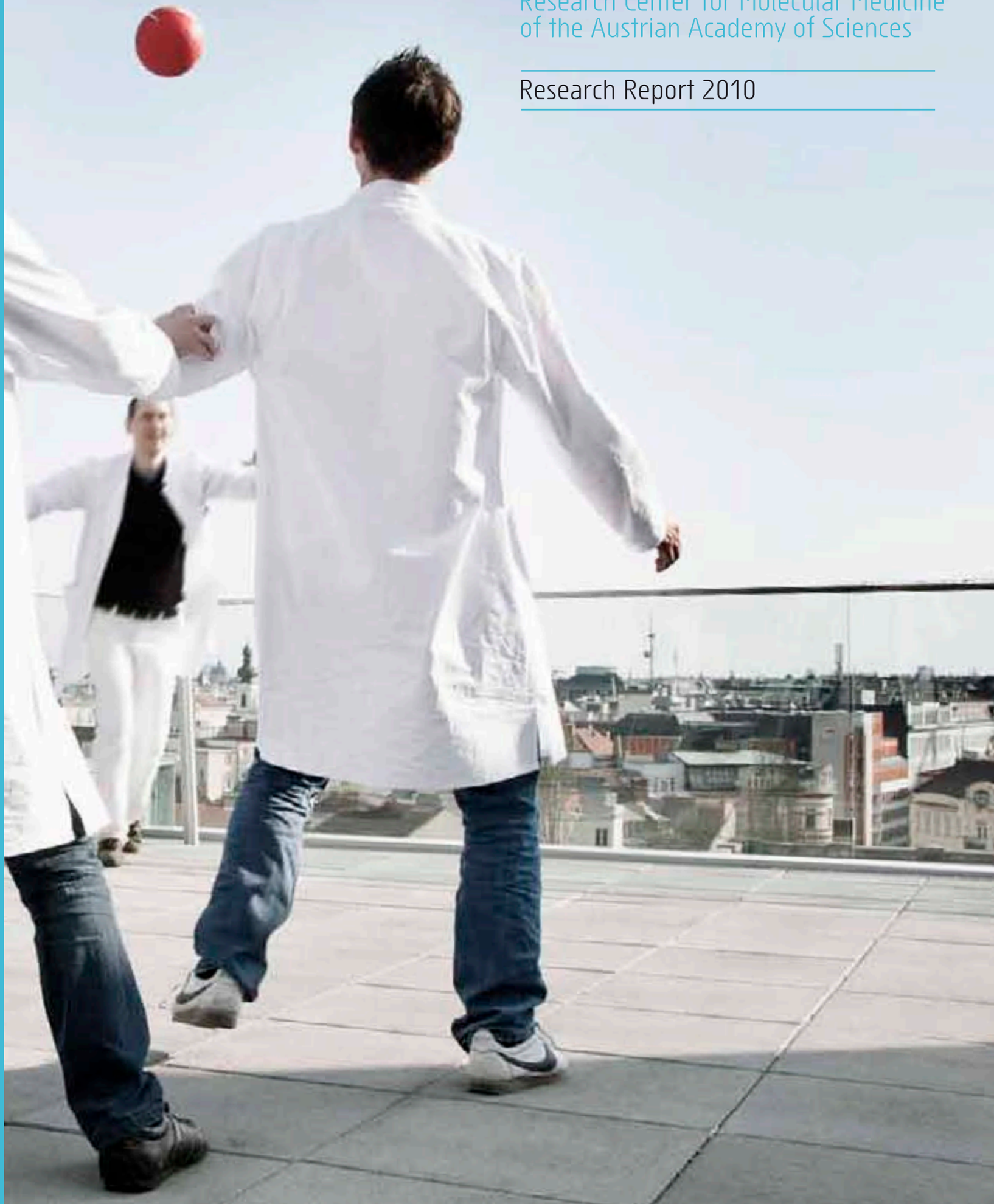
Ce–M–M–

Research Center for Molecular Medicine
of the Austrian Academy of Sciences

Research Report 2010



Ce–M–M– Research Report 2010

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Previous page:
Level 04, Room 04.205
Functional Genomics

Each and every CeMM member is crammed into one laboratory to symbolize many functions and talents superimposed and also to remember the crowded times in the Vienna Competence Center laboratories located in Lazarettgasse 19, where CeMM HQ were located until August 2010.

CeMM Research Report 2010

Introduction by Giulio Superti-Furga

Last year I began the introduction to the 2009 research report with "What a year!". So how then do I describe 2010: a period that saw CeMM finally move into and occupy a tailor-made beautiful building in the middle of the country's medical action? Finally all scattered CeMM research groups have come together under one roof! Apart from the minor upheaval of the actual move, a logistical challenge per se, and the difficulties associated with jump-starting the infrastructure necessary to serve a demanding community of hard-working researchers, what an exhilarating and up-lifting year 2010 has been! Jokingly, we said that the five years preceding the move were our "purgatory" years, testing our fitness and worthiness of the upgrade to first-class. Now that we can stand on our own terrace on the 8th floor, with views of not only the medical campus but the entire city, below us a stunning work of art in the form of a gigantic glass façade and above us, on a bright day, only some scattered fluffy clouds, we get paradisiacal emotions.

The building is full of light, due to the large windows and the "transparent" architecture of its creator, Ernst Kopper. Depending on the weather, the beautiful façade reflects sky, clouds, surrounding trees and buildings in a different way, interweaving it with its own pattern and inside illumination, leading to an attractive ever-changing appearance. When we come to work each morning, we still feel a bit incredulous that CeMM has such a superb home. The work of art by Peter Kogler, who designed the façade, immediately gained a lot of fans, not only among the fifty plus sponsors who each contributed to a "section" and whom I would like to thank here again, but also among students, campus visitors and even construction workers. Here is an example for illustration: on the day the last façade piece was put into place, the artist and I visited the building, which was at that time unfinished, with only concrete floors. We met a woman working on the first floor tiles in a room close to the façade window and asked her sceptically what it was all about. Not knowing who we were, she expressed her views frankly and produced a spontaneous, funny and charming approval. We knew then it was going to be a success.

The celebration of the opening of the façade in February set off the year magnificently. We had the honour of the presence of Minister Beatrix Karl in one of the first events she had attended since taking up office, and holding on to a nice glass of sparkling wine, despite the cold, everybody gladly drank with her to the new era that the event seemed to herald. During the week in July when the first people began to move into the new building, we welcomed scientifically curious and very supportive Federal President Heinz Fischer and his wife Margaret Fischer. It might easily have been the sunniest day of the year, as the photographs remind us, and in many respects the visit represented a particularly memorable and symbolic start of our newly accommodated research activities. Once these activities picked up pace, our main supporter and privileged partner, Minister Beatrix Karl, visited us again, this time inside the building. We discussed the research program and societal mission of CeMM and, importantly, inaugurated the laboratory ironically named PLACEBO (Platform Austria for Chemical Biology), the gateway to some of our translational activities. Stefan Kubicek, from Stuart Schreiber's laboratory at the Broad Institute of Harvard University/MIT, had just joined CeMM to head PLACEBO. Two events in the second half of the year characterize the outreach part of CeMM's mission. In October the fine-looking lecture hall on the 8th floor housed the first Constantin Spiegelfeld Lecture on drug discovery and development with all its technical, commercial and public health implications. George Poste, a towering figure in the field, inaugurated the lecture series with a "big bang" sort of talk that created a lot of resonance. In December we had the CeMM Science Day where research projects in the institute were presented to the public. The event was attended by the President of the Austrian Academy of Sciences and was very well received so we plan to repeat it annually. The Karl Landsteiner lecture, presented by the Howard Hughes Medical Institute Investigator Helen Hobbs in the great hall of the Academy building, was once again a resounding success.

An important milestone in 2010 was the graduation of the first wave of CeMM PhD students (Roland Jäger, Ana Zivkovic and Irena Vlatkovic) as well as the start of our third PhD programme. Also, we are exceptionally proud that Post-doctoral fellow Oliver Hantschel, from my own group, accepted a position as Assistant Professor in a new department headed by the American molecular cancer research pioneer Doug Hanahan, which is affiliated with the cancer research foundation at the Swiss Federal Institute of Technology (École Polytechnique Fédérale De Lausanne, EPFL) in Lausanne.

Thus, CeMM trains young researchers that are competitive at the highest international level! In return, 2011 will see the beginning of three new CeMM Principal Investigators (PIs): Kaan Boztug, from the University of Hannover Medical School, Joanna Loizou, from Cancer Research UK in London and Andreas Bergthaler, from the Institute of Systems Biology in Seattle. While this will not yet fill the new building entirely, it will bring additional life to the 6th and 7th floors and represent a phenomenal boost to CeMM research activities and competencies. We are also very happy to have secured as CeMM Adjunct Principal Investigator Thijn Brummelkamp, who in 2011 will join the Netherlands Cancer Institute from the Whitehead Institute of Biomedical Research in Cambridge, USA. At CeMM, Thijn will co-tutor PhD students and research projects.

Having our own building has also importantly increased our laboratory support facilities such as health and safety and administration (finances and public relations). Moreover, in many respects we have simply become better organized. Denise Barlow, a CeMM PI, has done a wonderful job in starting a regular and exciting seminar series (called CeMM-inars), weekly faculty lunches and, together with Eva Schweng, is also supervising common get-togethers and seminars with the adjacent Center for Translational Medicine in the Anna Spiegel building of the Medical University of Vienna. The enthusiasm and good will of Medical University of Vienna Vice-Rector Oswald Wagner and colleague Hans Wojta were critical for creating an inclusive and collaborative spirit between us. Mischa Pilz and his IT team have set up large flat screens in the entrance hall on the 3rd and 8th floors to advertise all events. I take the occasion to welcome and thank everybody, especially Gabriel O'Riordain. That we are getting better organized also became apparent on the occasion of a few social events that surprised us on account of the creativity and intensity that accompanied them. After a lukewarm after-barbeque party in the summer I had frankly wondered if CeMM, as a group, would be able to party at all. I was soon proven to be completely wrong by a phantasmagorical Halloween party organized by the CeMM PhD students, who decorated the building and themselves, as well as the entire CeMM community. Scientific advisory board (SAB) member Hidde Ploegh, of the Whitehead Institute in the USA, happened to be in town and willingly dropped by, and was immediately "transylvanized" and completely drawn into the party action. He left enthusiastic: "It was incredible, all SAB members should have experienced this!".

An even larger party, enlarged to include partners and families, was the Christmas get-together, with games, performances and the exchange of presents from a large potluck heap. I am deeply thankful to all the people who contributed to make CeMM a work hard/party hard place within such a short time, for this is a critical requisite of all successful research institutions I have experienced. So, how about our output?

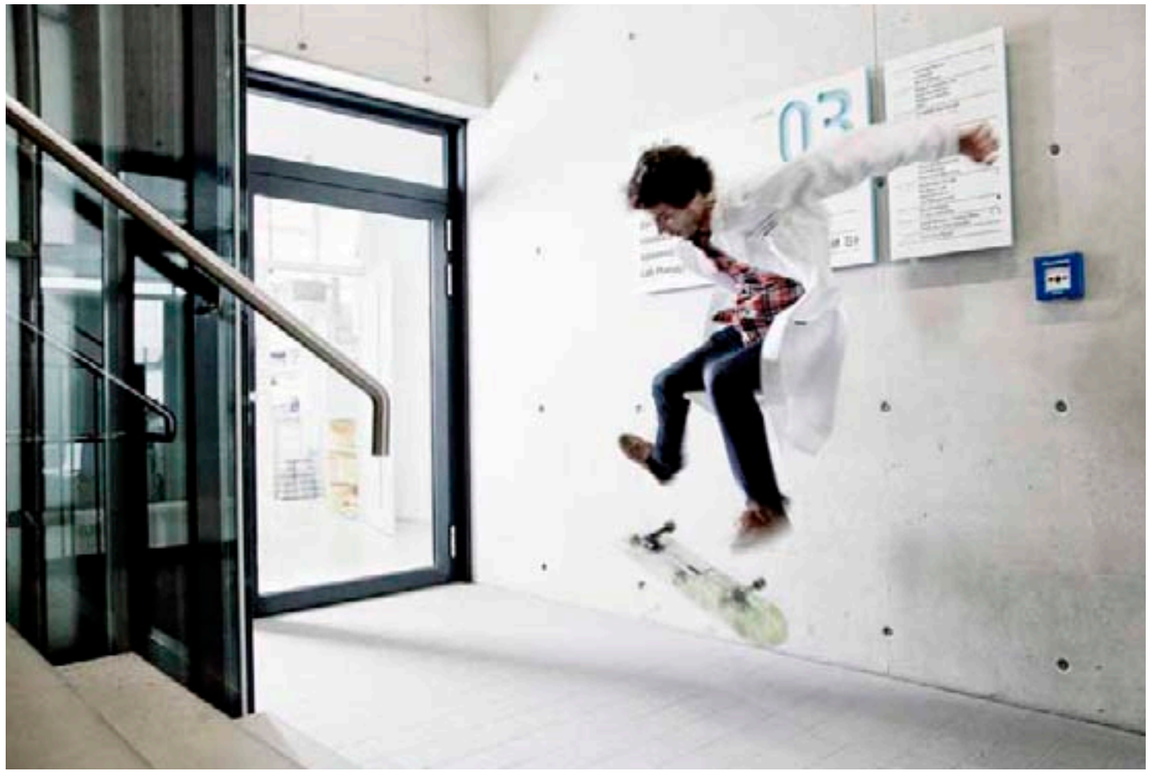
As the health activist and philanthropist Mary Lasker put it: "If you think research is expensive, try disease!". Nevertheless, research that aims to be competitive at the international level is indeed expensive. We are constantly working at leveraging the support we get from taxpayers through the Ministry of Science and Research (BM:WF) by applying for third-party funds. In 2010 we were very successful in securing some 2 million Euros to complement our 5 million Euro running budget. To these, one needs to add the funds required for the new laboratory furniture and equipment as well as our first large rent and building expenses. It is my privilege to thank Minister Beatrix Karl here again for the important support in these critical early years of CeMM.
Are we using this money wisely to create valuable knowledge? In 2010 we filed three patent applications and published a number of important papers, including the CD14 innate immunity paper published in the Journal of Experimental Medicine, and the paper in the journal Cell on the role of peroxisomes in innate immunity by our PhD student Evi Dixit and Harvard researcher Jonathan Kagan. The papers published in Leukemia by the Kralovics and the Superti-Furga laboratories, an innovative publication on predicting the mechanism of action of drugs captained by Jacques Colinge, as well as initial breakthroughs on medical proteomics by Keiryn Bennett's team in collaboration with Ursula Schmidt-Erfurth at the University Eye Hospital in Vienna also deserve to be mentioned. An increasing number of CeMM papers represent collaborations with the Medical University of Vienna and many deal with drugs and therapeutics. A journalist recently asked me whether CeMM would be as good as its paragon Institute of Molecular Pathology (I.M.P., in Vienna's 3rd district). I immediately said no, not for several years, give us time! I did mention though that if the I.M.P. was founded today, it would rather resemble CeMM, with its link to the medical research campus and more patient-oriented research. Afterwards, for curiosity, I checked the recent scientific impact of CeMM by monitoring the most highly cited papers (a measure of impact) listed in Thomson Reuter's ISI Web of Science. If one looks only at papers senior-authored in Austria, excluding reviews and clinical trials, it turns out that CeMM has produced the first and second most highly cited papers of the last two years in the whole of Austria (Bürckstümmer et al, *Nature Immunology 2009* and Olcaydu et al. *Nature Genetics 2009*). This is in all disciplines! While experts would caution that these results can be biased and may look different in the future, it clearly tells us that CeMM is on the right track! So young but already so clearly on the research map, and under sub-optimal conditions. Now that we have a building, just think what we can do!

Clearly, this has all been possible because of the help and contributions of a truly large number of people. A hopefully complete list appears at the end of this report. On behalf of all CeMM colleagues I wish to thank especially the Board of the Austrian Academy of Sciences, but also the entire Academy who supports CeMM through all challenges. We are also greatly thankful to the leadership of the Medical University of Vienna, constantly confirming their highly positive and collaborative stance towards the "CeMM experiment". In this "building year" it is particularly important to thank all Ministry collaborators, the construction and decorating groups, the Bundesimmobiliengesellschaft and its employees, the teams around architect Ernst Kopper, artist Peter Kogler and designer Kriso Leinfellner. Finally, I wish to personally thank the rest of the management team, Gerhard Schadler, Georg Casari and Anita Ender, who are the pillars of this institute. As in the past, my final and wholehearted gratitude goes to all CeMM researchers and collaborators. Your performance in 2010 was outstanding and your commitment will bring fruits for years to come.

After three research reports presented as "blue book" lab journals, this year we present our report by staging the wonderful new CeMM building. We hope that through our research report you will become curious and you will all visit us in person. The cover and the other "strange" pictures characterizing each level of the building are there to provoke thought and interest and to symbolically represent the variety of talents among CeMM's staff. Please do not try to do things like skateboarding in staircases at home! We take lab safety very seriously and do not advocate trespassing except in an intellectual sense! Imagination beyond boundaries.

Thanks to Helen Pickersgill and Ioannis Legouras for expertly weaving stories out of all titbits.

Giulio Superti-Furga
Scientific Director



Research at CeMM

Driven by talents

As the main theme of the research report, we have chosen the new building. It was only logical to structure the report by referring to the various floors of the building. And what better is there to represent CeMM and its qualities than the people who are responsible for the special mood, and most of all, for the success? Of course CeMM scientists are hand-picked out of many highly skilled applicants from all over the world. They are of course distinguished for their research track record and scientific capabilities. Yet there is much more to look at. CeMM has the pleasure to host a wide range of gifted people. There are enough musicians to form a big band, enough singers to build a choir, there are professional deejays, dancers as well as dancing instructors, groups of runners and soccer teams, cup cake bakers and acrobats. They all make CeMM very special and contribute to the "think outside the box and see the bigger picture" mission. The different chapters of this year's report are accompanied by pictures portraying extraordinary talents. We hope they will guide you through CeMM when you are reading our report. As mentioned in the introduction, these are symbolic pictures, do not try and play soccer on a roof!

Overview

Ce–M–M–
Research Center

Level **07**

Level 07
Where Genomes are Studied

Previous page:
Level 07, Room 07.101.1
Meeting Room

Into the groove
Giulio Superti-Furga, Scientific Director
playing a Höfner semi-acoustic bass
guitar from the 60's
André Müller, Staff Scientist
playing a Rickenbacker electric guitar
from the 70's

We have the pleasure of presenting you our 2010 research activities by taking you through a virtual tour of the new CeMM building and looking at the groups and people who work there. Our virtual tour starts on the seventh floor, the highest floor housing research laboratories. It is reachable by the CeMM staircase, the main elevator or the smaller service elevator. If you have a magnetic card you can also reach it through the corridor connecting the floor to the adjacent Anna Spiegel building of the Medical University. Of course, most people prefer the elevator. Walking out of the elevator on the seventh floor you can turn right, where you find the offices and the corner seminar room, or left towards the laboratories. The laboratories offer an impressive view of the Vienna skyline. This is the floor where medical genetics and genomics rule.

The laboratory of Principal Investigator Robert Kralovics is found here. Robert's team comprises five PhD students, one postdoctoral fellow, one research technician and two diploma students. They come from all over the world. PhD student Ashot Harutyunyan, for example, comes from Armenia and research technician Tiina Berg comes from Finland. Early in 2011, they will be sharing the floor with the group of new CeMM PI Kaan Boztug and, later in the year, with a new PI working on computational genomics. The Kralovics lab works mainly on identifying mutations that contribute to the initiation and progression of various blood cancers like leukemia. For this they use genomics approaches. To assist them, as well as other groups at CeMM, they have established a well equipped Genomics Facility on this floor.

The Genomics Facility

The Genomics Facility is a collection of state-of-the-art equipment for performing high-throughput genomics analyses. It includes a dedicated pre-PCR (polymerase chain reaction) laboratory, including robots for sample preparation, eleven standard PCR machines and a "real-time" PCR machine. Moreover, there is a complete Affymetrix microarray processing platform and, the lab's most coveted toy, the next generation DNA sequencer (HiSeq2000 from Illumina). This allows sequencing at a pace that would have been unthinkable some years ago. In the last few months numerous collaborations with researchers from both inside and outside CeMM, including the Medical University of Vienna, and the Universities of Pavia, Florence and Basel, have been established, mainly involving the use of the arrays and next generation sequencing. Particularly, members of Denise Barlow's lab on the third floor are common users of the sequencer for their studies on the epigenetics of cancer.

The Blueprint of Life

To create a new building one of the first steps is to produce a detailed outline of the design: a blueprint. DNA encodes a detailed outline for creating life and is sometimes called the 'blueprint of life'. Just like the blueprint of a building that guides its construction, by encoding genes, the DNA guides cells to construct a fully functioning organism. If there are mistakes in the blueprint, the result can be disease, but if the mistakes are only small, finding them can be quite a challenge. On the seventh floor of the CeMM building, using their new technology, the Kralovics lab searches through the genetic blueprints of cancer cells.

Reading the Genetic Proofs

Finding subtle differences in the genetic code between different cancer cells is like searching for a very small needle in a very big haystack. Fortunately, in the last few years, groundbreaking technology has been developed for sequencing whole genomes at a reasonable cost as well as accompanying computational tools. Whole genome sequencing allows us to determine the complete DNA sequence of an organism or cell in one go. DNA is made up of only four molecules known as adenine, guanine, cytosine and thymidine (usually depicted as A, G, C and T). These so-called nucleotides are linearly arranged in different orders on individual chromosomes. It is this sequence that together makes up the genome.

The first human genome sequence was completed in 2001 and was a landmark event, not least because it is composed of almost 2.9 billion nucleotides found on 23 chromosomes. It took one consortium of twenty centers in six countries over 10 years to complete and cost just under $3 billion. Since then, huge advances in technology have meant that large sections of DNA, such as those harbouring potential cancer-causing mutations, can be sequenced by individual labs in a relatively short space of time and at a fraction of the original cost. It has begun to change the face of cancer genetics and has directly influenced the research in the Kralovics lab. CeMM established this new technology in the seventh floor Genomics facility in July 2010, when the first scientists moved into the new building.

The Genome Architecture of Cancer Cells

DNA microarrays can read 1.8 million data points per genome and "paint a genome mosaic" for each leukemia patient.

Cancer is a disease characterized by a group of cells that have lost growth control. It originates from a single healthy cell that acquires a specific genetic mutation, changing the sequence of our DNA. Our cells acquire random mutations all the time, simply from dividing, or from environmental damage by chemicals such as those found in tobacco or UV from the sun. Fortunately, most of these mutations are relatively harmless and do not cause disease. However, a mutation that affects the function of certain important proteins, thereby enabling the cell to bypass normal mechanisms of growth control, can eventually lead to cancer.

In leukemia, the initiating mutation comes in various forms. It can be a large chromosomal rearrangement leading to misplaced, missing or multiplied sections, or a small point mutation in a single gene. Once the cell is transformed into a cancer cell it sets out to multiply, generating millions of copies of itself. Its progeny, the tumour mass, starts to compete for space and other resources with healthy cells of the surrounding tissues. As the cancer cells continue to divide and the tumour grows, more mutations occur. Although the vast majority of these newly acquired genetic mutations do not provide any benefit to the cancer, some may prove to be useful in the environment in which the cancer resides and thus provide a selective advantage. Therefore, selection is the main driving force behind the cancer genome in a given environment.

Painting Genome Mosaics

Different tissues have different selective forces that shape the cancer genome. Cancers of blood, particularly leukemias, are one of the focal points of research at CeMM. In leukemia, the cancer cells of each patient follow a unique evolutionary path. As a result, a mosaic of chromosomal changes can be seen in each patient. The Kralovics laboratory studies the genomic architecture of leukemic cells in hundreds of patients diagnosed with different forms of leukemia. In each patient, the leukemic genome is evaluated using DNA microarrays that can read 1.8 million data points per genome and "paint a genome mosaic" for each leukemia patient.

When this analysis is performed for hundreds of patients, the mosaics can be compared and used to identify a pattern that best describes each leukemic disease. Using this approach, several members of the lab, including PhD student Roland Jäger, have discovered a number of chromosomal defects that implicated a group of regulatory genes called transcription factors in leukemia, which may lead to the future development of new drug treatments. Some of this work was published in the journal *Leukemia*, in 2010. In addition, being able to detect some of these chromosomal abnormalities in new patients may be useful for predicting the severity of the disease. Interestingly, different types of leukemias tend to have fairly similar genome architectures. It seems that leukemic cells use related chromosomal defects during their genome evolution, most likely due to the similar tissue microenvironments they evolve in.

Unlucky Number 7

An example is illustrated by chromosome 7. Various chromosome 7 defects or lesions have been described in the past in different types of myeloid leukemias. However, which of the 1400 or so genes found on this chromosome were directly involved was not known. The group assembled "genomic mosaics" using cells isolated from many patients. By comparing the different mosaics they were able to make some striking conclusions. Indeed, two genes turned out to be important targets of these lesions; CUX1, which is located on the short arm of the chromosome, and Ikaros, which is found on the long arm. As chromosome 7 lesions are seen in almost all types of leukemia, this indicates that these two genes are prominent players in the pathways used by leukemic cells to promote their survival. Finding ways of manipulating these genes may lead to a new treatment for the disease.

Reading the Cancer Genome Letter by Letter

Although genome sequencing has only recently been established at CeMM, it has already contributed significantly to our understanding of cancer genomes. In the Kralovics lab, genome sequencing has complemented the DNA microarray data generated using patients' leukemic samples and filled in a substantial information gap. Genome sequencing can literally read more than 3 billion letters of the genome. Because large numbers of the chromosomal defects found in leukemia are point mutations changing only a single letter (or few letters) of the genome, this new technology allows scientists to essentially find the needles in the haystacks. Once these single-letter defects are detected, they contribute to the individual mosaics of defects of each cancer genome. Comparing many such high-resolution genome mosaics will enable the group to draw generalized conclusions on the evolution of the leukemic genome and decipher the genetic complexity of leukemias step by step or rather letter by letter.

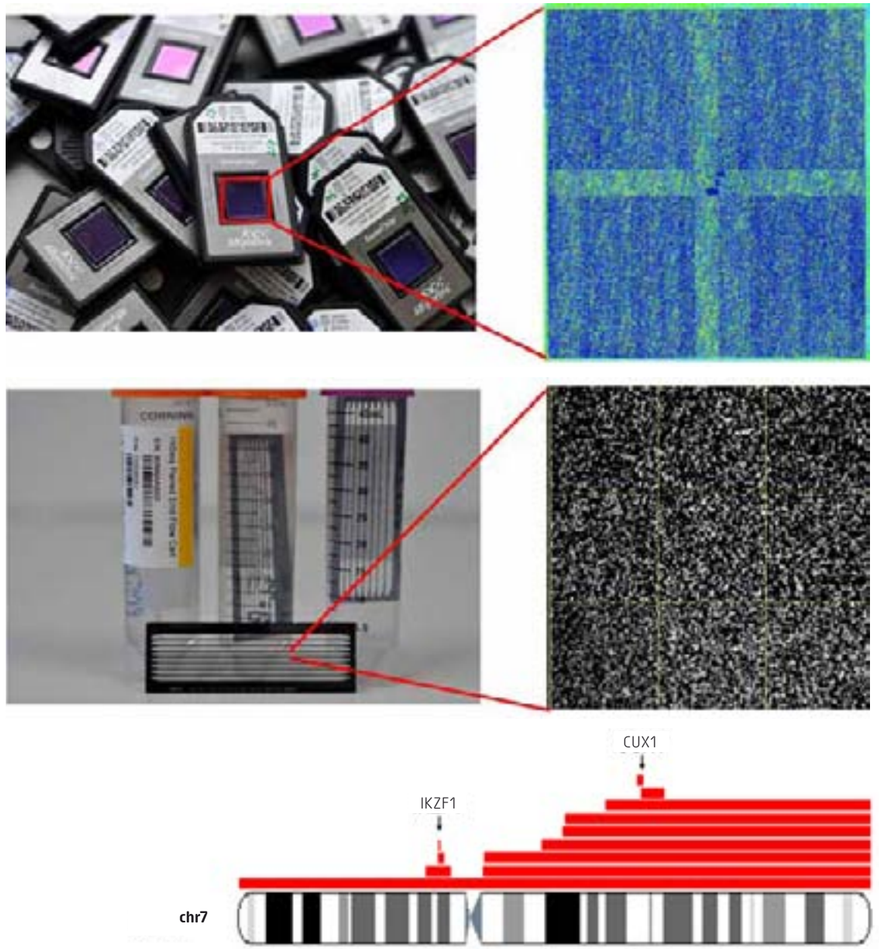


Fig. 1 Top: DNA microarrays and an image (right) of the thousands of data points they can analyze in a patients genome. Middle: Flowcells – the devices used to sequence whole genomes of cancer patients. Right: magnification of a small area on a flowcell where millions of DNA pieces are read. Bottom: a schematic view of chromosome seven. In leukemia, patients frequently lose fragments of this chromosome (indicated by the red bars). Comparison of these changes in different patients led to the identification of two important target genes IKZF1 and CUX1.

