
Ce-M-M-
Enjoy our 3rd Report!
Lab Journal
2009
No.
Name
Ce-M-M-
Research Center for Molecular Medicine
of the Austrian Academy of Sciences

Ce–M–M–

Research Center for Molecular Medicine of the Austrian Academy of Sciences

Offline Fractionation: O20090721-4
Pulldown: P20090406-1141

Cell Line: HS Cataract aqueous humor — M20090721-MP-213 (E-F)

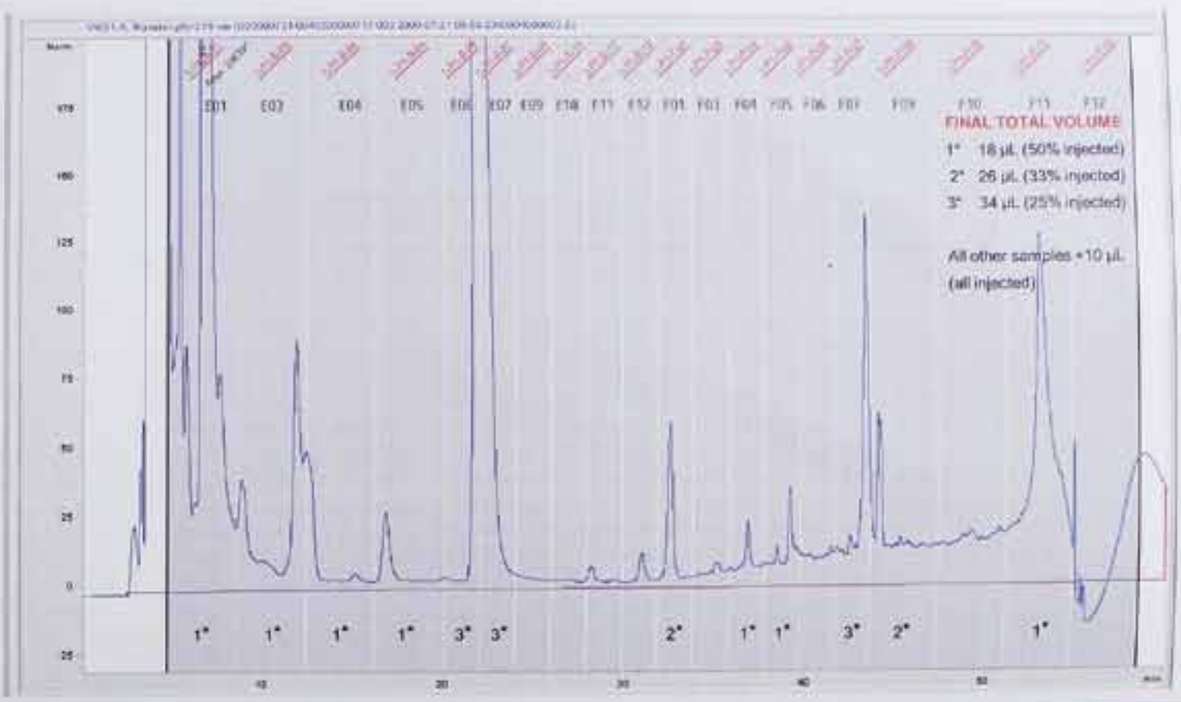
recorded Ulrich Planyavsky date 21.07.2009

witnessed date

Offline separation followed by clean-up as described on page 68! HP 21.07.09

from page no. 90

to page no. 90



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Cell Line: HS Cataract aqueous humor — M20090723-MP-229 (A-B)

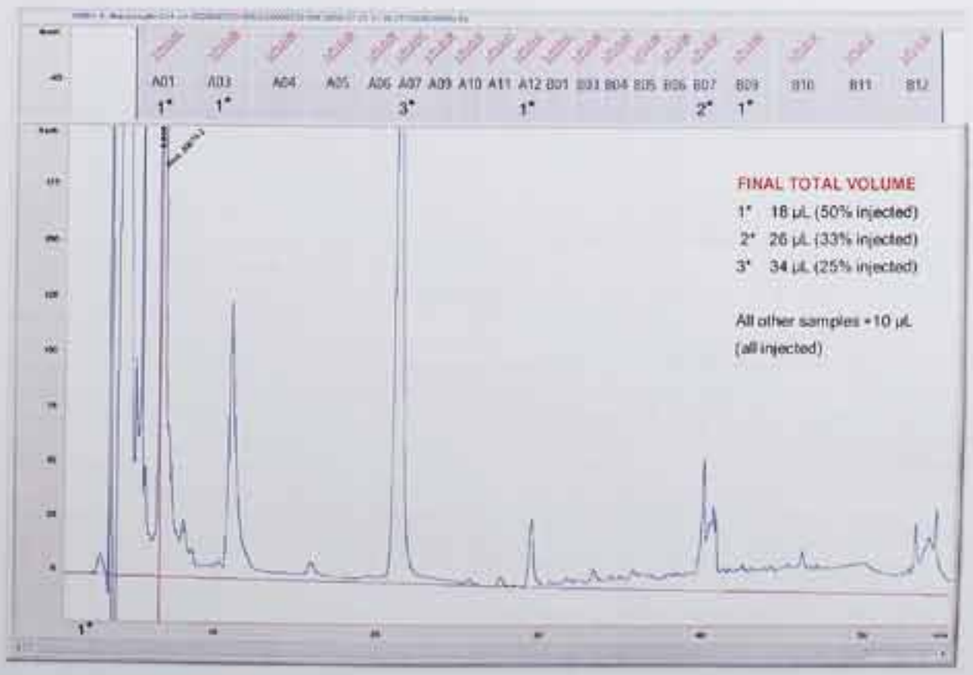
recorded Ulrich Planyavsky date 22.07.2009

witnessed date

Offline separation followed by clean-up as described on page 68!

from page no. 91

to page no. 91



MS Sample Preparation - Loading lists G302 & G303

Name: G302	Date: 26.05.2009	Contact: DH/IK TB	Western Blot	Silver Stain	Coomassie	MS
Lane:	1	2	3	4	5	6	7	8	9	10
Comment	M		P1256 2step TAP BB		P1257 2step TAP BB					
	W		Untreated		+Dasa					
	M		K562/Sts-1		K562/Sts-1					
	Pre		C235		C235					
Cell Line:										
Volume:	3µl		5.7 µl		5.7 µl					

Name: G303	Date: 26.05.2009	Contact: DH/IK + CG	Western Blot	Silver Stain	Coomassie	MS
Lane:	1	2	3	4	5	6	7	8	9	10
Comment	M		P1265 ProtG-purified anti-NRLP3		P1266 Affinity-purified anti-NRLP3				P1258 2step TAP BB Membr. prep	
	W									
	M									
	Pre								receptor	
Cell Line:			C296		C296				HEK293	
~~Volume:~~	~~3µl~~		~~34.2 µl~~		~~34.2 µl~~				~~22.8 µl~~	

Alkylation: IA stock = 133 mg / mL iodacetamide, 0.14µl IA stock per 1µl sample

P1256 & P1257: 5µl sample + 0.7µl IA stock = 5.7µl loaded

P1265 & P1266: 30µl sample + 4.2µl IA stock = 34.2µl loaded

P1258: 20µl sample + 2.8µl IA stock = 22.8µl loaded

All samples have been reduced and denatured before.

Silver staining

according to G_SOP0004_Rev2

with 1 hour Fixing at RT

Pictures are following page

recorded Melanie Planyavsky date 26.05.2009 from page no. 50

witnessed date to page no. 51

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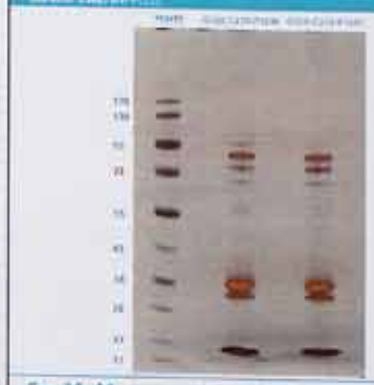


Ce-M-M-

MP 26.05.2009

Gel: G20090526-303
Pulldown: P20090522-1265, -1265 & P20090520-1258

Ce-M-M-

MP 26.05.2009

recorded Melanie Planyavsky date 26.05.2009 from page no. 50

witnessed date to page no. 51

CeMM Research Report 2009

Introduction by Giulio Superti-Furga

What a critical year! We almost completed construction of our new building, to be ready to move in late spring 2010. We witnessed an explosion of support on the whole concept of bridging basic molecular and post-genomic research with the chances and difficulties of the clinical realm. It is becoming more and more obvious that the revolutionary molecular knowledge on human individuals and on particular diseases will drastically change medicine. Most importantly, it may well change our basic philosophical perception on human individuality. We start evaluating in great detail not only the body plan (genome) as it is modified by our personal history with our environment (epi-genome), but also how this plan, by being relentlessly executed, results in the variety of molecular and cellular networks that make us unique as individuals. Diseases affect these networks by putting them out of balance. In essence, at CeMM we characterize these fundamental molecular networks, look at their pathological malformations and develop ideas on how to restore them.

Did we make enough progress this year? I believe we did. The young Principal Investigators were successful in establishing their laboratories, publishing their initial findings and obtaining additional funding from grants. Sebastian Nijman obtained two large grants and the "Wiener Zukunftspreis" (Vienna Prize for the Future), thus confirming the appropriateness of CeMM to bet on very young, internationally recruited, scientists. CeMM published important papers in cancer genetics and innate immunity, including the identification of a gene form that increases the likelihood of a blood cancer and the identification of a protein fighting infections. We also proposed a new experimental therapy for acute lung injury and pneumonia and published a warning paper on the use of digitalis-like drugs in cancer treatment. This shows that our translational-medical vocation is indeed becoming more evident. Most importantly, the organization has grown together through a nice and natural effort, with full awareness that special dedication had to go into forging relationships when groups are geographically separated. To all CeMM scientists and administration personnel goes our appreciation and gratitude. Thank you!

Giulio Superti-Furga, CeMM Scientific Director

If you were wondering how the perspective of this photograph in front of the academy building came about: Photographer Michale Sazel and I were allowed to jump on the stage of a tow-away truck that was idle in front of the building!

The Scientific Advisory Board, fearlessly captained by Prof. David Livingston of the Dana-Farber Cancer Research Institute and Harvard University, visited us in November. One of the recommendations expressed at the previous meeting was to push towards medicine. They were happy about the progress obtained and encouraged us to intensify the thrust. Our collaboration with the Medical University of Vienna (MUV), that sort of surrounds us like a womb, is of course critical for this and many events and initiatives in 2009 contributed to this goal. We were very happy that CeMM Principal Investigator Christoph Binder became Professor of Atherosclerosis Research at the Medical University and congratulate him. His dual appointment with the Department of Laboratory Medicine is, similar to Sylvia Knapp's dual affiliation with the Department of Medicine I, Division of Infectious Diseases and Tropical Medicine, one of the vital umbilical cords that link CeMM to the Medical University. We are indebted to Prof. Oswald Wagner and Prof. Christoph Zielinski who represent the pillars of this collaborative set-up. CeMM has also profited very much from the interdisciplinary fellows Stephan Blüml and Viola Bergdorff, who, working in both institutions, CeMM and the Medical University, have contributed to enhance the flow of cultural exchange. For this, we are grateful to Prof. Josef Smolen and Prof. Stephan Wagner for these interesting joint projects.

In the spirit of enhancing medical knowledge at CeMM it has been a privilege and also thrilling to host Prof. Eric Haura, Director of the Lung Comprehensive Research Center of the Lee Moffitt Cancer and Research Center in Florida, U.S.A, for a sabbatical period in the director's laboratory. Eric's experimental enthusiasm, personal drive and patient-oriented perspective had an inspirational effect on the laboratory and resulted in a few interesting successful studies on systems-level approaches to lung cancer therapy. We are hoping to establish an institutional tie with the "Moffitt" to continue the exciting collaboration. Along these lines are our efforts to use proteomics as a discovery tool in a clinical setting. We have started a large proteomics-based collaboration with the Department of Ophthalmology, led by Prof. Ursula Schmidt-Erfurt, to obtain a molecular characterization of the content of ocular fluids in healthy individuals as well as in patients with the most threatening and abundant eye disorders.

As in the previous years, CeMM has profited tremendously of the training of 22 PhD students, who participate in several PhD programs hosted by the MUV. They form the foundations of CeMM's trans-disciplinary knowledge base and are a constant source of creativity. As of 2010, we will also start a postdoctoral program aimed at offering the same degree of organized medicine-science cross-training to postdoc fellows. In 2009, we have had numerous attractive international speakers, offering to the entire MUV campus at the General Hospital, another chance to meet and discuss with CeMM members and with the speakers. CeMM's Landsteiner lecture, held by Dr. Vishva Dixit of Genentech has again been a highlight for the community. Probably the most important event of 2009 was the search for new Principal Investigators, operated with the help of colleagues from the MUV, the Vienna Biocenter and the Universities of Graz and Innsbruck. We had 184 applicants, many of which were excellent. Scientific achievements and vision, but also strategic fit with CeMM's focus on innate immunity, cancer, and vascular biology, were the important selection criteria. We will present the new Principal Investigators in next year's report, but I would like to already thank everybody involved in the long hiring process.

How to move towards therapy? Principal Investigator Christoph Binder is making important progress towards the identification of so-called "natural antibodies" that could be exploited therapeutically to treat or prevent cardiovascular disease. 2009 was the year where ideas on combination therapy came of age at CeMM, both from a theoretical point of view (including interesting discussions with visitor Joe Lehár), from an experimental point of view (for example with Principal Investigator Sebastian Nijman's search for cancer vulnerabilities) and also from a therapeutic perspective (where initial results from using different kinase inhibitors are very encouraging at the cellular level).

Without doubt, robust biological and pathological systems are more easily made vulnerable by simultaneous attacks. As part of the necessary toolbox, we have started gaining access to a chemical biology platform, partially financed by a grant of the GenAU program (Genome Austria, BMWF) respectfully called PLACEBO (for Platform Austria for Chemical Biology) that links chemistry, pharmacology and disease biology groups across Austria to do focused chemical screens on interesting assays and chemical proteomics to identify targets. The name makes it clear that chemistry is used as a research tool, but of course we envisage insights that can be exploited therapeutically. PLACEBO is part of a European network of chemical biology laboratories called EU-OPENSCREEN that is seeking infrastructure funds from the European Union.

To structure this year's report we have chosen to refer to the privilege of being associated with the Austrian Academy of Sciences. I wish to thank the entire Board of the Academy for constant support. The Academy, consisting of a philosophical/historical part as well as a mathematical/natural sciences part, has been a hearth of cross-disciplinary exchange for 162 years and allows a young and future-prone institution such as CeMM to draw from a very large spectrum of experiences and knowledge to gain some important historical perspective. The festive hall of the Academy with its perfect architectural proportions, its beautiful frescoed ceiling is one of Austria's most congenial and amiable baroque rooms. Most importantly, it is dedicated to science and scholarship. It also harbors four niches with fascinating long-limbed, elegant sculptures of unusual grace. The statues represent embodiments of pairs of classical virtues, (faith, constancy, justice, wisdom, prudence, vigilance, liberality). In times as these, where dire economic straits can lead to shortness of vision and the faith in the power of knowledge is questioned, we find inspiration for our work and for our science in these statues. In our mind, they link the present to the ancient world and 18th-century art of the age of enlightment to our modern science. The different chapters of this year's report are structured along these virtues. We hope that this Ariadne's thread will help you find your way when reading our report.

Finally, we again include our "CeMM Health Research Bond" to highlight our pact with society. We envision a society that is increasingly aware of the opportunities that the ongoing biomedical revolution is offering and that gives us input and feedback, and a society that is cheering on the sidelines for CeMM's team of mostly young researchers and that is willing to support it, also financially. Awareness about health and research can always be improved. CeMM wishes for a society that is serious about fighting infections, cancer and deaths from cardiovascular disease. In return, we promise our most serious engagement, fortified by the virtues mentioned above.

This is number three in the "Blue Books" series that symbolize the research lab notebooks that we use daily. As in the past, you hold in your hand the testimonial of our work. A very long list of people that we wish to thank is at the end of the book. Here, I want to thank Gabriel Ó Ríordáin and Helen Pickersgill for organizing and writing this report, respectively. I thank my co-directors Gerhard Schadler and Georg Casari for stirring finances and administration with dedication and expertise and Anita Ender for still being the person at which the buck stops most often.

Enjoy the reading!
Giulio Superti-Furga

The Statues in the Academy

Interview with Prof. Artur Rosenauer
by Prof. Giulio Superti-Furga

As an institute of the Austrian Academy of Sciences, CeMM refers to the historical building in the 1st district on Dr. Ignaz Seipel-Platz, formerly the main building of the University, as a sort of headquarters of immense prestige. The centerpiece is the magnificent festive hall on the first floor, in which not only distinguished scholars and scientists discussed and presented their work but also famous musicians such as Haydn, Beethoven and Schubert performed. A significant event in the Viennese history of music was the performance of Haydn's "Creation" on March 27, 1808, on the occasion of the composer's 76th birthday.

The subjects of its ceiling fresco, created by Gregorio Guglielmi in 1755, are the University's four faculties and the apotheosis of the imperial couple, Maria Theresia and Franz Stephan, as patrons of science and arts. The four groups of statues in the niches of the festive hall are believed to depict the virtues faith and constancy, justice and wisdom, prudence and vigilance, and liberality.

Inspired by the festive hall's artistic visualization of the different realms of knowledge, the different chapters of this year's CeMM report are structured along the above mentioned virtues of the four groups of statues. We are grateful to Artur Rosenauer, full member of the Section for the Humanities and the Social Sciences of the Academy, Chairman of the Academy's Commission of the History of Arts and Professor at the University of Vienna , who kindly shared his expertise with us. Giulio Superti-Furga interviewed him in the festive hall of the Academy building.

Giulio Superti-Furga: The statues standing in niches of the hall are ascribed to Mollinarolo. What do we know about the artist?

Artur Rosenauer: It was only a few years ago that my pupil and friend, Luigi Ronzoni, found out that the sculptures in the festive hall of the Academy were made by Jakob Gabriel Müller, known as Mollinarolo (1717–1780). Unfortunately, there exist hardly any documents about him and he only produced a few sculptures that we know of. One example of his work, an altar, can be found in the dome of Raab (Györ) and two sculptures made of lead are presented in the Liechtenstein Museum in Vienna. Another is the main altar in the cathedral of Wiener Neustadt. So he is somewhat of a well kept secret but in my opinion probably the best Austrian sculptor of the 18th century. His mentor Georg Raphael Donner was by far more famous. After the death of Donner in 1741, his pupils (Moll, Messerschmidt, Mollinarolo) and his brother Mathias continued to work in his style until late in the century.

GSF: Do you think if Donner had still been alive they would have engaged him? The figures are beautiful and you and I like them very much, but is there any reason to believe that Mollinarolo was a second choice?

AR: Maybe they would have asked Donner, but he was already dead and then Mollinarolo was the best choice. It was Wenzel Anton von Kaunitz-Rietberg, chancellor of Maria Theresia and a member of the Kuratorium of the University, who is likely to have given the permission to engage Mollinarolo. I would say, in the second half of the 18th century whoever gave the order must have been somebody who really was knowledgeable about sculptures with taste and judgment.

GSF: The statues by Mollinarolo in the Lichtenstein collection, are they new acquisitions?

AR: Yes. Once, in the 18th century, they belonged, I believe, to a Liechtenstein castle in Lower Austria. It is a similar story like the one of the virtues here in the Academy. When I saw them first, about 40 years ago, they were ascribed to another Donner pupil, namely Johann Georg Dorfmeister. It was again my student Ronzoni who was able to reattribute them to Mollinarolo while writing his thesis. He is perfectly right with the Liechtenstein sculptures as well as with the figures in the Academy building. Although there are no real documents for the latter, there is a kind of hint in a letter of the architect mentioning that he is going to engage Müller (Mollinarolo) for the façade of the new University building.

Details of the Statues: top left: the long neck of Constancy; right: the cross in the hand of Faith; bottom left: the hands of Generosity handing out coins

GSF: As a layperson looking at these statues, I am wondering whether it is customary to make virtues as couples?

AR: No, it is absolutely not. It is highly unusual, I don't know any other example. And also the iconography of these virtues is rather unusual. Even as an art historian I have to admit that it is not easy to identify the statues by their attributes. In some cases like faith it is obvious because of the cross and the other figure is with great probability constancy because of the lion. So faith and constancy are represented as twin sisters.

GSF: Is faith holding an orthodox cross?

AR: No, an orthodox cross would have an additional short skewed bar. This is a so-called Cross of Patriarchs or of Cardinals. It is very possible it is meant to honor the Viennese archbishop cardinal Johann Joseph Count Trautson, whom Maria Theresia had made the protector of the University and responsible for the new building. Trautson is the one who had commissioned Metastasio. It's curious that archbishop Trautson was made cardinal in April 1756 only a few days before the official opening by the imperial couple of the new building, so he was at the height of his influence and shortly before his death. Here he may be present to highlight his role as a sort of guarantor of the virtues and values for the entire new University. Look, in the statue representing constancy you can see this unique Mollinarolo style very well. It is really slender, very elegant.

GSF: Absolutely, it really reminds me of Parmigianino if you have a look at the neck.

AR: Yes! "La Madonna con il collo lungo"! It belongs really to the finest examples of middle European sculpture in the second half of the 18th century, although the surfaces of the sculptures suffered from the big fire in 1961. The whole fresco of the room is a copy of the lost original. I have seen it once before the fire. There was the birthday of the president of the Academy in February and they fired the stoves. Because of the old chimneys and a storm going on at that time it started a fire. Besides the ceiling also some of the attributes of the statues were destroyed and they had to be reconstructed. The photos which existed were not very good, so what we can see today may be a combination of poetry and truth.

GSF: So also the surface was damaged by the fire. What material are the statues made of?

AR: It is stucco and the figures should be bright and shining like the surface of porcelain.

GSF: Would there be somebody in Austria who knows how to restore them?

AR: Yes, it should be possible to find a competent team but it is more a matter of securing the necessary funds.

GSF: So the fact that they are pairs, could it be that the artist was paid per each statue done?

AR: No, I am sure there is another reason which maybe can be found in the fresco. Pietro Antonio Domenico Trapassi, better known by his pseudonym of Metastasio, created the fresco program. This fresco is different from most other baroque frescos. He wanted everybody to understand what the fresco means, so he wrote down the specification of the faculties. If you come to a typical fresco in the library of a monastery and look at all the figures, it is not very easy to figure out the meaning of the depicted persons and scenes. Not here.

GSF: Would you imagine that Mollinarolo was aware of the plan of Metastasio?

