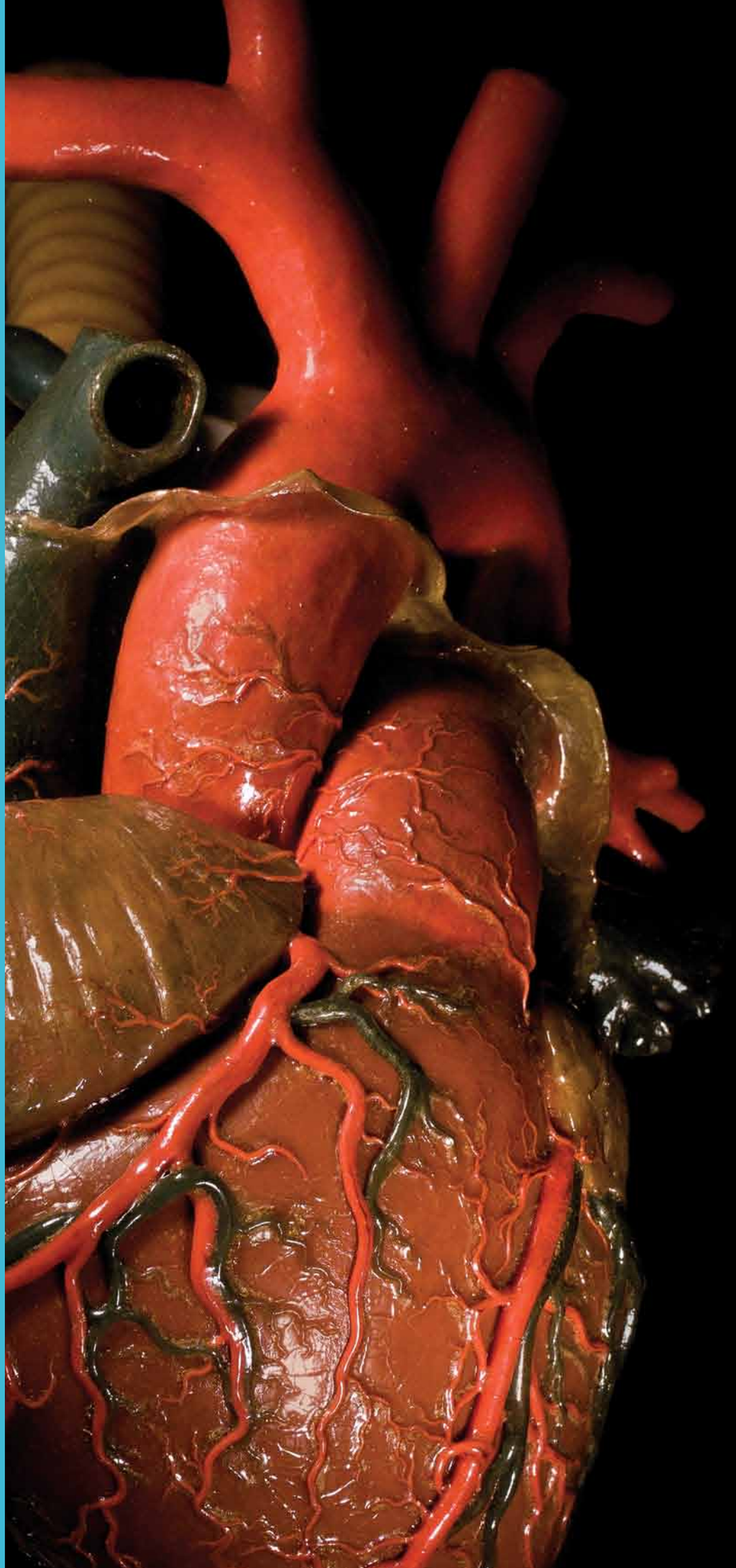

Ce–M–M– Research Report 2011

Research Report 2011

Ce–M–M–

Research Center for Molecular Medicine of the Austrian Academy of Sciences

CeMM Research Report 2011

Introduction by Giulio Superti-Furga

Year zero. That is what the President of the Section for Mathematics and the Natural Sciences Georg Stingl, one of the fathers of CeMM, agreed to consider 2011. Because on March 16th, the CeMM building was finally officially inaugurated by the Federal Minister of Science and Research Beatrix Karl, the city counsellor Andreas Mailath-Pokorny and the President of the Austrian Academy of Sciences Helmut Denk. There was a memorable ceremony involving a choir of CeMM students, a surprise aria by charlatan and molecular medical rival Dulcamara (from Donizetti's Elisir d'Amore, bass sang by Lars Woldt) and the band CeMMsons. On that day, our biggest dream came true. And on behalf of the entire CeMM tribe, I would like to thank everybody who has been involved.

But 2011 is also memorable for many other reasons, making it a true *annus mirabilis*. Out of all the papers that we published, one sticks out particularly: the discovery that an element of the innate immune system, complement factor H, binds an oxidation epitope known as malondialdehyde, and prevents inflammation in the retina. Lack of this protective function correlates with age-related macular degeneration, which is the leading cause of blindness in the Western world. This is a truly spectacular result from the laboratory of Christoph Binder and his collaborators at CeMM and at the Medical University of Vienna, as well as in Germany, the USA and the UK. The work was published as an article in *Nature*, probably the most coveted and cherished scientific publication spot in existence. What makes this special are many corollary facts: 1) it is the first *Nature* article on work mainly performed at CeMM, 2) it is the first *Nature* article since the Medical University of Vienna was spun off from Vienna University seven years ago, 3) Christoph was on the first round of CeMM Principal Investigator hires and is younger than 40, 4) the first author, David Weismann is a first-round CeMM PhD student, 5) the study has obvious implications in medical diagnostics and possibly therapy. These facts beautifully illustrate the essence of CeMM. And the discovery is based on an innovative technology practiced at CeMM (chemical proteomics), the medical and immunological expertise of one of its young leaders, who has a dual affiliation with the Medical University, and is validated by an extensive international collaborative network. In a generous recognition of this achievement, the new Minister of Science and Research, Karlheinz Töchterle, came to participate in our small internal celebration. So many reasons for a scientific director to be proud!

Many other important papers also helped to embellish this awesome year. My laboratory published important results in *Cell* that open the possibility of new targeting stratagems for Chronic Myelogenous Leukemia. We also identified a new class of innate immunity receptors (IFITs) and published it in *Nature Immunology*, likely to be in the long run one of the most important discoveries of CeMM. Robert Kralovics' laboratory also published a number of important papers, one of which described the frequency of genetic lesions in the tumour suppressor gene p53 in leukemia, which was published in the prestigious *New England Journal of Medicine*. Sebastian Nijman's group used its cutting edge technology to identify a mechanism by which cancer cells become resistant to an important anti-cancer drug in clinical use. All of these papers and others illustrate the themes that are increasingly dominating CeMM's research: personalized medicine, clarification of drug mechanisms of action and resistance, and elucidation of pathological mechanisms at the molecular level, including new diagnostic rationales and anti-infective processes.

But how are we doing overall and how does our efforts compare to work done in other places? A Scientific Advisory Board (SAB) that includes some of the most accomplished and highly active cancer scientists and immunologists in the world came to assess our science. They concluded that the progress we have made in the interval since the last SAB meeting 18 months before was truly impressive, which is significant praise given their standing and their obligation to give balanced feedback to the Board of the Academy. As it is our first year of official life we decided to print the general part of the SAB report, which you will find on page 105.

Yet 2011 was an extraordinary year also in terms of other forms of recognition. I was elected "Austrian of the Year" by an expert jury after readers of the daily newspaper "Die Presse" voted for me from a short-list of three (thank you all!). The televised awards ceremony on National Day was somewhat reminiscent of the Hollywood Oscars, and full of suspense also for Eva Schweng, who manages CeMM's public relations, and for Anita Ender, my assistant and CeMM's administrative genius-in-a-bottle, both of whom supported me through the whole thing. I also thank the jury, all voters, Die Presse for the prize, as well as Henrietta Egerth and Klaus Pseiner, CEOs of the FFG funding agency for applied research, who acted as sponsors. In this unforgettable year I also won the "Prize of the City of Vienna for Natural Sciences", an award previously received by giants such as Lisa Meitner, Erwin Schrödinger and Konrad Lorenz.

Of course these are recognitions for my entire team and for the whole of CeMM, who, with their merciless sense of humour, made sure that I stood nailed to the ground throughout the extravaganzas (who would know of these prizes outside of Austria?).

We also started, thanks mainly to the effort of CeMM Principal Investigator and faculty doyenne Denise Barlow, a regular series of CeMM-inars (note the pun) with a constant stream of international speakers who all congratulated us on the new building and the particular atmosphere at CeMM. We thank them all for coming and sharing their ideas with us. I also thank the CeMM postdocs and PhD students who have contributed to making the series a success, with both their passion and their many interesting questions. We also had four special lectures in 2011. In May, George Q. Daley of Harvard Medical School held the fifth CeMM Karl Landsteiner Lecture on stem cells in the Festive Hall of the Austrian Academy of Sciences, which was a huge success. Also in May, Greg C. Simon, Senior Vice President for Patient Engagement at Pfizer gave a Special Lecture, a breath-taking, eye-opening view on patient engagement and drug development. CeMM also had the privilege of hosting the 7th Special Lecture In Memoriam Laura Stingl, held by Harald zur Hausen, Winner of the 2008 Nobel Prize for Physiology or Medicine, for his pioneering work on cancer prevention by vaccination that triggered a real revolution in medical practice. The CeMM 8th floor lecture hall was filled to the rim with a fascinated audience, and the event was unforgettable. Finally, in October, we had the pleasure of hosting Bruce N. Ames, another pioneer of biomedical research. He not only spoke about drug safety, but also, passionately, on the role of human nutrition in health and disease. His talk left a strong mark on CeMM eating habits and dispelled several myths on food. A heart-felt thanks to all the speakers!

In addition, four technologies and tools that are likely to affect our research in a dramatic way were established in 2011. Principal Investigators Robert Kralovics, Kaan Boztug and Christoph Bock introduced next generation sequencing protocols and pipelines at CeMM. In collaboration with the Medical University of Vienna, we have established a common facility with two deep-sequencing machines that are in constant use. On the proteomics side, we established quantitation with chemical labels, allowing us, together with phosphoproteomics, to characterize samples in a much more precise and comprehensive way. In 2011 we also established a private-public partnership with the biotech company Haplogen, co-founded by scientists at CeMM and at the Whitehead Institute for Biomedical Research,

to generate a collection of human haploid cells with defined single gene defects. These cells have only one set of chromosomes, and therefore can reveal the physiological consequences of single gene inactivation. This now enables the testing of the function of human genes in the petri dish, something that was not feasible before. The collection already includes more than a thousand cell clones. Lastly, we have established the CLOUD collection (CeMM Library Of Unique Drugs) of 239 systemic bioavailable and FDA-approved small molecules representing 177 drug classes and 160 targets. This first compact and non-redundant library will make it possible to perform screens for activity on many of our cellular systems.

In line with CeMM's vocation to entertain an active and healthy dialogue with other disciplines and with society at large, we have started art & science projects. In March, a first gathering of artists and scientists at CeMM resulted in a "Wien Live" issue where seven pairs of artist-scientists confronted each other. Several projects ensued, among which is an art, science and society club that is still in the making, along with new ideas for the "brain lounge" on the eighth floor.

Following this, it may then not surprise the reader to learn that we have chosen an art & science project of legendary, important and gargantuan dimension to act as the thematic thread through this year's research report: the wax anatomical model collection of the Josephinum. A must for Vienna's visitors, school classes and medical students, it represents an invaluable treasure for the history of medicine and the history of art. We are in love with the collection and CeMM's first year PhD students since some years have had the privilege of a guided tour by Dontscho Kerjaschki, the owner of the same pathology chair at the Medical University as Carl von Rokitanzky, founder of the pathological anatomy discipline, one of the great medicine scholars of the 19th century, president of the Austrian Academy of Sciences and user of the Josephinum for didactical purposes. Putting the Josephinum collection at the center of CeMM's research report is not so far-fetched. Also CeMM in the 21st postgenomic century, like the anatomical wax collection of the late 18th century, aims to uncover the mechanisms taking place under the surface of the human skin, the pathobiology behind the wonders of the human body and the mystery of disease. What could be of greater symbolic value than the Josephinum to epitomize CeMM's value of scientific tradition, of art, and of its frienship with the Medical University of Vienna, who owns the collection? Vice-rector for clinical affairs Christiane Druml and myself have decided to use this CeMM report centered on the Josephinum as the kick-off for a campaign aimed at raising public awareness for this fantastic treasure, which is sadly in desperate need of renovation. The collection deserves to be rescued with 21st century conservation technologies and displayed in the most worthy of all possible manners, giving it safe access to even larger numbers of visitors and pupils. Therefore, the report contains an appeal for financial and political support for a rescue plan of the Josephinum, as inalienable priority of our cultural heritage.

To finish I would like to thank at least the most critical contributors to CeMM. The Board of the Austrian Academy of Sciences and the entire Academy need to be thanked for supporting CeMM particularly at times when it could have been popular to do otherwise, and the Ministry of Science and Research for its unabated and sustained help. The CeMM administration is thanked in its entirety. I would like to mention particularly the administrative director Gerhard Schadler, for smooth operations behind the scenes and essential strategic insights, but also Georg Casari for efficiently protecting our intellectual outputs and trying to turn it into money (it will take some time) and finally my assistant Anita Ender, who, as in the past, is the person who tirelessly and selflessly takes care of the CeMM baby with infinite love.

The CeMM research report is itself becoming a piece of art. A whole group of people take pride in making it not only a very readable publication, but something like a collectors' item. Eva Schweng coordinates the effort with passion and taste, Helen Pickersgill and Ioannis Legouras write up the text skilfully from the various contributions and make it highly readable, and the fabulous team at Lichtwitz Leinfellner provide the esthetical framework that culturally and ideologically fits the content just right. Only they can do it so well. This year we were helped by the extraordinary photographer Klaus Pichler.

This research report is especially dedicated to all CeMM scientists. It is a token of appreciation towards them and a promise to warrant those ideal working conditions that the entire circus around the science and medicine core needs in order to keep going. It is their engagement and hard work that makes it so worthwhile for faculty, for the Academy, for the Ministry, for the embedding Medical University and for me personally to come up with unconditional support and even fandom. The time is not far from when your supporting base will include patients who profited from your hard work.

Giulio Superti-Furga
Scientific Director

About Josephinum
The general idea

Interview with Christiane Druml,
Vice-Rector of the Medical University of Vienna
by Giulio Superti-Furga

Inspired by the priceless treasure of the Josephinum, this year's report is structured alongside pictures of a selection of the wax models to accentuate the main research topics at CeMM. We are grateful to Christiane Druml, Vice-Rector of the Medical University of Vienna, President of the Austrian Bioethics Commission and managing head of the Josephinum, who enabled us to connect a historical look into these crucial medical advances of the 18th century, which were led by great anatomists and innovators, together with the current insights of modern molecular medicine. Giulio Superti-Furga interviewed her in the library of the Josephinum.

Giulio Superti-Furga We are thrilled to be associated with this incredible collection, and very grateful that you are intent on doing everything that is in your power to support and preserve this institution for the public.

Christiane Druml We also feel very privileged that you chose the Josephinum for your annual report, which is a piece of design by itself. And there couldn't be any better idea at the moment than spotlighting this particular place. I do feel supported and I'm happy to have you as fellow campaigners. Of course there are restricted means, but we have to keep up with caring for the collections and also the building.

Giulio Superti-Furga What are the characteristics of the wax models? What was the original idea and what was their purpose?

Christiane Druml The fact that this collection was initiated by Joseph II in the 1780s makes it a very wise decision of an Emperor to order these pieces of art with a view to educate students of medicine. If you look at the wax models, it is clear that even to this day there could not be any better visualization of anatomical structures, even in digitalized form.

Giulio Superti-Furga I'm impressed with all the details the artists carved out. Also entries from recent visitors in the guest book of the Josephinum confirm their value as a training aid. For example, something like, "I wish I'd seen the waxes before my anatomy exam", you read quite often. Do we know what the models are made of?

Christiane Druml Yes, we know that the models are made of a mixture of turpentine and wax. But – as far as I know – we don't have the exact recipe. Obviously the secret of the formula was taken to the grave.

Giulio Superti-Furga They must have had a way of turning the wax into something time stable or sufficiently hard to last centuries. Quite a large proportion of the models are still in good shape in general. Of course they require restoration and also many colors may have altered but they are still quite distinct. So the creators of the Josephinum's wax models must really have mastered their art. Do we know of other collections that are similar?

Christiane Druml Well, the sister or brother collections are the wax models of La Specola in Florence and Palazzo Poggi in Bologna. But there I think some of the models were made by other artists. I am planning to visit the collections in Bologna and Florence, also to get ideas on how these institutions successfully manage the wax models. But beyond those two I don't know of any other collections comparable in size and masterfulness.

Giulio Superti-Furga So, you can imagine maybe organizing a conference about preservation, the science and art craft behind it. Has there been one?

Christiane Druml These aspects are especially important from an art history preservation view, but I don't have enough information on that. I think that our primary aim as a Medical University should be to be aware of our heritage and the reason why we have got it, and the use it had in the past and still has today. We should still encourage our physicians and teachers to make much more use of it as training aids. And, as we are not only in Austria, but also in the European Union, and as we have continuously good relations with Italy, also from a historical point of view especially with Joseph the II and Leopold, the Grand Prince of Tuscany being brothers, we should also emphasize both the historical and the modern aspects of this heritage.

Giulio Superti-Furga Absolutely! In this regard I am very curious about whether we have access to historical records that prove the usage of the models in teaching or in training of physicians already at the time the collection arrived. Do you think there is any documentation of that?

Christiane Druml I am not a historian, so I don't have detailed overview of the documentation. But education and training of physicians was the original reason why the Josephinum was built and the wax models were ordered. At that time two medical schools existed. The one at the Josephinum was for military purposes, which makes it funny in some way that it also housed the collection of obstetric wax models. The reason why the wax models were ordered was of course to teach anatomy and nothing could

Giulio Superti-Furga and Christiane Druml reading through the precious books of the Josephinum Library. Built in 1785, the library houses more than 6,000 books, the oldest of which was published in 1478. The majority of books were published in the 18th century.

have worked better. There were not only the wax models, but they also had watercolors depicting the same part of the body, organ or tissue. The illustrations were to be taken out of drawers, which are part of the display cases. With the combination of valuable showcases, wax models and the pictures, the Josephinum was providing an artistic synthesis, a "Gesamtkunstwerk" to the students of the military school!

Giulio Superti-Furga When the collection was ordered, was it ordered exactly for this building? Was each room and furniture conceived in a way so that the collection could be used for viewing and teaching?

Christiane Druml Yes, it was. I think there were originally almost 1,200 specimens. Now there is a bit less, but still up to a thousand. Respecting the entrusted treasure and the needs of modern museum education one could see many modern ways of connecting the collection with also digitalized visual and interactive tools.

Giulio Superti-Furga Do we have any documentation on whether there was any sort of bad reaction or negative stance towards the collection? As you remember the contemporary Body Worlds exhibition by Gunther von Hagen was met with some skepticism given we are not entirely sure where the preserved bodies came from. Of course this is not an issue for the Josephinum collection. But maybe the clergy or some moral people thought that seeing so much naked flesh or, even worse, seeing inside the body, would be unethical. Was it originally accessible to the general public or just to scholars?

Christiane Druml I don't know specific details but the church always had some problems with dissection courses. And at least for priests, such demonstrations were not accessible for some time. Aside from that, wax models like ours are just a complete ethical way of demonstrating some secrets of the bodies that are not accessible in any other way.

Giulio Superti-Furga Do we know more about the origin of the collection and do we know the artist?

Christiane Druml Yes, we do. There is also a historical book by Erna Lesky, who headed the Josephinum in the 1960's, about the medical school of Vienna in the 19th century, where we can find particular information about the building and the collection, including the costs of the wax models and transport details. They were built in Florence by the artists Paolo Mascagni and Clemente Susini and took a long and dangerous journey across the Alps and down the Danube to their final destination in the Josephinum. The artist's fees were about 30,000 gulden, which Joseph II paid from his private means.

Giulio Superti-Furga We are talking about an incredible investment and dedication of people who used art to illustrate science and medicine. Now, the two categories, the two disciplines have drifted apart a lot. It is not very common to ask an artist to help us understand or visualize medicine or science. Do you think there is still room for art to help us to understand nature?

Christiane Druml There definitely is. It would be a complete sign of failure ("Armutszeugnis") if we did not strive to incorporate art and the natural sciences. It could for instance help people to understand the construction of modern inventions like a bionic hand, combining the high tech approach of the artificial limb and the wax model of an arm, artistically showing the underlying anatomy.

We are talking about an incredible investment and dedication of people who used art to illustrate science and medicine.

Giulio Superti-Furga So maybe the Josephinum and certainly the wax collection can be part of an itinerarium, a sort of a parcours, an illustrative way to go from total ignorance about the making of the body into a more modern medical anatomical view, even down to the molecular level, down to individual types of genomic information. Do you think that the young public will find this historical step through the Josephinum a potentially attractive one?

Christiane Druml Why not? Of course it depends on the recipients, some have more background experience with museums, some not. Of course we have to make things interesting, and we have to find new concepts for how to incorporate medical themes and art in the education of young people. Also in my function as chair of the Austrian Bioethics commission I try to generate a more intellectual approach to things. I think we have to get away from our allotment gardens to a more integrative type of thinking and culture.

Giulio Superti-Furga I strongly believe that the youth will be interested in these multi-layered types of approaches. Is there money coming from the Cultural Heritage Protection Institute, or directly from the Ministry for Education or the Ministry of Science and Research to support the Josephinum?

The Treasure of the Josephinum

Portrait of Joseph II, Holy Roman Emperor from 1765 to 1790, remembered as an 'enlightened ruler'. During Joseph's rule, elementary education was made compulsory for boys and girls. The collection of the wax models was initiated by Joseph in the 1780's.

The museum of medical history, the so called "Josephinum", located in the heart of Vienna's 9th district houses a precious and unique collection: More than 1,000 wax models of the human body and its organs from the 18th century. There is enough to satisfy anatomists as well as art lovers. The building, a sight by itself worth visiting, was designed and built between 1783 and 1785 by the architect Isidore Canevale. Founder and patron of this pioneering institute was Joseph II, the eldest son of Habsburg Empress Maria Theresa, and **proponent of enlightened absolutism.** Modeled on the Académie Royale de Chirurgie in Paris, the Josephinum was meant as a novel education and training center for physicians and midwives for civil and military service. Joseph II's intention: To raise the standard of training of surgeons by establishing new methods.

Inspired by a visit to "La Specola", the **Reale Museo di Fisica e Storia Naturale in Florence,** Joseph II ordered a duplicate collection of the exhibited lifelike wax models. The models are made of a mixture of wax, resins, and coloring agents, and were designed to support the training of observers and raise their knowledge of human anatomy without the need for direct observation of corpses.

The extraordinarily gifted modeler, Clemente Susini (1754–1814), under the supervision of the noted anatomist Paolo Mascagni (1752–1815) assumed responsibility for the anatomical precision of the models. The personal imprint of Mascagni meant that the **Viennese wax models are a unique collection,** rather than a straight copy of the Italian specimens.

Joseph II not only had the idea to improve the study of medicine by creating accurate and artistic visual aids, he also paid for the models himself. The total expenditure was 30,000 gulden (equivalent to 640,000 euros today), which also covered the difficult transport cross the Alps. The famous wax models took a long and dangerous trip to Vienna, first via the Brenner Pass along the border between Italy and Austria using mules, than down from Linz to the capital by boat along the Danube. Their final destination at that time was to provide knowledge to the medical community. Ultimately, since becoming a public museum in the 1920's, they are providing knowledge and inspiration to everyone.

Josephinum, Währinger Straße 25, 1090 Vienna
www.josephinum.meduniwien.ac.at

Christiane Druml At the moment the Josephinum is only basically financed by the global budget of the Medical University. I am having at least one or two meetings every week with influential people to figure out how to get and what to do with specific money. I think there will be no other option but to establish a way of fundraising.

Giulio Superti-Furga I assume it requires a lot of money to ensure the type of preservation you like to do. I think it is very important to inform people that this incredible treasure requires a concerted effort from society not only to preserve it, but to make it really accessible and to bring it to the stage it deserves.

Christiane Druml There are two main things: First, I truly believe that it is part of our fundamental mandate as a Medical University to also maintain a collection of the medical history. I also think that it is important to have a professorship for medical history, medical theory, and medical ethics to give a foundation for the students. And we need to not only preserve this heritage, but also to make it accessible to the public. So, those are a few steps that have to be fulfilled, and each of them costs money. We need a concept. We need a concept that has to be widely published, and we have somehow to find the right persons who want to help us finance it in a transparent and sustainable way into the future.

Giulio Superti-Furga We wish you all possible success for this very important task. The Medical University as well as CeMM is trying to come to an understanding of diseases below every type of skin and surface to the inner core. This is something the Josephinum collection beautifully illustrates! The visit to the Josephinum is not only a yearly highlight in CeMM's PhD-program; we will also be happy if we can add to the re-discovery of the Josephinum to the wider community, starting with this annual report. Thank you for the interview!

A whole-body wax model, one of the most famous exhibits of the Museum. All exhibits are protected by glass cases and in many instances depict bodies and body members in dramatic postures.

Donate to the Josephinum

A more than two-century old tradition, a unique treasure to the history of medicine, an indispensable token of science and art working in harmony. The reasons to protect the Josephinum are multifaceted, and help is as pertinent as ever. All contributions are welcome. Be part of saving a rare pice of world's history:

Erste Bank
Bank number: 20111
Account number: 40410070714
Reason for Transfer/Verwendungszweck:
SO 102 500 12

For more detailed information, including the various kinds of sponsorship, please contact:
Angelika Wallner,
angelika.wallner@meduniwien.ac.at.

CeMM Research Section

From cancer to infectious diseases, and from atherosclerosis to childhood diseases, the multifaceted research at CeMM strives to be at the forefront of biomedical research. The next chapters delve into the research at CeMM with the exhibits of the Josephinum serving as an inspiration for young researchers and reminding us of our commitment to better understand human biology and contribute to the medicine of the future.

Cancer

Fig. A

Wax model of a human head and neck, with many of the underlying structures visible. Parts of the brain, the optical and oral cavity, as well as numerous muscles and blood vessels are visible. Especially impressive is the reconstruction of the intricate network of lymphatic vessels, a central player in the spread of metastatic cancer cells.

Finding What Lies Beneath Cancer

The late 18th century anatomical wax models displayed in the Josephinum at the Medical University of Vienna illustrate man's profound curiosity to explore inside a human being. By peering under the skin, the intricate details of organs and tissues displayed in the models helped physicians begin to understand the inner workings of the human body – how it is engineered and how it functions. Scientists at CeMM have a similar curiosity about human biology but focused more closely on the cells that form the organs and tissues. They peer inside these cells to see how genes and molecules such as proteins and lipids work to keep the cells working properly, which helps them understand what goes wrong in diseases such as cancer.

Our bodies are composed of trillions of cells that are programmed by DNA to keep us healthy and allow us to perform all sorts of complicated functions such as thinking, talking, running, reading and writing. However, occasionally something goes wrong with one of these cells and it stops doing what it is supposed to. Instead, it begins to divide, producing more and more copies of itself, damaging our healthy cells and organs, making us ill and sometimes causing death. This process is called cancer. It is one of the leading causes of death in the Western world, and one of the top research priorities for scientists at CeMM.

Cancer the disease takes its name from the sign of the Zodiac, Cancer the crab. It was named by ancient Greek physicians who thought that the solid tumors seen inside the human body resembled a crab, with a large central body and 'legs' spreading into surrounding tissues. Cancer was first documented more than 4,000 years ago, however it was still relatively rare up until the nineteenth century when life expectancy was low, as it often takes decades to develop. Even so, the Viennese physicians of the 18th century, who studied the wax works at the Josephinum, will certainly have been faced with the crab-like appearance of cancer inside some of the bodies they worked on.

Detailed Blood Work

Cancer can begin with a single cell from many different organs and tissues, including breast, lung and blood. Blood is pumped through our bodies via an extensive network of arteries and veins depicted beautifully in several of the wax models, providing a lifeline for all our organs and tissues. In the 17th century, scientists built the first microscopes to enable them to observe the blood cells that flow through this elaborate cardiovascular system carrying oxygen and nutrients as well as protecting us against disease. Now, zooming in even deeper, scientists at CeMM are working on understanding the genes and molecules involved in the development and function of these blood cells, and how blood cancers such as leukemia can start.