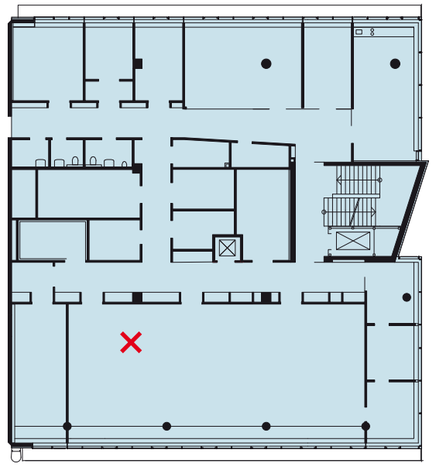
Ce–M–M–
Research Center

Level **06**

Level 06
Where the Weaknesses of Cancer and Immune Cells are Studied

Previous page:
Level 06, Room 06.203
Nijman Lab

Lust for life
Tillmann Burckstümmer, Postdoctoral Fellow
dancing Lindy Hop



We leave the seventh floor via the stairs. The walls are unpainted concrete, which, with the sober steps and metal railings, contribute to an industrial type of atmosphere. The steps are relatively high, so it's tough going, and enviously we watch the elevator go up and down within its glass enclosure. On the landing, we take the glass door on the left. On the glass is imprinted the shape of a female researcher with a ponytail holding a tube. The image is filled with white decals of the three-letter codes for amino acids, the building blocks of proteins encoded by the genome. From the head, the sequence reads Met-Glu-Glu-Pro-Gln-Ser-Asp-Val and so on. This is the beginning of the polypeptide chain of the human tumour suppressor protein p53 (P53_HUMAN), arguably the most important cancer-preventing protein in our genome. A surprising number of cancer types show mutations in this protein or in a protein associated with it. Cells become more susceptible to other changes leading to cancer, when mutated in p53. So, it is a symbolically relevant gate to the sixth floor where cancer "weaknesses" is one of the research topics.

The corridor parallel to the axis of the building has three doors to the open-space laboratory. One end leads to the tissue culture lab, and the other to one of the three small offices that are on the side of the art façade. We walk into the large, open-plan laboratory, which is full of light. The lab furniture, including benches and shelves, is white, while the stools and chairs are black. The bench surfaces are made out of thick glass. Along the tall windows lining the back wall, which are the source of all the light, there is a long desk for students and research technicians. The view may not be quite as good as from the seventh or eighth floor, but is still fantastic. Currently, the floor is only occupied by the laboratory of Principal Investigator Sebastian Nijman. In the summer, two more PIs will start; Joanna Loizou, joining from Cancer Research UK in London, and Andreas Bergthaler, currently at the Institute for Systems Biology in Seattle.

The Nijman lab, consisting of two Post-docs, two PhD students, two research technicians and a diploma student, occupies a third of the sixth floor. Most commonly people are found seated at one of the four sterile hoods in the tissue culture room adjacent to the open-plan lab, splitting cells into stacks of petri dishes for screening experiments. The group also employs two bio-informatics undergraduates from the Vienna Technical University, who sit at the desks in the Post-docs writing room on the other side of the floor, helping to analyze the large datasets that are produced from the high-throughput screens.

The general focus of the lab is cancer, which is often also the topic of the weekly journal clubs held by the group during lunch in their meeting room. Each week, one member of the group gets to choose a paper on any topic for detailed discussion. This helps teach the students how science should (or shouldn't) be done, and keeps them up to date with current literature. In the lab, most of the group are using a relatively new concept to find new ways to fight cancer.

Back-up Systems

The functioning or "homeostasis" of the new CeMM building is not easily disturbed. A comfortable indoor climate is maintained thanks to air conditioning, heating and window blinds regardless of the weather outside. Back-up systems avert problems even when things go wrong. For instance, the emergency electricity system prevents defrosting of freezers containing valuable reagents in case of a power outage. And the two lifts and staircase ensure that all employees can efficiently navigate the building, even if one of the lifts is out of order.

One could say that the building has a certain "robustness" that protects it and its users from changing conditions and the occasional malfunction of any single component. A defining characteristic of a robust system is that breakdown of a single part causes problems only in the case of an unlikely event. A failed computer back-up, for example, only becomes problematic when a server crashes that same day, which is highly improbable. A blocked staircase only becomes life threatening in case of a fire.

Testing for Weaknesses

These very same principles also apply to biological systems and play an important role in many diseases, including cancer. The hope is that they can offer new therapeutic strategies for treating these devastating diseases. During tumour formation, normal cells acquire numerous genetic and molecular changes that turn them into cancer cells and drive the growth of the tumour. These changes include the activation of growth signalling pathways, deregulated transcription, crippling of cell cycle checkpoints and so on. The consequence is cancer cells that are impervious to outside regulation and even spread to other sites in the body (metastasis). However, all these changes also make extra demands on back-up systems and the cancer cells become, in some ways, less robust than their normal counterparts. Selling the fire alarm system may have saved money and energy, but in case of a fire the whole building is now at risk.

Screening for New Cancer Drugs

In 2008, there were over 300,000 new cases of breast cancer within the European Union.

In the Nijman lab the principles of robust systems are now the basis for experiments aimed at finding new therapeutic angles for cancer therapy. One of these principles is known as "synthetic lethality": two molecular changes that are only detrimental to the cell when occurring in combination. Because cancer cells already have one of such a pair of alterations, they are now sensitive to a second whereas normal cells can still rely on the back-up system. In the Nijman lab, systematic explorations into these combinations aim to identify these Achilles' heels of cancer.

Breast cancer is a devastating disease with high incidence, mortality and morbidity. In 2008, there were over 300,000 new cases within the European Union, and mortality rates range from around 20-40%. This is despite intensive screening programs designed to catch the disease early in women who are at higher risk, such as those over the age of 50. There have also been significant advances in treatment. So why is it still causing such a problem?

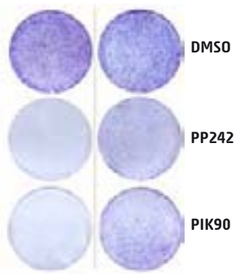
Once cancer cells have spread to other organs in the body by a process known as metastasis, chemotherapy is the principal treatment. However, a patient's response to treatment is highly variable and in most cases does not provide a cure. It is not clear what determines this variable response to therapy and why it is so difficult to find drugs that can kill cancer cells without affecting the patient. These are the areas that are the key focus of the Nijman lab. They are searching for more intelligent drugs by building on the extensive genetic knowledge of cancer that has already been generated over the past few decades.

Relationships Between Genes and Compounds

Most of the group is performing large-scale chemical genetic experiments. Chemical genetics is the study of the modulatory effect that genes and gene mutations have on the response of cells to chemicals such as drugs. In particular, the lab are investigating which cancer genes may influence a cancer cell's response to chemotherapeutic drugs. Cancer genes are normal genes that have undergone a specific mutation that changes the genes' function or switches it off. In some cases cancer genes can make cancer cells less sensitive (i.e. resistant) to a specific drug. This information is very important as it can help to make sure patients are not treated with strong drugs that will not work on them and often have severe adverse effects. The reverse – cancer genes that make cells more sensitive to drugs – is perhaps of even greater importance as this may guide new treatments and lead to therapies with fewer side effects.

Markus Müllner, a Post-doc in the lab, along with PhD student Iris Uras and diploma student Bianca Gapp, have set up a sophisticated screening platform to enable large numbers of drugs to be tested on many different genetic variants of cancer cells. By doing this they hope to tease out which cancer genes contribute to resistance or cause synthetic lethality when combined with drugs. This high-throughput technology means that members of the lab spend a lot of their time in the tissue culture room working with large stacks of dishes in which there are many combinations of cells and drugs. In 2010, several chemical genetic screens were performed using breast cancer cells engineered with specific cancer mutations. The results are promising and several weaknesses and mechanisms of resistance have been found that can be exploited with new drugs. The lab is now also planning to use lung cancer cells in similar screens using their new platform, with the hope of contributing to new therapies and better-informed treatment decisions.

Fig. 2 Colony formation assay showing pronounced resistance of a gene to two different PI3K inhibitors in breast cancer cells.



Protein Modifications and Cancer

Many proteins undergo chemical modifications involving the addition of small chemical groups or molecules that can alter their function. These modifications are dynamic, and their addition and removal enables the careful control of specific cellular processes. The best studied posttranslational modification is phosphorylation, whereby a phosphate group is added to a certain amino acid residue on a protein via the action of a protein kinase, and is removed by a phosphatase. A less well-studied modification is ubiquitination, resulting in the addition of a small molecule known as ubiquitin. The removal of ubiquitin from a protein is known as deubiquitination, and is performed by so-called deubiquitinating enzymes. The significance of ubiquitination in diseases such as cancer has only recently been illustrated, but it has now become accepted as playing a central role. Identifying which proteins are controlled by ubiquitination and how this is linked to disease is an ongoing pursuit in the Nijman lab.

Recently, an undergraduate student in the lab, Thomas List, discovered that a protein in a cancer signalling pathway is mono-ubiquitinated. This pathway plays an important role in many cellular processes such as cell death, cell growth and proliferation. This cancer signalling pathway is a particularly interesting pathway as its deregulation has been linked to a large number of human cancers such as glioblastoma, breast and prostate cancer. This makes its components important potential targets for therapy. Indeed, several inhibitors of individual members of this pathway have been identified and are showing promise in clinical trials.

Ongoing work in the lab by PhD student Iris Uras aims to uncover the importance of this ubiquitin modification for protein function, and particularly how this may be involved in cancer. Their results may provide evidence that mono-ubiquitination can be exploited as an alternative treatment for cancers caused by deregulation of this pathway.

The significance of ubiquitination in diseases such as cancer has only recently been illustrated.

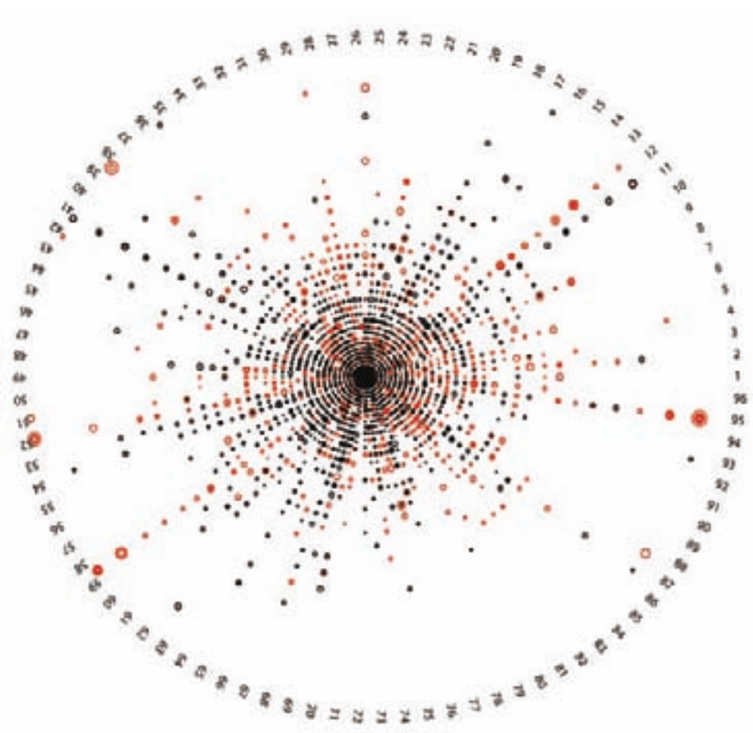


Fig. 3 Synthetic lethality and drug resistance screen in breast cancer. Each dot in the figure represents a drug vs. cancer gene combination. Dots further away from the center indicate more significant hits and dot size increases with the magnitude of the effect.

Inflammation and Atherosclerosis

The Binder laboratory is located in the Anna Spiegel Building of the Medical University of Vienna, which is directly adjoined to CeMM essentially forming one building. Christoph Binder has a dual affiliation with CeMM and the Department of Laboratory Medicine, headed by Oswald Wagner, where he also works as a Specialist in Laboratory Medicine performing diagnostics on blood samples.

Nearest Neighbours

The CeMM and the Anna Spiegel building share the same entrance and are connected on each floor via a corridor. The door leading to the sixth floor of the CeMM building where the Nijman lab is located is directly across from Christoph Binder's office. The group uses many of the facilities at CeMM on a daily basis, such as the cafeteria on the eighth floor, the seminar room, colour printer and bacterial shakers on the sixth floor and the liquid chromatographer on the fourth floor, which is used to separate and purify proteins. They also participate in the weekly Friday CeMM meetings, where, over the course of a year, all the CeMM scientists are expected to present their recent projects during a half hour slot, which is followed by intense open discussion.

Antibodies are glycoproteins that are normally produced by our blood cells in response to infection and act to protect our bodies from the inside.

Walking toward the Binder lab from CeMM one is greeted with the intense grass-green color of the walls on the landing. This green color is maintained throughout the entire sixth floor of the Anna Spiegel building, although closer to the labs it becomes a lighter green. The Binder lab is on the south side. The laboratory is designed differently from those at CeMM. Instead of an open-space layout, it is divided into bays. When quizzed, the Binder lab members prefer that to the CeMM layout as it allows scientists to have their desks close to their benches.

The Binder group currently consists of two research technicians, three diploma students (two Biology, one Medicine), five PhD students and one Post-doc.

Protection and Safety in the Lab

Safety is of utmost importance in any laboratory, especially considering that some very toxic chemicals and biological samples are used. There are many safety mechanisms in place to protect scientists from hazards at work, such as lab coats to protect their skin and clothing, and chemical fume hoods to protect against corrosive and toxic chemicals. Latex gloves are used both to protect hands, but also to protect experiments from being contaminated by bacteria, enzymes and other molecules found on our skin.

Internal Protection

Antibodies are glycoproteins that are normally produced by our blood cells in response to infection and act to protect our bodies from the inside. There are five antibody subtypes in mammals: IgA, IgD, IgE, IgG and IgM. The Binder lab's main focus is on so-called natural IgM antibodies, which have currently unknown functions. Natural IgM antibodies are pentameric (like gloves!) consisting of five immunoglobulin subunits and are the largest antibody type found in humans. The lab is studying how natural antibodies can help protect us from chronic inflammatory diseases such as atherosclerosis.

Natural IgM Antibodies

Antibodies are large proteins produced by our immune system, usually in response to pathogen infection, and help our bodies to fight disease. They are designed in such a way that they can each specifically recognise and bind to a target molecule known as an antigen, found for example on the surface of a bacterium or virus. However, so-called natural IgM antibodies, unlike other types of antibodies, seem to be produced without prior exposure to antigens and their function is currently unclear. The Binder team has been investigating the role of these natural antibodies in diseases such as atherosclerosis, a chronic cardiovascular disease where arteries become blocked.

The group has recently discovered that circulating microparticles are physiological targets of natural IgM antibodies. Microparticles are small fragments of membrane that are shed from both living and dying cells. They are found in our circulation, and increased levels of microparticles have been reported in various diseases, including cardiovascular disease. They are believed to be pathogenic by promoting vascular dysfunction, thrombosis, and inflammation.

Biological Protectors

Atherosclerosis is a leading cause of morbidity and mortality, particularly in Europe and the U.S. It is a chronic disease, caused by the slow buildup of material in blood vessel walls, forming plaques. Disruption of these plaques can lead to heart attack or stroke. Understanding how our body tries to protect us from this disease may help in the development of much needed new treatments.

The Binder lab have shown that many naturally occurring IgM antibodies recognize various lipid peroxidation-derived structures, which they found on up to 50% of circulating microparticles in healthy volunteers. Excitingly, these specific natural IgM antibodies were actually able to protect mice from developing atherosclerosis. They went on to show that natural IgM antibodies could neutralize inflammation caused by the microparticles, which is thought to contribute to chronic inflammatory diseases like atherosclerosis. In fact Dimitris Tsiantoulas, a PhD student in the lab, was able to show that microparticles stimulate the production of an important inflammatory mediator (chemokine) termed interleukin-8, in macrophages, and that in the presence of a specific natural IgM antibody this effect was completely abolished. This is highly relevant as interleukin-8 plays an important role in atherosclerotic plaque development by promoting the recruitment of inflammatory cells to the artery wall. Future work will aim to define other protective functions of these antibodies, e.g. in thrombosis, and evaluate if the production of these natural IgM antbodies can be stimulated.

Natural IgM antibodies seem to be produced without prior exposure to antigens.

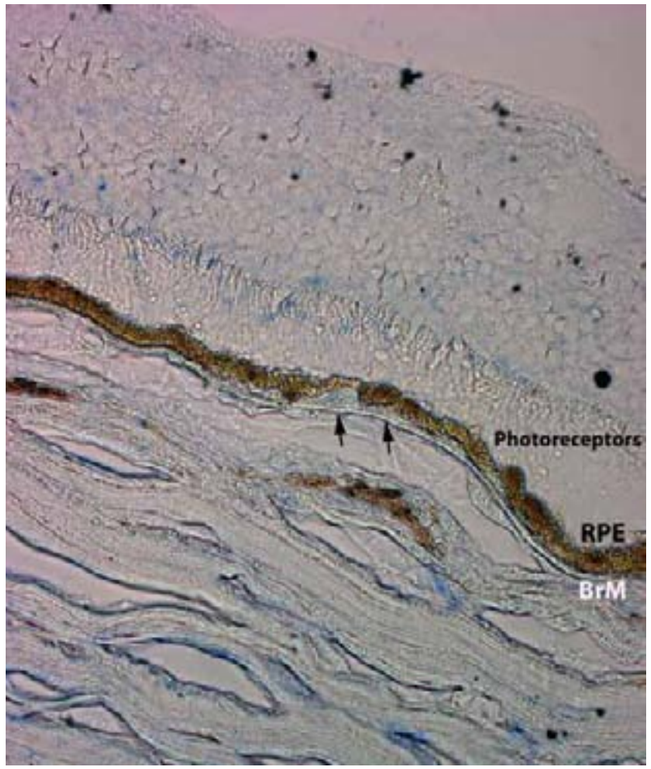
Protection against Oxidative Stress

Reactive oxygen species are produced as a by-product of oxygen metabolism and have important biological functions. Excess reactive oxygen species can be destructive and are normally neutralized by antioxidants. However, sometimes this protective system fails, causing a buildup of reactive oxygen species and subsequently a state of oxidative stress. Increased oxidative stress can lead to lipid peroxidation, which in turn generates various lipid-derived danger signals that alarm the innate immune system and cause inflammation. Indeed, oxidative stress is associated with many chronic inflammatory diseases.

Oxidative stress is associated with many chronic inflammatory diseases.

David Weismann, a PhD student in the lab, in collaboration with Joe Witztum at UCSD and Jim Handa of Johns Hopkins University, both in the U.S., Peter Zipfel of the International Leibniz Research School (ILRS Jena), and Giulio Superti-Furga and Keiryn Bennett's labs at CeMM, are trying to understand how cells can be protected from these lipid-derived danger signals and their proinflammatory effects. They believe that these signals may represent a common disease mechanism in many different chronic inflammatory diseases. While searching for serum proteins that could protect against these danger signals, the team, working with the mass spectrometry group led by Keiryn Bennett, uncovered complement factor H (CFH). CFH is a large glycoprotein that circulates in human blood plasma and helps mediate the innate immune response via controlling the complement system. A mutation in this protein has been linked with age-related macular degeneration (AMD), which is the leading cause of blindness in the elderly. However, the cause of AMD is currently unclear.

The Binder team was able to show that CFH binds a specific oxidative stress marker known as malondialdehyde, which accumulates in patients with age-related macular degeneration. Significantly, the binding of CFH was able to block the proinflammatory effects of malondialdehyde. This provides critical new insight into the cause of this devastating disease, which could be exploited in its prevention and therapy. Importantly, this information may also be applied to the treatment of other diseases and help protect our bodies from damage by chronic inflammation.



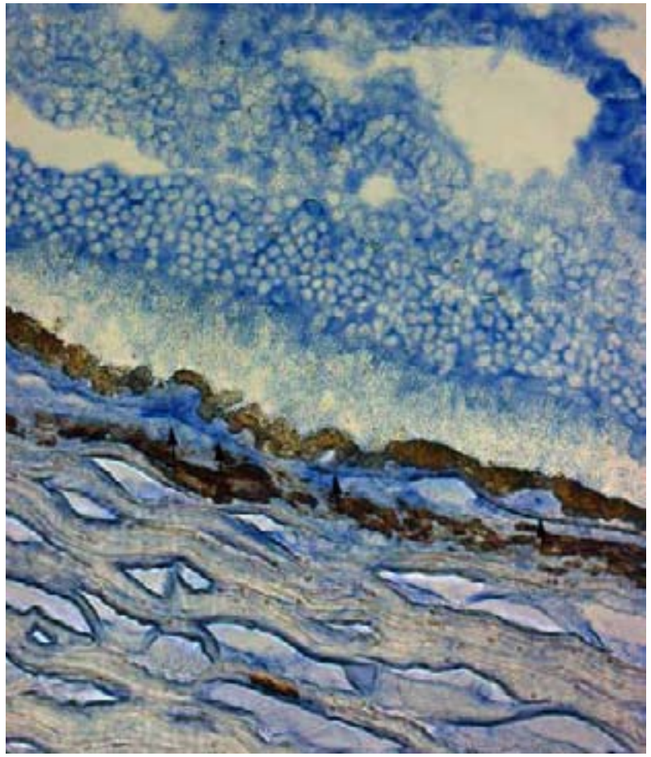


Fig. 4 MDA adducts are present in eyes of patients with Age related Macular Degeneration. Drusen of AMD lesions are typically composed of cellular debris and replete with products of lipid peroxidation. Using an MDA-specific monoclonal antibody, we detected MDA-epitopes in histological sections of patients with AMD. The presence of MDA-epitopes is indicated by the blue color. RPE = retinal pigment epithelium; BrM = Bruch's Membrane; arrows indicate drusen.

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Level **05**

Where Malfunctions of Molecular Networks are Investigated → p. 30

+ Systems Medicine
+ Innate Immunity: Anti-Viral Defence
+ Drug Effects on Cells

Level 05
Where Malfunctions of Molecular Networks are Investigated

Previous page:
Level 05, Room 05.213
Equipment Room

Air swirl
Vesna Krajina, Diploma Student performing a traditional dance in a Bosnian folk costume

Moving back to the staircase of the Anna Spiegel Building we walk up one flight of stairs. With our back to the two elevators, we go to the right and step through the glass door onto the landing that leads to the fifth floor Anna Spiegel laboratories, three offices and to the north corridor of the CeMM building. The entire fifth floor is occupied by Scientific Director Giulio Superti-Furga and his group. It is the center of the building and to a certain extent the center of the action – if one spends time on this landing, one is likely to meet most of the people at CeMM. Appropriately, it is also the floor where the human resources and public relations offices are located, which are two essential functions of the institute. Office and cell phones are permanently ringing as Anita Ender and Eva Schweng try to keep everything under control and to manage the flow of people and events, including the production of documents such as the report you are holding in your hands. In addition to this, Anita Ender is also the personal assistant of the Scientific Director, providing a connection between research strategy and implementation. This makes her the most popular person in the entire building.

A Large Interdisciplinary Group

The large open-plan lab is where the molecular biology and biochemical experiments take place. Music is often played over a radio or an MP3 player, and occasionally there is singing of varying quality, mostly early in the morning or after core hours. At regular intervals there is a loud "beep-beep" coming from one of the devices powering a Western blot experiment, which enables the immunological detection of specific proteins. Giulio's office is adjacent to the lab, separated by a glass door. For some reason, the desks and benches most distant to Giulio's office are considered the most attractive. Colleagues who have more recently joined the team occupy the rest. There are some 20 people working on this floor, consisting of a mixture of Post-docs, PhD students, MD trainees, diploma students and research technicians. The researchers that were in the Superti-Furga laboratory when it first moved to Vienna have started to leave for prestigious appointments in academia or biotech companies (see section on Post-docs). However, the laboratory continues to expand and diversify in both scientific disciplines and in nationalities. It now includes bioinformaticians working on data analysis, shared with Jacques Colinge's team. A new addition to the Superti-Furga lab is a chemical proteomics unit established on the fourth floor of the new building, which shares critical equipment and expertise with the PLACEBO lab housed on the same floor.

Linking Diverse Topics

Research activities in the group can be divided into three major topics: 1) leukemias and other hematological malignancies (blood cancers); 2) innate immunity and infectious diseases; 3) chemical proteomics and the mechanism of action of drugs. Although these topics seem diverse they synergize well within one laboratory because they share three important characteristics. Firstly, they are all strongly linked to medicine, and the Medical University of Vienna, CeMM's nearest neighbour, has a history of expertise and clinical successes in all three topics. Secondly, the three topics are all amenable to the suite of technologies and experimental approaches that have been optimized in the institute over the years, particularly proteomics-based pathway and network analysis. Lastly, the relationship between cancer, inflammation and infection is becoming increasingly intimate and these interfaces are current hot areas of discovery and innovation.

Connecting Cancer and Inflammation

Former CeMM SAB member Alberto Mantovani has proposed to add inflammatory status to the infamous six hallmarks of cancer – a move which has elicited strong resonance in the community (see *Cancer-Related Inflammation. Mantovani A et al., Nature. 2008, 454:436-44)*. Indeed the best-cited paper ever published in the journal *Cell* (*"The Hallmarks of Cancer". Hanahan D, Weinberg RA. Cell. 2000; 100:57-70*) has recently been updated and now includes inflammation. In addition, CeMM supporter Harald zur Hausen (see our 2009 Research Report) obtained the Nobel Prize for Physiology or Medicine in 2008 for his work on papilloma virus as the causative agent of cervical cancer, highlighting the infectious basis of certain malignancies. Other microbes like the bacterium *Helicobacter pylori* and the *Hepatitis B* virus are thought to represent only the tip of an iceberg of pathogens implicated directly or indirectly in the carcinogenic process.

Connecting People

Members of the lab are able to keep abreast of all these topics and associated technologies at biweekly meetings held in the fifth floor seminar room. Importantly, the meetings provide the opportunity to coordinate work between the Superti-Furga laboratory and cooperating laboratories. At these meetings, you can see some 10–15 people gathered around the table in the seminar room, with pens and notebooks, and coffee or tea. Different parts of the turn of last century buildings that face CeMM can be seen through the roundish shapes of the glass etchings on Peter Kogler's façade. Usually between two and four people present their latest results and consult the assembled project team about future plans. Discussions are entirely informal and participants are encouraged to interrupt wherever necessary. People sitting at the table come mainly from the Superti-Furga lab but also from the Bennett/Colinge/Kubicek teams and include visiting medical doctors and Post-docs. In this way, both the projects and the people in the lab remain connected.

Systems Medicine

The human body and its multitude of functions are controlled by information encoded in our genomes, which are the ensemble of all our genes. Genes contain the instructions for making individual proteins, but proteins do not act alone. They work by forming complexes with other proteins and molecules, which interact with other complexes and molecules to form pathways and networks. These networks perform specific and highly controlled cellular functions and can be thought of as the genome coming alive. Network perturbations are associated with diseases, and inflammation and cancer, which are themselves cellular functions, share molecular pathways, targets and signalling elements. The Superti-Furga laboratory is interested in exploring these interfaces for therapeutic intervention. Systems medicine is an approach applied to all three research areas investigated in the lab.

Network perturbations are associated with diseases, inflammation and cancer.

Teamwork and Networks

The Superti-Furga lab investigates the pathways and networks around individual proteins known to be associated with specific blood cancers or infectious diseases. This involves collecting individual puzzle pieces by experimentation, followed by a technology and informatics-driven assembly of the final molecular network. Defining complex molecular networks allows causal relationships and inter-dependencies between different parts of the network to be modelled, which may be important for treating disease. Indeed, medical information is integrated with genetic insight to annotate these molecular networks. For example, the networks are virtually and experimentally "marked" with chemical compounds to enable predictions of potential pharmacological intervention, which can then be experimentally tested.

This research strategy relies heavily on teamwork. The interaction- or affinity-proteomics methods are performed by or in close collaboration with the team from the mass spectrometry department headed by Keiryn Bennett, one of the first CeMM scientists recruited. The data generated by this approach are analyzed by the computers commanded by Jacques Colinge and his team of biomathematicians located on the second floor. Lastly, perturbation of the system by chemical agents requires Stefan Kubicek's team, who formulate biologically relevant functional assays and perform robotics-based chemical compound screens.

Innate Immunity: Anti-Viral Defence

During one of the first meetings in the new seminar room, Christoph Baumann, a Post-doc, summarized the data that has just been used to write a manuscript for publication. It involved a lot of work, which was done in close collaboration with the laboratory of CeMM PI Sylvia Knapp, and also with Keiryn Bennett's mass spectrometry group on the fourth floor. Under investigation was a new co-receptor for a Toll-like receptor, named IPOT4 in the 2009 report.

Toll-like receptors (TLRs) are membrane-spanning proteins that play a crucial role in our body's first line defense against invasion by pathogens. They are part of the innate immune system. Different conserved structures on pathogens, so called pathogen-associated molecular patterns or "PAMPs" are recognized by TLRs. One of the most prominent and most studied PAMPs is Lipopolysaccharide (LPS), which is found on the surface of many different types of bacteria including *Salmonella*, and is recognized by TLR4. A subset of TLRs (TLR3, 7, 8 and 9) reside in small membrane-enclosed organelles called endosomes inside cells, where they sense the RNA- or DNA-containing genomes of invading viruses and bacteria.

A Big Job for a Small Family

An important question involving TLRs is how this relatively limited set of receptors is able to identify such an enormous variety of pathogens. Perhaps they have ancillary proteins with which they function? To gain insight into TLR function, Christoph and other colleagues from the mass spectrometry and bioinformatics team set out to identify cofactors that interact with TLR and aid its function. To do this, the TLRs were given a molecular hook (i.e. tagged), which was used to fish for binding partners in immune cells known as macrophages. Binding partners that are fished out can then be identified by their molecular weight through a physical measurement using mass spectrometry.

A prominent partner of TLR7 and 9, members of the Toll-like receptor family known to recognize viruses in intracellular endosomes, was found to be CD14, a well-known macrophage surface "marker" (i.e. a protein used to characterize subtypes of immune cells). A physical interaction between CD14 and endosomal TLRs inside cells could also be observed under the microscope upon special labelling, supporting the earlier result. The team was also able to show that this physical interaction between TLR7 and CD14 had functional consequences. First, they showed that CD14 was important for the pro-inflammatory response induced by TLR7 and TLR9, using immune cells from mice that had a genetic inactivation of the CD14 gene. Secondly, and more importantly, they showed these proteins functioning together using an infection model in whole animals.