AR: They were contemporaries and worked for the same building, somehow he must have been aware, but I can only see one possible connection between the fresco and the figures. If you have a look at the middle of the fresco you will see a medallion with the pictures of Maria Theresia and Franz Stephan. We know from the program of Metastasio that Maria Theresia insisted that she and Franz Stephan are depicted as a couple. Initially she was alone. And it is possible that the idea of a pair is reflected in the figures, sort of consolidating the notion of the imperial pair.

GSF: Was this before she became a widow or afterwards?

AR: Before, this was in the fifties of the 18th century. Franz Stephan was still alive so he was represented. We know that the fresco was started in 1753 and the room was finished in 1755. There is a description of the room which also mentions the figures but it is not clear if the statues already existed or if there was only the project to create them.

GSF: Metastasio clearly had the mandate to represent the University in this program. But do you think that the statues are also linked somehow to the program?

AR: Yes, but rather to the virtues of the imperial couple, I would say. Liberality has to do with the University as an official intellectual institution which needs money. The word generosity would probably be better in this context.

GSF: Is it clear that it was meant monetarily? Are the little discs in the baskets undoubtedly coins? Should they not be cornucopias?

AR: Well I personally was thinking of some sort of cornucopia. You know in Florence for example there existed a famous figure by Donatello, Dovizia, which got destroyed, also a phenotype of the cornucopia. One has really to ask who in our case was responsible for such an unusual program.

GSF: Do you think that an artist in the 18th century would have had the freedom to choose and to propose?

AR: Usually the decision was made by a representative of the court. In this particular case it is thought to have been Franz Christoph von Scheyb, who was a secretary in the government, a very educated person who had relations to the enlightenment and who was in correspondence with Rousseau and Voltaire. He might have been responsible for this program.

GSF: Does it appear unusual that in the case of liberality two statues represent the same virtue? Do you think that it was a political act of Maria Theresia, who gave the money to realize this University, to say – I was generous so you have to show it somehow?

AR: Maybe the intention was to represent the generosity in a dualistic way. But maybe they simply did not know how to couple it another way. It is only speculation as unfortunately, there is nothing written on the pediments. It would be quite interesting to have a look at the coins of the same age and see if liberality was depicted and if so, if ever as a couple.

GSF: If we speak about modern times it is certainly not easy for ministers to find a way to show generosity, by for example giving money to research or to knowledge, as they themselves have a limited budget. It would be curious to know which attribute they would choose to represent their field today.

AR: Today it may be more important to be present in the newspaper and media by giving prizes, awards, and so on. There are other possibilities. Another difference is that in former times it was not the government alone who was endowing institutions, but possibly the Habsburg family with their private money from their personal treasure.

GSF: Because we have no records, we obviously do not know how much the artist was paid for it. Do you think that at that time the better part of the artists were considered as bourgeois, middle class?

AR: The artists were paid quite well but some of them also spent a lot of money and lived quite merrily. I honestly have no idea.

From left to right:

PRUDENTIA ET VIGILANTIA
Prudence and Vigilance

IUSTITIA ET SAPIENTIA
Justice and Wisdom

FIDES ET CONSTANTIA
Faith and Constancy

LIBERALITAS
Liberality

GSF: How much time and work might it have taken? Do you think Mollinarolo had assistance?

AR: I think so. Michelangelo might have been an exception, but I worked on Donatello and he had a big group of helpers. If you look at the figures, it is almost impossible to create them alone. It is difficult to make an estimate but I would say one took approximately up to two years.

GSF: If one would start a new search of documents, would you rather look in the archives of the court or the University?

AR: Well, I think all the documents of the University have been studied well and so I would be surprised if we would find something new on this subject. But we have to take the possibility into account that in some cases documents might not even exist.. There was a relation of trust at that time. Everything was done by shaking hands.

GSF: There are ornaments on the walls besides the statues. Do you think they were also done by Mollinarolo?

AR: Yes, there are the same attributes, for example the lion. After the fire the ornaments were removed and they stayed in the Denkmalamt for years. It was again Luigi Ronzoni who found them and since six or seven years they are back again in the festive hall.

GSF: The University at this time was quite linked to the church. Do you think that they were very critical in the way the attributes were chosen? In other words, would they have criticized that the artist had too much liberty?

AR: I can imagine. Especially, as this was a time of a lot of theological controversy. There was for example a pro- and anti-Jesuitic movement. But I would rather believe that the statues refer more to enlightenment and not so much to theological matters. Otherwise there would be more religious symbols.

GSF: Do you know if the Academy has changed anything about the iconography in the festive hall?

AR: No, the work of artists was already respected at that time and it simply does not look like anything has been changed.

GSF: Professor Rosenauer, thank you very much for the interesting interview. We hope that you and Luigi Ronzoni will give a talk in the Academy as a lot of people might look forward to learning more about this topic. Maybe we made some people interested to see the festive hall by themselves. Maybe this helps find somebody who is willing to give funds for the restoration of the statues. CeMM is happy to act as contact point.

AR: I am glad we are bringing attention to these beautiful sculptures.

"Molecular medicine has been well on the way, from the first sequencing of a protein, insulin, and from the original modeling of DNA structure, some 50 years ago, to present-day molecule-based diagnostics and therapeutics. Yet the enormous potential that this basic biomedical research bears for medicine still has to come to full fruition. CeMM has been established and shaped at the right time and in the right place: it has every chance and it has already shown to contribute substantially to the ongoing biomedical progress: gaining relevant molecular insights and helping to translate them into new and improved methods of prophylactic and clinical medicine. May civil society and polity amply support this promising and salutary endeavor."

Prof. Dr. Hans Tuppy
Chair of the Board of the University of Natural Resources and Applied Life Sciences Vienna
President of the Austrian Science Fund (1974-1982)
Rector of the University of Vienna (1983-1985)
President of the Austria Academy of Sciences (1985-1987)
Minister for Science and Research (1987-1989)

Research at CeMM

Exemplified by Classical Virtues

To structure this year's report we have chosen to refer to our privileged association with the Austrian Academy of Sciences. The Academy encompasses both a historical and philosophical element as well as the mathematical and natural sciences, and enables CeMM to draw from a large spectrum of experience and knowledge to gain some important historical perspective. The festive hall of the Academy with its beautiful frescoed ceiling is one of Austria's most congenial and amiable baroque rooms. Most importantly, it is dedicated to science and scholarship. It also harbors four niches with elegant sculptures of unusual grace. The statues represent embodiments of pairs of classical virtues (faith, constancy, justice, wisdom, prudence, vigilance, liberality). In times as these, where dire economic straits can lead to shortness of vision and the faith in the power of knowledge is questioned, we find inspiration for our work and for our science in these statues. The different chapters of this year's report are structured along these virtues. We hope that this Ariadne's thread will help you find your way when reading our report.

Prudence and Vigilance

Justice and Wisdom

Faith and Constancy

Liberality

Prudence and Vigilance

+ Two Cautionary Tales to Illustrate Prudence as a Virtue

+ The Immune System: A Vigilant Force

prudence
the exercise of sound judgment in practical affairs. Proverb: "Take care of the pennies and the pounds will look after themselves"

vigilance
the process of paying close and continuous attention

Paying Cautious Attention

Prudence is considered to be a classic virtue. The ancient Greeks considered prudence to be the "Father" of all virtues, so what better place to start than here. Although its original meaning was the exercise of sound judgment in practical affairs, in modern English it became increasingly associated with vigilance, with which it is paired in statue form at the Austrian Academy of Sciences.

The statues representing prudence and vigilance act as a reminder to be cautious and aware. These traits are especially important for a scientist when performing research and interpreting data to generate models, but they can also be used to describe the immune system in the human body, which acts as a guard against infection and disease. Both of these interpretations can be applied to research being carried out at CeMM. The groups of Sylvia Knapp and Sebastian Nijman have both made recent scientific discoveries that were unexpected, and which challenged dogmas in the fields of innate immunity and cancer, teaching us the importance of being prudent. Elsewhere at CeMM, ongoing work in Giulio Superti-Furga's lab is focused on understanding how the immune system senses infection to generate new approaches for treating disease.

Prudence: Being Aware as a Scientist

Scientific investigation involves the generation of data by experimentation, which is then interpreted in the context of available knowledge to form hypotheses. These hypotheses are used as a framework on which to build predictions about related biological systems and processes. Hypotheses are continually refined, making science dynamic and exciting. As technologies advance, more sophisticated studies generate data that may lend support to certain hypotheses or, as sometimes occurs, cause them to need reformulating or even abolishing, which can dramatically change the direction of a field.

The sorts of scientific discoveries that cause substantial changes to current thinking often generate much excitement as well as much frustration, particularly when dogmas are overturned and models need to be discarded and replaced with new ones. Regardless, they tend to have a big impact on science, which adds to the excitement for the people working in it. The scientific system does have its own internal controls because it consists of a large community of scientists who are constantly testing the same hypotheses using different systems and tools. However, it still pays to be prudent when interpreting data and to appreciate that there are limitations to what can be concluded from individual experiments.

Vigilance by the Immune System

Vigilance implies an awareness of certain dangers and the establishment of mechanisms to deal with those dangers. The immune system can be thought of as being vigilant as it is on constant alert throughout the body for disease and damage. The innate immune system is able to detect the presence of invading pathogens such as bacteria and viruses. It responds by producing a complex immune response consisting of many different types of cells and molecules that collectively fight infection and return the body to a healthy state. Understanding how the immune system senses infection can help generate new approaches for treating disease.

Two Cautionary Tales to Illustrate Prudence as a Virtue

"The conclusion that cardiac glycosides would be successful anti-cancer agents was premature."

Tale One:
The Myth of Cardiac Glycosides and Cancer

The careful design and control of scientific experiments is crucial. Overspeculation – when one makes interpretations unsupported by the actual data – can lead to incorrect assumptions, which can be particularly destructive in fields involving human diseases. The first tale of caution comes from an area of cancer biology that has concluded that cardiac glycosides, which are a class of drugs used successfully to treat chronic heart failure, could be useful for treating cancer. The experiments leading to this conclusion appear solid on the surface. However, a serendipitous discovery in Sebastian Nijman's lab, in collaboration with the lab of Matthias Mayerhofer at the Medical University of Vienna, directly challenges this view, and the field is now faced with a sudden drastic change of direction.

The discovery came from a genetic screen to search for new drugs that could inhibit a protein kinase called JAK2, which is mutated in a large number of patients suffering from Polycythemia vera; a hyperproliferative blood disorder. From this screen containing over one thousand diverse drugs, cardiac glycosides were identified as being able to specifically reduce the levels of JAK2. At first, this was an exciting surprise. One of these drugs, known as digitalis, was extracted from the flowering plant *Digitalis purpurae* (otherwise known as the Common Foxglove), and has been used as a medicine to treat heart disease for over two hundred years. The groups scoured the literature and discovered numerous reports beginning in the 1960s, which eventually concluded that cardiac glycosides have anti-cancer activity.

How Cardiac Glycosides Really Work

This previous literature had already led to the current testing of cardiac glycosides in clinical trials using cancer patients. However, the mechanism of action of cardiac glycosides in this context had never been reported, and there remained an absence of definitive proof that they indeed have anti-cancer activity. Thus, the conclusion that cardiac glycosides would be successful anti-cancer agents was premature. Further studies in the lab discovered that in fact, cardiac glycosides work by inhibiting the general synthesis of proteins, which is a fundamental process and one that influences many other cellular functions. Indeed, this discovery can explain the vast majority of the published work and demonstrates that there is no specific effect of cardiac glycosides on cancer cells. Their results were published in the journal *PLoS ONE* in 2009, and have serious implications for the clinical evaluation of these drugs.

Tale Two: The Alter Ego of TREM-1

In another unrelated story, Sylvia Knapp's group has been investigating the role of a cell surface receptor known as TREM-1, which was thought to contribute to the adverse effects of inflammatory diseases such as sepsis – a severe systemic inflammatory response syndrome caused predominantly by respiratory tract infections. TREM-1 is found on the surface of myeloid cells in the blood, where it amplifies inflammation mediated by the Toll-like receptor (TLR) during bacterial infections. TREM-1 has become an attractive target for drug inhibition to treat medical conditions like sepsis, however the biological function of TREM-1 at that point was poorly understood.

The group set about studying the role of TREM-1 in pneumonia caused by the bacteria *Streptococcus pneumoniae*. They first identified that TREM-1 was upregulated in infected lungs and human plasma, together with an augmented response by the immune system towards the bacteria. They found that in mice infected with *S. pneumoniae*, activation of TREM-1 using an agonistic antibody enhanced the early inflammatory response, which was associated with lower levels of negative regulators of TLR signaling in lung tissue. However, later in the infection, TREM-1 activation actually promoted the resolution of pneumonia and remarkably led to an accelerated elimination of bacteria and consequently improved survival. So, TREM-1 has a protective role in the innate immune response to a common bacterial infection, suggesting that caution should be exerted when modulating TREM-1 activity during certain bacterial infections. Their results were reported in the *Journal of Immunology* in 2009.

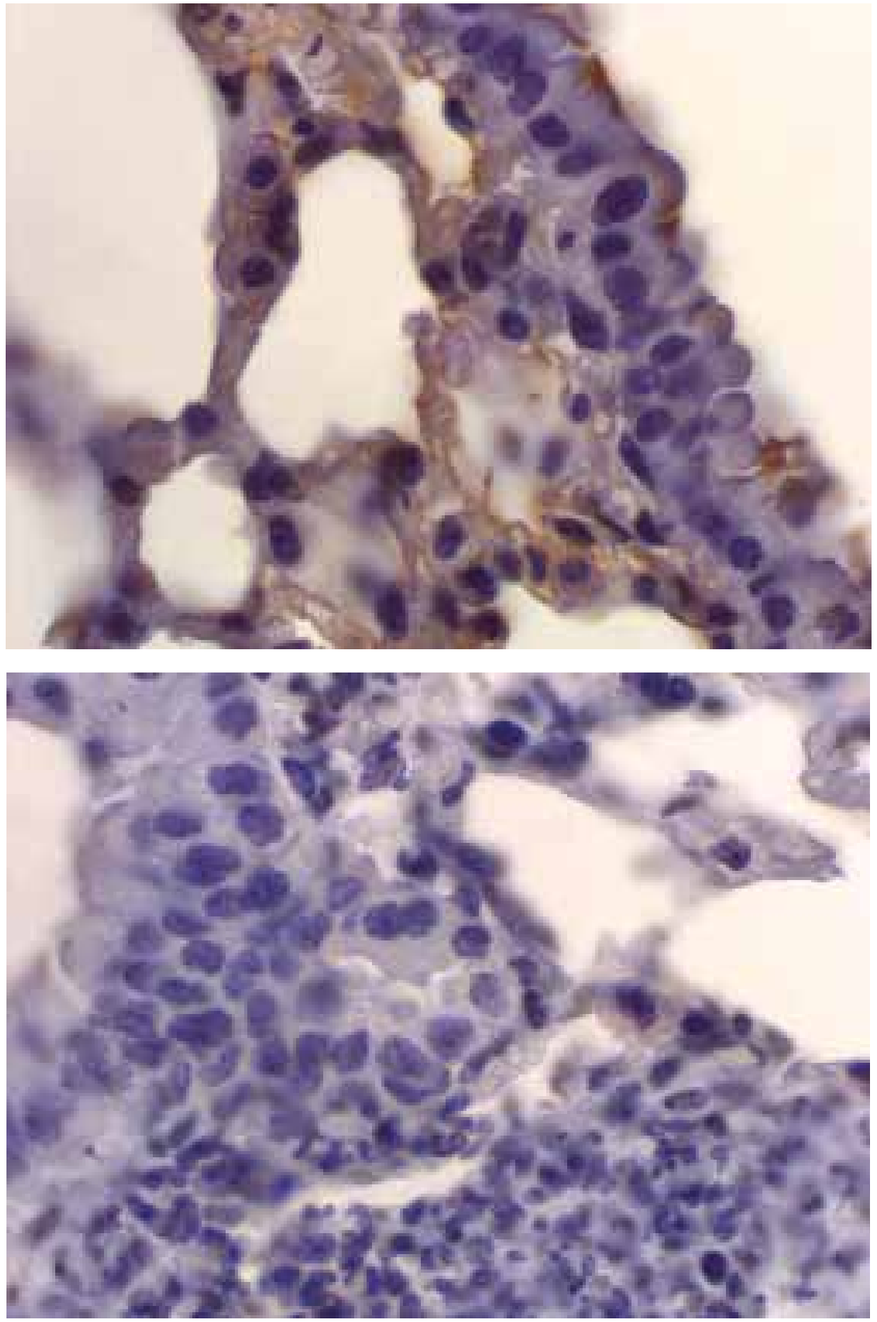


Fig. 1 Histology of mouse lung tissue 24 hours after infection. Top is stained with antibody against IRAK-M, bottom shows infiltrates

The Immune System: A Vigilant Force

"The goal is to find cellular proteins that can be modulated to increase the body's antiviral immune response."

Keeping a Watchful Eye out

The innate immune system employs a variety of strategies to recognize and fight invading pathogens. Crucial to this sensor function are the so-called pattern recognition receptor proteins such as Toll-like receptors (TLRs) that bind specifically to pathogen-associated molecular patterns, including viral and bacterial nucleic acids, proteins and carbohydrates. Many pathogens are sensed while they are circulating through the body by receptors found on the surface of cells. However, bacterial and viral nucleic acids (both DNA and RNA), which are one of the most important signals for activating the innate immune system, are recognized once these pathogens have actually entered individual cells.

Cell Patrol

Sensor receptor proteins patrol different parts of the cell to look for invading pathogens. They also search the endosomes, which are membrane-bound organelles that enclose extracellular material such as the various types of nucleic acids found in invading bacteria and viruses. A project led by Christoph Baumann in Giulio Superti-Furga's lab is focused on understanding how these foreign nucleic acids are taken up into endosomes and sensed by TLRs. This knowledge could be used to identify interesting candidates for drug targets to fine tune the immune response in diseases like chronic inflammation, sepsis, rheumatoid arthritis and cancer.

The group employed a proteomics approach, involving the isolation of proteins bound to endosomal TLRs and identifying them by mass spectrometry and bioinformatics analysis. This revealed a candidate list of seven interacting proteins for several different TLRs, which were named IPOT1-7 for Interacting Protein of endosomal TLRs. IPOT4 was subsequently found to act as a co-receptor required for the uptake and delivery of nucleic acids to all endosomal TLRs. This is interesting because it was previously unclear exactly how nucleic acids were taken up into this organelle. In contrast, IPOT7 was found to negatively regulate the secretion of cytokines, which are immune signaling molecules, and thus is an anti-inflammatory protein. Further experiments are planned to address the functional role of this protein in TLR signaling.

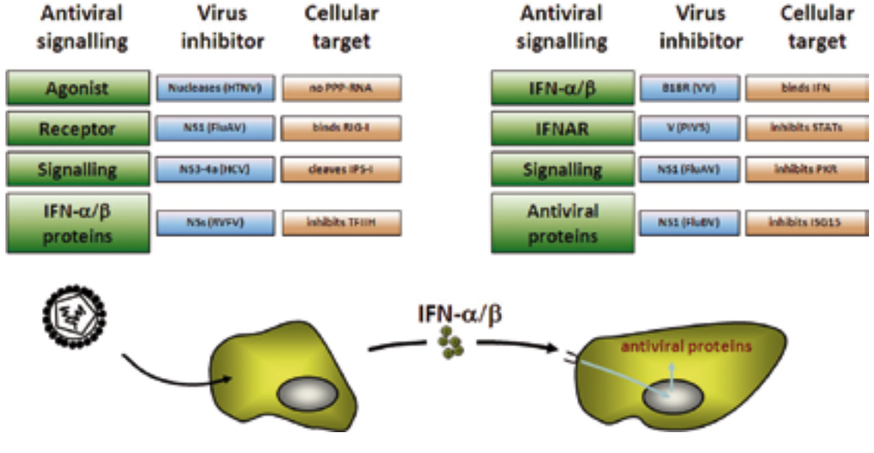


Fig. 2 Virus infection activates signaling cascades (green) that culminate in expression of type-I interferon (IFN-a/b), which is secreted to protect adjacent cells. Virus proteins (blue) inhibit the antiviral response at various levels (brown). Understanding binding partners of viral proteins may help to understand the innate immune system and may highlight possibilities for medical intervention.

Discovering New Vigilant Factors

Viruses such as Pox or Herpes contain DNA that is recognized by the body as foreign and acts as an alarm signal to trigger the production of proinflammatory cytokines and interferons to activate the immune response. Tilmann Bürckstümmer, also in Giulio Superti-Furga's group, has been developing a screen to discover new viral DNA sensor proteins. The group uses a proteomics screen to search for cytosolic proteins that have both an affinity for DNA as well as being produced in the cells upon viral infection. The screen has already proven successful as it led to the discovery of AIM2, a DNA sensor that triggers inflammation in macrophages, which was published in *Nature Immunology* in 2009. However, there is still ample evidence that additional sensors have yet to be discovered.

Another way of finding new vigilance factors is to use the viruses themselves. Fairly recently, an RNA helicase known as RIG-I was found to recognize virus-specific structures and initiate an immune response. Interestingly, different viruses have evolved specific mechanisms to respond to this. For example, influenza viruses can inhibit RIG-I whereas Bunya viruses instead inhibit the protein kinase PKR. So while scientists are trying to discover all the cellular proteins that can recognize viruses, the viruses themselves are already well aware of them, and use this information to find ways to survive. Andreas Pichlmair in Giulio Superti-Furga's lab has been expressing viral proteins to identify interacting host cellular proteins using mass spectrometry. Initial results are promising and suggest that different viruses bind to many of the same host proteins to escape immune detection. The goal is to find cellular proteins that can be modulated to increase the body's antiviral immune response and thus could be valuable for developing therapies to treat infectious diseases. Inhibition of these same proteins could also be of benefit during autoimmune diseases that are often characterized by an overreaction of the immune system.

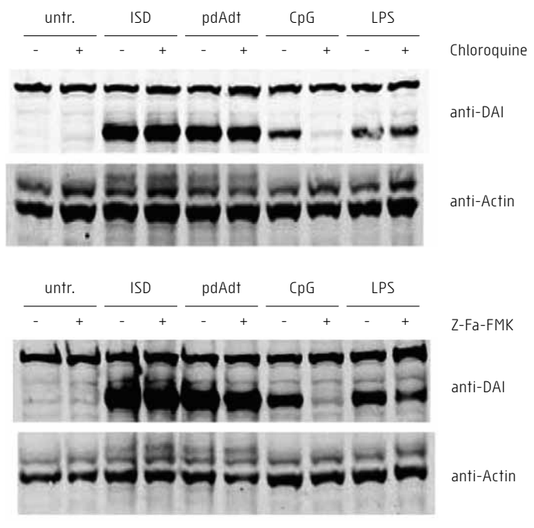


Fig. 3 Cytosolic DNA Recognition. Cultured mouse macrophage-like cells were pretreated with two inhibitors; chloroquine (inhibits endosome acidification – top panel) or Z-FA-FMK (inhibits lysosomal proteases called cathepsins – bottom panel) and stimulated with a set of pathogen-derived components: double-stranded DNAs (ISD), a repetitive DNA sequence (pdAdT), unmethylated CpG-DNA (CpG) or lipopolysaccharide (LPS - elicits an immune response). Untr. = untreated. Expression of the protein DAI, which can be visualized using Western blotting as shown here, indicates type-I interferon induction (i.e. an immune response). These results show that both inhibitors block recognition of CpG-DNA in the endosome, but not recognition of LPS on the plasma membrane. DNA (ISD or pdAdT) recognition is unaffected, suggesting DNA sensing occurs in the cytosol independently of cathepsin activity.