Dissecting DNA

Blood cells in humans and other vertebrates are made in the bone marrow by a process known as hematopoiesis. They are under rapid and constant turnover. In human adults, one thousand million red blood cells and one hundred million white blood cells are replaced every hour. When this process malfunctions it can cause severe blood diseases such as myeloproliferative disorders and leukemia, both of which are studied at CeMM. These diseases are often caused by specific mistakes or mutations in the blood cell's DNA. At CeMM, scientists are using new technology to analyse DNA and RNA sequences in patients, to discover the underlying genetic or epigenetic causes with a view to finding new ways to treat disease. In parallel, they are also studying how blood cells try to repair their DNA mutations, and how that can go wrong and cause cancer.

The Anatomy of Proteins

Proteins are the manual laborers of our cells, performing most of the physical work required for the cell to function properly. DNA mutations in protein-coding genes can lead to the production of faulty proteins that stop the cells from behaving normally and cause disease. These abnormal proteins also provide a unique target for small molecule inhibitors or drugs that can be used to treat patients with the disease. While these targeted drugs have been very successful in the fight against cancer, they often only provide a short-term solution as patients ultimately become resistant to them. To try to combat this, work at CeMM is concentrating on understanding why cancer drugs don't always work, and how drug resistance develops, particularly in breast and lung cancer. In addition, there is a focus on the structure and organization of certain leukemia-causing proteins, and how this makes them susceptible to inhibition by individual drugs. Thus, similar to the wax models exposing the anatomical features inside the body, CeMM scientists are exposing hidden details of the molecules inside cells to find new ways to treat disease.

Don't Judge a Book by its Cover

The well-known phrase "Don't judge a book by its cover" is a warning not to evaluate something based on its outward appearance alone. You need to look inside the book to find out what the story is about. Just as going beyond the external appearance of a human being and studying the structure of internal organs and tissues has helped clinicians to understand how the body works, so deciphering the physical sequence of DNA and looking at the structure of proteins can help scientists understand how cells work, and how they malfunction in genetic diseases such as cancer, which is an active area of research at CeMM.

At CeMM, work has focused on identifying the genetic causes of blood diseases such as myeloproliferative neoplasms (MPN) and leukemia, which are characterized by the excessive production of certain types of mature blood cells. They are often caused by mutations in the DNA of so-called stem cells, which are the precursors of mature cells. These mutations change the sequence of a gene, which leads to the production of an abnormal protein that can ultimately influence the state of the cell and potentially transform it into a cancer cell. To identify the genetic mutations involved in MPN and leukemia, Robert Kralovics's lab has been analyzing the DNA sequence of individual patients and comparing it with how the disease progresses.

Fig. 1 The picture intends to show a 3D rendering of blood cells as they are represented in a smear of peripheral blood from a patient with chronic myeloid leukemia (CML), a disease that is caused by the oncogenic fusion kinase Bcr-Abl. This disease is characterized by large numbers of immature cells in the blood, represented by cells stained in blue. The center of the picture zooms in to one leukemia cell. Within the borders of that cell, the ribbon representation of the active conformation of the SH2-Abl kinase module of Bcr-Abl is shown in purple. The corresponding CeMM paper (Grebien et al, 2011), describes a novel, allosteric mechanism of Bcr-Abl regulation via the SH2-kinase interface as shown in the structure. The authors use an engineered protein (a so-called monobody) that binds to this interface to inhibit Bcr-Abl activity, leading to apoptosis of CML cells. The structure of the monobody is shown in lucent yellow and its impact on the activity of the Bcr-Abl kinase is suggested by concentric waves covering the Abl kinase domain, originating from the monobody. The monobody's potential to inhibit Bcr-Abl activity and thereby leading to apoptosis of CML cells is represented by the monobody pushing the "power-off" button on the leukemic cell.

Taking a Closer Look at DNA Sequences for Cancer Mutations

Using high-resolution single nucleotide polymorphism (SNP) microarray analysis in over 600 patients with a variety of blood diseases, including myeloproliferative disease (MPD) chronic myeloid leukemia (CML) and de novo acute myeloid leukemia (AML), the Kralovics lab recently established a SNP and copy number database linked with the clinical data of patients, which they analyzed for specific mutations linked to disease progression. They identified several important new mutations, including a recurrent deletion of a gene on chromosome 7, which encodes for a transcription factor called Ikaros, amplification of the MDM4 gene on chromosome 1 and mutations in the TP53 gene. All of these mutations highly correlated with the transformation of chronic phase MPD to acute leukemia (Jäger et al., 2010, Harutyunyan et al., 2011), which is a far more serious disease. Being able to identify patients before that happens, using these new mutations as markers, means they can be more effectively monitored and treated. The mutations also provide new clues about the molecular mechanisms underlying these diseases, which can potentially lead to the development of new treatments.

Non-protein-coding RNAs, known as 'Macro ncRNAs', have the ability to silence closely linked genes on the same chromosome.

The Role of Long Non-Coding RNA Molecules in Cancer

The Barlow lab at CeMM has been looking in cells for the presence of RNA molecules called macro non-coding RNAs (ncRNAs), which regulate the expression of genes and have also been linked to the development of cancer (Barlow, 2011; Santoro and Barlow, 2011). The human DNA sequence is distributed over 23 chromosomes that are all present as two copies (one inherited from our father and one from our mother). Each chromosome wraps the DNA sequence around so-called chromatin proteins, such as histones. One layer of information contributing to the regulation of gene expression, and thereby which proteins are produced in a cell, is thought to arise from the relative position of chromosomes inside the nucleus and from the dense or loose organization of chromatin proteins. A second layer comes from biochemical modifications of the DNA sequence itself and of the histone proteins. These biochemical modifications are temporary and reversible and by adding extra information to the primary genetic code, are known as 'epi'genetic modifications. The Barlow lab has been concentrating on a third layer of information, which is the ability of gene neighbors that encode unusually long non-protein-coding RNAs, known as 'Macro ncRNAs', to silence closely linked genes on the same chromosome.

In collaboration with Johannes Haybaeck from the Institute of Pathology in Graz, Irena Vlatkovic and Alexandra Kornienko have been looking inside human cervical carcinoma cells for specific macro ncRNAs found in cancer cell lines but not in healthy tissues. Philipp Guenzl, Florian Pauler and Alexandra are now working on blood cells, and are sequencing RNA in different blood cell types (e.g. B cells, CD4 and CD8 T cells), to find out on a genome-wide level which macro-ncRNAs are present in each, and how they might function in blood cell development. As leukemia is caused by abnormal production of blood cells, the presence and dynamics of the identified macro-ncRNAs will also be analysed in patients, to see if they have disease-relevant gene regulatory functions.

Studying the Mechanisms for Repairing Damaged DNA

By building cancer models "from scratch", scientists at CeMM can determine the effects of single cancer genes on drug response.

When something breaks, we attempt to fix it, particularly if the damage may make the object dangerous such as a crack in a gas pipe. The same holds true for DNA mutations. All cells contain an in-built defense mechanism to repair damaged DNA and protect themselves against potentially lethal or transforming mutations. This DNA repair mechanism needs to be highly efficient considering our cells are constantly exposed to DNA damaging agents, such as sunlight and tobacco smoke, and it only takes one mutation to cause cancer. Other internal processes such as DNA replication can also generate unwanted mutations that need repairing. But, in addition to repairing adverse mutations, DNA repair is also used to restore programmed breaks to allow fordesirable changes specifically in the arrangement of certain genes in B and T lymphocytes, by a process known as somatic recombination. DNA repair of somatic breaks in these cells is essential for the maturation of the immune system, and our ability to combat infection and disease.

Joanna Loizou's lab at CeMM is interested in understanding how the DNA breaks formed during somatic recombination are resolved to generate functional B and T cells, or conversely, if these breaks are not properly resolved, how this can result in the development of lymphomas and leukemia. They are using mouse models of human diseases, as well as cells derived from patients with defects in DNA repair. High-throughput RNAi screens and proteomics approaches will also be used to identify new proteins and pathways involved in DNA repair, leading to insights into their molecular mechanisms of action.

Personalizing Treatment for Breast Cancer

One of the characteristics of cancer is that the DNA in cancer cells becomes more and more damaged and mixed up as the disease progresses. In addition, every patient and every tumor is genetically unique, and not all drugs work in every patient. Because of this, successfully treating cancer has turned out to be a major challenge. Sebastian Nijman's lab at CeMM has been working towards truly personalized anti-cancer therapy using a systematic approach to identify cancer vulnerabilities and drug resistance mechanisms in breast and lung cancer.

Despite population screening programs and significant treatment advances, breast cancer remains a devastating disease. This year more than 300,000 women will be diagnosed with breast cancer in the EU, making it the most frequently diagnosed malignancy, and over 50,000 will die of their disease. It is therefore not surprising that many pharmaceutical companies are trying to invent new therapeutics to treat breast cancer. One group of so-called "targeted drugs", known as PI3K/mTOR inhibitors, blocks a critical cell growth pathway, which is often overactive in a variety of tumors including breast cancer and pancreatic cancer.

However, these drugs don't work in all patients, and even for those patients who initially respond to the treatment, the effect is often short-lived as the cancer becomes resistant. The question is why.

In the Nijman lab, scientists have been investigating these and related questions by building cancer models "from scratch". This enables the determination of the effects of single cancer genes on drug response, and many thousands of so called "drug-gene interactions" are measured in high-throughput screens. In one such screen, postdoc Markus Muellner and colleagues have identified how breast cancer can become resistant to PI3K inhibitors. It turns out that activation of a protein known as c-MYC by the NOTCH signaling pathway renders cancer cells completely insensitive to these drugs (Muellner et al., 2011). This finding could be critical for making sure the right drugs are used to treat the right patients, potentially saving many lives as well as millions of euros. In collaboration with oncologists and scientists from the Vienna General Hospital (AKH) and the Medical University, the lab is investigating how this information can be transferred to the clinic, to match drugs to patients.

A New Mechanism for Treating Leukemia

Scientists in Giulio Superti-Furga's lab at CeMM have been working on understanding how individual mutations make cancer-causing proteins more or less vulnerable to certain drugs. They are studying chronic myeloid leukemia (CML), which was the first cancer shown to be caused by a genetic defect, back in 1960. This genetic mutation is actually a large rearrangement of two human chromosomes, which results in two genes, Bcr and Abl, being cut and pasted together. These fused genes produce an abnormal protein known as Bcr-Abl, which wreaks havoc in cells and causes leukemia.

While there are several drugs that can successfully target Bcr-Abl and treat patients with CML, they tend to only work in the short-term. Postdocs Florian Grebien and Oliver Hantschel discovered how the organization of the Bcr-Abl protein makes it particularly active in cancer cells, which is an important first step for finding new ways of inhibiting it. Abl is a tyrosine kinase and is divided into several different functional domains. Disruption of an intra-molecular interface between the SH2- and kinase-domains increased Bcr-Abl's sensitivity to clinical tyrosine kinase inhibitors, which are used to treat leukemia, and sensitized drug resistant Bcr-Abl mutants to their inhibition. In collaboration with the group of Shohei Koide at the University of Chicago, USA, they went on to develop a high affinity Abl SH2-binding protein (monobody), which was shown to disrupt the formation of the SH2-kinase domain interface (Fig. 1). Indeed, initial testing of the monobody in primary cells from CML patients, in collaboration with Peter Valent at the Medical University of Vienna, strongly supported this concept of targeting the SH2-kinase interaction for treating human CML (Grebien et al., 2011). Because this is a different approach for inhibiting the Bcr-Abl protein, it is likely that patients resistant to the classical drugs will benefit, and it may even turn out to bypass the problematic development of resistance.

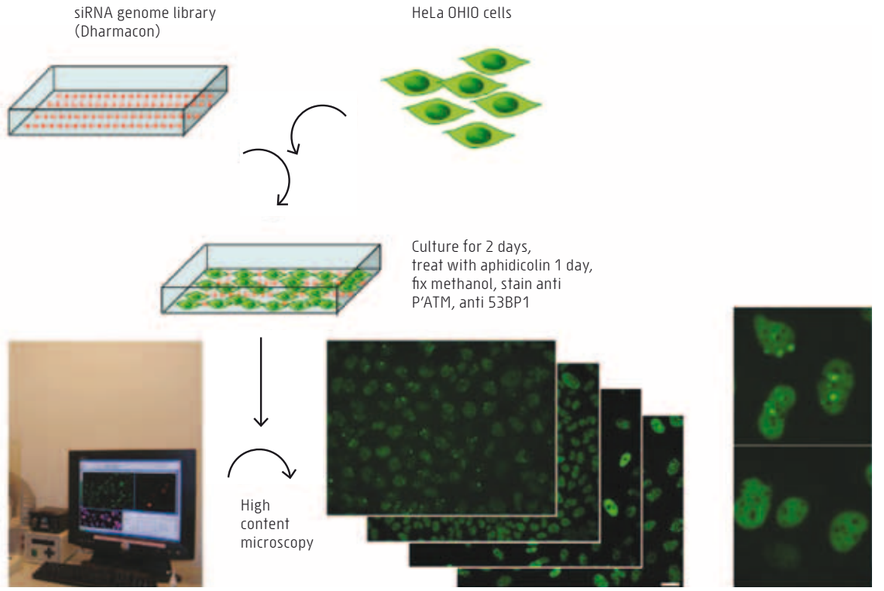

Fig. 2 Genome-wide si-RNA screen for regulators of the DNA damage response. HeLa cells were knocked-down for each gene of the human genome, treated with a replicative stress (aphidicolin), fixed and stained for markers of the DNA damage response (activated ATM and 53BP1). Analysis was by high-content microscopy.

Organs

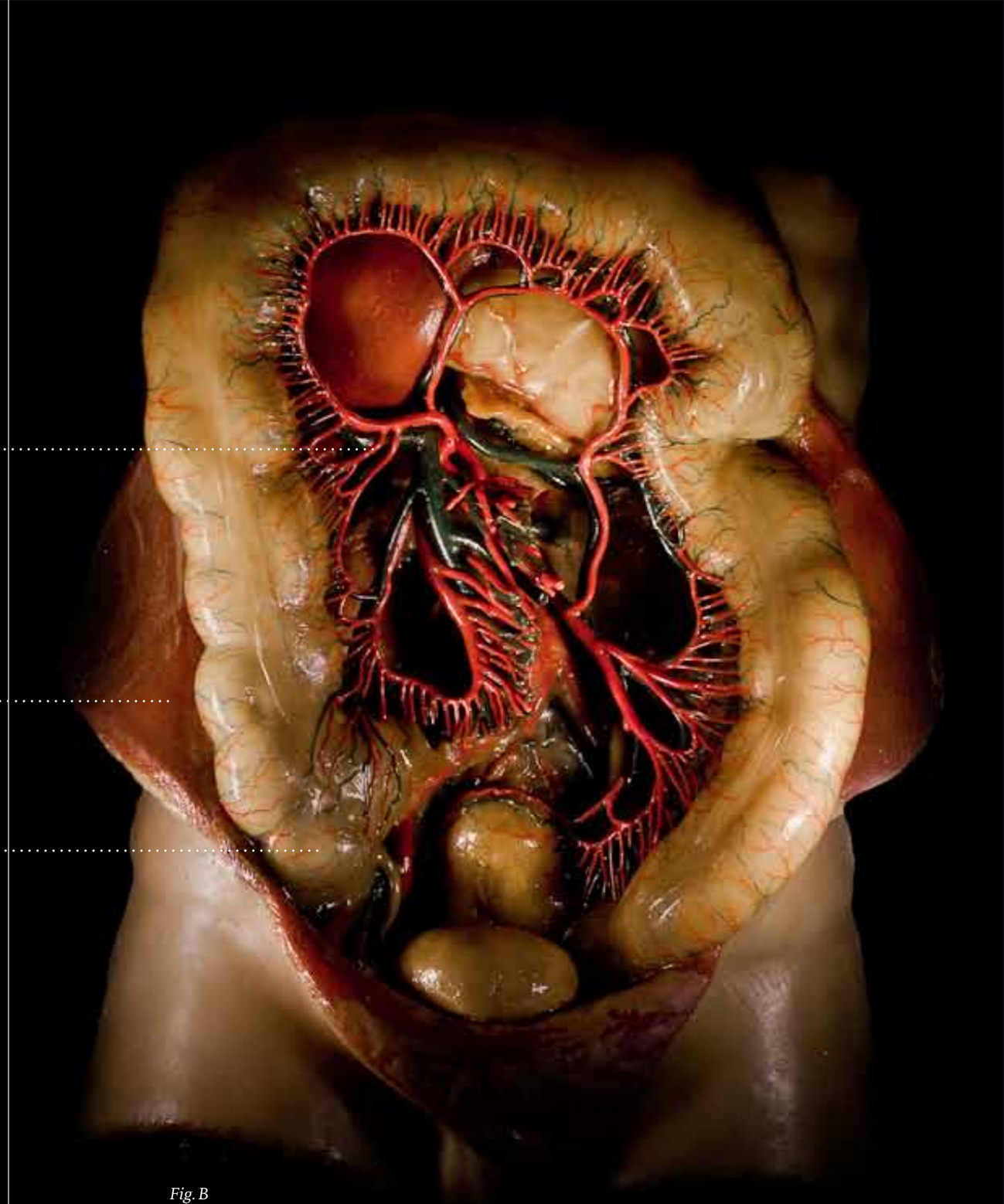

Fig. B

View of the abdomen with the large intestine and the intestinal arteries. Parts of the skin, as well as organs of the abdominal cavity can be seen. The arteries and the veins are colored differently (red vs. dark blue).

Individual Body Parts Make the Whole

The 52 different organs of the human body are an astonishing array of different shapes and sizes, revealed in exquisite detail by the wax models in the Josephinum. Together they form ten major organ systems, including the circulatory system, the cardiovascular system and the digestive system. Organs are essentially collections of different cells and tissues that serve a common function, such as the muscle and connective tissues of the human heart that pump blood around our bodies, and the acinar and endocrine cells of the pancreas that secrete digestive enzymes and insulin to enable us to digest our food. Sensory organs like the human eye and ear allow us to see and hear by incorporating cells and tissues with unique functions, such as the ability to respond to light or vibrations.

Keeping Up Appearances

The human organs displayed in the Josephinum are all healthy, but most adults have organs with some degree of visible damage. Our environment, along with unhealthy lifestyles, can have quite dramatic effects on the appearance of our internal organs. Smoking is by far the most dangerous human habit, and the lungs of a smoker are instantly recognisable. As opposed to a healthy pink, they become pale and grey, and are filled with tar deposits. However, even the lungs of non-smokers living in urban areas can show visible signs of damage. Another common culprit is alcohol, which causes the formation of nodules on the liver, and a high fat diet, which leads to hardening of the arteries. While the clinicians analyzed the physical appearance of the wax organs now displayed at the Josephinum, scientists at CeMM have been studying their molecular and cellular makeup, which is crucial for finding ways to treat many different diseases.

Getting Under the Skin

The largest organ in the human body is the skin, which can cover an area of up to 2m² and weigh around 4 kg. The seemingly superficial appearance of human skin masks critical and diverse functions, such as acting as a physical barrier between internal organs and the environment. Our skin protects us from infection by pathogens, harmful effects of the sun, and dehydration. It also maintains the shape of the human body, regulates heat, and contains millions of different sensory receptors that respond to heat, pain and touch. For something that acts as such a critical anatomical barrier, it is perhaps surprising that it is so soft and relatively easy to breach. Our skin cells regenerate rapidly, and there are robust mechanisms in place to quickly heal cuts and wounds in order to avoid infection.

There are thousands of different types of skin conditions, and while only relatively few are lethal, many cause discomfort or pain, and can be a source of embarrassment because they are difficult to conceal. In collaboration with the Department of Dermatology at the Medical University of Vienna, scientists at CeMM have been developing new techniques for identifying and monitoring proteins that are involved in skin diseases. A deeper understanding of the underlying mechanisms of skin disorders will ultimately lead to the development of improved treatments.

The human head is probably our most discerning feature, enabling us to easily distinguish between different people. It comprises sensory organs such as the brain, eyes, ears, nose and mouth. The human eye is made up of around 30 different structural components, including the pupil and retina. Together these components enable us to distinguish between a staggering 2 million different colors. At CeMM, scientists have been working on identifying the underlying molecular causes of two devastating diseases of the eye: Age-related macular degeneration and epiretinal membranes, both of which can cause blindness.

Changing Identity

In the abdomen, behind the stomach and just above the small intestine, lies the pancreas. It is a rather unique organ, being part of two different organ systems, the endocrine system and the digestive system. The pancreas is actually a large gland that makes and stores digestive enzymes and hormones such as insulin. It helps break down fats and starch, and regulates blood glucose levels. The pancreas has received a lot of attention in recent years because of a rapid rise in the incidence of type 2 diabetes, which is linked to excess weight. Both type 1 and type 2 diabetes are characterized by deficient insulin production. This leads to an increase in blood sugar that can damage many major organs, particularly the kidney, which turns from a deep healthy red to almost white. Insulin is made in the pancreas by so-called beta-cells, and scientists at CeMM have been working on mechanisms to regenerate these important cells using small molecules, which could lead to urgently needed new treatments for this increasingly common disease.

Studying the Molecular Causes of Eye Diseases

Detailed studies revealed how complement factor H protects cells from the inflammatory response towards malondialdehyde.

Age related macular degeneration (AMD) occurs due to the deterioration of tissue in the central part of the retina known as the macula, which provides particularly detailed vision. Although a major cause of irreversible blindness and vision impairment, particularly in adults over the age of 50, the underlying molecular cause was unclear. In the laboratory of Christoph Binder at CeMM, PhD student David Weismann has been working on the role of oxidative stress in disease. Along with Peter Zipfel in Germany, Jim Handa and Joseph Witztum in the USA, and other scientists at CeMM, the group had been studying the common lipid peroxidation product malondialdehyde, which is produced when membrane phospholipids become oxidized. In their search for malondialdehyde binding proteins, complement factor H was identified by mass spectrometry performed by the Bennett laboratory. Complement factor H is one of the most abundant proteins in blood. A specific mutation in the complement factor H gene is found in patients with AMD, and the corresponding protein was found to no longer bind malondialdehyde, which also accumulates in AMD lesions, indicating a critical role for the interaction in development of the disease. Indeed, detailed studies revealed how complement factor H protects cells from the inflammatory response towards malondialdehyde (Weismann et al., 2011). The identification of this molecular mechanism could lead to new approaches for the treatment of AMD and potentially other chronic inflammatory diseases such as atherosclerosis.

Another disease affecting the macula region at the center of the retina is known as epiretinal membrane. It is caused by the accumulation of cells from other areas of the eye to form a sheet of scar-like fibrous tissue on the macular region of the retina. Ultimately, this can lead to severely distorted vision. The most common risk factor for idiopathic epiretinal membrane is age. Indeed, prevalence estimates approach 20% by the age of 70. In collaboration with Andreas Pollreisz, Marion Funk and Ursula Schmidt-Erfurth from the Department of Ophthalmology at the Medical University of Vienna, Katja Parapatics and Melanie Planyavsky in Keiryn Bennett's group at CeMM have been performing quantitative proteomic analyses by mass spectrometry of aqueous and vitreous fluids from eyes with idiopathic epiretinal membranes. A total of 323 proteins were identified in the eye fluids, many of which were found to be involved in certain cellular processes, specifically in the activation of complement, proteolysis, and cell adhesion. The data were combined with multiplex bead assays, and overall the results revealed a similar array of proteins, including cytokines and growth factors, between these two eye compartments. Identification of the proteins that are involved in this disease offers new opportunities for disease management and could lead to important new treatments.

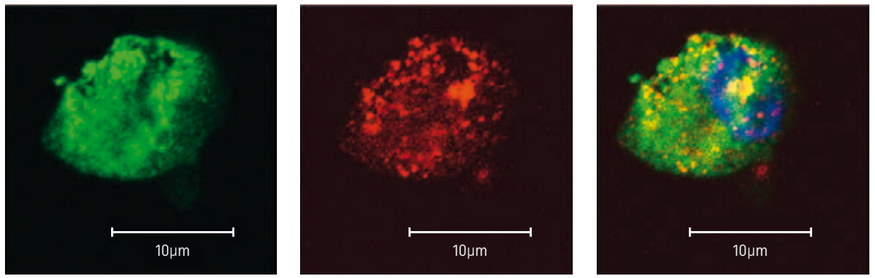

Fig. 3 MDA is present in the macula of AMD-patients. Histological sections of human maculas were stained with a non-specific control antibody (right) or the MDA-specific antibody MDA2 (left panel). Antibody binding is indicated by the blue color.

Identifying Proteins Underlying Skin Disease

Along with the development of new approaches, André Müller from the Bennett group has been using a similar method to comprehensively identify proteins present in skin suction blister fluid. To identify disease-related changes in protein composition within a specific area of skin, a quantitative method involving stable-isotype labelled chemical tags was set-up. In collaboration with Adelheid Elbe-Bürger, Christopher Schuster and Georg Stingl from the Department of Dermatology at the Medical University of Vienna, a pilot study was conducted whereby the proteins found in blister fluid from eight healthy volunteers were compared. Blisters were formed by prolonged application of suction to the forearm to physically separate the epidermis from the dermis. The compartment that forms is filled with interstitial fluid that can be aspirated with a fine syringe and processed for analysis by mass spectrometry. Over 740 proteins were identified in these experiments, many of which were specific for skin development or integral to tissue architecture. The robustness of the methods and the ability to meaningfully compare the skin-fluid profiles between human beings of different ages and gender illustrates the feasibility of comparing diseased and normal healthy skin for future clinical research.

Changing Cells in the Pancreas for Treatment of Diabetes

The human body is composed of more than 200 different cell types, almost all of which contain the identical DNA sequence. The different cell types form in the developing embryo by following specific environmental cues that selectively regulate the expression of genes in individual cells. These cells types are then stably maintained in the adult via epigenetic mechanisms. It was previously thought that once a cell developed an identity, it was fixed. However, over the last few years it has become increasingly clear that cell types are surprisingly plastic and can be interconverted upon the forced expression of a set of genes – so called master regulatory transcription factors. This process is known as transdifferentiation and it has generated much excitement in the field. Scientists at CeMM have been looking at how this works in the pancreas with a view to treating human disease.

Normally, beta cells in the islets of Langerhans in the pancreas produce insulin in response to elevated glucose levels in the bloodstream. In type 1 diabetes, insulin-producing beta cells are destroyed, and type 2 diabetes is often caused by insufficient insulin production and reduced beta cell function. Therefore, regenerating beta cell mass from other cell types has great potential for diabetes therapy. It has been shown that functional insulin-producing beta cells can be made from glucagon-producing alpha cells by the overexpression of a single transcription factor, Pax4. However, such transcription factor overexpression can only be achieved by genetic manipulation in mouse models or gene therapy approaches and is thus not suitable for the treatment of diabetes in humans. Stefan Kubicek's group at CeMM is working towards converting alpha cells into beta cells using small molecules, which can be more easily translated into the clinic. They have so far identified two compounds with promising properties and are now working together with researchers from Nice, Copenhagen, Goettingen and the Broad Institute of Harvard and MIT in the USA to further characterize and improve these compounds.

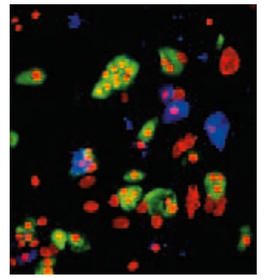

Fig. 4 Pancreatic islet
Dissociated pancreatic islet cells were visualized by immunofluorescence staining. In this image, histone methylation, which is found in all cells, is colored in red, alpha-cell specific hormone glucagon in blue and insulin in beta cells is detected in the green channel.

