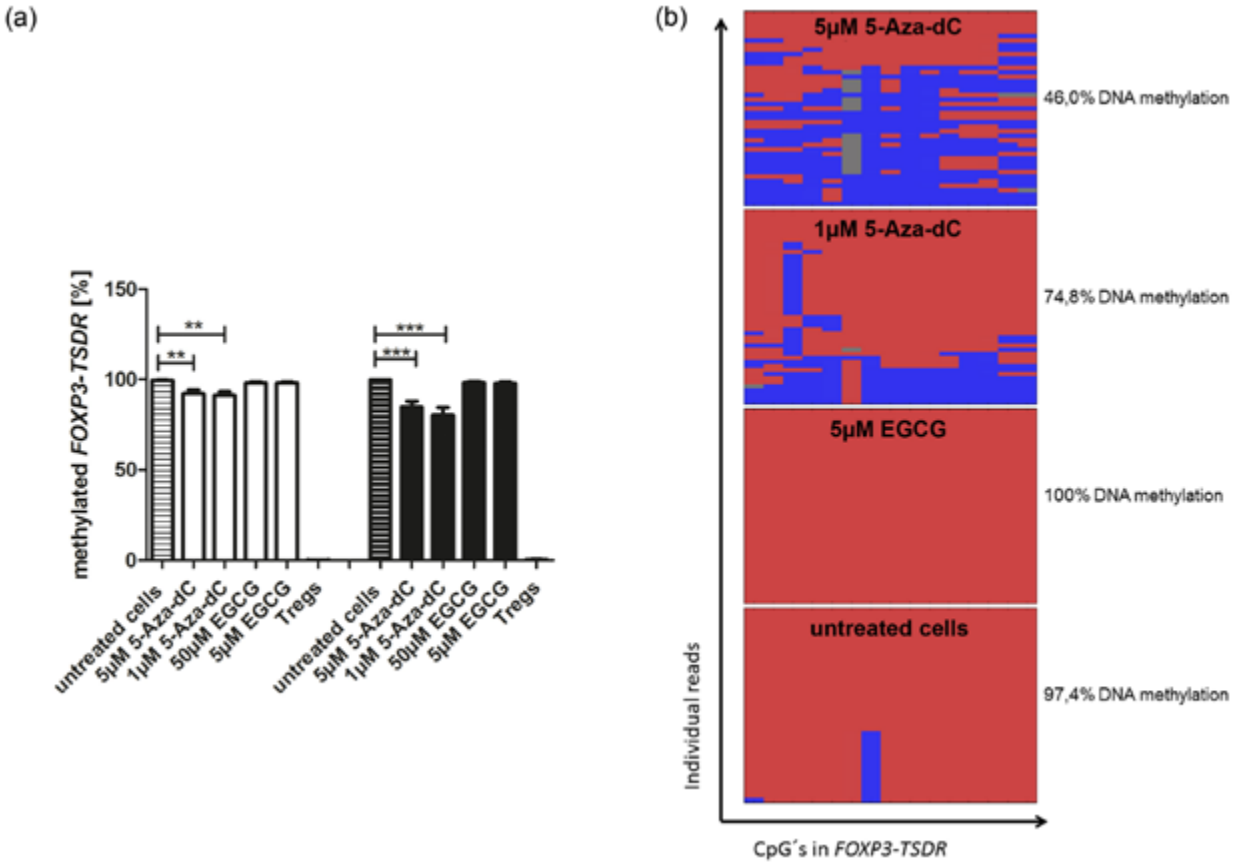


Figure 2: (a) FOXP3-TSDR methylation analysis by methylation sensitive qRT-PCR. Quantification of methylated and unmethylated DNA using specific Taqman probes in QAMA qRT-PCR. Cells stimulated with DNMT inhibitors for 4 days (white bars) and 7 days (black bars). (b) FOXP3-TSDR methylation by Next Generation Sequencing (NGS). Blue color indicates unmethylated CpG, red color indicates methylated CpG. Mean methylation of all CpGs and sequence reads is shown alongside.

5-Aza-dC induced hypomethylation within FOXP3-TSDR and expression of Treg cell specific genes FOXP3, LRRC32 and IL-10. Proliferation of 5-Aza-dC treated cells was reduced, but they did not suppress growth of responder T cells. Master transcription factors and leading cytokines of Th1 and Th17 cells were induced as well. EGCG did not induce hypomethylation within FOXP3-TSDR or expression of Treg cell specific genes. Although 5-Aza-dC treated cells phenotypically mimic Treg cells, they do not suppress proliferation of responder cells and acquire properties of Th1 and Th17 cells, which raises concerns for these induced cells being used for therapy.

Publication

Kehrmann J, Tatura R, Zeschnigk M, Probst-Kepper M, Geffers R, Steinmann J, Buer J. Impact of 5-Aza-2`-deoxycytidine and epigallocatechin-3-gallate for induction of human regulatory T cells. *Immunology*. 2014 Jan, doi: 10.1111/imm.12261

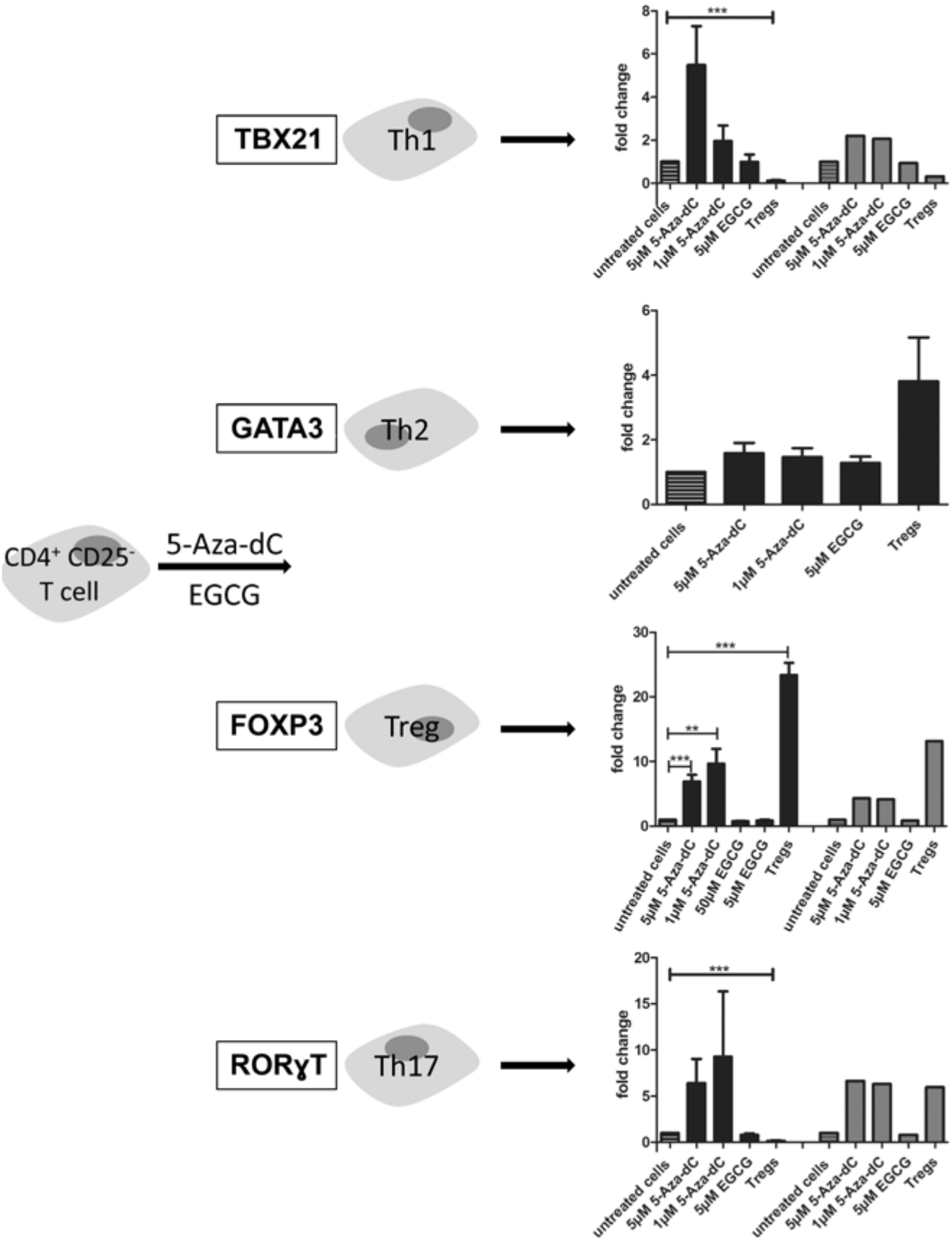


Figure 3: Expression analysis of Treg cell specific genes and FOXP3 protein expression. Expression of Treg cell specific genes and FOXP3 protein expression was analysed after four (white bars) and seven (black bars) days of stimulation with 5-Aza-dC and EGCG.

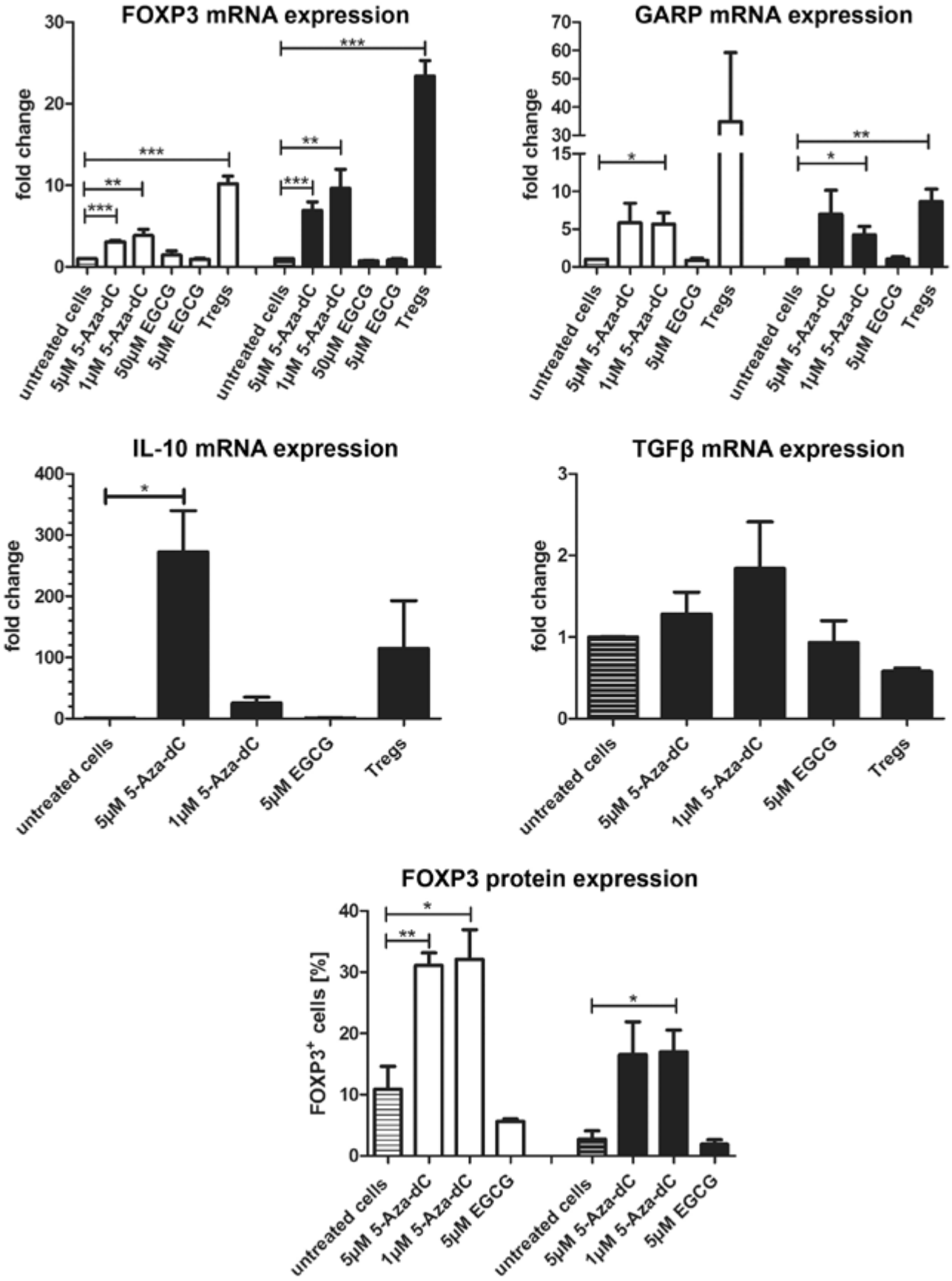


Figure 4: Effect of DNMT inhibitors on T cell lineage-specifying transcription factor expression was quantified by real-time PCR (black bars) and gene-array analysis (grey bars) after stimulation with 5-Aza-dC and EGCG for 7 days. Array data did not include GATA3.

Computational study of Sonic Hedgehog proteins: insights into the role of metal ions

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Group: Daniel Hoffmann

The morphogen function of Hedgehog (Hh) proteins is crucial for normal development in all higher animals. Hh molecules spread from localised sites of production to trigger differential cellular responses dependent on morphogen concentration. The basic physical process shaping the concentration gradient is the diffusion of Hh through the extracellular matrix, e.g. in the form of large oligomers or other agglomerates. The signalling activity of Hh ligands is intimately linked to several post-translational modifications and cleavage events that modify their activity and regulate their spread from producing cells through tissues. The tight control of secretion is a key step in the regulation of signalling activity. Mathematical modeling has pointed to self-enhanced degradation of the morphogen as one possible mechanism to establish the predicted concentration gradients. Molecular feedback loops that lead to self-enhanced removal of Hh, e.g. by receptor–ligand internalisation in the target cells, have indeed been found.

The first crystal structure of murine ShhN revealed the presence of a zinc ion tetrahedrally coordinated bound at the bottom of a solvent-accessible cleft. The arrangement of Zn2+ is very similar to that of zinc hydrolases such as thermolysin and carboxypeptidase A. However, later on, the presence of a double calcium binding site buried at the interface with CDO was shown. The two metal centres are separated by a distance of about 11 Å and connected by a long loop between two antiparallel b-sheets. Although in the beginning, the zinc centre was found to be a potential catalytic site no enzymatic activity has been uncovered so far. Besides, the role of calcium ions is not fully understood.

Despite the advances, there are still large gaps in our comprehension of the Hh signalling and many unsolved questions. For instance: What role do calcium ions play in maintaining the ShhN structure?, Is the zinc ion only implicated in the stability of ShhN despite this metal centre resembles a catalytic site?, Would it be possible that ShhN is a Ca2+ activated LAS peptidase?. These questions could be important for understanding the Hh signalling pathway. Therefore, the goal of this work was to study the effect of metal ions on the structure, dynamics and interactions of the ShhN protein. To accomplish such a task, molecular structures of ShhN proteins were analysed with a set of computational methods, revealing new features of ShhN proteins.

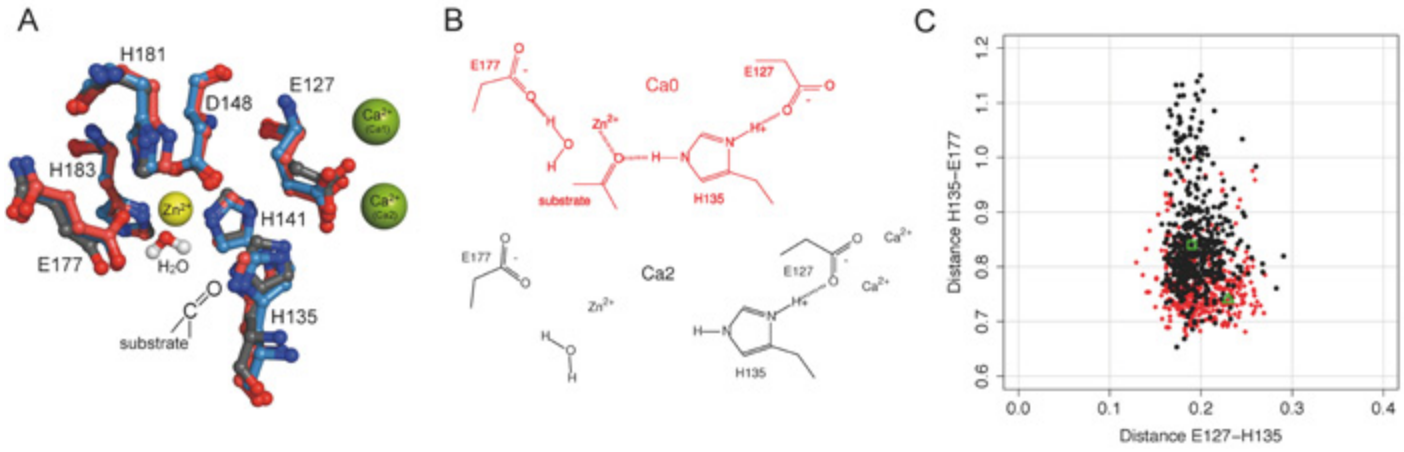

Figure 1: Switch mechanism triggered by Ca2 calcium ion. (A) ShhN zinc centre in states Ca0 (1vhh, red), Ca1 (3n1r, blue), Ca2 (3d1m, grey). Putative catalytic water from 1vhh is close to the zinc ion. From Ca0 to Ca1 and Ca2, E127 carboxylate is drawn towards Ca2+ and drags H-bound H135 side chain with it, away from substrate and the active E177. While Ca0 and Ca1 superimpose well, Ca2 is clearly different. (B) Central components of the switch mechanisms in states Ca0 and Ca2. (C) Distances between H-bonded E127 carboxylate-O and H135 imidazole-proton, and between substrate-clamping side chains of H135 and catalytically active E177. Black (Ca2) and red (Ca0) points are sampled by MD simulations. Green triangle (Ca0) and green square (Ca2) are the corresponding values directly taken from X-ray structures 1vhh and 3d1m, respectively.

In summary, our data suggest that ShhN is an enzyme with a zinc catalytic centre that is regulated by the binding of the calcium ions. The binding of the second calcium ion causes a conformational change that is accompanied by a significant perturbation of the putative catalytic centre, possibly affecting substrate stabilisation (Figure 1). A strong pH dependence of protease activity was confirmed by *in vitro* experiments. Electrostatic potential differences among calcium states suggest the possible binding of nonpolar substrates. Although the peptidase substrate has still to be determined, autodegradation could be an elegant mechanism to tune morphogen gradients. This possibility does not rule out, of course, the existence of other mechanisms that govern ShhN concentration gradient.