Citation: Karayel et al. Eur J Immunol. 2009 39(7):1929-36

"From the publications in the last years it is clear that in the short time of its existence CeMM has initiated world class research in its chosen areas and is poised, if supported adequately, to soon become a center of research excellence and a source of inspiration in the field of Molecular Medicine. I hope that CeMM will have the same energizing effect on the medical research community in Austria that the IMP has had for the basic biosciences."

Prof. Dr. Max L. Birnstiel
Founding Director of the Research Institute of Molecular Pathology (IMP)

justice
the quality of being just or fair

wisdom
the ability to think and act utilizing knowledge, experience, understanding, common sense, and insight

Justice and Wisdom

+ Two Ways of Gaining Wisdom

+ Justice: Wisdom in Action

Using Knowledge to Fight Disease

Justice and wisdom are paired together as statues at the Austrian Academy of Sciences building in Vienna. Their pairing seems particularly fitting given a quote from the English historian James Anthony Froude (1818-1894) who said, "Justice without wisdom is impossible." He could easily have been referring to the scientific quest for knowledge – wisdom – and the translation of that knowledge to fight disease – justice. It is within this framework that many projects taking place at CeMM can also be appropriately grouped.

Scientists generate knowledge about all aspects of whole organisms, including individual biological systems and groups of proteins and other molecules. Many sophisticated technologies have been developed to generate these comprehensive datasets, which can then be utilized by the scientific community to test hypotheses and help generate new drugs to treat diseases. Working together, the bioinformatic and mass spectrometry groups at CeMM have identified the individual proteins found in cells representing all three separate germ layers of the human body. These layers are composed of very different types of cells, which the bioinformatic group led by Jacques Colinge has used to generate a dataset comprising the so-called "core human proteome".

Learning about Molecules

Recently a new class of long nucleic acids known as macro non-coding RNAs (ncRNAs) have been discovered and the Barlow group at CeMM has been looking into their function. To do this, they have been studying how genomic imprinting regulates the activity of certain genes, which is a mechanism that is directly linked to the parent from which the copy of the gene was inherited. They have already discovered how macro ncRNAs are involved, and suspect the same mechanism works to silence tumor suppressor genes, which can lead to cancer.

Bringing Disease to Justice

Using knowledge to fight disease is an underlying principle that governs the majority of the research performed at CeMM. The mass spectrometry group led by Keiryn Bennett has been studying the protein composition of a biological system in humans, specifically the aqueous fluid of the eye. This type of project has only recently become technically feasible, and the group has had to introduce new technology to accomplish it. Importantly, they have been analyzing aqueous fluid isolated directly from the eyes of patients suffering from different eye diseases, which could generate new approaches for treatment. The Knapp group at CeMM is waging another honorable battle against disease. They have been studying why intensive care unit (ICU) patients often suffer from bacterial pneumonia caused by relatively harmless bacteria. Using mouse models they have already generated important insight into this process and have also found a therapeutic intervention that could prove life saving in humans.

Two Ways of Gaining Wisdom

"The core interactome is active in every human cell and implements a fundamental network of exchange and synchronization between biological processes."

A Comprehensive Approach Using comprehensive mass spectrometry datasets generated by Keiryn Bennett's team from various cell lines covering all three germ layers, Jacques Colinge and his group have identified over a thousand proteins universally expressed in all human cells. Using their own bioinformatic platform, they went on to analyze these proteins, grouping them according to their cellular function, as well as incorporating additional information on their structure and evolutionary conservation and their presence in certain networks and pathways. Their results reveal interesting properties of the so-called "core human proteome", particularly its flexibility, which probably reflects the ability of these common building blocks to operate in a wide variety of different environments. Statistical analysis of the interactions linking proteins of the core proteome showed that this network has evolved to synchronize protein synthesis with many other biological processes, suggesting that one important function of the core proteome is self-maintenance.

Learn How it Works
The Barlow group has been studying how macro non-protein-coding RNAs (ncRNAs), which are transcribed from DNA, work to silence genes that are found nearby on the same chromosome. This mechanism is also likely to be important in cancer. In normal human tissues, cells produce tumor suppressor proteins whose job is to control growth and block the formation of tumors. However, in many cancers these tumor suppressor genes are silenced by chemical methylation marks added directly to the DNA or to histone proteins that bind DNA. The Barlow group has been studying imprinted genes, which have parental-specific expression, to investigate how tumor suppressor genes gain these silencing methylation marks. Members of the group published two reviews on the regulation of imprinted expression by macro ncRNAs in the journals *RNA Biology* and *Development* in 2009.

Secret Mechanisms
Human chromosomes contain roughly 23,000 genes but only 200 of these show imprinted expression by inheriting an epigenetic DNA methylation mark from one of their parents. A major discovery by the Barlow group 8 years ago showed that the DNA methylation mark was used to silence a macro ncRNA, which was able to induce silencing of a gene involved in suppression of embryonic growth that lay close to it on the same chromosome. It has recently become clear that huge numbers of macro ncRNAs are made in human cells, even exceeding the number of protein-coding genes. In the Barlow group over the past year, two approaches have produced some particularly interesting results. In one study, the team has shown that areas of DNA containing genes silenced by macro ncRNAs gain different chemical methylation marks on histone proteins compared to regions containing genes that are silenced in a tissue-specific manner. These results were published in the journal *Genome Research* in 2009, and raise the possibility that macro ncRNAs could be selectively targeted by therapeutics, without disturbing the repression of other genes. In a second study, the team used mouse embryonic stem cells to analyze a change in the expression of a specific macro ncRNA and its target imprinted locus over time. They discovered that macro ncRNAs could silence genes specifically by blocking their upregulation. This important result was published in the journal *Development* in 2009. The group's findings explain many puzzling features of silent imprinted genes and also pave the way for future studies in cancer biology aimed at reactivating silenced tumor suppressor genes.

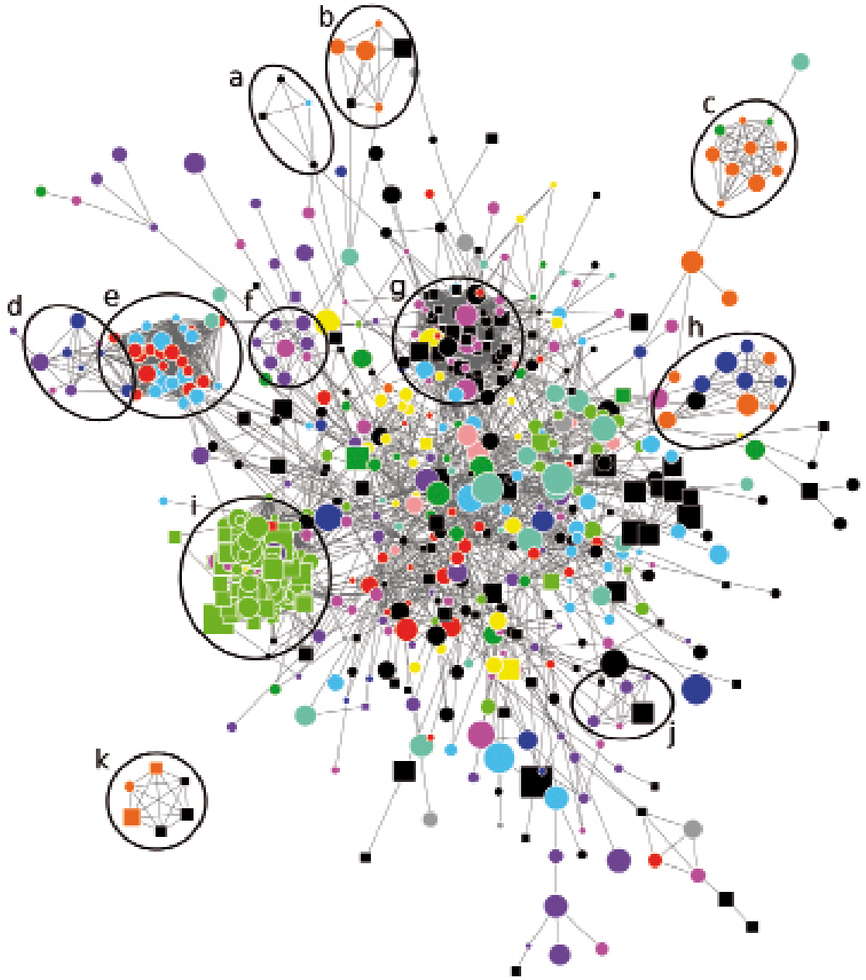


Fig. 1 Interactions taking place between proteins of the core proteome. This core interactome is active in every human cell and it implements a fundamental network of exchange and synchronization between biological processes. Each node is a protein, edges represent physical interactions, and the colors represent different processes, e.g green is translation, red is cell cycle, cyan is cell death, etc. The ellipses highlight known protein complexes – or molecular machines – that are recognized in the core interactome, e.g. (a) is the exosome, (e) is the proteasome, (i) is the ribosome, etc. Analysis of the topology of the core interactome indicates that this network has been "optimized" by evolution to synchronize translation with the other biological processes.

Justice: Wisdom in Action

"Characterization of the proteome in healthy and diseased eyes would potentially improve existing treatment options."

An Eye for Humour

At CeMM, Keiryn Bennett and her team have been analyzing the protein content of aqueous humour, a clear fluid filling the anterior segment of the human eye. Aqueous humour supplies parts of the eye with nutrients, as well as removing waste and participating in the immune response against invading pathogens. Importantly, defects in proteins found in aqueous humour are associated with several eye diseases, including age-related macular degeneration, which is one of the leading causes of vision loss in the industrialised world. The group reasoned that a thorough characterization of the proteome in healthy and diseased eyes would help to elucidate the disease process and potentially improve existing treatment options.

Due to the low volume of aqueous humour that can be isolated from the human eye, Keiryn's team had to design a strategy to ensure they could accurately and comprehensively identify all of the proteins present in the samples. Using this strategy, they were able to analyze the proteome of aqueous humour taken from an individual patient. They identified 198 protein groups, and found a low level of variability in protein type and concentration between the individual samples. This analytical approach will be a valuable tool for monitoring an individual's response to disease treatment, and could also be used to analyze other types of body fluids to gain further insights into many different diseases.

A Matter of Life and Breath

The reason why intensive care unit (ICU) patients often acquire secondary pneumonia caused by relatively harmless bacteria is poorly understood, although the incidence is high. This form of pneumonia is known as ventilator-associated pneumonia (VAP) and is one topic under investigation by scientists in the Knapp group at CeMM. They noticed that all ICU patients experience some form of mild lung injury before the onset of pneumonia, which has a variety of causes including aspiration of gastric contents, the ventilation itself or inflammation caused by an independent disease. The group reasoned that this prior lung challenge then predisposes the patients to secondary infection.

They addressed this using a mouse model of acid aspiration followed by infection with the pathogen *Pseudomonas aeruginosa*. Results revealed that as predicted a prior lung injury predisposes the animal to acquiring a bacterial infection. Following on from these studies, the Knapp group hypothesized that prevention or attenuation of this pre-existing lung injury might help prevent ICU patients from acquiring pneumonia, or at least help them to fight it. Indeed, using their mouse model, they found that the fibrin-derived peptide $B\beta_{15\text{-}42}$ could reduce vascular leak, which is a hallmark of acute lung injury, and could protect mice from both acute lung injury and secondary infection. This work was published in the *American Journal of Respiratory and Critical Care Medicine* in 2009. Further work, in collaboration with scientists in Austria, Russia and the UK, identified a potential therapeutic benefit for this same Bβ peptide in preventing shock syndrome, which was also published in 2009, in the journal *PLoS ONE*.

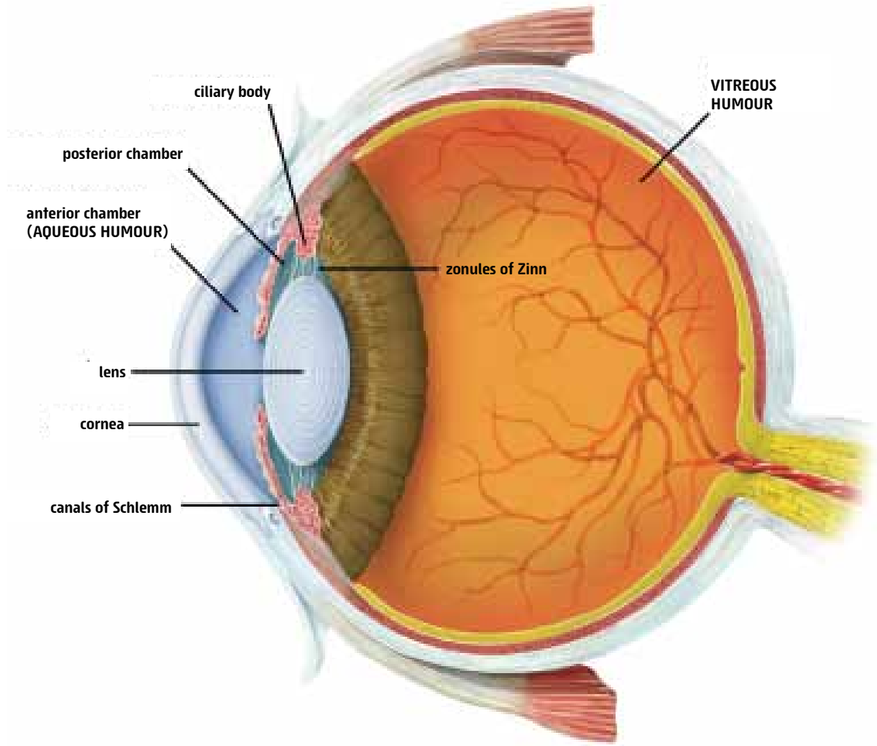


Fig. 2 Sagittal section of the human eye. The anterior chamber between the cornea and lens contains the aqueous humour and the firm, gel-like vitreous humour is located behind the lens in the posterior part of the eye.

Illustration by Kevin Sommerville, www.ksomervillemedicalart.com

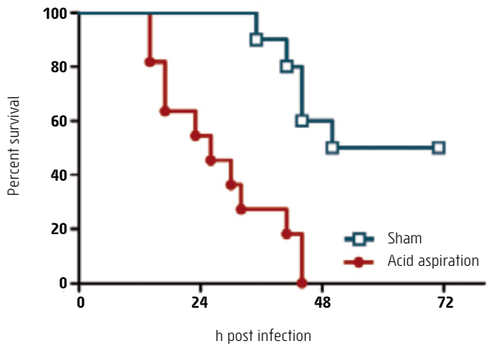


Fig. 3 Survival curve of healthy (sham) mice that were infected with Pseudomonas compared to mice that suffered from lung injury (acid aspiration) before bacterial infection.

"CeMM – just another research institution? No! CeMM was founded in close relation to the Medical University of Vienna to provide it with the unique opportunity of combining most advanced research technologies with burning medical needs. Looking back at the past years, CeMM has utilized these opportunities quite successfully and this is also what makes CeMM so special: Looking at inflammation as a disease entity and not as a mere symptom of a disease and at diseases as disturbed networks and not at each pathway separately. To accomplish this and to be at the forefront of research Principal Investigators were recruited, who are established members of their respective international research communities and represent a stimulating mixture of MD/PhDs and PhDs. In further pursuing this approach, I am confident that CeMM – although already very successful – will become an integral member of medical research in Vienna much to the benefit of all participating institutions."

Prof. Dr. Bernd Binder
Department of Vascular Biology and Thrombosis Research
Medical University of Vienna

Faith and Constancy

+ Keeping Faith and Gaining Knowledge

+ Fighting Disease to Maintain Constancy

faith
confident belief in the truth, value, or trustworthiness of a person, idea, or thing

constancy
freedom from change or variation; stability

Stable Beliefs

The statues representing faith and constancy are coupled at the Austrian Academy of Sciences. Faith is a solid trust in something that is not based on reason. In a way, this reflects curiosity driven research, where an experiment is performed to test a given hypothesis with no prior knowledge as to the outcome. Faith is also apparent in some fields, particularly in the medical realm, where drugs are used because they were previously shown to be effective, rather than because it is known exactly what they do. Here, the addition of knowledge to faith can result in a new generation of smart drugs that more effectively treat disease.

Joining Faith with Rationale

Many drugs are used to successfully treat patients in the clinic without firm knowledge about how they actually work. They just do. However, many existing drugs are in urgent need of improvement in both efficacy and safety, and there is a constant demand for new drug development. So, scientists in Giulio Superti-Furga's group at CeMM are working towards a comprehensive characterization of drug action in order to improve their value and help identify the next generation of drugs. Importantly, in 2009 CeMM scientists, along with collaborators in Vienna, Graz and Innsbruck, were awarded a competitive grant funded by the Austrian Genome Research Program (GenAU) for an innovative and large-scale project named PLACEBO (for PLatform Austria for ChEmical BiolOgy). This project aims to use sophisticated screens to develop a nationwide platform for identifying molecular targets for active drugs.

Keeping it Constant

While drugs require modifications and development to make them more effective, the body itself fights to maintain a constant state – homeostasis – in the face of continuous challenge by disease. So, constancy can represent the healthy state of the human body. Indeed, diseases such as cancer can be thought of as the very opposite of constancy: they have gained strength from being dynamic and maintaining the capacity for change. This gives cancer the upper hand when it comes to trying to cure it. Several groups at CeMM are rising to this challenge by using different approaches to find new ways to treat cancer, leading to a number of high profile publications in 2009.

Sebastian Nijman's lab uses a concept called synthetic lethality, to tease out the weaknesses of cancer cells and find drugs that can exploit them. Giulio Superti-Furga's group is following on from understanding the mechanism of action of drugs by finding new ways to inhibit disease-causing proteins. They are studying how the activity of an oncogenic fusion protein can be regulated, with a view to identifying new types of drugs that could be used to treat leukemia. Finally, scientists in the lab of Robert Kralovics are searching through DNA sequences for the genetic causes of Myeloproliferative Neoplasms, which could provide new targets for developing drugs.

Clearing out Disease

Our immune system helps to maintain our bodies in a healthy state using many different techniques. Christoph Binder's lab is studying the role of natural antibodies in keeping blood vessels clear and preventing conditions like atherosclerosis, which can lead to heart attacks and stroke. Maintaining the body in a constant and healthy state is not easy when faced with so many challenges, including infection by pathogens, harmful genetic mutations and our unhealthy lifestyles. If we can understand how the body manages it, we may find new ways to make us healthier.

Keeping Faith and Gaining Knowledge

"Most drugs bind to more than one cellular protein, which is why many of them cause side-effects in patients."

Determining how Drugs Work

Chronic Myelogenous Leukemia (CML) is caused by a rearrangement of chromosomes inside the nucleus of a cell, leading to the inappropriate fusion of two genes, known as Bcr and Abl. This generates an oncogenic protein, Bcr-Abl, with aberrant tyrosine kinase activity. White blood cells carrying the oncogenic Bcr-Abl fusion are able to divide uncontrollably, causing leukemia. Fortunately there are several drugs available to treat patients with CML. The pharmaceutical company Novartis launched the first of these, called Imatinib, in 2001. Imatinib directly inhibits Bcr-Abl's kinase activity leading to remission of the disease. However, mutations in Bcr-Abl have emerged in patients treated with Imatinib. These mutations make patients resistant to the drug and lead to cancer relapse. To address this, both second and third generation Bcr-Abl inhibitors have been recently developed.

Although these different drugs are all able to bind to mutant forms of Bcr-Abl, they don't all work in exactly the same way. Most drugs bind to more than one cellular protein, which is the reason why many of them cause side-effects in patients. Uwe Rix and colleagues, working in Giulio Superti-Furga's group, have been using a chemical proteomics approach to identify the cellular protein target profiles of a number of different Bcr-Abl tyrosine kinase inhibitors. One of those, INNO-406 (Bafetinib), has been reported to efficiently inhibit most Bcr-Abl mutants as well as another tyrosine kinase called LYN. Knowledge of the full target spectrum of Bafetinib would provide a molecular basis for understanding potential side-effects, and help develop novel therapeutic applications and possible combination therapies. Uwe and Giulio wrote a review article on chemical proteomics for the journal *Nature Chemical Biology*, in 2009. This review received substantial attention from the chemical biology community and became the most highly downloaded review article of the journal in that year.

Placebo

In addition to this, CeMM has established a solid infrastructure to begin a pioneering project on drug discovery that will provide an important expertise for diverse scientists throughout Europe. In 2009, a prestigious research grant by the Austrian Genome Research Program (GENAU) was awarded to CeMM, along with its collaborators, to develop their sophisticated chemical proteomics technology for the large-scale study of bioactive substances. The aim is to provide a comprehensive analysis of the cellular targets of many different drugs and to identify important new drugs for treating common diseases. Stefan Kubicek, who has been recruited from the esteemed Broad Institute in Cambridge, USA, will head this screening facility. It will be set up in custom-built laboratories in the new CeMM building and the first stages of equipment purchasing are already well underway. Furthermore, the European academic chemical biology and drug screening community has invited this facility to participate in the international EU-Openscreen consortium, which is an initiative pursued under the strategic roadmap for European Research Infrastructure.

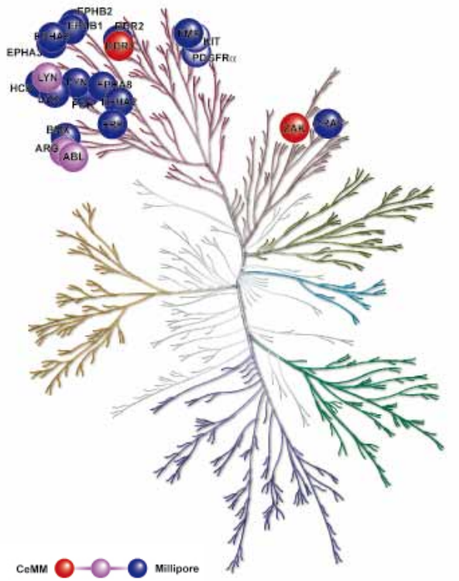


Fig. 1 Global protein target spectrum of the Bcr-Abl tyrosine kinase inhibitor INNO-406. Red: targets identified only by chemical proteomics with chronic myelogenous leukemia cells, blue: targets identified only by *in vitro* kinase assays; purple: targets identified by chemical proteomics and *in vitro* kinase assays. KIT/PDGFR: activity of INNO-406 against distinct disease-relevant kinase mutants.

