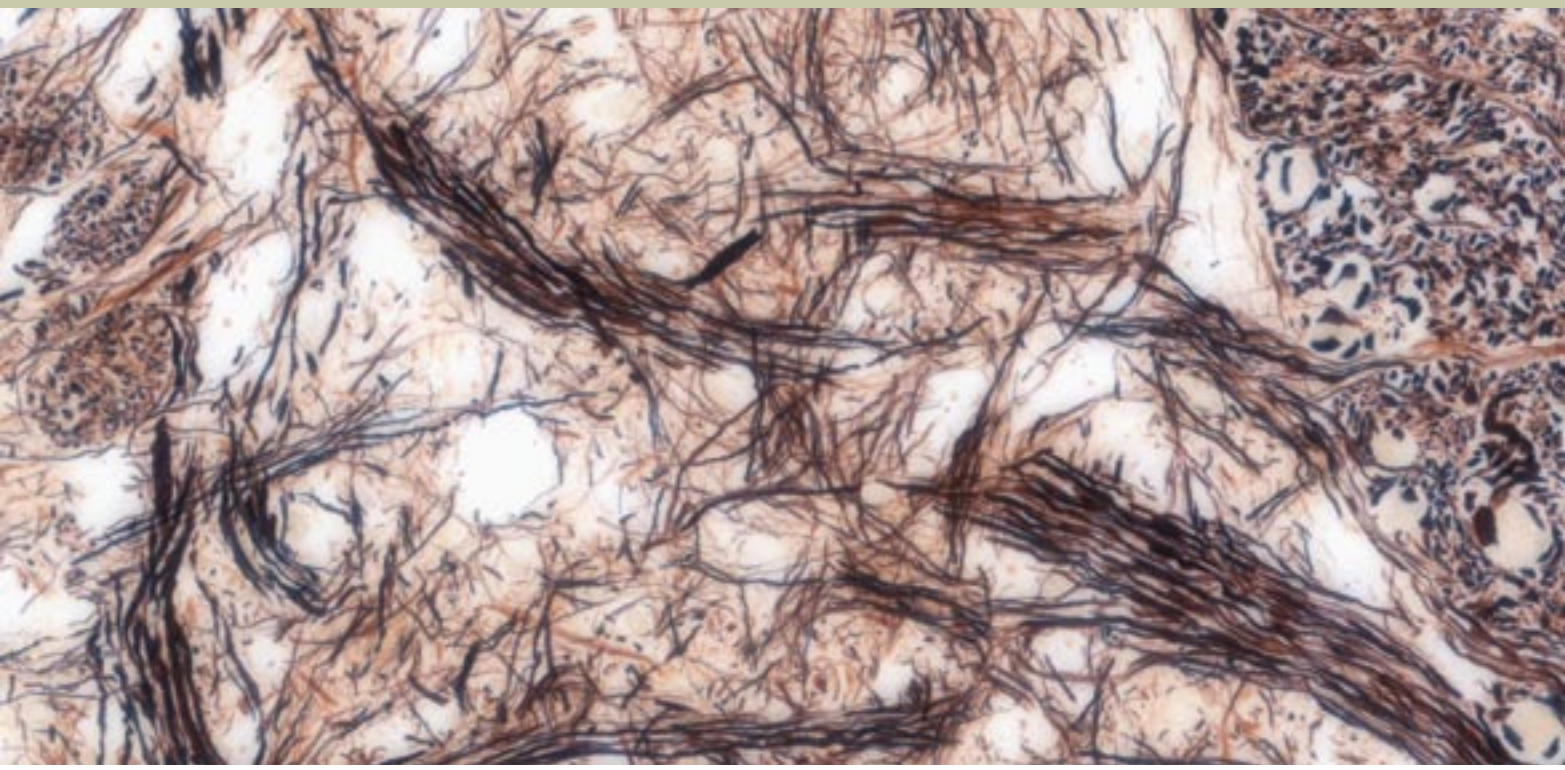
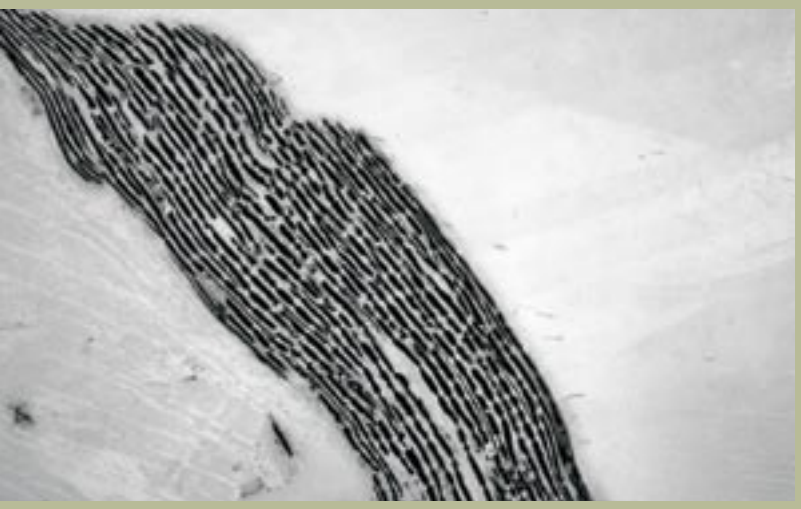
Intellectual Capital Report 2005



Karolinska Institutet

CMM | Center for Molecular Medicine

For research on the common diseases



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Ten years old and growing

In November 2005, the Center for Molecular Medicine, (CMM), celebrated The Ten Year Anniversary of its foundation. We could look back on 10 years of growth and progress that has taken CMM to a world-leading research and development position.

The CMM vision was to create a new type of operational R&D center for the study of common, chronic disorders; afflictions that at best could be given symptomatic relief, but not cure. These diseases are by definition leading causes of disability.

Why are common chronic disorders therapeutic failures? Their complex etiology with roots in the genetic disposition, and also in lifestyle; eating habits, exercise, smoking and alcohol, and in infections is a partial answer. Origins of these disorders that cross over diagnoses and disciplines is another. However, knowledge and experience indicated that at the level of the cell, mechanisms of disease are similar, maybe common.

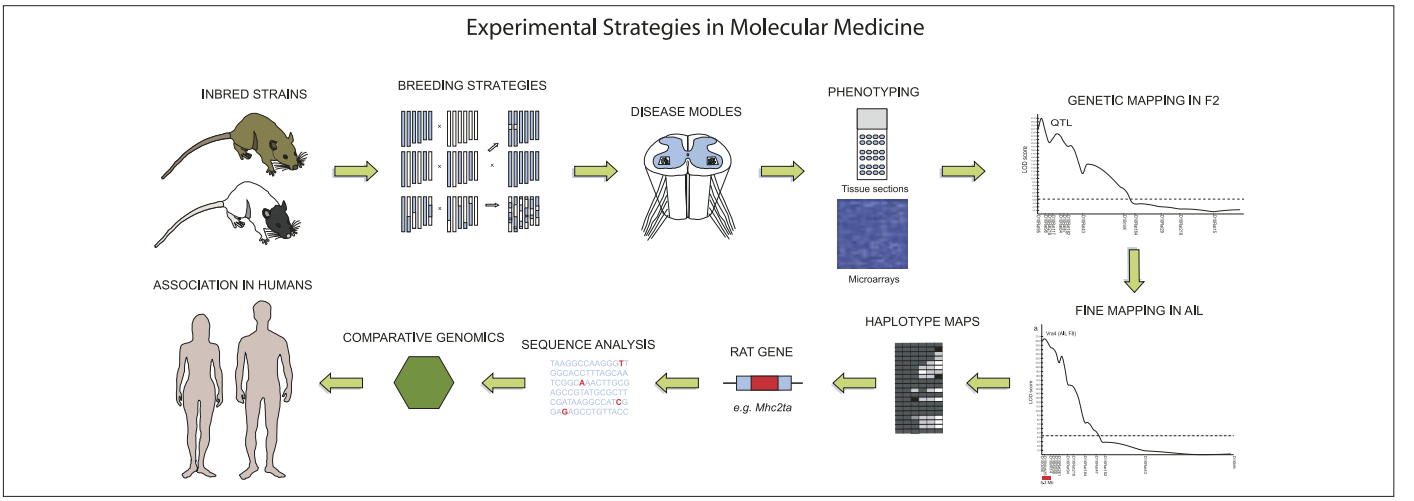
CMM was therefore designed and built for openness and knowledge interactions. A unique context has been established for laboratory research and clinical applications. The CMM leadership concept to share wisdom and insights works on two premises, first that the research groups are sufficiently diversified and second that a culture is created where exchange is promoted and natural. In fact, these conditions seem right for CMM as we have seen progress over the years, with the development of several successful cross-disciplinary programs. CMM has also attracted attention for its management from other organizations, including the EU-Commission for Small and Medium-sized Enterprises (SMEs) and the Austrian Ministry for Education, Science and Culture.