CD14: Immunity Booster

Previous work from others had shown that CD14 was an essential co-factor for TLR4 in the recognition of bacterial structures. Importantly, the Superti-Furga lab along with the Knapp lab, had now shown that CD14 could also enhance the ability of our cells to recognize viruses via TLR7 and TLR9, which is highly significant given the extensive risks viruses pose to human health. This was one of the most important findings of the Superti-Furga laboratory in 2010. Their discovery could lead to future monitoring of CD14 protein levels to predict the ability of patients to withstand viral infections. In addition, it may be possible to boost the levels of CD14 to improve our immunity to viruses. Unfortunately, Irene Aspalter, a CeMM diploma student involved in the project who now works at Cancer Research UK in London, was not able to attend the celebration that occurred when the paper was finally accepted for publication in the *Journal of Experimental Medicine*, which is one of the oldest and most prestigious journals in molecular medicine.

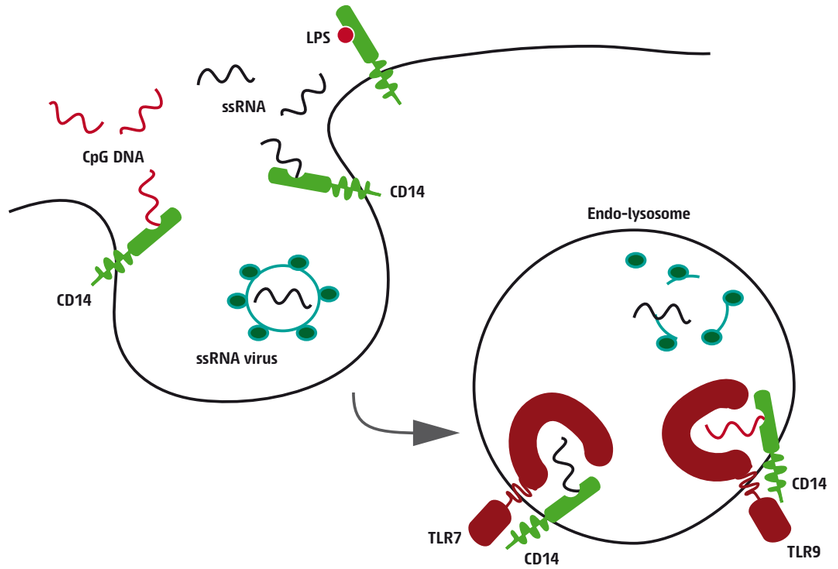

Fig. 5 Model: The CD14 membrane protein (green) associates with microbial nucleic acids (ssRNA and CpG DNA) at the plasma membrane (black line), which surrounds each cell. It promotes their entry into the cell (endocytosis) within the endo-lysosome organelle, which is also surrounded by a membrane. Other ssRNA viruses enter the endosome in a CD14-independent way, where the acid environment destroys the viral envelope (light blue circle) releasing the viral RNA genome (ssRNA). In the endosome, CD14 also functions as a co-receptor for TLR7 and 9 (red) in the recognition of microbial nucleic acids, initiating an immune response to fight the pathogen.

Drug Effects on Cells

On another day in the same seminar room it was the turn of Post-doc Uwe Rix to summarize his work on the use of chemical proteomics to study the effects of drugs on cells. Drugs that are absorbed through the gastrointestinal tract enter the bloodstream and are then distributed throughout the body, eventually reaching their target cells. When the drug receptor is at the surface of the cell, drugs can elicit their response from the outside. However, some drugs actually enter the cell where they encounter proteins that bind to them. More often than not, drugs bind many different proteins, either within the same cells or tissues, or even in different parts of the body. The usefulness of a drug for a given therapeutic purpose is the integration of all its effects, some of which are good, others of which have no consequence, while some effects are harmful and elicit adverse side effects.

Scrutinizing Cancer Drugs

Uwe, together with technician Manuela Gridling and the mass spectrometry team, is studying the full spectrum of effects of certain anti-cancer drugs. Cancer is characterized by the uncontrolled growth of certain mutant cells in the body and anti-cancer drugs generally work by inhibiting their growth. Inside the cells, the anti-cancer drugs being studied bind quite selectively to a class of enzymes known as protein kinases, which control the cells response to growth stimuli by attaching chemical phosphate groups to target proteins. Uwe and coworkers have been studying the anti-cancer drug dasatinib, which is used to treat patients with Chronic Myeloid Leukemia (CML). They have also been looking at the effects of dasatinib in different cell types, in collaboration with physician and scientist Eric Haura.

Cancer is characterized by the uncontrolled growth of certain mutant cells in the body.

Eric Haura works at the Moffitt Cancer Center in Florida, USA, and has been working at CeMM on sabbatical. He knows that dasatinib can inhibit the growth of lung cancer cells. Fighting lung cancer is Eric's mission and he is astonished that people in Austria are apparently happy to inhale cigarette smoke, the known cause of lung cancer, in public places. Uwe used cells that have been derived from patients with non-small-cell lung cancer, a particularly nasty type of lung cancer, to look for the potential binding targets of the drug dasatinib. It turns out from Uwe's experiments that there are some 40 kinase proteins binding to dasatinib. But they still didn't know which of these drug-target interactions was likely to be responsible for the growth-inhibitory effect of the drug. In other words, if the drug is the key and the kinases are locks to different doors, which doors need to be locked to prevent growth?

Going Back to Their Roots

It was already known from previous work that the cellular protein, Epidermal Growth Factor Receptor (EGFR), which is a protein kinase that is often hyperactive in lung cancer, was likely to play a role. To distinguish which of the other forty kinases were also involved, they looked at which was bound most strongly by the drug and correlated this with kinase function by analyzing the autophosphorylation status with phosphoproteomics. The so-called *Src* family kinases (from **s**a**rc**oma, a particular type of cancer), a group of related protein kinases involved in a variety of cellular functions, was heavily represented in the list of strong binders. The family is named after the first cancer-inducing gene ever identified, *v-src*. Interestingly, Giulio Superti-Furga spent the first part of his independent scientific career studying the molecular mechanism that makes *v-src* a cancer-inducing gene compared to the important but usually harmless cellular counterpart *c-src*. Giulio also contributed to solving the crystal structure of the chicken *c-Src* protein. Now, by coincidence, Uwe Rix and Eric Haura were focusing on the same enzyme.

The challenge was to find out if the drug dasatinib exerted its anti-cancer effect by inhibiting the *c-Src* protein. First it was confirmed that dasatinib could inhibit the enzymatic activity of *c-Src*. Next, Eric Haura and colleagues mutated a single amino-acid residue in the critical active site of the *c-Src* protein. They predicted this would prevent dasatinib binding, as this so-called "gatekeeper" residue is known in many other kinases. This trick had been often used in the Superti-Furga laboratory to test the biological consequences of disrupting a drug-protein kinase interaction. When lung cancer cells harboured an extra copy of this mutated *src* gene, the effect of dasatinib on inhibiting growth was significantly diminished. This strongly suggests that *Src*, like the EGFR protein, was a critical target of dasatinib in certain lung cancer cells.

A Rare Success Story: From Lab to Clinic

These results importantly suggested that dasatinib could also be used in the clinic to treat lung cancer. Indeed, the next time that Eric Haura visits CeMM and addresses his colleagues in the same fifth floor seminar room, he will hopefully report on some promising progress his group are making in this direction using patient groups. So, although the "molecular medicine" cycle of research leading specifically to medical applications is often slow moving and tedious, as this story shows, it is also powerful and worthwhile enough to keep persevering.

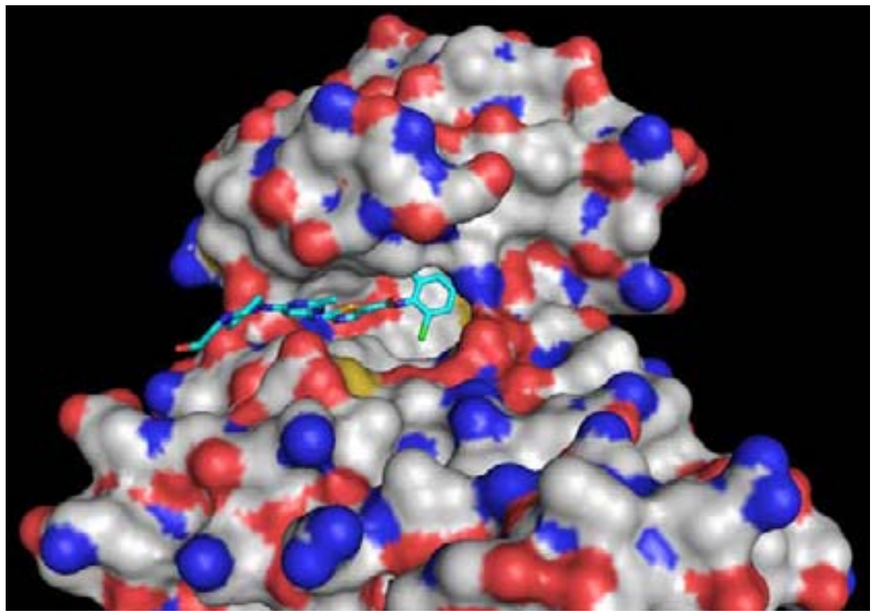

Fig. 6 A model showing the structure of the *c-Src* protein kinase (gray, with highlighted areas in red, blue and yellow) in complex with the anti-cancer drug dasatinib (cyan). Dasatinib binds very tightly to the ATP-binding pocket of *c-Src*, but in a competitive manner, with the terminal hydroxy group (red tip) protruding into solvent space.

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Level **04**

Level 04
Where Molecules are First Detected

Previous page:
Level 04, Room 04.207
Mass Spectrometry

Resonances
Elisabeth Salzer, PhD Student
playing the violin

We leave the fifth floor using the smaller "service" elevator. As the elevator door opens, we can see the sign of the PLACEBO laboratory, and the logo is a yellow and blue pill. What could it mean? And which other labs are found on this floor? It looks different to the other floors we have visited. Looking down the corridor one does not see the usual door to the tissue culture lab but instead sees a glass enclave. Could this be housing CeMM's famous mass spectrometry lab? Is this a super-technology floor? We enter the PLACEBO lab first.

A Joint Effort

PLACEBO sounds like an odd name for a lab focused on the discovery of small bioactive molecules. However, it is actually an acronym for *PLatform Austria for ChEmical BiOlogy*, a network project funded by the prestigious GEN-AU program of the Austrian Science Ministry. The project, which is coordinated by Giulio Superti-Furga, is a joint effort of researchers interested in innovative chemistry (Rolf Breinbauer, TU Graz; Bernhard Keppler, University of Vienna), finding new bioactive small molecules (Veronika Sexl, Michael Freissmuth, Medical University of Vienna) and characterizing the biological mode of action of compounds (Lukas Huber, Medical University Innsbruck, Walter Berger, Medical University of Vienna). While the goal is far from discovering placebos – compounds that by definition have no pharmacological effect – the name rather illustrates that the team are not so naïve to think they can easily develop drugs in an academic setting.

Industry in an Academic Setting

The pharmaceutical industry has longstanding expertise in drug discovery, as well as the resources to cover the high costs of drug development, which is currently close to one billion euro per drug. However, in recent years the numbers of novel approved drugs have stagnated despite increased research spending. This has incited the very recent and exciting trend for a small number of academic institutes to set up their own screening centers. This has the added advantage of bringing academia in general, and CeMM in particular, closer to the clinic, by enabling them to discover novel biological targets and thus more directly contribute to new therapies. In contrast to the often risk-adverse industry, the group can make best use of the innovative biology generated at CeMM and the other academic PLACEBO groups in Vienna, Graz and Innsbruck and implement it to discover active small molecules in a fast and flexible manner.

The screening system takes up the entire center of the PLACEBO lab on the fourth floor of CeMM, but with dimensions of around four by three meters it is still very compact for the multitude of functions included. This allows Stefan Kubicek and his Post-doc and PhD student to set up experiments, culture cells, and prepare compounds on the surrounding workbenches. The setup of the PLACEBO lab was only possible in the new CeMM building, and the fourth floor with its proximity to mass spectrometry and chemical proteomics is the ideal location, bringing together groups with strong technology and small molecule interests.

Consistent with the high-tech flavour of the fourth floor, also the other main laboratory, Mass Spectrometry, is tuned towards the discovery of molecules. 'MS' as it is often abbreviated, is a powerful analytical technique that measures the mass-to-charge ratio (m/z) of charged particles. At CeMM, MS is used to characterize the particular class of molecules called proteins and their smaller break-down products, the peptides. This analytical capability, when systematic, is called "proteomics". Essentially, biological samples are fed into the mass spectrometer and the resultant data are analyzed to identify the constituent proteins. Although the process sounds straightforward and simple, this is far from reality, as we will see further below.

No Placebo, No Drug

Chemical probes can be used to validate that targeting a certain biological pathway for therapy is feasible.

To set up a drug screening center at CeMM, the first step was to establish a high-throughput and high-content screening platform, involving an amalgamation of very sophisticated equipment. The platform has two robotic arms that can handle plates with 96, 384 or 1536 wells, which can each contain a different chemical. Other equipment is used to fill these plates, including acoustic transfer of volumes as low as 2.5 nanoliters (one millionth of a ml), and more standard pipetting robots, dispensers and washers. The most important aspect of the design and setup of the platform was maximum flexibility for different biological readouts, allowing the rapid transfer of biological assays from their original format to a high-throughput screening format. Therefore, the team installed several additional pieces of equipment that could directly analyze experimental assays that are commonly used in the lab, such as a fluorescence plate reader, a qPCR reader and a Luminex reader. Finally, a confocal automated microscope that can analyze images was also fully integrated into the system.

A Complex System

The entire system is housed in a biosafety cabinet, allowing the use of cell lines and primary material, which require specific safety protocols. In addition to the software and automation necessary for controlling the robots, lots of additional informatics support is necessary to work in a controlled and efficient way with the collection of 100,000 chemical compounds. Indeed, the group have barcodes on all labware, which is tracked by a lab information management system, chemistry tools, and data analysis software.

The aim of screening is to find 'hit' compounds that can be further developed to 'chemical probes', which are in many ways comparable to drugs. They can be used to validate that targeting a certain biological pathway for therapy is feasible, meaning that more appropriate drugs (in terms of cost and safety) can be developed. The screening platform was installed in September 2010, and by the end of the year had already generated more than 200,000 data points. The coming year will reveal how successful it can be at generating chemical probes, thereby transforming the basic research performed at CeMM to make the maximum translational impact on human health.

Fig. 7 The PLACEBO screening system allows the fully automated testing of thousands of chemical substances for their biological activity.

2010: Moving to New Chemical Space

For the successful identification of potential new drugs, the composition of the compound library is as important as the screening infrastructure. The group have put lots of effort into optimizing their collection of compounds to maximize the chances of screening success. The main target was to ensure maximum coverage in three areas: known drugs and bioactives, focused libraries, and a chemical diversity library.

Building the Optimal Chemical Screening Collection

To best cover all known drugs in the screening collection, the group first analyzed all 26,900 products that are currently approved for human treatment. Often different dosage forms contain the same active ingredient, and in total these drug products correspond to 2,171 unique compounds. Removing biologicals and compounds only used as diagnostics and in topical applications left 980 individual structures. Many of these are "me-too" compounds that are very similar to each other. Indeed, when the group analyzed the biological targets of these 980 compounds, they unexpectedly found only 180 proteins. This is very low, given the human genome contains ~22,000 protein coding genes, and together with posttranslational modifications and the selective targeting of protein-protein interaction, there are estimated to be hundreds of thousands of potential drug targets. Indeed, having drugs for only 180 of them further justifies the establishment of PLACEBO and similar academic chemical biology efforts. From the original list, the group have selected 221 compounds that hit all targets and show maximum chemical diversity to include in their screening collection.

In addition to approved drugs, so called 'tool compounds' exist that can modulate many proteins and biological pathways. These are either used in biochemical or cell biological experiments, or are currently at early stages of clinical development. Based on the work being carried out at CeMM, the group have established focused compound libraries containing such chemical tool compounds for two classes of enzymes; kinases and chromatin modifying enzymes. These can be used in screens to discover novel biological roles of the target proteins.

Maximizing Chances of Success

Finally, an important aspect of PLACEBO is the ability to identify novel chemical structures as probe compounds for biological pathways. To maximize the chance of identifying such novel compounds, optimal coverage of 'chemical space' in the screening library is essential. Chemical space, which covers all possible molecules, is vast. For example, 1060 molecules are possible when restricted to using a maximum of 30 atoms, and making them would require more mass than exists in the entire universe. Up to now, around 50 million molecules have actually been made by chemists, approximately half of which are commercially available. After analyzing different commercial libraries for their chemical diversity and drug-likeness, the team decided to acquire a 91,000 compound library in collaboration with the Dana Faber Cancer Institute in Boston, U.S. Furthermore, PLACEBO partner Rolf Breinbauer, at Graz University of Technology in Austria, will produce unique compounds for the screening platform.

Collectively, these libraries targeting known drugs, kinases, chromatin, and chemical diversity will total up to 100,000 compounds, thereby giving the group a good chance of identifying hit compounds.

An important aspect of PLACEBO is the ability to identify novel chemical structures as probe compounds for biological pathways.

Targeting the Fourth Level of Gene Expression Control

In cancer, control mechanisms fail at all these levels of transcriptional regulation, allowing cells to grow unrestrictedly and to invade other tissues.

Controlling the expression of genes in order to make specific proteins is essential for all cells to properly function. Because this process is so important, there are multiple mechanisms involved. First, for each gene, the DNA sequence is split into separate promoter, enhancer and coding sequences. Specific DNA-binding proteins, so-called transcription factors, can recognize and bind some of these sequences. Transcription factors also recruit other proteins that can chemically modify both the DNA and associated histone protein components of the chromatin. Finally, on what could be considered the fourth level of control, selective binding proteins recognize these chromatin modifications and regulate chromatin structure, the recruitment of RNA polymerase and thereby transcription.

In cancer, control mechanisms fail at all these levels of transcriptional regulation, allowing cells to grow unrestrictedly and to invade other tissues. Unfortunately, direct intervention to revert the genetic changes that cause cancer is currently impossible in the clinic. Similarly, the binding of transcription factors to DNA is not easily inhibited by drugs. Therefore, the changes to chromatin structure that cause erroneous expression of the pro-proliferative and invasive genes that can cause cancer, are among the most promising targets for innovative cancer therapy.

Stopping Cancer Cells with a PHD

With a strong background in epigenetics research, and a history in successfully developing selective chemical probes for histone methyltransferases and demethylases, the Kubicek lab is now focusing on methyl-binding domain proteins. Certain cases of acute myeloid leukemia (AML) are caused by chromosomal translocations that rearrange genes, causing the abnormal fusion of specific methyl-binding domains, so called PHD fingers, with common highly expressed partners. The resultant aberrant fusion proteins cause leukemia by maintaining the expression of certain key genes that should normally be switched off. Using molecular biology methods, it has been shown that preventing the binding of the PHD domains in these fusion proteins to their targets can stop the cancer cells from growing.

The group have performed a virtual screen for small molecule inhibitors of methyl binding proteins. Currently, no such compounds are available, and the limited success of targeting protein-protein interactions makes is unlikely that pharmaceutical companies are developing such compounds. Their results are promising, and they are now in the process of testing their hit compounds in cellular assays to determine if they can be validated to the point to become candidates for potential new treatments for certain specific cases of AML in the distant future.

As we leave the PLACEBO laboratory we turn left on the corridor and aim straight to the mysteriously-looking glass cubicle. We read the sign: “Mass Spectrometry”.

Fig. 8 Principal investigator Stefan Kubicek and his team with the robotic arm of the PLACEBO screening facility.

Chasing the Masses

Researchers, engineers and architects worked together to customize the laboratory.

As mentioned, mass spectrometry is a technology-intense endeavour. Coaxing the very best from these specialized instruments requires unsurpassed love, care and attention. The fourth floor of the new CeMM building is currently home to four machines: a quadrupole time-of-flight (QTOF) mass spectrometer from Waters, one LTQ Orbitrap XL and two latest-generation LTQ Orbitrap Velos mass spectrometers. All four instruments have an associated nano-HPLC (high performance liquid chromatography) system from Agilent that is used to separate mixtures of peptides prior to entry into the mass spectrometer.

A Designer Building

Modern day mass spectrometers are highly sensitive to perturbations in the environment. Therefore, careful attention was paid to the design of the new laboratory to ensure the team, led by Keiryn Bennett, could push the boundaries of the technology even further while still working to the highest possible standards. There are currently seven people in the group, and the team worked together with the architects and engineers to customize the laboratory. New plastic materials were to be avoided as the vapours generated are literally sucked into the mass spectrometers, contaminating the data. Thus, even the floor is designer-made and not the usual ‘plastic’ glued-down floor found in standard laboratories.

It is very common to find mass spectrometry departments hidden in the basement without any natural light. The reason for this is primarily due to the sheer weight of the equipment. At CeMM, an airy, ‘house-of-mirrors’-type glass laboratory on the fourth floor of the building was designed. Here the mass spectrometers are visible from every angle and can be shown off to visitors without having to physically enter the room. This design also takes into consideration the well-being and safety of the operators, who are working with equipment powered by high-voltage electricity.

Individual Spaces Allow Improved Control

The size of the new laboratory space meant that each mass spectrometer and associated HPLC system could be housed in its own cubicle. This design allows the generation of highly stable yet independent microenvironments around each system. Organising the instruments in this way makes it easier to maintain a stable air temperature of 20˚C (+/- 1˚C), which is of critical importance for optimal instrument performance. The main air conditioning has a backup in case of failure, as without cooling the temperature can increase by 15˚C within half an hour causing the mass spectrometers to overheat and ultimately break down. Each cubicle has a sensor, and any fluctuations in air temperature and humidity can be closely monitored.

There are individual laminar flow-like air conditioning systems in each cubicle to avoid disturbing the fine liquid spray that is generated at the interface between the HPLC and mass spectrometer. The spray contains the sample that is subsequently analysed by the mass spectrometer. Standard air conditioning systems generate a laboratory ‘breeze’ that is often a problem for mass spectrometry analyses, as each cycle causes small gusts of air turbulence. The inspiration for this design came from the Institute of Atomic and Subatomic Physics, Technical University of Vienna, located in the third district on the other side of the city. The engineers and members of the MS team visited a group of physicists from the institute that face similar problems as they run experiments using lasers that also require cool, stable temperatures with minimal air fluctuation. Based on these discussions, the idea was adjusted for the mass spectrometers and so far the laminar-flow systems function extremely well.

Keeping Things Moving

All four mass spectrometers can be operated from the comfort of the office by remote desktop access. At weekends the equipment is carefully monitored from outside the institute as it is in constant operation. The laboratory also has an uninterrupted power supply to compensate for power outages and avoid disruption of experiments and forced shutdown of the instrumentation. The move from the old building down the road to the new building required extensive and careful planning and took several weeks to complete, but ultimately was a clean, well-orchestrated process. An interesting observation was made when the instruments were moved into the new designer space. There was an order of magnitude reduction in interfering background noise, concurrent with a marked increase in detection sensitivity. It appeared as if the instruments were more than content with their new surroundings, and improved their performance.

Establishing New Methodology

The MS group is involved in numerous proteomic studies at CeMM and also with several external national and international collaborators. The team is constantly pushing and refining technological boundaries to complement the requirements that biological and medical progress demand. Two such recent advances are: (i) the introduction of chemical crosslinks to 'freeze' or 'trap' protein complexes; and (ii) chemical enhancement of peptide signals to improve the sensitivity of detection. The MS team has been optimising these steps to overcome some of the current limitations of the technology and have shown some promising results. These recent advances have enabled scientists to extract more sophisticated information from their biological experiments.

Building Protein Complexes

All biological functions are regulated by integrated interactions between multiple proteins. These interactions occur in different ways: some are dynamic and exist only transiently, while others are highly stable. A chemical crosslinking strategy can be used to 'trap' the protein interactors that work together with an individual protein to perform a function. This involves the physical introduction of strong covalent links between the individual proteins in a complex.

The mass spectrometry group have been establishing a methodology that is based on SH-tagged protein purification, followed by chemical crosslinking and mass spectrometric analysis. This approach increases the possibility of identifying weakly-binding proteins, and also reveals the physical organisation of the individual proteins that go together to form a working complex. This information can be used to build virtual three-dimensional images of intact protein complexes. From this information, it is possible to model the relationships between other protein complexes and help to understand how proteins act as a team to perform a specific biological function.

Standing out from the Crowd

In collaboration with lung cancer oncologist Eric Haura from the H. Lee Moffitt Cancer Center in the U.S., the MS group has also been experimenting with the iTRAQ reagent (isobaric tag for relative and absolute quantitation). This tag is normally used to label protein fragments with different chemical groups, thereby enabling the relative quantitation of the same proteins in several biological samples. Now, the group has investigated the use of these tags for something else: to enhance the signal of minute quantities of proteins. This new approach is a significant improvement over previous methods, and allows the detection of low-abundance proteins that were previously impossible to detect by conventional mass spectrometric methodology.

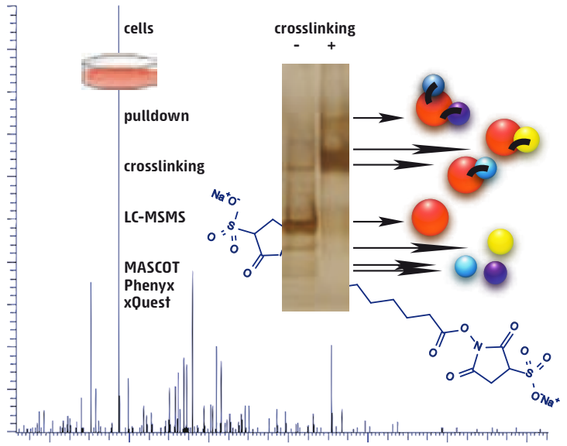


Fig. 9 Generic strategy for the chemical crosslinking and 'trapping' of stabilised protein complexes.

Proteomic Analysis of Body Fluids to Study Disease

Skin fluid samples provide valuable insights into disease initiation and progression.

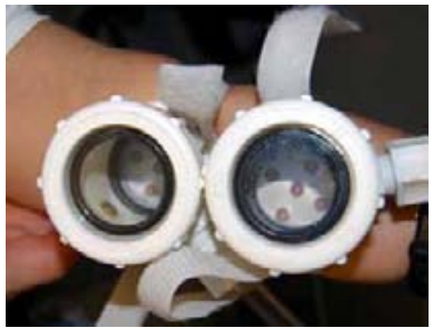
The proteomic analysis of any body fluid is hampered by the high complexity and dynamic range of the component proteins. To overcome this constraint, highly-abundant proteins can be removed using special depletion kits, thus enabling the detection of low copy number proteins. In addition, pre-fractionation techniques and iTRAQ-labelling improves the number of proteins that can be detected, and allows a relative quantitative comparison between different patient samples or disease states.

In collaboration with Adelheid Elbe-Bürger, Christopher Schuster and Georg Stingl from the Department of Dermatology at the Medical University of Vienna, the MS team has developed a proteomic strategy that allows not only a comprehensive identification of proteins present in a blister fluid, but also a comparison of the relative quantities of the same protein across different samples. A more thorough understanding of the proteins present in skin fluid samples from healthy and diseased skin could provide valuable insights into the underlying mechanisms responsible for initiation and progression of skin diseases. Ultimately, it is envisaged that such knowledge will lead to improvements in the treatment of skin disorders.

A Blistering Start

Using mechanically-induced suction blister fluid, the group have generated preliminary data from a single healthy control subject and identified a total of 354 proteins including several associated with skin function. Importantly, the approach identified many low-abundance proteins. Some of these proteins are found specifically in the epidermal layer of the skin, and are already known to be involved in certain cellular processes such as cell-to-cell interactions and pathogen defence. Other identified proteins have already been associated with certain inflammatory skin diseases, supporting the notion that such an approach can be used to monitor pathological conditions in the skin. The group will assess the utility of the approach for comparing different control samples before embarking on a comparison of control subjects with patients suffering from a range of skin ailments.

We leave the mass spectrometry laboratory and pass by the small chemistry laboratory that allows the chemical proteomics branch of the Superti-Furga team and PLACEBO to operate relatively simple chemical reactions such as the ones needed to "join" chemical compounds to matrices for chemical proteomics. Similar to the other floors, there is also a large office with a glass wall where lab members have their writing desks. Now it's time to walk back to the staircase and go down one more flight to see what's on the third floor.



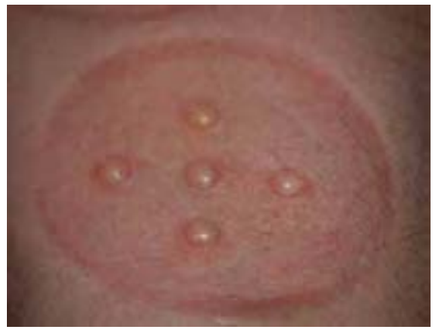


Fig. 10 Formation of mechanically induced blisters.
A) Pressure device for separating epidermis from dermis
B) Blister formation from interstitial fluid (5x5mm).