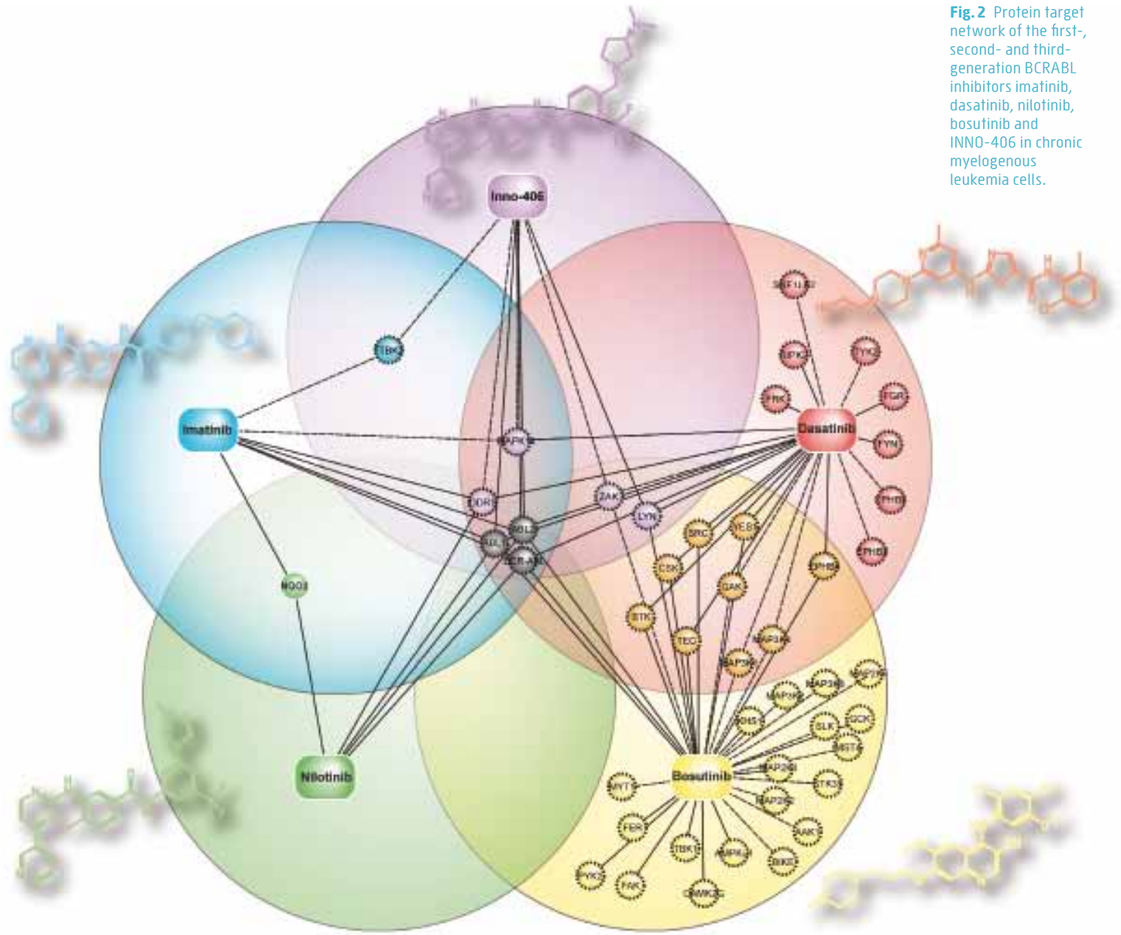


Fig. 2 Protein target network of the first-, second- and third-generation BCRABL inhibitors imatinib, dasatinib, nilotinib, bosutinib and INNO-406 in chronic myelogenous leukemia cells.

Fighting Disease to Maintain Constancy

"Synthetic lethality has been recently exploited to target genetic mutations found in human cancer cells."

Finding New Ways to Treat Leukemia

The causative molecular event of Chronic Myelogenous Leukemia (CML) in humans is the expression of the oncogenic fusion gene, Bcr-Abl. In the cells expressing Bcr-Abl, a large number of signaling pathways are active, involving many different proteins and molecules. Although Bcr-Abl inhibitors are available, resistance leading to disease relapse is still one barrier to finding a cure. Alternative approaches are needed to provide superior future therapeutic options for treating and hopefully curing CML.

Scientists working in Giulio Superti-Furga's lab have systematically mapped the protein complex centered around Bcr-Abl in leukemic cells. The work revealed a molecular machine composed of only seven proteins that bind to Bcr-Abl and was published in the journal *PNAS* in 2009. The group found that this Bcr-Abl complex is mostly disrupted by the classical drug Imatinib, although Bcr-Abl still interacts with some of its binding partners. This observation may lead to a novel way of looking at drug targets, specifically as protein complexes rather than just single proteins.

Florian Grebien and Oliver Hantschel in Giulio Superti-Furga's group have also been studying the molecular structure and dynamics of Bcr-Abl regulation. In collaboration with the laboratories of John Kuriyan (University of California, Berkley, USA), Tony Pawson (Lunenfeld Research Institute, Toronto, Canada) and Stefan Knapp (Structural Genomics Consortium, Oxford, UK) they have identified novel regulatory mechanisms of Abl activity through structural, biochemical and cellular studies. These insights could lead to alternative therapeutic approaches for the treatment of CML to cope with arising resistance in patients to the current tyrosine kinase inhibitors.

Searching for the Genetic Mutations that Cause Disease

It is widely recognized that cancers originate from somatic mutations that occur during life in different tissues of an organism. However, hereditary factors are also important, and a significant number of cancers and other diseases are familial. This means family members can inherit mutations that predispose them to a certain disease. Myeloproliferative neoplasms (MPN) are a group of sporadic disorders that in rare cases also occur in families, and are the focus of the Kralovics lab. MPNs are characterized by chronic hyperproliferation of blood cells leading frequently to transformation to acute leukemia. The lab has been searching for acquired and hereditary factors that lead to the development of MPNs.

The main genetic mutation found in patients suffering from MPNs lies in a gene encoding for the tyrosine kinase JAK2. Recently, the Kralovics lab demonstrated that an inherited version of the JAK2 gene significantly predisposes the person to this common JAK2 mutation and thus to the development of MPNs. This work was published in the journal *Nature Genetics* in 2009.

Two Approaches to One Problem

The Kralovics group has implemented two different approaches for identifying additional hereditary factors linked to MPNs. The first approach is to sequence DNA samples from patients who develop MPN sporadically without any prior family history of the disease. This is done using a sophisticated approach that enables the simultaneous genotyping of more than 900,000 markers distributed throughout the genome. A difference in one of these markers compared to a healthy control group may indicate that a nearby gene has some connection with MPNs, stimulating further and more focused study. They can also analyze the distribution of known mutations within a patient population. The second approach is to use familial cases of MPN to identify familial-type hereditary factors. The lab has already collected samples from individuals in over fifty families that suffer from MPNs, from three different countries. The DNA from all affected family members is then used to identify causative genetic mutations. This successful biobanking of rare samples was done in collaboration with scientists from Italy and Australia.

The identification of mutations causing MPNs enhances scientists´ understanding of cancer evolution in general, where both acquired and inherited genetic factors play a fundamental role. The mutations can also serve as important markers for early identification and potential prevention of MPNs in patients, and form a basis for the identification of novel drug targets and more rational therapies for this group of diseases.

Synthetic Lethality and Cancer

It is well known that the genetic and epigenetic changes in cancer cells cause them to grow uncontrollably and become invasive. Many of these individual mutations have already been identified and several large international projects are now dedicated to finding them all. However, it has become clear that having the information is not in itself enough to develop new treatments. This is partly because many mutated proteins are difficult to inhibit with a small molecule drug, and it is almost impossible to bring back deleted or inactivated proteins that are causing the disease.

To overcome these hurdles, Sebastian Nijman's group is taking a different approach. They plan to target cancer cells by taking advantage of synthetic lethality – a concept borrowed from classical genetics. Geneticists speak of a synthetic lethal interaction between two genes when disrupting or inactivating both of the genes together causes the cell to die, whereas inactivation of either gene on its own has no effect. This principle has been recently exploited to specifically target some of the genetic mutations found in human cancer cells.

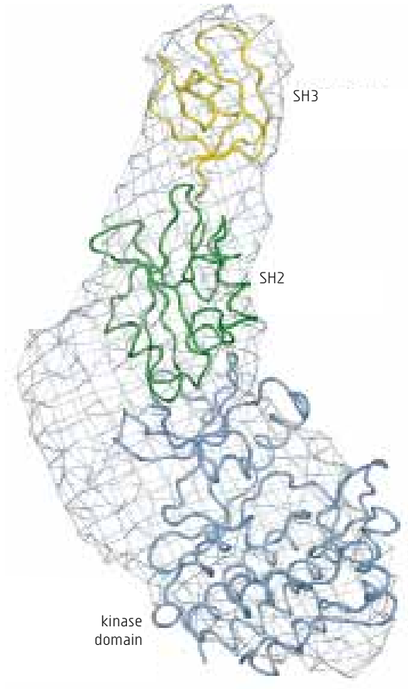


Fig. 3 Small-angle X-ray scattering shape reconstruction of the active Abl tyrosine kinases adapted from Nagar, Hantschel et al. (2006) Mol. Cell 21, 787-798. The kinase domain and SH2 and SH3 domains are colored blue, green and yellow, respectively.

"Cellular mechanisms have evolved to maintain the body in a homeostatic state in the face of change during aging and disease."

Finding Cancer Weaknesses

Unfortunately, synthetic lethal interactions are not easy to find. Therefore the Nijman lab is embarking on a systematic approach using high-throughput technologies to help to identify them. They can mimic the genetic changes found in cancer cells using molecular biology techniques and screen them against panels of drugs and drug targets. With this method the team can now measure tens of thousands of combinations between cancer genes and drugs and drug targets. Using this technology, the lab hopes to identify new synthetic lethal combinations that could lead straight to new cancer therapies that are also tailored to individual patients.

How Natural Antibodies Help Maintain the Status Quo

Many cellular mechanisms have evolved to maintain the body in a homeostatic state in the face of change in the form of cell turnover, aging, and disease. In Christoph Binder's group, they have been studying the role of natural antibodies, which, unlike other types of antibodies, arise spontaneously without apparent antigen exposure early on in life. Natural antibodies are produced by a subset of B-lymphocytes (a type of blood cell) and bind to a broad range of antigens from both external and internal sources. They have an important function in defending the body against invasion by pathogens. Work ongoing in the lab has focused on the role of natural antibodies in clearing waste material from the body, which is crucial for maintaining homeostasis.

Eliminating Waste

In collaboration with the group of Joseph Witztum at the University of California San Diego, USA, the lab recently identified an important property of natural antibodies. They showed that oxidation-specific epitopes are found on the surface of apoptotic (dying) cells, and were prominent targets of natural antibodies in both mice and humans. The recognition of these epitopes promoted the clearance of apoptotic cells. These findings revealed an important novel recognition pathway by which natural antibodies mediate homeostasis, which was published in the *Journal of Clinical Investigation* in 2009.

Oxidation-specific epitopes are also present during inflammatory conditions such as atherosclerosis, and may represent danger signals in other pathological settings. Likely, the omnipresent generation of these epitopes throughout life has contributed to the need and thus the positive selection of natural antibodies. By targeting these stress-induced cell-derived structures, natural antibodies may provide a generalized protective response against the consequences of oxidative stress.

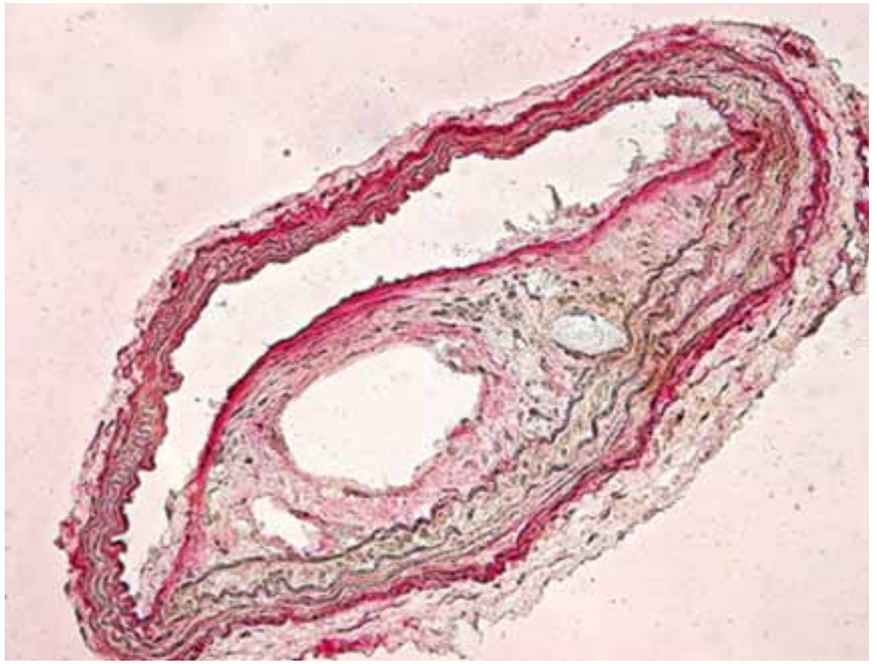


Fig. 4 Immunohistochemistry of an atherosclerotic lesion with the natural IgM antibody NA-17. Sections of the brachiocephalic artery from cholesterol-fed Ldlr–/–Rag1–/– mice were stained with NA-17, a monoclonal germline encoded natural IgM anitbody against Malondialdehyde-epitopes. NA-17 recognises oxidation-specific epitopes present in atheroschlerotic lesions. (Original magnification, x200)

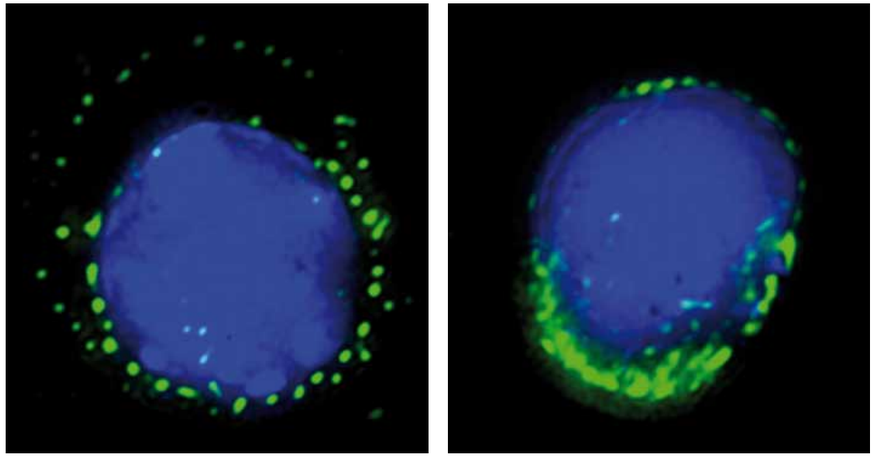


Fig. 5 Deconvolution microscopy of individual dying cells. Binding of total serum natural IgM antibodies (left) and the monoclonal natural IgM NA-17 (right) to the surface of apoptotic thymocytes (shown in green; nuclei are stained in blue)

"CeMM is about to become one of the leading centers of applied basic research in the city of Vienna and beyond. With its major and important scientific contributions, its close neighborhood to the MUV and its ingenious scientists under the intense leadership of Giulio Superti-Furga, CeMM is not only an international, highly esteemed site of biological science and the thrive towards our understanding of physiological and pathological processes within the human body, but has also developed into a patron of arts. Personally I am very enthusiastic about the hitherto extremely pleasant and successful scientific interactions between the MUV and CeMM, and welcome very warmly the institution into the immediate premises of the MUV and the General Hospital. The presence of CeMM within one common ground will give all three institutions a further boost to form a point of gravitation in biological science in our beautiful city."

Prof. Dr. Christoph Zielinski
Chairman, Department of Medicine I and Cancer Center
General Hospital – Medical University Vienna

Liberality

+ Tools for the Masses
+ Keeping Data Flowing
+ Generating Resources

liberality
the quality or state of being liberal or generous

Generosity

Of only four statues in the Austrian Academy of Sciences building, liberality was chosen to represent one of them. It stands alone, in comparison to the dual meanings of the other three statues, and perhaps rightly so. Liberality symbolizes sharing, kindness and generosity, which are important aspects of any society, and the statues themselves illustrate this by handing out coins. Liberality and science are connected on several different levels: by the individuals, organizations and governments who share wealth to fund it, as well as within the scientific community both in the form of collaborations and in the sharing of new technologies and valuable results. Science is also very much about the teaching and training of young people. The coins handed out by the statues could represent the handing out of knowledge and experience for others to invest.

Giving Back to Society

Patients are at the center of CeMM's focus, which is exemplified by their motto: "From the clinic to the clinic". The institute places a strong emphasis on giving back to society by focusing on the integration of basic research and clinical expertise, i.e. molecular medicine. They pursue innovative diagnostic and therapeutic approaches particularly focused on cancer, inflammation and immune disorders. Their motto and their research are driven by the medical needs of our society.

At CeMM, the research groups run by Keiryn Bennett and Jacques Colinge provide the facilities and expertise to develop the next generation of technologies that can be used by all the different groups in the institute, as well as for collaborations with researchers from other universities and institutes. The mass spectrometry group run by Keiryn Bennett has been pushing technology to the limits and beyond. They have been systematically testing new approaches to expand CeMM's mass spectrometry capabilities. These proteomic technologies generate substantial datasets that need sophisticated methods to handle and analyze them. This is where the bioinformatic group led by Jacques Colinge comes in. They provide and develop data analysis systems as well as integrated databases, so that scientists can efficiently and effectively analyze their experimental results.

Team Work

The Barlow group at CeMM has set up a collaboration with the Research Institute of Molecular Pathology in Vienna and the Nijmegen Center for Molecular Life Sciences in the Netherlands to undertake an ambitious project that will generate a large resource for further work in their laboratories, as well as for the entire scientific community. The collaboration enables the team to use very new technology to sequence the transcriptome (the RNA products copied from DNA) in different types of cells to search for a certain class of long non-coding RNAs known as macro non-protein coding RNAs (ncRNAs).

Ce–M–M– Research Report 2009

Tools for the Masses

"Such an advance would revolutionize proteomic analysis of human clinical samples."

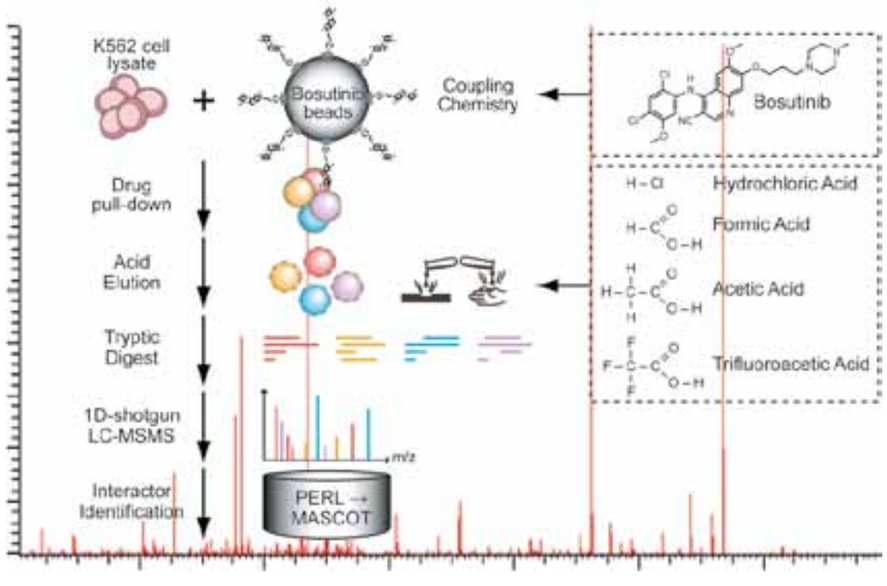
Analyzing proteomes (the protein content) of diverse biological system such as cells or tissues requires a combination of experimental protocols. These protocols require modifications and development depending upon the type of starting material used and the specific biological question being asked. As the instruments become more sophisticated and complex, the boundaries of what they can be used to analyze are continually challenged. To fully utilize these new capabilities requires the parallel modification of existing protocols, in particular, sample preparation and subsequent data analysis.

The mass spectrometry group has been working towards establishing new strategies to further increase analytical sensitivity and efficiency of protein identification. Previously, they used a conventional gel-based strategy to separate individual proteins so that they can be identified. A number of limitations, however, including contamination and speed of analysis, meant that there was a need to find a new approach. This came in the form of the 'shotgun' proteomic approach, pioneered by groups in the USA. This method removes the need for a protein separation step, and along with newer generation instruments enables them to offer a deeper and faster analysis.

How Low Can You Go?

Keiryn's group had new ambitions to analyze the proteomes of cells taken directly from individual patients. However, this meant they were severely limited by sample quantity, and the current protocols were inadequate. They set about establishing a rapid throughput method that was sufficiently sensitive to analyze the protein content isolated from individual patients and that could be used, for example, to follow a patient during a specific drug treatment to see how they responded. By testing different laboratory acids for preparation of the samples, as well as improving analytical sensitivity of the mass spectrometry step, they developed a robust approach to effectively analyze protein content in small quantities, such as those taken routinely from patients. The group plans to take this technique even further by downscaling the approach again. This has the potential to lead the group, and the rest of the scientific community, into the realm of analyzing minute quantities of material, such as those that are obtained from a fine needle biopsy. Such an advance would revolutionize proteomic analysis of human clinical samples.

Fig. 1 The target profile of the promiscuous kinase inhibitor bosutinib was investigated by an improved chemical proteomic approach to identify natural binders. It was clearly demonstrated that the approach could be successfully downscaled by a factor of one hundred. The entire methodology as described could lead us into the realm of using as little material as can be obtained from a needle biopsy, thereby revolutionizing proteomic analysis of human clinical samples.



Keeping Data Flowing

The mass spectrometry analyses performed by Keiryn Bennett's group generate large amounts of data, and their efficient interpretation in the context of a specific biomedical question requires highly specialized tools. The bioinformatic group led by Jacques Colinge at CeMM has developed a specialized platform for handling large proteomic datasets generated by the different mass spectrometers. This supports the scientists when they want to analyze their results, and helps them to make clear and accurate biological interpretations.

Analyze This, and That

Once the raw data have been generated from a mass spectrometer run, they undergo a first analysis to generate usable primary data, which is performed by a distributed computing system controlled by a laboratory information management system (LIMS). Then the primary data can be used to search against publically available protein databases, to reveal the content of biological samples. These database searches are performed by a sophisticated combination of two search engines, which provides enhanced sensitivity.