Progress can be measured in different ways. One approach is bibliometry, which shows that the impact of the average publication from CMM is now well above those from Swedish universities in general and reaches the publication level of the world-leading universities in the USA, Harvard and Stanford. A growing portfolio of patents and start-up companies emanating from research at CMM is another example of progress.

Ten years is still a beginning for a scientific institution. We still challenge great breakthroughs in diagnosis and therapy for chronic, common diseases and CMM is positioned to step forward. All who have contributed to making CMM a leading institution in molecular medicine should take pride in what has been achieved thus far. The center has shaped a foundation to meet future challenges.

Lars Terenius – *Professor at Karolinska Institutet and CEO Center for Molecular Medicine.*

Molecular Medicine—*The New Generation of Medicine*



Example of strategies used in research. Animal models are still necessary for certain studies, in order to confirm the results before transferring the studies to human objects. Modern research, though, has made it possible to do many kinds of studies on cell lines or other media without the need for animal testing. Ill. Olle Lidman.

The announcement of the first draft of the human genome on 26 June, 2000, marked a new era in medicine. The advancing knowledge of our genome, the genetic instructions that form our body and mind, will transform healthcare on a global scale. Our health care system can move away from an average dose of the average therapy suitable for the average patient. Instead the therapy can be tailored to efficiently target the exact molecular makeup of the disease and be adjusted to the patient's genetic constitution to minimize unwanted side effects.

While existing therapies use about 500 molecular targets; it is estimated that there are thousands of new potential targets to be discovered by future research in the field of molecular medicine. Therefore, investing in molecular medical research is investing in the future healthcare for us all.

At CMM the research focuses on the complex diseases which are influenced by both genetic and environmental factors. The molecular mechanisms are studied in four areas of common complex diseases: neurogenetics and psychiatric diseases, cardiovascular and metabolic diseases, inflammatory diseases and genetic diseases. As a result, improved diagnostic methods, treatments and preventive measures are continuously being developed to address clinical issues.

Swedish advantages in the forefront

Sweden is the European Union's biggest producer of biomedical research in relation to its population. The position is strongly promoted by a centralized public health system with unique sources of medical and genetic information. Sweden is also recognized for its ability to transform research progress into clinical practice. The transfer is facilitated by the 180 Swedish biotech companies, overall Europe's fourth-largest biotech industry.

These resources enable researchers to make important discoveries; results which the researchers own by Swedish law. All researchers who are participating in teaching at a Swedish university own the proprietary rights to their research results and inventions, a right called the "Teacher Exception".

These advantages are in focus at CMM. The unique organization of CMM forms an intellectual melting pot where experimental expertise from Karolinska Institutet meets clinical competence from Karolinska University Hospital. The researchers are internationally competitive and seven of them are members of the Nobel Assembly awarding the Nobel Prize in Physiology and Medicine.

The proximity to the hospital provides the researchers with rich material for research. The Swedish tradition of medical research combined with registers provides a multitude of biobanks. Other strong platforms are the core facilities and know-how shared among the research groups at the center.

In Sweden researchers own the proprietary rights to their research results and inventions, called the "Teacher Exception"

CMM researchers in the Nobel Assembly

Anders Hamsten
Göran K Hansson
Lars Klareskog
Catharina Larsson
Magnus Nordenskjöld
Tomas Olsson
Lars Terenius

Discoveries at CMM

Of the over 400 discoveries during 2005, here are a few examples to illustrate the scope and expected impact of CMM research.

Vaccine against myocardial infarction might be on its way

Cardiovascular diseases are by far the most common cause of death and are often caused by atherosclerosis. Göran Hansson, Professor in experimental cardiovascular research, and his group have made a discovery that may lead to prevention of atherosclerosis.

Professor Göran Hansson and his research team discovered in the 1980s that people suffering from atherosclerosis have an inflammation in their blood vessels. They have continued to investigate how the development of atherosclerosis is influenced by an inflammation caused by the immune system.

A number of risk factors for atherosclerosis are well known, i.e. smoking and diabetes, but the positive factors are not as well understood.

—Our new discovery, that certain cells in the immune system protect against atherosclerosis, was made together with a French research team in the European Vascular Genomics Network, says Professor Hansson. Our long-term goal is now to develop a vaccine against stroke and myocardial infarction.

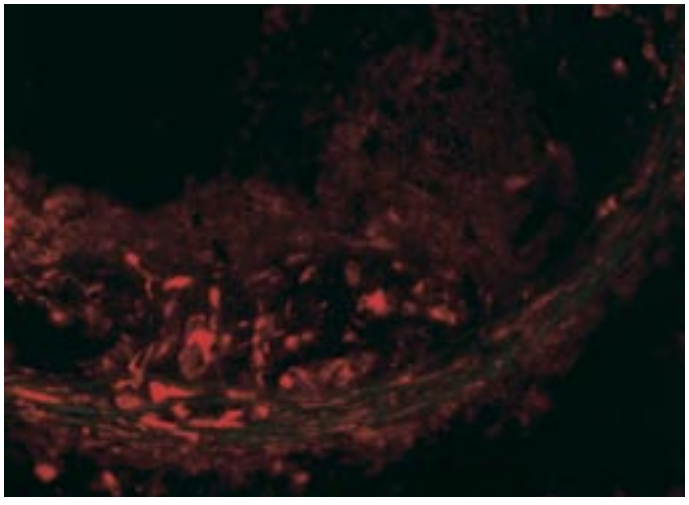
Normally, there is a balance between protective and aggressive immune defence. If the protection factors are reduced for some reason, atherosclerosis can accelerate. The identified protective cells are a subpopulation of T lymphocytes called natural T regulatory cells, or Treg. If Treg cells were absent, more atherosclerosis was developed, and if the number of Treg cells were increased, the atherosclerotic process was stopped.

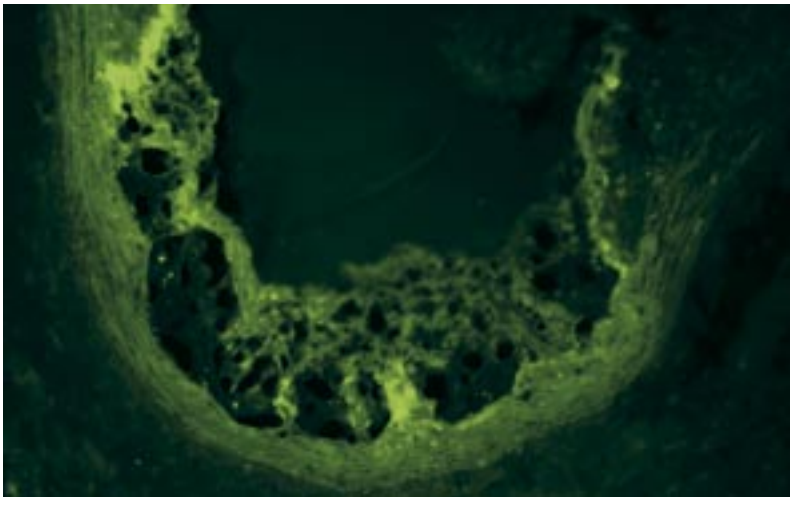
The discovery was further supported by a study where the Treg cells were inhibited by antibodies that blocked their activity. With inactivated Treg, the atherosclerosis increased again. Through gene technology the activation and deactivation of atherosclerosis could be coupled to a molecule made by Treg, called TGF-beta.