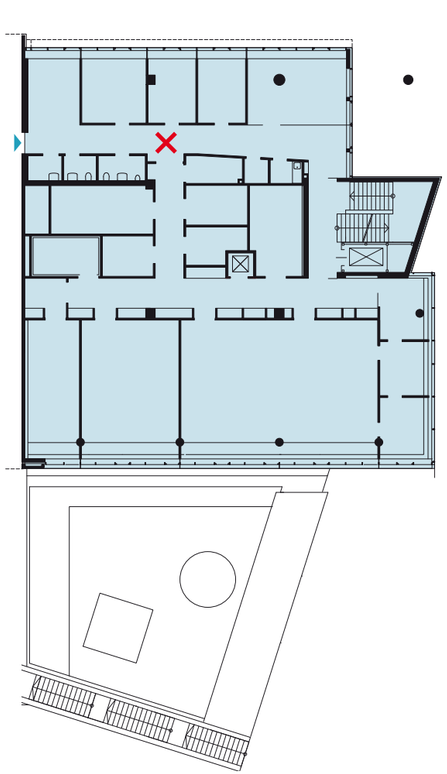
Ce–M–M–
Research Center

Level **03**

Level 03
Where Epigenetic Regulation and Infection Processes are Studied

Previous page:
Level 03
Corridor

Fast forwarding
Rui Martins, PhD Student
riding his skateboard



Level three is the most complex floor in the building. Across a small path in one of the research buildings of the General Hospital is the Knapp laboratory. Sylvia Knapp is a medical doctor and Associate Professor of Internal Medicine at the Medical University of Vienna, who still works in the intensive care unit of the hospital taking care of critically ill patients. The group signifies the close ties between CeMM and the clinic. Treatment in the intensive care unit of a hospital unfortunately makes patients more vulnerable to secondary infections, some of which can be life threatening. This is because most patients have weakened immune systems and are at significant risk for conditions such as sepsis. In the clinic, Sylvia Knapp works on the pathogenesis and treatment of sepsis and bacterial infections. These conditions are strongly associated with the innate immune response involving inflammation, which is also the primary focus of the Knapp research lab.

Before we move into the Knapp laboratory in the AKH, we look at level 3 in the CeMM building. In the CeMM building itself, there is the administration on one side and the Barlow lab on the other.

The Barlow lab is the second biggest group at CeMM. The open-plan lab is divided in two parts. One lab, corresponding to two thirds of the other floors, is occupied by the three Post-docs, four PhD students, and the two research technicians that currently form the Barlow team. The first activity in the morning is usually to switch on the computers. Scientists have become completely dependent on computers, both to generate and analyze data, and to access information. One of the most popular websites is PubMed, which is a searchable database of over 19 million citations from life sciences journals without which no one could keep up with the literature. Indeed there are more than 3000 papers published each year in the Barlow lab's topic area alone. There is a lab custom that if anyone finds an interesting paper they e-mail it around the lab.

On most days, at around 3 pm, you will find the majority of the lab crammed in to one office drinking black tea with milk. This gives them a chance to discuss what is coming up in the week, to brainstorm some experimental problems, or just to gossip. Occasionally someone makes a cake, particularly if there is a birthday or a paper has been accepted for publication. Everyone is looking forward to summertime when they can also go up to the CeMM terrace in the evening and enjoy the fresh air and the spectacular view of the city.

Keeping Things Organized
Even with the carefully designed layout of the CeMM building, scientific laboratories tend to become easily cluttered. This is because there is so much stuff required to perform a single experiment. Simply growing cells to use in an experiment requires a wide variety of different materials and equipment such as sterile dishes, tubes and pipettes, special liquid medium, heated incubators, a sterile 'culture hood' and a microscope. To keep laboratories functioning efficiently requires careful organization, and the Barlow lab is probably one of the most organized labs in the building.

All the equipment and materials have their own place in the Barlow lab, and shelves, drawers, fridges and freezers are all clearly labelled. Labelling is a useful way of keeping things organized and informing people what something is and how it should be used. Epigenetics, the main focus of the Barlow lab, also involves a sort of labelling but this time of DNA, which helps to organize it within the cell. Epigenetic labels are specific chemical modifications that act as information marks. They were added to the chromosomes in each of our cells when we were undergoing embryonic development in the uterus. These labels have an influence on when and where individual genes are expressed to make specific proteins, and thus how cells and organisms develop and function. Disruption of epigenetic marks can lead to severe developmental disorders and diseases such as cancer.

The Barlow lab is investigating how epigenetics controls the expression specifically of imprinted genes in the developing mouse embryo. Most of our genes have two copies; one inherited from our mother and one from our father, and both copies are normally used to make proteins. Imprinted genes are a special type of gene where only one copy is expressed, and the copy that is chosen depends upon the parent from whom it was inherited. Imprinted genes are becoming more and more important as an epigenetic regulatory model to help us understand how epigenetics control genes in human disease. The Barlow lab have been using imprinted genes to "break the epigenetic code" that is hidden inside the human genome. And now, using some of the latest high throughput technologies, which have been installed in the new CeMM building on the seventh floor under the guidance of Robert Kralovics, they are currently testing how epigenetic mechanisms are used in humans to silence genes in normal tissues and in cancer.

Breaking the Epigenetic Code

The visceral yolk sac is a novel model system for the study of epigenetics.

Evolution has led to the same biological process, such as cell growth or limb development, occurring in roughly the same way across diverse cell types and species. This means that fundamental information about a particular process, can be studied in a so-called 'model' system. Models are chosen based on various practicalities such as accessibility, ease of use and cost. The best models generate insight that can be directly applied to many other cell types or organisms, and all models should be critically assessed to ensure they produce accurate and useful information.

In the study of epigenetics, the mouse placenta is often used as a model to describe epigenetic processes in embryos and adult mice. However, the placenta is not part of the actual mouse embryo and also contains contaminating maternal tissue. At the beginning of 2010, Post-doc Quanah Hudson and PhD student Tomasz Kuliniski wrote a review to raise awareness of serious problems using the mouse placenta as a model, which was published in the journal Heredity. They have also now completed a study that confirms the placenta has serious drawbacks for epigenetic studies on imprinted genes.

Instead, the group found that the visceral yolk sac surrounding the developing mouse embryo in the uterus provided a much improved model system. They have now used this tissue to show, contrary to studies based on the placenta, that imprinted gene expression in the yolk sac is clearly regulated by one of the best-studied epigenetic marks – DNA methylation. As a result of this study, the lab have set a new and more accurate baseline for identifying additional factors responsible for epigenetic gene regulation in development and disease.

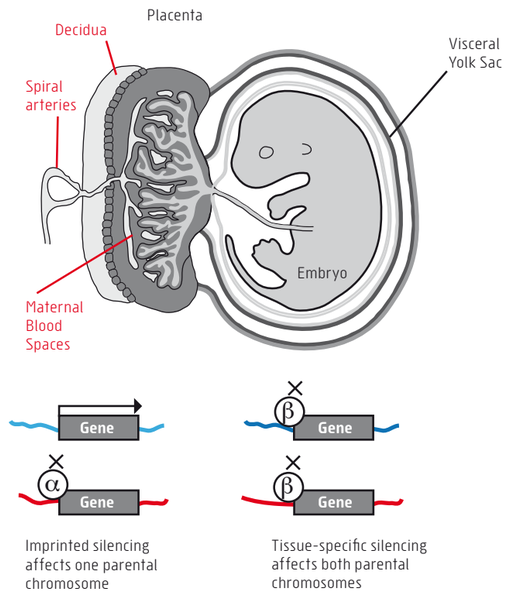


Fig. 11 Top: Illustration of a mouse embryo midway though development showing a close-up of the placenta and the contaminating maternal tissues (red), which cause problems in its analysis. Tissues that only contain embryonic cells such as the visceral yolk sac membrane are shown in grey.
Bottom: Genes can show imprinted-gene silencing or tissue-specific silencing that is controlled by different epigenetic marks (alpha & beta). Good model systems should not confuse these two types of silencing.

Crystallizing Ice Control

Recently, the regulation process of imprinted genes has started to be shown.

Imprinted genes – those that are expressed depending on the parent from which they were inherited – were discovered almost 20 years ago, but it was only recently shown how this process is regulated. A particular sequence of DNA called an ICE (for imprint control element) was found to be responsible for silencing small clusters of genes on only one of the two chromosomes. The ICE has two properties of special interest to epigeneticists. First, it turns on or activates an unusual, large 'macro' non-protein-coding RNA that actually causes the silencing. Second, in order to work, the ICE must itself avoid attracting DNA methylation, one of the most common repressive epigenetic marks in the human genome.

A few years ago the Barlow lab described how an ICE resembles another commonly occurring short stretch of DNA that overlaps the start of most human genes, which is known as a CpG island. The CpG island is so named because it is very rich in C and G nucleotides (as opposed to the alternative A and T nucleotides that altogether make up DNA), which is unusual for mouse and human chromosomes. CpG islands also turn genes on so that they can be used to make specific proteins, and like ICE must also avoid acquiring epigenetic labels themselves.

Mechanisms of Control
For the last few years, the Barlow lab has been trying to take one ICE apart to find out exactly how it works. Martha Körner, a PhD student in the Barlow lab, used "gene knockout" technology in mouse embryonic stem cells to remove two different parts of the ICE sequence, allowing her to then test if the ICE required these parts to function normally. These experiments revealed that only the first half of the ICE sequence is important for its function. One of the most surprising results from this study was that the DNA elements that turn genes on in CpG islands were unexpectedly found after the start of the gene. It is likely that this will be a common characteristic shared by all CpG islands that overlap the start of most human genes. This information will also help explain how epigenetic labels are attracted to CpG islands in human diseases such as cancer.

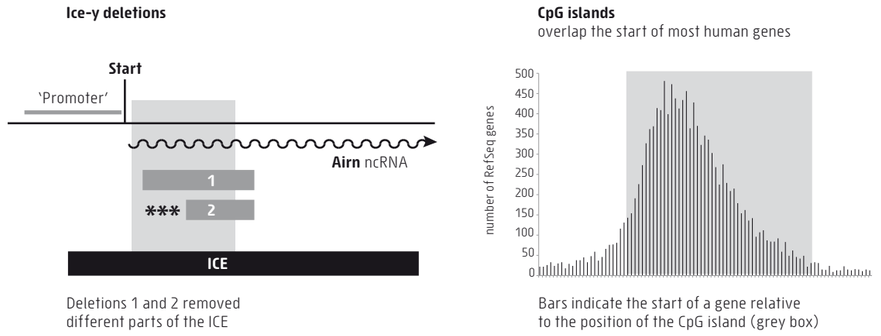


Fig. 12 Left: the segments of the ICE sequence that were deleted using gene knockout technology.
Right: the position of the start of a gene relative to its CpG island shows that the promoters of a large number of genes actually lie upstream to the CpG island.

Epigenetic Regulators in Human Disease

Macro ncRNAs may play an important role in the cancer process.

Disruption or deregulation of many biological processes can cause disease. Indeed, cancer is caused by a deregulation of cell growth, which is normally controlled by many different mechanisms, including epigenetics. Other work in progress in the Barlow lab is the implementation of a new approach to epigenetics in cancer. Their hypothesis is that molecules known as macro ncRNAs (non-protein-coding RNAs) mediate the epigenetic deregulation of genes in tumours. The rationale for proposing this comes from two observations. First, macro ncRNAs are known to epigenetically silence imprinted genes. Therefore they could also perform this same function but in an abnormal way in cancer cells. Second, there are many macro ncRNAs in mammals, and some are already known to be deregulated in other diseases.

The lab has experience with experimental methods involving custom NimbleGen tiling arrays and RNA-seq for identifying macro ncRNAs in mouse imprinted regions. Now they will apply this technology to cancer. The new Illumina sequencing machine located on the seventh floor of the CeMM building is used to perform the RNA-seq experiments. Tiling arrays and sequencing produce vast amounts of data, so Florian Pauler, a Post-doc in the lab, has been developing a new bioinformatics tool to help them identify the macro ncRNAs. The group are collaborating with the CeMM Bioinformatic group of Jacques Colinge and the Hofacker lab from the University of Vienna, to further improve these detection methods.

Valuable Neighbors

The Barlow lab plans to initially search for macro ncRNAs associated with tumour suppressor genes in leukemias and lymphomas. Hematological malignancies like leukemia are already intensively studied at CeMM, particularly in the Kralovics and Superti-Furga laboratories on the seventh and fifth floors, respectively. Thus, there are plenty of nearby resources and expertise. They also have collaborations with Robert Zeillinger and Iveta Yotova at the Vienna General Hospital (AKH) on the same campus as the CeMM building, as well as Kurt Zatloukal and Johannes Haybäck at the Medical University of Graz.

Understanding the function and regulation of the newly identified macro ncRNAs is an important long-term goal to improve our understanding of gene regulation in cancer. A PhD student in the lab, Irena Vlatkovic who recently successfully defended her thesis, has made a pilot study in colon cancer using genome tiling arrays to examine 2% of the human genome for macro ncRNAs. Of the 120 novel macro ncRNAs that she found, more than half changed their expression in colon cancer cell lines compared to normal colon tissue, and 22 were only expressed in the cancer cell lines. This suggests that these macro ncRNAs may play an important role in the cancer process and are a valuable starting point for future work on this topic.

To help fund this work, the Austrian Science Fund (FWF) has recently approved a new Special Research Program entitled "RNA regulation of the transcriptome" under the lead of Renée Schröder at the Max Perutz Laboratories (MFPL) in the third district of Vienna. This program aims to investigate how RNA molecules control the flow of genomic information from genes to function, and how these RNAs are regulated. Ultimately, this will improve our understanding of developmental disorders that arise from errors in these circuits. The program involves 11 research groups from Vienna based at the institutes, MFPL, CeMM, IMP, IMBA, GMI, as well as the University of Vienna and the Medical University of Vienna. It will be funded with approximately 4–3 million Euros over the next four years. This special research program is one of the most prestigious avenues for funding by the FWF. It supports the establishment of long-term and interdisciplinary research networks enabling scientists to conduct high-end research and helps to strengthen Austria's international stance in science.

The third floor differs from floors four to seven because the north axis is taken up by the CeMM administration. Walking from Denise Barlow's lab, you can either access the administration corridor though the staircase landing or through a double glass door if you have access with a magnetic card. We are now standing approximately in the middle of the building.

Connecting People Between Buildings

We leave the CeMM building through the entrance hall common to the Anna Spiegel/CTR laboratories of the Medical University and CeMM. Outside the door, we walk 35 meters in a straight line to the "East" entrance of the General Hospital. The path is bordered on both sides by two wings of the General Hospital/Medical University research buildings. We enter through the revolving door and, remaining on level three, enter the wing of the building of the "Forschungslabor der Klinischen Abteilung für Infektionen und Tropenmedizin" where the laboratory of Sylvia Knapp is situated. Although the Knapp lab is located in a separate building, the windows of the lab can actually be seen from the entrance to the CeMM building. Lab members often visit CeMM to use equipment, such as the virus room and the FACS machines, which enable to scan populations of cells. They also use the robots and the mass spectrometers in collaboration with Stefan Kubicek and Keiryn Bennett on the fourth floor. The Knapp lab holds their own weekly lab meetings as well as their weekly journal club in one of the CeMM seminar or meeting rooms, and often have lunch in CeMMs cafeteria. Thus, the group are integrated into every aspect of CeMM life, including the institute's scientific meetings, which are held weekly on the eighth floor.

In 2010, the outcome of a very successful collaboration between the Knapp and Superti-Furga groups was finally published in the *Journal of Experimental Biology*. The project, described in more detail in the fifth floor section on the Superti-Furga lab, uncovered a new role for proteins involved in detecting invading intracellular pathogens and initiating an innate immune response.

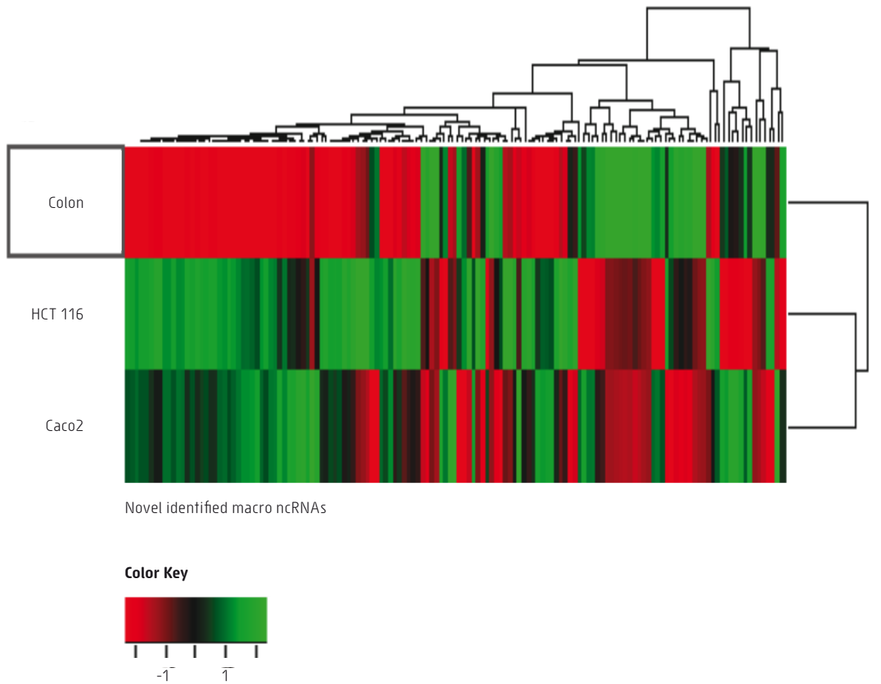


Fig. 13 Heat Map shows expression profiles of 143 novel and known macro ncRNAs in normal colon and in two colon cancer cell lines (HCT116 and Caco2).

Inflammation and Pneumonia

The tight regulation of inflammation during bacterial pneumonia determines the clinical outcome.

Certain species of bacteria are highly virulent and cause a serious threat to human health. *Streptococcus pneumoniae* (or pneumococcus) is a human pathogenic bacterium that can cause many different diseases. One of the most significant, in terms of human health burden, is pneumonia, an inflammatory disease of the lung. How inflammation is linked to the progression of pneumonia upon infection by *S. pneumoniae* has been one of the recent focuses of the Knapp lab.

Signalling Pathways: All About Teamwork

Researchers in the Knapp lab use mouse models to investigate mechanisms of disease. They were particularly interested in the role of an enzyme called PTEN, which has already been implicated in cancer. PTEN is part of an important intracellular signalling pathway, which is known as the PI3K pathway after one of its key members. Signalling pathways enable a cell to selectively respond to extracellular signals such as hormones and growth factors. They are composed of many different proteins and molecules, which perform a variety of functions.

Some of the proteins in a signalling pathway reside at the outer cell membrane where they detect the extracellular signals, while others relay the signal through the interior of the cell by binding and modifying each other. Eventually, other proteins in the pathway bind to the cell's DNA and induce the expression of even more proteins that finally mediate an appropriate cellular response, such as growth or differentiation. Depending upon the extracellular signal, the PI3K pathway can induce many different responses including cell death or cell growth. Indeed, PTEN has been shown to play multiple roles in cells, such as modulating the inflammatory response, and the physical elimination of bacterial pathogens.

The Role of Pathways in Disease

To investigate the function of PTEN in *S. pneumoniae* infections, researchers in the Knapp lab made use of a so-called conditional knockout mouse, meaning that a certain group of blood cells in the mouse, which mediate the inflammatory response, were unable to make the PTEN protein. Upon infection with *S. pneumoniae*, the group could analyze disease progression and compare it with normal 'wild type' mice to elucidate the role of the PTEN protein. They found that the knockout mice lacking the PTEN protein had improved survival rates. They concluded that PTEN both promoted inflammation but also inhibited the function of some blood cells to clear the lungs of bacteria. These data show that the tight regulation of inflammation during bacterial pneumonia determines the clinical outcome. Their results were published in the *Journal of Immunology* in 2010.

In addition to this, in collaboration with Gernot Schabbauer in the Department of Vascular Biology and Thrombosis Research, Center for Biomolecular Medicine and Pharmacology at the Medical University of Vienna, the group showed a role for two additional proteins in mediating inflammation via the PI3K pathway. This work was published in the *Journal of Leukocyte Biology* in 2010. In another collaborative project with the group of Wilfried Ellmeier from the Division of Immunobiology, Institute of Immunology, also at the Medical University of Vienna, the group studied the role of a kinase called Tec in the host response to *S. pneumoniae*. This work was published in the *Journal of Immunology* in 2010.

On a somewhat related topic, a collaboration with Mathias Müller from the Institute of Animal Breeding and Genetics, University of Veterinary Medicine in Vienna, uncovered a role for protein translation in controlling the production of the proinflammatory cytokine IL-1beta, which has a major role in many inflammatory diseases. Their results were published in the *Journal of Immunology* in 2010.

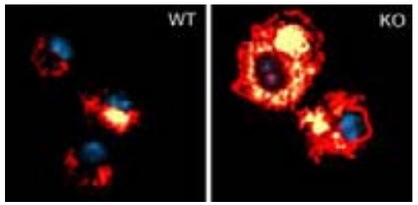


Fig. 14 Phagocytosis of Streptococcus pneumoniae (green) by primary alveolar macrophages from wild type (WT) and PTEN-deficient (KO) mice. Nuclei are stained blue with Dapi, and lysosomes stained red; the overlay of ingested bacteria with lysosomes appears yellow.

An Emerging Deadly Disease

Staphylococcus aureus literally translates as 'the golden seed'. However, this Gram-positive bacterium has been somewhat misnamed, given it is a leading cause of human disease worldwide. Recently, new strains of *S. aureus* have emerged that are resistant to the antibiotic methicillin. These strains (known as MRSA) have evolved as a result of decades of antibiotic use, and more significantly misuse, whereby antibiotics are prescribed for patients suffering from viral infections like flu, for which they are useless. These dangerous MRSA strains were originally confined to hospital settings, but the new strains (known as community acquired MRSA, or CA-MRSA) are also found in the general public and are highly virulent. The most dangerous site of infection by CA-MRSA is the lung, with severe necrotizing pneumonias in infected patients. Worryingly, high mortality rates have been reported, even in patients that were young and previously healthy.

Toxic Substances

Many bacteria cause disease by releasing toxins into the body. Panton Valentine toxin is a pore-forming bacterial toxin found in most CA-MRSA strains. Some scientists have predicted that this toxin is a key virulence factor in these new infections, and it has been shown to cause cell death. The Knapp lab wanted to know if and how Panton Valentine toxin was involved in lung inflammation. Ana Zivkovic, a PhD student in the lab first determined that this toxin indeed inflamed the lung. Furthermore they identified the constituent of the Panton Valentine toxin that mediated this inflammatory response, and the cellular factors required for this to happen. The novelty of this work lies in the discovery that parts of the bacterial toxin exert potentially protective inflammatory effects independent of their other function in pore formation. These findings might explain why antibodies that block the toxin have not been promising in preventing lethality in preclinical pneumonia models. This work was recently published in the *Journal of Immunology*, where it was available online in 2010.

In addition, Stefanie Sigel, a Post-doc in the Knapp lab, studied how molecules from *S. aureus* are recognized by human blood cells. She found that human antibodies are able to augment the inflammatory response to specific bacterial molecules. This work was published in the *Journal of Immunology*, in 2010.

Leaving the Knapp lab, we walk back to the CeMM building and step down to level 2.

Antibiotic resistant strains evolve as a result of antibiotic use and misuse.

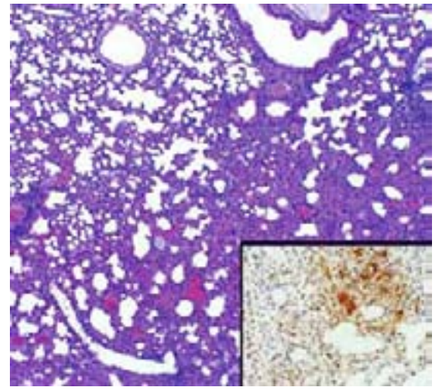


Fig. 15 Lungs from mice 48h after infection with *S. pneumoniae* bacteria were stained with Haematoxylin and Eosin and imaged under the light microsope. Inset shows neutrophils (in brown), a special form of blood cells that enter the lung during infection.

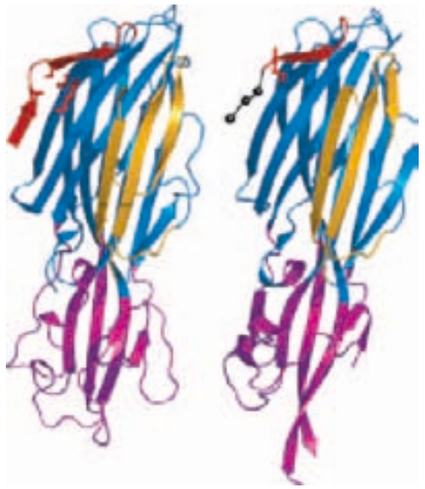


Fig. 16 Structure of Panton Valentine Leukocidin components LukF-PV (left) and LukS-PV (right). Adapted from (*Joubert et al*, JBB 2007).

Ce–M–M–
Research Center

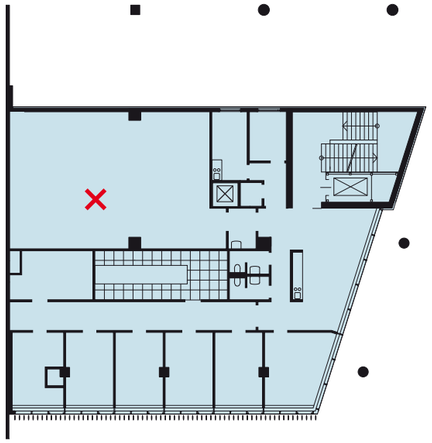
Level **02**

Level 02

Where Data is Gathered, Managed and Analyzed

Previous page:
Level 02, Room 02.204
Machine Room

Giving the beat
Philipp Hainzl, Technical Assistant
playing his drum kit



The second floor is the data center of the CeMM building. Here one can find the IT department, that keeps the electronics up and running, including the computers, printers and communication networks. Plants, computer screens, spare parts and lots of cables make up the kingdom of Michael Pilz and Joachim Tröster. It is not often that you find them both in at the same time, as one is often going around the building to install computers, fix problems or organize the projection in the seminar rooms. They also oversee the web pages, intranet and the infoscreens, announcing the seminars of the whole building in the third floor entrance hall and in the foyer on level eight. If you listen closely you can hear the computers humming in their cabinets in the server room across the corridor.

Walking down the corridor, you come across the three offices housing Jacques Colinge and the bioinformatics team.

The bioinformatics group led by Jacques Colinge is located along the southern axis of the building. This position, with all the laboratories above, symbolically reflects one important mission of the group: to support the other CeMM labs and first make sense of their data. The team has been setting up a computational infrastructure able to deal with the enormous data flows that are generated by some of the most sophisticated modern technologies available at the institute.

Establishing a Solid Infrastructure

Some of the research at CeMM utilizes two powerful in-house technologies; mass spectrometry for the identification of proteins, and so-called “next-generation” DNA sequencing. Both create large volumes of data, as much as 1 terabyte per week, that need storing and that also require computer-intensive data analysis. The move to the new CeMM building along with the acquisition of the most recent next-generation sequencing machine was a good opportunity to build a powerful computer cluster (>350 cores) and data management system. This set-up can handle 40 terabytes of digital information and runs the institute’s proprietary data workflow management software, databases, and data analysis programs.

A carefully designed computer infrastructure is critical for any modern biomedical research institute to function efficiently. At CeMM, the set-up enables first the customized analysis of any newly generated data, followed by its integration with existing data either from CeMM or from other institutes. The capacity of scientific technologies like mass spectrometry and sequencing continue to grow exponentially, as do available data collections from other institutes. Fortunately, computer and storage power are growing at a comparable pace.

Building Models

The bioinformatics group also develops statistical models that are used to analyze data generated by several CeMM research projects. Their aim is to build a collection of mathematical models that can perform rigorous data analyses on combinations of datasets originating from multiple technology platforms. These models are the foundation of deeper and more biology-oriented bioinformatics projects, and illustrate CeMM’s efforts to build cutting-edge data analysis tools.

Mathematical Modelling of Biological Data

Novel statistical models generate highly accurate protein complex predictions.

Many CeMM research projects generate vast quantities of data that need to be effectively analyzed to produce meaningful biological conclusions. Beyond establishing the infrastructure for managing the data, the bioinformatics group also develops diverse methods to properly model them, in order to generate novel conclusions. They focus mainly on statistical approaches, which also allow them to determine the level of accuracy of their results.

Recently, in collaboration with Karl Mechtler from the Protein Chemistry facility at the IMP/IMBA research institutes in Vienna, and Jean-Charles Sanchez from the Biomedical Proteomics Research group at the University of Geneva, the group has invented novel statistical models for quantitative proteomics analyses and for predicting the existence of protein complexes. Quantitative proteomics is a powerful analytical technique based on mass spectrometry. It simultaneously measures the protein content of several biological or patient samples as well as the relative abundance of the individual proteins, e.g. through iTRAQ™ and TMT™ technologies. This approach can reveal differences between individual samples, such as a disease and a control (healthy) sample, which can provide insight into why diseases occur, or how they respond to certain treatments. The new statistical model they have developed provides researchers at CeMM with a tool to use quantitative proteomics in a simple but highly sensitive way.

Using Algorithms to Identify Protein Complexes

In living cells, proteins usually act in groups known as protein complexes to perform specific biological functions. Identifying the individual proteins in these complexes is important for understanding their function. Pulldown experiments can isolate proteins in a complex by using a 'bait' protein to fish in a biological sample for all the other proteins (prey) to which it binds. These binders can then be identified by mass spectrometry. Data generated from these sorts of experiments, obtained for several bait proteins, constitute tricky puzzles that need analyzing by complex algorithms before the true protein complexes can be identified. The group has introduced a new advanced statistical learning method that explores all possible interaction configurations and generates highly accurate protein complex predictions.

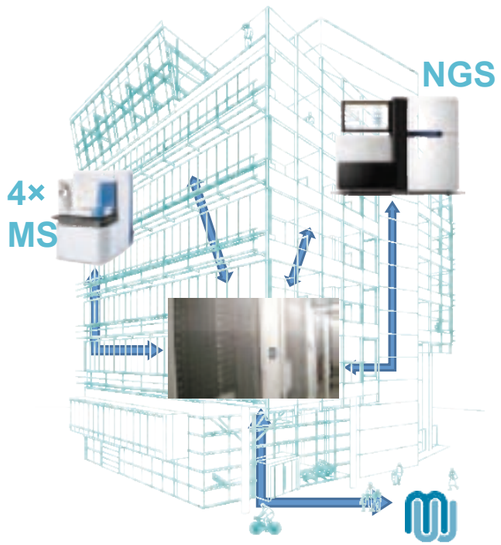


Fig. 17 The CeMM computer cluster is at the center of all scientific data flows. It processes the huge data volumes generated by four mass spectrometry (MS) instruments and one DNA next generation sequencing (NGS) platform (1 TB/week). CeMM IT infrastructure connects the research center to the world through the network from the Medical University of Vienna.