Infectious Disease

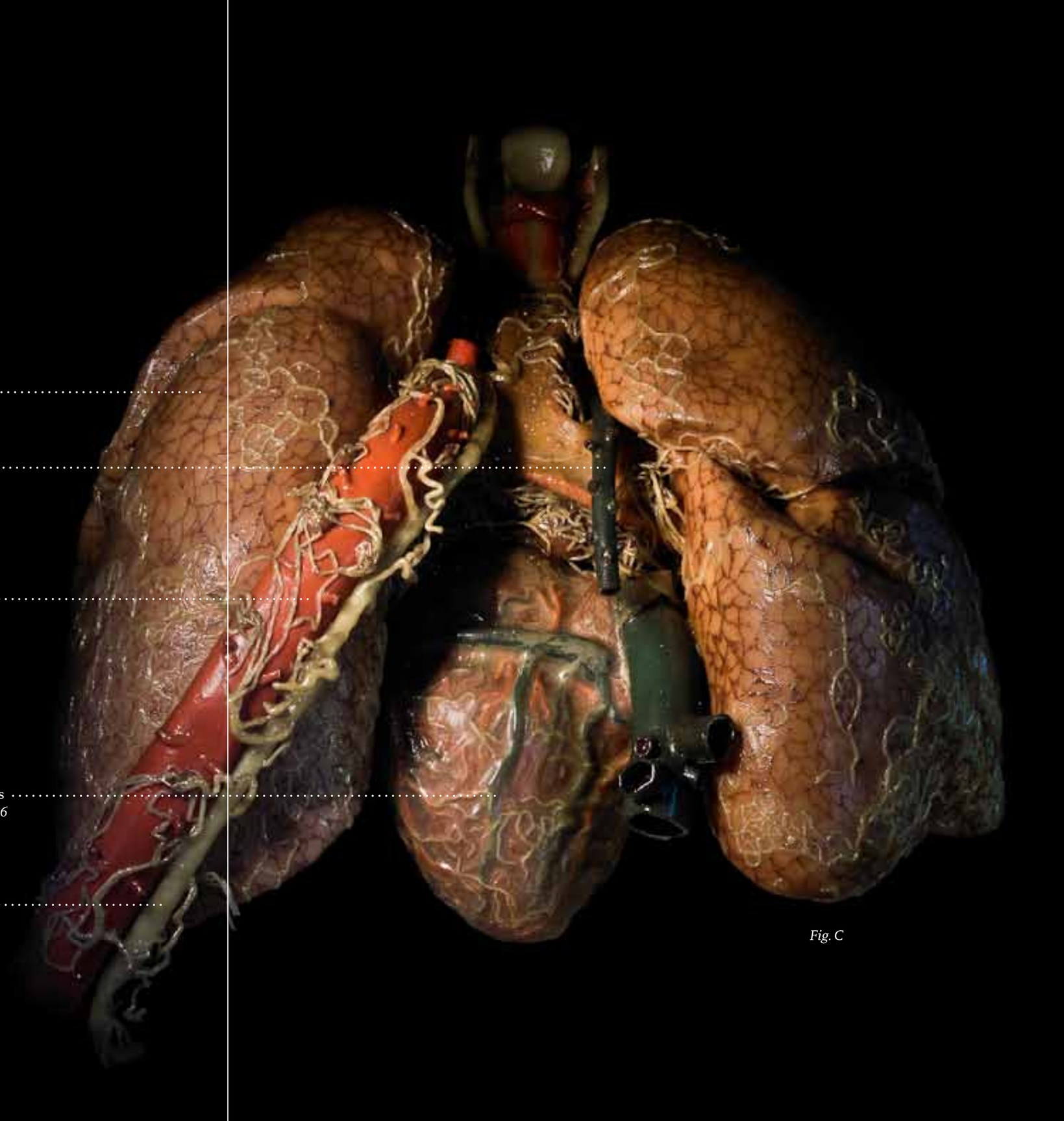

Fig. C

The lungs and the heart are central to human biology, as a multitude of diseases is manifested in these organs. In this view, the large aorta is also visible, with its many associated lymphatic vessels.

Investigating Self Defense

The famous wax models displayed in the Josephinum at the Medical University of Vienna beautifully illustrate our inherent fascination of the science underlying human life. They were originally used to educate physicians and midwives so that they could better promote, maintain and restore health. Scientists at CeMM are similarly fascinated by the life sciences, and also focus on tackling significant human health challenges, albeit different ones than those faced by physicians in the 18th century. Smallpox, for example, was one of the most deadly diseases in the 18th century, but was fully eradicated over 30 years ago after extensive vaccination campaigns run by the World Health Organization. However, infectious diseases in general, caused by a huge array of microorganisms including viruses and bacteria, remain a major cause of human mortality here in the 21st century.

There are thought to be tens, maybe hundreds of thousands of different types of bacteria and viruses on earth, and we only know the identity of a relative handful. Fortunately the majority don't infect humans, but there are many that do, and some of these we are exposed to every day. Microorganisms are smeared on the handles and surfaces that we touch when opening doors at work or when travelling by bus, and float around in the air that we breathe, carried by miniscule liquid droplets produced by people when they cough and sneeze. They are in the food that we eat, on our computer keyboards, and also already in and on our bodies. Some are too small to see without a microscope, but some of them can make us very ill or even kill us. Fortunately, the human immune system is exquisitely designed to protect us from pathogens, and scientists at CeMM are studying the immune response to a number of infectious diseases, to help find better ways to treat them.

Pathogens can enter the body by many different routes and cause infection and damage at any site. Fortunately, the extensive arrangement of the lymphatic vessels of our circulatory system, as illustrated by one of the wax models at the Josephinum, provide the cells of the immune system unlimited access to all parts of the body, where they patrol our tissues for signs of infection.

Self Defense

Once inside the human body, viruses and also many bacteria hijack our cells in order to propagate. At CeMM, scientists are trying to identify these cellular entry-points, which are often specialized protein receptors on the cell's outer membrane, with a view to finding ways to block them using drugs. They are also interested in how our innate immune system can detect these alien invaders, as viruses and bacteria are made, like our own cells, out of similar proteins, nucleic acids, lipids and sugars. Our immune detection system needs to be sophisticated, as pathogens are also masters of disguise, constantly changing their appearance to make detection more difficult. Once a pathogen has been detected by a cell, it sets off a chain reaction involving the production, modification and interaction of many different proteins and molecules, known as signaling pathways, which lead to a full blown immune response. At CeMM, they are also investigating the identities and functions of these molecules, which work together as part of our body's immune response to fight battles against infectious diseases.

The Specialized Human Body

The human body is an extraordinary feat of engineering, as can be seen from the array of wax models housed at the Josephinum. The models display intricate details of our internal tissues and organs, and show how they are interconnected via elaborate networks of blood and lymphatic vessels. Humans have evolved to this level of complexity due in part to our ability to survive a never-ending war against viruses and bacteria, who themselves are constantly evolving new ways to harm us. Cue the immune system, itself an elaborate network of specialized molecules, cells and systems that together form an armoury of weapons to protect us from potentially lethal infectious diseases.

Identifying the Molecules that Detect Viruses

Each member of the IFIT complex has an important role in blocking viral infection, constituting a novel anti-viral defense mechanism.

At CeMM, Giulio Superti-Furga's group, in partnership with the Bennett and Colinge laboratories, has been focusing on systematically identifying the body's anti-viral molecular repertoire. One of their main routes of discovery is using a trick called affinity proteomics. As postdoctoral fellow Tilmann Bürckstümmer has shown, one can take components of viruses, typically nucleic acids or proteins, and use them as baits to fish out the proteins or other molecules in human cells that can detect and bind to them. These binding components are likely to be involved in the initial detection of the intruding virus, and this approach has already led to the identification of a protein called AIM2 (see 2009 research report).

Continuing with this approach, postdoctoral fellow Andreas Pichlmair has been focusing on a particular structure that distinguishes the ribonucleic acid (RNA) of a virus, from human RNA. The difference is subtle. At the start of a viral RNA molecule are three small chemical groups called phosphates, which are normally cleaved or "capped" in humans. Using a short RNA bearing this 5' triphosphate, the investigators fished for human proteins that could specifically interact with it and, through mass spectrometry and bioinformatics, identified the protein "interferon inducible transcript with tetratricopeptide repeats 1 (IFIT1)", as well as three other members of the same family. These proteins were known to be strongly induced by interferon, which is a protein produced by cells of the immune system and released as a signal to other cells involved in the immune response. However, their molecular mechanism of action was unknown.

The IFIT proteins are thought to form anti-parallel alpha-helical structures consisting of several short segments of 34 amino acids, which are known as tetratricopeptide repeats. In the series of proteomic, biochemical and functional experiments that ensued, Andreas Pichlmair together with fellow postdoc Maria Gorna, and in collaborations with several other colleagues at CeMM, the Medical University of Vienna, the Vienna Veterinary University and the University of Freiburg, was able to show that IFIT1 binds to 5' triphosphate with high affinity, and engages IFIT2 and IFIT3 in a large multiprotein complex. Each member of this complex has an important role in blocking viral infection, constituting a novel anti-viral defense mechanism (Pichlmair et al., 2011 – see Fig. 5 – an illustration from a review by Veit Hornung on this work). The Superti-Furga group is now working hard to test possible medical applications of this work.

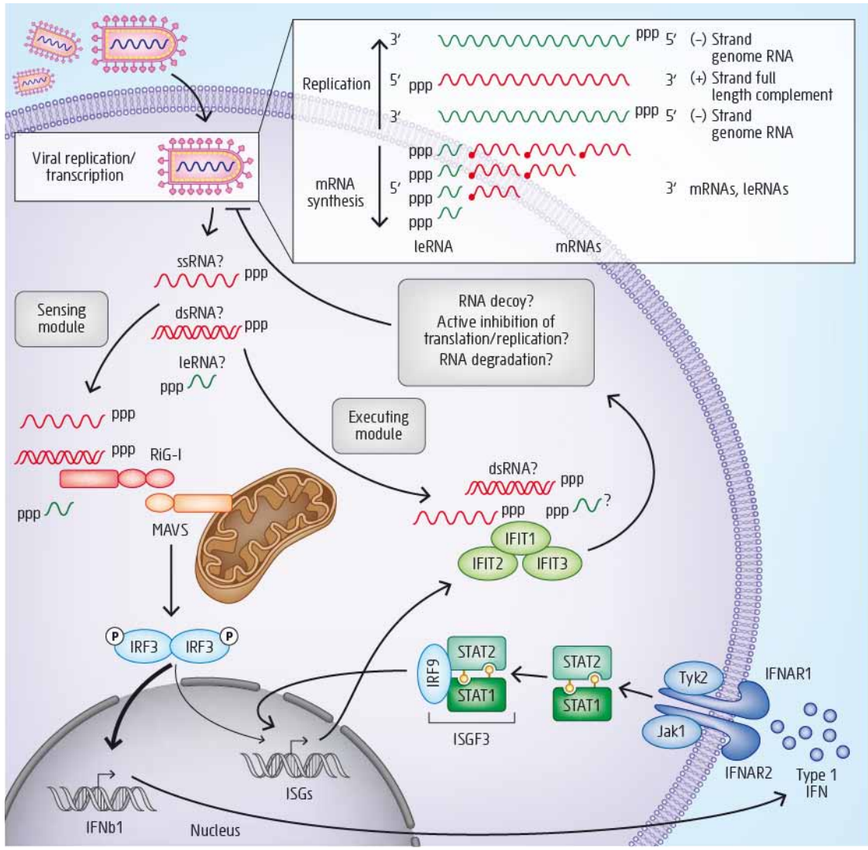

Fig. 5 The IFIT1 complex inhibits viral replication. A nonsegmented negative-strand RNA virus (such as vesicular stomatitis virus) serves as an example in this presentation of possible interactions of IFIT1 with viral RNA. After infection, the negative-strand (–) RNA genome of vesicular stomatitis virus, which is 5′ triphosphorylated (ppp), is transcribed by the virus-encoded RNA-dependent RNA polymerase. At some point, transcription is switched to replication and full-length complementary positive-strand (+) RNA (antigenome) is made. The antigenome serves as a replication template for the full-length negative-strand RNA genome. Activation of RIG-I by 5′ PPP-RNA (such as leader RNA transcripts, genomic single-stranded RNA (ssRNA) or double-stranded RNA (dsRNA) intermediates) leads to the translocation of interferon-regulatory factors (IRF3), which subsequently initiates the production of type I interferon (IFN) and also IFIT expression. Moreover, type I interferon, acting in a paracrine or autocrine way, boosts IFIT expression. IFIT1 binds to 5′ PPP-RNA of as-yet-unknown origin, which leads to the assembly of an IFIT complex and thereby inhibits viral replication. MAVS, adaptor protein; *Ifnb1*, gene encoding interferon-β1; STAT1 and STAT2, transcription factors; Tyk2 and Jak4, kinases; IFNAR1 and IFNAR2, interferon receptors.

Title: Where, in antiviral defense, does IFIT1 fit?
Author: Andrea Ablasser, Veit Hornung
Publication Name: Nature Immunology
Publication Date: Jun 20, 2011
Content ID: 10.1038/ni.2061
Issue Number: 7
Identification: Katie Vicari, "The IFIT1 complex inhibits viral replication"

Studying the Molecular Mechanisms of Viral Infection

CeMM is using a conceptually new approach that involves human cells with only one copy of the chromosomes (haploid).

Andreas Bergthaler has recently established his group at CeMM, and is also working on the complex molecular processes involved in the immune response, but with a focus on how our cells and bodies react to so-called persistent viruses, such as Hepatitis B virus, Hepatitis C virus and HIV. These viruses are long term residents in around half a billion people worldwide, managing to continually evade detection and clearance by our immune systems. The Bergthaler group utilizes a combination of approaches, including cell culture, and a mouse infection model with lymphocytic choriomeningitis virus (LCMV). LCMV closely mimics the pathophysiology of human diseases like hepatitis that are caused by persistent viruses, and is a classic model used by scientists for understanding infections in humans. Indeed, 80 years of research with LCMV have led to many seminal findings culminating in two Nobel Prizes. By merging this classic LCMV infection model with state-of-the-art systems biology tools, including transcriptomics and quantitative proteomics, they aim to gain new insights into both the cellular and organismal mechanisms associated with these permanent viral residents.

Identifying Human Proteins Required for Infection

The mechanisms by which viruses and bacteria get inside human cells is another active area of research at CeMM. The group of Thijn Brummelkamp, who is an adjunct Principal Investigator at CeMM, is using a conceptually new approach that involves human cells with only one copy (haploid) of the 23 human chromosomes, rather than the usual two (diploid – see also page 55). This finally allows scientists to efficiently disrupt large numbers of individual genes in human cells. The team have recently used this technology in combination with systematic screens, in collaboration with research groups in the USA, to uncover key insights into the entry route for one of the most deadly human viruses, the Ebola virus.

The Ebola virus causes a rapidly fatal haemorrhagic fever in humans, and there is currently no cure. Virus entry into human cells is mediated by the viral glycoprotein, which attaches to the cell surface and delivers the virus to intracellular vesicles called endosomes. It was known that other human proteins were required for this mechanism, however, despite considerable efforts using conventional methods, they remained unknown. Using a haploid genetic screen, the group identified 15 human proteins that were required for Ebola virus entry. Unexpectedly, they discovered that cells from individuals with a rare metabolic disorder known as Niemann-Pick C1 disease could not be infected by Ebola virus (Carette et al., 2011). In collaboration with the group of Klaus Aktories in Germany, they similarly uncovered novel host-pathogen interactions for one of the most frequent causes of infectious diarrhea in hospitals worldwide, *Clostridium difficile* (Papatheodorou et al., 2011). Identification of human proteins that are required for pathogens to enter our cells can lead to the development of much-needed new drugs to treat a multitude of infectious diseases.

The Immune Response to Bacterial Infections

Globally, infections are the second leading cause of death, the majority of which occur in the lungs. Indeed, there are several bacteria that cause serious lung infections, and despite the proper use of antibiotics, some still lead to death. Sylvia Knapp's laboratory at CeMM and at the Medical University has been studying immune defense mechanisms such as the inflammatory response that help us fight this deadly group of bacteria.

Each bacterium is equipped to attack the body with a specialized army of so-called virulence factors, which enables it to invade tissues like the lung and escape detection by the immune system. The group has been taking a closer look at these virulence factors, particularly the Panton-Valentin toxin from the bacterium Staphylococcus aureus, which can cause a range of human diseases, some of which can be lethal. PhD student Ana Zivkovic, along with postdoc Omar Sharif, found that this toxin not only kills cells, but also activates the immune defense system to attract more of them to its site of action in the lungs (Zivcovic et al., 2011). This double-attack mechanism illustrates the sophistication of this deadly toxin. In collaboration with Pavel Kovarik from the Max F. Perutz Laboratories, postdoc Stefanie Sigel in the Knapp Lab also helped to discover several different signalling pathways in various immune cells in response to infection by another pathogenic bacterium, Streptococcus pyogenes (Gratz et al., 2011). These discoveries provide important new targets for the development of effective treatments to improve survival rates for these potentially lethal bacteria.

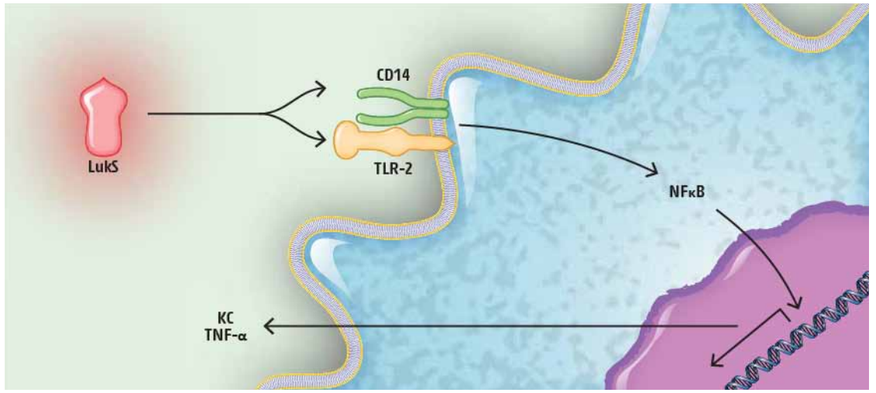

Fig. 6 The LukS component of the bacterial toxin Panton Valentine Leukocidin is recognized by TLR2 on macrophages and induces an inflammatory response (KC and TNF). (Zivkovic et al. J. Immunology 2011)

Inflammatory Disease

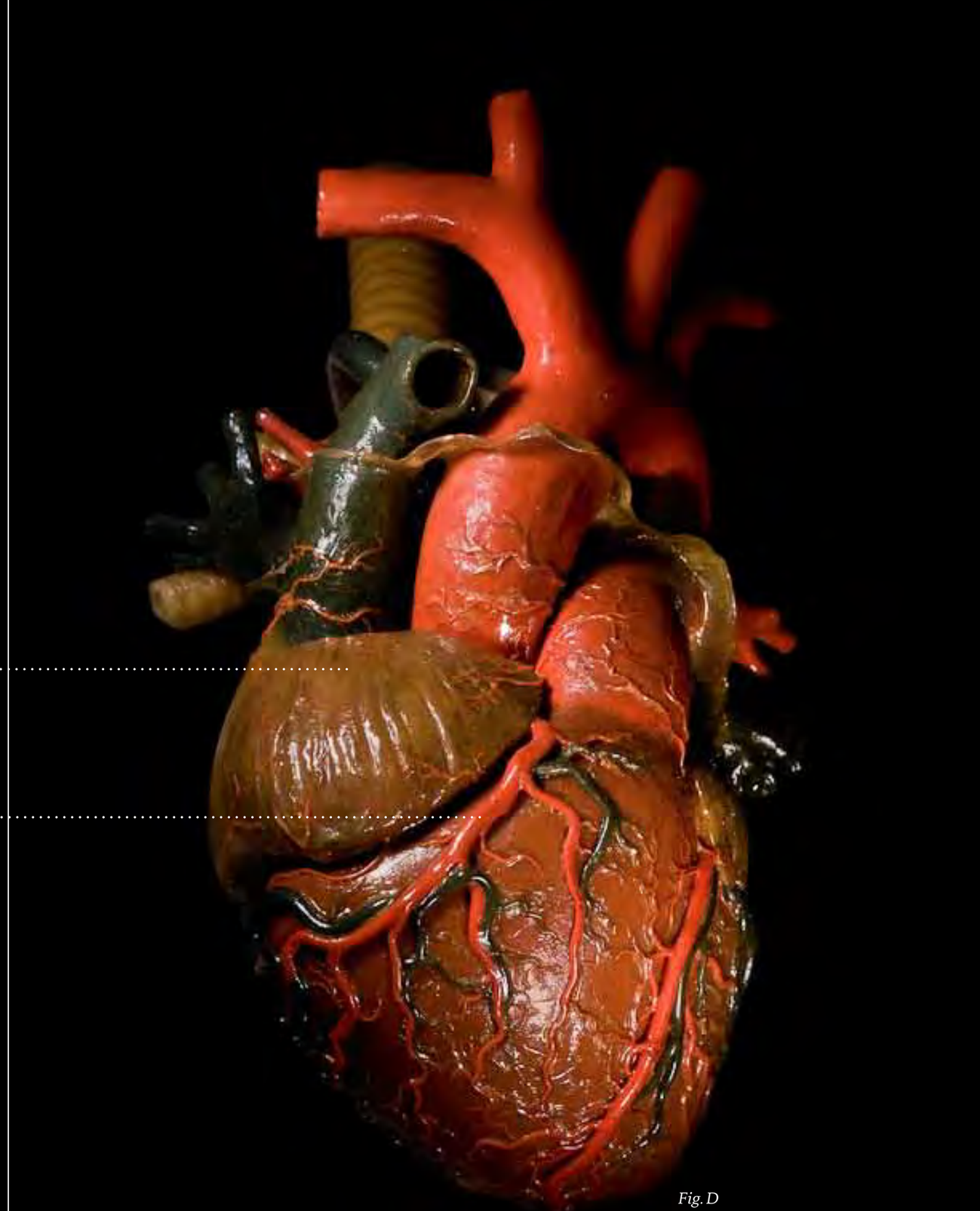

Fig. D

Fig. D

Indepth rendition of the heart, with impressive details. Mainly the right ventricle and atrium can be seen, as well as the aorta, the superior vena cava and the coronary arteries. Owing to its central role in human biology, the heart has for centuries fascinated humanity and heart diseases are still responsible for many deaths, making research into cardiovascular diseases even more pertinent.

The Heart of the Matter

Inflammation is probably one of the most well known signs of infection or injury. If we bang ourselves, cut our skin, or get bitten by a mosquito, the initial pain is usually quickly followed by a swelling of the local area due to the accumulation of fluids. Although we often associate it with pain and discomfort, inflammation actually works as a critical part of our innate immune system, protecting the body by treating the cause of the pain and repairing the damage. Clinicians studying medicine in the 18th century would also have easily recognized the five classic signs of acute inflammation: pain, heat, redness, swelling and loss of function, which are often readily apparent on the surface of the body. But one has to go beyond the surface to see the many other important signs. These include increased permeability of the blood vessels, reduced blood flow, and the influx of an army of cells such as white blood cells, or leukocytes. These cells are critical mediators of the inflammatory response, and possess a repertoire of defenses to target and destroy invading pathogens and to clear up the cellular debris caused by damage.

Although acute inflammation is protective, prolonged inflammation can be damaging and appears to underlie many chronic diseases such as atherosclerosis and diabetes, as well as being strongly linked to the progression of cancer. Scientists at CeMM have been delving even deeper inside the body to study the molecular mechanisms underlying the self-destructive side of chronic inflammation, in order to find new ways to treat these deadly diseases.

Breaking Hearts

Atherosclerosis is a chronic inflammatory disease and the underlying cause of heart attacks and stroke, making it the leading cause of death in the world. It is characterized by the build-up of fatty material in the arteries, which can ultimately lead to a life threatening disruption of blood flow. These days, sophisticated methods exist for imaging advanced atherosclerosis in affected arteries, including angiography and computerized tomography (CT) scanning. However, even without these modern day tools, the clinicians of the 18th century, who were studying the wax models of the human heart now displayed in the Josephinum, would also have been familiar with the visible signs of arterial damage, as most of us have it to some extent. Since that time, many scientific advances have led to a clearer understanding of the processes leading to this prevalent and life-threatening disease. It starts with the accumulation of lipids, cells and debris over many decades, which gradually thicken the blood vessel walls. High cholesterol is one of the main risk factors for atherosclerosis, and results in the accumulation of lipids called low-density lipoproteins (LDL). These trapped lipids become oxidized and trigger an inflammatory response contributing to the formation of lesions. At advanced stages of the disease, the lesions progress to form plaques that can restrict blood flow to the heart, causing chest pain and discomfort, which is diagnosed as angina. If the plaques rupture, blood clots can form and block blood flow to the heart, leading to a heart attack, or to the brain, causing a stroke.

Although it is clear that the inflammatory response plays an important role in the development and progression of atherosclerosis, little is known about the cellular factors that attempt to mitigate it. Scientists at CeMM have been focusing on this neglected aspect of the disease to find out how cells work to inhibit the formation of atherosclerotic lesions and stabilize the plaques to avoid catastrophe. Knowledge of these mechanisms may reveal attractive new targets for therapeutic intervention. They are also working on the development of vaccines by studying so-called autoantibodies against oxidized low-density lipoproteins, which can be detected in patients with atherosclerosis and are linked to cardiovascular disease risk.

Finding Protective Molecules in Atherosclerosis

In addition to high plasma cholesterol levels, which represent a major risk factor for atherosclerosis, inflammation has also been shown to be critically involved in the formation of atherosclerotic lesions. These lesions are characterized by the accumulation of oxidized low-density lipoproteins (OxLDL) and the infiltration of immune cells such as macrophages and T-cells. The secretion of small molecule cytokines in the microenvironment of evolving lesions also contributes to the development of plaques, which are characteristic of advanced disease. While the pro-atherogenic effect of the T helper 1 (Th1) cytokine interferon-γ is well established, the role of Th2 cytokines is less clear.

In collaboration with Oliver Söhnlein of Munich (LMU) and Herbert Stangl of the Medical University of Vienna, the laboratory of Christoph Binder at CeMM has previously shown that the Th2 cytokine IL-13 is induced when lesion formation is decreased by specific immunological interventions in mice. IL-13 is primarily made by haematopoietic cells making it relatively straightforward to generate atherosclerosis-prone IL-13 deficient mice by reconstituting them with bone marrow from available IL-13 knockout mice. PhD student in the Binder lab Larisa Cardilo dos Reis found that deficiency of IL-13 results in dramatically accelerated atherosclerosis in LDL receptor-deficient mice without changing plasma cholesterol levels. Importantly, IL-13 administration to mice with established atherosclerotic lesions stabilized their plaques by increasing the collagen content of the lesions and by halting the recruitment of new monocytes, resulting in decreased numbers of macrophages. This was accompanied by the induction of alternatively activated macrophages, which they found had an increased capacity for removing and disposing OxLDL in vitro. Thus, IL-13 not only protects from atherosclerotic lesion formation but also induces the stabilization of existing lesions. These discoveries may lead to the development of novel therapies for atherosclerosis, particularly for patients with advanced disease.

Fig. 7 Increased atherosclerosis in IL-13-deficient LDLR knock out mice. Mice were reconstituted with bone marrow from either IL-13+/+ mice or IL-13-/- mice and fed an atherogenic diet. Values represent μm²/section throughout the entire aortic origin (**p<0.01). Images show representative examples. Original magnification: 50x.

Mimicking Antigens in Atherosclerotic Lesions

Oxidized low-density lipoproteins (OxLDL) such as malondialdehyde-modified LDL (MDA-LDL) are critically involved in the development of atherosclerotic lesions. They are bound by specific autoantibodies that can be detected in the plasma of patients with cardiovascular disease. Because these autoantibodies influence disease progression, their concentrations could be used as potential biomarkers to identify patients at high risk for heart attacks and strokes. However, MDA-LDL contains many different epitopes that are highly variable. Therefore, Shahzada Amir, a PhD student in the Binder lab, in collaboration with Joseph Witztum in the USA, designed an approach to identify and characterize peptide mimotopes of MDA-LDL that could serve as standardized antigens to improve the reproducible detection of these specific autoantibodies.

To identify such peptide mimotopes, phage libraries displaying random peptides were screened with an MDA-LDL specific monoclonal antibody. Of 42 identified mimotopes, one 7 amino acid-long and one 12 amino acid-long peptide carrying a consensus sequence were synthesized. Both peptides bound specifically to murine and human MDA-specific monoclonal antibodies. Furthermore, the peptides were found to mimic epitopes on the surface of apoptotic cells, which also carry MDA-epitopes. Immunization of mice with a peptide mimotope resulted in the induction of MDA-LDL-specific antibodies, which strongly immunostained human atherosclerotic lesions. Finally, both IgG and IgM autoantibodies to both peptide mimotopes were detected in sera of healthy subjects and in patients with myocardial infarctions and stable angina. Importantly, autoantibody titres correlated significantly with respective antibody titres against MDA-LDL. Thus, these newly identified peptide mimotopes of MDA-LDL serve as highly reproducible antigens to accurately determine the concentration of disease-associated autoantibodies in patients, and will also be tested as antigens for producing therapeutic vaccines.