While the N-terminal of ShhN proteins (residues G25-K38) enhances ShhN dimerisation, the binding of calcium ions does not favor interactions between ShhN subunits due to an increment of positive charges in this region (Figure 2). Nevertheless, this fact can promote the interaction of ShhN dimers with heparan sulfate chains (a key player for HhN function) providing a large positively charged region which is the ideal scenario for the binding of these molecules. Results built on mutations of buried residues at the ShhN dimeric interface show the importance of hydrophobic residues for the maintenance of a stable complex. In addition, mutations within the calcium binding site can affect the ShhN multimerisation at the molecular level and thus, alter the ShhN signalling.

The identification of ShhN as a putative peptidase makes possible to test different hypotheses about this morphogen which might explain some of the still unsolved questions.

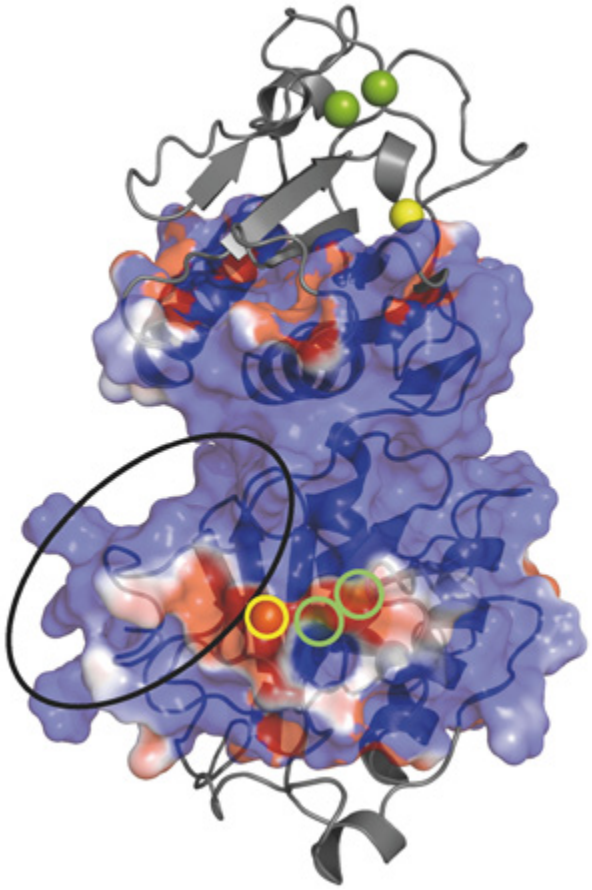

Figure 2: Electrostatics of ShhN-dimer with two calcium ions. The molecular surface of the proteins is colored according to the electrostatic potential; blue is positive and red is negative. The ellipse encloses the region where the N-terminal from one subunit interacts with loops from the adjacent subunit. Calcium (green) and zinc (yellow) ions are depicted as spheres and highlighted in the lower subunit by green and yellow circles respectively. Electrostatic potentials were scaled to the range of -1 (red) and 1 kT/e (blue).

Publication

Rebollido-Rios R, Bandari S, Wilms C and Jakuschev S *et al*. Signaling domain of Sonic Hedgehog as cannibalistic calciumregulated zinc-peptidase. *PLoS Comput Biol*. 2014. (in revision)

The AAA-ATPase VCP/ p97 in endosomal sorting of ubiquitinated CAV1

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Department of Molecular Biology I, ZMB
Group: Hemmo Meyer

The AAA (ATPases associated with diverse cellular activities)-type ATPase p97 (also called VCP) is best known for targeting and segregating ubiquitin-conjugated protein complexes for subsequent degradation by the proteasome. This activity is required for as diverse cellular processes as endoplasmic reticulum-associated degradation or cell cycle signalling (Meyer *et al.*, 2012). In these cellular processes, p97 cooperates with alternative sets of cofactors, including a group of ubiquitin-like (UBX)-domain containing proteins, which provide functional and spatial specificity. p97 missense mutations in humans cause a dominant late-onset sys-

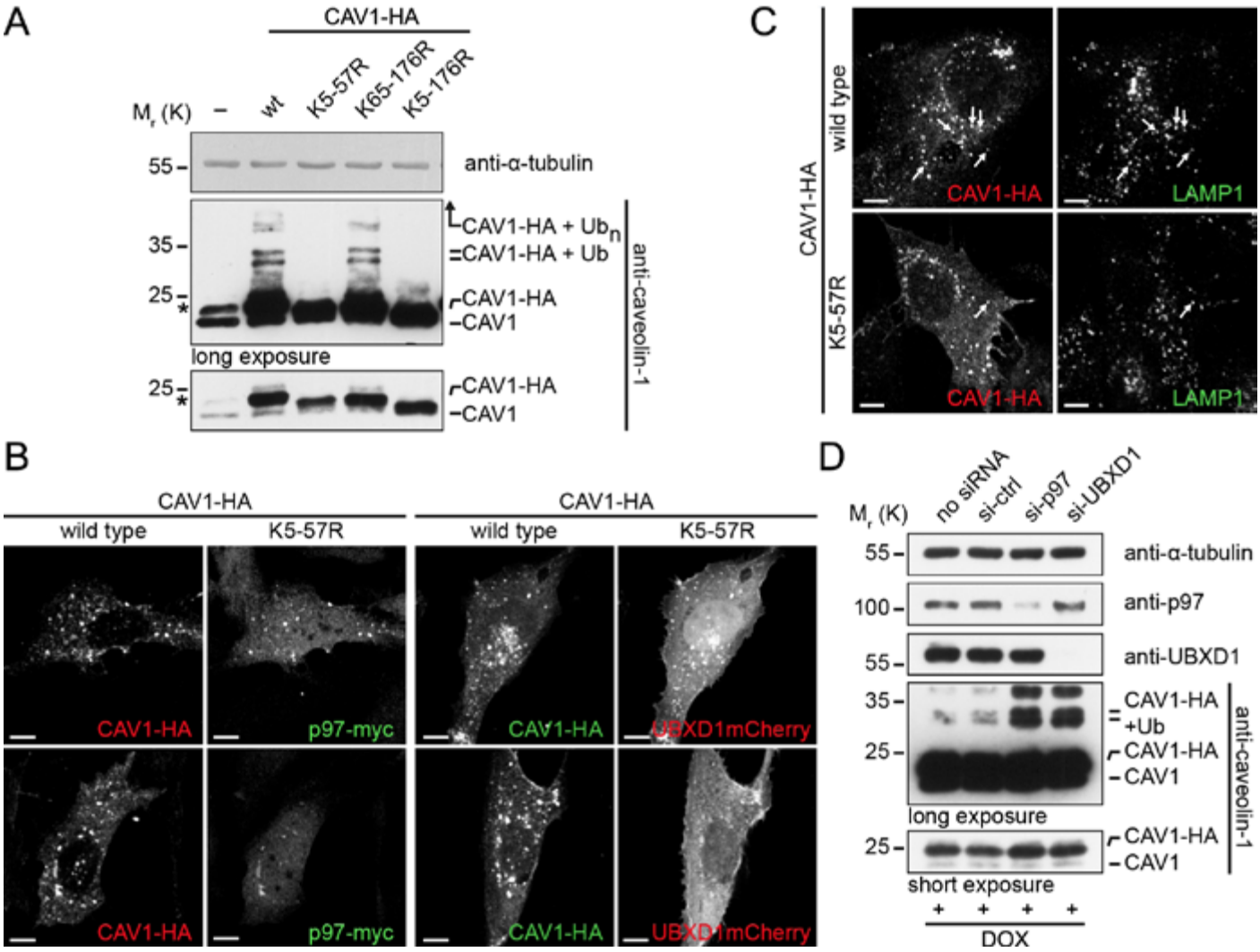

Figure 1: (A) Mutation of the six lysines in the N-terminal region of CAV1 to arginine (K5-57R) abolishes ubiquitination of CAV1. (B) Mutation of the N-terminal ubiquitination site affects recruitment of p97 and UBXD1 to CAV1-loaded endosomes. (C) The N-terminal ubiquitination site is important for transport of CAV1 to late endosomes. (D) siRNA-mediated depletion of p97 or UBXD1 leads to accumulation of ubiquitinated CAV1.

temic degenerative disorder, IBMPFD (inclusion body myopathy associated with Paget's disease of bone and fronto-temporal dementia), as well as Amyotrophic Lateral Sclerosis (ALS). However, the molecular pathogenesis of p97-associated disease is unclear.

We used an unbiased mass spectrometry approach and identified a p97 complex with the UBXD1 cofactor, which binds to the plasma membrane protein caveolin-1 (CAV1) and whose formation is specifically disrupted by disease-associated mutations (Ritz *et al.*, 2011). CAV1 is the main structural component of cholesterol-rich microdomains in the plasma membrane, called caveolae. Caveolae occur in most mammalian cells and are involved in the regulation of cell signalling, lipid homeostasis, and response to mechanical stress (Parton and del Pozo, 2013). We showed that the p97-UBXD1 complex targets ubiquitinated CAV1 complexes, which are en route to degradation in the lysosome. Furthermore, overexpression of mutant variants of p97 caused a block of CAV1 transport at the limiting membrane of enlarged endosomes in cultured cells. Consistently, we showed that p97 mutations are associated with mislocalisation of the muscle-specific caveolin isoform CAV3 in IBMPFD patient muscle that may contribute to IBMPFD pathogenesis.

In this context, we investigated the functional connection between CAV1 ubiquitination and endosomal sorting by the p97-UBXD1 complex (Kirchner *et al.*, 2013). We showed through site-directed mutagenesis that ubiquitination of CAV1 occurs at any of six lysine residues in the flexible N-terminal region of CAV1 but not at lysines in the oligomerisation, intra-membrane, or C-terminal domains (Figure 1 A). Given that ubiquitination occurs outside of the oligomerisation domain, it is unlikely that ubiquitination interferes with or even directly regulates formation of CAV1 oligomers or larger assemblies. However, the ubiquitination site in the N-terminal region controls binding of p97-UBXD1 to CAV1 and recruitment of the p97-UBXD1 complex to endosomes (Figure 1 B). Moreover, mutation of the ubiquitination site specifically interfered with trafficking of CAV1 to late endosomes (Figure 1 C). Conversely and consistently, depletion of p97 or UBXD1 led to accumulation of ubiquitinated CAV1 (Figure 1 D) suggesting that p97 acts downstream of CAV1 ubiquitination and is required for transport of the ubiquitinated form of CAV1 to intralumenal vesicles for degradation in the lysosome.

On late endosomes, p97 could be required to dissociate large protein complexes, for example CAV1 oligomers, prior to sorting into intralumenal vesicles or regulate the endosomal sorting machinery. Along this line, we observed that inhibition of p97 affects sorting and lysosomal degradation of the EGF receptor indicating that p97 has a more general function in endosomal sorting (Ritz *et al.*, 2011).

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Perfluorodecalin-based artificial oxygen carriers

Julia Laudien

Institute of Physiological Chemistry
Group: Herbert de Groot

The opponent steady decrease in blood donation and the current demographic trend will result in a lack of the blood supply of the population in the future (Henkel-Honke and Oleck, 2007). Thus, a focus of medical research lies on the development of artificial blood substitutes, e.g. perfluorocarbon-based artificial oxygen carriers. Perfluorocarbons (PFCs) are perfluorinated hydrocarbons, whereas liquid PFCs, such as perfluorodecalin (PFD), are highly effective in dissolving the respiratory gases oxygen and carbon dioxide. According to Henry's law, dissolubility linearly depends on the partial pressure of the correspondent gas and is irrespective of the presence of toxic gases, e.g. carbon monoxide, hydrogen sulfide or hydrogen cyanide (Riess, 2001; Dinkelmann and Northoff, 2002). Because of the very high carbon-fluorine bond energy, PFCs are chemically and biologically inert, making them interesting candidates for medical applications. PFD is one of the most investigated PFCs in biological systems (Lowe, 2003) and is already used for the ventilation of newborns in the form of liquid breathing (Curtis *et al.* 1991; Fuhrmann, 1991) or for vitreoretinal surgery (Mertens, 2000). A new approach to establish a PFD-based artificial oxygen carrier for intravenous application is to encapsulate the PFD with biocompatible polymers, such as poly(lactide-*co*-glycolide) (PLGA) or poly(*n*-butylcyanoacrylate) (PACA). Preclinical safety and biocompatibility of the prepared capsules was elucidated in

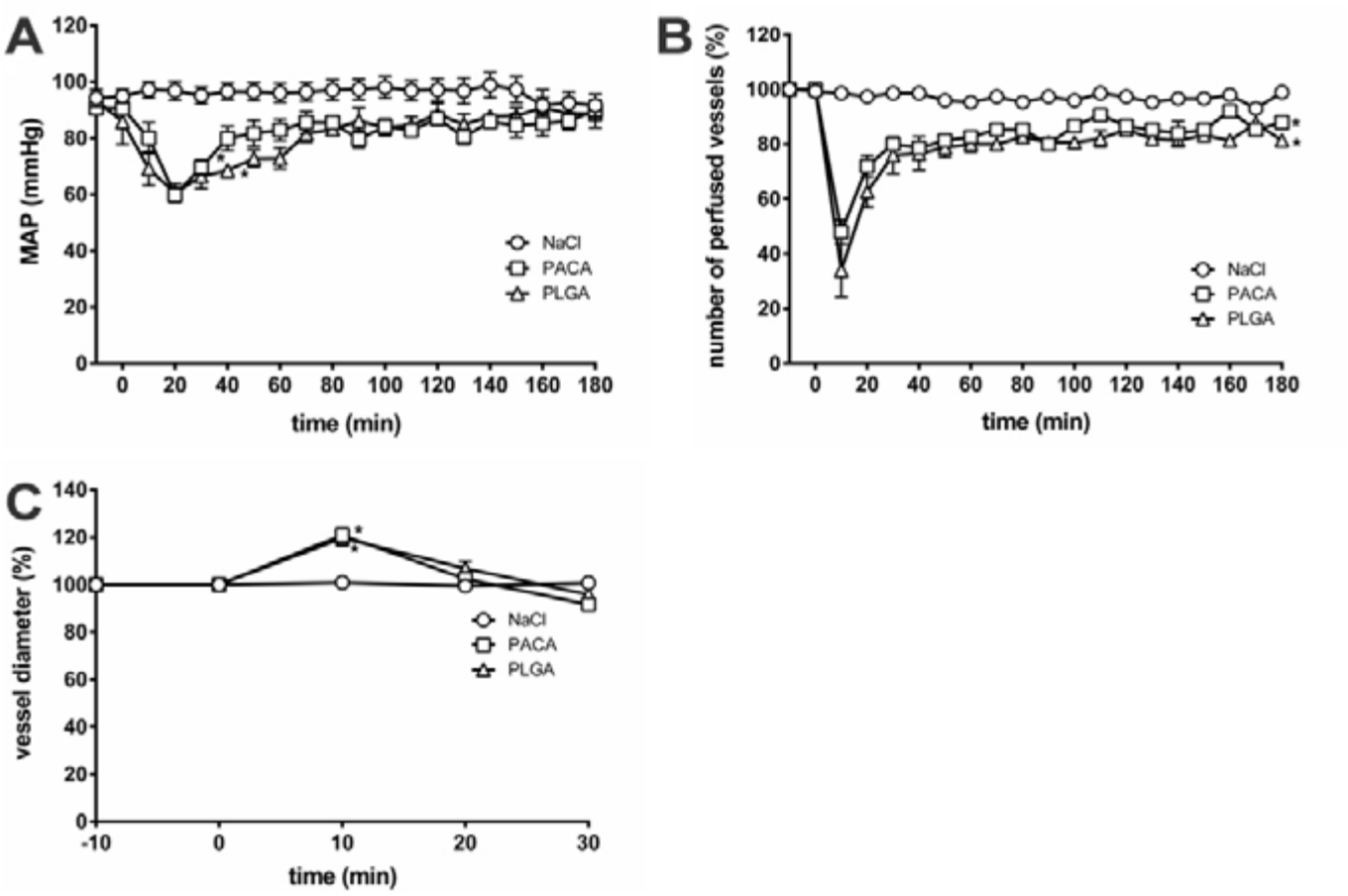


Figure. 1: Transient systemic hypotension and impairments of microcirculation. PACA and PLGA capsules caused a transient systemic hypotension (A), a decrease in number of perfused hepatic vessels (B) and a vasodilation in the liver (C).

rat model studies. Although all animals survived the studies, serious side-effects occurred after intravenous infusion of PLGA and PACA capsules. A transient decrease in systemic blood pressure (Figure 1A) and impairments of the microcirculation (Figures 1B and 1C) were caused. Furthermore, PLGA and PACA capsules displayed different biodistribution patterns due to organ specific accumulation (Figure 2).

To establish PLGA and PACA capsules as PFD-based artificial oxygen carriers further improvement is needed.