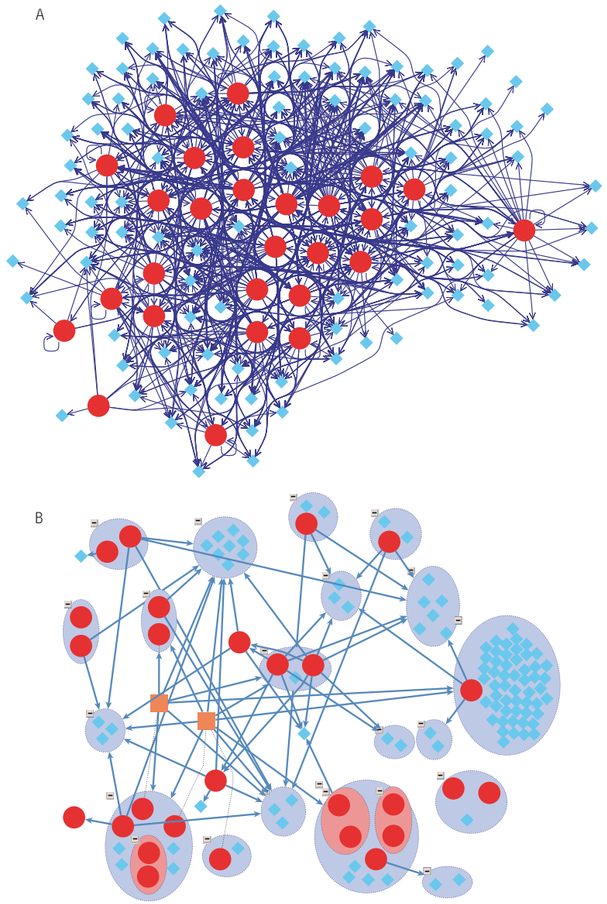


Fig. 18 (A) An original dataset comprised of the relationships between bait (red circles) and preys (blue diamonds). The original dataset is reduced to a more simplified structure (B) using the group's statistical method, which explores all possibilities and returns the most probable configuration. This is obtained when proteins are organized in modules (light blue ellipses), which can combine to form actual protein complexes (through arrows). (Data from Sardiu et al., 2008).

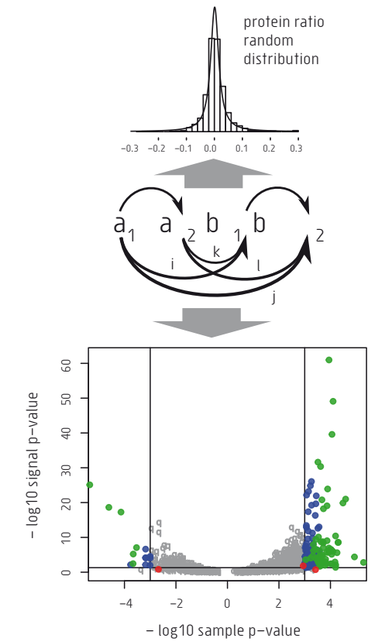


Fig. 19 A novel statistical model developed at CeMM is able to determine natural biological sample variability from quantitative proteomics data by integrating replicate analysis (top, 2 samples of classes a and b each). Significantly regulated proteins are then identified and a comparison with classical approaches reveals that the number of detected proteins is doubled (new= blue, classical ethod=green), while eliminating spurious cases (red).

The Power of Computing

In 2010, the bioinformatics group developed several computational methods that can predict actions of anti-cancer drugs using chemical proteomics data. Most drugs work by binding to a disease-causing protein thereby inhibiting its function. Unfortunately, many drugs are promiscuous, and also bind many other cellular proteins, sometimes causing unpleasant side effects. Identifying all the proteins to which a drug binds is an important challenge in biomedical research. It can help explain how the drug works and why it causes side effects, thus leading to the development of more effective drugs.

Translating Data into Clinical Results

Chemical proteomics measures protein-drug interactions and detects the protein targets of drugs in cells. At CeMM, this technique has been applied to several drugs that are primarily used to treat leukemia. They identified many new protein targets, some of which bound strongly to the drug and may be causing the unwanted side effects. In addition, identifying strong drug-protein interactions may reveal new uses for these approved drugs in other diseases. Thus, these new computational methods developed by the bioinformatics team help to bridge the gap between laboratory experiments and human health in the clinic.

The group could predict the likely benefit of treating lung cancer patients with two different drugs.

Identifying New Uses for Old Drugs

The bioinformatics group has developed an algorithm that can identify parts of a protein interaction network that are influenced by a disease or by the action of a drug. When these two areas coincide in a statistically significant manner, there is the potential to apply the drug to treat a new disease. Using this algorithm, the group could predict the likely benefit of treating lung cancer patients with two different drugs, and treating hepatocellular carcinoma with four drugs. Importantly, they were able to predict that bosutinib, a new compound not yet tested in humans, is likely to cause immunosuppression. These results were published at the International Conference on Computational Systems Biology in 2010 in Suzhou, China. They were also able to predict that the drug bafetinib, commonly used to treat patients with chronic myeloid leukemia (CML), may be useful for treating lung cancer, which was published in *PLoS Computational Biology* in 2010.

New projects have recently been set up in collaboration with chemical proteomics in the Superti-Furga lab and the PLACEBO compound screening facility run by Stefan Kubicek, both found on the fourth floor, to further explore these initial exciting results.

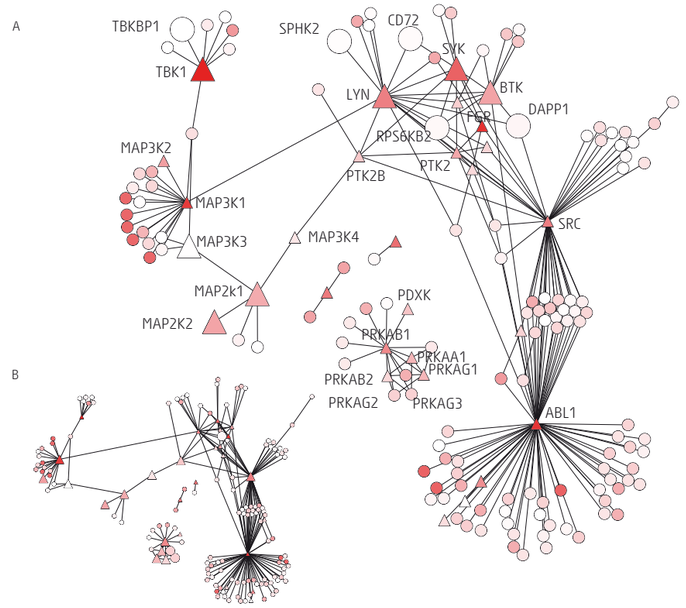


Fig. 20 Area of the human protein interaction network significantly influenced by bosutinib treatment in chronic myeloid leukemia (CML). The 43 proteins directly bound by the drug are depicted by triangles, 4 of which (SYK, BTK, LYN, and TBK1) are involved in immune system pathways. Given these proteins also bind other proteins involved in immunity (numbers in brackets), this augments the risk of an impact of the drug on the immune system. The protein target PRKAA1 is the likely cause of a potential side effect related to the endocrine system and BCR-ABL is the primary CML-relevant bosutinib target.

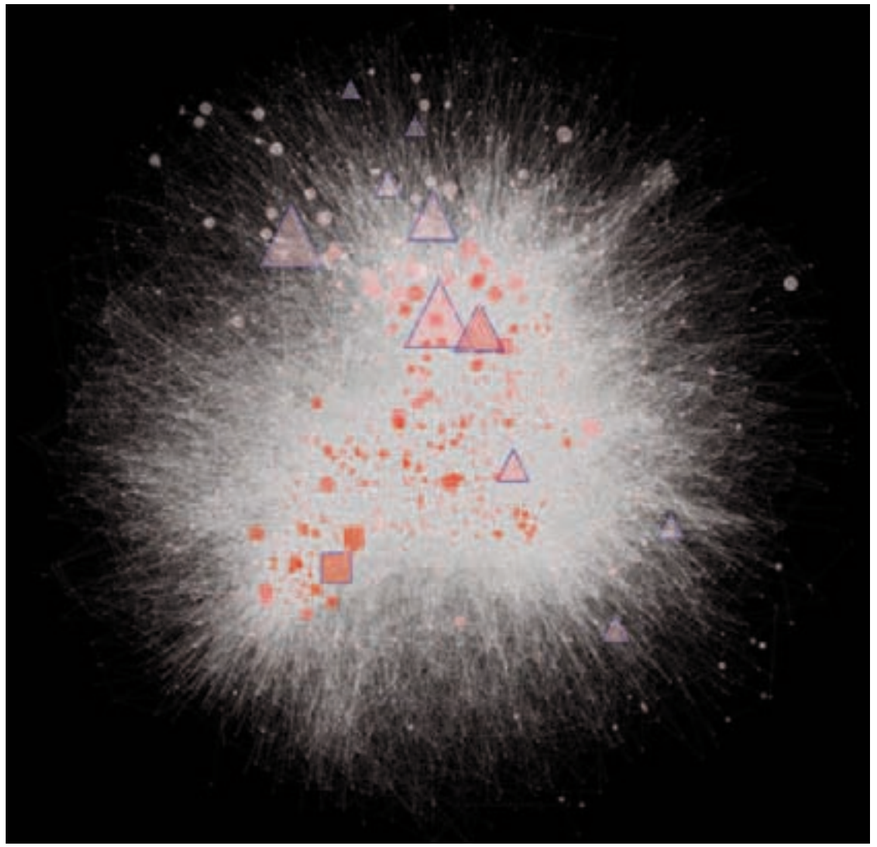


Fig. 21 Systemic effects of the disease and the drug treatment. Kinase inhibitors used against various cancers target many kinases and hence have a global influence on treated cells. The same is true for cancer that can impact a multitude of biological pathways and, therefore, the bioinformatics group of Jacques Colinge favors systems biology approaches to relate drug targets – as revealed by chemical proteomics – with diseases. The figure features part of the human interactome, i.e. all the known protein interactions, with node sizes representing the disease influence (Ph+ ALL in this case). The red color intensity indicates drug treatment (dasatinib) influence and we see, in this case, the good correlation between disease and drug treatment. Triangles stand for deleted genes (chromosomal aberrations) that cause the disease.

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Research Center

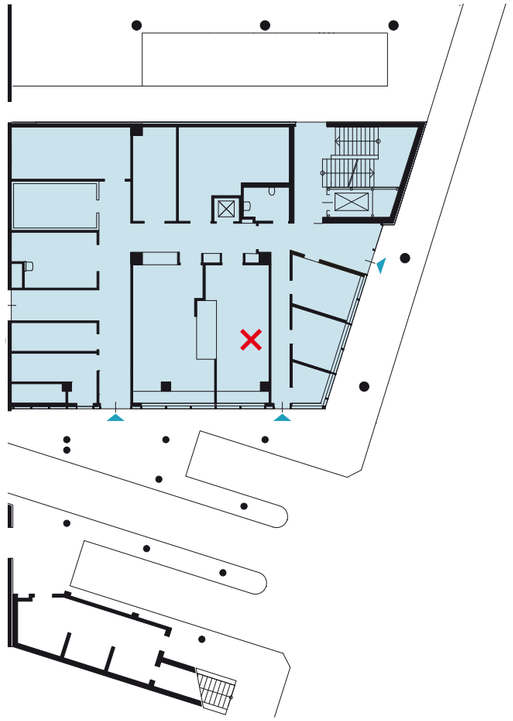
Level **01**

Where Support Comes From → **p. 66**

Level 01
Where Support Comes From

Previous page:
Level 01, Room 01.207
Wash Kitchen

Warming-up for peak performance
Ana Puda, PhD Student
dancing jazz ballet



Reaching the first floor, one is presented with the familiar choice between the left and right glass doors. The right door is an emergency exit, but one is tempted to move to the left, towards a room that is permanently busy. Parcels, boxes, deliveries and envelopes fill the room where Paul Kletzl takes care of all goods' arrivals and distributes them in the building. Further along the corridor, the room gets a more industrial feeling: the false ceiling disappears and all the utility lines become visible; ducts for AC, cables and pipes form an intricate network that spans the entire corridor and serves as a reminder of how many important functions of the building are not immediately clear to the visitor. One of these functions is the media and wash kitchens, supervised by Sylvia Bolz and Amisi Nyembo. The kitchens are composed of two rooms that are connected by a through-type autoclave, where used labware enters from one side, and comes out autoclaved on the other side after being exposed to 120 degrees Celsius at high pressure. The rooms are dotted with various other types of equipment, to prepare media solutions for all laboratories in the institute, to clean and decontaminate glassware, sterilise plasticware and purify water to produce the double distilled water that is going to be used in the various biological and chemical experiments. Apart from the kitchens, there are large rooms for storage, either at room temperature, 4 degrees or -20 degrees Celsius.

All the utilities that are visible on the ceiling of the corridor of the first floor need to originate somewhere, and this point of origin is found below the first floor. There are two more floors in the basement of CeMM, where the feeling is even more industrial: electricity control stations, battery rooms, heating and cooling systems for the radiators, fuse boxes and numerous storage areas, including a special one for flammable chemicals equipped with an extra powerful hood.

Keeping the things running at an institute with so many functions as CeMM requires some synergy between machines and people. The lower floors provide most of the machinery needed to keep things functioning, but actually most of the administration is located on level three. The feeling there is not industrial any more. On one end of the corridor, to the east, is a clear window. The art façade does not reach to this side of the third floor, as it is a bit shorter. This is because CeMM is built over a pre-existing electrical station. On the other end of the corridor, at the west end, is the public entrance. Walking past, we peek into the three small offices and in the larger, glass-enclosed corner office. Here in the finance department, books are balanced and bills are paid on time by Sigrid Strodl, Victoria Kulcsar-Mecsery and Stephan Boos-Waldeck. Angelika Eisner is also part of the team, managing grants and much of the third-party funding. The office next door is shared between Georg Casari, who guards the intellectual property rights and technology transfer, and Gerhard Schadler, who supervises the entire administration while overseeing ties with the administration of the Academy, the Medical University and the General Hospital. Sonja Baier and Verena Lichtenegger are responsible for the phones, for making travel arrangements for CeMMies and receiving visitors. Here you also find Gabriel O'Riordain, who manages the labs and is responsible for lab safety in the entire building. Gabriel is also in charge of the purchase and maintenance of equipment.

Clearly, an efficient and lean administration is critical for the success of the research organization. In many ways it is a challenge, as scientists occasionally have prima donna allures like artists. On the other hand, providing the best possible infrastructure and assistance can make the distinction between a mediocre institution and one that aims at competing internationally with the very best and wants to find new strategies to cures. As in Formula One racing, it is not only the driver that deserves credit when a car wins a competition. The CeMM administration sometimes is challenged like a Ferrari box on a race circuit.

Ce–M–M–
Research Center

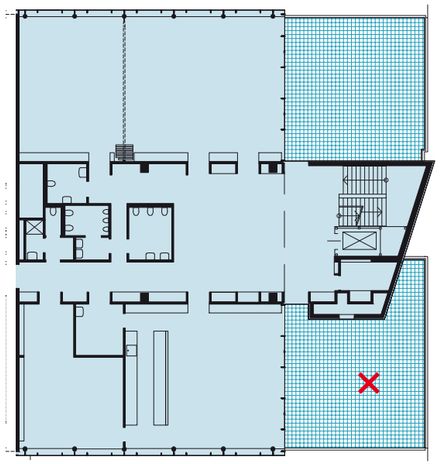
Level **08**

Where CeMM Meets the World → **p. 70**

Level 08
Where CeMM Meets the World

Previous page:
Level 08
Terrace

Enjoying team spirit
Philipp Günzl , PhD Student
Florian Pauler, Postdoctoral Fellow
Georg Winter, PhD Student
playing soccer



Having finished the tour through all the research floors of the new CeMM building, it is time to go up to the 8th floor, the floor that affords the most impressive view of the Vienna skyline. Getting out of the elevator or the staircase you are presented with three options: move straight ahead towards the foyer, or go to either right or left to the north- and south-facing terrace respectively.

The foyer welcomes you with a big electronic screen announcing current and upcoming events and seminars at CeMM. It is updated regularly and serves as a fast and effective way of communicated events to the CeMM community.
The 8th floor is highly frequented: institute meetings, CeMMinars, Impromptu seminars, and Constantin Spiegelfeld Lectures. To the right of the foyer you find the large seminar room of CeMM. It is accessible through three doors, which is quite convenient as it allows latecomers to enter the room and reach almost any available seat without disturbing the speakers. Upon entering the room, you are presented with a formidable design: wooden floor, round concrete pillars, bright red cupboards and of course a podium that is coloured in the notorious light blue colour that is a hallmark of CeMM. The room is surrounded by tilted glass windows on two sides, offering views of the city and also of the hospital. For people who are not comfortable with heights, the tilted glass walls are almost certainly going to create a slight feeling of vertigo. But one doesn't have to go to the end of the room. The chairs are located on the entrance side of the room and the audience can attend the presentations projected on the two whiteboards electronically controlled and folded out from the ceiling. The room is also equipped with shades to optimize the amount of light in the room on sunny days. In addition, it has the added versatility that it can be divided in two parts (one third, two thirds) through a foldable wall.

Every Friday morning at 9:00 a.m., the entire CeMM research community gathers in the seminar room to attend the regular scientific progress meeting. Normally two people present their latest scientific findings and they engage in an intense scientific dialogue. There is always a moderator to ensure that time slots are being adhered to and to get the questions from the audience. The atmosphere is kept informal and collegial. To avoid turning straight-off-the-lab presentations into a competition of performances, there is no clapping (sometimes a reflex hard to withstand).

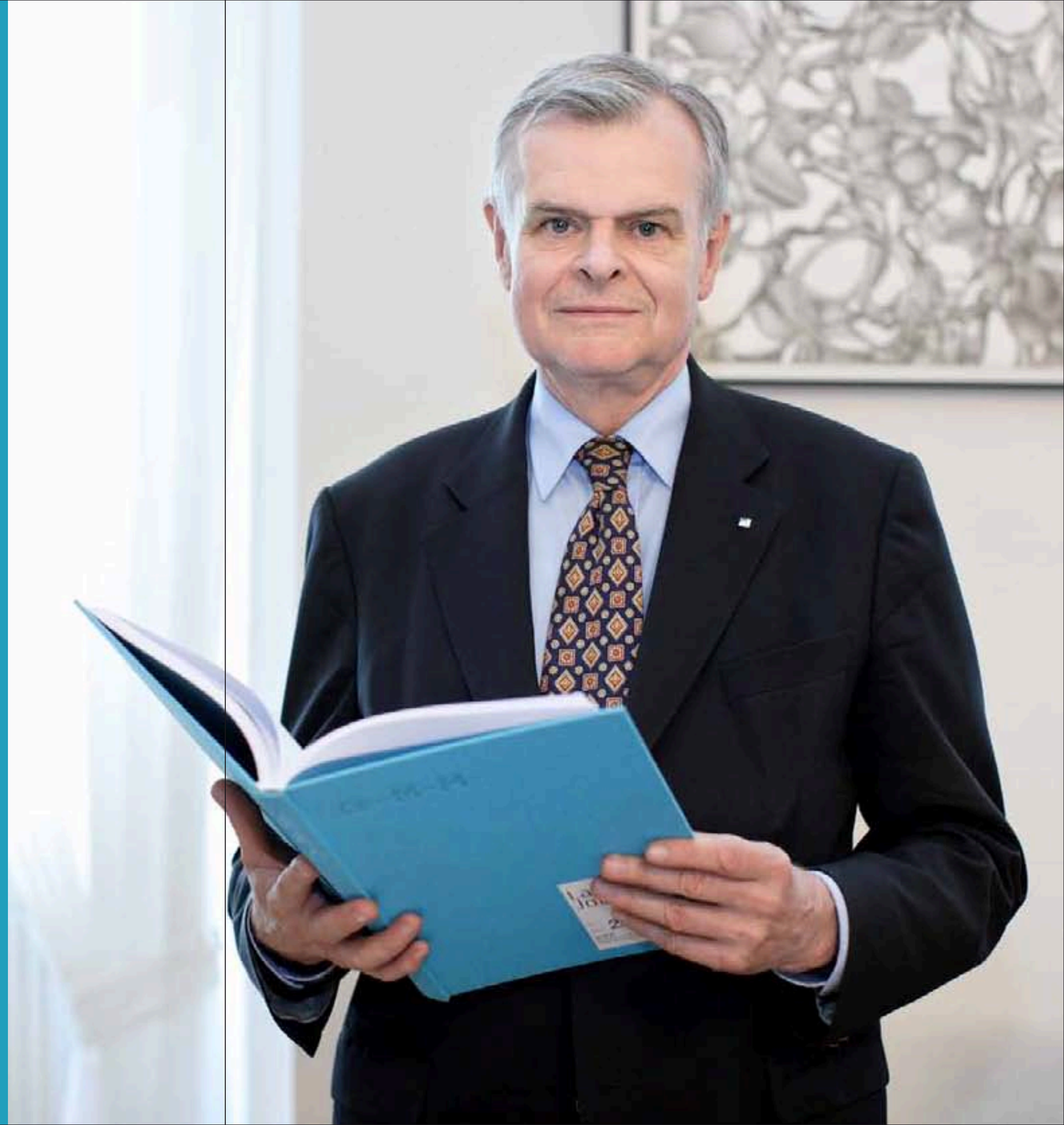
Getting out of the seminar room towards the foyer, depending on the occasion, one can expect to be presented with all the possible different uses of the room, with different furniture types and arrangements. On a Friday morning, coffee and tea are served on the big table in the center to cater for the people attending the Friday seminar and to foster discussions. During a conference break, numerous groups of people will cluster around tall, round tables exchanging views and ideas on the scientific data presented. On other occasions, cameramen and journalists will take photos and perform interviews with the participants of a meeting. Finally, on any day around twelve o'clock, many CeMM people will be rushing to the cafeteria for the coveted lunch.

The cafeteria mirrors the seminar room on the other (southern) side of the 8th floor. It has recently been upgraded and it caters successfully to the 120-people strong CeMM community that includes guests from the Medical University.
The room is the focal point of any culinary activity at CeMM: be it breakfast or lunch break, conference dinner, or the famous Friday get-togethers with the Anna Spiegel/CTR colleagues. This initiative takes place every couple of Fridays and aims at bringing together the CeMM with the adjacent medical community and involves short lectures with subsequent reception. The cafeteria has immediate access to the south-facing terrace, enjoying plentiful sunshine when available.
The room is designed to be well adapted to Vienna's climate. On bitter-cold winter days, the terrace is always empty, but the south-facing glass walls nevertheless guarantee that whatever little sun there is will enter the room unhindered. On temperate days, the terrace is very popular, offering a comfortable and relaxing experience. On hot summer days, a large adjustable sail will protect from the scorching sunlight, making the terrace a pleasant place to stay.

The whole of the 8th floor serves the purpose of enabling and maximizing scientific exchange and interaction, in an engaging and inspiring way.
What is central to the success of medical research, is not only hard work, but also groundbreaking ideas. To aid in that respect, an innovative project has been initiated at CeMM. The plan is, to build a room that can serve as a point of inspiration for the exploration of ideas, at the interface of arts and sciences. The 'Brain Lounge', as this room is called, is still in the making and is located adjacent to the cafeteria on the south side of the building. It will be designed in a thought-provoking way, by a team of artists, scientists and interior designers with the aim to provide the space for creative ideas about research approaches in molecular medicine. It will be a futuristic setting including designed carpets, couches, tables, lamps, mirrors, sculptures and paintings. Any donation is welcome, since the project can only take shape through the kind gifts from donors and benefactors (see Brain Lounge section at the end of the report).

"I am proud to say that the Research Center for Molecular Medicine (CeMM) is one of the pearls in the research portfolio of the Austrian Academy of Sciences. 'From bed to bench and back to bed' can be regarded as the motto of this institute indicating that the patient with his/her disease is the source of inspiration for the scientist who then analyzes and characterizes pathogenetic principles and networks with the help of all modern methods and technologies available. The insights flow back to the patient in the form of innovative and specific diagnostic and therapeutic procedures. Molecular medicine, therefore, is not a one-way street. A close interaction with the clinician is the basis of success. The position of CeMM at the campus of the Medical University of Vienna (MUW) and the Vienna General Hospital (AKH) is an ideal place to fulfil its mission in the sense of translational and individualized medicine. I congratulate the scientists, all members of CeMM and particularly its director Giulio Superti-Furga on their scientific achievements and I am convinced that the new institute will act as further stimulant and that our high expectations regarding scientific excellence will even be surpassed."

Prof. Dr. Helmut Denk
President of the Austrian Academy of Sciences



CeMM Principal Investigators

Giulio Superti-Furga

Pathological Networks in Leukemia and Immunity

CEO and Scientific Director
gsuperti@cemm.oeaw.ac.at

PhD (Molecular Biology),
University of Zurich (CH)
IMP Vienna (A)
Post-doctoral fellow, Team Leader
EMBL – European Molecular Biology Laboratory (D)
Scientific Director
Cellzome (D)

+ Italian nationality
+ Joined CeMM in January 2005
+ Group of 20 people
plus mass spectrometry team (5)
and bioinformatics team (4)

Main research interests
+ Mechanism of action of drugs
+ Molecular networks
affecting leukemias
+ Molecular basis of innate immunity

Giulio Superti-Furga is an Italian national and he joined CeMM as Director in January 2005. He performed his undergraduate and graduate studies in molecular biology at the University of Zurich, Switzerland, at Genentech Inc., South San Francisco, USA, and at the Institute for Molecular Pathology in Vienna (I.M.P.), Austria. He has been a post-doctoral fellow and Team Leader at the European Molecular Biology Laboratory (EMBL) until 2004. For several years he served as Professor of Biotechnology at the University of Bologna. In 2000, he co-founded the biotech company Cellzome, where he was Scientific Director. Some of Giulio's major achievements to date are the elucidation of basic regulatory mechanisms of tyrosine kinases in human cancers and the discovery of fundamental organization principles of the proteome of higher organisms. Giulio's work on the organization of the eukaryotic proteome is the most highly cited in the field. He is a full member of the Austrian Academy of Sciences, the German Academy of Sciences Leopoldina, the European Molecular Biology Organization and the European Academy of Cancer Sciences. He is chair of the EMBL Alumni Association. He uses and develops high-throughput 'omics' approaches to study several areas including the mechanism of action of proteins and drugs, the identification of molecular networks underlying leukemia and the molecular basis of innate immunity. In 2009 he received the prestigious Advanced Investigator Grant awarded by the European Research Council (ERC), and he was awarded the Knight Officer Order of Merit of the Republic of Italy for his contributions to science.

Relevant/Important publications

Functional organization of the yeast proteome by systematic analysis of protein complexes. Gavin AC, Bösche M, Krause R, Grandi P, Marzioch M, Bauer A, Schultz J, Rick JM, Michon AM, Cruciat CM, Remor M, Höfert C, Schelder M, Brajenovic M, Ruffner H, Merino A, Klein K, Hudak M, Dickson D, Rudi T, Gnau V, Bauch A, Bastuck S, Huhse B, Leutwein C, Heurtier MA, Copley RR, Edelmann A, Querfurth E, Rybin V, Drewes G, Raida M, Bouwmeester T, Bork P, Seraphin B, Kuster B, Neubauer G, Superti-Furga G. *Nature*. 2002. 415(6868): 141-7.

A network solution. Henney A, Superti-Furga G. *Nature*. 2008 Oct 9; 455(7214):730-1.

An orthogonal proteomic-genomic screen identifies AIM2 as a cytoplasmic DNA sensor for the inflammasome. Bürckstümmer T, Baumann C, Blüml S, Dixit E, Dürnberger G, Jahn H, Planyavsky M, Bilban M, Colinge J, Bennett KL, Superti-Furga G. *Nat Immunol*. 2009. March 10(3):266-72.

Denise P. Barlow

Epigenetic Mechanisms in Development & Disease

CeMM Principal Investigator
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Honorary Professor of Genetics,
University of Vienna (A)
PhD, **Warwick University** (UK)
Post-doctoral Fellow,
ICRF London (UK),
EMBL Heidelberg (D)
Group Leader,
IMP Vienna (A)
NKI Amsterdam (NL)
Head Dept. Developmental Biology,
IMB-OeAW Salzburg (A)

+ British nationality
+ Joined CeMM in 2003
+ Group of 12 people

Main research interests
+ Molecular basis and function of genomic imprinting in mice and humans
+ Identification and characterization of macro non-coding RNAs in the mouse and human genomes
+ The potential of macro non-coding RNAs as tumor biomarkers in human cancer

Denise Barlow is a British national who joined CeMM in 2003 and is an Honorary Professor at the University of Vienna. Denise initially trained as a State Registered Nurse in the UK and afterwards completed undergraduate studies at Reading University (UK) and a PhD on the interferon system in early mouse development at Warwick University (UK). Post-doctoral work studying mouse embryonic development followed at ICRF (London, UK) with Dr. Brigid Hogan, and on genome biology at EMBL (Heidelberg, D) with Dr. Hans Lehrach. Denise has also held group leader positions at the IMP (Vienna, A) and the NKI (Amsterdam, NL). On returning to Austria in 2000, Denise was appointed Head of the Dept. of Developmental Genetics at the Austrian Academy IMB Institute (Salzburg, A), and then returned to Vienna in 2003 as a Principal Investigator with CeMM.
One of the Barlow lab's major achievements was the discovery in 1991 of the first imprinted gene in mammals to show parental-specific gene expression. Their subsequent identification that epigenetic silencing of this imprinted gene is induced by expression of an unusual macro non-protein-coding (nc) RNA, has led them to investigate how macro ncRNAs act throughout the mouse and human genome as regulators of gene expression in development and disease. The lab continues to use the model of genomic imprinting to dissect how ncRNAs epigenetically silence genes, and uses this as a platform together with high throughput sequencing technology to extend these results into human diseases such as cancer.