The concentrations of autoantibodies could be used as potential biomarkers to identify patients at high risk for heart attacks and strokes.

Pediatric Disease

Fig. E

A wax model of a full-term preborn male fetus, likely measuring around 50 cm long and weighing around 3 kg. The appearance is of a newborn, with fully formed nails on the fingers and toes, and some hair on the scalp, and inside would be fully developed organ systems. The umbilical cord can also be seen, which connects the fetus to the placenta and supplies nutrient rich blood to the developing fetus, as well as removing waste.

Fig. E

Tackling Childhood Diseases

In the womb of a pregnant woman, over a period of around nine months, probably the most dramatic metamorphosis of the human body occurs. It begins with just a single cell known as a zygote, which first undergoes several rounds of cleavage to produce 32 identical cells. These cells then gradually change shape, differentiate and divide to form the three so-called primordial germ layers of the human body – the endoderm, mesoderm and ectoderm. These are the precursors of all our organs and tissues, which form over the coming months. Scientists and clinicians have long been fascinated by this unparalleled anatomical transformation, and it continues, albeit at a reduced rate, particularly during the very early childhood years. But it is not just our physical appearance that changes as we grow. Many of our biological systems also take years to develop properly. Our immune systems, for example, are quite rudimentary at birth, and it takes several years of being exposed to pathogens to build up enough immunity for protection against common infections. The neural circuits in our brains are also mostly formed after birth, with an estimated 700 new neural connections being made every second during our first few years of life.

Inherited Diseases

In contrast to viruses and bacteria, which cause infectious diseases, genetic diseases are caused by abnormalities or mutations in our genes, some of which can be inherited from our parents. These genetic mutations produce abnormal cells that interfere with the normal functioning of our bodies and ultimately affect our health. Inherited disorders of the immune system – so-called "primary immunodeficiency disorders" – constitute a heterogeneous group of diseases which have greatly facilitated our understanding of the hierarchical structure of the immune system. They are characterized by malfunctioning of the immune system, which can cause a substantially increased risk of infection and autoimmune disease. Work at CeMM is focused on identifying the genetic basis of these disorders using state-of-the art high-throughput genomics technologies. An enhanced molecular understanding of these conditions will enable the development of better classification systems for disease management, as well as new and more effective treatment strategies.

Susceptible Age Groups

Cancer is another genetic disease. Although it can strike at any age, it normally takes decades to develop and so is considerably more prevalent in the elderly. There are many different types of cancer, and most tend to be more common in certain ages or sexes. For men, prostate cancer is most prevalent between the ages of 70 and 75, whereas testicular cancer is more common in the 20–40 year age group. Childhood cancers are fortunately more rare than most adult cancers, and the survival rates are generally better. They tend to involve cells of the blood (leukemia), bone (sarcoma) or nerve cells (neuroblastoma), although the reason for this is not well understood.

The genetic aberrations underlying many types of cancers are now known, and for some cancers it appears that a shared set of genes and cellular pathways is involved. These are mostly linked with proliferation and the deregulation of growth control, both of which are common characteristics of all cancer cells. Understanding the molecular causes of cancer has led to the development of some very effective targeted drugs, but there is still a gap in knowledge for certain cancer types, and an urgent need for new treatments. To meet this need, scientists at CeMM have been working on childhood cancers that are currently associated with low survival rates, to help identify promising new drugs.

Identifying the Molecular Causes of Inherited Immune Disorders

Of the 23,000 genes in the human genome, it has been estimated that almost 5% plays a role in the immune system. However, for many of these genes, it is still unclear what their precise function is. Identifying the function of genes via forward genetics approaches using animal models have revealed important insights into the molecular processes controlling our immune systems. However, although genes are often conserved between different species, no model can fully replicate the precise physiological conditions found in humans, particularly in human diseases, making it hard to conclusively extrapolate the function of a gene from one organism to another. To combat this limitation, the laboratory of Kaan Boztug, who has a dual affiliation with the Children's Hospital of the Medical University of Vienna, has been studying the patients themselves, to find new ways of treating inherited disorders of the immune system, known as primary immunodeficiency disorders (PIDs).

PIDs such as congenital neutropenia are characterized by a defective innate immune response. Individuals with congenital neutropenia have low numbers of neutrophil granulocytes and are particularly vulnerable to bacterial and fungal infections. A severe complication of this disease is the development of myelodysplastic syndrome or acute myeloid leukemia in up to 30% of patients. Neutrophils from these patients often show an enhanced propensity to undergo apoptosis or so-called "programmed cell death". To identify the underlying molecular defects involved, the group employs high-throughput genomics approaches including Affymetrix SNP-array based mapping studies and whole exome sequencing, which have been established at CeMM. Identification of the respective candidate genes, molecular pathways and networks involved will provide deeper insights into the molecular pathophysiology of these disorders. These investigations will lay the foundation for the development of more specific, therapeutics to treat this group of diseases.

Looking for Similarities in Cancer

Cancer is characterized by specific molecular events that cause cells to behave abnormally. This altered behavior includes uncontrolled proliferation, which causes excessive tumor growth, and the ability to change cell type, potentially leading to metastasis. Due mainly to the advances in molecular biology, many of these tumor causing (oncogenic) mutant proteins have been identified for different types of cancer, and specific drugs have been developed to target them. As many different cancers activate the same growth promoting pathways, there is a good chance that drugs developed for one particular tumor type could also be used to treat other types with the same cellular lesions. To test this, Kilian Huber, a postdoc in Giulio Superti-Furga's group at CeMM, has launched a combined approach. By coupling chemical proteomics with screening clinically approved drugs against different cancer cell lines, all protein interactions of a selected drug can be identified. This could lead to the discovery of new drugs to treat this devastating disease.

Finding New Drugs to Treat Ewing Sarcoma

Mutations in the ALK protein kinase gene have very recently been identified as a strong driver of malignant transformation. Consequently, several drugs were developed to inhibit ALK activity, which have proven to be very useful in the treatment of certain types of lung cancer as well as childhood tumors such as neuroblastomas. As childhood cancers occur early in life and may have a common underlying molecular cause, the group investigated whether there were other types that may also respond to these newly developed ALK kinase inhibitors. They discovered that particularly cancer cells derived from the Ewing sarcoma family of tumors were highly sensitive to ALK inhibitors. Using chemical proteomics, the ALK inhibitors were found to target several important proteins driving proliferation and inhibiting apoptosis. Long-term survival of advanced disease can be less than 10%, and therefore new, effective therapeutic options are urgently needed. The group is currently trying to further validate their results and translate them quickly into effective new treatments for patients in the clinic.

In pediatric cancers, the success rate for the treatment of leukemias is now relatively high. However, therapeutic options for solid tumors often do not improve long-term survival rates, and the treatment of both still rely on chemotherapeutics, which are associated with substantial and toxic side effects due to their limited specificity for cancer cells. Hampering the development of "smarter" drugs that would specifically kill tumor cells is a limited understanding of the molecular biology underlying these tumors and their relatively low incidence, rendering them unattractive targets for the pharmaceutical industry.

To address this, PhD student Georg Winter and postdoc Uwe Rix, both from Giulio Superti-Furga's group at CeMM, have set out to systematically test hundreds of drugs and drug-like molecules in cell lines derived from patients that suffered from one of the most frequent pediatric sarcomas, Ewing's sarcoma. They found that the drug tozasertib was very effective at selectively killing these cell lines. Using chemical proteomics and genetic loss of function experiments, tozasertib was shown to affect some 20 proteins in the Ewing's sarcoma cell lines. Simultaneous impairment of only two of these had the most dramatic effect on cell viability. These two proteins are closely related and are called Aurora kinases A and B, which are important players in cell division. Further experiments also showed a synergistic effect of tozasertib with current chemotherapeutics, and a significant effect on the growth of Ewing's sarcoma-derived tumors in mice (Winter et al., 2011). Altogether this study reveals novel insight into the molecular mechanisms underlying this pediatric solid tumor, which has a very poor prognosis.

There are some 538 kinases in humans, making them the biggest family of enzymes, and they control diverse biological processes such as cell proliferation, DNA repair and cell death.

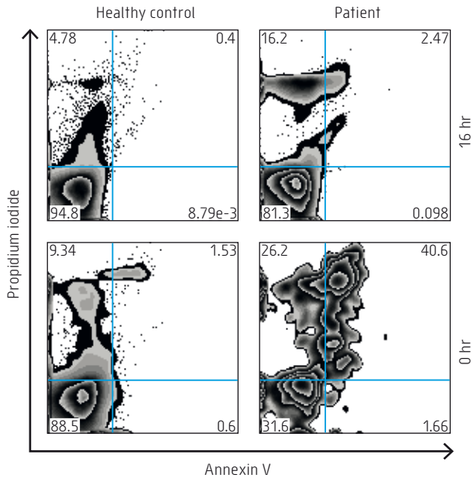

Fig. 8 Increased neutrophil apoptosis in a patient suffering from congenital neutropenia. The upper panels depict apoptosis (measurement using Annexin V as a marker) in freshly isolated peripheral neutrophils, the lower panel 16 hours after apoptosis induction using staurosporine. The results shown here suggest that the underlying genetic defect is associated with increased neutrophil apoptosis.

Research Tools

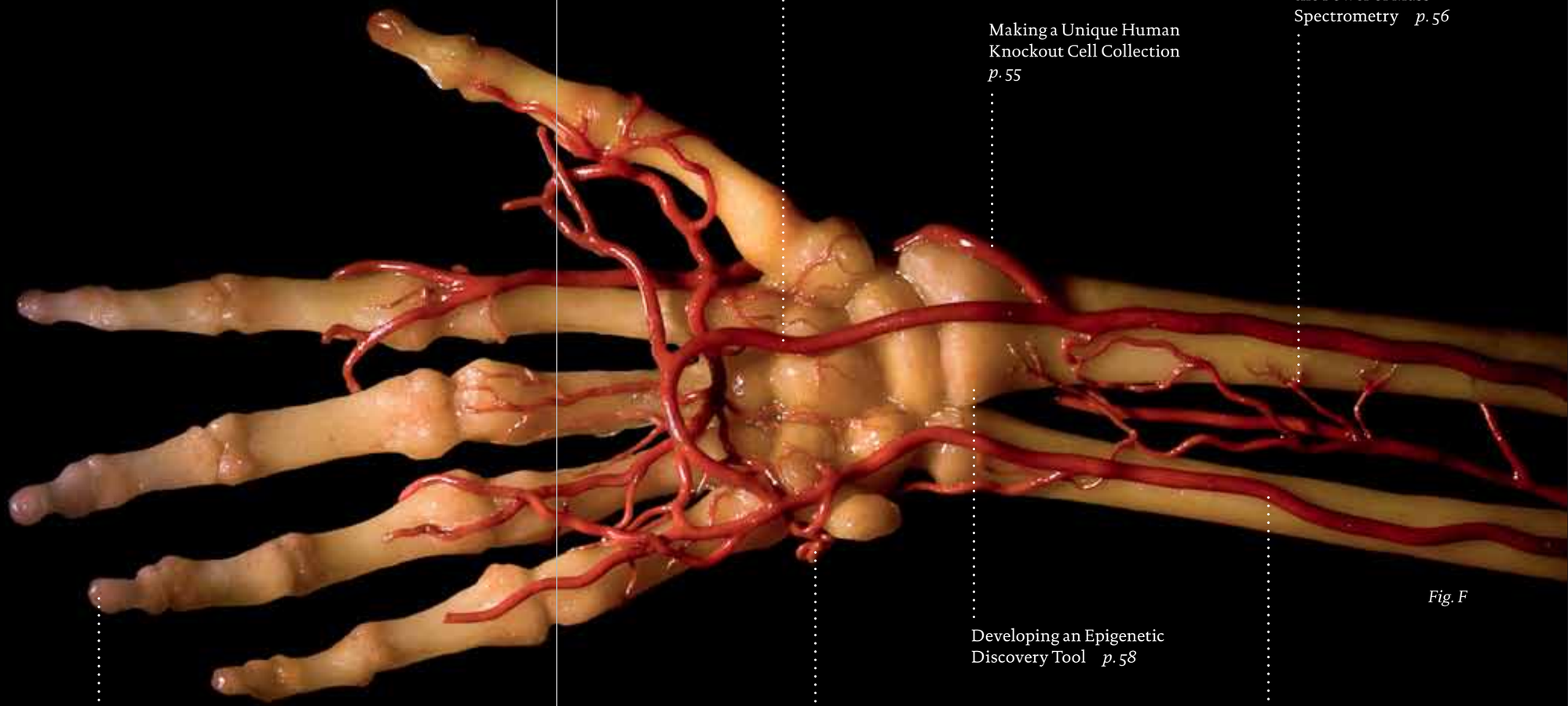

Fig. F

View of the proximal end of the human arm. The radius and the ulna with their associated radialis and ulnaris arteries are visible on the right. The carpus, metacarpus and the phalanges of the hand are composed of many small bones.

Helpful Hands

One of the most cited abilities of early humans that is said to have set us apart as a species from the other animals is our extensive use of tools. This ability was strongly supported particularly by one of our anatomical features, our hands. Compared to our most closely related cousins, the apes, human hands have shorter fingers and a longer thumb. Coupled with a flexible wrist, this handy set-up made tool making relatively easy, setting us on our distinct evolutionary path. Scientists at CeMM have been busy using their hands to make diverse scientific tools to help them investigate many different biological processes linked to human disease.

Hand-Made Tools

In the 18th century, 1,192 different wax specimens were made in Florence and sent to Vienna via the Alps as educational tools for physicians at the Academy of Medicine and Surgery to help them better understand disease. The collection is now housed in the Josephinum at the Medical University of Vienna. Tools are critical also in biology, and significant advances in knowledge often parallel great advances in technology. At CeMM, many of the research groups have been developing new tools to help generate knowledge and ultimately aid in the treatment of human diseases such as cancer and infections. For example, a custom designed drug library and an exclusive human knockout cell collection using haploid cells are being developed as unique tools to find new drugs to treat disease and to study the mechanisms of action of drugs. And mass spectrometry, used to identify proteins, and bioinformatics are both crucial tools being used in many projects in progress at CeMM, as well as for external collaborations.

Engineering Life

Today, most of us don't use our hands and fingers as much to specifically make tools, but we do use them for almost everything we do. They don't work in isolation though, requiring our brains to control them, along with an extensive set of muscles that extend up our arms, as shown in some of the wax models at the Josephinum. The muscles are split into sensors, flexors and rotators, but they work together in groups, allowing fine control of our fingers for performing delicate movements such as threading a needle or writing a letter. The fine control required for many biological processes such as cell migration or gene expression also requires its components to work together. Indeed, there are many connections between our molecules and our cells, and to fully understand particularly disease, one needs to consider the entire system. This so-called systems approach has become an important feature of many of the scientific projects being carried out at CeMM. And they have been tooling up, particularly in mathematics and computers, to support them in their endeavors.

The wax models reveal the intricate engineering behind our anatomical features, which helped the clinicians of the 18th century understand how they worked. Studying the detailed mechanisms behind biological processes is also necessary to build a comprehensive molecular framework for understanding exactly how the body functions and what goes wrong in disease. Projects underway at CeMM have been analyzing the intricate engineering behind gene regulation, particularly focused on macro non-coding RNA molecules, which underlie many different biological processes, in both health and disease.

Building a Customized Library of Approved Drugs

Sophisticated tools to identify small molecules for the potential treatment of many different diseases make up CeMM's PLACEBO (Platform Austria for Chemical Biology) screening platform, managed by Stefan Kubicek's group. PLACEBO is now running at full scale and has so far generated more than 1 million data points. Equally as important to the identification of new chemicals is finding additional uses for already approved drugs. In the absence of a representative collection of all clinically used small molecules, the Kubicek group has generated such a compound set, and named it CLOUD for CeMM Library of Approved Drugs. Approved drugs already have many known chemical, biological and medical properties. As such, they have enormous value in phenotypic high-throughput screening as they can identify the involvement of previously known biochemical pathways in new biological processes. Furthermore, all approved drugs have already been shown to be safe in humans, so the discovery of novel applications can rapidly be translated to the clinic.

To build this unique and valuable collection of compounds, the Kubicek group first analyzed all 26,800 FDA approved drug products and identified 962 unique small molecules. For 35 of these, the relevant cellular target (usually a protein) was unknown, but the remaining molecules could be classified into 164 groups based on their target and mode of action (e.g. activator or repressor). They also analyzed the chemical structure of these molecules and explored the maximum concentration achievable in human patients to make sure they would be screened at the relevant dose. The library is being physically assembled on a single 384-well plate and will be included in all high-throughput screens in the PLACEBO lab. It is also expected to become the reference standard for CeMM's collaboration partners in the EU-Openscreen project, as well as in industrial and academic screening centers around the world.

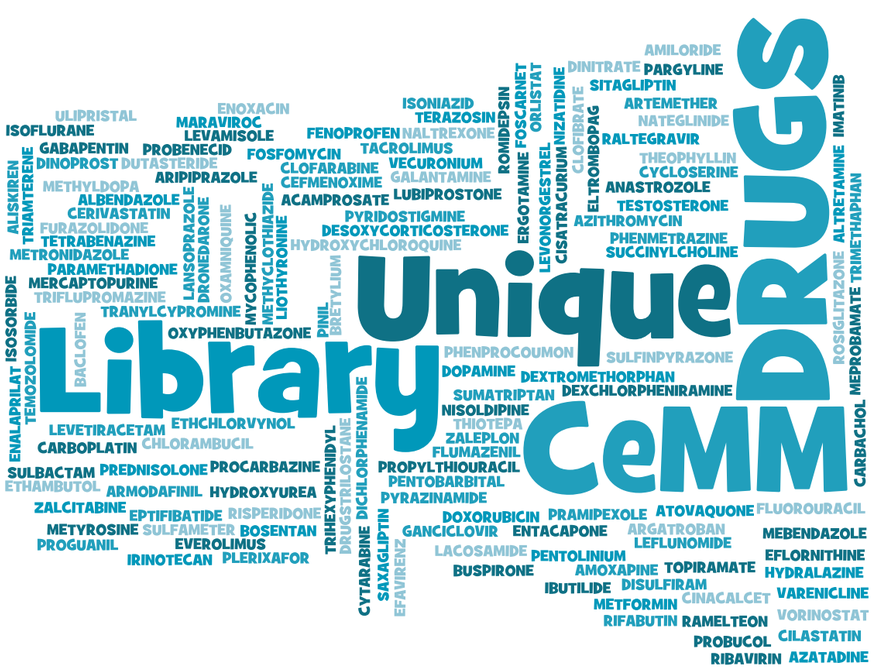

Fig. 9 The CeMM Library of Unique Drugs (CLOUD) was designed to contain a set of compounds that represent all approved drugs. These compounds, whose names make up this word cloud, maintain the chemical diversity and biological targets of all clinically approved drugs.

Making a Unique Human Knockout Cell Collection

Tools to genetically modify cells and organisms have revolutionized all aspects of modern biology and biomedicine. It began at the start of the 20th century, when Nobel laureate Hermann Muller showed that ionizing radiation caused heritable changes in fruit flies, thus founding the field of classical genetics using induced changes in genes, which are the units of heredity in living organisms. Today, studying cells or organisms after the removal (or knockout) of a single gene remains one of the most powerful approaches for understanding complex biological processes, as well as for identifying drug targets.

Collections of knockout cells for many of the model organisms such as yeast and Drosophila have long been available and are treasured by the academic and industrial communities. Thus, it would be highly valuable to have a collection of validated knockout cells for humans (arguably the most relevant 'model organism' for medical research) that are mutated for all the protein-coding genes in the genome. Unfortunately, human knockout cell collections are not yet available because gene disruption or mutation in human cells is notoriously complicated. This complexity arises from the fact that human genes are present in two copies or alleles (diploidy, which is also called 'the geneticist's nightmare'). Consequently, inactivation of one allele of a gene that is present in two copies will usually not cause an appreciable effect because the other functional allele can take over.

To overcome this hurdle, Thijn Brummelkamp, who recently moved from the Whitehead Institute for Biomedical Research to the Netherlands Cancer Institute in Amsterdam and is also Adjunct Principal Investigator at CeMM, has recently developed a method to generate fast and complete knockouts at unprecedented scale, called HaploTrap. This method utilizes a unique near-haploid human cell line in combination with insertional mutagenesis using a retroviral gene trap vector. As the cell line carries only one copy of most of its chromosomes, genes that are "trapped" and thus inactivated by the gene trap vector yield a complete loss of function knockout. In this manner, more than 97% of all expressed genes can be targeted (Carette et al., 2011). In a public-private partnership, CeMM and Haplogen have joined forces to bring the technology to the next level by generating a comprehensive human knockout cell collection, called the HaploSet. In the HaploSet, every cell clone will bear a single insertion of the gene trap in one human gene, leading to its specific inactivation in that particular clone. Over the past year, more than 10,000 clones have been generated and their identity is currently being mapped using an elaborate deep sequencing strategy. The HaploSet will not only provide CeMM and Haplogen with an unequaled technology platform for in-house studies of individual human genes and drug target discovery screens, but will also enable partnerships with academia and/or industry.

New Tools to Increase the Power of Mass Spectrometry

A new development will enable the mapping of protein-protein interaction networks from limited biological samples.

Keiryn Bennett heads the mass spectrometry research group at CeMM. In collaboration with Eric Haura and Jiannong Lee from the H. Lee Moffitt Cancer Center in Florida, André Müller from the lab has been establishing new ways to identify core protein complexes from limited quantities of material. Tandem affinity purification (TAP) is a method for enriching and isolating non-covalent protein complexes under near-physiological conditions. Coupling of TAP to mass spectrometry (TAP-MS) is a powerful tool for the generation of large-scale protein-protein interaction networks, however large quantities of input protein are generally required. Together with Roberto Sacco and Florian Grebien in the Superti-Furga lab, André has been establishing new ways to downscale TAP using stable expression of tagged versions of the EGFR and the Grb2 proteins in human cell lines. With this approach, all six major constituents of the EGFR complex were identified, and all ten of the Grb2 complex. This was achieved with just 5 to 12.5 mg total protein input, which is equivalent to approximately one 15 cm culture plate of cells and considerably less material than is usually required to successfully identify core protein complexes. This work will enable the mapping of protein-protein interaction networks from cells that are difficult to cultivate in large quantities and will be of considerable benefit for identifying molecular mechanisms of disease from limited human patient material.

Enabling Systems Biology with Mathematics and Computing

Individual proteins are designed to perform relatively elementary functions such as chemical modification of another protein or molecule, or binding to DNA. Working in isolation means they have limited capabilities, but proteins working together as molecular machines (complexes) are able to perform more complex biological functions, such as cell migration or activating an immune response. Individual proteins can be part of multiple complexes, and this modular design allows genomes of limited sizes to encode for an immense variety of molecular machines fitting the needs of very diverse cell types and tissues. Using mathematics and computing, Jacques Colinge's group at CeMM have been detecting the protein composition of these machines, in order to better understand cancer and the human immune system.

Molecular biology has developed powerful tools for measuring the physical interactions between a chosen protein, the bait, and other proteins, by mass spectrometry. By selecting appropriate baits, it is possible to map the interactions that underlie the assembly of protein complexes of interest. This procedure generates highly complex data sets that need analyzing by mathematical modelling and powerful computing. The Colinge group has been developing novel and sophisticated statistical models that rely on known properties of protein complex architecture to identify protein complexes from this type of data.

This new bioinformatics tool is being applied to a multitude of running projects both at CeMM and as part of external collaborations. For instance, by measuring protein interactions in cancer-associated protein complexes in healthy individuals and diseased patients receiving distinct treatments, they have been uncovering how defective molecular machines assemble. These experiments provide an extensive source of information for designing new therapies or indicating better uses for the existing arsenal of drugs. The group also use these computational methods to find new molecular machines involved in the processing of DNA or RNA by integrating large collections of DNA/RNA-protein interaction measurements. Some of these machines are involved in the innate immune system where they detect and combat the presence of infecting viral genetic material in human cells.

A Unique Technology Platform for Personalized Medicine

A unique technology platform has been developed at CeMM to predict treatment response.

In many diseases, particularly cancer, the genetic makeup of the patient determines the efficacy of certain therapies. Confounding this is the fact that most drugs induce complex and extensive perturbations in the cells and bodies of treated patients. Understanding the impact of drug treatment is clearly important and can be used to match a drug to an individual's genetic makeup, to ensure the most beneficial treatment response. It can also be used to explore new indications for existing drugs and to predict the potential side effects of individual drugs, some of which can be particularly harmful. The Colinge group, along with other groups at CeMM, has developed a unique technology platform to experimentally measure drug protein targets and predict treatment response. Data are analyzed using a systems biology approach, where all the known protein-protein interactions are assembled to build a comprehensive cellular model. The protein targets of the drug, as well as the genes known to cause the relevant disease, are mapped onto this network of protein interactions. Physical proximity within the network is then exploited to score the proteins for association with the disease or the treatment. The correlation of the two association scores can be computed to estimate treatment efficacy. This method was applied to chronic myeloid leukemia and the results were used to anticipate side effects of a new compound currently in clinical development, and to propose new indications for unrelated diseases (Colinge et al., 2010).

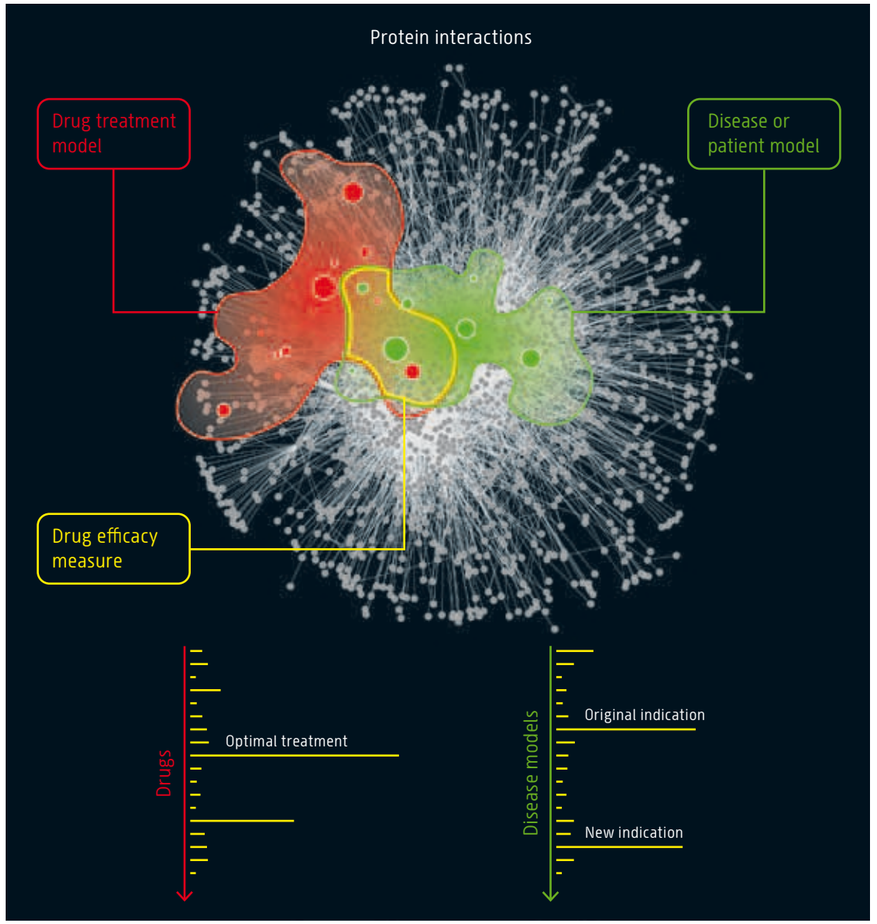

Fig. 10
Protein interactions
(A) Areas of the protein interaction network with significant influence of the drug treatment or the disease are computed independently (drug targets and disease genes as colored circles). On the overlap, a drug effacy score is computed. (B) Applications to compare therapeutic options for a patient or to repurpose existing compounds.