—This tells us that TGF-beta is an important tool by which Treg protects against atherosclerosis, says Professor Hansson. There could therefore be possibilities to develop therapies based on protective mechanisms in immune cells of the immune system. In order to do this, we need to continue to map the atherosclerotic process and the factors which increase as well as those that decrease development of disease.

In order to make the future research on atherosclerosis more effective, a large international network has been created, sponsored by the French Leducq Foundation. This network connects a number of research centers in both Europe and the US, with Göran Hansson and Anders Hamsten from CMM as active members, and it will hopefully help their teams contribute to new breakthrough discoveries.

—By using this network, an international effort can be made to solve the mysteries of atherosclerosis – the leading cause of death in the world, concludes Professor Hansson.





Enzymes that degrade collagen within atherosclerotic plaques may cause plaque rupture, thrombosis and ultimately myocardial infarction or stroke. The left picture shows the presence of collagen-degrading enzyme in red and the right one collagen degradation by active enzyme within the plaque in green.

New method to discover unknown human virus

Tobias Allander is working part-time as a physician at Karolinska University Hospital and is a part-time researcher at CMM, developing methods for identification of unknown viruses. Dr Allander's interest in unknown viruses is driven by the desire for new discoveries combined with an interest for medically relevant issues. Even though virus infections are among the greatest health problems in the world, the map of viruses that can cause disease in humans is far from complete. In 2005 he discovered a virus causing serious lower respiratory tract infection in children.

—Viral infections are one of the world's most serious health problems. They can cause everything from AIDS to the common cold, and they kill thousands of people every day. Despite this, we do not have a full picture of all the viruses that infect humans, says virus researcher Tobias Allander

Dr Allander and a collaborator therefore set out to develop a method to enable systematic scanning of samples for unknown viruses. Using this method, they discovered a previously unknown virus that has been found to affect children. The virus, called human bocavirus, was identified in respiratory tract samples drawn from children at Karolinska University Hospital in Stockholm. The bocavirus was detected in 3 per cent of cases of serious lower respiratory tract infection.

—We believe that the most important aspect of our discovery is that it will enable the discovery of many more viruses, and this may help us solve important medical questions. Identifying unknown viruses will probably help in developing diagnostics and treatment for diseases that are currently of unknown origin, says Dr. Allander.

Many scientists believe that as yet unknown viruses can be involved in the development of, for example, childhood diabetes and multiple sclerosis (MS). Tobias Allander voices the need for a project such as the human genome project, where all human genes were mapped. In analogy, a Human Virome Project could render important information on yet unknown viruses with an impact on human health.

—The support I have received from CMM was crucial for my research. The financial compensation from CMM to my clinic has enabled me to investigate viral pathology behind diseases on a part-time basis at CMM. My research could quickly be productive as I started working in a well-equipped and functioning laboratory and did not need to set up all the practical details from scratch, says Tobias Allander.

The impact of smoking and genes on rheumatoid arthritis

Professor Lars Klareskog and his research team explore the genetic and environmental factors influencing rheumatic diseases with the purpose to develop therapies aimed at the immunologic mechanisms involved.

Rheumatoid arthritis (RA) is one of the most common systemic autoimmune diseases, and one of the least understood. Smoking is the major known environmental risk factor for RA, though little is known about the mechanisms involved. A common gene type involved in the disease, HLA-DR shared epitope (SE) genes, is a widely recognized genetic risk factor for RA, but its effects on the autoimmune reactions are also not fully understood. Further research is needed to discover how these genes are involved in the cause of chronic inflammation and progressive joint and organ damage.

To better understand the interactions between smoking and genetics in RA, Professor Klareskog and his team focused on a frequent component of the disease; citrulline, an amino acid not normally present in protein.[1] While extremely rare in healthy individuals and relatively rare in other inflammatory conditions, citrulline-modified proteins are common in about two-thirds of RA patients and may be an underlying factor in the development of the disease. The team investigated patients with newly diagnosed RA and found that smoking and SE genes trigger immune reactions to citrullinated proteins.

The study's 930 early RA patients ranged in age from 18 to 70 years. 383 healthy controls, drawn from the blood bank of northern Sweden, were matched for age, gender, and residential area. The researchers found that a history of smoking increases the risk for RA, but only for individuals who test positive for anticitrulline antibodies, regardless of the presence of SE genes. Similarly, inheriting HLA-DR SE genes in a single copy, as well as in double copies, increases the risk for RA, but only for individuals who test positive for anticitrulline antibodies, including individuals who have never smoked. Yet, for individuals who test positive for anticitrulline antibodies, the interaction of smoking and carrying 2 copies of the SE gene dramatically increases the risk for developing RA--by 21 times.

—The remarkable gene-environment interaction observed in the case-control study, together with the immunostaining for citrullinated proteins, might now provide a clue to the molecular mechanisms of importance for disease development in a subset of RA patients. We may thereby be given some new opportunities to both predict and understand the onset of RA and to interfere with RA-inducing events before clinical symptoms are apparent, notes Lars Klareskog.

1. Klareskog L, Stolt P, Lundberg K, Källberg H, Bengtsson C, Grunewald J, Rönnelid J, Erlandsson Harris H, Ulfgren A-K, Rantapää-Dahlqvist S, Eklund A, Padyukov L, Alfredsson L och Epidemiological Investigation of Rheumatoid Arthritis Study Group. A new model for an etiology of rheumatoid arthritis: Smoking may trigger HLA-DR (shared epitope)-restricted immune reactions to autoantigens modified by citrullination. Arthritis & Rheumatism, January 2006, 54: 53-61.

A major EU-project – AUTOCURE – containing over 25 research groups, was initiated during 2005 with Professor Klareskog as co-ordinator. The project is starting in March 2006 and will be financed for five years to map immunologic mechanisms behind rheumatoid arthritis and myositis. The project will also lead to a system for exchange of research material for other research projects on inflammatory diseases.

Psoriasis—a complex disease linked to cardiovascular disease and breast cancer

Professor Mona Ståhle leads a research group studying skin diseases such as psoriasis and wound healing. Her interest in psoriasis is that the disease is quite common, about 2-3 per cent of the population in the western world has the disease, yet its cause is unknown. Her group is therefore investigating genetic and environmental factors which could influence the outbreak of the disease. To complicate the subject further, psoriasis is not one disease but can occur in different forms.

—We study a group of 700 affected individuals in Stockholm from the debute of the disease in order to identify the genetics, the disease progress and the efficiency of treatment, says Professor Ståhle. In this group two major forms of psoriasis could be found—guttate psoriasis and plaque psoriasis. The latter was present in 90 per cent of the patients and could be linked to severe stress or life crisis two or three months before the outbreak of the disease.

Psoriasis is also linked to other diseases. Twenty years ago researchers realized that psoriasis is not only a skin disease but also a condition which embraces the immune system and a systemic disease which can induce cardiovascular illness. Professor Ståhle and her group showed that patients with severe psoriasis have an altered blood fat metabolism, which could explain the increased risk for cardiovascular disease in this group.

Another discovery was the additional functions of the antibacterial protein, hCAP18 and its product after cleavage, LL-37. Healthy individuals have increased levels of hCAP18/LL-37 after a skin injury, whereas people with chronic ulcers lack hCAP18/LL-37 in their wounds. The protein was consequently found to stimulate growth in skin cells. People with impaired wound healing could therefore be treated with this protein. A step towards a solution is the group's discovery that vitamine D stimulates the production of the protein. Future treatments based on hCAP18/LL-37 are further developed through a company, Lipopeptide, which Professor Ståhle and her colleagues founded.