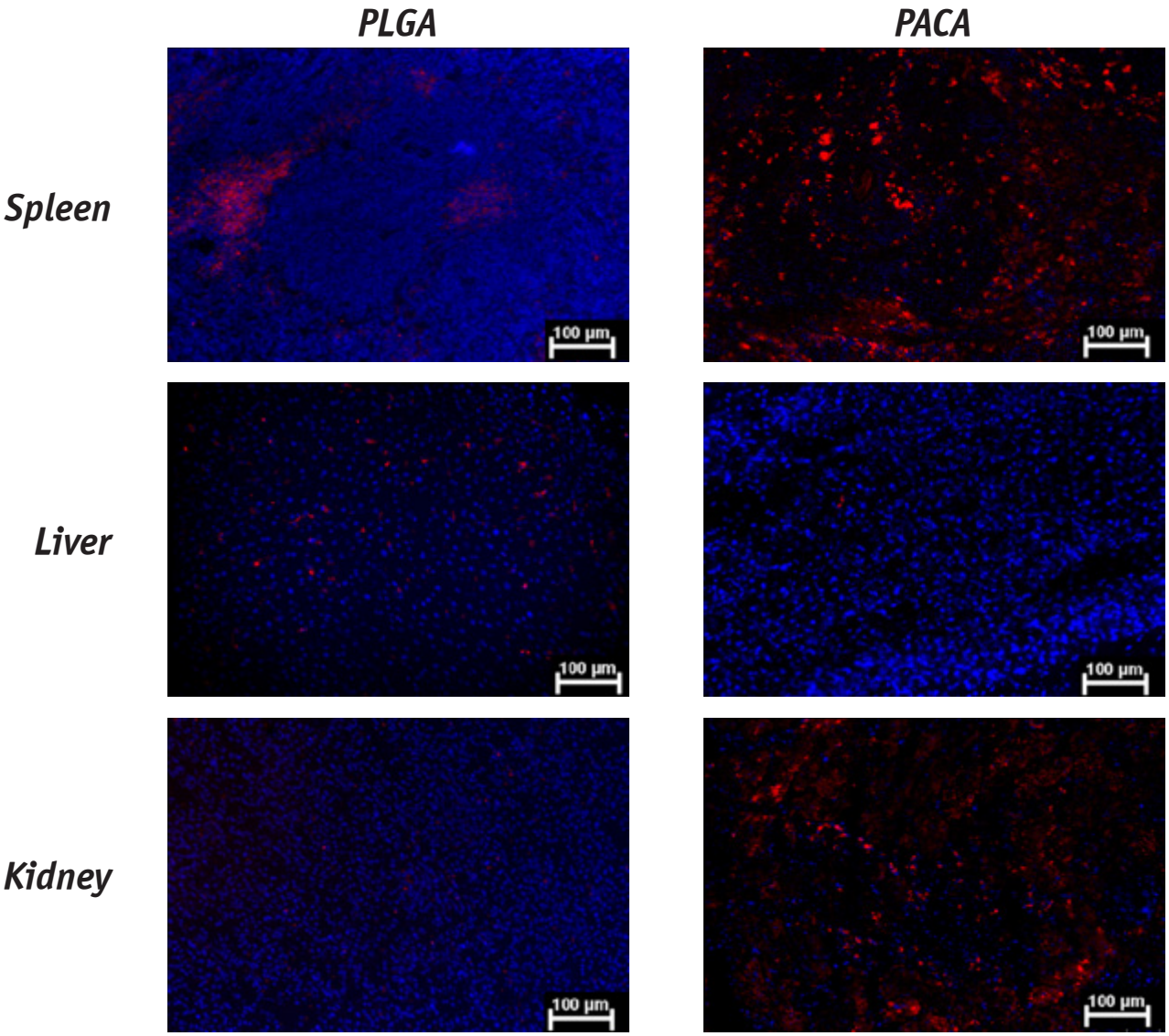


Figure 2: Biodistribution of PLGA and PACA capsules. PLGA capsules accumulated specifically in spleen and liver, whereas massive accumulation of PACA capsules were found in spleen and kidney.

The influence of mTor inhibitors on HCV reinfection after liver transplantation

Eva-Maria Ecker

Clinic for Gastroenterology / Hepatology
Group: Kerstin Herzer

The hepatitis C virus (HCV)-associated liver cirrhosis is one of the main cause for liver transplantation in the western world. Nearly 100% of those patients experience a HCV reinfection of the graft which results in episodic hepatitis with progressive fibrosis and the danger of re-cirrhosis and graft-loss. The standard therapy with alpha-interferon and ribavirin is poorly efficient and often not applicable. Investigations concerning the influence of immunosuppressive therapy on the course of reinfection created contradictory results, while an effect of mTOR-inhibitors has not been investigated so far.

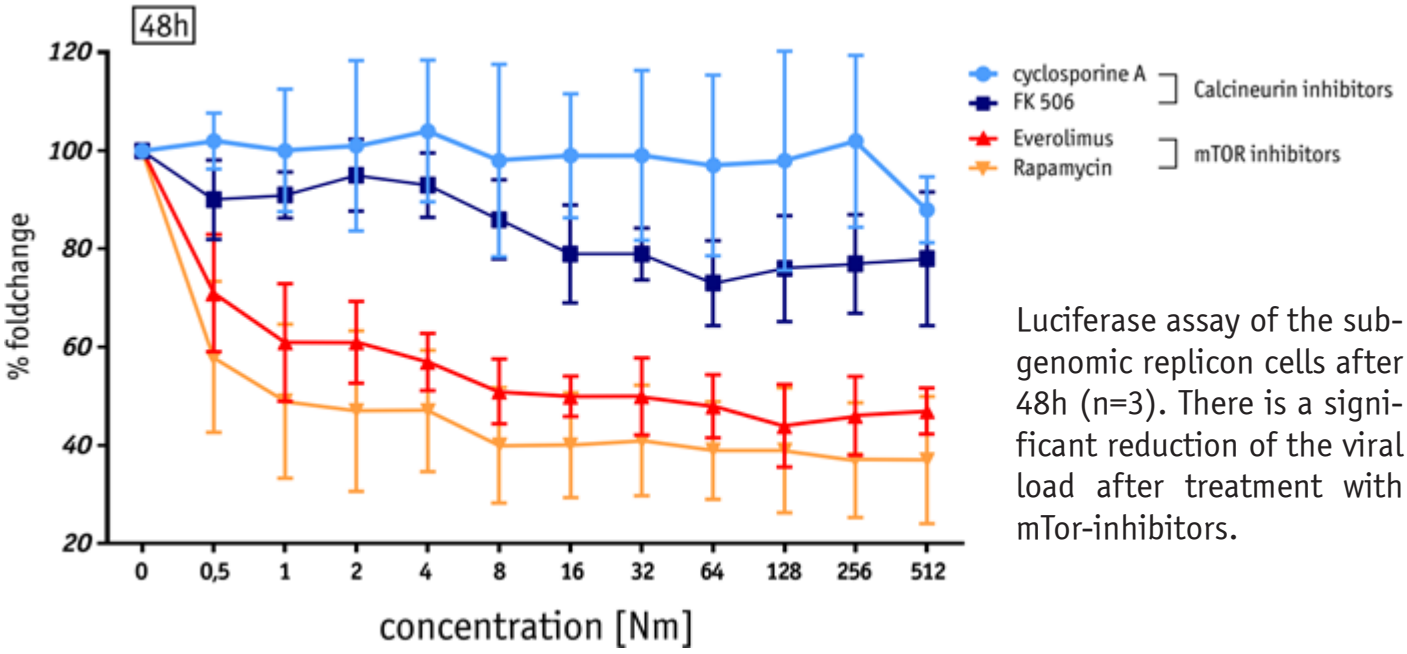
The effects of various immunosuppressive agents were analysed *in vitro* using a subgenomic HCVcc replicon system (gentoyp 2a) linked with a luciferase construct. Calcineurin inhibitors (cyclosporine A, tacrolimus) were compared with mTOR inhibitors (everolimus, sirolimus) with respect to their effect on viral replication. A significant impairment of replication can be observed upon application of mTOR inhibitors in therapeutic dose equivalent.

Cytotoxicitysassays and FACS-based CFSE cell proliferation analyses were performed in order to exclude anti-proliferative effects of the mTor-inhibitors in the cell culture system. Cell proliferation and viability was not compromised by the mTOR inhibitors.

As the tumour suppressor protein promyelocytic leukaemia (PML) has been shown to be involved in HCV infection, rtPCR and gene silencing by sh-Plasmids were used to study the influence of PML on mTor-inhibitor-induced impairment of HCV replication. Silencing of PML causes a significant reduction of viral replication. This effect appears to be associated with the mTOR pathway.

Currently, gene array analyses are on the way to identify other factors and shed more light on the underlying molecular mechanisms of the mTor-inhibitor effect on HCV replication.

This study provides initial evidence that mTOR-inhibitor-based immunosuppression after liver transplantation may have a positive effect on the course of reinfection with certain genotypes of HCV. The correlation with *in vivo* data, the analysis of further HCV genotypes and the identification of the underlying molecular mechanisms are subject of current investigations.



Luciferase assay of the subgenomic replicon cells after 48h (n=3). There is a significant reduction of the viral load after treatment with mTor-inhibitors.

Impact of the NOTCH1 (p.P2515R) mutation on pathogenesis and progression of patients with chronic lymphocytic leukaemia

Stefanie Rost

Clinic of Haematology
Group: Joachim Göthert

Chronic lymphocytic leukaemia (CLL) is the most common leukaemia in adults in the western world. The pathomechanisms leading to malignant transformation and disease progression are not fully understood up to now. Activating mutations in the gene for NOTCH1 are the most frequent oncogenic events in T-cell acute lymphoblastic leukaemia and have recently been implicated in around 10% of CLL cases as well (Fabbri *et al.*, J Exp Med, 2011 and Puente *et al.*, Nature, 2011).

The aim of this project is to analyse the oncogenic potential of the most frequent NOTCH1 mutation on a molecular level and thereby contribute to the understanding of the malignant transformation and clonal evolution of blood leukocytes to CLL.

The prevailing CLL NOTCH1 mutation is a deletion of a CT dinucleotide (N1ΔCT) which leads to an early truncation of the Notch1 protein (p.P2515Rfs*4) resulting in impaired degradation of activated NOTCH1.

We established two new screening methods – RFLP (restriction fragment length polymorphism) analysis and AS-PCR (allele-specific polymerase chain reaction) – for the N1ΔCT mutation and analysed a cohort of n=275 CLL patients. Using RFLP analysis, we

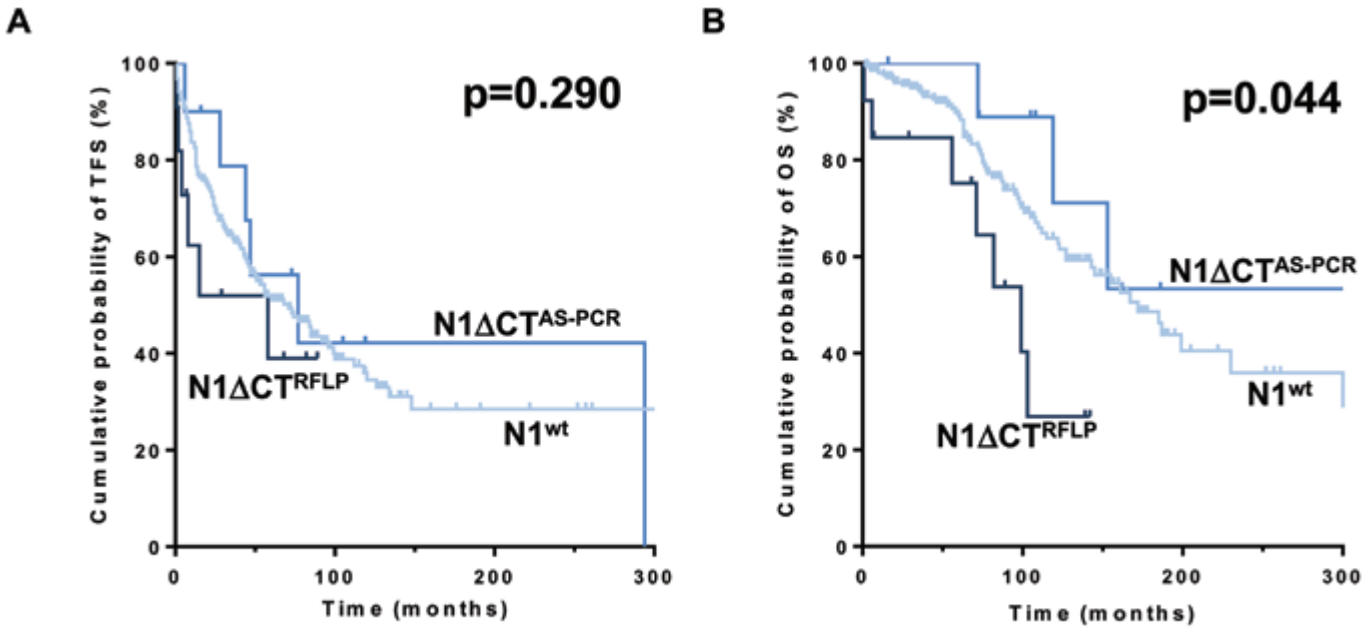


Figure 1: Kaplan-Meier estimates according to *NOTCH1* mutational status. (A) Treatment-free survival (TFS) of n=219 CLL patients was analysed revealing that size of the N1ΔCT mutation did not have a significant impact on treatment-free survival. (B) In contrast, overall survival (OS) analysis of n=230 CLL patients demonstrated that a larger N1ΔCT mutated clone (RFLP+) correlated with impaired survival (p=0.044).

detected the N1ΔCT mutation in n=17 CLL patients (6.2%), using the more sensitive AS-PCR, we were able to identify 12 additional presumably subclonally N1ΔCT-mutated cases, resulting in a total mutation rate of 10.5% (n=29/275) in the cohort.

To investigate the clinical impact of this mutation on CLL patients, we analysed the overall survival (OS) of both, patients with high (RFPL+) and low (RFLP-/AS-PCR+) N1ΔCT burden. The OS of RFLP+ patients was significantly shorter than the OS of N1ΔCT-unmutated CLL patients (wt) (mean OS; RFLP+, 87 months vs. wt, 218 months; p=0.017). In contrast, OS of AS-PCR-positive cases (RFLP-/AS-PCR+) did not differ significantly from the OS of wt patients (mean OS; AS-PCR+, 175 months vs. wt, 218 months; p=0.42) (Fig. 1).

In order to be able to precisely quantify allelic burden, we designed a quantitative real-time PCR (qRT-PCR) assay, which is capable of determining the size of the N1ΔCT-mutated subclones (allele frequency, %) in the CLL cohort. As expected, significantly different allele frequencies between RFLP+ (mean±SEM 27.1±3.4%), AS-PCR+ (3.7±0.6%) and wt patients (0.6±0.04%) were revealed by qRT-PCR (p<0.0001) (Fig. 2). In order to determine a methodology-independent cut-off which correlates with the clinical significance of the N1ΔCT mutation, we employed Receiver Operating Characteristics (ROC) analysis based on the survival status and calculated a N1ΔCT allele frequency cut-off of 15.2% (AUC=0.71). Next, we determined N1ΔCT allele frequencies over time to investigate clone dynamics within individual patients (n=15 patients, mean observation period 87.4 months; range 5-186 months). Unexpectedly, the N1ΔCT allele frequencies remained relatively constant and none of the patients with N1ΔCT allele frequencies below 15.2% rose above this cut-off over time.

In conclusion, our data demonstrate that a high abundance of a N1ΔCT-mutated CLL clone correlates with an aggressive disease course. In our CLL cohort a N1ΔCT allele frequency below 15% was of negligible clinical relevance. Thus, mere qualitative detection of a N1ΔCT mutation by PCR is not inevitably associated with shortened survival. Surprisingly, we did not observe that a minor N1ΔCT clone became dominant over time.

In future experiments we are going to analyse clonal behaviour and evolution *in vivo* to find out whether the N1ΔCT mutated clone possesses a selection advantage and expands over time and thereby contributes to disease progression of CLL.

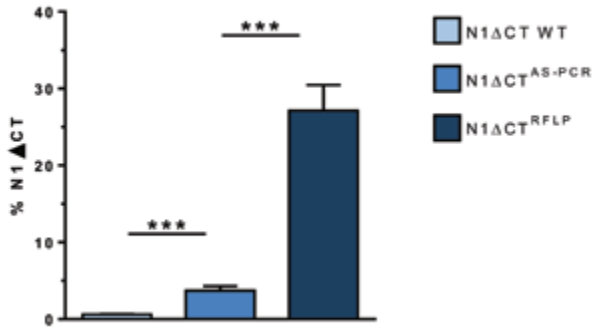


Figure 1: Real-Time PCR analysis. The N1ΔCT percentage was calculated as a proportion of all detected *NOTCH1* exon 34 alleles. This analysis revealed significantly different allele frequencies between RFLP+ (mean±SEM 27.12±3,3%), AS-PCR+ (3.7±0.6%) and wt patients (0.6±0.04) (p<0.001).

The AAA+ ATPase p97 in cell cycle checkpoint regulation

Anne Riemer

Department of Molecular Biology I, ZMB
Group: Hemmo Meyer

During the cell cycle, DNA replication in S-phase and chromosome segregation in mitosis are tightly coordinated and monitored by checkpoints. Important regulatory elements of the checkpoints are protein phosphorylation and the ubiquitin proteasome system (UPS). A key player of the UPS is the AAA+-type ATPase p97, which generally recognises substrates after they have been modified with ubiquitin by E3 ubiquitin ligases and targets them for proteasomal degradation. p97 acts in a number of different cellular processes with distinct cofactors, such as the Ufd1-Npl4 heterodimer. So far, the p97Ufd1-Npl4 complex has been associated with independent functions in regulating Aurora B kinase in mitosis, in orchestrating repair of ionising radiation-induced DNA damage as well as in the response to replication stress.

In this project we focused on the role of p97 in the regulation of cell cycle progression. We found that ionising radiation (IR) treated HeLa cells depleted of p97Ufd1-Npl4 showed increased segregation defects that originated from pre-mitotic errors indicating that the G2/M checkpoint is compromised. Indeed we showed that depletion of p97Ufd1-Npl4 leads to G2/M checkpoint failure upon treatment with IR with significantly more cells entering mitosis compared to control depletion. While upstream DNA damage signalling was unaffected, we observed a delayed degradation of the CDC25A phosphatase in Ufd1-Npl4-depleted cells. Consistently, mitotic entry after IR of Ufd1-Npl4 depleted cells was rescued by concomitant inhibition of the Cdc25 phosphatases. Co-immunoprecipitation experiments confirmed the interaction of p97 with the SCF-β-TrCP E3 ligase complex that mediates CDC25A ubiquitination, as well as with CDC25A itself. This led us to conclude that the p97Ufd1-Npl4 complex facilitates efficient degradation of CDC25A downstream of ubiquitination by β-TrCP to prevent cells with damaged DNA from entering mitosis and thus maintain genome integrity.