Developing an Epigenetic Discovery Tool

Some of the most important tools for basic scientific research are models of specific diseases, organisms or biological processes, which provide various practical advantages for answering important questions. Denise Barlow's group at CeMM works in the field of epigenetics, and has developed a plethora of tools to help them understand the molecular details underlying this sophisticated mechanism for controlling gene activity. They have been investigating the potential of the mouse yolk sac endoderm as an in vivo epigenetic discovery tool. The yolk sac is a membrane that surrounds and nurtures the developing mouse embryo. Both the yolk sac and the placenta have a short but very dynamic existence, and this is reflected in their epigenetic profile i.e. total DNA methylation levels, which are low compared to the embryo. This is a similar state to cancer cells, suggesting that insights into gene regulation gained in these tissues may help explain disease related epigenetic changes. Reflecting this unusual epigenetic state, the placenta and yolk sac show unique parental-specific silencing of a large number of genes, which is known as imprinting. In the past, the placenta was used to study regulation of these imprinted genes, but it has the disadvantage that it contains both embryonic and maternal cells. The Barlow lab has developed an efficient method to separate the yolk sac into the mesoderm and endoderm layers, and shown that yolk sac specific imprinted expression is restricted to the endoderm layer (Hudson et al., 2011), and provides an important new model for studying mechanisms particularly of long-range gene silencing by macro ncRNAs.

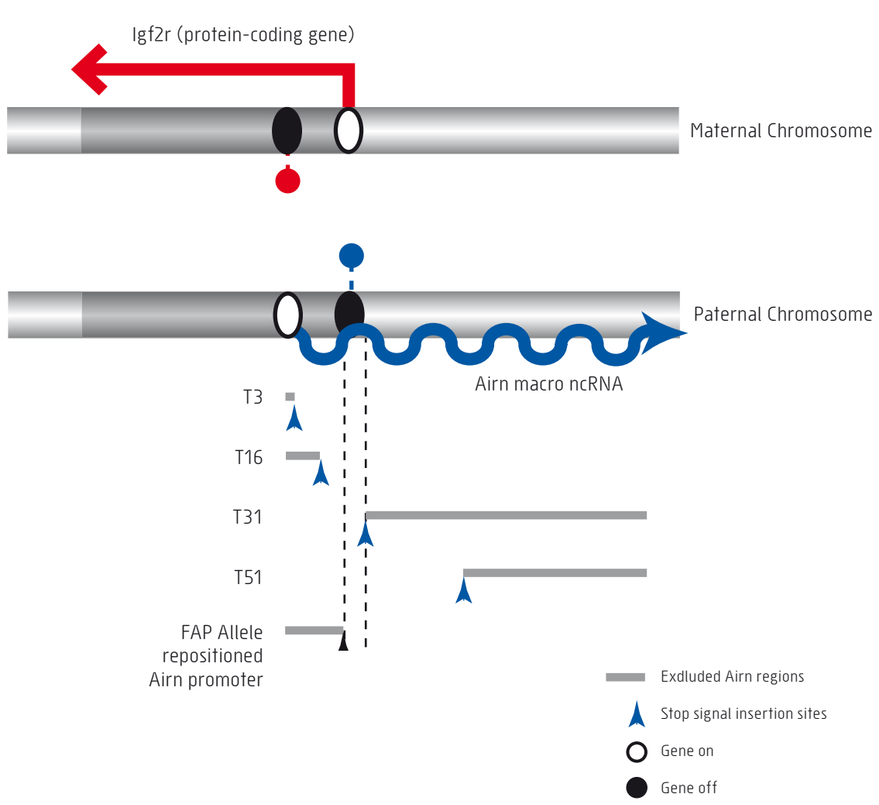

Fig. 11
Transcriptional interference
Genetic manipulation of mouse stem cells to carry a signal to stop the transcription of the Airn ncRNA at different positions along its length (T3-T51), show that 97% of the Airn ncRNA product could be removed without affecting its ability to silence the Igf2r gene, providing the remaining Airn transcript runs across the Igf2r promoter.

Mechanisms of Regulating Gene Expression

Macro ncRNAs are long, non-protein coding RNA molecules that can work as "gene switches". Just as an electric switch is used to turn devices such as a computer or a light on and off, cells use macro ncRNAs to switch genes on and off. This enables them to control many different biological processes. An example of such a gene switch is the *Airn* macro ncRNA, which represses its neighboring protein-coding gene *Igf2r*. So whenever *Airn* is off, *Igf2r* is switched on, and vice versa. The Barlow group have also been using mouse embryonic stem cells (mESCs) as a model for mouse embryo development to show that they could manipulate this gene switch by modifying the DNA sequence to control *Airn* (Santoro and Barlow, 2011). Their results reveal that gene silencing by the *Airn* macro ncRNA is reversible. Importantly, *Airn* is just one example of an expanding class of macro ncRNAs that act as "gene switches" to control the on/off status of protein-coding genes. Some of them play a role in human disease by turning off anti-cancer genes in tumors. Thus, it may be possible to design anti-repressor therapies to shut off macro ncRNAs and treat diseases.

Other work in the Barlow group has been revealing more details behind the complex engineering of gene regulation. ncRNA genes are very different from protein-coding genes as their DNA sequence is not used to code for a product such as a protein. This allows the intriguing possibility that the process of making the ncRNA could be part of the silencing mechanism, while the ncRNA product plays no role. Members of the Barlow group have recently completed a long-term experiment to investigate this possibility by studying how the *Airn* macro ncRNA silences the *Igf2r* protein-coding gene, which plays an important role in regulating embryonic growth. The *Airn* and *Igf2r* genes face towards each other and their transcripts – the copy of the DNA sequences that encode for them – partly overlap. They genetically manipulated mouse stem cells to carry a gene signal (called a polyadenylation site) to stop the transcription of the *Airn* ncRNA at different positions along its length. These experiments tested which part of the *Airn* ncRNA product was required to silence *Igf2r*, and they produced some very new and unexpected results. First they showed that 97% of the *Airn* ncRNA product could be removed without affecting its ability to silence the *Igf2r* gene, providing it overlapped with the *Igf2r* promoter. Second, that *Airn* transcription only needs to cross over the *Igf2r* promoter to turn off the *Igf2r* gene. This implies that, as predicted, transcription of the *Airn* macro ncRNA is more important than its product. This is the first time that so-called transcriptional interference by macro ncRNA overlap has been shown to operate in mammalian cells. The group is now examining gene expression patterns in human differentiation and cancer to see if this is a common mechanism of gene silencing.

Airn is just one example of an expanding class of macro ncRNAs that act as "gene switches" to control the on/off status of protein-coding genes.


WME

Principal Investigators

Giulio Superti-Furga

Pathological Networks in Leukemia and Immunity

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+ Italian nationality
+ Joined CeMM in January 2005
+ Group of 22 people

Main Research Interests
+ Mechanism of action of drugs
+ Molecular networks affecting leukemias
+ Molecular basis of innate immunity
+ Systems Pharmacology

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. In 2011 he received the Prize of the City of Vienna for Natural Sciences, and was honored as Austria's scientist of the Year.

Relevant/Important Publications

Functional organization of the yeast proteome by systematic analysis of protein complexes. Gavin AC, et al., Superti-Furga G. *Nature.* 2002 Jan 10;415(6868):141-7.

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

IFIT1 is an antiviral protein that recognizes 5'-triphosphate RNA. Pichlmair A, Lassnig C, Eberle CA, Górna MW, Baumann CL, Burkard TR, Bürckstümmer T, Stefanovic A, Krieger S, Bennett KL, Rülicke T, Weber F, Colinge J, Müller M, Superti-Furga G. *Nat Immunol.* 2011 Jun 5;12(7):624-30.

Targeting the SH2-kinase interface in Bcr-Abl inhibits leukemogenesis. Grebien F, Hantschel O, Wojcik J, Kaupe I, Kovacic B, Wyrzucki AM, Gish GD, Cerny-Reiterer S, Koide A, Beug H, Pawson T, Valent P, Koide S, Superti-Furga G. *Cell.* 2011 Oct 14;147(2):306-19.

Denise P. Barlow

Epigenetic Mechanisms in Development and Disease

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+ 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 joined CeMM in 2003. She completed a PhD on the interferon system in early mouse development at Warwick University (UK). Post-doctoral work followed at ICRF (London, UK) and on genome biology at EMBL (Heidelberg, D). Denise has also held group leader positions at the IMP (Vienna, A) and the NKI (Amsterdam, NL). 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

Extra-embryonic-specific imprinted expression is restricted to defined lineages in the post-implantation embryo. Hudson QJ, Seidl CI, Kulinski TM, Huang R, Warczok KE, Bittner R, Bartolomei MS, Barlow DP. *Dev Biol.* 2011 May 15;353(2):420-31.

An RNA-Seq strategy to detect the complete coding and non-coding transcriptome including full-length imprinted macro ncRNAs. Huang R, Jaritz M, Guenzl P, Vlatkovic I, Sommer A, Tamir IM, Marks H, Klampfl T, Kralovics R, Stunnenberg HG, Barlow DP, Pauler FM. *PLoS One.* 2011;6(11):e27288.

A Downstream CpG island controls transcript initiation and elongation and the methylation state of the imprinted Airn macro ncRNA Promoter. Koerner MV, Pauler FM, Hudson QJ, Santoro F, Sawicka A, et al. *PLoS Genet.* 2012 8(3): e1002540.

Developmental control of imprinted expression by macro non-coding RNAs. Santoro F, Barlow DP. *Semin Cell Dev Biol.* 2011 Jun;22(4):328-35.

Genomic imprinting: a mammalian epigenetic discovery model. Barlow DP. *Annu Rev Genet.* 2011;45:379-403.

Christoph J. Binder

Atherosclerosis and Immunity

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+ Joined CeMM in April 2006
+ Group of 10 people

Main Research Interests
+ Role of innate immunity in inflammation and oxidative stress
+ Elucidate the protective capacities of natural IgM antibodies in atherosclerosis
+ Discover ways to modulate natural immunity as therapy for cardio-vascular diseases

Christoph Binder's Group is located at
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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 Athero-protective 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, Dewan A, Witztum JL. *Nat Med.* 2002 Nov;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, Goodyear CS, Shaw PX, Palinski W, Witztum JL, Silverman GJ. *Nat Med.* 2003 Jun;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.

Complement factor H binds malondialdehyde epitopes and protects from oxidative stress. Weismann D, Hartvigsen K, Lauer N, Bennett KL, Scholl HP, Charbel Issa P, Cano M, Brandstätter H, Tsimikas S, Skerka C, Superti-Furga G, Handa JT, Zipfel PF, Witztum JL, Binder CJ. *Nature.* 2011 Oct 5;478(7367):76-81.

Sylvia Knapp

Innate Immunity and Bacterial Infections

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Main Research Interests
+ Exploit molecular mechanisms of host-pathogen interactions
+ Identify the impact of bacterial toxins

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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

TLR 2 and CD14 mediate innate immunity and lung inflammation to staphylococcal Panton-Valentine leukocidin in vivo. Zivkovic A, Sharif O, Stich K, Doninger B, Biaggio M, Colinge J, Bilban M, Mesteri I, Hazemi P, Lemmens-Gruber R, Knapp S. *J Immunol.* 2011 Feb 1;186(3):1608-17.

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 Aug 1;183(3):2027-36.

CD14 is a coreceptor of Toll-like receptors 7 and 9. 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#. *J Exp Med.* 2010 Nov 22;207(12):2689-701.

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Robert Kralovics

Genetics of Hematological Disorders

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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 dis orders 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.

Genome integrity of myeloproliferative neoplasms in chronic phase and during disease progression. Klampfl T, Harutyunyan A, Berg T, Gisslinger B, Schalling M, Bagienski K, Olcaydu D, Passamonti F, Rumi E, Pietra D, Jäger R, Pieri L, Guglielmelli P, Iacobucci I, Martinelli G, Cazzola M, Vannucchi AM, Gisslinger H, Kralovics R. *Blood.* 2011 Jul 7;118(1):167-76.

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. *Nat Genet.* 2009 Apr;41(4):450-4.

A gain-of-function mutation of JAK2 in myeloproliferative disorders. Kralovics R, Passamonti F, Buser AS, Teo SS, Tiedt R, Passweg JR, Tichelli A, Cazzola M, Skoda RC. *N Engl J Med.* 2005 Apr 28; 352(17):1779-90.

Sebastian Nijman

Functional Cancer Genomics

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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 NF-kappaB. Brummelkamp TR*, Nijman SM*, Dirac AM*, Bernards R. *Nature.* 2003 Aug 14;424(6950):797-801.

The deubiquitinating enzyme USP1 regulates the Fanconi anemia pathway. Nijman SM*, Huang TT*, Dirac AM, Brummelkamp TR, Kerkhoven RM, D'Andrea AD, Bernards R. *Mol Cell.* 2005 Feb 4; 17(3):331-9.

A genomic and functional inventory of deubiquitinating enzymes. Nijman SM, Luna-Vargas MP, Velds A, Brummelkamp TR, Dirac AM, Sixma TK, Bernards R. *Cell.* 2005 Dec 2;123(5):773-86.

Synthetic lethality: general principles, utility and detection using genetic screens in human cells. Nijman SM. *FEBS Lett.* 2011 Jan 3;585(1):1-6.

A chemical-genetic screen reveals a mechanism of resistance to PI3K inhibitors in cancer. Muellner MK, Uras IZ, Gapp BV, Kerzendorfer C, Smida M, Lechtermann H, Craig-Mueller N, Colinge J, Duernberger G, Nijman SM. *Nat Chem Biol.* 2011 Sep 25;7(11):787-93.

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Kaan Boztug

Malignant Hematological Disorders of Childhood

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Hannover Medical School (D)

+ German Nationality
+ Joined CeMM in January 2011
+ Group of 7 people

Main Research Interests
+ Molecular genetics of primary immunodeficiencies and congenital bone marrow failure syndromes
+ Molecular genetics of malignant hematological disorders of childhood

Kaan Boztug, born in 1977, has been appointed as a Principal Investigator at CeMM starting in January 2011. He studied Medicine at the Universities of Düsseldorf, Freiburg and London. For his MD thesis, he spent a year of research in the laboratory of Iain L. Campbell at the Scripps Research Institute, La Jolla, CA, USA, where his work was focused on neuroimmunology. From 2005 until 2010, Kaan Boztug worked at Hannover Medical School in the Department of Pediatric Hematology/Oncology headed by Christoph Klein with a dual affiliation combining clinical training and postgraduate laboratory work. He developed a strong interest in the molecular genetics of primary immunodeficiency disorders and was able to elucidate a novel primary immunodeficiency which combines congenital neutropenia and complex organ malformations, caused by deficiency in the glucose-6-phosphatase catalytic subunit 3 (G6PC3). In another sentinel work, he was one of the lead authors in the identification of the first monogenic causes of childhood inflammatory bowel disease (IBD), caused by mutations in the genes encoding the interleukin-10 receptor. At CeMM, Kaan Boztug works on the genetics of primary immundeficiencies and congenital bone marrow failure syndromes but has also broadened his interest to genetics of malignant disorders of childhood. He holds a dual appointment with the Children's Hospital of the Medical University of Vienna.

Relevant/Important Publications

A syndrome with congenital neutropenia and mutations in G6PC3. Boztug K, Appaswamy G, Ashikov A, Schäffer AA, Salzer U, Diestelhorst J, Germeshausen M, Brandes G, Lee-Gossler J, Noyan F, Gatzke AK, Minkov M, Greil J, Kratz C, Petropoulou T, Pellier I, Bellanné-Chantelot C, Rezaei N, Mönkemöller K, Irani-Hakimeh N, Bakker H, Gerardy-Schahn R, Zeidler C, Grimbacher B, Welte K, Klein C. *N Engl J Med.* 2009 Jan 1;360(1):32-43. *Erratum in: N Engl J Med.* 2011 Apr 28;364(17):1682.

Inflammatory bowel disease and mutations affecting the interleukin-10 receptor. Glocker EO*, Kotlarz D*, Boztug K*, Gertz EM, Schäffer AA, Noyan F, Perro M, Diestelhorst J, Allroth A, Murugan D, Hätscher N, Pfeifer D, Sykora KW, Sauer M, Kreipe H, Lacher M, Nustede R, Woellner C, Baumann U, Salzer U, Koletzko S, Shah N, Segal AW, Sauerbrey A, Buderus S, Snapper SB, Grimbacher B, Klein C. *N Engl J Med.* 2009 Nov 19;361(21):2033-45.

Stem-cell gene therapy for the Wiskott-Aldrich syndrome. Boztug K, Schmidt M, Schwarzer A, Banerjee PP, Díez IA, Dewey RA, Böhm M, Nowrouzi A, Ball CR, Glimm H, Naundorf S, Kühlcke K, Blasczyk R, Kondratenko I, Maródi L, Orange JS, von Kalle C, Klein C. *N Engl J Med.* 2010 Nov 11;363(20):1918-27.

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Andreas Bergthaler

Viral Immunobiology

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Postdoctoral fellow,
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+ Joined CeMM in July 2011
+ Group of 5 people

Main Research Interests
+ Viral pathogenesis (e.g. virus persistence, immunosuppression, hepatitis)
+ Antiviral immune responses (CD8 T cell, innate immunity, B cells)
+ Mouse infection models
+ Systems biology

Andreas Bergthaler, born 1977, studied veterinary medicine at the University of Veterinary Medicine in Vienna and spent clinical and research stays at the Royal (Dick) School of Veterinary Studies, Edinburgh, the University of Tokyo, the University of Zurich and the Danish Veterinary Institute, Copenhagen. For his graduate studies he joined the Institute of Experimental Immunology at the University/ETH Zurich (Profs. Hans Hengartner and Nobel Laureate Rolf Zinkernagel). After postdoctoral work in Zurich and in the laboratory of Prof. Daniel Pinschewer at the University of Geneva he joined Prof. Alan Aderem's group at the Institute for Systems Biology in Seattle, WA. In 2010 he co-founded a Swiss/Austrian vaccine start-up company. Andreas Bergthaler's research is focused on the molecular mechanisms which govern virus-host interactions. To this end the Bergthaler laboratory studies viral infections in mouse models through an interdisciplinary approach of pathology, molecular biology, virology, immunology and systems biology. The employed experimental models are well-defined and bear great patho-physiological relevance to human disease. This enables his group to dissect novel molecular determinants and inter-action networks that impact viral pathogenesis and the antiviral immune system. Eventually, this may pave the way for the development of much-sought clinical treatments against viral diseases in man.

Relevant/Important Publications

Impaired antibody response causes persistence of prototypic T cell-contained virus. Bergthaler A, Flatz L, Verschoor A, Hegazy AN, Holdener M, Fink K, Eschli B, Merkler D, Sommerstein R, Horvath E, Fernandez M, Fitsche A, Senn BM, Verbeek JS, Odermatt B, Siegrist CA, Pinschewer DD. *PLoS Biol.* 2009 Apr 7;7(4):e1000080. *Erratum in: PLoS Biol.* 2009 Aug;7(8).

Interferons direct Th2 cell reprogramming to generate a stable GATA-3(+)T-bet(+) cell subset with combined Th2 and Th1 cell functions. Hegazy AN, Peine M, Helmstetter C, Panse I, Fröhlich A, Bergthaler A, Flatz L, Pinschewer DD, Radbruch A, Löhning M. *Immunity.* 2010 Jan 29; 32(1):116-28.

Innate and adaptive immune control of genetically engineered live-attenuated arenavirus vaccine prototypes. Pinschewer DD, Flatz L, Steinborn R, Horvath E, Fernandez M, Lutz H, Suter M, Bergthaler A. *Int Immunol.* 2010 Sep;22(9):749-56.

Viral replicative capacity is the primary determinant of lymphocytic choriomeningitis virus persistence and immunosuppression. Bergthaler A, Flatz L, Hegazy AN, Johnson S, Horvath E, Löhning M, Pinschewer DD. *Proc Natl Acad Sci U S A.* 2010 Dec 14;107(50):21641-6.

Joanna I. Loizou

DNA Repair and Genomic Stability

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Main Research Interests
+ Signaling and repairing DNA damage
+ Repair of physiological DNA breaks generated in immune T and B cells during somatic recombination
+ DNA damage response as a barrier to leukemia and lymphoma

Joanna Loizou joined CeMM in September 2011. Joanna completed undergraduate studies in the UK, having moved there from Cyprus. Subsequently, she joined the laboratory of Prof. Caldecott at the University of Manchester, and later the University of Sussex, to commence PhD work investigating mechanisms of DNA repair, with a focus on DNA single-strand break repair. During this time Joanna identified for the first time a requirement for the kinase CK2 in the DNA damage response (Loizou et al., 2004). Postdoctoral work followed at the International Agency for Research on Cancer (IARC), World Health Organization (WHO), France where Joanna investigated the role of epigenetic modifications, mainly histone acetylation, in DNA repair. Joanna was able to show that cells use shared molecules both in transcription and in repairing DNA lesions (Murr* & Loizou* et al., 2006). It was also during this time she chose to work on the immune system and showed that histone acetylation is important in maintaining haematopoietic stem cells (Loizou et al., 2009). Joanna wanted to build on the experience she gained from working on the immune system but now aimed to understand the role of genomic instability leading to cancers of the blood, hence she joined the London Research Institute (LRI) at Cancer Research UK (CR-UK), where she continued to work on DNA repair and its importance in developing a functional immune system, as well as suppressing leukemia and lymphoma (Loizou et al., 2011). At CeMM, Joanna's group investigates the signalling cascade that occurs in cells as a result of DNA damage in order to maintain genomic stability and suppress tumorigenesis. Physiological DNA breaks are generated during the maturation of immune T and B cells in order to allow for VDJ recombination, class switch recombination or somatic hypermutation to occur. Joanna is interested in understanding the pathways responsible for the repair of such breaks that allow for the generation of an immune response and the suppression of leukemias.

Relevant/Important Publications

The protein kinase CK2 facilitates repair of chromosomal DNA single-strand breaks. Loizou JI, El-Khamisy SF, Zlatanou A, Moore DJ, Chan DW, Qin J, Sarno S, Meggio F, Pinna LA, Caldecott KW. *Cell.* 2004 Apr 2;117(1):17-28.

Histone acetyltransferase cofactor Trrap is essential for maintaining the hematopoietic stem/progenitor cell pool. Loizou JI, Oser G, Shukla V, Sawan C, Murr R, Wang ZQ, Trumpp A, Herceg Z. *J Immunol.* 2009 Nov 15;183(10):6422-31.

ATMIN is required for maintenance of genomic stability and suppression of B cell lymphoma. Loizou JI, Sancho R, Kanu N, Bolland DJ, Yang F, Rada C, Corcoran AE, Behrens A. *Cancer Cell.* 2011 May 17;19(5):587-600.

Thijn Brummelkamp

Genetics of Cancer and Infectious Diseases

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MS (Biology), **Free University of Amsterdam** (NL)

+ Dutch nationality
+ Joined CeMM in January 2011

Main Research Interests
+ Cancer research
+ Infectious disease
+ Drug action

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Thijn Brummelkamp uses genetic approaches to identify genes that play a role in human disease. His primary interests are cancer research, infectious disease and drug action. Brummelkamp has developed technologies to accelerate genetic analysis of cultured mammalian cells. A 'stable RNA interference' process, which he and his colleagues first described, is now widely used to manipulate and study gene function in mammalian cells. Brummelkamp has used stable RNA interference to inhibit thousands of human genes, in order to find specific genes that play a role in human disease. More recently he has developed an approach for haploid genetic screens in human cells using insertional mutagenesis. He has used this approach to identify host factors used by a variety of pathogens. He received his MS in biology from the Free University, Amsterdam, in 1998. He did his graduate research at The Netherlands Cancer Institute in the laboratory of Rene Bernards and received his PhD cum laude from Utrecht University in 2003. He was appointed as a Whitehead Fellow in 2004 to initiate his independent research program at the Whitehead Institute for Biomedical Research in Cambridge, USA. In 2011 his laboratory moved to the Netherlands Cancer Institute and he became an Adjunct PI at CeMM. For his studies he received the Antoni van Leeuwenhoek Award (2003), The Annual NVBMB Award (2004, Dutch Association for Biochemistry and Molecular Biology), he was chosen as one of the world's top 35 Young Innovators by MIT's technology Review magazine (2005) and received the Kimmel Scholar Award (2006).

Relevant/Important Publications

A system for stable expression of short interfering RNAs in mammalian cells. Brummelkamp TR, Bernards R, Agami R. *Science.* 2002 Apr 19; 296(5567):550-3.

YAP1 increases organ size and expands undifferentiated progenitor cells. Camargo FD, Gokhale S, Johnnidis JB, Fu D, Bell GW, Jaenisch R, Brummelkamp TR. *Curr Biol.* 2007 Dec 4;17(23):2054-60. Epub 2007 Nov 1. *Erratum in: Curr Biol.* 2007 Dec 4;17(23):2094.

Haploid genetic screens in human cells identify host factors used by pathogens. Carette JE, Guimaraes CP, Varadarajan M, Park AS, Wuethrich I, Godarova A, Kotecki M, Cochran BH, Spooner E, Ploegh HL, Brummelkamp TR. *Science.* 2009 Nov 27;326(5957):1231-5.

Ebola virus entry requires the cholesterol transporter Niemann-Pick C1. Carette JE, Raaben M, Wong AC, Herbert AS, Obernosterer G, Mulherkar N, Kuehne AI, Kranzusch PJ, Griffin AM, Ruthel G, Dal Cin P, Dye JM, Whelan SP, Chandran K, Brummelkamp TR. *Nature.* 2011 Aug 24; 477(7364):340-3.

Keiryn L. Bennett

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PhD (Chemistry),
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University of Southern Denmark (DK)

+ Australian national
+ Joined CeMM in October 2004
+ Group of 8 people

Main Research Interests
+ Proteomics of protein-protein interactions including chemical crosslinking; and protein-drug interactions
+ Phospho- and quantitative proteomics
+ Proteomic applications with an emphasis on medical/clinical field
+ Liquid chromatography mass spectrometry (technical advancement and applications)
+ Integration of mass spectrometry with biology and bioinformatics

Keiryn Bennett, PhD, obtained her Bachelor of Science with First Class Honours from the University of Tasmania; and her PhD in protein mass spectrometry (under the supervision of Professor Margaret Sheil) from the University of Wollongong, Australia. She spent 2.5 years as a post-doctoral fellow in the laboratory of one of the forefathers of modern-day protein mass spectrometry, Professor Peter Roepstorff, (Odense, Denmark). This was followed by 4 years under the supervision of Matthias Mann at MDS Proteomics (Odense, Denmark). Keiryn has more than 15 years of experience including in the field of protein mass spectrometry and proteomics, with more than 4 years managing a high-throughput industrial proteomic laboratory. She joined the laboratory of Giulio Superti-Furga in 2004 and established the mass spectrometry research group at CeMM. Since 2009, Keiryn has an independent group leader position and currently the laboratory consists of 8 people. Maintaining close ties with the laboratories of Giulio Superti-Furga, Jacques Colinge and several national and international collaborators, the mass spectrometry research group is involved in a number of interdisciplinary fields.

Relevant/Important Publications

Systematic identification of protein complexes in Saccharomyces cerevisiae by mass spectrometry. Ho Y, et al. *Nature.* 2002 Jan 10;415(6868):180-3.

An efficient tandem affinity purification procedure for interaction proteomics in mammalian cells. Bürckstümmer T, Bennett KL, Preradovic A, Schütze G, Hantschel O, Superti-Furga G, Bauch A. *Nat Methods.* 2006 Dec;3(12):1013-9.

Acid elution and one-dimensional shotgun analysis on an Orbitrap mass spectrometer: an application to drug affinity chromatography. Fernbach NV, Planyavsky M, Müller A, Breitwieser FP, Colinge J, Rix U, Bennett KL. *J Proteome Res.* 2009 Oct;8(10):4753-65.

Using iTRAQ combined with tandem affinity purification to enhance low-abundance proteins associated with somatically mutated EGFR core complexes in lung cancer. Haura EB, Müller A, Breitwieser FP, Li J, Grebien F, Colinge J, Bennett KL. *J Proteome Res.* 2011 Jan 7;10(1):182-90.

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, et al. *J Proteomics.* 2011 Feb 1;74(2):151-66.

Jacques Colinge

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Serono Pharmaceutical Research Institute (CH)
Group Leader,
GeneProt Inc. (CH)
FH-Professor,
University of Applied Science Upper Austria (A)
Habilitation (Adjunct Professor),
Technical University Graz (A)

+ 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

A computational approach to analyze the mechanism of action of the kinase inhibitor bafetinib. Burkard TR, Rix U, Breitwieser FP, Superti-Furga G, Colinge J. *PLoS Comput Biol.* 2010 Nov 18;6(11):e1001001.