—We are now developing a pharmaceutical, based on this protein, to treat wounds with impaired healing in elderly patients, says Professor Ståhle. The product is now in a preclinical stage and has yet to be tested in patients.

Not only skin cells proliferate when stimulated with hCAP18/LL-37. Even cancer cells were shown to use the protein to stimulate growth, which the research group now studies in breast cancer. Previously, the protein was recognized as a defence mechanism for tumors. However, Professor Ståhle and her group have demonstrated that the protein is present in higher levels in breast cancer cells compared to normal breast cells. A possible future treatment for breast cancer could therefore be to block this protein.

Besides conducting research at CMM, Professor Ståhle also works at the Dermatology Clinic at Karolinska University Hospital and teaches medical students at Karolinska Institutet.

—It is a great advantage to work as a physician as well as researcher. My contacts with the patients greatly benefit my research, says Mona Ståhle.

Psoriasis in the skin can occur in different parts of the body and display a variety of symptoms. Photo: Swedish Psoriasis Association.

Highlights of the Year

H. M. Queen Silvia and Stig Larsson, chairman of the CMM board.

Royal Visit on the10 Year Anniversary of The CMM Cornerstone

On November 17, 1995, the cornerstone of the CMM building was laid. In celebration, a seminar on molecular medicine was held on December 1, 2005 attended by H. M. Queen Silvia and a number of CMM donors.

Professor Bengt Samuelsson, former President of Karolinska Institutet and Nobel Prize Laurate in 1982, expressed a positive opinion on the CMM model and how valuable research is accomplished.

—Research is like the activity in a beehive. There is no honey unless the bees co-operate. Likewise, there are no research results unless researchers collaborate. Multidisciplinary research centers are therefore a key to outstanding results.

The Director of the center, Professor Lars Terenius, described the concept of CMM.

—We have a common platform for molecular research on the major diseases. The same biotechnology basis and molecular methods are applied to investigate the exact molecular mechanisms behind a variety of diseases. Better preventive methods, diagnostic tools, and treatments can then be developed.

A selection of the discoveries on common diseases was presented. Professor Magnus Nordenskjöld explained how research on chromosomal changes can help couples having difficulties in having children. Professor Tomas Olsson presented his research on MS and factors that can increase the risk for the disease. Then Professor Göran K Hansson revealed the silent disease, atherosclerosis, where his group has shown that anti-inflammatory treatment can prevent cardiovascular disease. Next Professor Martin Schalling explained how renal failure is associated with premature cardiovascular aging.

Positive opinion from Harvard

The American talk-show host Montel Williams donates to a number of American universities but Tomas Olsson's research team is a Swedish exception. Olsson's group has for instance contributed to the discovery of a gene variant that increases the risk for MS, RA and cardiac infarction.

—Tomas Olsson's group has made important contributions for the treatment of MS which is why I am happy to support him, says Montel Williams.

Montel Williams is supported by his research advisor, Allen Counter from Harvard University.

—The research conducted here at CMM is in many ways better than the research at Harvard.

New donations

The Stichting af Jochnick Foundation granted two three year full-time positions (3,4 MSEK). The funding is allocated to young researchers with PhD degree and postdoctoral qualifications, the latter preferably from abroad, and the appointments for the positions are to be based on scientific qualifications. The 46 applicants who applied for the positions were reviewed by external experts, who chose a selected few for interviews. The selected researchers will start at CMM in the fall of 2006.

CMM in national media

CMM hosted a press conference on April 8, where the discovery of a common risk factor for cardiovascular disease, rheumatism and MS was presented.[2] It is the first identified gene to link autoimmune diseases with cardiovascular disease and up to a quarter of the population might be affected. Public newspapers and national television as well as the trade press were represented and the research had great impact in the different media.

CMM researcher among the most cited in the world

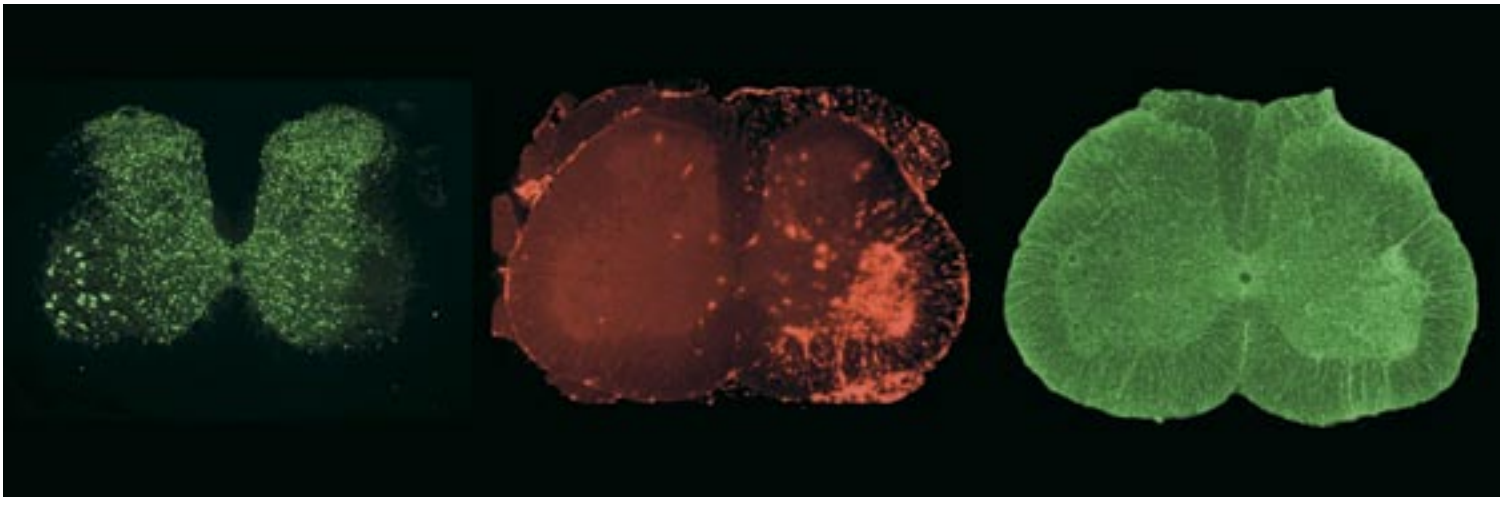
Lars Terenius, CEO at CMM, is listed on the Thomson Scientific International List of the world's most cited authors of scientific publications. Since his PhD degree in 1969 Professor Terenius has a publication list of 522 articles on discoveries in neuroscience.

Prizes and awards

CMM group leader Catharina Larsson was awarded the Eric K. Fernström's prize to young and promising researchers. Her research on mapping hereditary tumor diseases, including the identification of genes and genetic changes behind hormone-producing tumors, has been used for new diagnostics, treatments and preventive measures.

The Swedish Governmental Agency for Innovation Systems, VINNOVA, awarded two companies founded by CMM researchers 300 000 SEK each. Mohammed Homman is co-founder of Intelligent Virus Imaging, based on a method to analyze virus production through electron microscope imaging. Johan Björkegren is co-founder of Clinical Gene Networks, which is developing a novel technology to identify genetic networks, in particular regarding cardiovascular disease.

The Dmitris N. Chorafas Prize to distinguished PhD students was awarded to Stina Salomonsson at CMM. Stina received 4 000 USD for her thesis "The role of Ro52 autoantibodies in congential heart block".



Immunolabeling for NeuN, MHC class II, and GFAP in the lumbar spinal cord 21 days following unilateral ventral root avulsion in the DA rat.