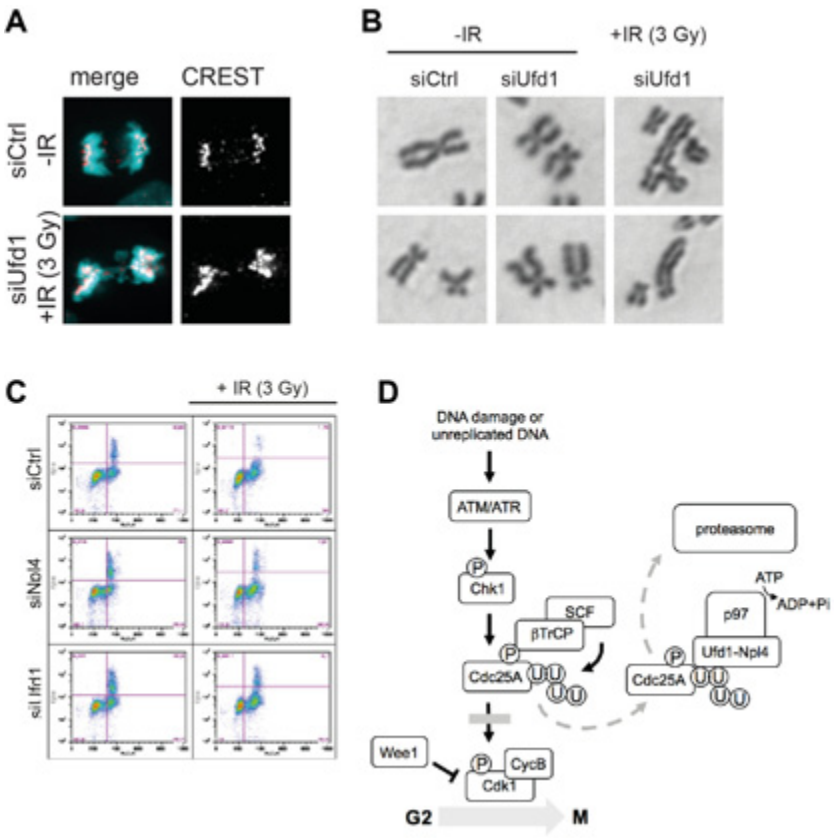
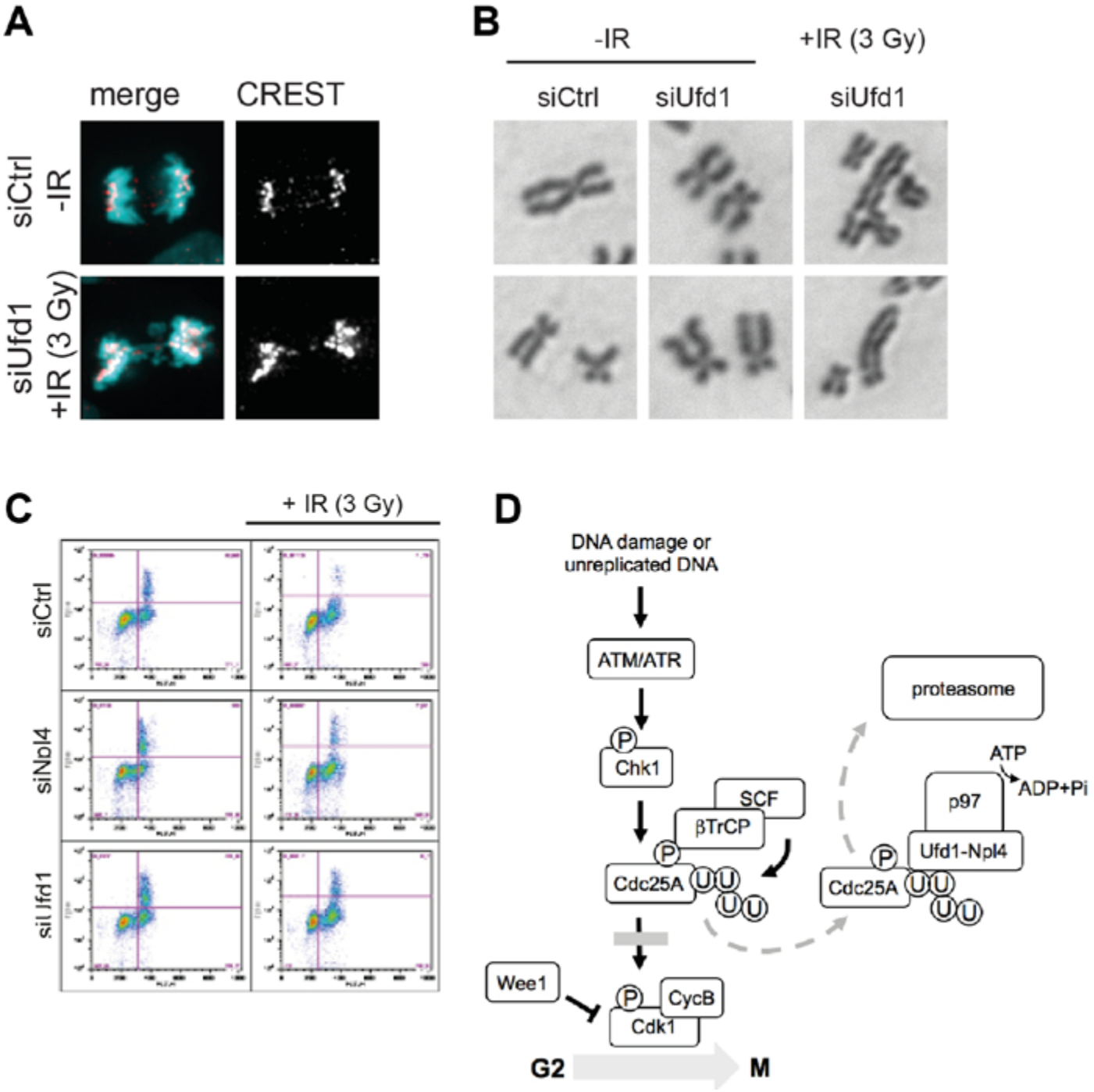


Figure 1: A) Schematic illustration of mitotic and pre-mitotic defects in anaphase. Blue depicts chromatin, red dots depict centromeres. Ufd1 depleted cells show an increase in pre-mitotic errors after IR. **B)** Magnifications of chromosome spreads of cells siRNA-treated and irradiated with 3 Gy. Note the prominent chromosomal aberrations including fragments and acentric chromosomes in irradiated Ufd1-depleted cells. **C)** Flow cytometry of HeLa cells stained with propidium iodine and pH3(S10) antibodies. Cells were depleted of indicated proteins, mock-treated or irradiated as indicated and then subjected to a nocodazole trap for 10 h prior analysis. Ufd1 and Npl4- depleted cells show significantly more mitotic cells after IR compared to control depletion. **D)** Model: Inactivation of CDC25A is initiated upon DNA damage or unreplicated DNA through phosphorylation by Chk1. Phosphorylated CDC25A is recognised and ubiquitinated by the SCF-βTrCP ubiquitin ligase. The p97-Ufd1-Npl4 ATPase complex binds ubiquitinated CDC25A and facilitates its degradation by the proteasome. Efficient degradation of CDC25A blocks activation of CDK1 and thus G2/M transition.



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Dissecting the role of the radioresistance factor Survivin in DNA repair

Elisabeth Schröder

Institute of Molecular Biology II
Group: Shirley Knauer

Survivin, also known as BIRC5 (baculoviral IAP repeat-containing 5) is the smallest member of the inhibitor of apoptosis protein (IAP) family with a molecular weight of approximately 16,5 kDa (Figure 1 A). It conducts a dual role by displaying anti-apoptotic functions as an IAP and by being necessary for the proper segregation of chromosomes during mitosis as part of the chromosomal passenger complex (CPC) (Figure 1 B). For both functions, integrity of its nuclear export signal (NES), interacting with the export receptor Crm1, has proven to be essential (Knauer *et al.*, 2006).

Survivin is expressed during embryonic development as well as in dividing cells, but is absent in normal differentiated tissues. Its upregulated expression in all cancer entities studied is known to be associated with an increased resistance against radio-/chemotherapy and a decreased radiosensitisation. This makes Survivin not only a potential diagnostic or prognostic tumour biomarker but also a promising target for cancer therapy. Recent data furthermore indicate that Survivin could be directly or indirectly involved in DNA repair, contributing to therapy resistance (Capalbo *et al.*, 2010; Reichert *et al.*, 2011). As the underlying molecular details still remain unclear, the present project aims to dissect the role of Survivin in the repair of irradiation-induced DSBs.

During interphase, GFP-tagged Survivin localises to the cytoplasm in untreated cancer cells. Analysis of microscopic images obtained from A431 cells stably expressing Survivin-GFP revealed a relocation of the GFP-tagged protein to the nucleus after irradiation as well as the formation of distinct nuclear foci which occurred within 30 min after treatment and persisted for at least 24 h (Figure 1 D). Likewise, ionising radiation induced formation of endogenous Survivin foci (Figure 1 C) as well as an increased protein expression in A431 cells, as detected by immunostaining and immunoblot analyses, respectively. Even though these Survivin foci resemble those harboring members of the DNA repair machinery, no distinct co-localisation with e.g. γH2AX (phosphorylated histone H2AX), phosphorylated ATM or phosphorylated DNA-PKcs could be detected. Also no direct interaction of Survivin with members of the DNA repair machinery could be detected in biochemical co-immunoprecipitation assays. However, immunostaining of the other members of the CPC revealed that especially Aurora B and INCENP, and to a lesser extent also Borealin, localised to the same irradiation-induced nuclear foci as Survivin (Figure 1 E). An induction of Aurora B expression after irradiation could be confirmed via immunoblot.

Since the CPC foci seemed to occur in distinct parts of the nucleus, including peri-nucleolar regions, the precise localisation of these foci within different subnuclear territories of the chromatin was further investigated. Irradiation-induced CPC foci co-localised with heterochromatin protein 1α (HP1α), a marker protein

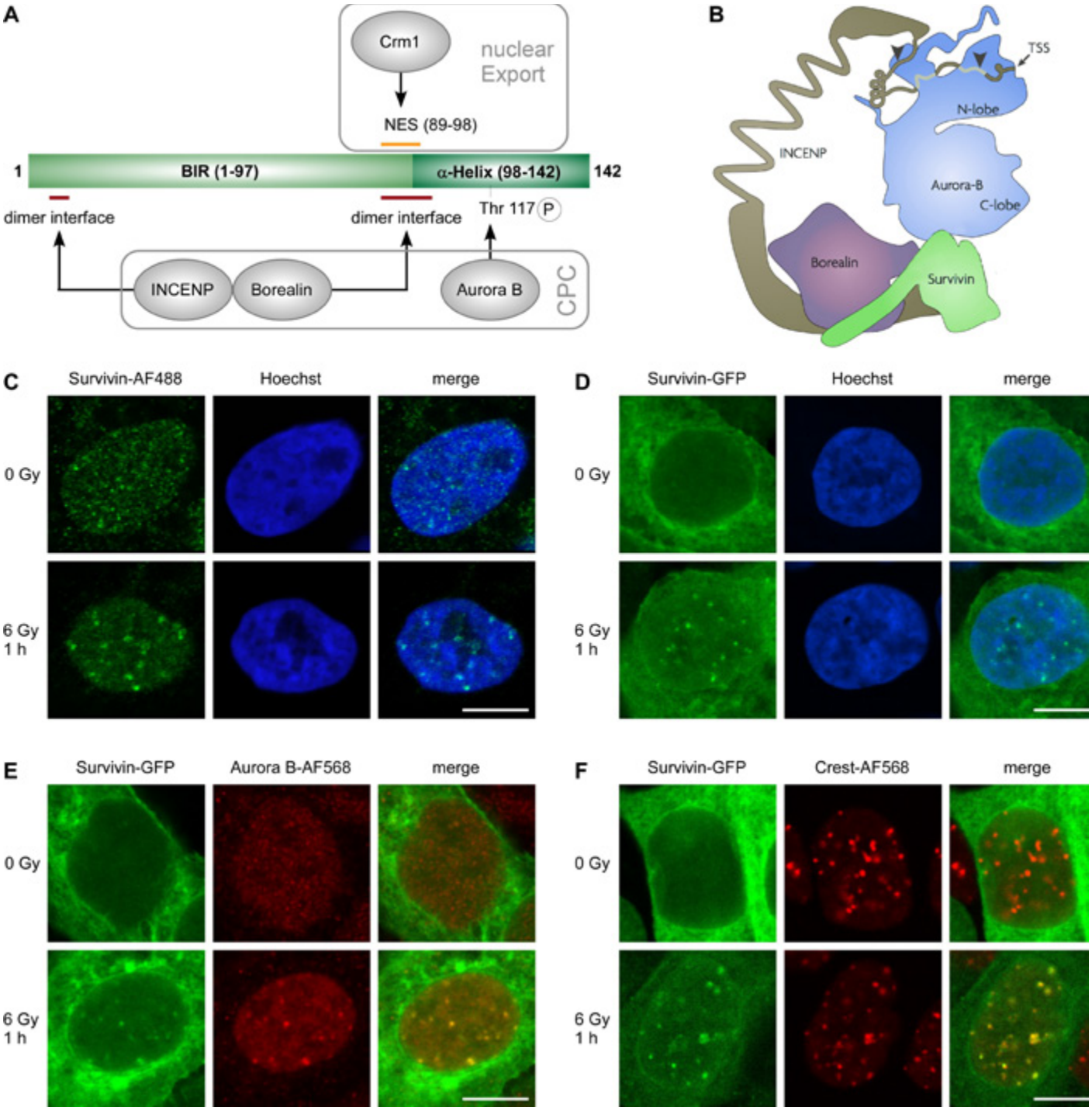

Figure 1: Survivin localises to irradiation-induced nuclear foci together with the other CPC proteins. A) Domain organisation of Survivin. B) Schematic diagram of the CPC modified after Ruchaud et al., Nat Rev Mol Cell Biol, 2007. C) A431 cells were irradiated with 6 Gy, fixed 1 h after irradiation and stained with an α-Survivin antibody and Hoechst. D-F) A431 cells stably expressing Survivin-GFP were irradiated with 6 Gy, fixed 1 h after irradiation and stained with Hoechst (D), an α Aurora B antibody (E) or an α-Crest serum detecting centromeric chromatin (F), respectively. Scale bar, 10 µm.

for heterochromatic DNA. More precisely, a staining with an anti-centromere antiserum (Crest) revealed a specific localisation within centromeric chromatin (Figure 1 F). Reduction of heterochromatic regions by using Trichostatin A (TSA), an inhibitor of histone deacetylases (HDACs), resulted in a decreased occurrence of Survivin foci after irradiation. As detected by immunostaining and immunoblot, siRNA-mediated knockdown of Survivin and Aurora B kinase resulted in an increase in γH2AX, which as a marker of DSBs hints towards a lowered cellular DNA repair capacity.

The CPC proteins were also found in nuclear foci during S-phase, and knockdown of Survivin led to a reduced replication fork speed (Figure 2 C), as determined by the DNA fiber assay method (Figure 2 A) established during a stay abroad in the laboratory of Eva Petermann at the University of Birmingham financed by the RTG 1739 (Jones *et al.*, 2013). These findings might indicate a participation of the CPC in DNA repair specifically during S-phase. To unravel the potential role of the CPC members in this process, siRNA-mediated knockdown should be combined with irradiation to find out at which point DNA repair is hampered and whether this might be mediated by changes in activating phosphorylation. Detailed analysis of foci localisation in only centromeric versus whole heterochromatin should further help to understand the connection between the CPC and cell cycle checkpoint control.

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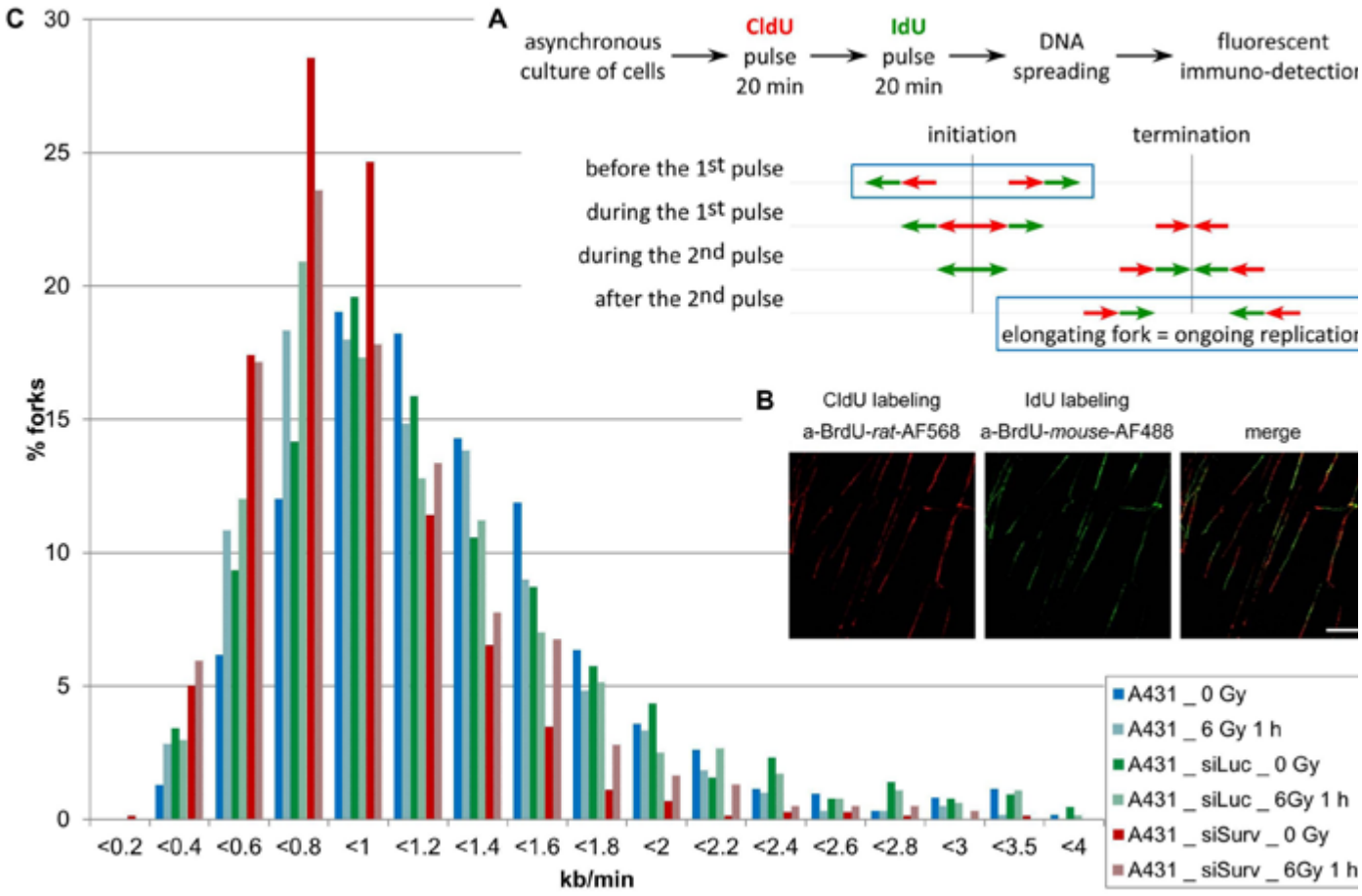


Figure 2: Knockdown of CPC proteins reduces replication fork speed. A and B) DNA fiber assay. A431 cells were transfected with 20 nM siRNA against Survivin or Luciferase as a control, and irradiated with 6 Gy 72 h after transfection. 1 h later, cells were labelled with CldU and IdU for 20 min each, trypsinised and spotted on microscopic slides. The cells were lysed to subsequently spread their DNA content by tilting the slides. Following fixation of the DNA, fibres were stained with two different α-BrDU antibodies specific for CldU and IdU, respectively, and visualised microscopically. Scale bar, 10 µm. C) The length of the stained fibers from elongating forks was measured with ImageJ, and the speed of the replication fork was calculated.