Using iTRAQ combined with tandem affinity purification to enhance low-abundance proteins associated with somatically mutated EGFR core complexes in lung cancer. Haura EB, Müller A, Breitwieser FP, Li J, Grebien F, Colinge J, Bennett KL. *J Proteome Res.* 2011 Jan 7;10(1):182-90.

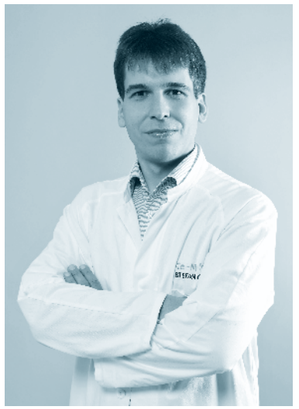
Initial characterization of the human central proteome. Burkard TR, Planyavsky M, Kaupe I, Breitwieser FP, Bürckstümmer T, Bennett KL, Superti-Furga G, Colinge J. *BMC Syst Biol.* 2011 Jan 26;5:17.

General statistical modeling of data from protein relative expression isobaric tags. Breitwieser FP, Müller A, Dayon L, Köcher T, Hainard A, Pichler P, Schmidt-Erfurth U, Superti-Furga G, Sanchez JC, Mechtler K, Bennett KL, Colinge J. *J Proteome Res.* 2011 Jun 3;10(6):2758-66.

Systems biology analysis of protein-drug interactions. Colinge J*, Rix U, Bennett KL, Superti-Furga G. *Proteomics Clin Appl.* 2011 Dec 27.

* corresponding author

Stefan Kubicek



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Broad Institute of Harvard and MIT (USA)

+ Austrian nationality
+ Joined CeMM in August 2010
+ Group of 4 people

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.

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, Schreiber SL. *Proc Natl Acad Sci U S A.* 2010 Aug 24;107(34):15099-104.

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, Rea S, Mechtler K, Kowalski JA, Homon CA, Kelly TA, Jenuwein T. *Mol Cell.* 2007 Feb 9; 25(3):473-81.

A selective inhibitor and probe of the cellular functions of Jumonji C domain-containing histone demethylases. Luo X, Liu Y, Kubicek S, Myllyharju J, Tumber A, Ng S, Che KH, Podoll J, Heightman TD, Oppermann U, Schreiber SL, Wang X. *J Am Chem Soc.* 2011 Jun 22;133(24):9451-6.

* equal contribution

Technology Transfer & Intellectual Property Management

During the last few years there has been an increased focus on technology transfer (TT) and intellectual property (IP) management at CeMM. This department promotes the transfer of external technologies for internal use, as well as securing inventions and transfer technologies developed at CeMM for use by other institutions and commercial partners.

As a first and important measure, CeMM researchers are given basic training on intellectual property and patenting. This is offered as part of the PhD program and as an in-depth course, held in co-operation with established patent law firms.

When an interesting invention or finding is made at CeMM, the technology transfer office offers advice and supports the process of capture and protection, including evaluating the commercial viability of the invention. To provide these services at the highest level, IP and TT work closely together with well-established patent and law firms. A commercialization strategy is outlined, which may involve technology licensing to a for profit organization. In certain instances, IP and TT will support the formation and technology transfer to a spin-out company.

During 2011: Three patent applications were prepared and filed. The preparations for one spin-out company were made, which is set to be fully established in early 2012.

PhD Program

The CeMM PhD program is 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.

PhD Program – CeMMtastic!

The 2011 Selection

The selection for the 4th CeMM PhD Program identified 10 female and 2 male students out of 30 invited students and around 400 applicants. The 12 highly motivated new students come from 6 different countries and have a keen interest in genomics and medicine:

Anannya Bhattacharya, India
Andreas Bergthaler

Clara Jana Busch, Germany
Christoph Binder

Ciara Cleary, Ireland
Robert Kralovics

Marielle Klein, Germany
Giulio Superti-Furga

Jin Li, China
Stefan Kubicek

Barbara Maier, Austria
Sylvia Knapp

Barbara Mair, Austria
Sebastian Nijman

Nina Prengemann, Germany
Kaan Boztug

Andreas Schönegger, Austria
Christoph Bock

Nicole Them, Austria
Robert Kralovics

Dijana Vitko, Croatia
Keiryn Bennett

Zhewen Zhu, China
Joanna Loizou

This may only be the fourth year that the CeMM PhD program is running, however the course is proving very popular as seen from the number of applications – over 400 submitted for the 2011 entry. Competition for places was tough and after the first round in the selection process, thirty potential students were invited to Vienna in May, for an intensive two day PhD hearing. The candidates introduced themselves and gave short presentations about their research interests and after a tour through the labs, had several interviews with the PIs. The candidates were also given the opportunity to find out more about the individual research projects of the PIs and they met current CeMM PhD students who provided the low-down on what life was really like at the institute. Although the selection process was extremely difficult given the high calibre of students, after arduous discussions the PIs selected the twelve best candidates whom they hope will engage in a promising career in science. What makes these young researchers so ambitious to come to CeMM?

The CeMM PhD program incorporates basic lectures and soft skill courses from the Medical University of Vienna, with exceptional state-of-the-art equipped practical training and mentoring provided at CeMM. Students have a solid scientific foundation upon which their ideas and creativity can grow, enabling independent minds to tackle important questions in molecular medicine.

Administrative support helps students to settle into their new demanding environment. For the first six months, first-year PhD students are accommodated in convenient one-room apartments, which are located close to the institute*. In October there is a full-program which, as well as enabling new students to get to know their peers, also prepares them for conducting research at CeMM. Orientation courses inform students of the practical things such as how to survive in the lab, how to keep a good lab notebook and how to successfully navigate University bureaucracy. Students also participate in short-term projects in different research groups; this enhances the strong link between CeMM groups and gives rise to future collaborations.

There are currently 38 PhD students (22 females and 16 males) from 16 different nationalities at CeMM; all are eager to unlock life's fundamental mysteries at the molecular and cellular levels. In 2011 the first students graduated from CeMM; they are reaping the benefits of a first-class research education and are equipped with the skills and knowledge needed to conduct intellectually challenging research which is clinically relevant – a must for 21st century medical research.

* We are thankful to the Medical University of Vienna/Vienna General Hospital.

Lecture Series

CeMM understands its role not only as a research institute but also as a cultural center for biomedical issues of relevance to the society. The CeMM Lectures series are important events in the year and a source of inspiration to many.

5th CeMM Karl Landsteiner Lecture

The annual CeMM Karl Landsteiner Lecture is held to honour Karl Landsteiner, the Austrian biologist and physician who is widely recognized as the father of transfusion medicine. The lecture is aimed at the wider scientific community as well as the general public and is presented by international leaders in Biology whose discoveries are shaping the scientific landscape. This year, Prof. Dr. George Q. Daley, a world-leader in the field of stem cells, haematology and oncology, was the guest speaker of the 5th CeMM Karl Landsteiner Lecture. George Daley is Associate Professor of Biological Chemistry and Pediatrics at Harvard Medical School in Boston, USA. He studies stem cells of the blood to define the molecular basis of human leukemia and to gain insights into normal blood development. He has won several important awards. In 2003, his germ cell research was cited as a "Top Ten" breakthrough by Science magazine. The CeMM Karl Landsteiner lecture took place on May 2nd, in the festive hall of the Austrian Academy of Sciences. Attended by around 300 scientists and interested lay people, the seminar was entitled: "Stem cells and regenerative medicine: breakthroughs and battles".

Before the start of the talk there was an impressive and inspiring performance of Franz Liszt's Hungarian Rhapsody no. 13 in A-minor by Prof. Jan G. Jiracek von Arnim. The introductory speech was given by Giulio Superti-Furga, and commemorated Karl Landsteiner as the person who embodies better than anybody what molecular medicine is. He made special mention of David Baltimore, George Daley's PhD supervisor, as a person who has been extremely influential to CeMM and its principles. Giulio reminded the audience that George Daley made the first ever demonstration of a human oncogene causing cancer in mice and was the inaugural winner of the NIH Director's Pioneer Award for highly innovative research.

Importance of Stem Cell Research

George Daley began by saying that the festive hall of the Austrian Academy of Sciences was the most impressive setting he has presented his science in and that he was very happy to be invited by CeMM, a vibrant institute performing fabulous science. He stated that he is a proponent of respecting embryos and that he agrees to use fertilized eggs for research only after failed in vitro fertilization that would otherwise be discarded. He stressed the importance of stem cell research, explaining that for some diseases animal models do not suffice, giving the example of Fanconi's anaemia, a genetic disease of autosomal recessive type for which animal models do not phenocopy the human disease, which necessitates the use of human stem cells.

The Problems of Rushed Commercialization

George Daley wanted to raise awareness in the audience concerning the dangers of a rush to commercialization of early stem cell research. There have been many cases of companies magnifying the benefits and trivializing the risks of stem cell treatment. He gave examples from company advertisements that used misleading information concerning the benefits of stem cell technologies with the sole aim of making profit. In order to minimize the risks, the International Society for Stem Cell Research is developing guidelines for the proper conduct of stem cell research.

A New Cautious Approach

Moving on to research practices, George said that he is a strong advocate of a slow, step-wise and prudent approach to stem cell research. He feels that the participation of the public in the dialogue on stem cell research is imperative. When asked about the tumorigenicity of stem cells, which is a current significant concern, he advises society to be patient. His view is that we will see the first cell replacement therapy available soon, but this will most likely not occur in the anatomically complex tissues like heart, brain or lung.

George Daley posing with Giulio Superti-Furga after being given the commemorative plate for the Karl Landsteiner Lecture.

Special Lecture
Greg Simon

The biannual Special Lecture series are intended to publicize the key issues surrounding drug development and healthcare, with a focus on drug safety and societal impact. It is aimed at both the scientific community and interested layman, and is awarded to world leaders who can expand our views on these topics.

Greg Simon, Senior Vice President for Patient Engagement at Pfizer presented a Special lecture on May 24. Greg has been described as one of a handful of people keeping the wheels of biomedical science turning. He was the Founding President of the non-profit organization *FasterCures*, which develops strategies to accelerate new medicines into the clinic. During his lecture, entitled "How Patient Engagement can Improve Health, Happiness and Productivity for Patients and Companies", he explained to the packed lecture hall how he thinks we can cut the 15+ years and billions of dollars it currently takes to cure a disease.

The Problem of Culture

Greg Simon's lecture began blaming culture, not science, for preventing faster and cheaper cures for disease. He explained that science carries the illusion of objectivity, but is actually influenced by multiple biases from the people working in it. For example, the progression of biomedical science is influenced by views from both scientists and governments. A critical omission however has been the patients' views, but it is their perspective, Simon argued, that is vital, particularly for the future of drug development. He stressed the need to talk to patients and find out what they want in terms of treatment for their particular disease, and not just offer them what the scientists and drug companies have developed, which is based on their own biases and perspectives.

Ideas for Research Funding

Having extensive experience as a Policy Advisor for the US government, as CEO of FasterCures, which is an "action" tank dedicated to shortening the time required to find cures, improved treatments and effective prevention of many destructive diseases, and now as patient engagement senior vice president at Pfizer, Inc., he is suggesting a new way to fund medical research. He reminded the audience that most Nobel Prize scientists carried out their acclaimed research whilst below the age of forty. However, under current funding schemes, it is very difficult for young researchers to attract large grants. A system where projects are funded on the basis of collaboration, i.e. young scientists working together with established researchers, could prove to be more efficient.

Finding Out What the Patient Wants

Simon then talked about his current work at Pfizer; engaging patients in the drug development pipeline. He has been finding out what the patient wants from participating in clinical trials, and has been offering them feedback on the results. It was interesting to learn that although the scientists and pharmaceutical companies formally decide whether a drug trial has been successful, the people in the trials will often disagree. Failure to detect a clear 'medical' effect will halt clinical trials, often to the great dismay of patients. It is exactly this difficult measure of the impact of a drug on the patient's quality of life that necessitates enhanced involvement of patients in the process. He went on to explain that people are usually not followed-up after the end of a clinical trial, leaving a huge potential unexploited since many long-term effects of drugs remain hidden. The companies need to acknowledge that the patients are the real customers of a drug and not the insurance companies. He also pointed out the importance of making sure drugs are available to the people that need them, as well as ensuring patients properly take drugs prescribed to them.

Change in the relationship between pharmaceutical companies and individual disease societies was highlighted as being a requirement for moving forward. These societies can offer valuable patient viewpoints to a forward-thinking company, as well as financial capital and potential participants for selected trials. This would help to ensure the patients' perspective rightfully becomes an integral part of the drug development process.

Special Lecture
Bruce Ames

Bruce Ames was hosted on October 24, and he presented a special lecture entitled "A Diet for Health and Longevity: How do we get there?". Bruce Ames has been doing innovative multidisciplinary science for 60 years and has developed the famous "Ames test" to screen for the mutagenic potential of a drug. His invention has undoubtedly saved hundreds of lives and has led to faster and safer drug development. A major focus in the last 15 years has been on understanding the mechanisms involved in linking micronutrient deficiencies, aging and diseases of aging. He is currently a senior scientist at the Children's Hospital Oakland Research Institute, in Berkeley, California (US).

Bruce Ames explained in his talk the importance of epidemiology in health research through providing insightful associations between diseases and underlying causes. He notes however that both scientists and policy makers should be careful when they interpret epidemiological correlations, as they only rarely establish causality. An example he used had to do with a healthy diet and its potential correlations with a healthy life. He argued that people that do healthy things tend to do many healthy things, and it is very difficult to discriminate which of these healthy behaviours are directly responsible for disease progression and overall quality of life.

Prioritizing Micronutrients

Ames emphasized that an organism is in constant need of a diverse range of micronutrients. These micronutrients, including vitamins, small minerals and metabolites, are essential for the proper physiological functioning of the organism, but the effects of their deficiency are not easy to investigate. He proposed that there is a continual competition between two essential functions of the organism: day-to-day survival (involving processes such as wound healing, reproduction, any other house-keeping functions), and long term well-being (promoted by for example tissue regeneration and oxidative stress). He postulated that at any time the available pool of micronutrients has to be allocated to the different proteins and tissues that would perform one of these two essential functions of the body. And when there is a nutrient deficiency, the body would allocate the scarce micronutrients to the day-to-day survival functions, which would potentially increase the probability of developing long-term mostly degenerative diseases, namely diabetes, cancer and neurodegenerative disorders.

The Dangers of a Limited Diet

He presented some results concerning micronutrient deficiencies in the US, where 95% of African Americans have a vitamin D deficiency, and approximately 56% of the whole population are deficient in magnesium. He advocated food supplements particularly for groups at high risk of deficiencies, but he warned that caution is needed given the importance of absolute amounts and the combinations of certain micronutrients. For example, iron can cause increased oxidative damage when present at levels both above and below the recommended concentration. In addition, there is evidence that a balance in the levels of calcium and magnesium, as well as the levels of iron, copper and zinc, are required for proper bodily functions. "You are what you eat" seemed to be a strong underlying message from the talk, and it is becoming clear that also the progression of diseases is closely linked with nutrition. Ames aptly ended his insightful lecture by emphasizing to all of us the value of a well balanced diet.

Greg C. Simon (top) and Bruce Ames (bottom) presenting the Special Lectures.

Overview
CeMMinar/Impromptu Series

12.01.2011
Impromptu
Giorgio Colombo
Istituto di Chimica del Riconoscimento Molecolare, Milano
"Investigating protein functions and interactions through computational biology"

17.01.2011
CeMMinar
René Bernards
Netherlands Cancer Institute, Amsterdam
"Uncovering mechanisms of cancer drug resistance through functional genetic screens"

24.01.2011
CeMMinar
Rüdiger Klein
Max-Planck-Institute of Neurobiology, Martinsried, Germany
"Molecular mechanisms regulating cell-cell communication by repulsion"

08.02.2011
Impromptu
Uttam Surana
Institute of Molecular and Cell Biology (A*STAR: Agency for Science, Technology And Research)
"Coping with the wounded chromosomes: Arrest, Recovery and Adaptation"

07.03.2011
CeMMinar
Blagoy Blagoev
Department of Biochemistry and Molecular Biology, University of Southern Denmark
"Cell signaling and stem cell differentiation: a view from system-wide quantitative proteomics"

14.03.2011
CeMMinar
Bernhard Küster
Chair of Proteomics and Bioanalytics, Technische Universität München and Center for Integrated Protein Sciences Munich (CIPSM)
"Quantitative chemical proteomics reveals new drug targets in head and neck cancer"

21.03.2011
CeMMinar
Bernhard Horsthemke
University of Duisburg-Essen and Institute of Human Genetics at the University Hospital Essen, Germany
"Species-specific differences in genomic imprinting"

28.03.2011
CeMMinar
Adrian Hill
University of Oxford and Jenner Institute
"Targeting bacterial killers: humans genetics and vaccines"

27.04.2011
Impromptu
Tassos Perrakis
The Netherlands Cancer Institute, Molecular Carcinogenesis
"Targeting a phospholipase for inflammation, cancer and fibrotic disease: the story of Autotaxin"

03.05.2011
Impromptu
William Kaiser
Emory University
"RIP1-RIP3 mediate the embryonic lethality of caspase-8-deficient mice while DAI-RIP3 drive programmed necrosis induced by viral infection"

13.05.2011
Impromptu
Manuele Rebsamen
University of Lausanne
"Signalling and regulation of innate viral recognition receptors"

16.05.2011
CeMMinar
Bhushan Nagar
Department of Biochemistry, McGill University, Montreal, Canada
"Structural basis for 5' nucleotide recognition by Argonaute proteins"

06.06.2011
CeMMinar
Emmanouil Dermitzakis
Department of Genetic Medicine and Development University of Geneva Medical School
"Cellular genomics in human populations"

08.06.2011
Impromptu
Thomas Frogne
Hagedorn Research Institute, Copenhagen
"Nanoscale isoelectric focusing identifies post-translational modifications on the homeodomain transcription factor Pdx1"

19.07.2011
Impromptu
Dietrich Rebholz-Schuhmann
Research Group Leader EBI European Bioinformatics Institute, Cambridge
"Semantic Interoperability between literature and data resources: from genes to diseases"

20.07.2011
Impromptu
Johannes Zuber
Group Leader, Institute of Molecular Pathology, Vienna Biocenter
"A chromatin focused RNAi screen using improved shRNAmir technology identifies Brd4 as a drug target in AML"

22.08.2011
Impromptu
Menno Creyghton
Epigenetics and stem cell development Hubrecht Institute, Utrecht
"Comparative epigenomic profiling of distal enhancers during lineage commitment"

23.08.2011
Impromptu
Anne Dell
Imperial College London
"Glycomics and glycoproteomics: windows to glycan function"

05.09.2011
CeMMinar
Roland Schüle
Department of Urology and Head of Research, Center for Clinical Research, University of Freiburg Medical Center
"In vivo functions of the histone demethylase LSD1"

14.09.2011
Impromptu
Philipp Kügler
Johann Radon Institute for Computational and Applied Mathematics (RICAM), Vienna
"Applications of sparsity enforcing regularization in systems biology"

19.09.2011
CeMMinar
Alain Fischer
Université Paris Descartes-Hopital, Necker-Inserm
"Human genetic defects in T cells: some causes and consequences"

20.09.2011
Impromptu
Rasmus Prætorius Clausen
Department of Medicinal Chemistry, Faculty of Pharmaceutical Sciences, University of Copenhagen, Denmark
"Development of chemical probes for Histone Demethylases"

26.09.2011
CeMMinar
William Vainchenker
INSERM U1009
"Hématopoïèse normale et pathologique", Institut Gustave Roussy, Villejuif France
"Myeloproliferative neoplasm from JAK2 to TET2"

03.10.2011
CeMMinar
Zhao-Qi Wang
Leibniz Institute for Age Research – Fritz Lipmann Institute, Jena
"MCPH1 regulates cell division mode of neuroprogenitors via the Chk1-Cdc25-Cdk1 pathway"

10.10.2011
CeMMinar
Ziad Mallat
Division of Cardiovascular Medicine, University of Cambridge
"Immuno-modulatory pathways in atherosclerosis"

11.10.2011
Impromptu
Fabian Hauck
INSERM U768
"Laboratoire du Développement Normal et Pathologique du Système Immunitaire", Hôpital Necker Enfants-Malades, Paris
"Primary T cell immunodeficiency with immunodysregulation caused by autosomal recessive LCK Deficiency"

02.11.2011
Impromptu
Alexander Stark
The Research Institute of Molecular Pathology (IMP), Vienna
"Regulatory genomics – decoding Drosophila regulatory sequences"

07.11.2011
CeMMinar
Stylianos Antonarakis
Department of Genetic Medicine and Development, University of Geneva Medical School and University Hospitals of Geneva
"Aneuploidies and chromatin dysregulation"

10.11.2011
Impromptu
Jarrod Marto
Department of Cancer Biology, Dana-Farber Cancer Institute Biological Chemistry and Molecular Pharmacology, Harvard Medical School
"The role of high performance fractionation in proteomics"

14.11.2011
CeMMinar
Michael Washburn
Stowers Institute for Medical Research, Kansas City, Missouri
"Deletion network analysis for capturing protein complex architecture and elucidating protein function"

21.11.2011
CeMMinar
Günter Weiss
Division for Clinical Immunology and Infectious Diseases, Department of Internal Medicine, Medical University of Innsbruck
"Regulatory networks between iron homeostasis, immunity and infection"

05.12.2011
CeMMinar
Jan-Michael Peters
The Research Institute of Molecular Pathology (IMP), Vienna
"How cohesin helps to organize and segregate the mammalian genome"

07.12.2011
Impromptu
Admar Verschoor
Institute for medical Microbiology, Immunology and Hygiene, Technical University Munich
"Delivering the goods: roles of the complement system in antigen trafficking and capture"

12.12.2011
CeMMinar
Luigi Naldini
Division of Regenerative Medicine, Stem Cells and Gene Therapy San Raffaele del Monte Tabor Foundation, Milano
"Recent advances in hematopoietic stem cell gene therapy: from microRNA regulation to targeted gene transfer"

19.12.2011
CeMMinar
Josef Penninger
Institute of Molecular Biotechnology (IMBA), Vienna
"ACE 2-from heart function and SARS infections to amino acid transport"

"As the famous roman playwright Terence let one of his characters say: 'Nihil tam difficile est, quin quaerendo investigari possit.' Nothing is so difficult that it cannot be found out by seeking. Surely, finding out the mechanistic causes of disease and fighting it in a way that best suits the individual patient is not only a noble cause, but also an extremely difficult endeavour. CeMM was founded to provide the scientific rationale for a more personalized, more precise medicine and propose mechanism-based therapeutic innovations. From the early success and the impressions during my visits it is already clear that CeMM can fulfil this ambitious and socially-relevant mandate with bravery and passion. For sure we are fully committed to supporting this young institute of very high potential in the following important years."

Prof. Dr. Karlheinz Töchterle
Austria's Federal Minister of Science and Research

“I think there is a link between the science, art and society vocation of CeMM and its success. I’ve learned to know this leading Viennese institute as a mainspring for new concepts, and out-of-the-box thinking. With this mindset, the excellent scientific expertise and the location in the middle of the General Hospital campus, CeMM is a destined hotbed for the personalized medicine of the future a think-tank for new, more holistic type of approaches to understand the nature of humankind.”

Dr. Andreas Mailath-Pokorny
City Councilor for Culture and Science, Vienna

Conferences

Apart from providing ideal forums for communicating all recent scientific developments to fellow researchers, conferences provide a fertile ground for conceiving new ideas. CeMM scientists are active in the organization of international conferences, and 2011 saw a number of them organized on CeMM premises. Support was secured from the Federal Ministry for Science and Research (BMWF), the Austrian Research Promotion Agency (FFG), the European Molecular Biology Organization (EMBO) as well as the Federation of European Biochemical Societies (FEBS).

Austrodrugs Conference

In March 2011, more than 80 researchers are interested in using and developing small molecules as biological probes and potential new drugs gathered at CeMM from all over Austria for the first Austrodrugs meeting. The one day conference was organized by Stefan Kubicek and Giulio Superti-Furga, along with Christina Glöckel from the Medical University of Vienna. It kicked-off with a keynote lecture by Prof. Christian Noe from the University of Vienna, who presented both his own research and the Innovative Medicines Initiative of the European Union that he is guiding as chairman of the scientific committee.

The meeting was organized akin to "speed dating", consisting of short 10-minute presentations from seven industrial and eleven academic chemical biologists. It ended with an evening reception that enabled intense interaction and laid the foundation for several collaborations. Based on the success of this first Austrodrugs meeting, a continuation is planned for 2012, when CeMM will additionally host the European Chemical Biology Symposium.

EMBO Workshop: Synthetic Lethality – From Yeast to Man

In June, Sebastian Nijman organized a conference together with Louis Staudt (NIH, USA) and Guri Giaever (University of Toronto, Canada) on synthetic lethality. In model organisms such as yeast synthetic lethality has already been extensively explored, but in biomedicine it has only recently attracted attention as an approach that can reveal novel opportunites for treating cancer. The aim was to bring together for the first time scientists working on synthetic lethality in different contexts and organisms. Thus, world leaders working in yeast, worms, fruit flies, cancer and bioinformatics presented their latest work. In particular, the two keynote lectures by Charles Boone (Canada) on yeast genetics and Alan Ashworth (UK) on the application of synthetic lethality in the clinic were truly outstanding and inspiring.

The relatively small size of the conference allowed ample interactions between speakers, post-docs and students, which is often difficult at large meetings, and the poster session was well attended, with several social events further contributing to the collaborative and open atmosphere. Besides a grant from EMBO, the conference was made possible by sponsoring from CeMM, Luminex and Boehringer Ingelheim.

FEBS Workshop: Protein Modules and Networks in Health and Disease

The FEBS Workshop on Protein Modules and Networks in Health and Disease took place in Seefeld in Tirol, Austria, September 14–18, 2011. Organized by Anne-Claude Gavin (EMBL, Germany), Marius Sudol (Weis Center for Research in Pennsylvania, USA) and Giulio Superti-Furga (CeMM) and supported by FEBS, it follows a series of successful FEBS workshops in Seefeld that started in 2001 and has continued unabated with renewed excitement. The workshop fills a niche as, to date, there is no comparable conference in or outside of Europe that deals with modular protein domains as the basic units of the canonical code of cellular signalling.

A wide range of topics was covered in the conference and the opening plenary lecture was given by Peer Bork (EMBL, Germany), one of the pioneers of bioinformatics and modular protein domains. He talked about function prediction at different spatial scales and reviewed the past, present and the future of research on modular domains from the perspective of a single domain, single genome and single interactome, andthrough the analysis of mega-genomes. The program extended to new technologies, and human diseases caused by mutated domains were discussed in detail. The conference was closed with a talk by Mike Yaffe (MIT, USA), an avid participant of these workshops who has contributed at many levels, as a lecturer and active member of the Protein Modules Consortium, a poster judge and a valuable adviser to young researchers. The conference received exceptional evaluations from the participants and more than twenty of the speakers have agreed to contribute to a special issue of FEBS letters that will appear in the spring. The Board of the Protein Modules Consortium also had a meeting during the conference taking key decisions about the future of the consortium as well as laying the framework for the next Seefeld meeting to be held in 2013, which Mike Yaffe and Wendell Lim (UCSF, USA) will play a key role in organizing.

9th Austrian Proteomic Research Symposium: Special Focus on Clinical Proteomics

On November 8 and 9, 2011, the 9th Austrian Proteomic Research Symposium was jointly held at CeMM and the Center for Translational Research, Medical University of Vienna (MUV). The symposium had a special focus on clinical applications and was co-organised by Keiryn Bennett from CeMM, and Goran Mitulovic, Klaus Kratochwill and Rudolf Oehler from the MUV. The two day event consisted of eight scientific sessions, two poster sessions and an industrial exhibition from fourteen sponsors. Topics of the symposium covered broad-ranging aspects of clinical proteomic applications including leukemia, drug resistance in melanoma cells, drug target profiling, and ageing.

The international keynote speakers were Jarrod Marto (Dana Farber Cancer Center, Boston, USA), and Harald Mischak (University of Glasgow, UK). National keynote speakers were Lukas Huber (Medical University of Innsbruck), Christian Huber (University of Salzburg), Ruth Birner-Grünberger (Medical University of Graz), Guenter Allmaier (Technical University of Vienna), Ingrid Miller (University of Veterinary Medicine) and Giulio Superti-Furga (CeMM). A total of 182 people registered from Europe and the USA. During the meeting, the new members of the Austrian Proteomic Association board were elected. The 10th Austrian Proteomic Research Symposium is scheduled for September 2012 and will be held in Graz.