A central repository stores all the protein identifications and allows the users to access and compare the content of any combination of samples. This can be done using tools integrated with a large range of public protein annotations and resources, which helps to summarize results and understand complex datasets. Because of the strong interest in protein interactions at CeMM, the bioinformatic group has also implemented an integrated database of protein interactions to complement their other tools. This interaction database is also designed to represent protein interaction networks identified by scientists at CeMM, and it provides an interactive graphical interface for ease of visualizing these networks.

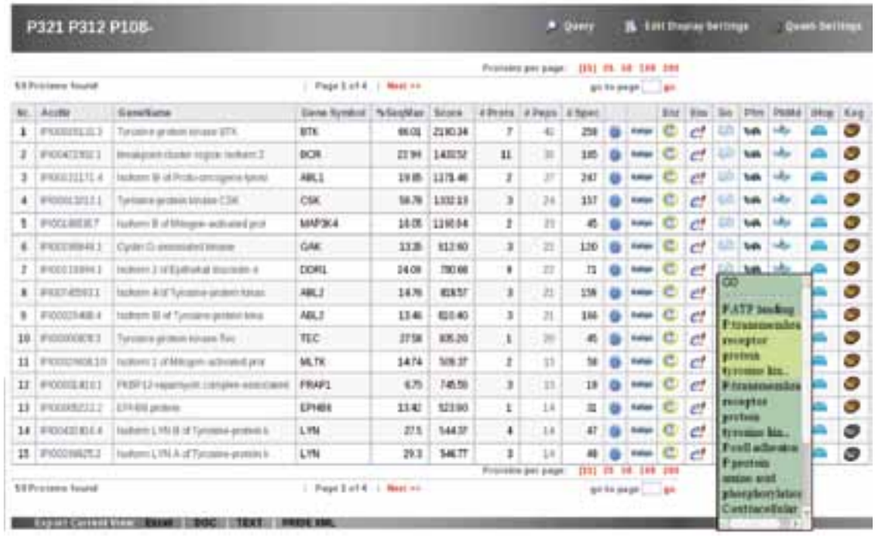


Fig. 2 MASPECTRAS, a proteomics data integration system developed in collaboration with TU-Graz (Prof. Z. Trajanoski), is used to link our protein identification data with information related to proteins and scientific literature, which we collect from public databases. MASPECTRAS can also be used to perform various types of sample comparisons and analyses of the resulting protein lists.

Generating Resources

"The stage is now set for future work to screen the transcriptome of human cancers."

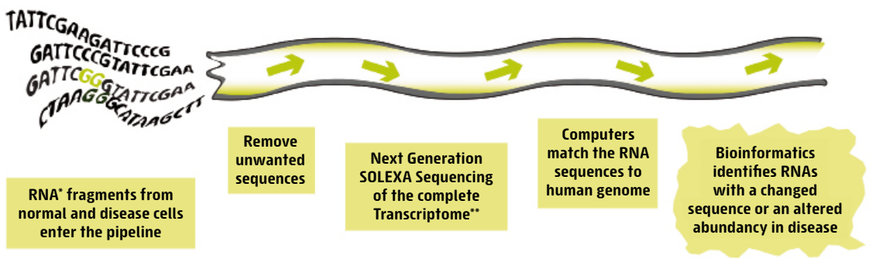
Generating large comprehensive biological and medical datasets can provide a rich source of information for scientists around the world to utilize and integrate into their own experimental systems. The Barlow group is planning on generating its own comprehensive dataset of macro non-protein coding RNAs (ncRNAs) and has been developing an RNA sequencing pipeline to lead them straight to disease gene discovery. Previous work has revealed that the total number of macro ncRNAs in a cell exceeds the total number of genes that code for proteins, which is about 23,000. Although the function of the majority of ncRNAs is unknown their abundance suggests that they likely play many important and diverse roles within the cell. Given also the known association between macro ncRNAs and tumor suppressor genes, which cause cancer when they are silenced, macro ncRNAs could be important agents in human diseases, particularly during cancer development.

Setting the Stage

To generate their datasets, the group has joined forces to set up an RNA-sequencing pipeline. They want to analyze the transcriptome (the total cellular RNA content) of both normal and tumor cells using new technology termed 'next generation whole genome sequencing' that utilizes the Solexa-Illumina platform. The pipeline included optimization steps both for the preparation of RNA samples for sequencing, and to determine how much sequencing will be needed to view the entire cell transcriptome in a quantitative manner. One final essential step was the development of new bioinformatics tools that can search through the RNA sequencing data to specifically identify the macro ncRNAs amidst the other protein-coding RNAs.

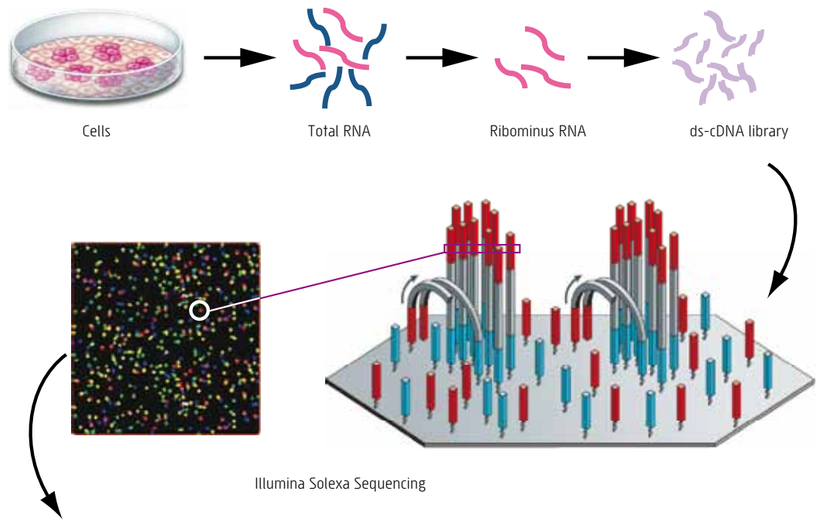
Full Steam Ahead

These steps have already been successfully completed and the RNA-sequence pipeline is currently flowing smoothly and producing transcriptome data from normal mouse and human cells. The stage is now set for future work to screen the transcriptome of human cancers. The data obtained will enable the identification of macro ncRNAs that could be associated with silencing the many tumor suppressor genes identified in the human genome that cause cancer. The data will also enable the identification of disease-associated genes that are expressed at aberrant levels in these cells, as well as providing a rich resource to help answer many other biological questions.



*RNA: genome messengers coding for proteins or initiating epigenetic modifications on chromosomes
**Transcriptome: a description of all RNA molecules present in a living cell

Fig. 3 An RNA-seq pipeline for disease gene discovery
Five steps in this discovery pipeline are indicated by which RNA from diseased and normal tissue is sequenced by next generation whole genome sequencing that uses the Solexa-Illumina platform. Each step requires optimization experiments that have the goal of determining the minimal number of sequence reads that would allow the characterization of the entire transcriptome and ultimately identify genes responsible for specific human diseases.

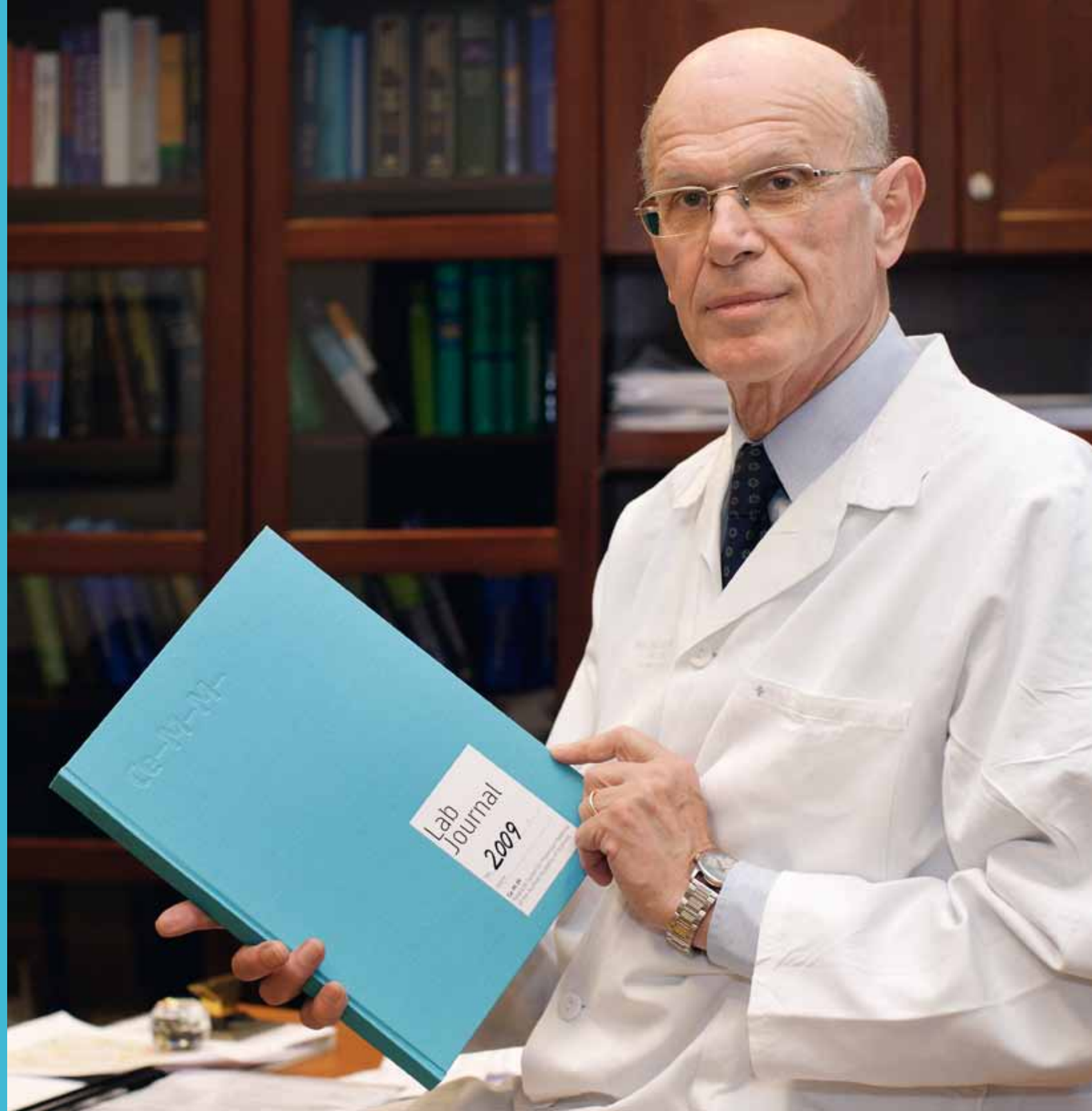


RNA-Seq data visualized in UCSC Genome Browser

Fig. 4 Ribominus RNA Sequencing
Total cellular RNA was depleted of Ribosomal RNA using the Ribo-Minus™ Eukaryote Kit (Invitrogen) and then hydrolyzed to 200~500nt before conversion to ds-cDNA. The ds-cDNA library was amplified and sequenced using an Illumina Solexa Genome Analyzer. The data was aligned to the mouse genome, and visualized using the UCSC genome browser. The displayed region shows expression of the *Malat1* non-coding RNA in two tissues.

"Molecular Biology is very central to many modern aspects of pediatrics, from diagnosis to therapy. At St. Anna, we have recently opened a new state-of-the-art research center with a special focus on the molecular causes of pediatric cancers. The Center for Molecular Medicine of the Austrian Academy of Sciences is a wonderful addition to the medical research scene and adds to our international visibility and competiveness. As an Academy member, I have followed and supported CeMM from the beginning and am very happy that many collaborations between our institute and CeMM have been built already over an intense and particularly friendly relationship of collaboration and exchange."

Prof. Dr. Helmut Gadner
Director, St. Anna Children's Cancer Research Institute



Sabbatical Visiting Scientist at CeMM

Eric Haura was a visiting scientist in the group of the director, Giulio Superti-Furga, at the Research Center for Molecular Medicine (CeMM) of the Austrian Academy of Sciences in Vienna from June to November of 2009 (see Eric Haura at http://www.moffitt.org/site.aspx?spid=1868A49EC35848BCAADC81CB6CAB7EC6&SearchType=Physician). During this time, Viennese and American scientists at CeMM developed a possible new strategy for target-oriented therapy combining two drugs that have a synergistic effect. The findings of this successful cooperation have been published in the renowned journal *Nature Chemical Biology*.

The buzz words of the moment for oncologists are target-oriented therapies. Insights of modern molecular biology have made it possible to develop drugs that target a specific molecular lesion in cancer cells. However, drugs are much more unspecific than generally recognized and the exact molecular understanding of *why* a drug is actually exerting its effects often remains obscure. Working together, scientists at CeMM and the H. Lee Moffitt Cancer Center and Research Institute were able to identify several target proteins of the kinase inhibitor drug dasatinib, which is currently used for treatment of imatinib-resistant patients with chronic myelogenous leukemia (CML) and also for the treatment of lung cancer.

The CeMM director, Giulio Superti-Furga, is enthusiastic: “For six months, we had the pleasure of hosting Eric Haura from the Lee Moffitt Cancer Center in Tampa, Florida, one of the fastest growing cancer research centers in the USA.”

During this time, analytical methods have been applied that had previously been developed at CeMM. Eric Haura, Uwe Rix, Keiryn Bennett, Jacques Colinge and Giulio Superti-Furga focused the study on the mode of action of the kinase inhibitor dasatinib and its possible (NSCLC) application in treating non-small cell lung cancer.

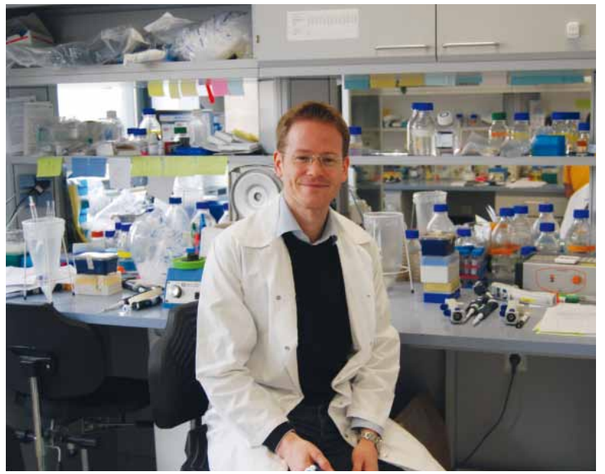
The joint study demonstrated a strategy for comprehending signalling pathways that are active in lung cancer cells and that are targeted by dasatinib. Nearly 40 different kinase targets of dasatinib were identified. Using a branch of proteomics that identifies, catalogs, and characterizes proteins containing a phosphate group as a post-translational modification – called quantitative phosphoproteomics – the scientists identified peptides corresponding to autophosphorylation sites of tyrosine kinases that are inhibited in a concentration-dependent manner by dasatinib. Using drug-resistant (“gatekeeper”) mutants of these proteins, they were able to show that SRC, and also the Epidermal Growth Factor Receptor(EGFR), is a relevant target for dasatinib action in these cells. The combined mass spectrometry–based approach provided a system-level view of dasatinib action in cancer cells and suggested both targets to be of functional relevance and a rationale for combinatorial therapeutic strategies.

Exactly this could have consequences for the future treatment of patients with NSCLC illnesses. Superti-Furga: “Dasatinib could really have synergistic effects with the therapies already in use, such as the EGFR-inhibitor erlotinib.” It would be one of the first combination therapies with drugs as target-oriented therapy and also one with a rational scientific basis. Based on these findings, the American oncologist Eric Haura is already conducting a clinical study with lung cancer patients that takes advantage of this mechanistic relationship.

Sabbatical
Visiting Scientist
Eric Haura with
his family

CeMM/MUV Interdisciplinary Postdoctoral Fellows

One of CeMM's primary goals is to train young men and women in the field of molecular medicine. As one means of achieving this, CeMM and the Medical University of Vienna (MUV) founded the Interdisciplinary Postdoctoral Fellows Program in 2008. Participants of this program work in a clinically-oriented laboratory at the Medical University with access to the respective clinical department. They are also a full member of CeMM, and benefit from all of CeMM's technologies and facilities, including the seminars. This unique partnership enables fellows in the program to tackle areas that would not be easy to address at either CeMM or the MUV alone, providing new research opportunities. We'd again like to express our thanks to our partners at the MUV, who have supported this project and shared our enthusiasm for this endeavor. Last year, we reported on the progress of the Fellows who began in the program. This year, we have revisited two of them, to see how they have been getting along.



Left: CeMM/MUV Interdisciplinary Postdoctoral Fellow Dr. Viola Borgdorff

Right: CeMM/MUV Interdisciplinary Postdoctoral Fellow Dr. Stephan Blüml

Dr. Viola Borgdorff is in the Department of Dermatology with Prof. Stephan Wagner at the MUV. Viola has been working on characterizing the transformation of melanocytes, which is a molecular process that leads to skin cancer, and how this might be pharmacologically exploited. This last year, she has been continuing these studies on melanoma by investigating the role of the transcription factor MITF in the initiation and progression of the disease. She has recently generated immortalized melanocytes over-expressing a double-tagged version of MITF for efficient identification of MITF-interacting proteins by mass spectrometry. This type of project is performed routinely at CeMM, utilizing the expertise of Keiryn Bennett's group, who develop and implement mass spectrometry techniques for identifying protein complexes, and Jacques Colinge's group, who generate bioinformatics platforms for data analysis. In addition, Viola has begun another collaboration with the chemical proteomics group at CeMM, to screen for drugs preferentially targeting melanoma cells overexpressing MITF. This could lead to the identification of novel therapeutic strategies for treating this serious disease.

Dr. Stephan Blüml has recently completed his Interdisciplinary Postdoc project, which he performed in collaboration with Prof. Josef Smolen, in the Department of Rheumatology at the Medical University. We caught up with him in person, to ask him a few questions about his experience.

What was your motivation for doing an Interdisciplinary Postdoc at CeMM and the Medical University of Vienna?

Coming from the Department of Rheumatology, a clinical department with a strong interest in translational science, I was very happy to be given the opportunity to join an institution like CeMM, which is a basic research facility with a strong interest in translational science. For me, it was the perfect opportunity to gain technical and experimental skills to approach specific questions.

What was your research project about?

My project was to try to define the roles of the two receptors that mediate the arthritogenic properties of TNF. The role of TNF in the pathogenesis of rheumatoid arthritis is well established. However, the role of its two receptors is not well defined in this context.

. . . and what were the main results?

We could show that the two TNF receptors possess non-overlapping and even opposing roles in the pathogenesis of a TNF-mediated animal model of rheumatoid arthritis, with TNFR1 being the major culprit in the development of arthritis. TNFR2, on the other hand, seemed to have a protective role in this process. These results might even have clinical implications, since one could start to speculate whether selective blockade of TNFR1 would be a therapeutic opportunity in rheumatoid arthritis.

What did you find particularly beneficial about being an Interdisciplinary Postdoc, for both your research and your scientific/medical training?

There are a couple of things that I really found very helpful and that I benefited a lot from. First of all, I was lucky to end up in a group (the innate immunity team at CeMM) with excellent scientists, who I really enjoyed working with. I was able to discuss ideas and problems in a very productive way with basically everyone, not only in the innate immunity team, but also with other people working in totally different areas at CeMM. I also had the opportunity to participate in projects of other members of CeMM, and some of those collaborations are still going on. In addition, CeMM is an institution with excellent technical resources, from which I also benefitted a lot.

Did you observe a difference in culture between the Medical University and CeMM?

I think one of the main differences is the very interactive way of doing things at CeMM, which is promoted by the way the lab is structured. The fact that basically everyone at CeMM has his/her computer and desk in the main room really promotes interaction among all the members. In addition, CeMM is a professional research institute with full time scientists, whereas at the MUV there is also the clinical work.

Was the experience how you expected, better or perhaps worse?

My experience at CeMM was definitely better than I expected, which was in part due to the fact that there were excellent scientists at CeMM, from whom I could learn a lot. In addition I felt that the climate was very good and I was able to make friends while I was there.

What are you doing now?

Last October I returned to the Department of Rheumatology at the AKH [Vienna General Hospital] to continue my residency in internal medicine. However, there are still some experiments planned for my project and in addition to that there are also collaborations with members of CeMM going on.

Will you continue your relationship with CeMM?

I certainly will continue my relationship with CeMM. Nevertheless, the amount of time I will be able to work on the ongoing projects will be less than it used to be, because of the clinical work I have been resuming at the AKH. But, as I mentioned before, there are some very interesting collaborations still running.

Would you recommend other Medical Doctors (MDs) to do an Interdisciplinary Postdoc at CeMM?

I definitely would recommend doing an Interdisciplinary Postdoc at CeMM to any MD with a strong interest in basic science. It is an excellent opportunity to get in touch with excellent researchers and to broaden one's horizon in many ways.

CeMM Postdoctoral Fellows

Scientists who have completed a doctoral degree and continue in research are known as post-docs. There are currently 17 post-doctoral fellows working at CeMM. We picked a handful and asked them a few questions about their experiences.

Dr. Omar Sharif
(Supervisor: Sylvia Knapp):

What was your personal motivation to do a post-doc at CeMM?

Having carried out my PhD in the UK in the area of innate immunity and transcription, I wanted to move abroad to conduct a post-doc. My personal motivation to apply at CeMM was that I wanted to learn more about mouse models of infectious diseases and the laboratory of Sylvia Knapp (one of the principal investigators at CeMM) seemed to be an ideal place to achieve this. Additionally, I liked the idea of working at a research centre that lies at the heart of one of the largest hospitals in Europe, providing a bidirectional channel between basic research and clinical applications. Working in the area of infectious diseases this is very helpful as there is direct access to clinicians and clinical material, which is useful for translating and correlating results obtained from mouse and cell culture models to humans. This is one of the unique things about CeMM.

What is special/different about a post-doc at CeMM?

As it is a relatively new research centre, there is a lot of effort directed towards providing an open and collaborative environment. This has provided an ideal forum that has allowed me to foster collaborations with several post-docs at CeMM and at the Medical University of Vienna on various different problems all related to understanding how the body defends itself against foreign "invaders".

Would you recommend CeMM to others for a post-doc and why?

Importantly, Vienna is one of the cultural capitals of Europe, with a great nightlife, and has one of the highest standards of living in the world. I feel that my time in Vienna working at CeMM has so far been very productive and would recommend it as an institute to other post-docs for the aforementioned reasons.

Dr. Christoph Baumann
(Supervisor: Giulio Superti-Furga):

What was your personal motivation to do a post-doc at CeMM?

After my doctoral studies I wanted to do a post-doc working in a place where basic research is more motivated by medical needs. CeMM seemed a very good option to do that. It was and still is a young and rising institute in Europe, working on subjects such as innate immunity, infection, leukemia and cancer and located at the general hospital in the center of one of the most beautiful cities in the world.

What is special/different about a post-doc at CeMM?