Activation and expansion of Vβ5+ regulatory T cells is dependent on membrane-bound TNFα and TNFRII during retroviral infection

Jara Joedicke

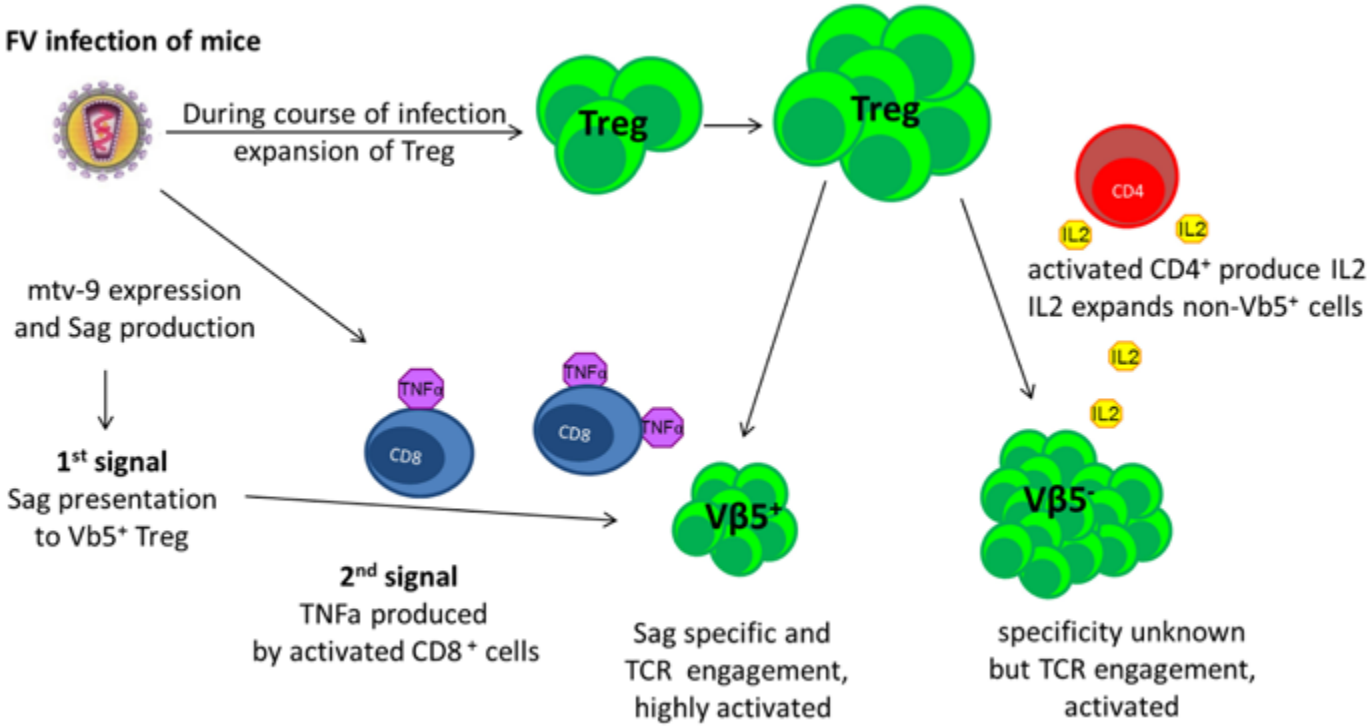
Institute for Virology
Group: Ulf Dittmer

CD4+Foxp3+ Tregs constitute a major subset of suppresser T cells. The function of Tregs is essential in both the prevention of autoimmune diseases in healthy individuals and protection from immune response-mediated tissue damage during viral infections. While generally beneficial, these suppressive effects can be limiting for anti-viral immune responses, resulting in a delayed or incomplete clearance of the pathogen. The immunosuppressive role of Tregs in virus-specific immunity was first described using the FV model, but has also been reported for viruses causing human infections such as HBV, HCV and HIV.

The aim of this PhD project was to better define the molecular characteristics of FV-induced Tregs. For this purpose it was of importance to determine the phenotype acquired by Tregs during acute and chronic FV infection by analysing the expression of various activation, differentiation, and proliferation markers. Furthermore, it was of great interest to determine the specificity and origin of the Treg population and the molecular mechanism of expansion during viral infection. This was especially important as knowledge on this topic will provide new concepts to therapeutically interfere with Treg cell expansion.

Infection of mice with Friend retrovirus (FV) induces the expansion and activation of regulatory T cells (Tregs) during acute infection, which remain throughout the chronic phase of infection. Tregs are responsible for the suppression of FV-specific CD8+ T cell responses, leading to the establishment of this chronic infection. In our recent study, we have shown that the Tregs responding to FV-infection were actually natural nTregs rather than induced iTregs. We observed a disproportionate expansion of T cell receptor (TCR) Vβ5+ Tregs in FV-infected mice during the acute phase of infection, which were specific for an endogenous retroviral superantigen (Sag) of the mouse tumour virus 9 (mtv-9). Investigation into the characteristics of this Vβ5+ Tregs subset showed that they were highly activated, suppressive, and had the unusual characteristic of being independent of IL2. Furthermore, their expansion was dependent on activated CD8+ T cells, rather than viral loads, and most intriguingly, the presence of TNFα.

TNFα is a pleiotropic cytokine present in two forms: a soluble (solTNFα) and a membrane-bound form (mbTNFα). Both forms can bind the two TNFα receptors, TNFRI and TNFRII. The solTNFα preferentially binds to TNFRI, whereas mbTNFα has a higher affinity for the TNFRII receptor. TNFRII was recently described as important for Treg development and suppressive activity. Interestingly, we were able to show that TNFRII, but not TNFRI, was significantly up-regulated on Vβ5+ Tregs during FV-infection. Furthermore, we have shown that the expansion of Vβ5+ Tregs was dependent on the presence of TNFRII, but not TNFRI. Intriguingly, we found that FV-specific CD8+ T cells produced substantial amounts of mbTNFα after *in vitro* stimulation, providing a potential source of TNFα for Vβ5+ Treg activation. The use of iRhom2-KO mice, which only express mbTNFα and not solTNFα, revealed that Vβ5+ Tregs expand more in response to CD8+ T cells of these mice. Finally, the treatment of naïve mice with solTNFα did not induce expansion of Vβ5+ Tregs as expected, whereas treatment with a synthetic TNFRII ligand was able to induce Vβ5+ Treg expansion. These results reveal a new mechanism for the expansion and activation of different Treg subsets, and their intercellular communication with CD8+ T cells during viral infection. Although it remains to be determined whether humans have infection-induced, Sag-specific Treg subsets, circumstantial evidence points in that direction. If such cells are involved in the immunological control of human diseases they make good targets for intervention since they could be regulated independently of other Treg subsets.



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BIOME Experiences

Clinical Grand Rounds for PhDs: exploring the bench-to-bedside gap

Jolanthe Baingo

The clinical grand rounds were initiated and encouraged by Prof. Dr. Elke Winterhager who was a scientific coordinator of the BIOME core Tumour and Signalling until June 2013. This translational programme addressed PhD students from the BIOME cores Tumour and Signalling and Cellular and Molecular Immunology. The aim of the clinical grand rounds was to offer PhD students the prospect of having a look beyond the "bench" and getting in contact with clinical approaches. Participation was voluntary and the first trial was performed in January/February 2013. About 15 young biomedical researchers were interested in taking part in this interesting programme and wanted to explore the space beyond their own nose! The Clinic for Neurosurgery, the West German Tumour Centre/ Paediatrics, the Department of Otorhinolaryngology, the Children's Hospital as well as the Clinic for Gynaecology and Obstetrics agreed to participate in this experiment. Each organisation was visited for three days by three PhD students.

Two colleagues and I visited the Clinic of Gynaecology and Obstetrics. We were allocated to a ward physician or resident physician so that we could pass through various wards of the clinic. Every morning I joined the ward rounds. The ward physicians shortly explained the anamnesis of the patients, especially of patients suffering from complicated diseases. Although the medical doctors had tight time schedules there was enough time to ask some questions about the patients' diseases and therapy options. As I changed the wards every day, the rounds were exciting and multifaceted. I got to learn about various disease patterns as well as about ailments affecting expectant mothers. During the clinical grand rounds I was also introduced into the everyday life of surgery: preparation of the operating room, surgery procedure, cleaning of the operating room and again preparation of the operation room for the next surgery. During surgery I was involved in patients' diseases and the operating surgeon explained each step of the surgery to me, so that I was able to follow up the surgery procedure. I became acquainted with different surgery types as classical surgery, minimally invasive surgery and robotic surgery, which was really impressive. Furthermore, the operating surgeon declared the assets and drawbacks of the different surgery types.

I am very glad I took the chance to attend the clinical grand rounds. It was a great experience that I did not want to have missed. However, I think there is also room for improvement in this translational programme. As we are young biomedical researchers it would be great to be more incorporated into an intense debate of therapeutic options on the basis of case studies. The clinical grand rounds were a successful first trial and I hope that more clinics will participate to improve mutual understanding between biomedical researchers and medical doctors.

Reflections on BIOME's MD/PhD programme: a pioneer's tale

Ilseyar Akhmetzyanova

I am Ilseyar Akhmetzyanova and I would like to reflect upon some of my experiences as an MD/PhD student at the University of Duisburg-Essen.

My time in Germany so far has been an amazing academic and professional journey. I started my MD doctoral work in July 2009 at the Institute for Virology with the innovative topic of regulatory T-cells' influence on effector CD4+ T-cells during tumour formation. In 2010, the Faculty of Biology set up a novel MD/PhD programme which provides a deep immersion in the world of science while stressing the valuable connection with the medical field. After successfully obtaining my MD title, I was offered to enrol into this programme. Notably, it also required a successful participation at one of the cores of the university's graduate school. The high levels of support I received at the BIOME graduate school pleasantly surprised me. There I had the chance to attend not only interesting lectures but also to participate in the clinical grand rounds which stressed the possible connections between the researcher's and physician's worlds.

The MD/PhD included not only the work on my research topic but also a chance to intern at other laboratories. This gave me the chance to get a broader view and pick some useful techniques through which I improved my own research.

I also felt the seminars, which were incorporated into the programme, were an extremely beneficial as they aided the students in their efforts to expand their views and to continuously learn new material and job-related skills.

Similarly, the numerous conferences which I attended like the Meeting of the German Society for Virology in 2012 and the Annual Meetings of the Association for Cancer Immunotherapy in 2012 and in 2013 (CIMT), allowed me to exchange views and ideas with some of the leading experts in the field and to meet some of the brightest scientists in Europe. I was extremely glad to have my work recognised on such a high level by being

awarded the poster prize in the section "Improving Immunity" at CIMT 2012.

My current work at the MD/PhD programme continues my investigation of immune response to virus-induced tumour formation by focusing on enhancing the CD4+ T-cell function through treatment with co-stimulatory antibodies. I do believe that this opportunity is very rewarding as it has a great potential for future development and various medical applications.

I am especially thankful to my supervisor, Prof. Dr. Ulf Dittmer, who made sure I had everything I needed to conduct my research in this challenging but fascinating field.

With ELAN towards the doctoral degree

LISA STROHBÜCKER is a 22-year old medical student who, in her fifth semester, intensely focused on her MD degree. To non-physicians, this sounds terribly like a turbo degree – usually people first finish one course of study before doing their doctorate on top. In medicine in Germany, this has traditionally not been the case. The lengthy training to be a doctor – and then a medical specialist – leaves no time at the end for the usual doctoral phase. Thus, one does one's MD work relatively early on, parallel to one's other medical studies. It is easy to imagine one can end up feeling heavily pressurised. Lisa not only has the necessary élan, but has ELAN backing her up during the doctoral process.

ELAN is short for the *Essener Ausbildungsprogramm „Labor und Wissenschaft" für den ärztlichen Nachwuchs*, a laboratory and science training programme for young MD students. The doctoral course was established in 2012, and Lisa was one of its first eleven fellows. Prof. Dr. Ursula Rauen belongs to the three-headed ELAN management team and explains the initiative's background. On the one hand, the new approbation regulations with their rigorous demands makes it more difficult than ever for students to write a challenging doctoral thesis alongside their medical studies. On the other hand, the university hospital urgently needs to encourage good students to become future experimental researchers in the academic context.

Close supervision, structured programme

Hence, ELAN. The doctoral course merges outstanding students with excellent doctoral projects. It offers doctorates close supervision as well as support through a comprehensive, clearly structured training programme. Last but not least, an ELAN stipend enables MD students to take one or two semesters off from their regular studies to dedicate themselves to science. ELAN is grateful to the Else Kröner Fresenius Foundation for its grant of maximum € 750 000 for three years.

The theme of Lisa Strohbücher's thesis is, "Role of the infection-associated danger signal $HMGB_1$ in the immunopathogenesis of *Psoriasis vulgaris*". With a bit of luck, the average person may have read "psoriasis" on a shampoo bottle and is able to guess it has something to do with dandruff. Smiling, the young doctorate tries to explain the complicated rest. The protein $HMGB_1$ is the ground soil in which not only the uncontrolled immune reactions of psoriasis play a role, but also of other infectious courses of disease such as tumours and cancer therapy. Lisa's doctoral supervisor, PD Dr. Christoph Bergmann (Otorhinolaryngology), is one of many researchers looking into $HMGB_1$.

The young MD started her "semester off" with a three week crash course on the theoretical and practical aspects of laboratory work. Then the experimental phase began during which all ELAN fellows spend a year as integrated members of BIOME's academic programme: clinicians and biologists work together in groups, listen to lectures, and visit meetings. And Lisa took the skin and blood samples from the patients she was examining for her thesis on $HMGB_1$.

One feels a little more secure

In the winter semester 2013/2014 Lisa ended her work-intensive "break" from regular studies, and in the sixth semester the normal semester count began again. This is the phase in which one has to speedily finish the thesis and translate it into written form. This again is parallel to regular studies, yet ELAN supports its fellows in this phase too – with seminars about writing a doctoral thesis and how to present one's research to a scientific public and so on. The latter can then be put into practice at a scientific conference; Lisa will be presenting her data at an international immunological conference soon.

"One feels a little more secure with ELAN," says the young doctorate. This is because ELAN tested not only her but also the doctoral project for feasibility; because the funded semester-long break enabled concentrated work on the thesis; because one intensively practised working experimentally under close supervision. It is also more than likely that Lisa Strohbücher and all the other ELAN fellows will fulfil their reciprocal obligations sovereignly by very soon completing their MD degrees with excellent grades and published results.

Fairly enough, ELAN forces no obligations on its fellows as certified doctors to later do research at the university hospital. Rather it is hoped that, after the ELAN experience, the already motivated students will feel inspired to become the next-generation researchers at Universitätsklinikum Essen. The second ELAN round begins in March 2014.

P.S.: At the time of going to press, Lisa was on her second month-long exchange, collaborating on research at Irma Joosten's medical immunology lab at the Radboud University Nijmegen in the Netherlands.

Peeking at the German research culture through Chinese eyes

EJUAN ZHANG and Zhiyong Ma were young researchers in Essen between 2008 and 2013. Ejuan Zhang came out to Germany on a bursary funded by the Chinese Scholarship Council, while Zhiyong Ma was one of the first PhD exchange students of the Transregio 60: *Mutual interaction of viruses with cells of the immune system: from fundamental research to immunotherapy and vaccination* (TRR 60), an international, German-Chinese research cooperation based in Essen between the universities in Duisburg-Essen, Bochum, Wuhan and Shanghai. Ejuan Zhang reveals her personal experiences of the initial cross-cultural shock commonly felt by most Chinese scientists living and working in the west for the first time.

It was the end of 2007 when I got the information about the National Natural Science Foundation of China (NSFC) project for the joint PhD programme. This project was aimed at sending the best students from Chinese universities to the best universities or research groups all over the world. After discussions with my advisor, Prof. Mengji Lu, we decided to apply to the Institute of Virology at the University Hospital Essen to continue my experiments with the hepatitis virus woodchuck model. I started my life in Essen in September 2008, and stayed in Essen for 2.5 years in total. It gave me a store of impressive memories with a wealth of new experiences.

Generally, research life in Germany is not that different from that at the University of Wuhan. One also has to spend most of the time in the lab, cafeteria and dorm, which we called the "three points in line". However, life is a little more difficult in Germany than in China because one has to make one's own living arrangements. In Wuhan, one can spend all day in the lab and just go out of the school at any time to find food. But in Essen, finishing work too late at night always meant the cafeteria and shops were closed. Thus, my first new task was to calculate and set my experiment times, shopping times, cooking times and remaining time. At the beginning it puzzled me quite a lot. After a whole day of hard work, I was so sad to find nothing to eat in the fridge. Friends always had to wait for me to go shopping because I could not finish my experiments on time. It took me several weeks to get used to this independent lifestyle.

Independence is a difficult and new word for me in not only in life but also in research. In many big labs in China, the lab is divided into several small groups. A group leader and several students will be included, and the leader will discuss and help the students with the experiments. Moreover, if the experiment needs cooperation with other groups or labs, the leader will communicate with them. Thus, the students don't have to jump to the front, play the major role and discuss or make decisions. Students are passive in the cooperation procedure, and tend to be shy and introverted when sharing and discussing their results. However, the advisor in Essen also discusses the experiment, gives you suggestions, points out the person with whom you have to discuss, but doesn't help you to communicate with them. I was such an introverted person at the beginning of my Essen days. When I was asked to discuss my data with a postdoc in another institute, it took me several days to prepare the result and organise my sentences. Through this suffering, I started to become more conversable, and learned to communicate and cooperate with the colleagues, which is one of the most important skills in scientific research.

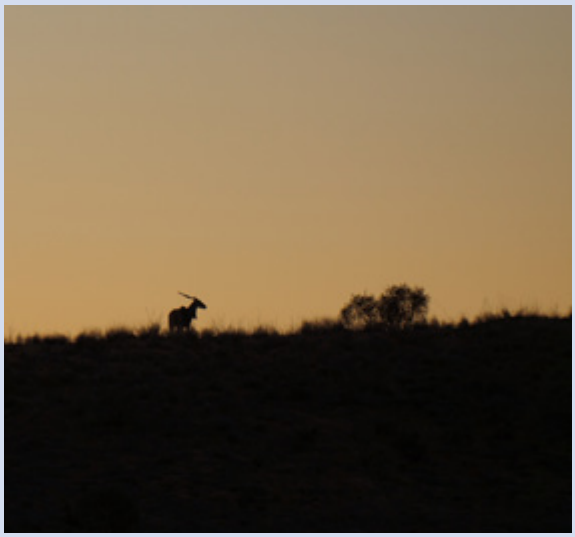
An independent researcher should know how to present his/her data to other people. Attending international meetings is a very rare chance for Chinese PhD students in Wuhan. Most of the time the students are not allowed to go abroad for meetings or, if they do, they just sit silently in the audience. I was very glad to be able to show our results at international meetings. One has many chances to attend different meetings if the grant allows, and of course, one must have enough results.