2. Swanberg M, Lidman O, Padyukov L, Eriksson P, Akesson E, Jagodic M, Lobell A, Khademi M, Borjesson O, Lindgren CM, Lundman P, Brookes AJ, Kere J, Luthman H, Alfredsson L, Hillert J, Klareskog L, Hamsten A, Piehl F, Olsson T. MHC2TA is associated with differential MHC molecule expression and susceptibility to rheumatoid arthritis, MS and myocardial infarction. Nat Genet. 2005 May;37(5):486-94.

The CMM Intellectual Capital Report Model

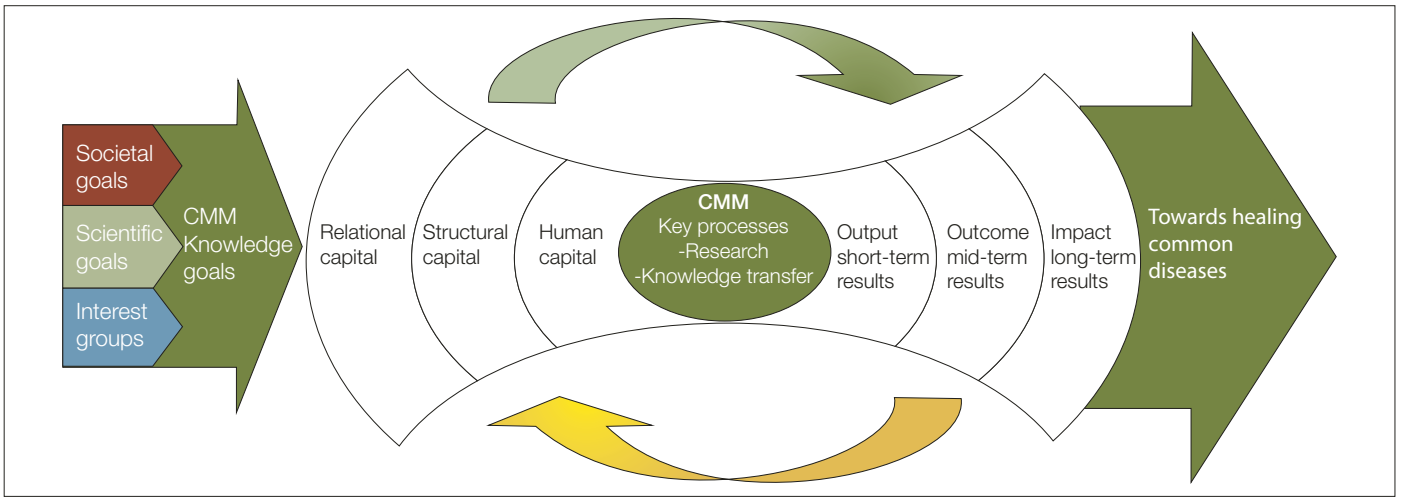


Figure 1. The Intellectual Capital Report Model illustrating the input and output of research and knowledge transfer.

New knowledge makes our society evolve. This is the ultimate purpose of research. The research at CMM is therefore aimed at the goals of society, science, and various interest groups, such as patient organizations. In order to reach these goals, human, structural, and relational capital is invested in the key processes of CMM - research and knowledge transfer (see figure 1).

The results can be viewed in a short-, medium- and long-term perspective. The immediate result of a discovery is a published article to spread the new knowledge. The discovery can in time be developed to new diagnostics and treatments. In the long run, improvements in the health care system lead to healthier individuals and lowered societal costs for illness.

Thus, investing in medical research can reduce societal illness costs. This can be described as an opportunity cost or indicate the potential value contribution of CMM research. A calculation of the costs caused by cardiovascular disease in Europe showed a loss of 169 billion € annually.[3] The expenditure was primary, outpatient, emergency, and inpatient care, as well as medications. Costs of unpaid care and lost earnings due to morbidity and premature death were also included in the study. In Sweden cardiovascular disease costs 4.8 billion € every year, and the cost of cancer in 2004 was 3.5 billion €, which equals 7-8 per cent of the total cost of medical care in Sweden.

> Non-profit institutions tend not to give priority to performance and results. Yet performance and results are far more important—and far more difficult to measure and control—in the non-profit institution than in a business."

Peter F. Drucker (1909—2005) "Managing the non-profit organization".

3. Economic burden of cardiovascular diseases in the enlarged European Union. Leal et al. Eur Heart J. 2006; 27:1610.

CMM Profile Areas

CMM has three profile areas. The strategy to focus support in the profile areas strengthens both the human and the relational capital as well as the productivity and implementation of the research results. The interdependency between the areas creates a synergy rendering rapid research results with high relevance to patients.

Translational research

CMM strives to stimulate the mutual benefit between clinical competence and experimental experience, and aims to disseminate knowledge on medical technology and methodology relevant for molecular medicine in the clinical practice. Therefore, CMM forms an arena for knowledge exchange between researchers from Karolinska Institutet and clinicians from Karolinska University Hospital. Funded by Torsten and Ragnar Söderberg Foundation, CMM has been able to offer clinicians an opportunity to spend 50 per cent of their time on research (see also page 7). Their research areas are closely linked to patient needs and situations and the results have the potential of greatly improving the medical care.

Supporting young researchers

All experts have been beginners. To secure future generations of researchers in molecular medicine, CMM needs to recruit young outstanding researchers and support their development. The strategy is therefore to emphasize the intellectual, relational, and structural infrastructure for this group in particular. Many of the clinical researchers, mentioned above, are young and in the beginning of their careers, and will benefit from the opportunity CMM provides them with.

Transferring research results to society

Research results make a difference only once they leave the lab bench. At CMM the transfer of research results to society is strongly supported; disseminating new knowledge and developing results into methods and treatments for health care is highly focused.

During 2005, CMM initiated a support system for collaboration projects with pharmaceutical and biotech companies, a majority of which were small and founded by researchers at CMM.

Furthermore, CMM offers patent support to stimulate entrepreneurship and facilitate for the researchers to further develop their research results. The recently introduced patent support has so far led to the creation of one start-up company (see also page 16).

Research fields of the clinical researchers

Methods for identification of unknown viruses
Tobias Allander, MD, PhD

The potential of stem cell treatments in neuroinflammatory diseases
Lou Brundin, MD, PhD

Immunological mechanisms in atherosclerosis and hypertension
Johan Frostegård, MD, PhD

Gene expression at heart failure
Anders Gabrielsen, MD, PhD

The genetics behind autism
MaiBritt Giacobini, MD, PhD

Molecular medicine and prenatal treatment of androgenital syndrome
Svetlana Lajic, MD, PhD

Immune-modulating substances in rheumatoid arthritis
Per Larsson, MD, PhD

Mechanisms and genetics of nerve injury-induced inflammation and neurodegeneration
Fredrik Piehl, MD, PhD

Kidney failure and its relation to atherosclerosis and malnutrition
Peter Stenvinkel, MD, PhD

Genetic and environmental factors regulating neuroinflammation
Erik Wallström, MD, PhD

CMM Intellectual Capital

Relational Capital

CMM has continued building relations both within the center, with the clinic and with other researchers worldwide. The number of collaborations of all kinds has increased since 2004 and since many of the former PhD students now continue their careers abroad, the strong international network will increase.

The internal co-operation within CMM groups has increased by 3 per cent, and an overview of articles published during 2004-2005 shows that the researchers overlap each other's areas in an elaborate network (figure 2). Some areas are more strongly connected to certain groups but most of the researchers publish results in a number of different subareas of molecular medicine. Even though CMM has four major research areas; neurogenetics and psychiatric diseases, cardiovascular and metabolic diseases, inflammatory diseases and genetic diseases, it is in reality not so easy to divide the research into these areas. Most of the groups feel connected not to one but two or more of these areas, which indicates the strong foundation of multidisciplinary research.