The main difference to me is the timing: CeMM has been founded just a few years ago and this year we will move to our own building. A lot of highly qualified and motivated people have gathered here and are about to create something special and unique.

What does molecular medicine mean to you?

Basically all of the drugs we use to treat a certain disease are not really understood in terms of their molecular targets and side effects. In addition, the disease causing aberrations in individual patients are still largely elusive. Molecular medicine addresses these questions, translating the acquired understanding of basic research into medical perspective, offering new possibilities for therapies.

Would you recommend CeMM to others for a post-doc and why?

Yes I would and have. The atmosphere is great, everybody is motivated, the lab and PIs have a good reputation, the new building is cool and the funding is good.

Name one highlight of 2009 for you – personal or work related?

One of the highlights of 2009 was a beautiful hike in the Dolomites followed by an evening in the arena of Verona watching the Puccini opera Tosca.

Dr. Quanah Hudson
(Supervisor: Denise P. Barlow):

What does molecular medicine mean to you?

To my mind molecular medicine involves investigating the genetics and cell biology of development and disease to provide a knowledge basis that can be further developed for the diagnosis and treatment of disease.

Would you recommend CeMM to others for a post-doc and why?

I would recommend CeMM as a good place to do a post-doc, because of the good working atmosphere and well-resourced labs. People at all levels of the organisation are friendly, but also passionate about their science and willing to help and give constructive suggestions about each other's work.

Name one highlight of 2009 for you – personal or work related?

A rewarding experience for me in 2009 was writing a review examining the different mechanisms regulating genomic imprinting in embryonic and placental tissues.

Dr. Sandrine Tonon
(Supervisor: Christoph J. Binder):

What was your personal motivation to do a post-doc at CeMM?

I was charmed and fascinated by the dynamism and potential of CeMM – a research institute offering such broad, complementary and multidiscliplinary teams. Real cross-interaction in between all teams is still not optimal yet but I do believe that a common location will be extremely emulative by gathering together brains, techniques and equipment.

What does molecular medicine mean to you?

It means adapting and shaping the molecular world which is microscopic and extremely complex to allow human beings to live better and longer in the third millennium.

Name one highlight of 2009 for you – personal or work related?

I realised more than ever that art and science are feeding each other. And only excellence and convergence of both universes will lead to great discoveries.

CeMM Postdoctoral Fellows
Christoph Baumann
Tilmann Bürckstürmer
Thomas Burkard
Florian Grebien
Oliver Hantschel
Quanah Hudson
Markus Müllner
Florian Pauler
Andreas Pichlmair
Uwe Rix
Elena Rudashevskaya
Roberto Sacco
Omar Sharif
Stefanie Sigel
Mathew Sloane
Alexey Stukalov
Sandrine Tonon

Dr. Oliver Hantschel
(Supervisor: Giulio Superti-Furga):

What was your personal motivation to do a post-doc at CeMM?

When I started my post-doc, CeMM only existed as a "virtual" institute consisting of the ten founding groups from the MUV. So it was on us, the five founding lab members (Keiryn, Angela, Lily, Uwe and myself) and Giulio to decide on our scientific direction, order equipment, hire the first technicians, establish the first collaborations with clinicians etc. It was an exciting time to witness the immense growth of our lab, to see so many people coming, some others leaving, with each person bringing their own diverse scientific expertise, personality and cultural background. My motivation to help to get CeMM started was a logical step in my own scientific development. After having spent my PhD at an institution with a strong focus on basic biological research and mainly having worked on structural aspects centered around the regulation of the proto-oncogene Abl, I became more and more interested in the medical implications of my work. In particular the rising problem of tyrosine kinase inhibitor resistance of Bcr-Abl in the clinics and the two emerging second generation Bcr-Abl inhibitors attracted me to"join" CeMM in order to attempt to bridge basic and clinical research.

What is special/different about a post-doc at CeMM?

I think one of the main differences to post-doc positions at other places is the strong collaborative aspect of most projects and the possibility to integrate different expertise and technologies. This comes along very quickly after one starts as a post-doc with tutoring responsibilities for technicians, diploma or PhD students, which requires that you are able to plan and execute your projects beyond your own work at the bench. So you learn to manage your own micro- or mini-lab, which I believe is an extremely good way to qualify for a future career as an independent PI.

What does molecular medicine mean to you?

Molecular medicine for me means the aim to understand the molecular basis of disease, which I strongly believe is the first step towards the development of targeted molecular therapies that attack the cause of the disease rather than interfering with its consequences.

Name one highlight of 2009 for you – personal or work related?

One great highlight of 2009 was the very successful and rapidly progressing collaboration with Shohei Koides lab from the University of Chicago, which included a six week scientific visit to our lab of John Wojcik, an MD/PhD student from Shohei´s group. In addition, the invitation to participate in the conference celebrating the tenth anniversary of the first clinical results of imatinib/Gleevec, the first approved tyrosine kinase inhibitor, was an extremely exciting experience.

Dr. Uwe Rix
(Supervisor: Giulio Superti-Furga):

What was your personal motivation to do a post-doc at CeMM?

My personal motivation to do a post-doc at CeMM was mainly driven by the strong drug proteomics focus, but I was also attracted by the chance to be part of such a pioneering new institute. Finally, the opportunity to work with my wife Lily decided it for me.

What is special/different about a post-doc at CeMM?

The interdisciplinary and highly interactive nature of the organization makes it unique when compared with other institutes. The cooperation between the groups is great and will be better again in the new building.

What does molecular medicine mean to you?

Molecular medicine is a novel discipline aiming at molecular approaches to understanding diseases, which will hopefully allow us to develop better therapies and diagnostics.

Would you recommend CeMM to others for a post-doc and why?

I would definitely recommend CeMM to other post-docs because of the focus on state-of-the-art technology and the combination of different approaches. On top of that CeMM is now starting a comprehensive post-doc program including multidisciplinary activities to develop a wider range of skills.

Name one highlight of 2009 for you – personal or work related?

My highlight for 2009 was being an invited speaker at Harvard Medical School!

CeMM PhD Program

The CeMM PhD program is a program for students planning a career in biomedical research. The program is designed to develop creative, independent research scientists, who will be well-equipped to study molecular medicine in the post-genomic era. Strong emphasis is put on the understanding of fundamental physiological and pathological processes to identify the most relevant questions of molecular medicine and study them with the best technologies available.

The Medical University of Vienna is the home academic institution for the CeMM PhD program, which has a minimum duration of 3 years. Laboratory work is performed in the laboratories of the CeMM PIs. There is mandatory course work, particularly in the first year. By the second year a thesis committee consisting of at least three members is appointed for each student. Students have to meet with this committee on a regular basis and ultimately defend their thesis in front of it. The PhD thesis is required to yield at least one publication in a peer-reviewed journal.

The internationally advertised PhD program began in 2006, when thirteen students from eight different nationalities were selected. These first years have clearly reassured us about the importance of having a graduate training program within our young institute, as our students are probably the single most important factor that ties us all together. They are indeed our best investment, and their contagious enthusiasm and inquisitive minds were a driving force over the past few years.

Second Year PhD Students

Joanna Warszawska (Supervisor: Sylvia Knapp): It has been 1 year since I joined CeMM. So far, it has been a great time for a number of reasons. As a medical doctor, I started with less experience in basic research than my non-medical colleagues. Over this last year, I received lots of support and encouragement, which helped me to greatly improve my technical skills as well as my knowledge in molecular medicine. For me, CeMM is the ideal place to start a career in molecular medicine and – last but not least – the best place to have fun!

Thorsten Klampfl (Supervisor: Robert Kralovics): It has been now 1.5 years since I started my work on the genomics of the myeloproliferative neoplasms in Robert Kralovics' lab as a PhD student. So far I can really say it proved to be a good decision to work with Robert and at CeMM in general. It is challenging to learn how to perform cutting-edge research especially in a highly competitive field, but CeMM is a good place to do that. On the one hand, the access to the latest technologies not only for genome research, but also for the various other fields at CeMM sets the technical basis for exciting and creative experiments. On the other hand, the CeMM community and the close contacts between the people of the different labs serves for lively exchange of knowledge and development of new ideas and research strategies. Especially the latter is expected to become even more exciting when we all move together into the new CeMM building which will definitely be one of the highlights of the upcoming year.

Roberto Giambruno (Supervisor: Giulio Superti-Furga): This is my second year at CeMM and it is amazing how fast my scientific experience is growing. There is always the possibility to learn new techniques and to increase your scientific background thanks to seminars, meetings and journal clubs. Moreover the nice atmosphere and the people working in the institute give you the strength to go forward with your research, especially during the several difficult moments of your PhD.

Damla Olcaydu (Supervisor: Robert Kralovics): Being now in the second year of my PhD, I am more than ever convinced that applying at CeMM for my postgraduate studies was just the right thing to do. I am grateful to have the chance to work in an exceptionally friendly, supporting, motivating and productive atmosphere at CeMM, which definitely aids one to successfully cope with the challenges of scientific everyday life. I have learned a lot in the last years, not only concerning scientific knowledge, but also to be independent in research work, have and defend my own ideas, work hard, make your own experiences, withstand drawbacks and keep your motivation high, despite all the difficulties you encounter. As a PhD student in Robert Kralovics' research group, I am working on the genetics of myeloproliferative neoplasms and enjoying the opportunity to conduct basic science in such close vicinity to the clinic – which makes CeMM a unique place to do research work, especially for me as a medical doctor with a great interest in basic and translational research.

Ashot Harutyunyan (Supervisor: Robert Kralovics): In the second year of my PhD, I got deeply engaged in the research at CeMM, which is at the same time exciting and challenging. I gained significant experience in designing projects and learnt what difficulties and obstacles lay on the way towards their accomplishment. The availability of most modern technologies at CeMM makes it possible to conduct research projects that would have been unthinkable a couple of years ago. On the other hand, close collaboration between different CeMM groups helps one find interesting solutions to many research questions. So doing research here is always hugely interesting and also fun, though it requires a lot of hard work. I have rather high expectations for the coming year: it promises to be even more exciting as we are all looking forward to moving to the state-of-the-art new CeMM building and working even closer with the other CeMM groups.

Dimitris Tsiatoulas (Supervisor: Christoph Binder): 2009 at CeMM! The highlight of the year?! Our retreat in Budapest. We had a very nice time as we combined very successfully the well organized scientific part of the retreat with a so-called 'social event' (party until late in the morning). All the good impressions from the previous year regarding the exceptionally friendly international environment and the freedom to develop your own scientific ideas have been totally confirmed. I am sure it is going to be even better in the future as soon CeMM is moving to a brand new building.

Iris Uras (Supervisor: Sebastian Nijman): One more year at CeMM has passed and I am proud to say that my initial high expectations are still being fulfilled. I am in the right place at the right time because a PhD is not only a thesis, but also a step forward in becoming a grown-up by improving both your personality and personal skills, thinking independently, being mature in your judgement and standing up for your ideas. I experienced how exciting and enthusiastic science can be and also learnt how to deal with the challenges – by being motivated, hard working, patient and optimistic. CeMM therefore represents a unique place with its friendly atmosphere and great support by extraordinarily talented people and stimulating discussions. It definitely provides both competitive and encouraging spirit for scientists who stand at the very beginning of their careers.

Georg Winter (Supervisor: Giulio Superti-Furga): Being now at CeMM for around one and a half years, my resume still is a very positive one. I think the environment that CeMM provides for PhD students is optimal in many regards as it offers on the one hand access to a variety of different state-of-the-art technologies and on the other hand, so many different scientific expertises ranging from mathematical modeling to in vivo mouse experiments. Trying to incorporate those assets represents a wonderful possibility but also a challenging task for young researchers and provides us with all the resources that are necessary to be internationally competitive.

Second Year PhD students
from left to right:
Dimitris Tsiatoulas
Damla Olcaydu
Thorsten Klampfl
Iris Uras
Georg Winter
Joanna Warszawska
Roberto Giambruno
Ashot Harutyunyan

Third Year PhD students
from left to right:
Roland Jäger
Irena Vlatkovic
Adriana Goncalves
David Weismann
Ana Zivkovic

Third Year PhD Students

Irena Vlatkovic (Supervisor: Denise P. Barlow): The three years as a part of CeMM were among the most interesting and rewarding years of my life. The years compacted with science, friendships and traveling while every day was bringing something new and exciting. As a part of CeMM I learned how to do both basic and disease related science, how to think scientifically, how to always aim to get the bigger picture and in the same time to understand the each small part. This year I am coming to the end of my CeMM journey finishing my PhD thesis about mapping and characterization of novel macro non-protein coding RNAs in human normal and cancer cells and tissues. I am sure that for my future scientific carrier the knowledge and skills I obtained in CeMM will be the excellent basis, and that I will always aim to find the CeMM spirit at any institute I go.

Roland Jäger (Supervisor: Robert Kralovics): When I started my training as a PhD student in Robert Kralovics's lab at CeMM three years ago, I took a lot of motivation from the optimistic atmosphere in the lab and at CeMM. I soon realized that people at CeMM aim at a very high standard in communication, knowledge, technology and science in general. Working on the genetics of Myeloproliferative Neoplasms, I could experience the hard competition in science and how fast things change in the field, but also how exciting science can be. I could participate in starting up a lab, facing a lot of challenges, but in the end making big progress in organization as well as in productivity.

Ana Zivkovic (Supervisor: Sylvia Knapp): Discovering logic behind the act of bacterial toxins and a response of host organism was my main preoccupation during last several years. Throughout this time I have been hunting to further my knowledge and contribute to the progression of science in this field. Today I'm in my final year of PhD. I believe I learned a lot about basic science and the importance of Molecular and Translational Medicine. Discovery of unknown pathways is hard and creative work but remarkably exciting. For me and my professional ambitions, CeMM presents an open-minded and inspiring platform, a great chance to develop intellectually and to be appreciated wherever you come from.

Adriana Goncalves (Supervisor: Giulio Superti-Furga): It was very encouraging to see how much CeMM grew and expanded in the last year: many new colleagues, a new building and a beautiful art façade, new projects and grants, fruitful conferences and many interesting events. It is therefore not difficult to imagine that also for me, 2009 became in many ways a decisive year, marked by a strong personal and scientific development. I was not only able to consolidate my knowledge but also to bring it to a further level of understanding. I have no doubts that both CeMM and myself will continue to grow in the following year!

David Weismann (Supervisor: Christoph Binder): Of all the years I spent at CeMM, I enjoyed the last one in particular. Mainly because my PhD project finally set off and yielded more than just interesting observations. But importantly, it was also during this last year that my scientific as well as my personal bonds within the institute eventually stabilized and opened the prospect for connections that will outlast my time here.

CeMM Principal Investigators

Giulio Superti-Furga

Pathological Networks in Leukemia and Immunity

Giulio Superti-Furga's group
is renting lab space:

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

+ Italian nationality
+ Joined CeMM in January 2005
+ Group of 19 people
plus mass spectrometry team (5)
and bioinformatics team (4)

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

Giulio Superti-Furga is an Italian national and he joined CeMM as Director in January 2005. He performed his undergraduate and graduate studies in molecular biology at the University of Zurich, Switzerland, at Genentech Inc., South San Francisco, USA, and at the Institute for Molecular Pathology in Vienna (I.M.P.), Austria. He has been a post-doctoral fellow and Team Leader at the European Molecular Biology Laboratory (EMBL) until 2004. For several years he served as Professor of Biotechnology at the University of Bologna. In 2000, he co-founded the biotech company Cellzome, where he was Scientific Director. Some of Giulio's major achievements to date are the elucidation of basic regulatory mechanisms of tyrosine kinases in human cancers and the discovery of fundamental organization principles of the proteome of higher organisms. Giulio's work on the organization of the eukaryotic proteome is the most highly cited in the field. He is a corresponding member of the Austrian Academy of Sciences, the German Academy of Sciences Leopoldina and the European Molecular Biology Organization. He follows Angus Lamond as chair of the EMBL Alumni Association. After joining CeMM, he continues to use and develop 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 November 2009 he received the prestigious Advanced Investigator Grant awarded by the European Research Council (ERC).

Three relevant/important publications

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

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

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

Robert Kralovics

Genetics of Hematological Disorders

Robert Kralovics' group
is hosted by:

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

+ Czech nationality
+ Joined CeMM in June 2006
+ Group of 5 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 Ph.D. in Biophysics at the Academy of Sciences of the Czech Republic in Brno. He did his postdoctoral work on the genetics of myeloproliferative disorders working with Josef Prchal at the University of Alabama at 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 New England Journal of Medicine and fostered Robert's interest in deciphering the genetic complexity of MPD. More recently, Robert's group discovered that 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.

Three relevant/important publications

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

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

Genetic complexity of myeloproliferative neoplasms. Kralovics R. *Leukemia*. 2008. 22(10):1841–8.

Denise P. Barlow

Epigenetic Mechanisms in Development & Disease

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at Vienna University
PhD,
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Post-doctoral Fellow,
ICRF London (UK), **EMBL Heidelberg** (D)
Group Leader,
IMP Vienna (A)
NKI Amsterdam (NL)
Head Dept. Developmental Biology,
IMB-OeAW Salzburg (A)

+ British nationality
+ Joined CeMM in 2003
+ Group of 15 people

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

Denise Barlow is a British national who joined CeMM in 2003 and is an Honorary Professor at the University of Vienna. Denise initially trained as a State Registered Nurse in the UK and afterwards completed undergraduate studies at Reading University (UK) and a PhD on the interferon system at Warwick University (UK). Postdoctoral work studying mouse embryonic development followed at ICRF (London, UK) with Dr. Brigid Hogan, and on genome biology at EMBL (Heidelberg, D). Denise has also held group leader positions at the IMP (Vienna, A) and NKI (Amsterdam, NL). On returning to Austria in 2000, Denise was appointed Head of the Dept. of Developmental Genetics at the Austrian Academy IMB Institute (Salzburg, A), and then finally returned to Vienna in 2003 as a Principal Investigator with CeMM. Amongst the Barlow lab's major achievements are the discovery of the first imprinted gene in mammals and the elucidation of the epigenetic mechanism underlying imprinted expression. The lab uses the model of genomic imprinting, i.e. parental-specific gene expression, to dissect how epigenetics change the behavior of our genes, which has important consequences for normal human development and when things go wrong, for diseases such as cancer.

Three relevant/important publications

The mouse insulin-like growth factor type 2 receptor is imprinted and closely linked to the Tme locus. Barlow DP, Stoger R, Herrmann BG, Saito K, Schweifer N. *Nature.* 1991. 349(6304): 84–7.

The non-coding Air RNA is required for silencing autosomal imprinted genes. Sleutels F, Zwart R, Barlow DP. *Nature.* 2002. 415(6873): 810–3.

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

Sylvia Knapp

Innate Immunity and Bacterial Infections

Sylvia Knapp's group
is hosted by:

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

+ Austrian nationality
+ Joined CeMM in April 2006
+ Group of 11 people

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

Sylvia Knapp was born in Austria and studied Medicine at the Free University in Berlin and at the University of Vienna. She obtained her M.D. degree in 1993 and did her Ph.D. with Professor Tom van der Poll at the University of Amsterdam studying the inflammatory response to severe bacterial infections. Sylvia received her License in Internal Medicine in 2000 and in 2004 she obtained a "Habilitation" in Internal Medicine at the Medical University of Vienna. After several residencies, mostly in areas of Internal Medicine like Infectious Diseases, AIDS and Intensive Care Units, she became a Research Fellow in Tom van der Poll's laboratory at the University of Amsterdam for four years. Sylvia's most important achievements include the identification of the anti-inflammatory role of alveolar (lung) macrophages in *Streptococcus pneumoniae* pneumonia. Sylvia joined CeMM in April 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 part-time responsibilities in the Intensive Care Unit at the MUV.

Three relevant/important publications

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

Toll-like receptor 2 plays a role in the early inflammatory response to murine pneumococcal pneumonia but does not contribute to antibacterial defense. Knapp S, Wieland CW, van ´t Veer C, Takeuchi O, Akira S, Florquin S, and van der Poll T. *J Immunol* (2004) 172, 3132-3138

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

Sebastian Nijman

Cancer Genomics

Sebastian Nijman's group
is renting lab space:

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

+ Dutch nationality
+ Joined CeMM in October 2007
+ Group of 4 people

Main research interests
+ Identify novel strategies to treat cancer (cancer vulnerabilities)
+ Unravel molecular mechanisms that drive tumorigenesis
+ Functional genetic screens to identify cancer-related genes

Sebastian Nijman was born in the Netherlands (1975). He obtained his university training in Utrecht where he specialized in Molecular Biology and Biochemistry and acquired a Masters of Arts degree from the University of Maastricht (Science, Society and Technology Studies). After a short "detour" through industry where he was involved in clinical research, he started his Ph.D. with Professor Rene Bernards at the Netherlands Cancer Institute in Amsterdam. With the help of the first RNAi screen in mammalian cells he assigned a function to the familial tumor suppressor gene CYLD, which was published in Nature, and has been one of his major achievements so far. This work has led to a rational therapeutic approach for treating the tumor syndrome that is caused by mutations in this gene. In 2006 he joined the lab of Dr. 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. Much of Sebastian's research can be considered as technology driven. His main interest includes the molecular mechanisms underlying cancer, particularly cancer vulnerabilities and the identification of new components of cancer pathways using genetic screens in mammalian cells.

Three relevant/important publications

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

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

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

Christoph J. Binder

Atherosclerosis and Immunity

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Post-doctoral fellow,
University of California San Diego (USA)

+ Austrian nationality
+ Joined CeMM in April 2006
+ Group of 8 people

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

Christoph Binder was born in 1973 in Vienna, Austria. He obtained his M.D. 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 Ph.D. program at the University of California in San Diego, working with renowned atherosclerosis researcher Professor Joseph Witztum, where he obtained his Ph.D. degree in 2002 for the thesis entitled: "Defining Innate and Adaptive Immune Mechanisms in the Atheroprotective Effect of Immunization with Oxidized Low-Density Lipoproteins". He continued with Professor Witztum as a Postdoc to study the role of IL-5 in atherosclerosis, which was where he made one of his major discoveries to date, namely that IL-5 is an atheroprotective cytokine. In 2005, he joined the Department of Laboratory Medicine at the Medical University of Vienna, where in 2009 he was appointed Professor of Atherosclerosis. 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 IL- 5 and of natural antibodies in atherogenesis and how immune recognition of oxidized lipids link autoimmunity and atherosclerosis.