In a few words, I am very thankful for experiencing research life in Essen. It brought me many new friends and collaborators. More importantly, I became more independent and developed a more active attitude in research. That is the best gift I received from my time in Essen.

A BIOME travel blog: The divide between corridors of pain and plains of game

Philipp Gödel

PHILIPP GÖDEL is a former BIOME MD student who joined his brother in embarking on a medical internship abroad and spent six adventurous months gathering practical clinical experience as well as international partying expertise in South Africa, Australia and Guadeloupe. In 2012, he was an intern for two months on the ward for General Internal Medicine at Tygerberg Hospital in the Cape Town area. Tygerberg Hospital is the University of Stellenbosch's Faculty of Medicine and Health Science campus and is South Africa's second largest hospital. Here, in a travel blog, he shares some of his impressions of the dazzling country, its contradictory society, and having to face the harsh and humbling local health challenges.



When I'm thinking of my trip...

I'm thinking of road trips, endless gravel roads, heat and dust in the desert. About hiking and climbing, squeezing through narrow cracks in giant rocks. Magic morning game drives in the Kalahari. A steenbok being chased by cheetahs and our small car being chased by rhinos in Kruger. Intended border-hopping and real-life cross-border control. Of that mind-blowing view from Lion's Head, the sun immersing oceans, cities, mountains in the gleaming warmth of a vanishing day. I am thinking of white dunes and dark whales, heavy rains und bitter cold. Of me, washed away by that huge wave, freezing for the rest of a stormy day. Star-bright desert nights and the mighty Milky Way.

I'm thinking of the endless corridor of the emergency room, packed with people waiting for help. Silhouettes of dead bodies lying in covered beds in the hallway. Young doctors doing their best to save lives and relieve pain. Ward rounds crowded with young and even younger medical students hungry for knowledge, eager to treat their own patients. I am thinking of highly sophisticated radiology and the worn out faces of end-stage patients, excellent clinical diagnostics and limited therapeutic options.

I am thinking of prehistoric German cars stuffed with jolly students and vibrant sounds waiting to be lifted to the beating heart of the city. Thinking of those mad Brits at our lodge, shouting and fighting, drinking and making a mess, who ended up being pretty decent blokes, actually. Of endless parties at our flat share, that morning when our kitchen was covered with the white dust of the fire extinguisher. Mountains of meat, just waiting to be roasted at the weekly *braai** or at Mzoli's. Watching the Springboks rule Argentina in a sport I didn't quite understand.

I'm thinking of tremendous villas and lousy shacks, wealthy men playing with high-priced cars and small

* *Afrikaans for barbecue*

children playing in ice-cold water. Ritzy glitzy, sickly filthy and lots of in-betweens. Stagnation and progress, past and future in a puzzling society. I am thinking of exceptionally pleasant cemetery keepers and less patient police officers. Of our cleaning lady addicted to Coke and chocolate and our Norwegian comrade addicted to Nina.

I am thinking of new friends, great adventures and an unforgettable experience.

When I'm thinking of my trip, I think I haven't thought enough... About South Africa.

Feeling inspired and would like to find out more? The Gödel brothers' German language blog can be found at:
http://krautsoverseas.wordpress.com/category/sudafrika/

Anybody wishing to get in touch with Philipp directly for more information about doing an internship at Tygerberg Hospital is welcome to approach BIOME's coordination office for his contact details.

BIOME Coordinators and Speakers

Chair

ULF DITTMER studied Biology at the University of Bremen from 1987 until 1992 and went on to do both his diploma and doctoral theses at the German Primate Center in Göttingen, receiving his PhD from the University of Göttingen in 1995. Ulf then headed the Viral Immunology group at the same German Primate Center for two years, after which he spent a further two years as a visiting scientist at the Rocky Mountain Laboratories, National Institutes of Health, Hamilton, USA. In 1999 he returned to Germany to obtain his *venia legendi* in Virology at Hannover Medical School and to head the Retroviral Immunology group at the Institute of Virology, University of Würzburg. In 2002 Ulf was appointed to the Institute of Virology, University Hospital Essen, firstly as an associate professor for Viral Immunology and then as a full professor for Experimental Virology in 2009. Since 2009 he has been closely involved with the Sino-German Transregio 60: "Mutural interaction of chronic viruses with cells of the immune system" both as vice speaker (first term of funding) and since 2013 as main speaker (second financial phase). In 2009 the idea of BIOME took form and shape in Ulf's mind, and he became its chairman once it was established. During the first half of 2011 Ulf took sabbatical leave to collaborate with Kim Hasenkrug on developing a humanised mouse model for a proposed HIV vaccine trial at the Rocky Mountain Laboratories, NIH, Hamilton, USA, returning to Europe to take over the directorship of the Institute of Virology in Essen in October 2011.

Ulf's research focuses on the basic cellular and molecular mechanisms of immunity against retroviruses as well as vaccine development against retroviruses. He is also interested in immunotherapy against retroviral infections and virus-induced cancer, persistent viral infections and retrovirus-induced immunosuppression.

Chair

SVEN BRANDAU studied Biology in Hamburg and Los Angeles and conducted his PhD studies from 1993 until 1996 at the Bernhard-Nocht Institute for Tropical Medicine in Hamburg. From 1996 until 2007 he worked as a postdoctoral fellow and later as a senior scientist and independent group leader at the Research Center Borstel. During his habilitation period he started focusing on cancer immunotherapy and obtained his *venia legendi* in Immunology and Cell Biology at the University of Lübeck in 2003. In 2007 he moved to the University of Duisburg-Essen where he became an associate professor in 2009.

Sven is the head of the Experimental Research Division of the Department of Otorhinolarnygology, University Hospital Essen, and co-chairman of the BIOME graduate school. He has received several awards for his work on experimental and translational aspects of tumour immunology.

Sven´s main research area is the immunological tumour-host interaction with a focus on myeloid cells. Additional research projects aim at developing novel immunotherapies for head and neck cancer and investigating the role of mesenchymal stromal cells in cancer and infection.

Chairs
Ulf Dittmer
Sven Brandau

General Coordinator
Delia Cosgrove

Scientific Coordinators

Cellular and Molecular Immunology
Sven Brandau, *Otorhinolaryngology*
Cornelia Hardt, *Immunology*
Wiebke Hansen, *Medical Microbiology*
Annette Paschen, *Dermatology*

Computational Biomedicine
Sven Rahmann, *Genome Informatics*
Daniel Hoffmann, *Bioinformatics, UDE*
Axel Mosig, *Bioinformatics, RUB*

Genetics and Cell Biology
Verena Jendrossek, *Molecular Cell Biology*
Hemmo Meyer, *Molecular Biology*
Perihan Nalbant, *Molecular Cell Biology*
Bernd Giebel, *Transfusion Medicine*

Ischaemia, Reperfusion and Angiogenesis
Herbert de Groot, *Physiological Chemistry*
Rabea Verhaegh, *Physiological Chemistry*
Dirk Hermann, *Neurology*
Anja Bienholz, *Nephrology*

Transplantation Medicine
Ursula Rauen, *Physiological Chemistry*
Oliver Witzke, *Internal Medicine, Nephrology*
Monika Lindemann, *Transfusion Medicine*
Katharina Fleischhauer, *Cell Therapy Research*

Tumour and Signalling
Alexandra Gellhaus, *Gynaecology and Obstetrics*
Joachim Göthert, *Internal Medicine, Haematology*
Hannes Klump, *Transfusion Medicine*
Laura Steenpass, *Human Genetics*

DFG Research Training Group Speakers

RTG 1431: Gene Transcription
Hemmo Meyer, *Molecular Biology*

RTG 1739: Radiation Sciences
Verena Jendrossek, *Molecular Cell Biology*

RTG 1949: Innate and Adaptive Immunity
Jörg Timm, *Virology*

General Coordinator

DELIA COSGROVE studied English and Environmental and Geographical Science at the University of Cape Town, South Africa, with a third major in Botany which included independent research on the difference in flammability of plants both within and external to the fynbos biome. She graduated from UCT in December 1989. From 1990 until 1999 she lived and worked in Genoa, Italy and Essen, Germany where she gathered experience and expertise in transferring English language business and cross-cultural skills to globally-oriented professionals at various international companies as well as to trainees on educational programmes at state-approved academies. The birth of twins in 1999 led to a career break until 2004 when Delia was appointed as the coordinator of the then newly established RTG 1045: Host-Pathogen Interaction at the University of Duisburg-Essen. In 2009 she moved on to her present position to focus on the detailed formation of BIOME and has been responsible for the daily management and general development of the graduate school since then.

Important to Delia is facilitating to ensure that there is an open and dignified rapport between all members of the graduate school and the faculties. Creativity of vision for BIOME, respect for graduate issues and integrity as well as the symbiotic investment in long-term international interdisciplinary scientific exchange are further aspects to be especially cultivated in the current academic terrain.

Cellular and Molecular Immunology

WIEBKE HANSEN studied Biology at the Carolo-Wilhelmina University Braunschweig. From 1997 until 2000 she did her PhD studies at the German Research Centre for Biotechnology in Braunschweig on the optimisation of retroviral vectors for human gene therapy. In 2000 Wiebke Hansen started to focus her research on molecular immunology as a postdoctoral scientist in the Mucosal Immunology group at the Helmholtz Centre for Infection Research. In 2007 Wiebke moved to the University Hospital Essen, where she has been working as a group leader of Immunregulation at the Institute of Medical Microbiology. Wiebke Hansen received the *venia legendi* in Medical Microbiology and Immunology in 2010. Since 2013 she is a W2 professor for Molecular Infection Immunology at the University Hospital Essen.

Wiebke's main research focus is on regulatory T cells which are well known key players in immunological homeostasis and thought to be involved in the regulation of different immune responses. By molecular and functional analysis she could identify molecules and microRNAs highly expressed by this immunosuppressive T cell subset. In further studies her group is currently developing new approaches to modulate regulatory T cells function *in vivo* for the treatment of dysregulated immune responses during chronic infections and cancer.

CORNELIA HARDT completed her medical doctor's degree in Cellular and Molecular Immunology at the University of Mainz in 1990. She received the *venia legendi* in Molecular Medicine in 1999 at the Ruhr University Bochum. She became a university professor in Immunolgy in 2002 at the University Hospital Essen. She is a member of the editorial board of the journal "Genes and Immunity". Her research background is cellular and molecular immunology, human genetics and immunogenetics. The main focus of Cornelia's research is on genomics, epigenomics, pharmacogenomics and immunregulation of complex diseases such as multiple sclerosis.

ANNETTE PASCHEN studied Biology at the University of Bielefeld where she also conducted her PhD studies in bacterial genetics. In February 1998 she started her work in the field of cancer biology as a postdoctoral fellow of the German Cancer Research Center in Heidelberg and the University Medicine in Mannheim. Her research concentrated on different aspects related to the immunology and immunotherapy of malignant melanoma and was honoured with different awards. In February 2007 she obtained the *venia legendi* in Experimental Dermatology at the Faculty of Medicine Mannheim of the University

Heidelberg. In summer 2009 Annette moved to the University Duisburg-Essen as a head of the laboratory of the Department of Dermatology and leader of the research group "Molecular Tumour Immunology"

Annette's research aims at understanding the interaction between immune cells and melanoma cells. Of particular interest is the question how tumour cells escape the recognition by autologous cytotoxic lymphocytes, as these escape mechanisms strongly interfere with the effectiveness of cancer immunotherapy.

SVEN BRANDAU

Please refer to the "Chairs" section for this biography.

Computational Biomedicine

SVEN RAHMANN has held the Chair of Genome Informatics at the Faculty of Medicine at Duisburg-Essen University since June 2011 and was appointed as the UAMR Professor for Computational Biology in 2014.

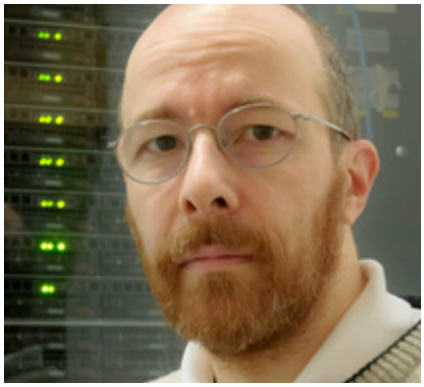
The chair focuses on inventing new algorithms and statistical methods for the analysis of next-generation sequencing data. In collaboration with other groups, the methods are applied towards medical and biological questions. For example, how can we identify the genetic causes for rare diseases? How do different subtypes of a tumour differ in their gene expression patterns? How does EHEC differ from a "standard" *E.coli* bacterium?

In both his research and teaching activities, Sven continues to maintain a strong collaboration with the Faculty of Computer Science at TU Dortmund. There, he leads a project on resource-constrained analysis of spectrometry data within the DFG collaborative research center 876: "Providing Information by resource-constrained data analysis". He is an associate editor for the journals IEEE/ACM Transactions on Computational Biology and Bioinformatics and for BMC Bioinformatics and has served in the programme committee of different bioinformatics conferences, including ISMB, WABI, ISBRA, Integrative Bioinformatics and CSB.

Between October 2007 and May 2011, Sven was professor for Bioinformatics for High-Throughput Technologies at the Chair of Algorithm Engineering, Computer Science Department, TU Dortmund. Between August and December 2007, he spent four months at HHMI Janelia Farm Research Campus as a visiting scientist in Gene Myers' lab. Sven was an independent Junior Research Group leader of the Computational Methods for Emerging Technologies (COMET) group, formerly known as the Algorithms and Statistics for Systems Biology group, at Bielefeld University from March 2004 till September 2007. The group closely collaborated with the Genome Informatics group at the Faculty of Technology at Bielefeld University. During this time, Sven was also a member of the Institute of Bioinformatics (IfB) at the Center for Biotechnology (CeBiTec), and part of the faculty of the Graduate School in Bioinformatics and Genome Research at Bielefeld University.

From 2001 until 2004, Sven wrote his doctoral thesis on oligonucleotide design for microarrays in the Computational Molecular Biology group at the Max Planck Institute for Molecular Genetics in Berlin under the supervision of Martin Vingron.

Between 1994 and the end of 2000, Sven studied Mathematics and Computer Science with a focus on statistical methods in bioinformatics at the Universities of Göttingen, UC Santa Cruz, and Heidelberg. During this time, he also worked as a freelance programmer for an insurance company and as a student assistant in the Theoretical Bioinformatics group of the German National Cancer Research Center (DKFZ), where he wrote his Diploma (M.Sc.) thesis on word statistics in random texts.



DANIEL HOFFMANN holds a diploma in Physics from the University of Heidelberg with a minor in Astronomy. He obtained a doctoral degree in Chemistry from the Free University of Berlin where he started his computational research on proteins with Walter Knapp. For several years he worked as a postdoctoral researcher with Thomas Lengauer at the German National Center for Information Technology, Sankt Augustin. In 2000, he started his first group at the Center of Advanced European Studies and Research, bringing together experimental and computational methods of protein research. In parallel, he was Professor of Bioinformatics at the Bingen University of Applied Research from 2004 to 2006. He then became Full Professor for Bioinformatics at the University of Duisburg-Essen, Faculty of Biology. He has initiated and co-founded the BIOME core Computational Biomedicine. At the Faculty of Biology, he was elected Vice Dean of Research in 2011, and Dean in 2012.

In his research, Daniel Hoffmann develops and uses computational methods to study mechanisms of evolution at the molecular level, including viral and microbial evolution, and evolution of antibody diversity.

AXEL MOSIG received his diploma and PhD degree in Computer Science from the University of Bonn in Germany. He finished his PhD work on algebraic approaches to pattern recognition in 2004, which took him to join the University of Leipzig's Bioinformatics Department as a postdoc to work on the structure, function and evolution of noncoding RNA genes. In 2005, he joined PICB, the Partner Institute for Computational Biology of the Chinese Academy of Sciences and the German Max Planck Society, in Shanghai as a founding member. First as a postdoc and later as a principal investigator, he worked on multispectral image analysis and developed a particular interest in vibrational microscpectroscopy.

In spring 2011, he joined the Ruhr University Bochum's Department for Biology and Biotechnology, where he since leads the Bioinformatics group and is particularly involved with biomarker discovery research in the PURE initiative funded by the federal state government of North-Rhine-Westphalia in Germany.

Genetics and Cell Biology

VERENA JENDROSSEK studied Pharmacy at the University of Würzburg and Cell Biology at the Ecole Pratique des Hautes Etudes, University of Paris. From 1988 until 1992 she did her PhD studies at the University of Göttingen on the analysis of NADPH-oxidase in immune cells from patients with chronic granulomatosis. She then started focusing her research on the molecular mechanisms of stress-induced apoptosis as a postdoctoral scientist at the Department of Paediatric Oncology, University of Göttingen. In 2000 Verena moved to the University of Tübingen where she continued her work on stress-induced apoptosis at the Departments of Physiology and of Radiation Oncology where she received the *venia legendi* in Physiology in 2003. In 2007 she obtained a full professorship for Cell Biology at the University Hospital Essen, where she established the Molecular Cell Biology group at the Institute for Cell Biology (IFZ). Verena is one of the coordinators of the BIOME core Genetics and Cell Biology and directs the research training group (RTG) 1739 "Molecular determinants of the cellular radiation response and their potential for response modulation" as its speaker. The RTG 1739 is a novel German Research Foundation (DFG) funded training programme at the University of Duisburg-Essen launched in April 2012.

Verena's main research focus is the analysis of molecular mechanisms of the cellular response to chemo- and radiotherapy with a focus on the signalling pathways involved in therapy-induced cell death and associated intrinsic and microenvironment-mediated resistance mechanisms. Moreover, the molecular details of radiation-induced normal tissue damage are explored with a focus on the regulation of radiation-induced tissue inflammation and fibrosis. These studies aim at identifying novel targets for a modulation of the cellular radiation response. The promising approaches to improve treatment outcome are tested *in vitro* as well as in animal models.