Relevant/Important publications

Active and Repressive Chromatin Is Interspersed without Spreading in an Imprinted Gene Cluster in the Mammalian Genome. Regha K, Sloane MA, Huang R, Pauler FM, Warczok KE, Melikant B, Radolf M, Martens JH, Schotta G, Jenuwein T, Barlow DP. *Molecular Cell*. 2007. 27(3): 353-66.

An in vitro ES cell imprinting model shows that imprinted expression of the Igf2r gene arises from an allele-specific expression bias. Latos PA, Stricker SH, Steenpass L, Pauler FM, Huang R, Senergin BH, Regha K, Koerner MV, Warczok KE, Unger C, Barlow DP. *Development*. 2009 Feb;136(3):437-48.

The function of non-coding RNAs in genomic imprinting. Koerner MV, Pauler FM, Huang R, Barlow DP. *Development*. 2009 Jun;136(11):1771-83. Review.

Genomic imprinting mechanisms in embryonic and extraembryonic mouse tissues. Hudson QJ, Kulinski TM, Huetter SP, Barlow DP. Heredity. 2010 Jul;105(1):45-56. *Epub* 2010 Mar 17. Review.

Christoph J. Binder

Atherosclerosis and Immunity

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MD, **University of Vienna** (A)
PhD (Molecular Pathology)
University of California San Diego (USA)
Post-doctoral fellow,
University of California San Diego (USA)

+ Austrian nationality
+ Joined CeMM in April 2006
+ Group of 10 people

Main research interests
+ Role of natural immunity in inflammation and oxidative stress
+ Elucidate the protective capacities of natural antibodies in atherosclerosis
+ Discover ways to boost natural immunity as therapy for cardiovascular diseases

Christoph Binder's group is hosted by
Department of Medical and Chemical Laboratory Diagnostics
Medical University of Vienna
Anna Spiegel Forschungsgebäude
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1090 Vienna, Austria

Christoph Binder was born in 1973 in Vienna, Austria. He obtained his MD degree from the University of Vienna Medical School (MUV) in 1997, working as an intern in the Clinical Pathology department with Professor Dontscho Kerjaschki. Later, he entered a PhD program at the University of California in San Diego, working with renowned atherosclerosis researcher Professor Joseph Witztum, where he obtained his PhD degree in 2002 for the thesis entitled: "Defining Innate and Adaptive Immune Mechanisms in the Atheroprotective Effect of Immunization with Oxidized Low-Density Lipoproteins". He continued with Professor Witztum as a Post-doc to study the role of natural IgM antibodies and IL-5 in atherosclerosis, which was where he made one of his major discoveries to date, namely the atheroprotective capacity of natural antibodies. In 2005, he joined the Department of Laboratory Medicine at the Medical University of Vienna, where in 2009 he was appointed Professor of Atherosclerosis Research. His interests are clearly interdisciplinary and span vascular biology, lipid oxidation, natural antibodies and innate immunity. In particular, he aims to define the role of B-1 cells and natural antibodies in atherogenesis and how immune recognition of lipid peroxidation derived structures promotes chronic inflammatory diseases, such as atherosclerosis.

Relevant/Important publications

Innate and acquired immunity in atherogenesis. Binder CJ, Chang MK, Shaw PX, Miller YI, Hartvigsen K et al. *Nature Medicine*. 2002. 8(11): 1218-26.

Pneumococcal vaccination decreases atherosclerotic lesion formation: Molecular mimicry between Streptococcus pneumoniae and oxidized LDL. Binder CJ, Hörkkö S, Dewan A, Chang MK, Kieu EP et al. *Nature Medicine*. 2003. 9(6): 736-43.

Oxidation-specific epitopes are dominant targets of innate natural antibodies in mice and humans. Chou MY, Fogelstrand L, Hartvigsen K, Hansen LF, Woelkers D, Shaw PX, Choi J, Perkmann T, Bäckhed F, Miller YI, Hörkkö S, Corr M, Witztum JL, Binder CJ. *J Clin Invest*. 2009 May;119(5):1335-49.

Sylvia Knapp

Innate Immunity and Bacterial Infections

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MD, **University of Vienna** (A)
Internist, **Vienna General Hospital, MUV** (A)
PhD (Experimental Medicine), **University of Amsterdam** (NL)

+ Austrian nationality
+ Joined CeMM in April 2006
+ Group of 7 people

Main research interests
+ Exploit molecular mechanisms of host-pathogen interactions
+ Identify the impact of bacterial toxins

Sylvia Knapp's group is located at the
Department of Internal Medicine I
Division of Infectious Diseases & Tropical Medicine
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1090 Vienna, Austria

Sylvia Knapp was born in Austria and studied Medicine at the Free University in Berlin and the University of Vienna. She obtained her MD degree in 1993 and started her residency in Internal Medicine at the University Hospital Vienna. In 2000 she received her License in Internal Medicine and in 2004 she obtained a "Habilitation" in Internal Medicine at the Medical University of Vienna. After several residencies, mostly in areas like Infectious Diseases, AIDS and Intensive Care Units, she became a PhD student in Tom van der Poll's laboratory at the University of Amsterdam and studied the inflammatory response to severe bacterial infections. Sylvia's most important achievements include the identification of the anti-inflammatory role of alveolar (lung) macrophages as well as the biological function of several pattern recognition receptors during Streptococcus pneumoniae pneumonia. Sylvia joined CeMM in 2006 and continues her work on the innate immune response to bacterial infections, focusing on the molecules involved in the initiation and resolution of the innate immune response to clinically relevant pathogens and on the role of bacterial virulence factors and their interactions with host structures and pathways. Sylvia keeps her responsibilities at the Intensive Care Unit at the Medical University Vienna.

Relevant/Important publications

Alveolar macrophages have a protective anti-inflammatory role during murine pneumococcal pneumonia. Knapp S, Leemans JC, FlorquinS, Branger J, Maris NA, Pater J, van Rooijen N, and van der Poll T. *Am J Respir Crit Care Med* (2003) 167, 171-179.

TREM-1 activation alters the dynamics of pulmonary IRAK-M expression in vivo and improves host defense during pneumococcal pneumonia. Lagler H, Sharif O, Haslinger I, Matt U, Stich K, Furtner T, Doninger B, Schmid K, Gattringer R, de Vos AF, Knapp S. *J Immunol* (2009) 183, 2027-2036

Baumann CL*, Aspalter IM*, Sharif O*, Pichlmair A, Blüml S, Grebien F, Bruckner M, Pasierbek P, Aumayr K, Planyavsky M, Bennett KL, Colinge J, Knapp S#, Superti-Furga G#. CD14 is a coreceptor of Toll-like receptors 7 and 9. *J Exp Med* (2010) 207: 2689-2701.
* equal contribution
# corresponding authors

Robert Kralovics

Genetics of Hematological Disorders

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PhD (Molecular Biology)
Czech Academy of Sciences (CZ)
Post-doctoral fellow
University of Alabama at Birmingham (USA)
Assistant Professor
Baylor College of Medicine, Houston (USA)
Project Leader
University Hospital Basel (CH)

+ Czech nationality
+ Joined CeMM in June 2006
+ Group of 9 people

Main research objectives and questions
+ Identify mutations in early steps of disease development in hematological malignancies
+ How mutant stem cells evolve genetically, how they respond to therapy?
+ What gene mutations cause familial predisposition to hematological malignancies?
+ How does genetic variability contribute to disease?
+ How to diagnose the diseases in early stages of development?

Robert Kralovics, born 1970, is Czech and joined CeMM in June 2006. He obtained his first degree in Molecular Biology and Genetics at the Comenius University in Bratislava and later his PhD in Biophysics at the Academy of Sciences of the Czech Republic in Brno. He did his post-doctoral work on the genetics of myeloproliferative disorders working with Josef Prchal at the University of Alabama in Birmingham, USA. He followed Prchal as an Assistant Professor at the Baylor College of Medicine in Houston. From mid 2001, Robert was a project leader with Radek Skoda in Basel. Robert's research interests are primarily in myeloproliferative disorders (MPDs) and in myeloid malignancies in general. One of his major achievements so far has been the identification of a gain-of-function mutation in the JAK2 kinase gene (V617F), which plays an important role in MPD pathogenesis. This was prominently published in the New England Journal of Medicine and fostered Robert's interest in deciphering the genetic complexity of MPD. More recently, Robert's group discovered a common JAK2 gene variant that confers susceptibility to MPD. Robert continues this work at CeMM to identify new mutations causing familial predisposition to hematological malignancies using advanced genomics approaches, and is working towards understanding how genetic variability contributes to the disease.

Relevant/Important publications

p53 lesions in leukemic transformation. Harutyunyan A, Klampfl T, Cazzola M, Kralovics R. *N Engl J Med*. 2011 Feb 3;364(5):488-90

Deletions of the transcription factor Ikaros in myeloproliferative neoplasms. Jäger R, Gisslinger H, Passamonti F, Rumi E, Berg T, Gisslinger B, Pietra D, Harutyunyan A, Klampfl T, Olcaydu D, Cazzola M, Kralovics R. *Leukemia*. 2010 Jul;24(7):1290-8

A common JAK2 haplotype confers susceptibility to myeloproliferative neoplasms. Olcaydu D, Harutyunyan A, Jäger R, Berg T, Gisslinger B, Pabinger I, Gisslinger H, Kralovics R. *Nature Genetics*. 2009. 41(4):450-4

A gain-of-function mutation of JAK2 in myeloproliferative disorders. Kralovics R, Passamonti F, Buser AS, Teo SS, Tiedt R et al. *N Engl J Med*. 2005. 28;352(17): 1779-90

Sebastian Nijman

Functional Cancer Genomics

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PhD (Molecular Carcinogenesis)
Netherlands Cancer Institute (NL)
Post-doctoral fellow,
The Broad Institute of Harvard and MIT (USA)

+ Dutch nationality
+ Joined CeMM in October 2007
+ Group of 6 people

Main research interests
+ Chemical genetics of cancer
+ Identify novel strategies to treat cancer (cancer vulnerabilities)
+ Functional genetic screens to identify cancer-related genes

Sebastian Nijman was born in the Netherlands (1975). He studied medical biology at Utrecht University and specialized in Molecular Biology and Biochemistry in the labs of Hans Bos and Rene Medema. Sebastian also holds a Masters of Arts degree from the University of Maastricht (Science, Society and Technology Studies) and was involved in clinical research at a Contract Research Organization. In the lab of Rene Bernards at the Netherlands Cancer Institute, he performed his PhD work, focusing on functional genetic screens in cancer-relevant pathways. He performed the first RNAi screen in mammalian cells that led to the identification of the cylindromatosis tumor suppressor as a regulator of NF-kappaB signaling. This work has led to a rational therapeutic approach for treating cylindromatosis and is one of his major achievements so far. In 2006 he joined the lab of Todd Golub at The Broad Institute of Harvard and MIT, USA. There he developed novel genomic approaches to discover the functions of genes and identify new angles for cancer treatment. Since joining CeMM, Sebastian's research is mostly focused on the identification and understanding of cancer vulnerabilities using chemical genetic screens.

Relevant/Important publications

Loss of the cylindromatosis tumour suppressor inhibits apoptosis by activating NFkappaB. Brummelkamp TR, Nijman SM, Dirac AM and Bernards R. *Nature.* 2003. 424(6950): 797-801.

The deubiquitinating enzyme USP1 regulates the Fanconi Anemia pathway. Nijman SM*, Huang TT*, Dirac AM, Brummelkamp TR, Kerkhoven RM et al. *Molecular Cell.* 2005. 17(3): 331-9.
* equal contribution

A genomic and functional inventory of deubiquitinating enzymes. Nijman SM, Luna-Vargas MP, Velds A, Brummelkamp TR, Dirac AM et al. *Cell.* 2005. 123(5): 773-86.

Synthetic lethality: general principles, utility and detection using genetic screens in human cells. Nijman SM. *FEBS lett.* 2011

Keiryn Bennett

Head of Mass Spectrometry
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+ Australian nationality
+ Joined CeMM in October 2004
+ Group of 7 people

Main research interests
+ Proteomics, with an emphasis on medical/clinical field
+ Liquid chromatography mass spectrometry (including technical advancement and applications)
+ Integration of mass spectrometry with biology and bioinformatics

Keiryn Bennett, heads the mass spectrometry unit at CeMM. Australian by birth, she obtained her Bachelor of Science with Honours at the Department of Biochemistry, University of Tasmania and her PhD at the Department of Chemistry, University of Wollongong, Australia, under the supervision of Professor Margaret Sheil. She further trained in some of the most renowned protein mass spectrometry laboratories of the world, including Professor Peter Roepstorff in Odense, Denmark. Keiryn was the Director of Analytical Applications at Protana A/S in Denmark (later called MDS Proteomics). Her hands-on experience with different systems include: Sciex prototype MALDI QqTOF, PerSeptive Voyager Elite MALDI-rTOF, TSQ 700 triple quadrupole mass spectrometer, Sciex QSTAR equipped with nano-electrospray, and nanoLCMS coupled to Thermo-Fisher hybrid LTQ Orbitrap XL and Micromass/Waters Q TOF mass spectrometers. Author of more than 40 publications, during her time at MDS, she was involved in the large-scale analysis of yeast protein complexes published in Nature along with the analogous effort from Cellzome. She brings to CeMM more than 17 years of experience in protein mass spectrometry and 4 years experience in managing a high-throughput industrial proteomic laboratory.

Relevant/Important publications:

Proteomic analysis of human cataract aqueous humour: comparison of one-dimensional gel LCMS with two-dimensional LCMS of unlabelled and iTRAQ®-labelled specimens. Bennett KL, Funk M, Tschernutter M, Breitwieser FP, Planyavsky M, Ubaida Mohien C, Müller A, Trajanoski Z, Colinge J, Superti-Furga G and Schmidt-Erfurth U. *J Proteomics.* 2011. 74, 151-166

An orthogonal proteomic-genomic screen identifies AIM2 as the cytoplasmic DNA sensor for the inflammasome. Bürckstümmer T, Blüml S, Baumann C, Dixit E, Dürnberger G, Jahn H, Planyavsky M, Bilban M, Colinge J, Bennett KL and Superti-Furga G. 2009. *Nature Immunol.* 10, 266-272

Systematic identification of protein complexes in Saccharomyces cerevisiae by mass spectrometry. Ho Y, Gruhler A, Heilbut A, Bader GD, Moore L, Adams SL, Millar A, Taylor P, Bennett K, Boutilier K, Yang L, Wolting C, Donaldson I, Schandorff S, Shewnarane J, Vo M, Taggart J, Goudreault M, Muskat B, Alfarano C, Dewar D, Lin Z, Michalickova K, Willems AR, Sassi H, Nielsen PA, Rasmussen KJ, Andersen JR, Johansen LE, Hansen LH, Jespersen H, Podtelejnikov A, Nielsen E, Crawford J, Poulsen V, Sørensen BD, Matthiesen J, Hendrickson RC, Gleeson F, Pawson T, Moran MF, Durocher D, Mann M, Hogue CWV, Figeys D and Tyers M. 2002. *Nature.* 415, 180-183

Jacques Colinge

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+ Swiss and French nationality
+ Joined CeMM in September 2006
+ Group of 6 people

Main research interests
+ Computational proteomics
+ Protein interaction network analysis
+ Systems biology and OMICS data integration
+ Drug mechanism of action and side-effects modeling
+ Protein complex predictions from mass spectrometry data
+ Application of computational statistics and mathematics

Jacques Colinge was born in Switzerland and heads bioinformatics at CeMM since 2006. He obtained a PhD in mathematics from the University of Geneva, Switzerland, in collaboration with the Swiss Institute of Technology. After completing his PhD, Jacques joined the Serono Pharmaceutical Research Institute as a bioinformatician to work mainly on differential gene expression data analysis. In 2000 he moved to GeneProt Inc. to head a group in charge of mass spectrometry-related bioinformatics and parallel computing. In 2005, he joined the Upper Austrian University of Applied Sciences at Hagenberg to serve as a Professor of Bioinformatics before moving to CeMM in September 2006. In 2009, Jacques obtained a Habilitation in bioinformatics from TU Graz.
The bioinformatics lab does research to develop data analysis methods aimed at understanding the biological function of networks of interacting proteins. The group also develops and maintains data processing pipelines and databases to analyze and manage mass spectrometry data, and to support protein interaction network analyses.

Relevant/Important publications:
Initial characterization of the human central proteome. Burkard TR, Planyavsky M, Kaupe I, Breitwieser FP, Bürckstümmer T, Bennett KL, Superti-Furga G, Colinge J. *BMC Syst Biol*. 2011. 5(1):17

Using iTRAQ combined with tandem affinity purification to enhance low-abundance proteins associated with somatically mutated EGFR core complexes in lung cancer. Haura EB, Muller A, Breitwieser FP, Li J, Grebien F, Colinge J, Bennett KL. *J Proteome Res.* 2011, 10(1):182-190

Proteomic analysis of human cataract aqueous humour: Comparison of one-dimensional gel LCMS with two-dimensional LCMS of unlabelled and iTRAQ(R)-labelled specimens. Bennett KL, Funk M, Tschernutter M, Breitwieser FP, Planyavsky M, Mohien CU, Muller A, Trajanoski Z, Colinge J, Superti-Furga G, Schmidt-Erfurth U. *J Proteomics* 2011, 74(2):151-166

Stefan Kubicek

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Group Members
Patrick Markt (Post-Doc),
Marco Licciardello (PhD-Student)

Main research interests
+ Chemical Epigenetics
+ Identification and development of small molecule probes for biological processes
+ Contribution of histone lysine methylation to cancer development and progression
+ Role of chromatin in the specification of pancreatic cell types

Stefan Kubicek, born 1978, is Austrian and joined CeMM on August 1st, 2010. He obtained an MSc in synthetic organic chemistry from Vienna University of Technology following a diploma thesis at ETH Zürich. For his PhD in Thomas Jenuwein's lab at the IMP in Vienna, he changed fields to Molecular Biology. He then performed post-doctoral research working on Chemical Biology with Stuart Schreiber at the Broad Institute of Harvard and MIT. Stefan Kubicek heads the chemical screening platform and PLACEBO (Platform Austria for Chemical Biology), a task he is well equipped for based on previous screening experiences with Boehringer Ingelheim and at the Broad Institute. These activities have resulted in the identification of the first selective histone methyltransferase inhibitor, BIX-01294, and a small molecule inducer of insulin expression in pancreatic alpha cells, BRD7389. The Kubicek lab is working on the role of chromatin in the definition of cell types and cell states. Projects focus on defining the contribution of histone methylation to cancer development and progression and its potential for transdifferentiation of celltypes. We use functional genomics to identify chromatin modifying enzymes as potential targets for cancer therapy and develop small molecules against these proteins. Currently we focus on the role of histone methyl binding proteins in acute myeloid leukemia. Additionally, we are interested in targeting epigenetic marks for cellular transdifferentiation, with the goal of generating insulin-producing beta cells from other cell types. In a project funded by the Juvenile Diabetes Research Foundation JDRF, we make use of the recent discovery that Pax4 overexpression can convert alpha cells into functional insulin-producing beta cells. We identify the chromatin changes underlying this transdifferentiation event and work on novel genes and compounds that induce insulin expression.

Relevant/Important publications
Small molecule inducers of insulin expression in pancreatic alpha cells. Fomina-Yadlin D*, Kubicek S*, Walpita D, Dancik V, Hecksher-Sørensen J, Bittker JA, Sharifnia T, Shamji A, Clemons PA, Wagner BK, and Schreiber SL. PNAS,107(34):15099-104 (2010)

Transient reversal of H3K9me2 by a small molecule inhibitor for the G9a histone methyltransferase. Kubicek S, O'Sullivan RJ, August EM, Hickey ER, Zhang Q, Teodoro ML, Mechtler K, Rea S, Kowalski JA, Homon CA, Kelly TA, and Jenuwein T. Mol. Cell 25, 473-481 (2007)

Jmjd2b antagonizes H3K9 tri-methylation at pericentric heterochromatin in mammalian cells. Fodor BD*, Kubicek S*, Yonezawa M, O'Sullivan RJ, Sengupta R, Perez-Burgos L, Opravil S, Mechtler K, Schotta G, and Jenuwein T. GenesDev. 20, 1557-1562 (2006)
* equal contribution

"Knowing and understanding the pathological mechanisms of diseases is a central need of medical research and of key importance for all future diagnostic and therapeutic developments. To fill the existing knowledge gaps a close interaction between basic and clinical research is an indispensable precondition. The Center of Molecular Medicine – CeMM – is one of Austria's prime locations for molecular research in medicine with an excellent research focus. CeMM's crew of dynamic and highly motivated specialists, its critical mass of young researchers, and the superb leadership of Prof. Giulio Superti-Furga ensure scientific output of the highest quality. Since its existence, CEMM has provided important contributions to the better understanding of the molecular pathomechanisms of several diseases. The location amidst the Medical University Vienna and the General Hospital Vienna allows optimal interaction with clinical partners and will lead to continued success in spearheading the progress of Molecular Medicine in Austria's scientific community."

Prof. Dr. Christine Mannhalter
Molecular Diagnostics, Medical University Vienna
Vice President of the Austrian Science Fund

CeMM PhD Program

Caution! CeMM-students @ work…

The President of Austria Dr. Heinz Fischer visiting the new CeMM building, a few weeks ahead of moving.

Starting at the top

There is a lot of noise and the sound of "sekt" corks popping on the 8th floor of CeMM. We are outside the seminar room at the end of 2010 and two CeMM PhD students are really celebrating! Roland Jaeger and Irena Vlatkovic joined the first CeMM PhD program at the end of 2006 and are the first students of this intake to obtain their doctorate. They are both well known in the CeMM community as intelligent, hard working and collegial young scientists who are great role models for our latest group of PhD students.

CeMM has now run three PhD programs that have taken in 34 students from 10 countries into a program that includes a unique blend of practical training, lectures and mentoring that builds on the guidelines for PhD programs of CeMM's home academic institution, the Medical University of Vienna. Students begin to arrive in September or October and for the first six months, live close by on the hospital campus in small, comfortable and very affordable one-room apartments. In October they spend the first 4 weeks in the 8th floor seminar room getting to know each other and the CeMM Principal Investigators by learning practical things like how to survive in a lab, how not to annoy your supervisor by keeping a good lab notebook, how to enjoy your PhD experience and how to successfully navigate the University bureaucracy. This is combined with basic science courses, some organized by the Medical University and some by the CeMM PIs that are given by a selection of prominent leaders, scientists and medical professors from the Viennese science and medical community and biotech industry. The days are very full but there is still time to attend the weekly CeMM work discussions that are held every Friday morning, where they get to know who is who and what is going on @ CeMM. What seems to be more important is that the students accepted into the program each year, because of this common induction program, tend to stay in contact throughout their PhD period.

A better perspective – the view from the terrace
The next 6 weeks are lab rotation time in floors 2–7. Here the students and their PI select three CeMM labs where the student spends two weeks on a small project to learn techniques and skills that will be useful for their future project. At the same time, the student gets a good idea of the type of research that is going on at CeMM and gets to know a wider group of scientists and interests. Some lectures and courses continue during this time, and one of the earliest lessons that all scientists need to learn is how to plan your day to do your experiment and go to the seminar. CeMM students also get a better perspective of the relationship between research and medicine and the privileged position of the CeMM Institute on the main hospital site by meeting clinicians at the main hospital.

Who you gonna call? CeMM students!
The CeMM PhD program looks for exceptionally motivated PhD candidates with a keen interest in molecular medical research at the forefront of new system and genome technologies. We expect a lot from our new students – they need to be good in the lab, they must not be afraid to learn new and difficult things or to ask challenging questions, and they need to learn to work together in teams. At the same time CeMM is offering a lot – the CeMM Faculty is committed to the training of young scientists that we hope will shape the future of molecular medicine.
We monitor the progress of each student. We do this in a formal way using a PhD committee that meets annually to advise both the students and their PI about the chosen research project. And we do it informally through the use of a mentoring system that pairs students with a PI who is not their supervisor, who meet more regularly for lunch or coffee time discussions. This seems to be a successful formula – CeMM students are just like Roland and Irena, committed, enthusiastic, good colleagues and great fun to work with.

CeMM PhD Students visiting the Josefinum with Dontscho Kerjaschki.

CeMM as Springboard for Careers

Part of CeMM's mission is to train young investigators in molecular medicine. CeMM is very proud of a highly active community of Postdoctoral fellows. Two such fellows, Oliver Hantschel and Tilmann Bürckstümmer, have left CeMM at the end of 2010. We report here their testimonials.

Dr. Oliver Hantschel
How should I start? It is pretty hard to try to summarize more than six years as a Post-doc at CeMM, that were scientifically challenging, formative, exciting, productive, collegial, supportive, often hard work, sometimes disappointing and annoying, but most of the time relaxed and fun.

Overall the 'package', if you start as a Post-doc is very good and very competitive compared to many other places in the world: I guess that I do not have to argue too much that Vienna is a fantastic (in terms of quality of life) and quite affordable (rent, culture, sports, eating/drinking) place to do a Post-doc. What is probably more important is that I never had to worry about money when planning an experiment and therefore could concentrate my energy on science and did not have to make any compromises. Of course, the majority of Post-docs are funded at least for most of their time at CeMM by fellowships or through grants that they apply for. This is not only something important to learn, but also gratifying. Something else that is worth mentioning and different from many other places is a relatively early level of independence and responsibility one gets as a Post-doc in Giulio's lab. Tutoring and mentoring of diploma/Master's and PhD students, as well as technicians, became an integral and pleasant part of my everyday duties and is a very good preparation to start your own lab. In a way, I always described my time as a Post-doc in Giulio's lab as being semi-independent. It was a bit like running my own small group with all the good things (scientific freedom, strong mentoring, having enough people and money), but almost none of the bad things (administrative burdens, worries on long-term stable financial support). This environment enables to prepare for an independent career and hopefully will prevent me to make certain mistakes in my own lab that will inevitably happen if you do things for the first time.

In terms of scientific projects, another distinctive feature of being a Post-doc at CeMM is the strong support and encouragement for both CeMM-internal, as well as external collaborations. For me, especially the very successful collaborations with the laboratories of Wilfried Ellmeier, Peter Valent, Veronika Sexl (all MedUniVienna), Jan Cools (University of Leuven) and Shohei Koide (University of Chicago) were among the very highlights of my time at CeMM. The latter two collaborations included visits of two months by Kim de Keersmaecker and John Wojcik in Vienna that, despite their short duration, set the foundation for a number of papers that were published or are in the process of preparation. Both visits were strongly encouraged and supported by Giulio, and both Kim and John have been cordially welcomed by our lab.

Finally, what advice can I give to those who plan to find a PI position after their Post-doc time at CeMM? Is there 'the right time' to start looking for a job? From my experience, this is hard to evaluate. Clearly, the time shortly after having published a good paper is a good time. On the other hand, you need to be flexible and be ready to apply for jobs once they are advertised. Especially in the these times of financial insecurities in science funding world-wide, the institute you are interested to work at may not have advertised positions for the last two years and probably will not do so for the next two years. So, do not miss chances. Furthermore, although we do not want to admit this, we are all much more specialized than we think we are, and most institutes that offer jobs have already a very specific set of qualifications in mind. So one needs to be patient and it might take longer than you think. After searching for jobs for almost two years and rejecting a few offers, I can say that it was worth waiting! I have now a position as a tenure-track assistant professor at the Swiss Institute for Experimental Cancer Research under the new directorship of the world-renowned cancer researcher Doug Hanahan at the École polytechnique fédérale de Lausanne and was awarded the first ISREC Foundation Chair in Translational Oncology. I have a long-term job perspective, excellent quality of life, secure and generous funding, and I am working at a prime research university with a dynamic, international and interdisciplinary faculty. Here, I am trying to continue what I have learned at CeMM (and which was the reason I wanted to work there) – to bridge basic and clinical research in haematology. I am recruiting PhD students and Post-docs and it would be fantastic if I could attract some CeMMies to join my lab. I look forward to maintain ties with CeMM and Vienna through ongoing and future collaborations.

http://hantschel-lab.epfl.ch/

Dr. Tilmann Bürckstümmer
Five years of Post-doc at CeMM, five years that changed my life. When I started in Giulio Superti-Furga's laboratory, the lab had just moved to Vienna and consisted of a handful of brave people. When I left, CeMM had become a flourishing eight-story institute with a beautiful façade and more than 100 scientists from 29 countries. I was surprised how well people from scientific backgrounds as diverse as clinical medicine, chemistry, bioinformatics or proteomics can actually interact and cooperate, although this cooperation always required an extra effort. I was also surprised to witness a team spirit grow that at least for now is unsurpassed in my professional life. Scientifically, I felt that CeMM provided almost unlimited resources for my research, both in terms of advice from mentors as well as in terms of funding, that allowed me to address fundamental questions in current immunology. I especially appreciated the chance to co-tutor PhD students as it was a great experience to share the excitement of a novel finding as well as the frustration about an experiment that did not work out as anticipated.

With beginning of 2011, I decided to cease the opportunity to lead a spin-off company. While initially located on "CeMM grounds", the company may move to a different place by the end of the year. Based on my Post-doc experience, I feel prepared to start something new, prepared to mentor other people as I have been mentored and prepared to create a working atmosphere that will foster exciting discoveries.

Left:
Dr. Oliver Hantschel,
Post-doctoral Fellow in
Giulio Superti-Furga's
laboratory at CeMM
from 2004 to 2011
Nationality: German
Age: 34
Research Interests:
Signaling mechanisms
and novel treatment
strategies for hematological
malignancies
Major publications in
PNAS (2009) and
Molecular Oncology (2008).