Three relevant/important publications

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

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

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

Keiryn Bennett

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PhD, Department of Chemistry,
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Director of Analytical Applications,
Protana AS, (later called)
MDS Proteomics (DK)

+ Australian nationality
+ Joined CeMM in October 2004
+ Group of 5 people

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

Keiryn Bennett, PhD, heads the mass spectrometry unit at CeMM. Australian by birth, she obtained her Bachelor of Science with Honours at the Department of Biochemistry, University of Tasmania and her PhD at the Department of Chemistry, University of Wollongong, Australia, under the supervision of Professor Margaret Sheil. She further trained in some of the most renowned protein mass spectrometry laboratories of the world, including Professor Peter Roepstorff in Odense, Denmark. Keiryn Bennett has been Director of Analytical Applications at Protana AS in Denmark (later called MDS Proteomics). Her hands-on experience with different systems include: Sciex prototype MALDI-QqTOF, PerSeptive Voyager Elite MALDI-rTOF, TSQ-700 triple quadrupole mass spectrometer, Sciex QSTAR equipped with nanoelectrospray, and nanoLCMS coupled to ThermoFisher Orbitrap and Micromass/Waters Q-TOF mass spectrometers. Author of approximately 40 publications, during her time at MDS, Keiryn Bennett was involved in the large-scale analysis of yeast protein complexes published in *Nature* along with the analogous effort from *Cell-zome*. She is known and respected world-wide in the field of protein mass spectrometry. She brings to CeMM more than 15 years of experience in protein mass spectrometry and 7 years´ experience in managing a high-throughput industrial proteomic laboratory. Keiryn Bennett has established the protein mass spectrometry capability at CeMM.

Three relevant/important publications:

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 and Bennett KL. *J Proteome Res.* 2009: 8, 4753–4765

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

Jacques Colinge

Jacques Colinge's group
is renting lab space:

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Bioinformatician,
Serono Pharmaceutical
Research Institute (CH)
Head of Bioinformatics,
GeneProt Inc (CH)
Professor of Bioinformatics,
Upper Austrian University
of Applied Sciences,
Hagenberg (A)

+ Swiss and French nationality
+ Joined CeMM in September 2006
+ Group of 4 people

Research Interests
+ Computational Proteomics
+ Computational Statistics and Statistical Learning
+ Systems Biology Data Analysis

Jacques Colinge is a Swiss and French national, and is head of the bioinformatics team at CeMM since he arrived in September 2006. He performed mathematics graduate studies in Geneva, Switzerland. He then did his Ph.D. with Professor G. Wanner, also in Geneva, in the field of numerical analysis of partial differential equations. This was a joint project with both Swiss Institutes of Technology. After completing his Ph.D., Jacques joined 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 of nine in charge of mass spectrometry-related bioinformatics. Four years later, he joined the Upper Austrian University of Applied Sciences at Hagenberg to serve as a Professor of Bioinformatics. Jacques Colinge's main contributions are solution methods for strongly nonlinear elliptic PDEs arising in glaciology, management of high-throughput proteomics data flows, statistical models for SAGE data analysis, MS data identification, and MS-based quantitation analysis, and recognition of biological functions represented in protein interaction networks, integration of proteomics results with transcriptomics, interaction, and pathway data.

Three relevant/important publications:

OLAV: Towards high-throughput MS/MS data identification. Colinge J, Masselot A, Giron M, Dessingy T and Magnin J. *Proteomics*. 2003. 3:1454–1463.

Peptide fragment intensity statistical modelling. Colinge J. *Anal. Chem*. 2007. 79:7286–7290.

Global target profile of the kinase inhibitor bosutinib in primary chronic myeloid leukemia cells. Remsing Rix LL, Rix U, Colinge J, Hantschel O, Bennett KL, Stranzl T, Müller A, Baumgartner C, Valent P, Augustin M, Till JH and Superti-Furga G. *Leukemia*. 2009. 23:477-485.

CeMM Retreat

The center-wide retreat is a particularly important event for CeMM because the laboratories are not currently situated close together, and so many people do not meet on a daily basis. Therefore, particular care goes into the organization of the yearly retreat. The CeMM retreat of 2009 was held from Thursday 26th to Saturday 28th of February at the Hotel Gellért in Budapest, a two-hour coach journey from Vienna. All members of CeMM were invited and there were 82 participants. The retreat began with an afternoon sightseeing tour by boat down the Danube River, which splits the city into two halves. The main scientific schedule began the first evening and continued throughout the Friday. This year, all the postdoctoral fellows were asked to present their research in 15-minute talks. In total there were 18 talks over 6 sessions. Particularly memorable was the very intense poster session in the evening, at which the PhD students presented and discussed their work to the rest of the institute.

As usual, there was some time set aside for more social activities, which involved experiencing at least one of the two things Budapest is most famous for: its extraordinary architecture and its thermal springs. Whatever the choice, there wasn't far to travel as the hotel was situated close to the city center. Itself a famous late Art Nouveau building, the Gellért also houses the famous spa, one of the most beautiful thermal baths in the city. As has become customary, evenings centered around food and drinks, and also music on the Friday night, which didn't go on long enough for some people, although they might not have admitted that in the morning! Fortunately for them, things wound down the next morning and the bus took people back to Vienna, with a few groups remaining to explore more of the city's attractions.






Photos from the CeMM retreat in Budapest, Hungary.

CeMM Karl Landsteiner Lecture

4 May 2009
Austrian Academy of Sciences, Vienna, Austria

Karl Landsteiner: Founder of Blood Groups
In 1900, Karl Landsteiner, an Austrian biologist and physicist working at the University of Vienna, published a short article in the *Zentralblatt für Bakteriologie, Parasitenkunde und Infektionskrankheiten*. In it, he described his observation that there were individual differences in the properties of human blood. In a second paper published a year later, Landsteiner presented the results from a study where he mixed blood taken from six individuals, including himself, which in certain combinations caused agglutination. This led to the identification of the AB blood group classification system in humans, for which Landsteiner was awarded the Nobel Prize in 1930.

The significance of his major discoveries are succinctly illustrated in the words of the late Prof. Dr. Hermann Chiari, an Austrian pathologist and previous Vice President of the Austrian Academy of Sciences, during his speech at the opening of the Karl Landsteiner memorial at the University of Vienna in 1961. He said: "Wherever a blood transfusion is performed in the world today, wherever a worried mother's threatened child is saved, Karl Landsteiner is virtually present".

To honor Landsteiner's extraordinary achievements, CeMM established the Karl Landsteiner Lecture series in 2007. The speaker is selected using a structured process by all members of CeMM, for being a pioneer in molecular medicine. In 2009, the honor was awarded to the Kenyan-born molecular biologist, Vishva Dixit.

Previous Awardees
2008 Kári Stefánsson: "Genetics of Common Diseases in the Context of Human Diversity".
2007 John Kuriyan: "Regulatory Mechanisms in Protein Tyrosine Kinase Signaling".

Death Receptors, Ubiquitin Editing and Inflammasome Function

Dr. Vishva Dixit is currently vice president of Physiological Chemistry at the biotechnology company Genentech in San Francisco. Genentech encourages the study of basic scientific research and is accredited as the founder of the entire biotechnology industry. Dixit was recruited to Genentech as director of the Molecular Oncology department in 1997 from the University of Michigan, where he had become full professor in 1995. Before that, Dixit began his career studying medicine at the University of Nairobi, and he completed his medical training at the University of Washington, where he also became a postdoctoral fellow. Some of his most notable scientific achievements to date are within the field of cell death, where he characterized the molecular components of the cell death receptor pathway and discovered new mechanistic paradigms for intracellular signaling cascades. On May 4th 2009, in the main lecture hall of the Austrian Academy of Sciences, Vishva Dixit took the audience on a journey through his scientific discoveries.

It began in the early 1990's, when people seemed more interested in studying cell survival and growth rather than cell death. However, today cell death is known to be a critical process both for the early development of an organism as well as to maintain homeostasis during life. Members of a family of proteins found on the surface of cells, known as the TNFR superfamily, had been shown to induce cell death upon activation by extracellular signals, and were named death receptors. Previously, these receptors were thought to work by serving as ion channels in the cell membrane or by regulating phosphorylation of target proteins. Dixit and his group found that these death receptors induced cell death via a new signaling mechanism, which involved the recruitment and activation of so-called death proteases.

In the process of characterizing this complex signaling cascade, involving many different proteins and leading subsequently to cell death, they uncovered another novel signaling mechanism known as 'ubiquitin editing'. Ubiquitin is a small molecule which is attached to proteins to mediate either their degradation or to modulate their activity. Ubiquitin can be attached as diverse chains to form polyubiquitin, the composition of which can be interpreted (or decoded) by proteins known as ubiquitin binding proteins (UBPs). Ubiquitin editing involves the replacement of one type of polyubiquitin chain with another, thus altering the protein's function.

In parallel to the work on cell death, Dixit's group also studied the molecular mechanisms of inflammation. Upon microbial infection, cells in the body respond very rapidly, which suggested the presence of an intracellular detection sensor to act as an alarm system. Along with other groups, they found that these sensor proteins also contained specific death domains that could recognize microbial components and induce the assembly of a large multiprotein complex known as the inflammosome, thereby activating the inflammatory response. This process represents one of the first defense mechanisms of the innate immune system, and is highly conserved, being found in both plants and animals.

Vishva Dixit made the decision to work in industry because it gave him the opportunity to turn his scientific results on basic cellular mechanisms into therapeutic opportunities to impact the lives of patients. Indeed, his work on cell death is highly relevant for understanding the molecular mechanisms underlying cancer cell survival. This guiding principle, as well as the topics of his research, fit well with the mission of CeMM to use basic research to pursue innovative therapeutic approaches focused on cancer, inflammation and immune disorders, making him clearly a pioneer in molecular medicine as well as a highly suitable choice to present CeMM's 2009 Karl Landsteiner Lecture.

Dr. Vishva Dixit during his lecture presented in the festive hall of the Austrian Academy of Sciences.

Scientific Advisory Board Members

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
Deputy Director, Dana-Farber/
Harvard Cancer Center, Boston, USA

Prof. Dr. William E. Paul
Chief, Laboratory of Immunology,
National Institute of Allergy and
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Prof. Dr. Hidde Ploegh
Member, Whitehead Institute for
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Prof. Dr. Louis M. Staudt
Head, Molecular Biology of
Lymphoid Malignancies Section,
National Institutes of Health,
National Cancer Institute, Bethesda, USA

Dame Prof. Dr. Janet Thornton
Director, European Bioinformatics Institute
in Cambridge, UK
Group Leader, EMBL- European Molecular
Biology Laboratory, Hinxton Outstation,
Cambridge, UK

Meeting 2009

The CeMM scientific advisory board (SAB) was invited to CeMM for the second time on Friday November 13th 2009, for a two day meeting to give a formal appraisal of the research being conducted at CeMM as well as offering their support and expert guidance. This time, nine members made the journey to Vienna. They were David Livingston, James Griffin, Louis Staudt, Hidde Ploegh, William Paul, Richard Flavell, Denis Hochstrasser, Carl Henrik Heldin and Nadia Rosenthal.

The scientific presentations began on the Saturday with the six Principle Investigators and two technical department heads introducing their research, followed by discussions. The rest of the day was focused on the Postdocs and PhD students, some of whom had been chosen to present their work to the SAB in ten-minute talks.

The SAB deliberated their observations that evening and on the final morning, they provided detailed feedback, first to the entire faculty of CeMM, then to the management, followed by a presentation to the Board of the Academy. In general they were delighted with the progress made and particularly praised the quality of the presentations by the junior members as well as the collegial and cooperative spirit. Detailed written feedback was sent later to the Academy Board and the CeMM directors.

Representatives of the CeMM Scientific Advisory Board at the Meeting in Vienna in November 2009.

The SAB and members of CeMM in the lecture room where the meeting was held.

CeMM Christmas Party

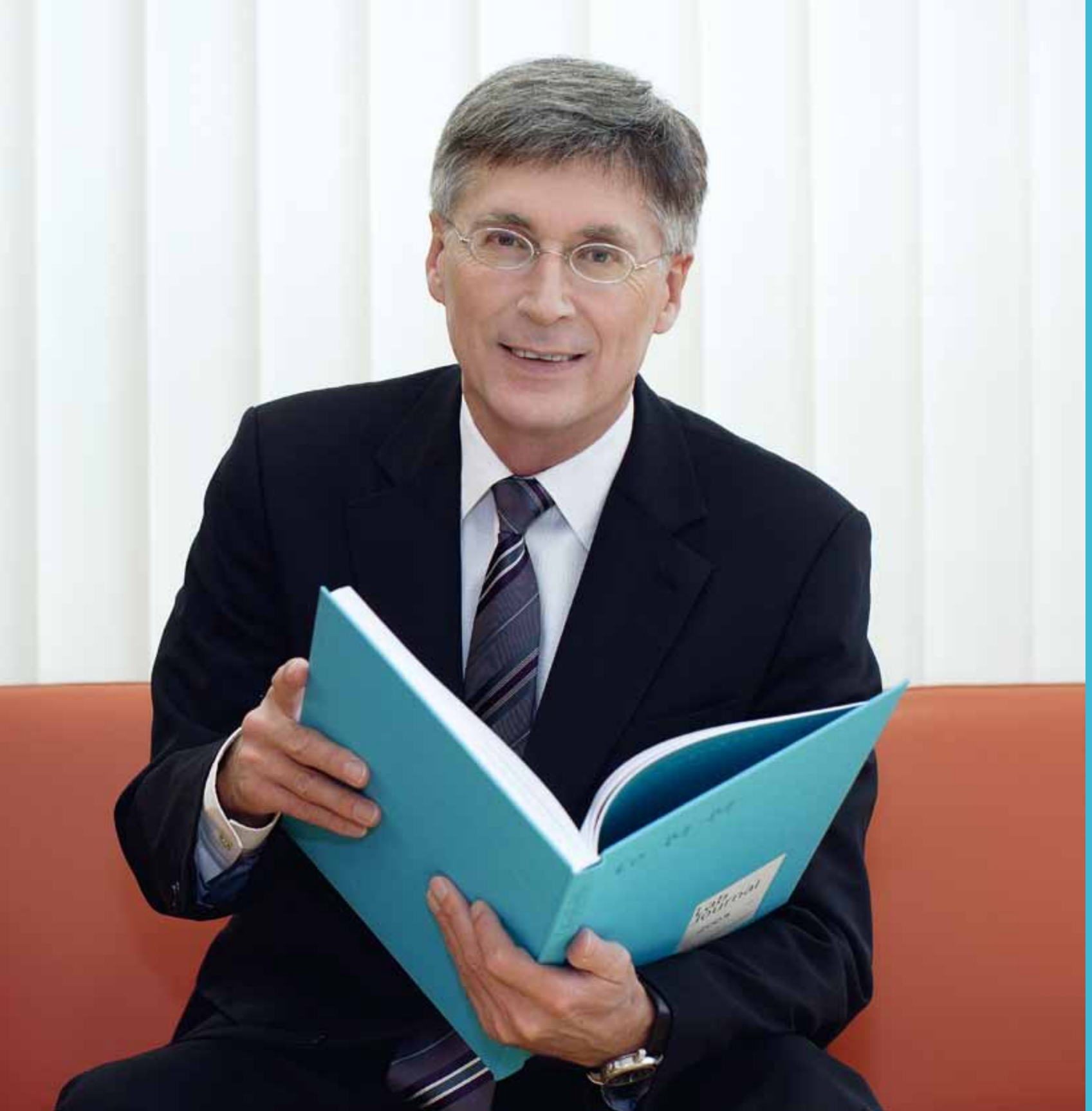
The 2009 CeMM Christmas Party was held at the Trummelhofbar (a wine tavern) in the 18th District of Vienna. Family and friends of CeMM were also invited to enjoy the buffet meal and appreciate some of the unique dancing styles that went on display later that evening. Taxis were ordered well after midnight, and partygoers traveled home accompanied by some of the first snow of the season.








Both young and old(er) enjoying the CeMM Christmas party, with food, drink and presents aplenty.



"CeMM has been a dear and important project for us. I am proud of the fact that the new CeMM building is currently under construction on the premises of the General Hospital and I am sure that under the leadership of Giulio Superti-Furga, CeMM will fulfill all the expectations of the surrounding community. It is a unique and remarkable example of how different institutions can cooperate effectively if the goal is better research for the benefit of patients."

Prof. Dr. Reinhard Krepler
Director of the Vienna General Hospital (AKH)

The New CeMM Building: Ready by Spring 2010

The entire concrete structure of the new CeMM building was completed at the beginning of 2009. A nine floor-high skeleton had grown from a deep hole in the ground over a period of less than a year. The construction workers and CeMM's faculty, along with the Minister of Science and Research, Johannes Hahn, and many supporters and friends of CeMM, celebrated the topping out ceremony on March 24th at the site.

Since then the appearance of the building has again changed dramatically and construction work is now (as of February 2010) almost complete. The outside is finished and the inside has been equipped with the technical infrastructure for power, computer network cabling, and air conditioning. The laboratories and offices are undergoing the finishing touches before they can begin being furnished. The current rate of progress indicates that the moving date for researchers into the new building will be as planned, in June of 2010.

A fabulous glass facade by artist Peter Kogler represents the interface between CeMM and the city beyond. You can find out more about the art facade and the building inauguration in the 2010 Research Report.

CeMM Building Facts:
The CeMM building has eight floors with a total floor space of more than 5,600 m² , including a cafeteria, lecture hall, several small meeting rooms and two large terraces on the top floor overlooking the city. Out of more than 3,400 m² of usable space, two thirds will be devoted to laboratories, which are organized as open-plan to encourage interactions between the different groups. The whole building will provide space for up to 100 people.

The building is located at the very heart of the Vienna General Hospital (AKH), which is one of the largest general hospitals in Europe. This privileged location will enable CeMM researchers to interact closely with clinicians and the medical faculty at the Medical University of Vienna. Crucially, the CeMM building is physically linked to a new research building of the Medical University by connecting doors on each floor, which is also connected to the main buildings of the hospital via an underground corridor.

CeMM Principal Investigators and Minister Josef Hahn celebrate topping out

Top:
The construction site in spring 2009

Bottom:
CeMM construction site at the end of 2009

CeMM Directory

Armenia, Australia, Austria, Belgium, Brazil, China, Czech Republic, Finland, France, Germany, Greece, Ireland, Italy, Liechtenstein, Mexico, New Zealand, Pakistan, Poland, Portugal, Romania, Russia, Serbia/Montenegro, Spain, Switzerland, The Netherlands, Turkey, United Kingdom, USA

28 Nationalities

Management

Giulio Superti-Furga
Scientific Director

Georg Casari
Administrative Director

Gerhard Schadler
Managing Director

Administration

Sonja Baier
Assistant

Angelika Eisner
Assistant

Anita Ender
Scientific Office & Human Resources

Verena Lichtenegger
Assistant

Leopold Liechtenstein*
Public Relations & Sponsoring

Edith Müller-Primeßnig
Finance & Controlling

Michael Pilz
IT Administrator

Simone Duve*
Public Relations & Sponsoring

Gabriel Ó Ríordáin
Scientific Support

Principal Investigators

Denise Barlow

Christoph Binder

Sylvia Knapp

Robert Kralovics
MPD New Investigator Award

Sebastian Nijman

Giulio Superti-Furga

Department Heads

Keiryn Bennett

Jacques Colinge
BWK0003 (GENAU APP II)

Postdoctoral Fellows

Christoph Baumann
EUP0004
(Marie Curie Fellowship)

Stephan Blüml*
MUV-CeMM

Viola Borgdorff
MUV-CeMM

Tilmann Bürckstümmer

Thomas Burkard

Florian Grebien

Oliver Hantschel
FWF P18737

Quanah Hudson
EUP0002 (HEROIC)

Markus Müllner

Florian Pauler
BWK0005 (GENAU EPI III)

Andreas Pichlmair
EMBO Long-Term Fellowship

Lily Remsing Rix°
PRI0001 (LLS Fellowship)

Uwe Rix
BWK0004 (GENAU DRAGON),
BWK0008 (GENAU PLACEBO)

Elena Rudashevskaya
BWK0007 (GENAU APP III)

Roberto Sacco
BWK0007 (GENAU APP III)

Omar Sharif

Stefanie Sigel
FWF I289-B09

Mathew Sloane

Alexey Stukalov
BWK0006 (GENAU BIN III)

Sandrine Tonon

PhD and Diploma Students

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KIMCL-MUV/FWF CCHD

Irene Aspalter*

Diego Barcena

Mario Biaggio
MUV

Marc Jochen Brehme*
FWF P18737

Larissa Cardilo dos Reis
KIMCL-MUV/GENAU DRAGON

Evelyn Dixit
FWF W1205 (CCHD)

Gerhard Dürnberger

Immanuel Elbau
MUV

Patricia Ganger*

Emanuel Gasser*

Riem Gawish
MUV

Roberto Giambruno

Adriana Goncalves

Philipp Günzl
EUP0002 (HEROIC)

Ashot Harutyunyan
FWF P20033

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EUP0002 (HEROIC)

Stephan Hütter
EUP0002 (HEROIC)

Roland Jäger
FWF P20033

Evren Karayel
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Thorsten Klampfl

Martha Körner
EUP0002 (HEROIC)

Tomasz Kulinski
EUP0002 (HEROIC)

Thomas List

Ulrich Matt*
FWF P18232-B11

Philipp Meng
MUV

Damla Olcaydu
Doc-fFORTE Fellowship

Lucas Rudigier*
EUP0002 (HEROIC)

Federica Santoro
FWF W1207 (RNA Biology)

Ruth Scheicher*

Basak Senergin
FWF F1718

Dimitris Tsiantoulas
FFG BRIDGE 815446

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Georg Winter
BWK0004 (GENAU DRAGON)

Ana Zivkovic

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Cristina Melinte

André Müller

Nils Craig-Müller

Katja Parapatics
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Melanie Planyavsky

Adrijana Stefanovic

Karin Stich
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Norbert Venturini

Katarzyna Warczok°

* left CeMM in 2009
° maternity leave

Legend to grants

BWK0003
GEN-AU Project
"Austrian Proteomics Platform II"

BWK0004
GEN-AU Project
"DRAGON-Drug Action
by GenOmic Network(s)"

BWK0005
GEN-AU Project
"Epigenetic regulation of
cell fate decisions"

BWK0006
GEN-AU Project
"BIN III-Bioinformatics
Integration Network"

BWK0007
GEN-AU Project
„APP III-Austrian
Proteomics Platform"

BWK0008
GEN-AU Project
"PLACEBO-Platform Austria
for Chemical Biology"

EUP0002
EU Project "HEROIC-
HighthroughputEpigenetic
Regulatory Organisation
In Chromatin"

EUP0004
Marie Curie Fellowship
"Dissecting pathogen recognition
complexes of Toll-like receptors"

FFG 815446
BRIDGE Programme
"Microparticles and novel therapeutic
approaches for thrombosis"

Foundation Leducq
Transatlantic Network of
Excellence "Immune Modulation
of Cardiovascular Disease"

FWF P18737
FWF Project "Physical
and Functional Map of
Bcr-Abl Signalling"

FWF P20033
FWF Project
"Genetic basis of
myeloproliferate disorders"

FWF F1718
FWF Special Research
Program "Modulators of
RNA Fate and Function"

FWF W1205
FWF Doctoral Program
"CCHD-Cell Communication
in Health and Disease"

FWF W1207
FWF Doctoral Program "RNA Biology"