HEMMO MEYER studied Human Biology and Medicine at the University of Marburg, Germany, where he also received his PhD working on the molecular cell biology of human cytomegalovirus maturation. He then moved on to work at the Imperial Cancer Research Fund in London and Yale University Medical School, USA, as a postdoctoral fellow. During this time, he became interested in a regulatory system that is governed by the p97 ATPase. His work revealed the basic principles of the system and contributed to establishing p97 as a central element of the ubiquitin-proteasome system. He then moved to ETH Zurich, Switzerland, as an independent group leader. During this time, his group revealed that p97 constitutes a novel regulatory layer in chromatin-associated processes that ensures the genomic stability of proliferating cells. In 2009, Hemmo Meyer accepted a professorial position at the Centre for Medical Biotechnology in Essen. Since August 2013, he is the speaker of the research training group 1431: "Transcription, chromatin structure and DNA repair in development and differentiation".

His goal is to tackle key questions in the molecular biology of cell cycle regulation relevant for cancer development and aging using state-of-the-art technology in an international network of collaborations. With regard to young academia, he hopes to transmit his own excitement about basic research in molecular cell biology.

PERIHAN NALBANT studied Chemistry at the Technical University Dortmund. She completed her PhD studies from 1997 until 2000 at the Max-Planck Institute for Molecular Physiology on the characterisation of sodium/phosphate co-transporters and their regulation by naturally occurring antisense mRNAs. During her postdoctoral studies at the Scripps Research Institute (La Jolla, CA, USA) she focused on the development of live-cell fluorescent biosensors to measure the activities of Rho GTPase proteins most prominently known to control the dynamics of the actin cytoskeleton. In 2007 she visited the Cardiff School of Biosciences as an independent researcher to establish fluorescence-based high-throughput screens for RNAi based pathway analyses. Perihan moved to the University of Duisburg-Essen in 2008 as a junior professor for Molecular Cell Biology up until the present.

Perihan's research is mainly focused on Rho GTPase signalling pathways controlling the dynamics of the actin cytoskeleton during cell migration and other cellular processes related to cancer cell invasion. Her group is using a multifaceted approach including fluorescent biosensors, RNAi and high-resolution live-cell imaging to dissect how the complex network of upstream regulators affects localised Rho protein signalling and how this is translated into normal as well as aberrant cell migration.

BERND GIEBEL studied Biology at the University of Cologne and received his PhD in 1996 at the Institute for Developmental Biology in Cologne. In his thesis he investigated aspects of the Notch signalling pathway during early neurogenesis of *Drosophila melanogaster*. In 1999 he moved to the Heinrich Heine University Düsseldorf and started to work with human haematopoietic stem and progenitor cells. There, he also established his research group focusing on the mechanisms which control the decision of self-renewal versus differentiation of human somatic stem cells. In 2008 he received the *venia legendi* in Molecular Medicine. In November of the same year he moved with his group to the Institute of Transfusion Medicine, University Hospital Essen where he has continued his studies on human somatic stem cells. Via the identification of two asymmetrically segregating proteins in dividing human haematopoietic stem and progenitor cells, the tetraspanins CD53 and CD63, he became interested in exososomes, small vesicles participating in intercellular communication. Currently, as a second topic, his group is establishing techniques to purify and analyse exosomes for clinical applications.

Ischaemia, Reperfusion and Angiogenesis

HERBERT DE GROOT studied Biology and Medicine at the RWTH Aachen and the University of Düsseldorf. He received his PhD in 1982 and his MD in 1987. From 1982 to 1988 he worked in Düsseldorf at the Institute of Physiological Chemistry I. This work was interrupted in 1986 by a research stay at the University of Rochester Cancer Center, New York, and completed in 1988 by receiving the *venia legendi* in Physiological Chemistry (Biochemistry). From 1989 to 1992 he served as a Heisenberg fellow leading one of the two working groups of the clinical research group "Liver Injury" at the Institute of Physiological Chemistry I and the Department of Gastroenterology, University of Düsseldorf. In this period he also spent a nine-month clinical period at the Department of General Surgery, University of Tübingen. In 1992 Herbert was offered the chair in Physiological Chemistry at the University Hospital Essen.

Herbert de Groot's research focus is on the mechanisms of cell and tissue injury, especially those induced by ischaemia (oxygen deficiency). Current projects include studies on the injury of the intestine, kidney and other organs by ischaemia and subsequent reperfusion, on tissue injury by haemorrhagic and septic shock, and on muscle injury by trauma. In addition, he is developing nano- and microcapsules for the use of artificial oxygen carriers (blood substitutes).

RABEA VERHAEGH studied Biology at the University of Cologne, where she also received her PhD in 2011 working on the role of novel transcripts on cardiomyogenesis and function of cardiomyocytes in zebrafish and murine embryonic stem cells. From 2011 until 2012 she worked there as a postdoctoral fellow. In 2012 Rabea Verhaegh started to focus her research on mechanisms of cell and tissue injury as a postdoctoral scientist at the University Hospital Essen, where she is still working as a group leader and research associate at the Institute of Physiological Chemistry.

Rabea Verhaegh's research focus is on the tissue ischaemia/reperfusion injury, e.g., of the small intestine as well as under conditions such as haemorrhagic shock. In addition, current projects include studies on muscle injury by trauma. The aim is a better insight into pathobiochemistry, pathophysiology, diagnostics and treatment. Based on clinically relevant and well-controlled animal models, the consequences of tissue ischaemia/reperfusion, mechanistic aspects, diagnostic parameters and therapeutic/protective strategies are being studied.

DIRK M. HERMANN studied Medicine at the Justus Liebig University Gießen, where he received his MD in 1995. He worked in Munich at the Max Planck Institute of Psychiatry from 1994 to 1995 and in Cologne at the Max Planck Institute for Neurological Research from 1995 to 1998. From 1998 to 2001, Dirk Hermann received his clinical training as a neurologist at the Eberhard Karls University Tübingen, where he obtained his neurology specialisation in 2001 and his state doctorate in 2002. Following a position as a senior consulting neurologist (*Oberarzt*) at the University Hospital Zurich (Switzerland) from 2002 to 2008, he is the Chair for Vascular Neurology and Dementia at the University Hospital Essen since 2008.
Dirk Hermann's research focus is the pathophysiology and therapy of brain injury, with a strong emphasis on post-ischaemic brain remodelling following exposure to risk factors and during ageing. Current experimental projects include studies on blood-brain barrier integrity, neuronal plasticity and angiogenesis using *in vitro* and *in vivo* models of stroke and neurodegeneration. Clinical projects evaluate risk factors contributing to cognitive impairment under conditions of ischaemia, neurodegeneration and ageing.

ANJA BIENHOLZ studied Medicine at the Ruhr University Bochum from 2003-2009. She received her Dr. med. for conducting genetic association studies on idiopathic sudden hearing loss in 2010. Since January 2010 Anja Bienholz has been working as a research fellow and clinical doctor at the Department of Nephrology, University of Duisburg-Essen. This work was interrupted in 2011 by a research stay at Ann Arbor's laboratory, University of Michigan, USA, supported by a grant of the Dr. Werner Jackstädt Foundation.

Anja Bienholz`s research focus is on acute kidney injury focusing on mechanisms of cell and tissue damage following ischaemia and reperfusion including settings involving allogenic organ transplantation (kidney, liver).

Current projects include studies on mitochondrial damage in isolated proximal tubular cells following ischaemia and reperfusion as well as cold storage, and on renal and systemic effects following isolated kidney ischaemia and haemorrhagic shock *in vivo*.

Besides her clinical and research work, Anja is actively involved in organising and managing various educational training programmes.

Transplantation Medicine

URSULA RAUEN studied Medicine in Düsseldorf and in Aberdeen, Scotland, from 1984 until 1991. She did her internship (AiP) in Tübingen (Department of General Surgery, Eberhard Karls University) in 1991/92 and received her MD in 1993 (Heinrich Heine University Düsseldorf) with a thesis on the preservation injury of liver endothelial cells. From 1993 until 2008 she worked as a group leader at the Institute of Physiological Chemistry, University Hospital Essen, where she focused her research on the mechanisms of cold-induced cell injury and the prevention of preservation injury. She received the *venia legendi* in Physiological Chemistry in 2000 with a thesis on cold-induced apoptosis. Since 2008 she is the professor of Physiological Chemistry at the Medical Faculty of the University of Duisburg-Essen and, from 2008-2011, she was a research coordinator of the DFG-funded clinical research unit "Optimisation of Living-Related Liver Transplantation" (KFO 117).

Current research interests focus further on the intracellular mechanisms of cold-induced cell and tissue injury and the mechanisms of preservation and cryopreservation injury. New mechanistical insights have already led to the development of a new cardioplegic/organ preservation solution (currently in its first clinical studies), a vascular preservation solution (approved for clinical use) and a solution for the hypothermic storage of cells for experimental uses. A better understanding of the molecular mechanisms leading to injury or compromising post-storage function is aimed at to provide a basis for the further refinement of the methods for the transport and storage of cells and tissues for clinical (and experimental) purposes.

Ursula Rauen is also a speaker of the ELAN programme established for medical students in 2012.

MONIKA LINDEMANN studied Medicine at the then University of Essen until 1994. From 1990 until 1992 she did the experimental part of her doctoral thesis at the Institute of Immunology and, from 1994 until 1995, at the Clinic for Internal Medicine (Endocrinology and Nephrology), both at the University Hospital Essen. In 1996 she completed her doctoral thesis on the molecular analysis of tumour necrosis factor gene loci in humans and, thereafter, worked as a research assistant at the Institute of Immunology in Essen. She rotated between Medical Microbiology, Virology and Clinical Chemistry from 1996 until 2001. Since 2001 she is a specialist in Laboratory Medicine. In 1996 she started to focus her research on cellular immunity in immunocompromised patients and, since 1998, she has been working as the group leader of Cellular Immunity. In 2006 Monika Lindemann received the *venia legendi* in Immunology. Since 2009 she has continued her research at the Institute of Transfusion Medicine in Essen where she is currently also a lecturer. In the German Society for Immunogenetics (DGI), Monika Lindemann has been a member of the educational committee since 2005, a board member since 2009 and chairman of the examination board since 2012. In 2012 she was appointed as a professor. She has received the following specialist training qualifications: Laboratory Medicine (Ärztekammer, 2004), Immunogenentics (DGI, 2006) and Immunology (German Society for Immunology, DGfI, 2011), Transplantation Immunology (European Federation for Immunogenetics (2013) Monika Lindemann's main research focus is on transplantation medicine and T cell immunity. She is especially interested in immune transfer via transplantation, cellular vaccination responses in transplant recipients, immune reconstitution after transplantation and *in vitro* markers of rejection.

OLIVER WITZKE studied Medicine at the University Hospital Essen, receiving his medical doctorate in 1996. From 1997 until 1999 he conducted research at the Nuffield Department of Surgery, Transplant Immunology, University of Oxford on tolerance induction after organ transplantation. Back in Germany, from 2000 until 2003, Oliver worked as a researcher at the University Hospital Essen while earning a specialist qualification in internal medicine. In September 2003 he became the senior physician at the Clinic for Renal and Hypertension Diseases in Essen. A further specialist qualification in nephrology was acquired in 2004, followed by the *venia legendi* in Internal Medicine in 2005 with a thesis on the mechanisms of T cell immune tolerance and T cell immune deficiency. In 2006 Oliver was appointed head of the Outpatients' Clinic for Nephrology and Transplantation and, a year later, the deputy medical director of the Clinic for Nephrology, University Hospital Essen. Between 2006 and 2010 Oliver Witzke increased his expertise in the area of infectiology and became increasingly involved in Eurotransplant through the German Transplantation Society (DTG). Since 2011 Oliver is the head of the section for Clinical Infectiology at the University Hospital Essen and was an initiator of the West German Centre for Infectious Diseases established in June 2013 as the central coordinating institution for all clinical and scientific areas of infectious disease.

Oliver's main research interests are transplantation immunology and infectiology as well as T cell function under immunosuppression.

KATHARINA FLEISCHHAUER studied Medicine at the University of Bonn from 1982 to 1988 and received her doctorate with a thesis on the immune response to *Toxoplasma gondii*. From 1988 to 1992 she worked as a postdoctoral fellow at the Memorial Sloan Kettering Cancer Center in New York, where she got acquainted with the immunobiology of haematopoietic stem cell transplantation, also known as bone marrow transplantation, a procedure that since then has become a standard treatment of patients with genetic and malignant disorders of the blood system. Katharina was involved in the first pioneer studies exploring the functional role of donor-recipient mismatches for human leukocyte antigen (HLA) molecules in the clinical outcome of haematopoietic stem cell transplantation, as well as in the development of the first protocols of molecular HLA typing. In 1992, she transferred this expertise to Italy where she joined the Laboratory of Experimental Haematology at the San Raffaele Hospital in Milan to work as research fellow in tumour immunology, and to implement molecular typing techniques in the HLA diagnostics laboratory. In 2002, Katharina became director of the San Raffaele HLA Tissue Typing Laboratory and Italian Commissioner for Accreditation of HLA Laboratories by the European Federation of Immunogenetics (EFI). After the seminal discovery of HLA haplotype loss as mechanism of immune escape by leukaemia relapsing after haematopoietic stem cell transplantation, she became head of the Unit of Molecular and Functional Immunogenetics of the San Raffaele Hospital as off 2010. Since January 2011, she has been Reviews Editor for the journal Tissue Antigens, and in May 2013 she was elected chair of the Scientific Committee of EFI. In October 2013, Katharina was appointed Full Professor and Director of the newly created Institute for Experimental Cellular Therapy at the University of Duisburg-Essen.

Katharina´s scientific interests are focused on translational research aimed at unravelling the biological mechanisms underlying the clinical success or failure of transplantation, with particular regards to haematopoietic stem cell transplantation. This includes the characterisation of cellular and humoral alloreactivity and its role in transplantation, as well as the molecular and functional polymorphism of the HLA system and immune-related genes.

Tumour and Signalling

ALEXANDRA GELLHAUS studied Biology at the Carl von Ossietzky University of Oldenburg. From 1999 until 2003 she did her PhD at the Institute of Anatomy at the University Hospital Essen, investigating the effect of different gap junction channels on the proliferation and invasion capacity of malignant trophoblast cells. In 2003 Alexandra Gellhaus continued her work as a postdoctoral scientist in the Institute of Anatomy and focused her research on the regulation of CCN family proteins and connexins in human trophoblast proliferation and invasion behaviour. She works in close collaboration with the Department of Gynaecology on the pathomechanisms of preeclampsia, a pregnancy disease which is characterised by intrauterine growth restriction and preterm birth. After two breaks (2007-2008 and 2010-2011) during which she was on maternity leave, she continued her work as a postdoctoral researcher and, in 2008, moved to the Institute of Molecular Biology in Essen. At the end of 2013 she changed to the Department of Gynaecology and Obstetrics where she focused on changed gene patterns in pregnancy diseases until present. In 2012 Alexandra Gellhaus finished her *venia legendi* for Molecular Biology.

Alexandra's main research focus is the regulation of trophoblast proliferation and invasion processes which are indispensable for proper placenta and embryo development. Furthermore, she is interested in the identification of deregulated placental genes in preeclampsia which is associated with impaired trophoblast invasion and often results in intrauterine growth restriction. Meanwhile, it has become clear that this in turn seems to programme coronary heart disease and hypertension in adults. She could show that CCN3, a matricellular protein which is expressed in the trophoblast and in placental endothelial cells, is deregulated in preeclampsia and might be associated with the deficient trophoblast invasion. In addition, she identified the CCN3 dependent signalling pathways regulating trophoblast proliferation and invasion.

JOACHIM GÖTHERT studied Medicine at the Universities of Bochum, Hamburg, Lübeck, London (University College, UK) and Yale (New Haven, CT, USA). He obtained his medical doctorate by studying the function of immune cells in preterm infants from 1996 until 1998 at the Institute of Immunology and Transfusion Medicine, Medical University Lübeck. From 1998 until 2000 he started his medical training as a resident physician at the Department of Haematology and Oncology, University Hospital Hamburg. In 2000 he commenced his postdoctoral training as a scholar of the German Research Foundation (DFG) at the Cancer Biology Division (Institute for Child Health Research) in Perth, Australia. The focus of his research was studying normal and malignant haematopoietic development in genetically modified mouse models. From 2002 until 2003 he continued his studies at the same Australian institution as a senior research fellow. In 2004 he returned to Germany and started his own research group at the Department of Haematology, University Hospital Essen. In 2008 he was awarded a junior research group grant from the Stem Cell Network of North Rhine Westphalia. In 2009 he completed his specialised training in internal medicine.

The main focus of his research is on the molecular regulation of normal blood development as well as genetic events leading to the development of leukaemia. Amongst other findings he demonstrated in genetic studies that adult bone marrow stem cells are primarily of foetal origin.

HANNES KLUMP is a principal investigator and physician at the Institute for Transfusion Medicine, University Hospital Essen. He received his diploma (equivalent to an MSc degree) and PhD in Genetics from the University of Vienna for his studies on picornaviral proteinases. From 1998 until 2003 he worked as a postdoctoral fellow at the Heinrich Pette Institute for Experimental Virology and Immunology in Hamburg. His studies focused on the development of a novel, picornaviral 2A-esterase based co-expression system for retroviral gene therapy vectors and the *in vitro* development and expansion of haematopoietic stem and progenitor cells (HSPCs) mediated by ectopic expression of the homeodomain transcription factor HOXB4. From 2004 until 2008, he pursued and extended his work on these topics in the Department of Experimental Haematology at Hannover Medical School (MHH) where he became a group leader within the cluster of excellence "REBIRTH" (JRG Differentiation). After receiving his medical degree at MHH in 2008 he moved to the Institute of Transfusion Medicine in Essen. Since then, his laboratory has continued to work on the *in vitro* development and expansion of HSPCs from pluripotent embryonic stem cells and the molecular mechanisms underlying the stem cell supporting activities of HOXB4. Furthermore, he initiated work on the reprogramming of mouse, marmoset and human cells back to the pluripotent state as a starting point for studies on autologous somatic gene and cell therapy of the haematopoietic system.

LAURA STEENPASS studied Biology at the Albert-Ludwigs University in Freiburg im Breisgau. From 1999 to 2002 she did her PhD thesis at the Children's Cancer Research Institute (CCRI) at the St. Anna Kinderspital in Vienna, focusing on protein-protein interactions of the oncogenic fusion protein EWS-Fli1. Switching from proteins to non-coding RNAs and their role in the regulation of genomic imprinting, she did her postdoc work in the lab of Denise P. Barlow at the Center for Molecular Medicine (CeMM) of the Austrian Academy of Sciences in Vienna. Laura developed an ES cell based *in vitro* differentiation system to study mechanisms at the murine imprinted gene locus Igf2r/Airn. Genomic imprinting is the reason why mammals need a maternal and a paternal genome for proper development. Imprinted genes are marked by DNA methylation in the germ line of one of the two sexes but not the other, resulting in parent-of-origin dependent gene expression. After her maternity leave from 2006 to June 2008 she started working part-time in the lab of Prof. Arndt Borkhardt at the Department of Paediatric Oncology, Haematology and Clinical Immunology at the Heinrich Heine University Düsseldorf, supporting a project dealing with micro RNAs in leukaemia. Coming back to the fascinating theme of genomic imprinting, she joined the Institute of Human Genetics at the University Hospital Essen in October 2009, which has a long standing expertise in diagnostics and research on imprinting diseases.