With 165 participants, the 9th Austrian Proteomic Research Symposium was a big success. There was a special focus on clinical proteomics, a field CeMM is investing heavily on.

The Grand Opening – or: How CeMM Celebrated it

On March 16, 2011, CeMM proudly held the inauguration of its new purpose-built building, at the heart of Vienna, right next to the General Hospital. Touching and thought-provoking opening addresses by Federal Minister Beatrix Karl, City Councilman Andreas Mailath-Pokorny and the President of the Austrian Academy of Sciences Helmut Denk, made the ceremony a particularly memorable event.

Had the 140 ceremony guests awaited a stiff festivity, they would have definitely been disappointed. Amongst them were Wolfgang Schütz, Rector of the Medical University, Reinhard Krepler, Medical Director of AKH, Carl-Henrik Heldin, director of the Ludwig Institute for Cancer Research in Uppsala and member of the CeMM Scientific Advisory Board as well as Alexander van der Bellen, member of the National Council and Vienna's special commissioner for University matters. Everything was going well with the formal welcome and the introductory speeches, until an uninvited guest rushed in the room causing confusion: "Molecular medicine? You are talking about molecular medicine? Let me tell you all about molecular medicine".

He interrupted the Scientific Director's speech and caused some sort of confusion to the audience. It took a while before the audience realized that the intruder was in fact the opera singer Lars Woldt. His surprise appearance in a lab coat as quack doctor Dulcamara (from *L'elisir d'amore* by Gaetano Donizetti) bewitched Beatrix Karl and the audience. Other highlights of the evening were a student's "bus choir", having originated from an improvised song contest at an institute-wide outing, and a big band, "the CeMMsons", consisting of students and postdocs intonating the Simsons' title theme and dedicating it to the amusement of the audience.

All CeMM colleagues followed the grand opening via video transmission in a party area on the ground floor. After a cocktail reception at the rooftop rooms, overlooking Vienna's skyline, most guests decided to join the party downstairs. An outstanding live band inflamed the party atmosphere. A birthday cake was dedicated to the new building as well as to all CeMM collaborators and supporters.

The opening ceremony of the new building had it all: from talks by politicians and researchers and the traditional commemorative photographs, to a surprise visit by an opera singer and performances by a spontaneously formed choir and music band of students and postdocs.

The party that followed the ceremony was impressive. A large cake, in blue of course – CeMM's favorite color, being cut by Ernst M. Kopper, the architect that designed CeMM. The event will be remembered for years to come!







Celebration of CeMM's first Nature Article

A rare event took place on October 18, 2011 at CeMM. Federal Minister of Science and Research, Professor Karlheinz Töchterle, visited the institute to celebrate the first ever Nature Article of CeMM in collaboration with the Medical University of Vienna (Weismann et al, Nature 2011). In this landmark study, the research group led by Christoph J. Binder identified a pathogenic mechanism of age-related macular degeneration (AMD). AMD is the most common cause of blindness in Western societies, and through this study it was found that complement factor H, a very abundant protein of the innate immune system plays a crucial role in the development of the disease. An article in Nature is one of the highest recognitions of the quality of scientific research, and CeMM feels proud to have achieved this at the same year of moving to the new building, setting the standards for the discoveries yet to come. Apart from Minister Töchterle, Professor Wolfgang Schütz, rector of the Medical University of Vienna, and Professor Oswald Wagner, vice-rector of Research were also present as well as many other friends and collaboration partners.




Minister Töchterle and Rector Schütz, congratulating the CeMM scientists that led the landmark study.

Giulio Superti-Furga is “Austrian of the Year 2011”

“I don’t stand the ghost of a chance”, was the first reaction of Giulio Superti-Furga to the request of the newspaper “Die Presse”. They asked for permission to nominate him for “Austrian of the Year”. The title is given to persons who fulfill outstanding contributions to Austrian society in various fields. It took some persuasiveness to weaken his arguments. In the end, readers of “Die Presse” and a top-class expert panel honored the Italian citizen as Austria’s scientist of the Year. The prize was awarded at a gala event on Austria’s national day, on October 26, by the FFG general managers Henrietta Egerth and Klaus Pseiner. Among the congratulators: Federal Ministers Karlheinz Töchterle and Beatrix Karl. In the “thank you” speech, Giulio Superti-Furga also appealed to all young women and men in the country to consider a career in research, as it can be exciting and entertaining.

Prize of the City of Vienna

On December 15, in a ceremonial event, city councilman Andreas Mailath-Pokorny awarded to CeMM Scientific Director Giulio Superti-Furga the Prize of the City of Vienna for Natural Sciences. The prize is meant as a recognition of lifetime achievement and is awarded yearly to people with outstanding accomplishments in the fields of music, literature, journalism, arts, science and education. Among the awardees were also Dontscho Kerjaschki, a close friend of CeMM and mentor of the PhD students and the Germanist Ingrid Cella, recipients of this year’s prizes in medical sciences and humanities respectively.

Retreats

Institute-wide retreats provide a unique opportunity for scientists and members of the administration team alike to interact and dedicate significant time into delving deeper into the different projects and latest scientific developments, as well as to promote team building.

Scientific Retreat

Research Group (as of Feb 2011)
Item representative of the group:

Barlow
nAir tank

Bennett
keratin protection gear

Binder
microtitre plate picture puzzle

Boztug
flow cytometry tubes

Colinge
USB bug

Haplogen
gene trap

Knapp
glowing *E.coli*

Kralovics
gene sequencing chips

Kubicek
chemical screening microtitre plates

Nijman
bar-coded ping-pong balls (Luminex beads)

Superti-Furga
Bcr-Abl

The 2011 scientific retreat was held over two days at the Wienerwaldhof Rieger in Tullnerbach just 45 minutes outside of Vienna. The location offered a quiet setting to get away from the hectic every-day life of a busy research institution; and all the amenities necessary for a growing institute including seminar rooms, a large dining and social room area and sleeping quarters. This year's organizers, Keiryn Bennett and Christoph Binder, arranged a scientific and social program to keep everyone busy, active and interactive. After arrival, checking into rooms, lunch and a welcome speech by the scientific director; there were team-building exercises held outdoors. Amidst the frivolities, getting people to work together in either an effort to untangle a human knot, run an amoeba race or win at tug-of-war was the goal that was successfully reached. These activities were followed by the first block of scientific presentations where each research group was given time to present their work and a snapshot of some of their projects.

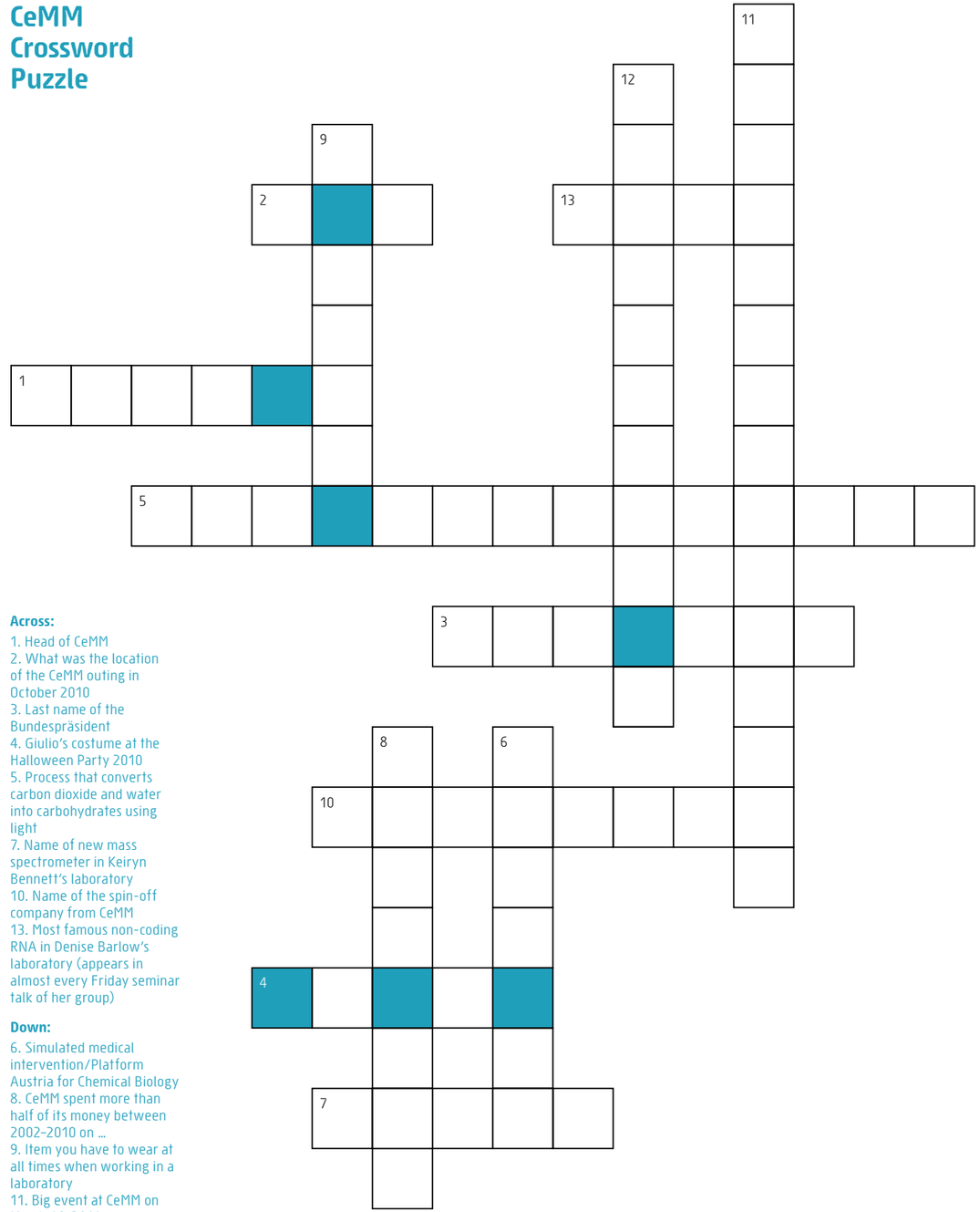
After series of intense scientific talks the following day, the scientific presentations continued before lunch and after another enjoyable meal, teams were once again formed for an exciting and surprisingly competitive treasure hunt. The teams had to accomplish different tasks in order to gain points and obtain clues to hidden objects, representing each of the research groups at CeMM.

After 2 days full of talks, the team was joined by two distinguished guest speakers, Professor Dr. Hans Lassmann and Professor Dr. Dontscho Kerjaschki, who both gave excellent and stimulating presentations on medical topics close to their heart. Prof. Lassmann showed highly-interesting findings on multiple sclerosis and oxidative stress. Prof. Kerjaschki talked about breast cancer, that received wide-spread interest and attention from not only those working on this topic at CeMM.

The last evening was filled with music, dance and entertainment. The scientific retreat was a great success thanks to wonderful organization, willing participants and an overall motivation of CeMM'ies to strive to give their utmost best, whether it be for presentations, posters, experiments or even folding paper aeroplanes!

1st place winners of the treasure hunt: Sabrina Gruber, Ioannis Legouras, Andreas Pichlmair, Tilmann Bürckstümmer, Thorsten Klampfl, Ana Puda, Oliver Stein, Tomasz Kulinski, Riem Gawish, Florian Pauler

CeMM Crossword Puzzle



Across:
1. Head of CeMM
2. What was the location of the CeMM outing in October 2010
3. Last name of the Bundespräsident
4. Giulio's costume at the Halloween Party 2010
5. Process that converts carbon dioxide and water into carbohydrates using light
7. Name of new mass spectrometer in Keiryn Bennett's laboratory
10. Name of the spin-off company from CeMM
13. Most famous non-coding RNA in Denise Barlow's laboratory (appears in almost every Friday seminar talk of her group)

Down:
6. Simulated medical intervention/Platform Austria for Chemical Biology
8. CeMM spent more than half of its money between 2002–2010 on …
9. Item you have to wear at all times when working in a laboratory
11. Big event at CeMM on March 16, 2011
12. Study of heritable changes in phenotype (appearance) or gene expression caused by mechanisms other than changes in the underlying DNA sequence – main focus of Barlow laboratory

Warning! Spelling error! Substitute 'C' for 'K'

What is the biggest fear in Mass Spectrometry?

Administration Retreat




On March 3rd the administration and management team of CeMM went to Seminarhotel Schloss Hernstein for a retreat. This beautiful, freshly renovated castle is located in the south of Vienna, close to the town of Hernstein, in a wonderful park area. As the number of persons working in CeMM's administration department increased, due to the increasing number of scientists and also to positions connected with the new building, which opened that year, the main focus of this one-day event was to set up new mechanisms to improve support activities. Support can be divided into different areas: the management of the building (cleaning, repair works, media kitchen); back office work (telephone, post, travel organization); IT-support; PR activities including the organization of all events (seminars, lectures, celebrations etc.); and finances/accounting. There was a particular focus on identifying areas where the different sub-departments could cooperate to provide an enhanced level of support and additional capabilities to the institute.

The main goals of the one-day meeting were:

+ Team building
+ Identification of measures that can increase work efficiency
+ Optimization of the management workflow to define individual and collective competencies
+ Promotion of open communication within departments

The team also worked on defining a total of eight principles for cooperative work between the separate sub-departments. One outcome was to identify the areas where collaboration could be more efficient and productive. Teams were built for follow-up discussions also concerning basic items like written work descriptions, sketches for optimal communication flow, priorities assigned, as well as necessary timetables.

After a full day's work, the participants were rewarded with dinner and entertainment in Vienna. As it was also Anita Ender's birthday (Human Resources and Assistant to the Scientific Director), there was a surprise cake and a birthday serenade with some 100 guests! We would like to take the chance to thank the moderator, Mrs. Claudia Osterer and the CeMM Management who made this retreat possible.

Scientific Advisory Board

The third evaluation of the Scientific Advisory Board (SAB) took place from June 19–21, 2011, the first time in the new CeMM building. Seven members made the journey to Vienna. They were Richard Flavell, PhD, James Griffin, MD, Carl-Henrik Heldin, PhD, Denis Hochstrasser, MD, David M. Livingston, MD, Chair, William Paul, MD, and Hidde Ploegh, PhD. The CeMM Faculty, Postdocs and PhD students took the opportunity to present their research achievements and goals, and to talk to the SAB members. In the next pages, the general part of the report is presented.

Report of the CeMM Scientific Advisory Board

"Overview: This (June 2011) was our third visit to CeMM, the last being 20 months ago. Since that time, CeMM is now a physical reality, having occupied its own, beautiful, and highly functional building, in which we spent two full days. This is a remarkable feat and, we suspect, will likely prove to be a transformative one.

We make these and other comments in this report as a committee of senior scientists, each of whom bears and/or has born major leadership responsibility for one or more leading, international scientific enterprises. Moreover, collectively, we sit and have sat over many years on the Scientific Advisory Boards (SAB) of numerous mature and emerging American, European, and Asian independent research institutes, like CeMM. Each of us attends yearly meetings of other such SAB groups. Thus, our views are conditioned by a detailed knowledge of and hands-on experience with the activities of a large number of other top quality biomedical research institutions in the international community. Moreover, each of us maintains a productive and vibrant scientific laboratory that focuses on problems that are closely related to the scientific interests of CeMM. Our views are also entirely consensual. Finally, we offer them against a backdrop of two prior visits to CeMM. The first occurred soon after CeMM had evolved from the concept stage and Dr Superti-Furga had been installed as Director. Subsequently we visited at a time when CeMM had appointed multiple new faculty who were, by that time, fully engaged in their own CeMM-based research. Thus, we have a longitudinal view of CeMM development, and it, too, has served as an important reference point for our current views.

The ability to colocalize all of the CeMM faculty in one site has long been a prime goal, and its achievement is an unmitigated success. One among several immediate benefits of the new building and the physical amalgamation of the entire faculty is an ability to recruit new round of superb, young faculty members such as Drs Bergthaler, Boztug, and Loizou. Each of them shows great promise of future success in independent science.

We also detect clear evidence of growing scientific cohesion and interaction among the existing and new faculty, alike; and overt scientific interactivity with the Medical University of Vienna faculty is rising. The movement to the new building has undoubtedly maximized these trends.

Research productivity is also growing, as reflected in an in increasing stream of excellent papers from CeMM that are appearing in excellent journals. Many of these papers represent collaborations not only among CeMM faculty but also between CeMM faculty and members of distinguished institutes from other parts of the world. The message is clear. CeMM is now on the map. Since we have long-standing and ongoing experience with and intimate knowledge of the major scientific themes of CeMM-research in innate immunity and on molecular cancer science– we make this comment with confidence.

In addition, CeMM is already on its way to fulfilling the dream of its founders, originally articulated at our first meeting in 2008. Its goal is to imprint, deeply, the study of molecular medicine. For example, CeMM has become a respected center of excellence in the study of hematopoietic neoplasms – no small feat in this intensely competitive landscape where the leaders have, traditionally, been very large academic medical centers and institutes, including some in which one or more of us is located. CeMM, through its growing chemical biology and proteomics focus, has also become a center of excellence in the study of innate immunity and inflammation, which has, in turn, led to significant advances in the analysis of infectious disease and the role of inflammatory phenomena in the evolution of arteriosclerotic cardiovascular disease.

The expertise at CeMM in chemical biology and drug discovery science is also a novel counterpart to its focus on cancer, immune, and inflammatory disease development and is likely to enrich these endeavors considerably over time. The recent relocation of Dr Barlow to CeMM and the addition of her invaluable expertise in the study of epigenetic mechanisms and non-coding RNA function has added yet another dimension of considerable value and significantly enriched the ongoing research programs at CeMM.

Among the Institute's most appealing qualities has been an ability to attract extraordinarily intelligent, ambitious, and energetic students and postdoctoral fellows to its midst. CeMM is now a very attractive place at which to receive one's graduate education in biological and medical science. Moreover, post-doctoral candidates of distinction are beginning to fill its training ranks. We have met with nearly all of the CeMM graduate students and post doctoral fellows who, as a whole, would have been highly desirable candidates for training at any of our own institutions. Moreover, to have attracted such talented and enthusiastic young trainees, is, in our experience, a rare attribute at newly formed research institutes.

The proximity to the Medical University of Vienna adds yet another positive dimension to CeMM's focus, especially because it offers unusual opportunities for valuable translational research. Medical University of Vienna and CeMM faculty interact, increasingly, which offers advantages to both institutions that did not exist until recently. The very opening of the CeMM building has provided additional energy to these interactions.

CeMM is grounded in both the excellence of its faculty-driven science and in the parallel excellence of its shared/core research laboratories. Superb proteomics, bioinformatics, and high throughput screening differentiate CeMM from many other institutes – both local and distant – in making it feasible for individual investigators to pursue systems-wide analysis of very complex problems in medical science. Elegant molecular and biological screens have yielded remarkable insights into disease mechanisms and drug action that were not conceived before. Newer facilities are being devoted to next generation DNA sequencing that has already led to new insights into the genetic basis for fascinating forms of inherited hematological disease. They have also led to observations that give license to new and highly incisive approaches to understanding cancer drug action. These outcomes are not unexpected. We detected their first signs of life on our first and second visits to CeMM. Indeed, we believe that they can trace their origins to visionary leadership that, in a very short period of time, has transformed into reality its aspiration for the institution to practice outstanding science.

With the addition of a suitably robust and creative genomics-directed computational biology effort, CeMM will have created a disease-focused genetics and genomics powerhouse that has moved from conception to reality in less than 3 years. This is a remarkable accomplishment, and, especially so, given that CeMM was founded less than 10 years ago.

The systematic approaches made possible by the current and developing experimental capabilities at CeMM will be extended considerably by the development of 21st century proof of concept experimentation. Success here will, inevitably, depend upon state of the art animal experimentation developed on site. Indeed, there are plans afoot to create the attendant animal care facilities that will be crucial for the success of this key endeavor.

All of these remarkable developments have been conceived and shepherded by CeMM's extraordinary leader, Giulio Superti-Furga. We have commented most favorably on his gifted leadership in the past, but at no time has it been more obvious that he is a treasured asset of CeMM than now, when all of the necessary elements for the Institute's operation have finally coalesced and are operating as a whole. We believe that only a rare individual who is as talented, committed, and visionary as Dr Superti-Furga could have equaled his accomplishments at CeMM. We also believe that this is a moment when his leadership position at CeMM needs to be cemented for the foreseeable future, for he has done spectacularly well in developing CeMM and would be extremely difficult to replace. With him as leader of CeMM, the security of the Institute and its ability to play a major role in deconvoluting some of the greatest mysteries in medicine will be maximized.

Finally, high-level financial investment in and tangible support of CeMM will, in our view, insure a very bright future for the Institute and add to the luster of the Austrian Academy. More specifically, we consider it imperative that the CeMM budget be increased now to meet its growing needs. Such an investment will insure that CeMM retains its well-earned status as an Austrian national treasure and becomes a widely admired, worldwide leader in translational science."

Richard Flavell, PhD
James Griffin, MD
Carl-Henrik Heldin, PhD
Denis Hochstrasser, MD
David M. Livingston, MD, Chair
William Paul, MD
Hidde Ploegh, PhD

Members of the CeMM Scientific Advisory Board

In strategic and scientific questions CeMM is advised by a board of international top-scientists:

Prof. Dr. Richard Flavell
Chairman, Section of Immunobiology,
Yale University School of Medicine,
New Haven, USA

Prof. Dr. James D. Griffin
Chair, Department of Medical Oncology,
Dana Farber Cancer Institute, Boston, USA

Prof. Dr. Carl-Henrik Heldin
Director, Ludwig Institute for Cancer Research,
Uppsala University, SE

Prof. Dr. Denis Hochstrasser
Head, Central Clinical Chemistry Laboratory,
Geneva University Hospital, CH

Prof. Dr. David Livingston (Chair)
Deputy Director, Dana-Farber/
Harvard Cancer Center, Boston, USA

Prof. Dr. William E. Paul
Chief, Laboratory of Immunology,
National Institute of Allergy and
Infectious Diseases, Bethesda, USA

Prof. Dr. Hidde Ploegh
Member, Whitehead Institute for
Biomedical Research, Cambridge, USA

Prof. Dr. Nadia Rosenthal
Australian Regenerative Medicine Institute,
Melbourne, AU

Prof. Dr. Louis M. Staudt
Head, Molecular Biology of Lymphoid
Malignancies Section, National Institutes of Health,
National Cancer Institute, Bethesda, USA

The Austrian Academy of Sciences

The Austrian Academy of Sciences, founded in 1847, is the most prestigious and important organization in Austria for the promotion of non-university-based academic research. The mother organization of CeMM is both a learned society, comprising highly qualified researchers from Austria and abroad, and a scientific organization promoting innovative research. It is currently promoting 65 research institutions, which are located in several federal states of Austria, with the headquarters located in the Old University in the center of Vienna. At present, the Academy employs about 1,100 people. The Austrian Academy of Sciences has developed from a mere learned society to an organization including the management of modern scientific research institutions. By founding basic research centers such as IMBA – Institute of Molecular Biotechnology and GMI – Gregor Mendel Institute of Molecular Plant Biology as limited liability companies under Austrian law, the Austrian Academy of Sciences embarked on a new approach to institutional organization. The connection between basic research and clinical research is being established by setting up CeMM.

In 2011 CeMM was honored twice by a distinguished delegation of the Austrian Academy of Sciences. President Prof. Dr. Helmut Denk was one of the laudators of the opening ceremony on March 16. While he officially opened the new home of the youngest “baby” of the Academy, Vice President Dr. Sigrid Jalkotzy-Deger, some former presidents and mentors of the CeMM project, amongst them Prof. Dr. Peter Schuster and Prof. Dr. Peter Tuppy, took their place in the first row during the ceremony and enjoyed the inauguration of the new research center with pride and excitement. Two months later, on May 10, 2011, CeMM had the privilege to host the Presidential Dinner. About 80 exalted representatives of the Austrian Academy of Sciences as well as of Academies of Sciences from neighboring countries enjoyed the breathtaking view over Vienna while drinking their aperitifs on the CeMM terrace. The seminar rooms on the rooftop of the research building were rearranged as a banquet hall and the cafeteria was turned into a gourmet kitchen: all in all a wonderful ambience for an inspired conversation.

The Presidential Dinner with guests from the befriended Academies of other countries was held at CeMM to present the new building and institution.

Sponsor us! Obtain a CeMM Health Research Bond

CeMM can be considered a People's Biotech Company that is predominantly run by taxpayers' money that funds scientific research.

To enable all individuals to contribute to the advancement of science, we are issuing the symbolic CeMM Health Research Bonds that you can purchase by donation. The bonds stand for our deal with society: You support us with these bonds and we do everything we can to advance knowledge about the molecular basis of disease and to identify innovative therapeutic and diagnostic options.

If you think that the research into future medicines should not be left entirely in the hands of businesses, then these bonds are for you. If you think that society needs to take a better informed and more active role in the health management options of the future, then these bonds are for you. If you think that knowledge is our biggest asset for the future, then these bonds are for you.

We have an entire sponsoring program, with the ability to support individual research projects, professorships, fellowships, training projects or important research instrumentation. We also have the possibility to give names to rooms, laboratories and even the whole institute ("Your name" Center for Molecular Medicine).

At minimum, for your donation, you will receive a symbolic CeMM Health Research Bond certificate, that you can treasure or give as a gift.

For the sponsorship program
please contact Eva Schweng
(eschweng@cemm.oeaw.ac.at,
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Social Activities

CeMM young researchers and employees (called CeMMies) come from many different nations, some very far away, and have very diverse cultural backgrounds. It is part of CeMM's mandate to organize social activities to favor integration of all members, expose them to some of Vienna's and Austria's cultural heritage and create a friendly and familiar atmosphere for the team spirit.








Outing to Wachau – Meeting Architectural and Viticultural History

The impressive Wachau landscape with its hilly vineyards was the location for CeMM's annual outing on October 6, 2011. Wachau is a small valley along a stretch of the Danube river that is famous for its natural beauty and rich history. Winemaking has had a continuous presence in this area for centuries, and the valley is also a UNESCO World Heritage site chosen for its high visual quality. CeMM scientists and employees visited also the Dürnstein castle, the site where Richard the LionHeart, King of England was held captive on his return from the Holy Lands in 1192. The visit included a traditional Austrian lunch at a local Heurigen, which enabled people to interact and socialize. The new CeMM PhD Students (many of whom are from outside Austria) were particularly enthused by the trip.

Halloween Ball
The stars of the 2011 CeMM Halloween party were the "Dead scientists". The event was organized by the new PhD students who drew inspiration from laboratory life and dressed up in a variety of lab related costumes such as research equipment and animal models. After two successful parties in 2010 and 2011, the Halloween party is now a well-established tradition at CeMM.




Christmas Party
During CeMM's 2011 Christmas party, the highlight was of course the children. A decorated Christmas tree awaited them along with Santa Claus who first told them a fairy-tale and then handed out the coveted gifts. The party took place at the Ottakringer Brauerei, a brewery with a two-century long history located in Vienna's 16th district. It houses a large events room where the party took place, and there was also a particularly tough quiz about many different aspects of CeMM (with questions such as how many steps are there in the entire building), which was followed by dancing.




CeMM Alumni


CeMM is a relatively young and still growing institute, so the number of students who have already finished their PhD is low. Four Principal Investigators started in 2011 or the beginning of 2012 and still need to build up their own groups. Nevertheless, we already had to part from several highly accomplished and appreciated colleagues – who went on with their scientific career – and had as many heavy-hearted farewell parties. This section is dedicated to them. We miss them and are grateful for their invaluable input and support in these very first years of CeMM, transforming the institute and its projects from a virtual idea to reality. There is no doubt that they will further contribute to CeMM's growing good international reputation and that they are the first of long list of successful scientists yet to come.

We are especially proud that five CeMM postdocs won very prestigious and internationally competitive independent positions. We would like to mention them as representatives of all colleagues and friends who left CeMM in 2011 and wish them all the best for the future!

A key component of CeMM's mission is to be a world-class training laboratory for molecular medicine, not only for students but also on the postdoc and faculty level. Apart from a solid research education, CeMM employees are trained at and get exposure on issues that have to do with responsibility towards society (inclusiveness, gender issues, public relations, communication, ecology, economy, ethics, and arts) as well as intellectual property and patenting. We strategically invest money in guest lectures, conferences and public relations initiatives which help us find the best possible students and researchers available.