One aim at CMM is to increase the interaction between the clinician and the researcher. Two ways of stimulating this are to encourage the staff to work both at the clinic and in the laboratory and to interact with other groups in the surroundings. Since 2004, the number of staff and students with clinical training has increased by 5 per cent and 6 per cent respectively and the collaboration with other groups at Karolinska Institutet or Karolinska University Hospital has increased by 38 per cent.

The national and international networks are also on an up going trend. The collaboration with other Swedish partners has increased from 106 in 2004 to 112 in 2005 and international collaborations from 164 to 192. The strong connection with the international research community can be seen in the number of faculty (29 per cent or 46) and students (41 per cent or 62) from other countries and also that 27 previous PhD students have started an international career during 2005, increasing the total number from 50 to 72.

Co-operation with other research institutes does not suffice, the industry is also an important collaboration partner. The number of PhD students or postdocs who are working for the biotechnology industry in Sweden or abroad remains high, 50 in 2005, and there are 39 reported collaborations with various biotechnological or pharmaceutical companies, which is an increase of 5 per cent from 2004.

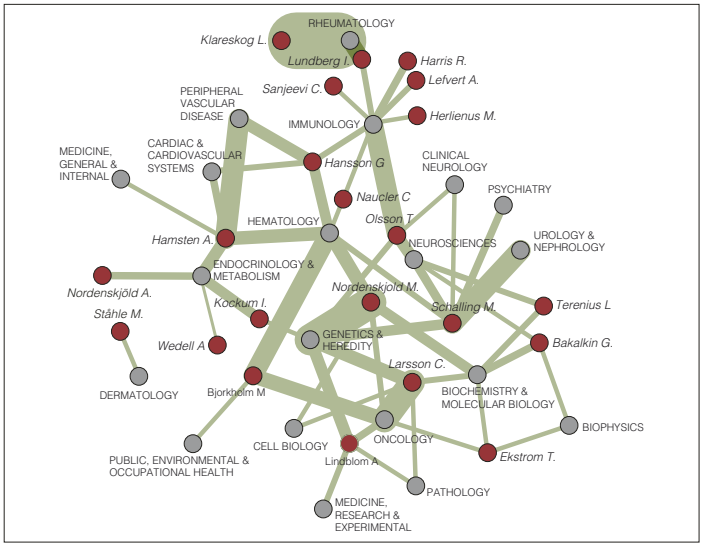


Figure 2. Publications pattern of the CMM research groups. Data produced by Catharina Rehn, Karolinska Institutet Library.

Structural Capital

Structural capital is not easily defined, but can be described as everything that is left after the people has gone home. It can be diverse items, ranging from computers and coffee tables to chemicals and cell samples.

Clinical material obtained from biobanks remains very important. The researchers gather their biological material from over 60 biobanks, Swedish as well as international, which provide them with e.g. tissue samples and blood from patients and healthy volunteers. Of the total budget, 8.5 per cent or almost 1.3 MSEK is spent on technical infrastructure, such as cell separators, DNA sequencing facilities, IT etc. Since the research demands very advanced apparatus, CMM is strongly dependent on both governmental and non-governmental funding. During 2005, 60 per cent of the total research budget derived from non-governmental funding (92.9 MSEK) and 40 per cent from governmental funding (61.7 MSEK). Companies funded CMM with 27 MSEK, or 17 per cent of the total budget.

Two other areas of importance are IT, which is getting more and more important as bioinformatics plays a greater part in biological research, but also the meeting places of the CMM building. One example of the latter is the restaurant, situated in the ground floor. This is an attractive and natural place for formal as well as informal meetings and an excellent venue for knowledge exchange.

Human Capital

Compared to 2004, CMM has grown with nearly 6 per cent, from 343 people to 363. The senior staff consists of 23 professors and 55 assistant professors, while the younger researchers are divided in 83 postdocs and 153 PhD students. This age distribution is consistent with efforts at CMM to support young researchers and to give them an opportunity to evolve in their role as scientists. The remaining 49 staff members consist of laboratory technicians, laboratory assistants and administrators.

CMM has a relatively even distribution of male and female researchers (figure 3). In Faculty the ratio male/female staff is 51/49, and of the PhD students the same ratio is 26/74. This can also been seen among the group leaders, 16 groups with a mean size of 15 members have a male leader, while 11 groups with a mean size of 10 members have a female leader. The distribution between group leaders over and below the age of 50 has a similar distribution, with 11 and 16 groups, respectively and with an mean size of 16 group members with more senior leader and 10 group members with younger leaders

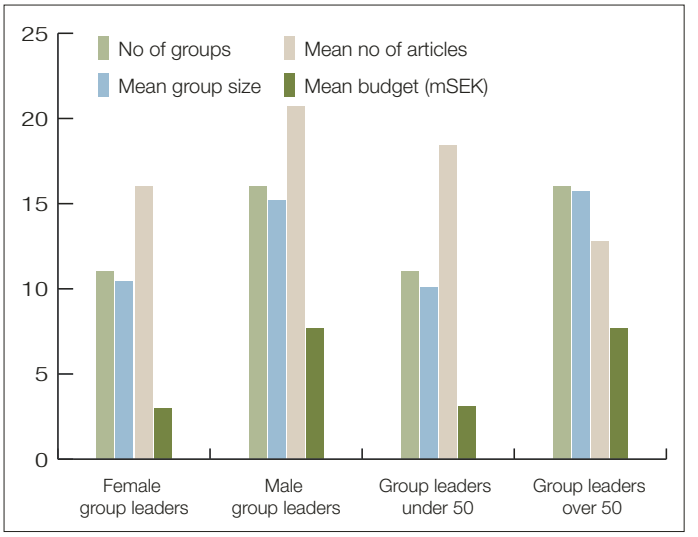


Figure 3. Distribution of staff, created articles and budget between different categories of group leaders.

Financial capital

CMM is funded by private donors, governmental organs, pharmaceutical companies and various types of charity organisations. Compared to 2004 the funding has increased by 35.1 MSEK, mainly due to larger contributions from the Swedish Research Council, Heart-Lung Foundation, Child Cancer Foundation and AFA Insurance.

Major grant donors (MSEK) 2005	
AFA	27.0
Cancer Fund	7.0
Child Cancer Foundation	13.0
EU	6.5
Heart-Lung Foundation	16.9
Karolinska Institutet	15.1
Pharmaceutical companies	6.4
Stockholm County Council	2.6
Swedish Foundation for Strategic Research	6.8
Swedish Research Council	21.9
Söderberg's Foundations	6.1
Wallenberg Foundations	0.8
Miscellaneous	27.5
Total:	**157.4 MSEK**

CMM Results

Output

Research at CMM is highly productive. Over 400 discoveries were published during 2005 and 46 dissertations were defended. The quality of the research is also strong. A comparison of the extent to which articles are cited by other researchers shows highly competitive research at CMM. The CMM articles are cited much more than the average article from all Swedish univerities—32 per cent more than the average article from Karolinska Institutet. On the international level, CMM has recently surpassed Imperial College in London and Stanford University and meets that of Harvard University (figure 4).[4] An overview of the development of average impact factor over time displays a very positive trend (figure 5).[5]

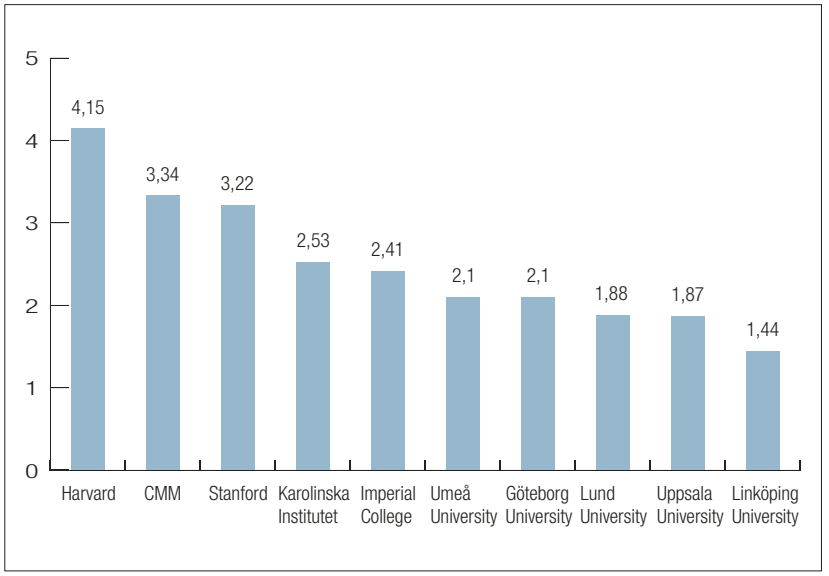


Figure 4. Average citations of articles published 2004—2005 from CMM and a selection of national and international universities.