Currently Laura is studying the mechanism of imprinting of the retinoblastoma gene 1 (RB1) and of the UBE3A gene using murine embryonic stem (ES) cells and human induced pluripotent stem cells. For RB1 imprinting targeted ES cells were used to generate knock-in mice, which are currently under study. Defects of the UBE3A gene copy inherited from the mother lead to the Angelman syndrome (AS), with patients presenting an absence of speech, ataxia and a happy demeanor. Laura's studies focus on the role of a paternally expressed long non-coding RNA which epigenetically silences UBE3A on the paternal allele. She received funding for her projects from the DFG and the intramural IFORES Collaborative Research Centre (*Sonderforschungsprogramm*) of the University Hospital Essen (together with Hannes Klump).

RTG 1431: Gene Transcription

HEMMO MEYER

Please refer to the "Genetics and Cell Biology" section for this biography.

RTG 1739: Radiation Sciences

VERENA JENDROSSEK

Please refer to the "Genetics and Cell Biology" section for this biography.

RTG 1949: Innate and Adaptive Immunity

JÖRG TIMM studied Medicine at the University of Münster from 1992 until 1994 and at the University of Bonn from 1994 until 1999. In Bonn he also finished his MD thesis as a scholar of the research training group "Pathogenesis of Diseases of the Nervous System" at the Institute of Pharmacology and Toxicology in Bonn. In 2002, Jörg started as a clinical fellow at the Ruhr University Bochum (Knappschaftskrankenhaus Bochum) in the Department of Gastroenterology and Hepatology and went on to work as a research fellow at the Partners AIDS Research Center at the Massachusetts General Hospital/Harvard Medical School in Boston, USA. In Boston Jörg began to work on the impact of CD8 T cell immunity on the evolution of the hepatitis C virus. After he returned to Germany in 2005, he established a research group on the immunology of viral hepatitis at the Institute of Virology, University Hospital Essen. In 2010, he obtained the *venia legendi* in Virology from the Medical Faculty of the University of Duisburg-Essen and was appointed as an associate professor for virology in 2011. Since 2007, he has been involved in the research training group 1045 and, since 2009, in the German-Chinese Transregio 60 as a principal investigator. In a collaborative effort between the Universities or Duisburg-Essen, Düsseldorf and Bochum Jörg coordinated as the main speaker an application for a novel research training group 1949 with a focus on the regulation between innate and adaptive immunity in infectious diseases. Funding was approved for the research training group by the German Research Foundation in 2013, and the research programme will start in April 2014.

Jörg's research focuses on cellular immunity against human hepatitis viruses and the implications of viral sequence diversity for immune control and vaccine development. He is also interested in viral evolution and the mechanisms of positive and negative selection of viral sequence polymorphisms in the context of the host immune response.

A BIOME Farewell

ELKE WINTERHAGER studied Biology at the RWTH Aachen, Germany, and did her PhD studies in the field of vision research at the Research Centre Jülich. From 1980 she started working as a postdoctoral researcher at the Department of Anatomy, RWTH Aachen, where she focused on membrane biology in the field of reproductive biology and received her *venia legendi* in Anatomy in 1986. In 1986 Elke took over the position of a study director and head of Department of Reproductive Toxicology at the company Grünenthal, Aachen.

In 1990 she moved to the University of Duisburg-Essen's University Hospital as a professor in Anatomy and Embryology and switched to the Institute of Molecular Biology in 2008. Her main research focus is on the cell biology of the endometrium during embryo implantation, embryonic signalling during implantation and hormonal regulation of endometrial genes. Towards the end of her research career, she focused on placental function and development in mice and humans. Besides using several knockout and transgenic mouse models, she also used trophoblast stem cells as a model for the regulation of trophoblast lineage development. Her main interest was deciphering the role of direct cell-cell communication via connexion channels for this process. In close collaboration with the Department of Gynaecology she worked on the pathomechanisms of preeclampsia. In May 2004 she became a reviewer on the DFG board for the study section "Molecular Biology".

Besides her research work, Elke held different political positions: from 1996 to 2000 she was Vice President for Research of the University of Duisburg-Essen and from 2001 to 2003 Associate Dean for Research at the Medical Faculty of the University of Duisburg-Essen.

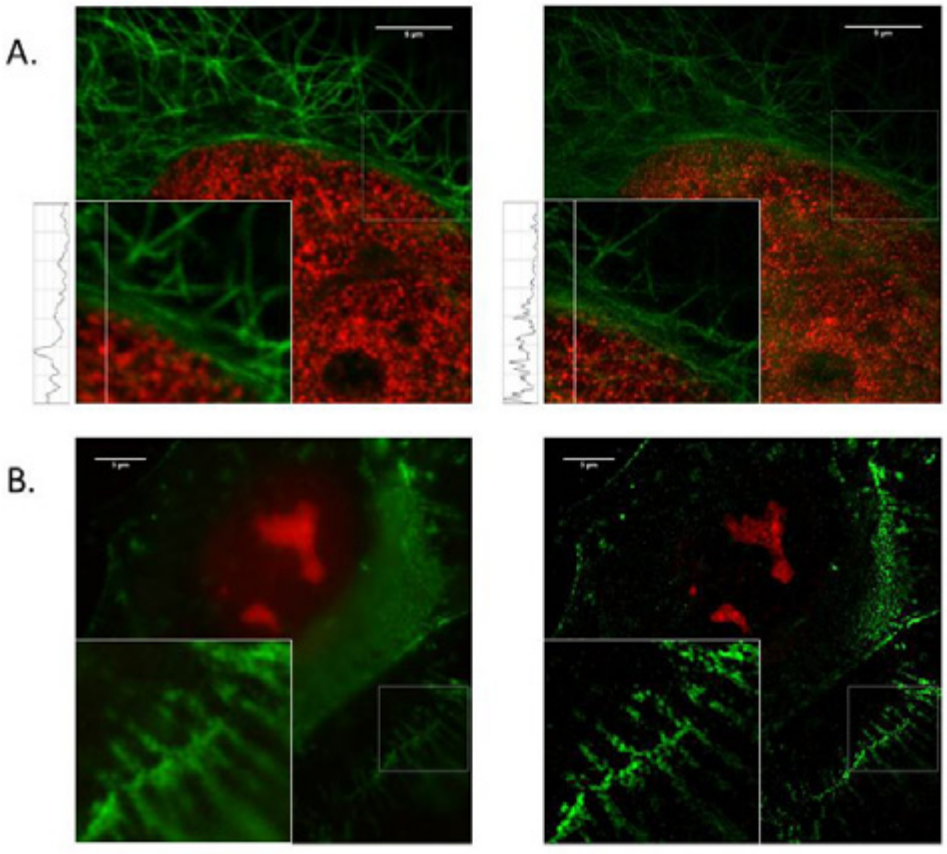
On the eve of her retirement, BIOME paid tribute to Elke Winterhager for her unfailing support, inspiration and input as a scientific coordinator of the core Tumour and Signalling. Prof. Winterhager's dedication and commitment have contributed greatly towards the success of the graduate school since its establishment in 2010. Amongst other things, she initiated the clinical grand rounds.

To strengthen research on reproduction biology in Germany and to further young researchers in this field, she initiated and organised the International Conferences on the Female Reproductive Tract seven times. In honour of her retirement, the 7th International Conference on the Female Reproductive Tract was held for the first time at the medical campus of the University of Duisburg-Essen on 6 July 2013. The focus of this particular conference was on hormone-dependent disease of the cervix and ovaries as well as placental and foetal programming.

Happily, since her retirement from active research in July 2013, Elke is still a figure contributing towards academic life. She is currently a manager for electron microscopy at the newly-established Imaging Center Essen at the University of Duisburg-Essen's University Hospital.

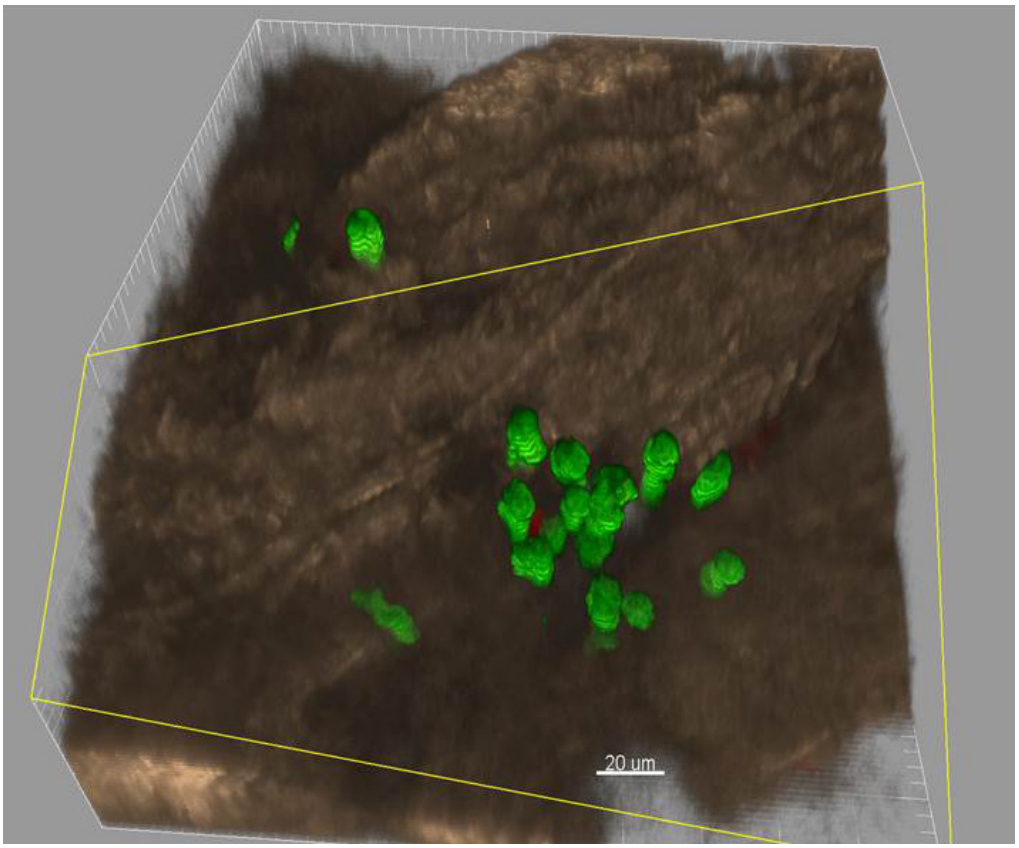
IMCES - Imaging Center Essen: Advanced Imaging Possibilities

Over the past twenty years there have been great advances in light microscopy, both in terms of improvements in imaging instrumentation as well as the development of radical new imaging approaches and techniques. These advances together with an ever increasing array of new molecular probes, such as genetically expressible fluorescent proteins, and the sophisticated manipulation of cells and organisms using modern genetic techniques has helped drive a revolution in modern biology. In particular the need to study not just the spatial organisation but also the temporal dynamics of living systems from the molecular scale upwards has resulted in an increasing need for more quantitative imaging and analysis, which in turn has driven the development of more sophisticated imaging instrumentation capable of acquiring multi-dimensional data sets that include time, as well as additional properties of light such as spectral properties, fluorescence lifetime or polarisation. The Imaging Center Essen (IMCES) is a recently established core imaging facility housed within the Institute for Experimental Immunology and Imaging, and located both at the Medizinisches Forschungszentrum (MFZ) at the Universitätsklinikum Essen and at the Zentrum für Medizinische Biotechnologie (ZMB) at the University of Duisburg-Essen. As director, the imaging center was established by Prof. Matthias Gunzer with the aim of bringing such state-of-the art imaging platforms and the latest imaging know-how to the local research community. As well as training and supporting researchers and medics in the use of such instruments, IMCES also aims to provide information and instruction in imaging techniques, as well as image processing, reconstruction and analysis, either on an individual basis or through the organisation of workshops and symposiums. IMCES currently houses 11 imaging platforms in 170 m^2 of dedicated lab space operating with S2 safety permission, providing a broad range of imaging services and catering for a diverse range of imaging requirements, from whole animal preclinical studies to the imaging of cellular ultrastructure by electron microscopy. In particular, with substantial funds from a DFG infrastructure grant the



A. Example of 2 Colour super resolution by STED confocal imaging acquired with a Leica SP5 white light gSTED platform. Fixed cell sample with Tubulin-V500 (green) and Histone3-Chromeo505 (red) antibody labeling. Both the conventional confocal (left) and gSTED (right) are shown for comparison.

B. Example of 2 Colour super resolution by widefield SIM imaging acquired with an Elyra PS.1 and LSM780 confocal platform. Fixed cell sample with DAPI nuclear staining (red) and Alexa488 labelled antibody against CarcinoEmbryonic-Antigen-related Cell Adhesion Molecule 1 (CEACAM1). Both the conventional widefield (left) and reconstructed SIM image (right) are shown for comparison. Sample provided courtesy of Dr. Nico Ullrich, Dermatology, University Hospital Essen



Intra vital two photon excitation microscopy of a mouse femur. Image shows two photon second harmonic generation (SHG) of bone (brown), vascular staining with Alexa594 labeled tomato lectin (red) and neutrophil granulocytes with GFP (Lys-EGFP, green).

Sample supplied courtesy of Anja Hasenberg and Anika Klingberg,

imaging center has recently installed cutting edge imaging platforms providing superresolution microscopy, high resolution intravital imaging by two photon microscopy, and a modern high speed FACS cell sorter.

Superresolution microscopy encompasses a range of new and revolutionary fluorescence imaging techniques designed to surpass the classical diffraction limit which prevents the imaging of structures smaller than half the wave length of light (~200 nm) in the light microscope. In general, three classes of superresolution techniques have become commercially available in the last 5-6 years. Structured Illumination Microscopy (SIM), providing a twofold improvement in resolution (~100 nm), Stimulated Emission Depletion (STED) microscopy with the capability to image structures down to 50 nm, and single molecule localisation methods such as Photoactivated Localisation Microscopy (PALM) and Stochastic Optical Reconstruction Microscopy (STORM), which with 20 nm resolution offer a tenfold improvement over conventional light microscopes, going some way towards bridging the resolution gap between light and the electron microscopy (<1.5 nm). With the recently installed Zeiss ELYRA PS.1 imaging platform and the Leica SP8 gSTED confocal, all the superresolution techniques are available at IMCES and examples of images acquired by SIM and STED are shown in Figure 1. Another imaging revolution has been in the area of high resolution intravital imaging by 2 photon microscopy. The use of pulsed infrared laser excitation sources in 2 Photon microscopy enables deeper tissue imaging with reduced fluorescence bleaching (and thus toxicity) and more efficient fluorescence detection than can be achieved with a conventional confocal microscope. Thus the 2 photon microscope is particularly well suited for cellular imaging up to several hundred microns deep into the organ tissue of living animals, enabling the dynamic behaviour of cells to be observed under the near physiological conditions of the living organism. A Leica SP8 MP microscope set up for intravital imaging in mouse models is now available at the IMCES ZMB site and an example of intravital imaging can be seen in Figure 2.

Stiftung Universitätsmedizin Essen

Fostering health together – going beyond basic medicial care in research, training and patient care

In 2006, Germany's first foundation to be created jointly by a university hospital and a medical faculty was chartered – the Stiftung Universitätsmedizin Essen. And for the first time this university foundation was launched by professors – both conceptually and financially. Since then, the foundation finances important projects with little or no public funding in the areas of research, training and patient care at Universitätsklinikum Essen.

Funded projects for patients
Projects in patient care financed by the foundation include art therapy for cancer patients, visits of clowns in the paediatric clinic, an internet project connecting isolated children to their families, friends and school classes as well as patient-centered care for premature infants in their home environment. The foundation also assists in the acquisition of urgently-needed medical equipment e.g. for children with hearing disabilities.

StiftungUniversitätsmedizinEssen

www.universitaetsmedizin.de

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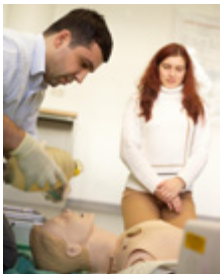

Funding of student training
Also students stand to profit from the foundation's initiatives. Thus, every year 14 eligible medical students are granted study bursaries. In addition, to support clinical training in a practical and contextual manner, the foundation funds the patient-simulation progamme as well as the "Skills Lab" training centre. Furthermore, a number of diverse smaller projects are funded which help to make students' lives easier.

Funding of research projects
The foundation focuses on important aspects in the field of research. Research on dementia disorders, the risk factors influencing premature birth as well as the side-effects of cancer therapy on child bone health is supported amongst other things.

Within the framework of the Medical Prize Awards 2013 the foundation has started awarding innovative research projects with start-up funding for two years to the sum of € 100 000. Short films introducing these projects can be viewed under the following link:
www.universitaetsmedizin.de/medizinpreis.php

In its support of the Graduate School of Biomedical Science which amounts to € 15 000 to date, the Stiftung Universitätsmedizin Essen would like to express how worthy it believes the BIOME idea is: the doctoral school brings young and experienced researchers together at an interdisciplinary level where they may enjoy an excellent and internationally-directed academic education.

It is of particular importance to the foundation to be able to continue contributing towards such innovative ideas and projects in research, training and patient care at the University Hospital Essen. In order to keep up its good work, the foundation is extremely dependent on external donations.

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- Stiftung Universitätsmedizin Essen, University Hospital Essen, University of Duisburg-Essen
- Kulturstiftung Essen
- International Research Universities Network (IRUN)
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- Werkstatt Wissenschaftskarriere
- West German Tumour Centre
- Mediment Programme

We would also like to express our sincere thanks to all those various colleagues at the University of Duisburg-Essen and the European partner universities and research centres who have collaborated with us with refreshing willingness and drive to make shared visions and projects work.

Credits

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biome [bī-ōm] *n.* a collective term used to describe a distinctive regional biotic community; an acronym for the Graduate School of Biomedical Science at the University of Duisburg-Essen established in 2010, an academic association offering state of the art doctoral training to young scientists, the heritage of a recent innovative research renaissance in the Ruhr region.

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