Christoph Baumann
Research Group Leader,
Boerhringer Ingelheim, Vienna

Tilmann Bürckstümmer
Principal Scientist,
Haplogen, Vienna

Oliver Hantschel
Assistant Professor,
Swiss Institute for
Experimental Cancer Research,
EPFL Lausanne

Andreas Pichlmair
Research Group Leader,
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Uwe Rix
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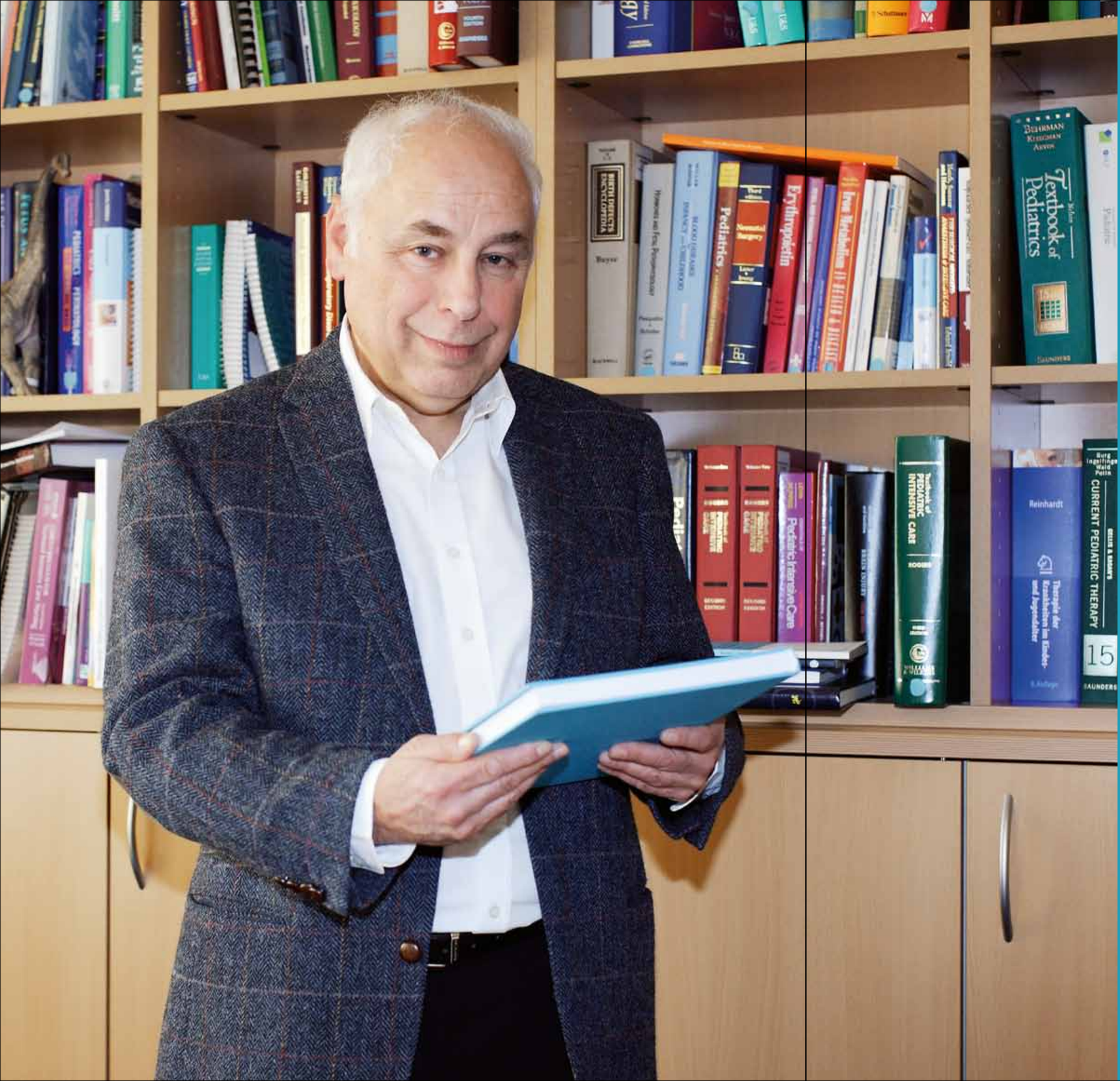


"Pediatric research has a strong tradition in Vienna and the Pediatrics Department is very active in both research and clinical innovation. I am very happy that Kaan Boztug, a highly talented medical researcher with dual affiliation at CeMM and in our clinical department, embodies the joint effort of CeMM and of the Medical University to boost collaborative research aimed at bridging cutting-edge molecular technologies and clinical needs. It is imperative that we continue to extend our collaboration; for the best possible use of resources and the benefit of science, patients and society."

Prof. Dr. Arnold Pollak
Head of the Department of Pediatrics and Adolescent Medicine,
Medical University of Vienna

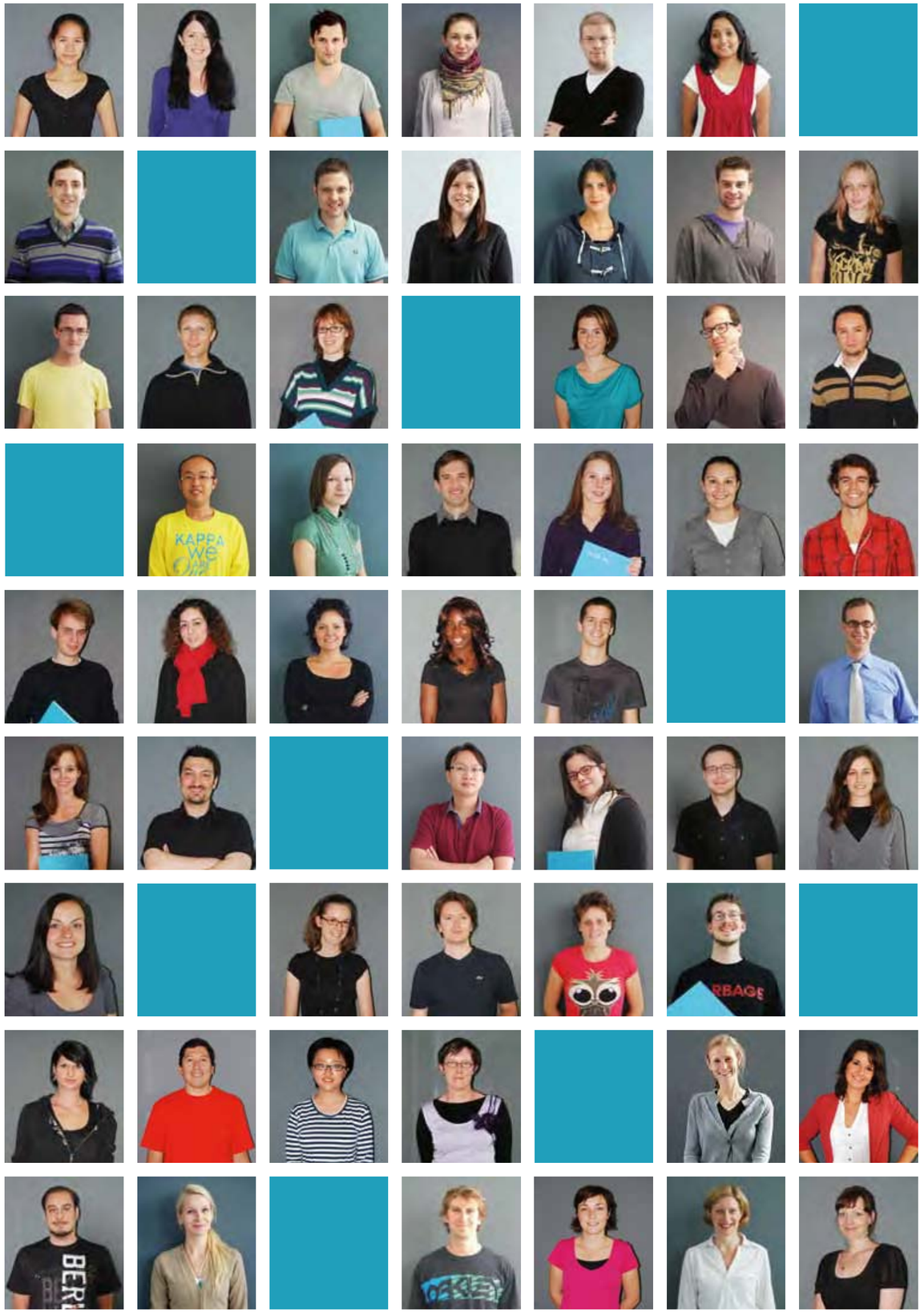
"Being competent, professional, and very concentrated on one's goals, are key factors to success in sports, business and, I am sure, also in science. From what I know, CeMM is a formula one racing house in medical research that we are already proud of."

Niki Lauda
F1 World Champion and Airline Founder

Employees

Armenia, Australia, Austria, Bolivia,
Brazil, China, Croatia, Cyprus,
Czech Republic, Finland, France, Germany,
Greece, India, Iran, Ireland, Italy,
Netherlands, New Zealand, Pakistan,
Poland, Portugal, Republic of the Congo,
Russia, Serbia, Singapore, Spain,
Switzerland, Turkey, United Kingdom

30 Nationalities



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graduated 2011
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° maternity leave

Legend to grants

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

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

EU Open Screen
European Infrastructure of Open Screening Platforms for Chemical Biology

Fondation Leducq
Immune Modulation of Cardiovascular Disease

DOC Fellowship
Austrian Academy of Sciences

DOC-fForte Fellowship
Austrian Academy of Sciences

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

FWF W1207 DK
Doctoral Program
"RNA Biology"

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

FWF 4302
Special Research Program
"RNA regulation of the transcriptome"

FWF I289B09 ERA-NET
PathoGenoMics
"Innate immune responses to Streptococcus pyogenes"

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

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

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

FWF P23257
Stand Alone Project
"Heriditary Predispositions to Myeloproliferative Neoplasms"

FWF P23991
Stand Alone Project
"The Role of Oxidative Stress in Viral Hepatitis"

FWF SFB Lipotox F30
"Lipotoxicity:
Lipid-induced Cell Dysfunction and Cell Death"

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

Gen-AU APP III
"Austraian Proteomic Platfom"

Gen-AU BIN III
"Bio Informatics Integration Network"

Gen-AU EPIGENETIC CONTROL III
"Epigenetic Regulation of Cell Fate Decisions"

Gen-AU PLACEBO
"Platform Austria for Chemical Biology"

JDRF Grant
Juvenile Diabetes Research Foundation, Canadia

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

OENB-14107
Austrian National Bank

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

“For sure there is a correlation between vigorous investments in innovative research and the economic health of nations. This may become particularly important for health-related research in times of demographic shifts. CeMM is a research institution the whole nation is becoming proud of. I, for sure, have been cheering on the sidelines all along as institutes like CeMM can be crucial for the social and economic development of Austria.”

Prof. Dr. Bernhard Felderer
Director, Institute for Advanced Studies, Vienna

"I have followed the developments of CeMM from the outset. Under Giulio's leadership, the CeMM has become a true world-class institute. For IMBA, to have the sister institution CeMM located close to the general hospital, ensures a bridge towards clinical application of our research findings. CeMM has developed technologies in drug screening and proteomics that are truly unique and combined with our expertise in functional genomics IMBA and CeMM will be unbeatable."

Prof. Dr. Josef Penninger
Scientific Director, Institute of Molecular Biotechnology (IMBA)

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Social Media

CeMM is a young institution full of young researchers. Social media are in constant use and videos are becoming increasingly important. The decision to extensively use the social media came naturally as a result of the passion of our young researchers to discuss, comment on, and communicate their thoughts on science and research. Therefore, a strong media presence has been an integral component of CeMM's communication strategy, that can be illustrated among others by two videos that were created to explain the results of scientific works in 2011 in the fields of innate immunity and leukemia. (www.youtube.com/watch?v=ve6AO35IW-0, www.cell.com/abstract/S0092-8674(11)01067-1) These two videos aim at explaining the recent scientific discoveries in an audiovisual way, and they are targeted more at a general audience. They ensure that viewers can go one level deeper in the science than with reading a summary of the research carried out at CeMM.

In addition, CeMM is present in the social media landscape. Social networking has become an integral component of the day to day communication, and especially for the younger generations it accounts for a large share of information acquiring. It is still at its early days, but CeMM is committed to giving the opportunity to the community to comment on questions and express ideas responding to news from CeMM, conferences organized, scientific talks, science and society events as well as scientific discoveries. All major CeMM events will have a place on the social media, either as short posts, or pictures and videos. If you want to follow the exciting new discoveries at CeMM, the events in Science Coordination, and the projects of Science and Society among others, you can find us on the following social media: facebook, twitter and linkedin.

Links:

http://www.youtube.com/watch?v=ve6AO35IW-0
http://www.cell.com/abstract/S0092-8674(11)01067-1

https://www.facebook.com/pages/CeMM/164718773581500

https://twitter.com/#!/CeMM_News

http://www.linkedin.com/company/cemm

Facts & Figures

Inclusiveness at CeMM

CeMM has a strong intellectual environment that stems from the international nature of its employees. Diversity and different cultural backgrounds are a clear advantage to successful research, collaborations, and the day-to-day business, as long as everyone follows a few basic principles, which at CeMM are: Professionalism, Politeness and Persistence. The working language at CeMM is English.

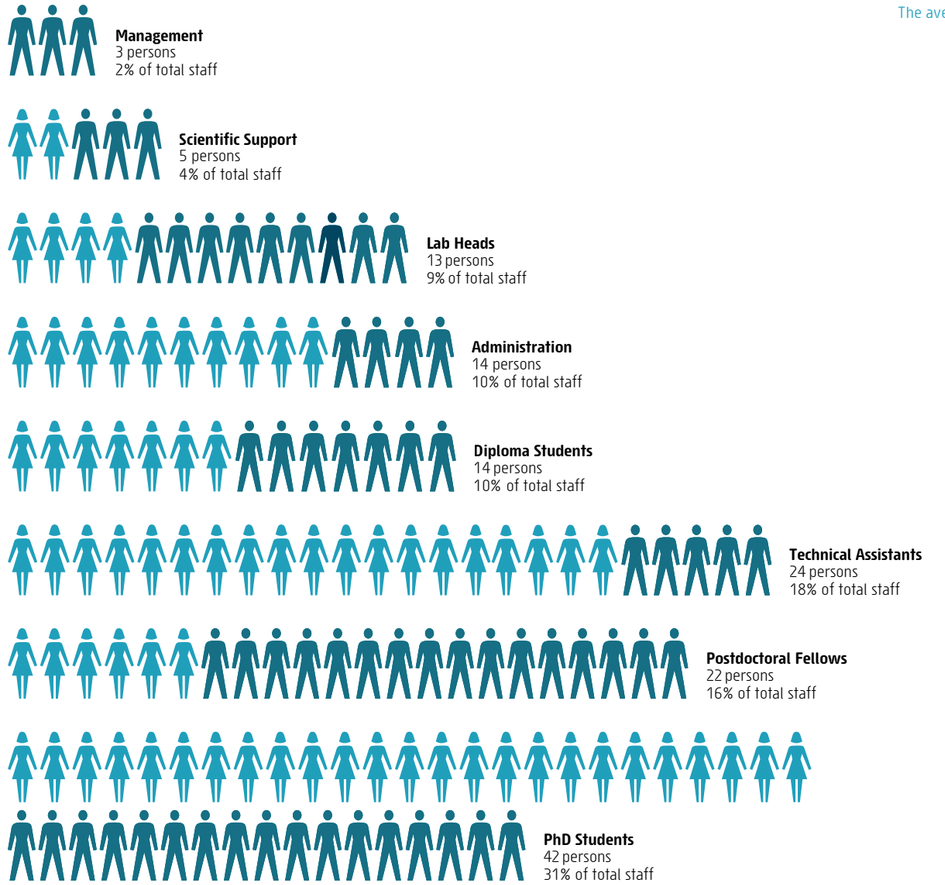
At CeMM, emphasis is given to mentoring independent young investigators and scientists early in their careers, through freedom, availability of infrastructure and a strong support system. A flat hierarchy, where the input of every single person is appreciated and required, leads to an enjoyable work environment and an increase in productivity and ideas.

CeMM is particularly interested in supporting and fostering women scientists in areas where the gender bias is more evident (like chemistry, screening, proteomics, bioinformatics).
In recruiting new scientists, a dedicated effort is made to engage female scientists and foster their career development as much as possible. Among faculty, 30% are female (Denise Barlow, Keiryn Bennett, Sylvia Knapp and Joanna Loizou). Currently the gender balance at CeMM is equitable (54% women in total) as one can see from the statistics in the annual report.

Staff

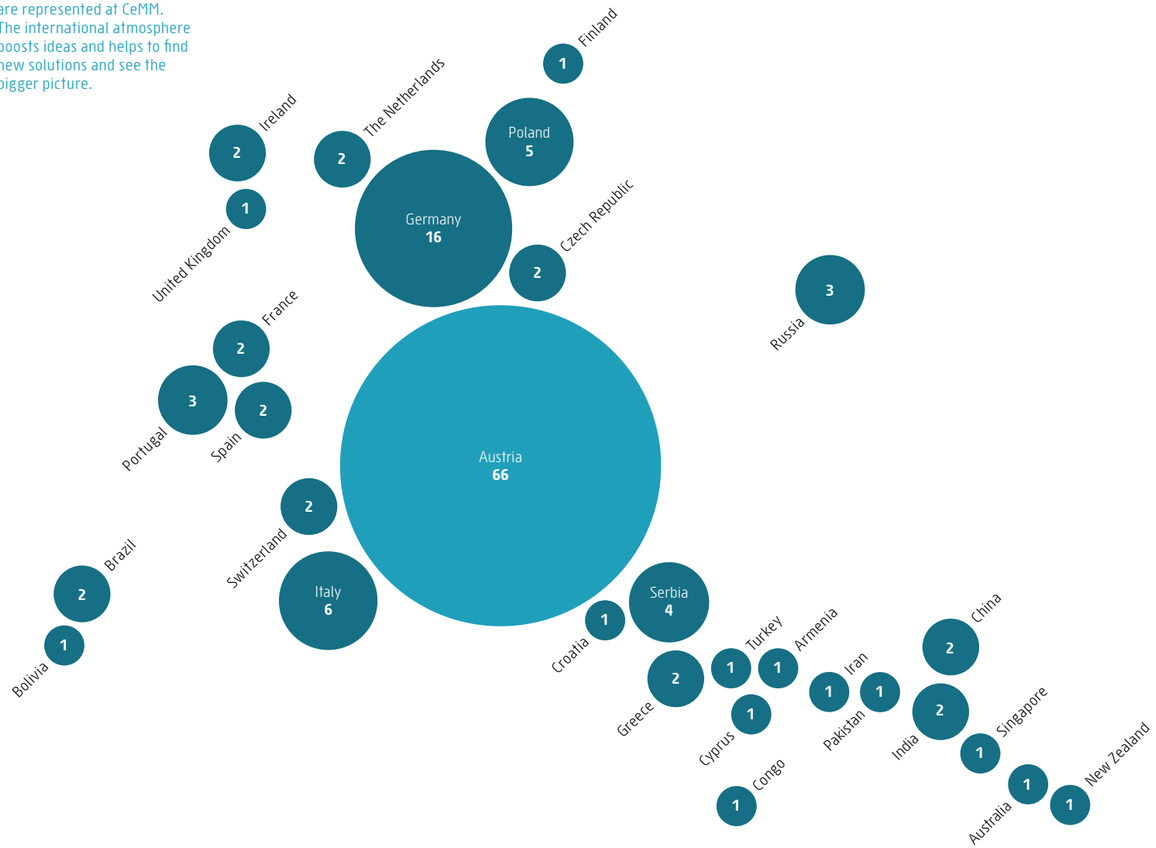
Listed by number of persons per field of work

CeMM stresses keeping the administration very lean and efficient. We have a very good gender balance, with a small surplus of women. The average age is 31 years.



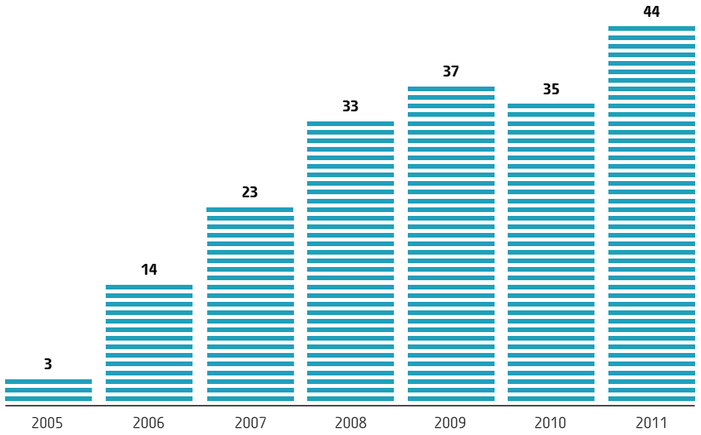
Nationalities at CeMM

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

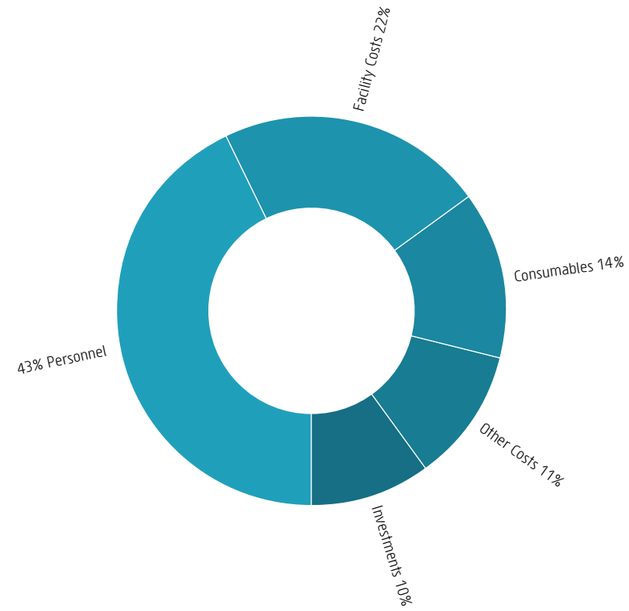


Publications

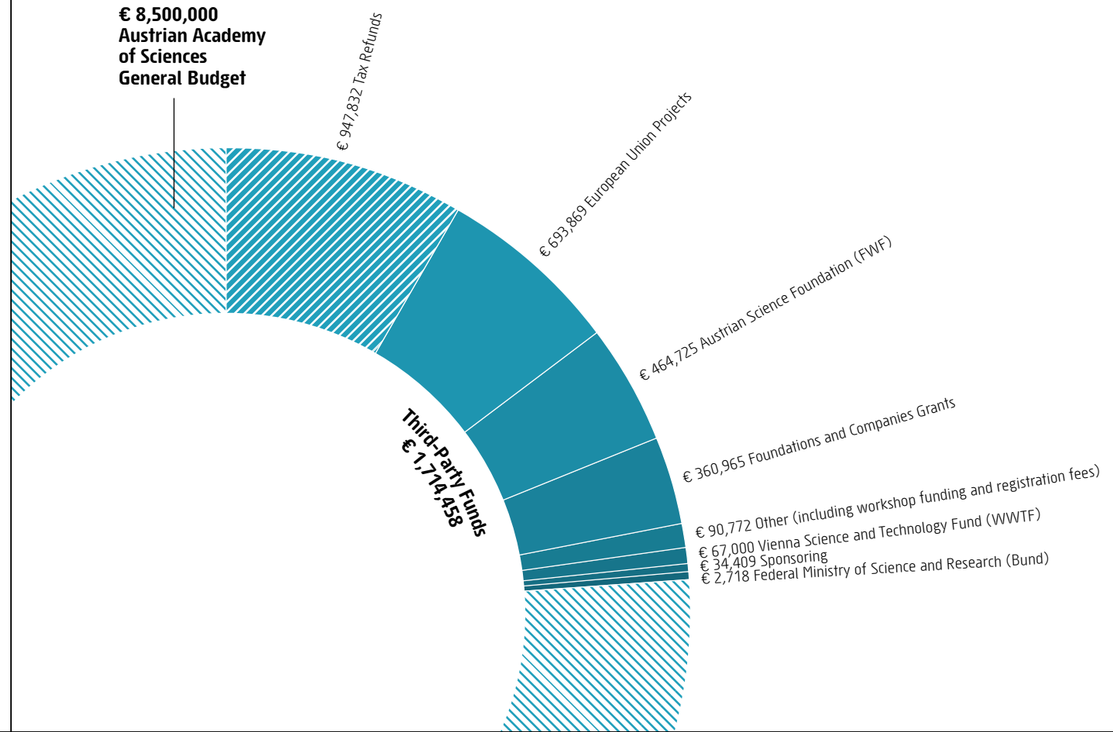
Includes all publications by CeMM staff members from the date of joining the institute.

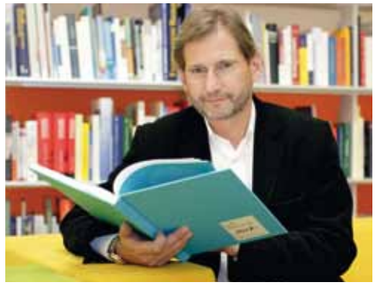


Expenses in 2011



Money Sources in 2011





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Austria's Federal Minister of Justice

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Mayor of the City of Vienna

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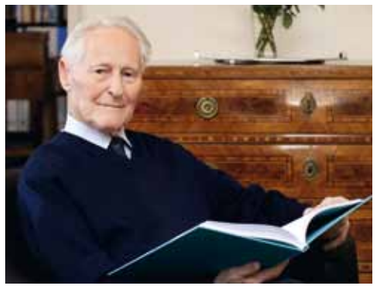

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MUV Medical University of Vienna
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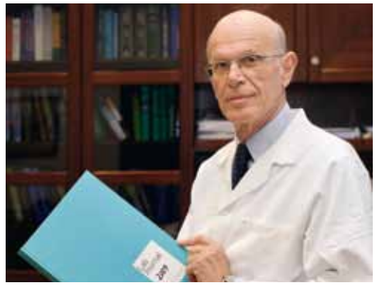

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Sponsors of the Constantin Spiegelfeld Lecture

Robert Palfrader, Austrian comedian in his most famous social satire role as the (fictitious) Austrian Emperor

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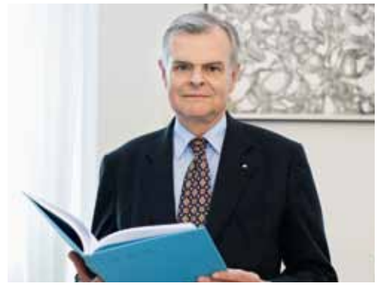
Former President of the Austrian Academy of Sciences



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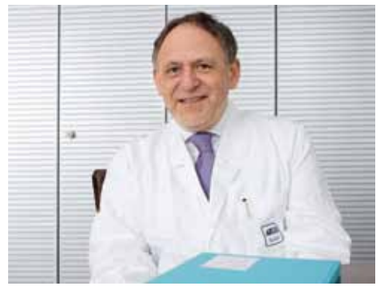

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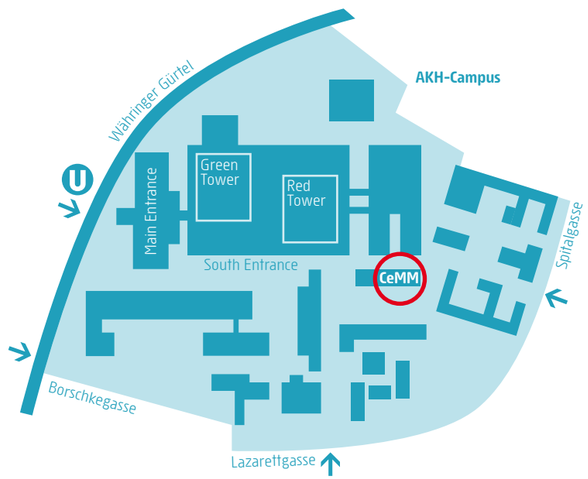

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3. FISCHER
4. NURSE
5. PHOTOSYNTHESIS
7. VELOS
10. HAPLOGEN
13. AIRN

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