Right:
Dr. Tilmann Bürckstümmer,
Post-doctoral Fellow in
Giulio Superti-Furga's laboratory from 2005 to 2010
Nationality: German
Age: 33
Research Interests:
Innate immune sensing
of foreign DNA
Major publications in
Nature Methods (2006) and
Nature Immunology (2009).

“Despite the economic turmoil in the last years, the government has been able to still strengthen the financial support for Science in Austria. CeMM is one of the lightning towers in Austria devoted to close the gap between basic research in molecular sciences and the needs of patients. The new building crowns the Government’s dedication to this extra-ordinary project, the support to the Austrian Academy of Sciences and the collaboration between the city government and the Ministry of Science and Research. CeMM is not only a place to do excellent science but it is also an investment in the education of the next generation’s medical doctors and biologists. We have great hopes for the success of CeMM maybe as a role model for collaborations with the other medical universities in Innsbruck and Graz, but also in different fields. We will continue to support CeMM, following the rule ‘only the plants tendered can bring fruits one can harvest’.”

Dr. Beatrix Karl
Austria’s Federal Minister of Science and Research

CeMM Karl Landsteiner Lecture

Karl Landsteiner:
A Formidable Hero of Molecular Medicine

Karl Landsteiner was born in Vienna, Austria in 1863. Although he trained as a chemist and earned his medical degree from the University of Vienna at the age of 23, Karl Landsteiner is best known as an immunologist. In 1930, he received the Nobel Prize in Physiology or Medicine for discovering the four different human blood groups. Furthermore, his work with Alexander Weiner uncovered the rhesus factor in blood cells in 1940. Along with other colleagues, he was one of the first to convincingly demonstrate that polio was caused by a virus, as well as being the first to successfully culture the causative agent of typhus, both of which dramatically advanced the study of these serious human diseases.

Following his death in 1943, an obituary was published in the journal *Science*, written by Michael Heidelberger who has been described as one of the fathers of immunology. Indeed, throughout his life Heidelberger was proud to state that he first learned immunology from Landsteiner. In the obituary, Heidelberger presents Landsteiner's most remarkable scientific achievements, as well as painting a picture of a man who was both an energetic scientist and a competent piano player with a love of music.

In honor of Karl Landsteiner's remarkable achievements, CeMM established the Karl Landsteiner Lecture series in 2007, as an annual event held at the Austrian Academy of Sciences. The speaker is selected by all members of CeMM for being a pioneer in molecular medicine. In 2010, the honor was awarded to the American geneticist, Helen Hobbs.

Previous Awardees
2009 Vishva Dixit: "Death Receptors, Ubiquitin Editing and Inflammasome Function".
2008 Kári Stefánsson: "Genetics of Common Diseases in the Context of Human Diversity".
2007 John Kuriyan: "Regulatory Mechanisms in Protein Tyrosine Kinase Signaling".

Speaker Helen Hobbs with Giulio Superti-Furga and the young artist Benedikt Hellsberg during the lecture in the Festive Hall of the Austrian Academy of Sciences.

Helen Hobbs is a Howard Hughes Investigator at the University of Texas Southwestern and Director of the McDermott Center for Human Growth and Development, in the U.S. She previously worked with Michael Brown and Joseph Goldstein, who jointly received the Nobel Prize in Physiology or Medicine in 1985 for their discoveries of the regulation of cholesterol metabolism. Now independent, Dr. Hobbs' main research interest is the genetics of lipid metabolism and its link to obesity and associated human diseases such as atherosclerosis, which is directly related to the research of Christoph Binder at CeMM.

Understanding lipid metabolism is indispensible for the research in the Binder lab. Dyslipidemia and inflammation are partners in crime in atherogenesis. They cooperate and can modulate each other's function. Understanding this interaction will help uncover the mechanisms by which cholesterol leads to atherosclerosis and help explain why certain individuals with identical cholesterol levels develop coronary disease differently.

Two Memorable Performances

Both Dr. Hobbs and her husband were invited to Vienna, where they were taken to the famous Musikverein to hear a memorable performance of Beethoven's Ninth Symphony by the Vienna Philharmonic Orchestra conducted by Christian Thielemann, without any doubt one of the highlight musical events of the year. The following day, Helen produced her own memorable performance by presenting the Karl Landsteiner Lecture entitled: "Genes Versus Fast Food: Eat Drink and Be Wary".

The event was held in the Festive Hall of the Austrian Academy of Sciences. There was classical music performed on the cello by Benedikt Hellsberg, the sixteen year old son of the current Chairman of the Vienna Philharmonic Orchestra, accompanied by Eva Ulrich on the piano. They played Robert Schumann, Fantasiestücke op. 73, and Camille Saint-Saëns "The Swan" from "Carnival of the Animals". The lecture was attended by some 200 people, and was followed by an after-party with finger food and wine to accompany the interesting discussions.

The Lecture

Hobbs first informed the audience, consisting of both scientists and the general public, that she always begins her genetics lectures to the undergraduate students at the University of Texas Southwestern by introducing Karl Landsteiner and his work, and proclaimed him to be a hero of hers. She went on to tell a couple of stories about her work linked to two important human diseases: fatty liver disease and coronary heart disease.

Identifying Genetic Causes of Fatty Liver Disease

Fatty liver disease is characterized by triglyceride deposits that accumulate in liver cells, and is caused by multiple factors including obesity and excessive alcohol consumption. The disease progresses from steatosis to steatohepatitis, which is characterized by inflammation, and finally to life-threatening cirrhosis and irreversible liver damage. Hobbs was interested in identifying genes that may influence the deposition of fat in the liver and thus affect an individual's susceptibility to the disease. Along with Ronald Victor and other investigators in Dallas they designed the Dallas Heart Study to identify ethnic differences in cardiac health. Over a period of 8 years, the scientists performed over 3,500 measurements and interviews on around 5,000 Dallas residents to search for genetic variants linked to liver fat content. They found that over a third of the individuals had excess fat in their liver, which is perhaps not surprising given there are 35 fast food restaurant of a particular famous chain in Dallas alone, and cities in Texas consistently rank at the top of obesity tables in the US (Source: American Obesity Association).

In this cohort, Hobbs identified ethnic differences in the prevalence of hepatic stenosis. Hispanics were more likely than those of European descent to suffer from the disease, with African Americans the least likely. By comparing the fat levels in the liver to genetic markers in each individual they identified a correlation between fatty liver disease and sequence variations in a gene encoding for PNPLA-3, of largely unknown function. They found that having a specific variation in PNPLA-3 could strongly predispose an individual to fatty liver disease, particularly in association with a poor diet. Further investigations on the actual cellular function of PNPLA-3 have also been performed in the lab, and uncovered an increase in protein levels on eating, and localization to lipid droplets in liver cells.

Cholesterol and Coronary Heart Disease

The second story focused on the contribution of genetic variation to plasma cholesterol levels. It is clear that industrialized populations have higher levels of cholesterol in their blood that increase with age. Previous work by Brown and Goldstein had shown that mutations in the LDL (low density lipoprotein; a cholesterol transporter) receptor causes an increase in blood cholesterol levels and a subsequent increased risk of coronary heart disease. In fact, there is a fifteen-fold increase in the incidence of coronary heart disease in the US as compared to rural China. Hobbs wanted to find out why.

Earlier work had shown that the levels of a protein known as PCSK9 was closely linked to cholesterol levels in mice. Using the individuals from the Dallas Heart Study, Hobbs and colleagues looked for mutations in the PCSK9 gene that were associated with blood cholesterol levels. They found a loss-of-function mutation predominantly in African Americans that was associated with a 28% decrease in plasma LDL levels. Life-saving drugs such as statins lower cholesterol levels and are widely prescribed to individuals at risk of heart disease. The goal now is to use the knowledge about PCSK9 to develop new therapeutics to further reduce an individual's risk of developing these progressive and chronic diseases, and to do so at an early stage of development, perhaps in combination with statins and better education on healthy eating and lifestyle changes.

Finally, Hobbs made it clear that these are diseases of dietary excess, but changing the diets of Westerners has not proven to be so easy. Her work has led to significant insight into the contribution of our genes to several severe human diseases, and as such makes her truly a pioneer in Molecular Medicine and a popular recipient of the 2010 Karl Landsteiner lectureship.

CeMM Constantin Spiegelfeld Lecture

In 2010, Dr. Benedikt and Beatrice Spiegelfeld founded the Constantin Spiegelfeld Lecture in memory of their son. The lectures will be bi-annual events held at CeMM. The lecture series addresses the complex world of therapeutics, from the research challenge to their impact on society. Topics will range from the drug discovery and development process to marketing and health costs issues, including drug compliance, adverse effects, safety and ethical aspects. The series wants to help familiarize the community and interested laymen with the complexity of the issues in question and provide education on the responsibility that society and politics share with the research community and the pharmaceutical industry. After each lecture, the events foster a forum for debate of controversial issues.

The world-renowned scientist and health manager George Poste from Arizona State University, U.S., gave the first Constantin Spiegelfeld Lecture. “Genomics, Demographics, Epidemics, Economics and Ethics: The Complex Forces Shaping Therapeutic Innovation and Investment” was presented at CeMM on November 8th 2010, an event which was co-managed by three CeMM PhD students. The Spiegelfeld family joined an audience of around 150 physicians, scientists, sociologists and artists for the lecture, which was held in the 8th floor lecture hall.

George Poste during his lecture in the seminar room of CeMM.

The First Lecturer

George Poste is currently Chief Scientist of the Complex Adaptive Systems Initiative (CASI), which addresses global health challenges by promoting cross-disciplinary relationships. He is also Professor of Health Innovation at Arizona State University (ASU). From 1992 to 1999, Dr. Poste was President of Research and Development at SmithKline Beecham, one of the world’s largest pharmaceutical companies, where he led the registration of 31 clinical products for marketing approval. He has won several high profile awards including the 2009 Scrip Lifetime Achievement award, which honors the brightest stars of the pharmaceutical and biotechnology industry, and in 1999 was awarded the title Commander of the Order of the British Empire by Queen Elizabeth II.

The decision to ask George Poste to hold the first Constantin Spiegelfeld Lecture was made by a panel consisting of Giulio Superti-Furga from CeMM, Michael Freissmuth and Markus Müller, both pharmacologists at the Medical University of Vienna, along with CeMM PhD students Dimitris Tsiantoulas, Iris Uras and Georg Winter. Upon his arrival, Dimitris, Iris and Georg showed George Poste and his partner around the city, before they met with Giulio and the Spiegelfeld family for dinner and a concert. On the day of the lecture, Dr. Poste had lunch with the rest of the CeMM PhD students and met with the CeMM PIs, as well as giving an interview for the Austrian newspaper “Der Standard”.

The Key Present and Future Aspects of Global Healthcare

George Poste’s lecture focused on a changing world, both from a disease and a treatment perspective. In terms of disease, there has been a continual emergence of new diseases, such as SARS (severe acute respiratory syndrome), which became a near pandemic in 2002, and the worrying increase in drug resistant pathogens. Changes in global parameters, such as increased transport and trade, and the average age of the population, also contribute to shifts in the impacts of current diseases.

Not only is the disease landscape changing, but also the technologies that are available to the healthcare community for diagnostics and treatments. There has recently been a rapid development of new technologies in the scientific community, which nevertheless, must still fit in with available healthcare resources. Within this context, George Poste spoke of the increasing cost of healthcare and highlighted the importance of using the limited resources to promote healthy living as well as managing disease. Indeed, as he pointed out, twenty percent of the population spends eighty percent of the healthcare costs, so it pays to keep the healthy people healthy.

Around 150 guests joined the first Constantin Spiegelfeld lecture of George Poste.

George Poste with Deborah Carstens and the students committee.

Personalizing Medicine

The lecture highlighted an important factor shaping the future of healthcare: the development and implementation of so-called personalized medicine. This concept has emerged from the knowledge that no two diseases are exactly the same, and indeed neither are the individuals carrying those diseases. Both of these factors directly and critically influence our ability to successfully treat disease. It is becoming clear that a 'one-size-fits-all' approach to disease treatment is no longer appropriate. Indeed, high costs are associated with using treatments that are ineffective in certain patient groups, as well as, more importantly, a high risk to patients, given the potential for toxic or even lethal side effects.

The advent of 'next generation' technologies means diagnostics have become more sophisticated, thereby enabling detailed profiling of individual patients at the genomic and proteomic levels. This means each patient can be measured for factors such as specific genetic mutations or protein levels that may influence how they respond to a specific drug or how a disease will progress. This information can then be used to design a customized treatment approach. So, drugs will only be used in patients where they are most likely to work and to be safe, ultimately saving lives and costs.

Connecting with CeMM

CeMM is investing in technologies and research that add to the knowledge base that will be critical for the development of truly personalized medicine. For example, Sebastian Nijman's group is investigating how genetic mutations that cause cancer can influence the response of cells to certain drugs, which could reveal which cancer types respond best to specific treatments. Scientists in Giulio Superti-Furga's lab have been analyzing the effects of drugs on cells by identifying the proteins to which they bind, which can help identify potentially severe side effects or new disease indications.

Science Fiction or Science Fact?

The lecture provided an interesting glimpse into how we will likely be dealing with our daily health in the future. Although it sounds like science fiction, some of this technology is already available. For example, there are companies developing wireless devices for monitoring an individual's health status in real time. This will involve the use of microchips implanted in our bodies, measuring parameters such as heart rate, blood pressure and cholesterol, which will enable the external monitoring of our health and lead to a rapid response upon detection of any abnormalities. This type of approach could also be used to help us monitor our own health status, by for example linking the sensors to a mobile phone or similar device to tell us if we are eating the right foods and getting enough exercise. In another area, there are many approaches being developed for tackling the serious problem of individuals not taking their medication properly. One company has designed smart caps for medicine dispensors, so that, rather than having to remember what pills to take when, our medication has its own timer and alert system to help remind us.

Conclusions

George Poste's lecture was incredibly well received and has set the bar for the next Constantin Spiegelfeld Lecture very high. It was followed by an exciting roundtable and forum discussion, chaired by Giulio Superti-Furga with a panel consisting of CeMM PhD student Iris Uras, and Michael Freissmuth and Markus Müller from the Medical University. Discussions focused on personalized medicine – what it is and why it's needed, as well as how society needs to better prepare for the associated ethical, political and biosafety issues. Finally, discussions continued more informally over cheese and wine in the adjacent room, accompanied by a tremendous evening view over the city of Vienna.

CeMMinar Series

A new system for Seminars and Lectures has been installed in 2010. CeMM has a dedicated budget to invite international speakers on a regular basis to give a talk to CeMM members and the scientific and medical community of Vienna. In addition the guest is asked to participate in a lunch meeting with CeMM Post-docs, a "Meet and Greet" session with the students right after the seminar. The duties and honor of being a host is shared within the Faculty.

In 2010 we had the pleasure to invite and host the listed CeMMinar and Impromptu speakers.

25.01.2010
Roderick L. Beijersbergen
"The RNAi strategy in target identification: Hitting cancer where it hurts most!"
The Netherlands Cancer Institute; Amsterdam, NL

15.02.2010
Barbara Kazmierczak
"The cost of virulence: Innate immune recognition of the type 3 secretion system of Pseudomonas aeruginosa"
Yale University School of Medicine, New Haven CT, USA

08.06.2010
Thomas Rattei
"In silico interpretation of microbial (meta-) genomes and its improvement through proteomic data"
Department of Computational Systems Biology, University of Vienna, A

02.08.2010
Tobias Stuwe
"The FACT Complex is a Multi Histone Chaperone-containing Chromatin Reorganization Complex"
European Molecular Biology Laboratory (EMBL), Heidelberg, D

14.10.2010
Francesca Ciccarelli
"Genomic Instability and the Evolution of Cancer"
European Institute of Oncology, Milan, I

28.10.2010
Impromptu
Jörg Hackermüller
"Cell cycle, oncogenic and tumor suppressor pathways control the expression of long and macro non-protein coding RNAs"
Fraunhofer-Institut für Zelltherapie und Immunologie IZI in Leipzig, D

09.11.2010
Ajay Chawla
"Immune Determinants of Metabolism and Regeneration"
Stanford University School of Medicine, USA

10.11.2010
Impromptu
Young-Hwa Song
"Novel molecular insights into the old tuberculin skin test and its association to secretion machinery"
European Molecular Biology Laboratory (EMBL), Heidelberg, D

16.11.2010
Impromptu
Francesco Gervasio
"Combining Free Energy Computations and Experiments to Study Large Scale Dynamics and Conformational Selection in Proteins"
Head Computational Biophysics, Spanish National Cancer Research Center, Madrid, E

29.11.2010
Hamid Bolouri
"Making the most of personal genomics in medicine"
Fred Hutchinson Cancer Research Center in Seattle, USA

10.12.2010
CeMM Science Day
The Science Day is meant to provide an overview of the research projects at CeMM and to present current themes accessible also to lay people

13.12.2010
Stefan Knapp
"Selective targeting of protein kinases using parallel screening and large scale structural comparison"
Nuffield Dept. Clinical Medicine, University of Oxford, UK

15.12.2010
Impromptu
Roel Verhaak
"Integrated genomic analysis of data from The Cancer Genome Atlas provides clinical and biological insights in serous ovarian cancer and glioblastoma"
MD Anderson Cancer Center, Houston, USA

20.12.2010
Andrew Bowie
"Sensing and signalling in anti-viral innate immunity"
School of Biochemistry and Immunology Trinity College Dublin, IRL

CeMMinar Speakers Hamid Bolouri signing books, Francesca Ciccarelli, Young-Hwa Song with students, CeMM student Damla Olcaydu at the Science Day.

"With its reputation for scientific excellence and its prime location within the Vienna medical campus, CeMM provides the perfect framework for a popular lecture series aimed at raising awareness of the world of pharmaceuticals, from discovery and development to use, misuse and side effects, as well as general issues on ethics and society. We would like to thank CeMM and especially Prof. Dr. Giulio Superti-Furga and the members of the board for their help and for organizing the Constantin Spiegelfeld Lectures in memoriam of our son. We believe the first lecture by well-known scientist Prof. George Poste made an impressive contribution to fostering a better understanding of the effects of drugs."

Dr. Benedikt and Beatrice Spiegelfeld
Sponsors of the Constantin Spiegelfeld Lecture

CeMM Retreat

In 2010, the institute's annual retreat was held in Brno in the Czech Republic, which is around 130km north of Vienna. Brno was chosen because of its strong link with genetics: Gregor Mendel performed his infamous experiments on plant breeding in a monastery in Brno between 1856 and 1863. Mendel was both a monk and a scientist, and is hailed as the father of modern genetics. By cross-breeding individual pea plants, he was able to follow the inheritance patterns of various traits, such as flower color and seed shape, the results of which he used to generate several laws of inheritance. These experiments and Mendel's laws are taught to every genetics student at university, and a visit to the monastery site and Mendel museum was an incredibly special start to the retreat.

CeMM students enjoying Brno, visiting Mendel museum and discussing self-definition posters.

The retreat was held in a modern city center hotel with a generously sized conference hall for all the talks, discussions and social gatherings. After dinner on the first evening, following Director Giulio Superti-Furga's opening address, each PI and team leader gave a short 10 minute scientific presentation. Each described his or her research in a broad context, linking it to molecular medicine and the mission of CeMM, as well as outlining the major challenges in the field and his/her scientific ambitions for the coming five years.

The following morning there was a brainstorming session where people were split into four groups. Each group was given a specific topic for discussion:
1. "Making CeMM more medical"
2. "Systems biology at CeMM"
3. "How to best use CeMM's technology"
4. "CeMM and my career"

The aim was to generate concrete strategic ideas to address the points above and it was followed by a flip-chart presentation and an open discussion. It shows how the opinion of each person working at CeMM is valued, and that the success of the institute is viewed as a collaborative effort. There were also two special guests who gave talks in the afternoon and joined in with some of the discussions. Gottfried Himmler, a biotech start-up veteran, gave a fascinating talk on his experiences in the biotechnology industry, and Helen Pickersgill, editor at the journal *Science*, gave some tips on how to write manuscripts for publication.

Everyone was required to make a small portable poster, including administration and members of the IT department, to briefly and clearly describe his/her work at CeMM. A 'speed dating' session involved randomly pairing individuals and giving them 10 minutes to try to find some common ground and a potential new collaboration.

As expected, the social program rivaled the scientific one. There was a lot of elaborate fancy dress and various party games, including a talent show, and some very interesting medieval dancing where all PIs and senior staff were dressed up in traditional costumes. The retreat lasted 2 days, and it is an important event in the Institute's calendar as it enables close interaction between all CeMM members in a more informal setting, as well as being a lot of fun.

CeMM
Social Activities

CeMM first Barbecue
On a balmy August night CeMM fellows, families and friends met to celebrate the more or less stressful but in the end exceedingly pleasing move into the new building. The breathtaking view over Vienna, a tasty barbecue, relaxed parents and lucky children made the first get-together on the terrace a memorable event.

Outing to Rax
2 coaches, 1 hour bus trip, 10 minutes cable car ride, 50 minutes walk, 2.000 meters above sea level, no effort for passionate hikers and no sweat for 100 CeMMies – on October 8, 2010 CeMM took pleasure in "climbing" Rax, one of the high mountains near Vienna. Bright sunshine and high spirits were the best background for a competition between two choirs that were spontaneously assembled in the buses. No doubt: CeMM people once more showed their talents, their capacity for team work and creativity in finding the best solutions within a limited time.

Halloween Ball
"Work hard, party hard", could have been the slogan for the 1st Halloween ball at CeMM. The organization was part of the duties and responsibilities of the new PhD. students. And they did it exceptionally well: with fancy dresses from horror (not suitable for children) to lambkin, an amazing buffet with regional specialties, a perfect dance show and a motivating DJ! Even CeMM SAB member Hidde Ploegh, who was giving a lecture in town and passed by, was very impressed. One might say they set a new benchmark for social events at CeMM.






Get-together Anna Spiegel/CTR – CeMM
CeMM is working next door to the Center of Translational Research (CRT) in the Anna Spiegel Research building of the Medical University of Vienna. To be accurate: CeMM and Anna Spiegel/CRT share a combined building with a common entrance. To encourage a collaborative spirit and to keep on good terms with each other, a monthly get-together was established. Starting with a jolly feast in October 2010 the monthly event has grown to be a scientific as well as a social highlight for both Institutes. CRT people have free access to CeMM with their door cards. Many informal meetings happen during lunch in the CeMM Cafeteria.









Christmas Party
No doubt: The Christmas party in the new building was the highlight of the first season in the new CeMM building. Families and partners were also invited to join the buffet, the show program and the subsequent dancing party. Santa Claus brought presents for children, but also each adult found a present under the tree through an entertaining potluck system to which everybody contributed. The amusement lasted well after midnight. And it seems, that CeMM was born under a lucky star.

"Investment in education and research is critical for the progress of a modern and just society. The Austrian Academy of Sciences fulfils an important role in providing a powerful source of independent research and innovation. One of its latest institutes, CeMM, promises to help bring about the translation of knowledge into medical practice and to energize medical research."

Dr. Hannes Androsch
Chair, Austrian Council for Research and Technology Development
Senator, Austrian Academy of Sciences

CeMM Art Façade

At the geometric center of one of the largest medical sites in Europe now stands the new custom-designed nine-floor CeMM building, which, by the end of summer 2010, was filled with research groups and open for business. The building itself is striking. It was designed by architect Ernst Kopper who created a building full of light with much open space for the needs and comfort of modern molecular biology laboratories as well as room to house sophisticated high-tech scientific equipment. One side of the building is adorned by a stunning glass façade, designed by Austrian multi-media artist Peter Kogler. This modern look makes it stand out in sharp contrast to the neighbouring buildings of the Medical University of Vienna, which were built around the turn of the last century, and the adjacent looming towers of the Vienna General Hospital.

Planting a Seed
One could say that the CeMM building seed was planted when its location was first proposed, in December 2000. The city authorities offered the Austrian Academy of Sciences a site on the premises of Vienna's General Hospital (AKH), which was supported by the Austrian Council for Research and Technology Development and the Ministry of Science. The site had originally been earmarked for the dental clinic in the 1970s. However, the dental clinic was eventually built on a different site, leaving the area free, and with the help of the Mayor of Vienna Michael Häupl and city counsellor Brigitte Ederer, it was finally allocated to CeMM.

After planting the seed, the building could begin to grow. The ground-breaking event took place on 19th September 2002 and, after some unforeseeable delays, the concrete shell of the building was eventually completed at the beginning of 2009. This topping-out event was celebrated by the construction workers and CeMM's faculty, along with the then Minister of Science and Research, Dr. Johannes Hahn, on March 24th, 2009. From mid 2009 till completion, the appearance of the building kept evolving, as it got covered in glass little by little. The large windows now provide substantial amounts of natural light for the people working inside.

The Art Façade
Architect Kopper had always envisaged the large glass façade at the eastern end of the building as a sort of membrane representing the interface between what had to occur inside the building and its environment. The art façade has its own story. CeMM scientific director Giulio Superti-Furga was inspecting the construction site in November 2008 as the first floors were emerging, because it occurred to him that such a prominent building deserved a strong esthetic statement. He consulted his wife Stefanie, an art historian, who listed a few artists that would be particularly suitable. One in particular, Tyrolean and Viennese artist Peter Kogler, was having a large retrospective show at the MuMOK that month. Superti-Furga visited the exhibition the same day, got transfixed by what he saw and immediately became obsessed with the possibility of winning the artist over for a CeMM art project. As fate would have it, the same evening, Martin Böhm, director of the Dorotheum, was able to seat Giulio vis-à-vis Peter at a charity dinner. This is where the first contact occurred. Discussions early in 2009, between the artist, the architect and the scientific sponsor, soon focused on the façade as an ideal surface for an object of art. Reportedly, the enthusiasm was so strong that Superti-Furga became confident that a sponsoring campaign would be feasible.

So, how does one come up with a design that would literally become the face of a biomedical scientific institute? Fortunately artist Peter Kogler had always been interested in the history of science and what goes on in research. His design was inspired by some of the topics that are studied at the institute, namely networks of molecules and cells. The artist was known for having depicted networks at the Documenta Kassel, when awareness of the Internet first started to emerge in the 90s. As CeMM Director Giulio Superti-Furga explained, proteins, which are the molecules that perform most of the functions in cells and organisms, work in groups that are interconnected to form large molecular networks. CeMM scientists have been uncovering the composition and function of some of these networks, which in turn can help scientists understand why and how disease occurs. However, the façade deliberately does not attempt to reproduce a particular network. It is rather a model of a possible, theoretical biological network, ranging from the microscopic to the macroscopic and even organism scale.

Assembly of the 400m2 glass façade took 12 months, and its completion was celebrated in a style to match the grand design. Because of its location, the façade can be seen by hospital visitors, patients, staff and students, amounting to many thousands of spectators each year, and will likely become a city landmark. CeMM is especially grateful to the 50 individual sponsors that supported this art and science project. The existence of the façade also symbolizes the determination and support of the Ministry of Science and Research, the Austrian Academy of Sciences, the Medical University of Vienna and the Vienna General Hospital, which together have made CeMM a new collaborative paradigm for medical research.

The Finishing Touches
The rest of the building was completed in summer 2010, when the research labs were able to move in. The first in was the Barlow lab, which moved from across the city in the third district where they had been renting space in the Max F. Perutz Laboratories. The rest of the labs came from closer by, and most of the equipment was wheeled or carried through the medical campus and into the new building. Moving some of the larger and more sensitive pieces of equipment, such as the mass spectrometers, required careful planning to ensure minimum disruption of ongoing experiments. The last of the groups were installed in September 2010, in time for some informal celebrations on the roof terraces in the last of the summer sun. The official opening of the CeMM building took place in 2011.

The Building Architect: Ernst M. Kopper

Location, Location, Location
The CeMM building is situated at the heart of a medical research campus housing the Vienna General Hospital (AKH) and the Medical University of Vienna. The building itself is physically linked to the Anna Spiegel research building of the Medical University by connecting doors on each floor, and is also linked to the hospital via an underground corridor. This prime location enables CeMM researchers to interact closely with clinicians and the medical faculty, which supports CeMM's mission to "combine insight obtained from basic and clinical research and use it to implement the development of innovative therapeutic and diagnostic strategies".

Building Facts and Figures
The main entrance of the CeMM building is shared with the complementary laboratory of the Medical University of Vienna. There is an additional entrance leading to the main stairway and the "service" elevator, for persons and goods. There are eight floors with an overall floor space of 5,620 m2. A similar floor plan repeats itself on almost all levels. The laboratories face south and are open-plan, with working places for some 20 people. Along the windows there are desks with computer workstations. On the north side of most floors are rooms for specialized laboratory facilities as well as more offices for scientists and administration, and a small seminar room. On the top floor are two lecture rooms, a cafeteria and a common office. Two large terraces provide exceptional views over the city. For a 'virtual' tour of the building, please turn to the research pages of this report.

The Façade Artist: Peter Kogler

Technical aspects of the façade
Duration of façade building:
February 2009–February 2010
Material: 400 m² enameled glass
Graphics applied by screen printing, the motif is applied to the glass surface using enamel, which is subsequently baked onto the glass
Glass thickness: 44.2 mm
Glass weight: 57.4 kg/m²
Production: Steindl Glas GmbH
Sponsoring project management:
Giulio Superti-Furga
Number of sponsors: 50

The following list of sponsors is also visible on a stainless steel plaque in front of the façade.