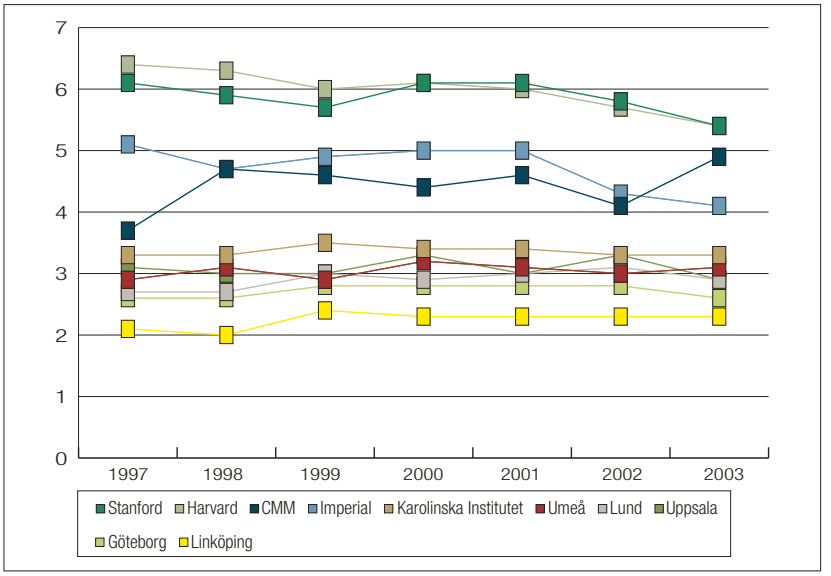


Figure 5. Development of average impact factor over time 1997—2003.

4. Data produced by Karolinska Institutet Library. The impact of the respective journals is collected from English journals in Web of Science in 2004 and 2005.
5. Data from 1997-2003 produced by Jonas Lundberg, Centre for Medical Innovations, Karolinska Institutet. The impact factors of the journals where articles are published is collected from Journal Citations Reports in 2002.

Outcome

Besides research and education, Swedish universities must by law contribute further to societal knowledge and welfare, our "third task". One aspect of this is to let research results contribute to the local, national and international development and healthcare through companies offering new products or services as well as new job opportunities.

At CMM, we take this third task seriously. In 2005, three new companies were founded by CMM researchers. All in all, nine companies have been started, rendering about 50 part- or full-time positions.

From discovery to company

Research used to be conducted by solitary geniuses in closed laboratories, but the modern scientist has a duty to transfer his results to the surrounding community. Mohammed Homman is one CMM researcher who has taken this obligation to heart.

—CMM has always encouraged me to develop products from my research results. I believe that the largest benefit of science is if the results can contribute to the development of the society, for example by improving health care or generating a company. It is clear that these values are shared by CMM, says Mohammed Homman

Mohammed Homman has studied the cytomegalovirus, a herpesvirus that can cause severe illness in patients with weakened immune defense systems, e.g. AIDS sufferers. He has developed a method, based on computerized image analysis, for determination of how virus particles mature in the cell. The method can also be used to study how the virus is affected by a drug, which makes it possible to determine at what point in virus development the drug will be most effective. One of the major advantages with the method is that the computer, as opposed to the human eye, produces exact, objective valuation of the image every time, which makes it possible to repeat experiments and compare results.

Mohammed Homman has created a large network, including business people and researchers from other universities, which has helped him during the founding of the company Intelligent Virus Imaging. The company offers systems for basic analyses and modules for result interpretation, as well as consulting services regarding the method. So far the business has been partly financed by different grants and prizes, but during 2005 Mohammed Homman closed an agreement with IBM, who will develop the computers required for the advanced calculations of the image analysis. Apart from this, there are also co-operations with other companies in different parts of the world

—My biggest motivation with my research is to find new methods that can be used in practice. There is a large satisfaction in the fact that the discoveries made by me and my fellow researchers can make areas in the pharmaceutical industry more efficient.

Companies created by CMM researchers

Actar
Develops target molecules for drug candidates.

Appetite Control
Drug development for obesity, bulimia and anorexia. Sold in 2004.

Biolipox
Drug development for respiratory and inflammatory diseases.

Clinical Gene Networks
Seeks target molecules for drug development for atherosclerosis

Intelligent Virus Imaging
Develops a system for virus quantification

Lipopeptide
Develops novel drug candidates to facilitate wound healing

MCeMED
Develops oral delivery of protein-based drugs

Molecules of Man
Develops human antibodies

NovaSaid
Develops orally available antiinflammatory drugs

Impact

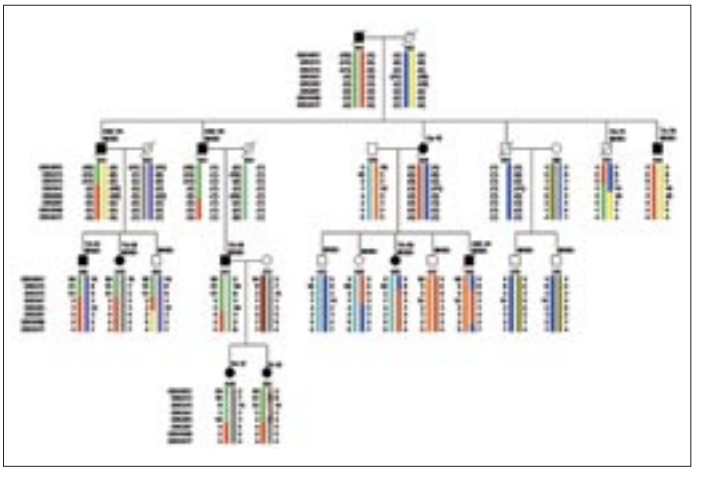
After a discovery is made in the laboratory, it is still a long way to go before it can be transformed into a new treatment or product. Here are a few examples of the results which research can render in a long-term perspective.

Eliminating the risk for colon cancer in high risk families

Professor Annika Lindblom and her group are investigating the genetics of cancer, with a focus on breast and colon cancer. These common cancer forms are often hereditary in contrast to more uncommon cancer diseases which are caused by spontaneous mutations in the DNA.

Professor Lindblom's group has managed to identify a few of the genes involved in hereditary colon cancer. These genes are now used as markers to identify individuals at risk in families with a history of this disease. These people can be offered regular coloscopy, a method where the colon is investigated for polyps, which can develop into cancer if not removed. The regular controls and removal of any detected polyp have reduced the risk of contracting colon cancer from 50 per cent to virtually non-existing for these families.

—The families who are included in the patient registers are very grateful for the possibility to be examined regularly for precaution. Using the genetic markers to identify individuals at risk saves important resources in our health care system and distress for the individual patient, says Professor Lindblom.



Skoglund J, Djureinovic T, Zhou XL, Vandrovcova J, Renkonen E, Iselius I, Bisgaard ML, Peltomaki P, Lindblom A. Linkage analysis in a large Swedish family supports the presence of a susceptibility locus for adenoma and colorectal cancer on chromosome 9q22.32-31.l. J Med Genet, 43:e7, 2006.