FWF I289-B11
FWF International Project
"Innate immune responses to
Streptococcus pneumoniae"

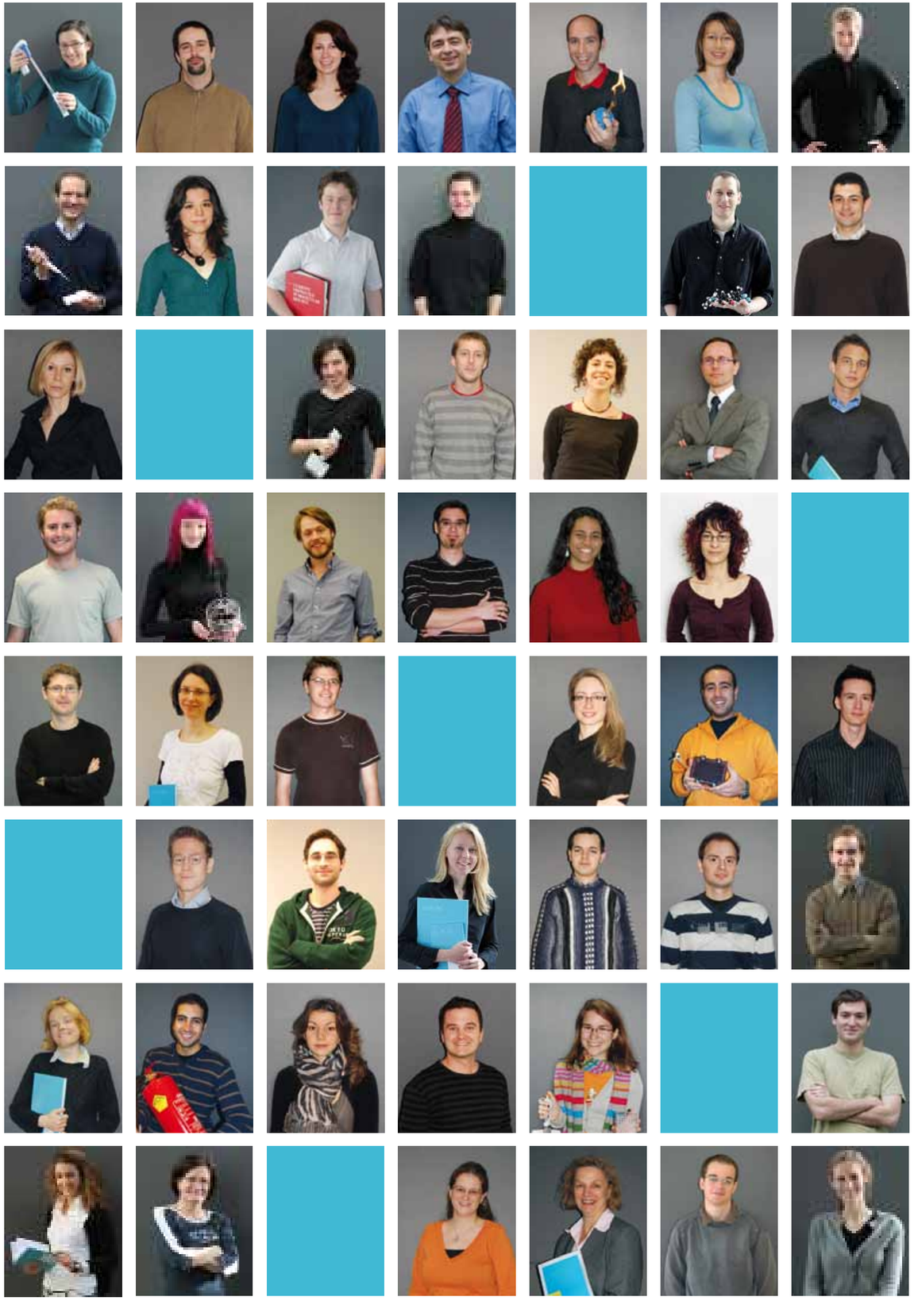
FWF 18232-B11
FWF Project
"Immunodulatory role of
oxidized phospholipids"

PRI0001
Fellowship of the
American Leukemia and
Lymphoma Society

Doc-fFORTE Fellowship
Austrian Academy of Sciences

EMBO Long-Term Fellowship
European Molecular Biology
Organization

MPD New Investigator Award
American MPD Foundation



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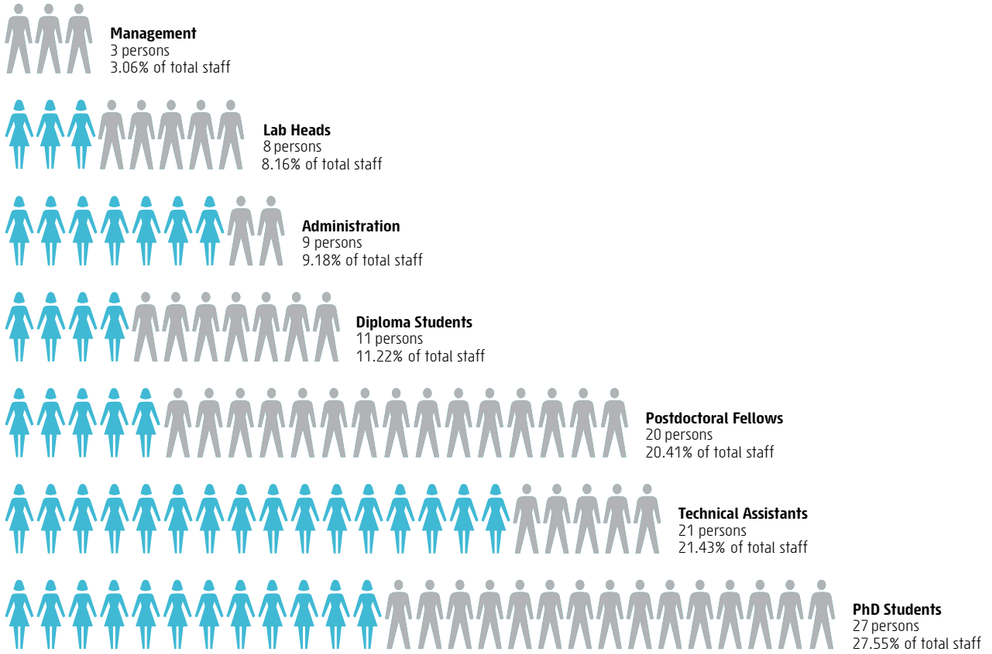
CeMM
Facts & Figures

CeMM Staff

Listed by number of persons per field of work

The CeMM administration is very lean in relation to the total staff (98 employees as of December 2009). We have a good gender balance. The average age at CeMM is 30.5 years.



Management
3 persons
3.06% of total staff

Lab Heads
8 persons
8.16% of total staff

Administration
9 persons
9.18% of total staff

Diploma Students
11 persons
11.22% of total staff

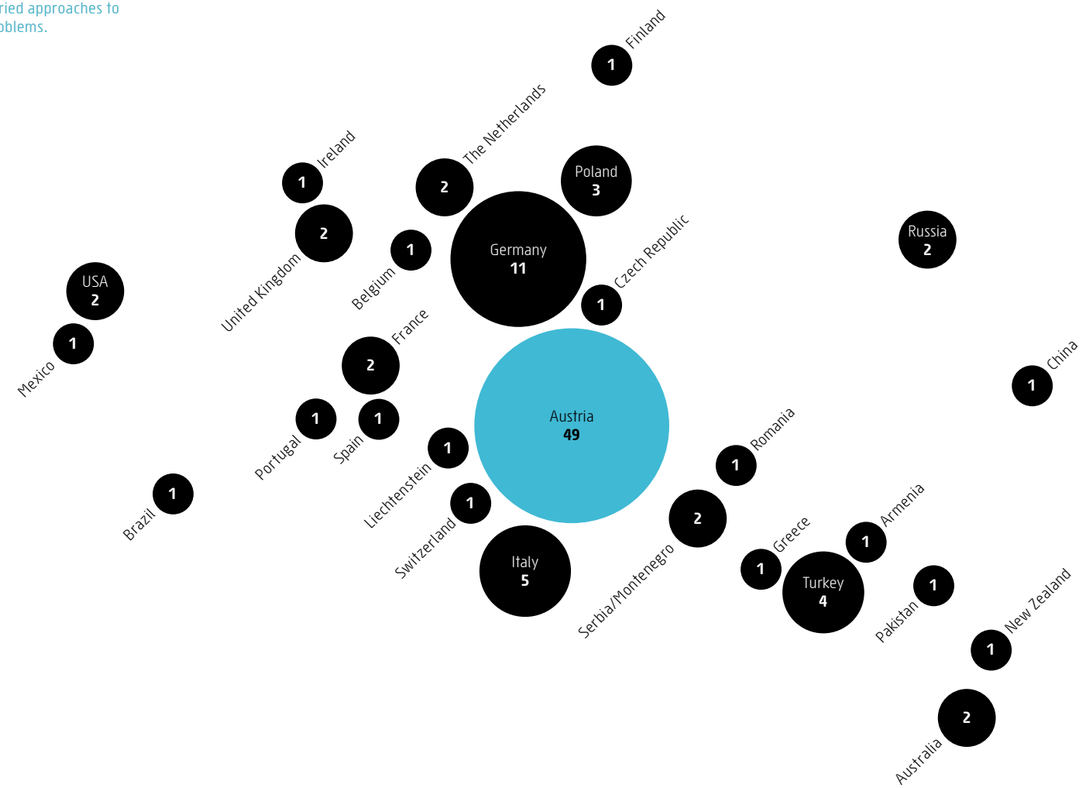
Postdoctoral Fellows
20 persons
20.41% of total staff

Technical Assistants
21 persons
21.43% of total staff

PhD Students
27 persons
27.55% of total staff

Nationalities at CeMM

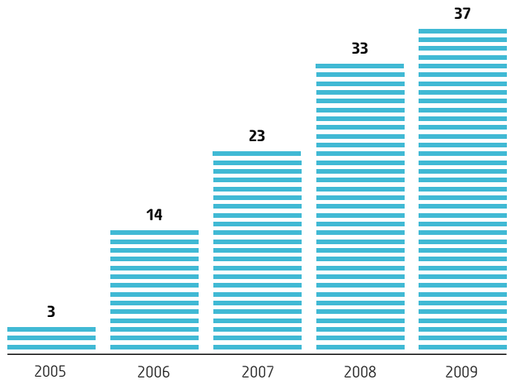
28 different nationalities are represented at CeMM. The international atmosphere spurs ideas and enables scientists to find varied approaches to problems.



CeMM Publications

The number of scientific publications at CeMM is still increasing year on year, a sign of the consistent development of the institute.

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



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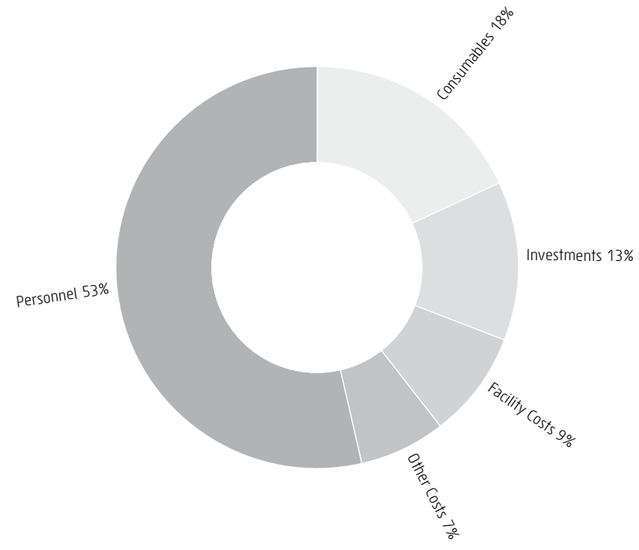

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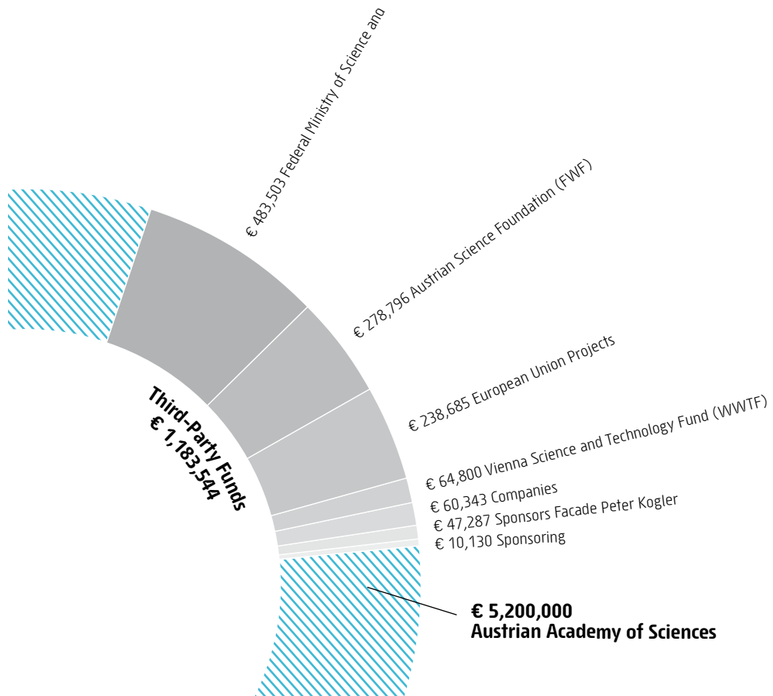

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CeMM can be considered a People's Biotech Company that is predominantly run by tax money. But maybe you wish to invest in CeMM on top of that. Therefore, we are issuing symbolic CeMM Health Research Bonds that you can purchase by donation. The bonds 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.

For your donation you will receive a symbolic paper CeMM Health Research Bond certificate, that you can treasure or give as a gift. Contact anybody at CeMM or directly at bonds@cemm.at.

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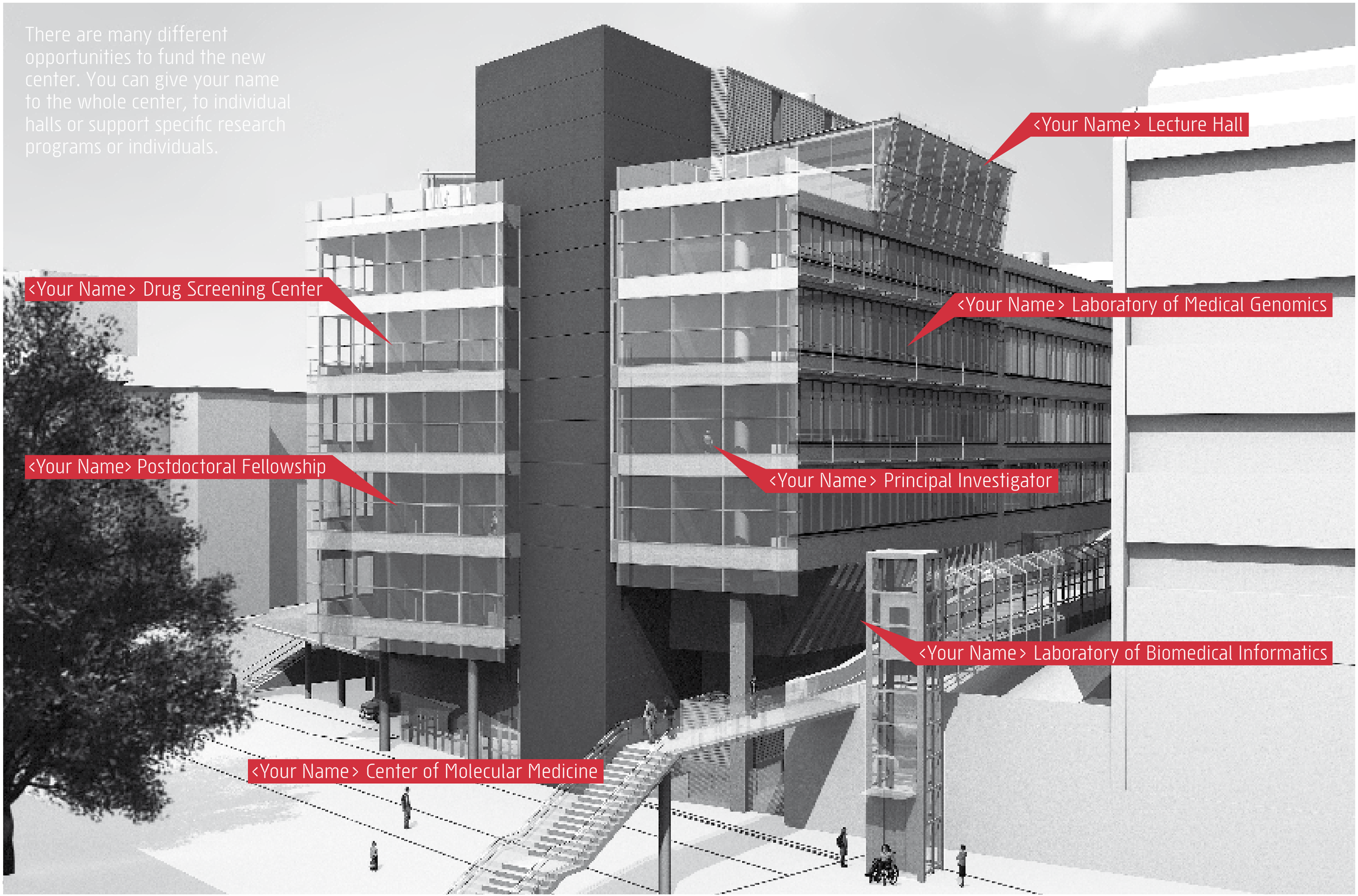

Glossary of Molecular Medicine

Antigen
A molecule capable of being recognized by an antibody, triggering an adaptive immune response.

Atherosclerosis
A medical condition involving thickening of the artery wall, which can lead to a variety of serious diseases such as heart attack and stroke.

Bioinformatics
The application of information technology, computer science, and mathematics to the field of biology.

Biological System
A group of multiple biological components, such as proteins or cells, which can be on many different levels such as molecular or organismal.

Blood Malignancies
A form of cancer characterized by uncontrolled proliferation of one of the diverse types of blood cells.

Cardiac Glycosides
A group of drugs related to Digitalis, a molecule derived from the Foxglove plant, used to treat chronic heart failure.

Cancer
A group of diseases caused by uncontrolled cell growth usually associated with invasion into healthy tissue, which is often life threatening.

Chemical Proteomics
The study of the physical interaction between drugs and cellular proteins.

Chromosome
A dense physical structure found in cells made up of DNA and proteins. Human cells contain 23 pairs of chromosomes, so that each gene is present in two copies.

Chronic Myelogenous Leukemia (CML)
A cancer of white blood cells characterized by uncontrolled growth of cells in the bone marrow.

Cytokine
A group of signaling molecules secreted by cells of the immune system to communicate with other cells.

DNA
Deoxyribonucleic acid. A self-replicating chemical structure found in all cells that carries the genetic information to specify life.

Drug
A chemical substance that can affect the function of a cell.

Drug Resistance
The ability of cells and organisms to become insensitive to the action of a specific drug.

Endosome
A membrane-enclosed structure that transports molecules inside cells.

Epigenetics
Heritable changes in genome function that occur without alterations in DNA sequence.

Genomics
The study of the entire DNA sequence (genome) of an organism.

Genotyping
Determining the DNA sequence at a specific position on one chromosome pair.

Gene
A functional unit of heredity found in the genome encoded by DNA.

Gene Expression
Generation of a functional product from a gene.

Genetics
The study of genes.

Histones
A class of proteins that bind and wrap up extended DNA molecules to form chromosomes.

Homeostasis
The natural balance of a biological system or organism.

Imatinib
A drug used to treat chronic myelogenous leukemia.

Immune System
A group of cells and molecules within an organism that protects against disease and damage.

Imprinting
The expression of certain genes in a parent-of-origin specific manner.

Inflammation
A biological response to disease or damage, involving a variety of cells and proteins, and characterized by swelling, redness and pain.

Innate Immunity
A branch of the immune system found in plants and animals comprising various cell-types that respond non-specifically to infection.

Interferon
A type of cytokine.

Leukemia
A cancer of the bone marrow or blood, characterized by uncontrolled growth of blood cells.

Macrophage
A type of tissue immune cell that engulfs pathogens and stimulates an immune response.

Macro Non-Coding RNAs
A class of long non-protein-coding RNAs.

Malignant Tumor
A tumor capable of invading other tissues.

Mass Spectrometry
An analytical technique to determine the elemental composition of a biological sample.

Molecular Medicine
A field of study integrating basic research with clinical investigation.

Mutation
A chemical change in DNA, which can lead to the expression of abnormal proteins.

Myeloproliferative Neoplasms
A group of diseases of the bone marrow characterized by chronic hyperproliferation of blood cells.

Natural Antibodies
Type of antibody present from birth and not produced in response to infection.

Oncogene
A gene that has been mutated or is expressed at high levels, which causes cancer.

Oxidative Stress
A usually harmful situation caused by abnormally high levels of reactive oxygen species.

Pathogen
An infectious agent such as a virus or bacteria that causes disease.

Pattern Recognition Receptors
Proteins commonly found on the surface of cells that recognize pathogen-associated molecular patterns and trigger an immune response.

Pneumonia
An inflammatory disease of the lungs caused particularly by infection by pathogens.

Proteins
Organic molecules consisting of a chain of amino acids that are encoded by genes and perform diverse cellular and extracellular functions.

Proteome
The entire protein content of a biological system such as a cell or organism.

Proteomics
The study of the protein products of a biological system.

RNA
Ribonucleic acid. A chemical structure found in most cells that can function in diverse processes, or be translated to make protein.

Synthetic Lethality
A process that occurs when loss of function of two genes causes cell death, whereas loss of each gene individually does not.

Transcriptome
All the RNA molecules that are produced by the genome in a biological system such as a group of cells, a tissue, or an entire organism.

Toll-Like Receptors
A class of pattern recognition receptors that recognize pathogen-associated molecular patterns and trigger an immune response.

Tyrosine Kinase
An enzyme that can transfer a phosphate group onto a tyrosine amino acid residue on a target protein, thus modifying its function.

Tumor Suppressor Gene
A gene that normally protects cells from becoming cancerous. Mutation or loss of expression of a tumor suppressor gene can cause cancer.

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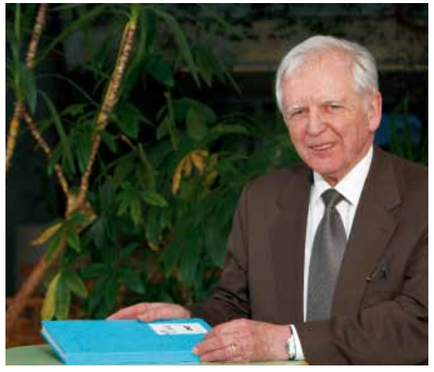

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