Gustav Ammerer
Bernd and Christa Binder
Christoph Binder
Max and Margaret Birnstiel
Martin and Lucrezia Böhm
Erhard Busek
Meinrad and Irene Busslinger
Georg and Maria Rita Casari
Helmut and Helga Denk
Heinz and Margit Fischer
Michael and Margarita Freissmuth
Annabelle, Tara, Constantin and Paul Habsburg-Lothringen
Johannes Hahn
Michael Häupl
Christian J. Herold
Erika Jensen-Jarolim
Beatrix Karl
Reinhard Krepler
Ernst M. Kopper
Klaus Lechner
Jürgen Meier
Laurenz and Waltraud Niel
Sebastian Nijman and Helen Pickersgill
Primus and Katharina Österreicher
Elisabeth and Helmut Pockberger
Maria Polsterer-Kattus
Barbara Prammer
Georg and Martina Prantl
Ursula Schmidt-Erfurth
Wolfgang Schütz
Constantin Spiegelfeld
Georg Stingl
Erich W. Streissler
Giulio and Stefanie Superti-Furga
Peter Swetly
Witold and Claudia Szymanski
Iris, Zambak and Abdurrahman Uras
Erwin Wagner
Herbert Watzke
Klaus Wolff
Nikolaus and Gabriele Zacherl
Franz Zwickl
General Hospital of Vienna
CeMM Administration
CeMM Barlow Lab
CeMM PhD Students
CeMM Post-doctoral Fellows
Medical University of Vienna
Austrian Academy of Sciences
STRABAG AG
Department of Psychiatry and Psychotherapy of the Medical University of Vienna
Vossius & Partner

Celebrating the New Landmark Façade

With a flash, the façade was completely bathed in light: sponsors and prominent guests gathered in front of CeMM and cheered at the first illumination of Peter Kogler's 400 m² piece of art. It was the climax of the ceremonial inauguration of the CeMM art façade, which took place with some 200 participants in a tent at the foot of the new building. Following the welcome addresses of CeMM scientific director Giulio Superti-Furga and artist Peter Kogler, a speech by Federal Minister of Science and Research, Dr. Beatrix Karl, hailed the importance of basic research for medicine and innovation, stressed the pivotal role of CeMM on the medical campus and congratulated on the successful merger of art and science.

Among the well-wishers were the Rector of the MUW Prof. Wolfgang Schütz, AKH Director Prof. Reinhard Krepler, former presidents of the Austrian Academy of Sciences, Prof. Werner Welzig and Prof. Herbert Mang, the newly-elected president of the ERC Prof. Helga Nowotny, numerous architects, museum directors and artists, including Anna Jermolaewa, Herwig Kempinger, Hans Kupelwieser, as well as far too many research partners and friends to be all mentioned. Following behind a press conference in the morning, which was widely covered by the media, the evening event was an extremely successful testimonial for cross-cultural integration and a celebration of the creative impetus common to art and science.

Well-wishers and sponsors followed the welcome addresses of Minister Karl, Peter Kogler and Giulio Superti-Furga and enjoyed a memorable festivity.

Round Table Discussion

The architect, the artist, the scientific director: a conversation on the building and the façade

Giulio Superti-Furga From our point of view, the CeMM building is tailor-made and almost ideal for its purposes. We had an opportunity to take part in floor plans and lab features. But the planning started long before. What was the focal idea of the building?

Ernst Kopper The idea was to fit the building into an important urban axis, which runs from west to east across the campus. The 66 meter long building includes two laboratory sections. Two thirds of the building are provided to the Medical University, one third to CeMM.

Giulio Superti-Furga Two entities, one building – are there particular challenges?

Ernst Kopper For the architect, the complexity was to have one body with two distinguishable entities. So it was clear for me to form the concept of the main building for CeMM to implement certain features: It is the crown, the "headgear" of the building, an additional floor with wing-shaped walls reaching outward to house the seminar rooms and the cafeteria and two terraces. Here happens everything that is exciting. It is indeed an essential part of any research building: space for communication and space for relaxation, with a view over Vienna. Another very prominent feature is the enclosure of the staircases, that holds the hollow of the rest of the building like a spine, like the ribs of a corpus. But architecture is always a combination of function and form, and the concrete structure of the staircase has to fulfil the earthquake standards for large buildings. The twist, as can be seen from the small side of the building facing east, depicts the bending of Spitalgasse outside the area.

Giulio Superti-Furga What about the wings and the spine. Is it an idea within a split second or the result of long deliberations?

Ernst Kopper There were some specifications, not least because of the involvement of the future user. An asymmetric construction of the building, north higher than south, causes a special dynamic. It was David Pasek who had the underlying idea for the east façade. It came swiftly and was workable over years.

Giulio Superti-Furga Were there any changes during the construction phase?

Ernst Kopper The entrance to the east was originally planned two stories high as it can still be seen from the outside. It was only decided later to abandon the main entrance on the east side in favour of a joint access to both parts of the building. But nevertheless the east façade is the eye catcher for all visitors, all the more because of Peter Kogler's work of art.

Top picture: Giulio Superti-Furga
with Ernst Kopper and Peter Kogler
Bottom left: Ernst Kopper
Bottom right: Peter Kogler

Giulio Superti-Furga While there were some tailbacks in the planning and construction phase, we quickly stepped forward in realising the art façade. Considering all the obstacles which had to be pushed aside before this building took shape, it was almost magical to experience the enthusiasm on the part of AKH director Dr. Krepler, the ministry, the academy, the BIG, to have this piece of art as a façade.

Ernst Kopper A lot is said in Austria about "Kunst am Bau" for public buildings. I believe that CeMM is one of the best examples of how to integrate great art into a building. From the beginning, there was a feeling that the CeMM building is situated right at the beginning of the AKH campus and that the façade should act like a membrane. It was this discourse between the strictly regulated rectangular form and the often chaotic life around a hospital. This lucky combination with Peter Kogler's imagination to fit the envisioned membrane sculpture led to the perfect combination we can admire now.

Giulio Superti-Furga For us the art façade is totem and symbol. It inspires us. Inward it provides shade, outwards it is sometimes transparent, sometimes reflecting. Depending on the angle of light one can observe the pattern mirrored on the building in front. When the sun sets on the other side, through the glass "ears" one sees a stripe of Emmentaler holes projected. The façade is alive, has its own dynamics.

Peter Kogler One important aspect was that Giulio gave me a lot of scientific pictures, a lot of input, which I mixed with my formal language. So the form is nothing real, but sort of a model – a visualization, a tool to uncover the unseen universe, which can only be detected with instruments and is brought to our everyday world in the form of a model. So I was also experimenting on how to translate the world of science into my own formal language. It is an approximation, a replica repeating itself. The whole structure is based on generated information and not on reality.

Giulio Superti-Furga It is amazing how it keeps changing all along, as one always finds a new pattern. This may be due to the fact that each part holds much information. The eye has a lot to discover. One always finds different facets. It could be a jungle, algae, cells, molecules. Later, I discovered human body parts. I had not noticed this before, but then they became quite present. Reflections influence the way I look at and perceive it.

Peter Kogler Probably it is rather reflecting the way the tools were invented. You can compare the simplicity of computer graphics in early times when only lines and circles were available, the information visualized was sort of like a caricature. The developments in this field were tremendous, and nowadays one can calculate all kinds of shapes, forms, angles, views as one wishes to. In architecture, a house drawn with a ruler and a pen is totally different to the one modern architects are constructing with CAD – computer aided design. Look at the films in Hollywood. Without computer graphics you hardly can make a film anymore. So to assemble the forms for the façade I used computers. If you look at it you will be sucked into it or the picture is popping out. You find a three-dimensional structure, even hidden parts of the human body like arms, shoulders etc.

Giulio Superti-Furga What else was determinant?

Peter Kogler For me the huge dimensions were quite a challenge in choosing the right forms. Of course, as an artist one is always developing one's own style and moving on to new unknown areas. The cognitive projection from the small form to a 400-fold magnification is daring even with the experience I had gained. A façade also has to fulfil technical aspects, so that as an artist you are limited in your choice of materials.

Giulio Superti-Furga It would be interesting what people think. Do they see any relation to the hospital, do they think it is frivolous, a kind of extravagance, which does not fit the sobriety of patients and disease? Do they see a relation to research and education? And will it last?

Peter Kogler How long it will last is a question that coming generations will have to decide on. As an artist I hope that this piece of art will survive. It was made within a certain time setup in a certain cultural context. And it is also perceived out of this context. But the perception changes constantly, so it is really hard to tell what people will feel and think in 20 or 50 years from now. But still, it will always serve as a façade. For the art, interpretations may change.

Giulio Superti-Furga The whole project started when I saw your exhibition at MUMOK and fortunately became acquainted with you. I got the idea that a piece of art might suit the CeMM very well. And it did.

Ernst M. Kopper was born 1945 in Schulberg near Graz. After studying architecture at Graz University of Technology he spent some diploma and internship years in Rome and Munich. Since 1975 he lives in Vienna. Since 1984 he works as an independent architect, but also in co-operations, within the scope of projects. He is specialized in research buildings and has realized among other things the Vienna Biocenter, the Center for Medical Research in Graz, lab buildings of the General Hospital of Vienna and CeMM.

Peter Kogler was born in Innsbruck, Austria in 1959, and currently lives in Vienna. He was one of the first artists to work with computers, and is described as one of the most influential artists of the nineties. Kogler has exhibited his work internationally, including exhibits at the 46th Venice Biennale (1995), the MOMA, New York (2006), and in the Galerie Crone, Berlin (2004). His work is also often displayed at the MUMOK (Museum of Modern Art) in Vienna.

"When I was Vienna's financial city counsellor, I remember vividly the initial discussions with Mayor Häupl and Academy President Welzig on the merit of starting an institute to tackle some of the research hurdles for the medicine of the future. Now molecular medicine, increasingly powerful diagnostic capabilities and virtual patient models are becoming more important by the day.
I wish CeMM and its brand new building all possible success."

Mag. Brigitte Ederer
Member of the Executive Board of Siemens AG

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Armenia, Australia, Austria,
Belgium, Brazil, China,
Congo, Czech Republic,
Denmark, Finland, France,
Germany, Greece, India,
Ireland, Italy, New Zealand,
Pakistan, Poland, Portugal,
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* left CeMM in 2010
° maternity leave

Legend to grants

DOC-fForte Fellowship
Austrian Academy of Sciences

ERC i-Five
European Research Council
Advanced Investigator Grant
"Interferon-focused Innate
Immunity Interactome
and Inhibitome"

EU ASSET
EU Project "Analysing and
Striking the Sensitivities
of Embryonal Tumours"

EU Project HEROIC
"Highthroughput Epigenetic
Regulatory Organisation
In Chromatin"

EU Marie Curie Project SMART
"Small Molecule Antagonists
of chromatin modifying
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Transcription, proliferation
and differentiation"

EU Marie Curie Project ToILiCoR
"Dissecting pathogen
recognition complexes
of Toll-like receptors"

FWF 1207 DK
Doctoral Program
"RNA Biology"

FWF 1718
Special Research Program
"Modulators of RNA
Fate and Function"

FWF W1205 DK
Doctoral Program
"CCHD – Cell Communications
in Health and Disease"

FWF P22282-B11
Stand Alone Project
"Regulo-Interactome Modules
of Hematopoietic Stem Cells"

FWF I291B09 ERA-NET
PathoGenoMics
"Pathogen-host metabolomics
and interactomics"

FWF P21768-B13
Stand Alone Project
"Searching for Cancer
Achilles' Heels"

Gen-AU Project APP III
"Austrian Proteomics Platform"

Gen-AU Project BIN III
"Bioinformatics Integration
Network"

Gen-AU Project
Epigenetic Control III
"Epigenetic Regulations
of Cell Fate Decisions"

Gen-AU Project PLACEBO
"Platform Austria
for Chemical Biology"

MPD Foundation
New Investigator Grant
"Genetic complexity of
myeloproliferative neoplasms"

WWTF LS09-009 Project
"Searching for Cancer
Archilles' Heels"


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"Exactly 30 years ago, the immunologist Dr. William Paul – at that time President of the ASCI – heralded the advent of a golden era of clinical investigation. He predicted that the availability of certain new technologies would lead to a deep and meaningful insight into the mechanisms operative in a whole variety of different diseases. Based on this, one would expect that therapeutic strategies are developed that should exhibit a much higher degree of specificity and, as a consequence, higher efficacy and lesser toxicity than the 'old remedies'. The history and, I am convinced, even more so the future of CeMM is an excellent example for the validity of Dr.Paul's forecast. A group of brilliant investigators led by the enthusiastic and charismatic Giulio Superti-Furga, a newly built institute with many important in-house technologies and a major academic medical center surrounding it, are ideal conditions for the pursuit of high-level biomedical research and true accomplishment. The Academy is very proud of having CeMM under its umbrella. Be assured that we will do our very best to help bringing its enormous potential to full fruition, for the benefit of true scientific progress of the biomedical research scene in Austria, and most importantly, of the patients seeking help for their disease."

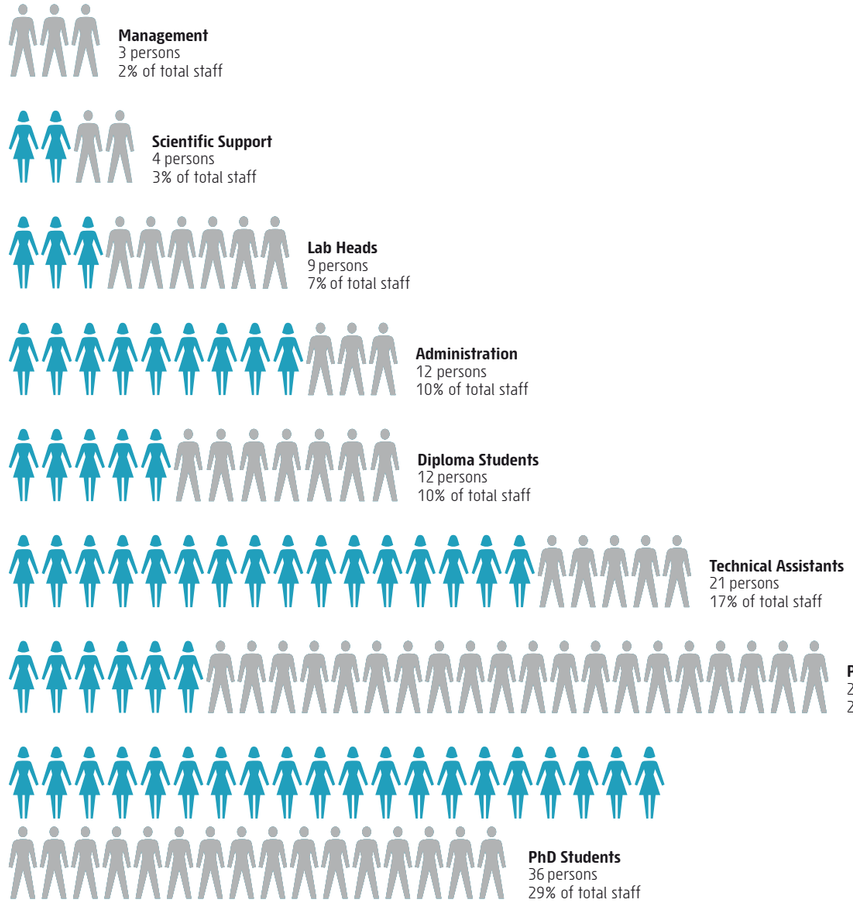
Prof. Dr. Georg Stingl
President of the Section for Mathematics and the Natural Sciences
of the Austrian Academy of Sciences

CeMM Facts & Figures

CeMM Staff

Listed by number of persons per field of work

The CeMM administration is very lean in relation to the total staff (124 employees as of December 2010). We have a very good gender balance. The average age at CeMM is 31 years.



Management
3 persons
2% of total staff

Scientific Support
4 persons
3% of total staff

Lab Heads
9 persons
7% of total staff

Administration
12 persons
10% of total staff

Diploma Students
12 persons
10% of total staff

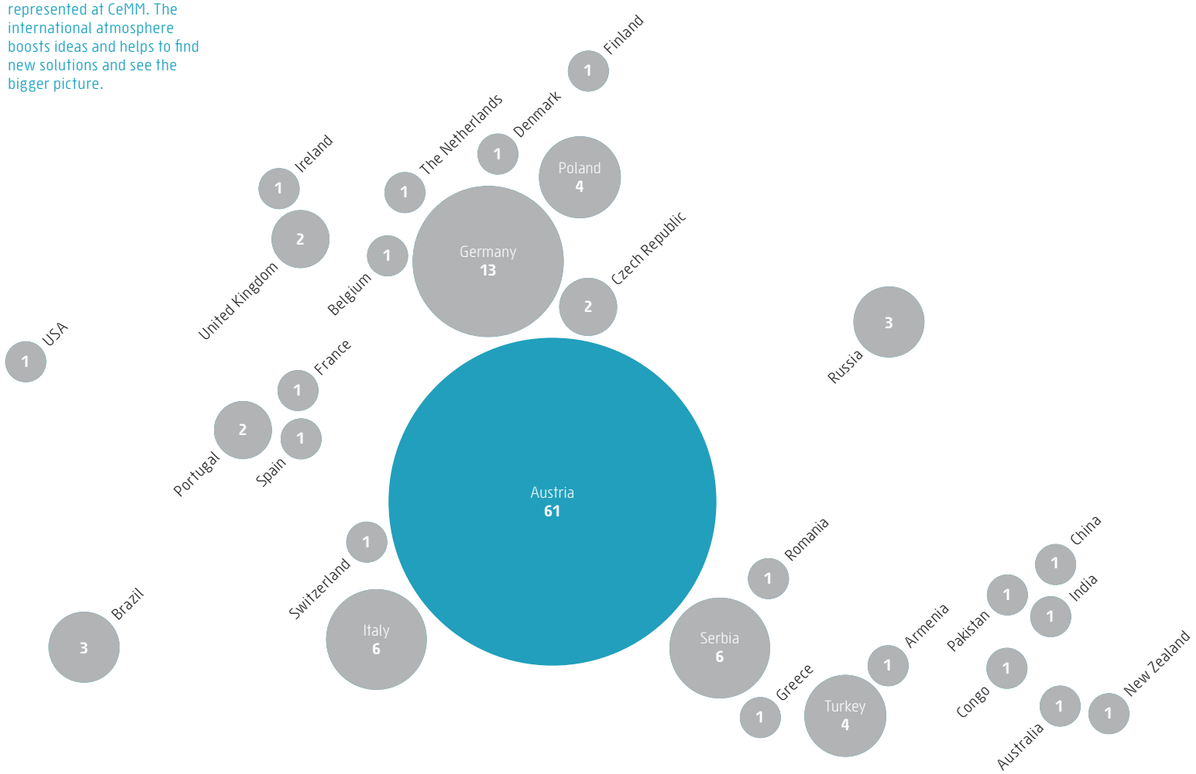
Technical Assistants
21 persons
17% of total staff

Postdoctoral Fellows
27 persons
22% of total staff

PhD Students
36 persons
29% of total staff

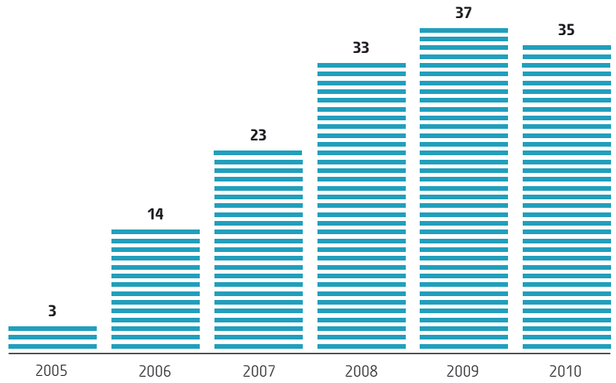
Nationalities at CeMM

29 different nationalities are represented at CeMM. The international atmosphere boosts ideas and helps to find new solutions and see the bigger picture.



CeMM Publications

Includes all publications by CeMM staff members from the date of joining the institute.



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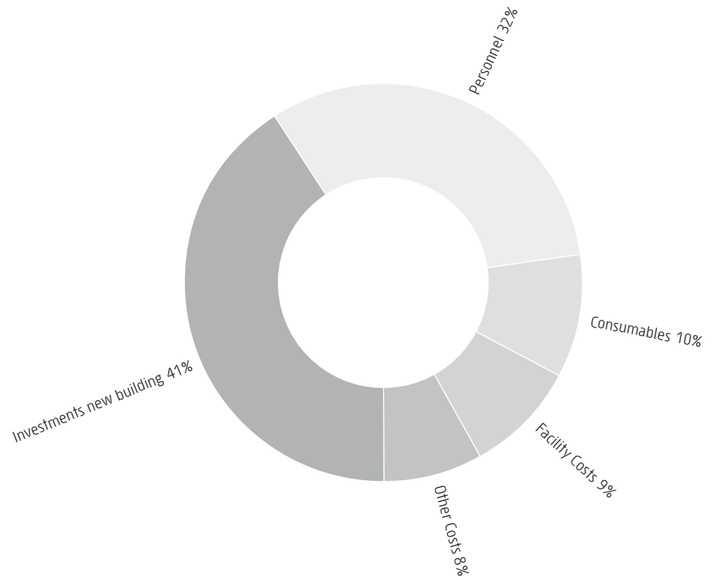

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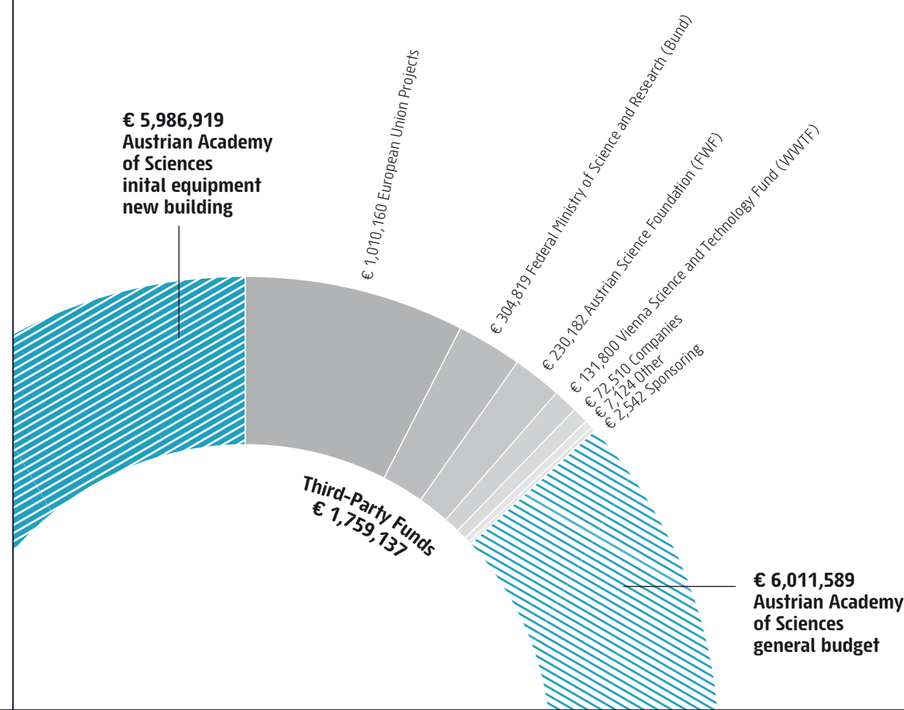

Sponsor the CeMM Brain Lounge

Critical to the much-needed development of innovative research approaches in molecular medicine are independence and space for creative ideas. Where do people obtain their best ideas? Can the process be facilitated? If an idea can save the planet or lead to a cancer cure, is it not worth doing all we can to let that idea crop up? The new building of CeMM will house a room with a breathtaking view over the center of Vienna. The concept for the so-called Brain Lounge has grown out of emotional and multi-disciplinary discussions with artists, scientists and designers who bring in their different insights, expertise and experiences. It aims to facilitate unusual thoughts in a relaxed, futuristic and thought-provoking setting. A carpet designed by Peter Kogler will lay the ground-work for the artistic design and tailor-made furniture, and lights are carefully selected for the desired inspiring atmosphere. As the project can only be done with sponsors and donors, CeMM needs to raise at least 50,000 Euro – best twice as much would be even better. Any donation is welcome!

For your donation you will be men-tioned on the CeMM web site and on a plaque in the room. And you can reserve the room for your own thinking sessions. Generations of thinkers will be thankful. If the donation is large enough, the room can bear your name.

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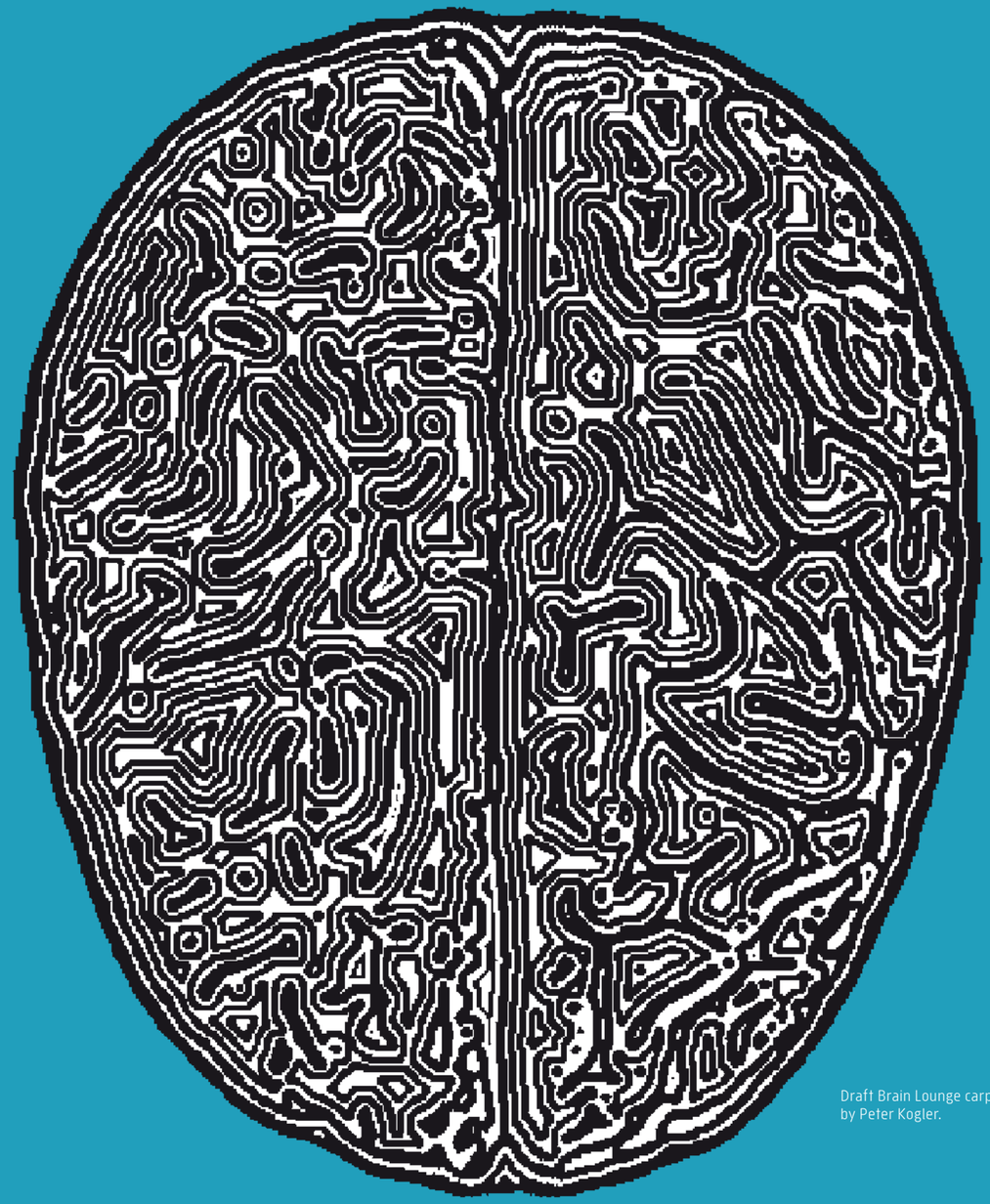
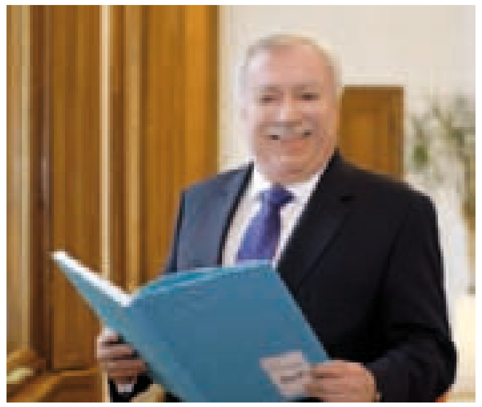


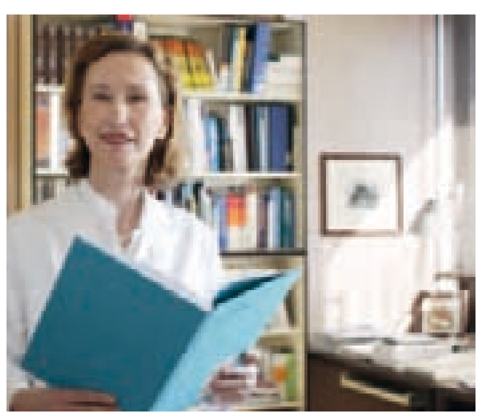
Draft Brain Lounge carpet by Peter Kogler.



















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CeMM thanks all friends and colleagues for their past and future support.

Acknowledgements
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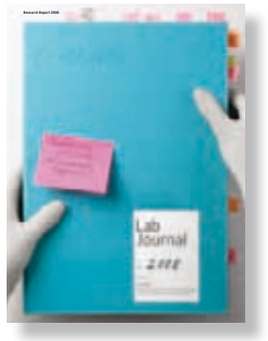

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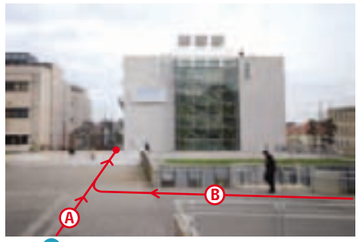

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