Today, the register comprises over 2000 individuals in Sweden and is accelerating in size. Including an entire population in such a program is not feasible, but Professor Lindblom's goal is to develop a cost-efficient test which could be offered for the middle-aged at health care centers.

One of Professor Lindblom's future projects is to identify more genes involved in colon cancer. An additional 70 families have been identified where the genetic influences are yet unknown. The interplay of environmental factors and the genetics is also an important area for future focus.

Unexpected connection between Hodkin lymphoma and asthma

The research conducted by Professor Magnus Björkholm and his group is focused on clinical and experimental studies in lymphomas and leukemia, with a special interest in Hodgkin lymphoma (previously referred to as Hodgkin's disease). This malignancy has a strong inflammatory element and the group is investigating which genetic and environmental factors are involved in the cause of the disease and also certain mechanisms in the inflammatory process.

Hodgkin lymphoma is one of the most common cancers in young adults. The disease has an exceptional age distribution, since it is rare in childhood and middle age. Its cause is yet unknown, but it has been proposed that a virus might be involved, especially in young patients. The current treatment is most often effective, but can give rise to both early and late side effects, such as reduced fertility and an increased risk to develop other cancers.

Professor Björkholm has, in co-operation with Professor Hans-Erik Claesson and MD Jan Sjöberg, investigated which inflammatory substances are important in blood tumor diseases in general, and have found a group of related substances in tissue from Hodgkin lymphoma patients. Some of these might also be involved in other inflammatory diseases. This discovery led to the foundation of the pharmaceutical company Biolipox AB, with focus on development of novel drugs against inflammatory diseases—in particular asthma, chronic obstructive pulmonary disease, allergic rhinitis, and pain in inflammatory joint disorders. The company has more than 40 employees and is situated at Karolinska Institutet campus.

Recently, additional substances with major inflammatory activity have been found in Hodgkin and certain other lymphoma tumors, which may also be therapeutic targets.

Intellectual Capital 2005

	Total	Average per group
Human Capital		
Number of staff	363	13
Number of professors	23	1
Number of assistant and associate professors	55	2
Number of postdoctoral employees	83	3
Number of doctoral students	153	6
Percentage of male/female doctoral students	26/74	
Percentage of male/female faculty	49/51	
Relational Capital		
Number of PhD students with a clinical background	54	2
Number of researchers who have clinical appointments	86	3
Number of collaborations within CMM	93	3
Number of collaborating groups at Karolinska University Hospital (KUS)	128	5
Number of collaborating groups at KI (apart from CMM)	99	4
Number of Swedish collaborating groups/departments outside KUS/KI	112	4
Number of collaborating groups abroad	192	7
Number of previous doctoral students now working in a research group abroad	72	3
Number of doctoral students from other countries	62	2
Number of faculty with undergraduate study background outside Sweden	46	2
Structural Capital		
Number of bio banks used	63	2
Total amount of funds spent on technical framework conditions (MSEK)	12.6	0.5
Key Process Reserch		
Ratio of basic/disease/patient oriented research[1]	24/56/20	
Percent of budget derived from external funds	79	
Percent of budget derived from companies	18	
Research budget (MSEK)	157.4	5.7
Key process "Knowledge transfer"		
Percentage of researchers' working time spent in the clinic	36	
Research leader in information meetings with patient organizations	54	2
Number of public debates in which the group leader participated	22	1
Number of interviews that the group leader gave to a journalist	107	4
Previous doctoral students or postdoctoral employees who now work in a company	50	1
Short-term Results		
Number of dissertations completed in the group	46	2
Number of published articles in refereed international journals during 2005	408	15
Total number of prizes and awards during 2005	32	1
Mid-term Results		
Number of patents approved during 2005	7	
Number of spin-off companies created	4	
New medical treatment or diagnostic programs in progress	~30	

1. Proportion of Bar/Dor/Por with the sum of the proportions=100, e.g 10/60/30.

   Bar=Basic research; the investigation of new knowledge with no clear application but can lay the foundation for disease-oriented or patient-oriented research.

   Dor=Disease oriented research, research that is targeted toward the understanding of the pathogenesis or treatment of a disease, but does not require contact between the patient and the scientist. It may use patient specimens.

   Por=Patient-oriented research, performed by physicians who observe, analyze, and manage individual patients.
   (see Goldstein and Brown (1997) J Clin Invest 99:2803-2812)

The 27 Research Leaders and their goals

Georgy Bakalkin
To understand the molecular and cellular mechanisms behind chronic pain and alcohol dependance.

Magnus Björkholm
To improve therapies for blood diseases.

Kristina Broliden
To investigate mucous immunity against HIV infection and mechanisms involving parvovirus, which is the most common infectious disease behind fetal death.

Nothing shocks me. I'm a scientist.

Harrison Ford (1942–) as Indiana Jones

Tomas Ekström
To study chromatin-modifying molecules that reduce the growth of brain tumors.

Anders Hamsten
To discover new genes and the molecular mechanism behind cardiovascular disease.

Göran Hansson
To generate new knowledge for better prophylaxis and therapies for atherosclerosis

Bob Harris
To produce therapeutic measures for MS and other inflammatory diseases.

Per-Johan Jakobsson
To characterize the importance of the eicosanoid system in the origin and healing of inflammatory diseases.

Lars Klareskog
To understand the mechanisms behind inflammatory rheumatic diseases in order to prevent or slow down disease development.

Science may set limits to knowledge, but should not set limits to imagination.

Bertrand Russell (1872–1970)

Ingrid Kockum
To discover new genes and molecular mechanisms behind type 1 diabetes and other diseases.

Catharina Larsson
To study the genetics of patients with tumors in endocrine organs.

Ann-Kari Lefvert
To accumulate knowledge of immunological reactions in autoimmune diseases.

Annika Lindblom
To identify families with a high risk for breast and colon cancer and thus find better treatments than those offered today.

Ingrid Lundberg
To study the mechanisms leading to chronic rheumatic muscle inflammation or myositis.

Agneta Nordenskjöld
aTo study molecular mechanisms in congenital malformations

Magnus Nordenskjöld
To study different genetic diseases caused by a change in gene dose.

Gunnar Norstedt
To study the influence of hormones on metabolic diseases, growth disturbances and old ageing.

Tomas Olsson
To identify the mechanisms behind MS.

Mats Persson
To study the immune response to hepatitis C virus, and microglia interactions in the CNS.

Carani Sanjeevi
To increase the knowledge of the immunogenetic factors behind type I diabetes.

There are no such things as applied sciences, only applications of science.

Louis Pasteur (1822—1895)

Martin Schalling
To search for the genetic factors behind e.g. depression and eating disorders.

Thomas Sejersen
To map the mechanism behind hereditary muscular disease.

Mona Ståhle
To study the genetics of psoriasis and its association with cardiovascular disease.

Cecilia Söderberg-Nauclér
To study cytomegalo-virus and its association with cardiovascular diseases.

Lars Terenius
To map risk genes behind alcoholism, memory disorders, and Alzheimer's disease.

Marie Wahren-Herlenius
To study the protein Ro52 and its involvement in rheumatic and dermatologic autoimmune diseases such as Sjögren's syndrome.

Anna Wedell
To investigate mutations that cause disorders of the reproductive system in children.

The CMM building.

Steering Board

Stig Larsson (Chairman), Leif Edvinsson, Ingela Gardner Sundström, Lennart Låftman, Ralf Pettersson, Nina Rehnqvist, Stig Åhs, Staffan Josephson

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National Public Health Institute, Helsinki

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R W Johnson Pharmaceutical Research Institute, New Jersey

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Karolinska Institutet, Stockholm

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Annica Arnberg, Anna Persson, Annika Wihlborg, Annika Rosell, Ingrid Kindahl, Leif Edvinsson, Lars Terenius, Olle Lidman

Photos

Front page	Spinal cord neuronal axons labeled by Bielschowsky silver staining.
Page 1	Bielschowsky silver staining of dorsal nerve root.

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