THE Crafoord PRIZE

Crafoord *Days* 2013

2–3 MAY, STOCKHOLM, SWEDEN

The Crafoord Prize in Polyarthritis 2013

Abstracts

Programmes

PETER K. GREGERSEN

LARS KLARESKOG

ROBERT J. WINCHESTER

Anna-Greta and Holger Crafoord Fund

THE FUND WAS ESTABLISHED in 1980 by a donation to the Royal Swedish Academy of Sciences from Anna-Greta and Holger Crafoord. The Crafoord Prize was awarded for the first time in 1982. The purpose of the Fund is to promote basic scientific research worldwide in the following disciplines:

- Mathematics
- Astronomy
- Geosciences
- Biosciences (with particular emphasis on Ecology)
- Polyarthritis (e.g. rheumatoid arthritis)

Support to research takes the form of an international prize awarded annually to outstanding scientists and of research grants to individuals or institutions in Sweden. Both awards and grants are made according to the following order:

year 1: Mathematics and Astronomy
year 2: Geosciences (2014)
year 3: Biosciences (with particular emphasis on Ecology, 2015)
year 4: Mathematics and Astronomy (2016)
etc.

The Prize in Polyarthritis is awarded only when the Academy's class for medical sciences has shown that scientific progress in this field has been such that an award is justified.

Part of the Fund is reserved for appropriate research projects at the Academy's institutes. The Crafoord Prize presently amounts to SEK 4 million. In addition to the prize, financial support is granted to other researchers in the same field in which the prize is awarded for that year.

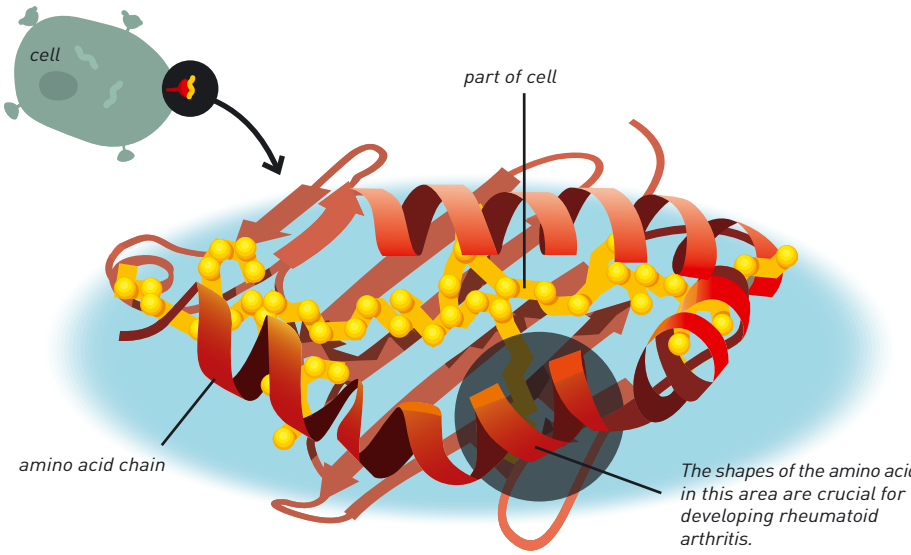
The Crafoord Prize is awarded by the Royal Swedish Academy of Sciences.

Lars Klareskog, Photo: Gustav Mårtensson
Robert J. Winchester, Photo: Columbia University Medical Center

Content

Rheumatoid Arthritis: risky genes become dangerous when you smoke

The knowledge acquired by the 2013 Crafoord Laureates opens new possibilities for the prevention and better treatment of rheumatoid arthritis. Their focused detective work has resulted in a hypothesis that the disease arises from the interplay between genetic inheritance and environmental influences. According to this premise, joint problems from rheumatoid arthritis may start in another part of the body: the lungs.



An illustration showing how the amino acid chains of HLA molecules (red) are folded. They form a pocket, which reveals different parts of the cell to immune cells. Winchester and Gregersen discovered that the shape of this pocket is crucial to the risk of developing rheumatoid arthritis. The amino acids marked with a grey dot are particularly important.

Rheumatoid arthritis was once thought of as one disease. But researchers now discriminate between two distinct forms. Through their work, **Robert J. Winchester**, **Peter K. Gregersen** and **Lars Klareskog** have contributed to a basic understanding of how the most common and serious form of rheumatoid arthritis develops.

In the 1980s, Winchester and Gregersen found an explanation as to why certain genes increase the risk for rheumatoid arthritis. These genes control the generation of proteins called human leukocyte antigen (HLA). These HLA proteins sit on the surface of all cells; they form a pocket in which molecules from the cell get stuck.

Immune cells, on patrol to defend the body against viruses and bacteria, constantly check the contents of this pocket. If a virus infects a cell, parts of the virus will get stuck in the pocket. The immune system reacts immediately and eliminates the diseased cell. Winchester and Gregersen found that certain variants of HLA proteins increase the risk for rheumatoid arthritis because their pockets form a special shape.

The next big breakthrough came 20 years later. By then, smoking was known to moderately increase the risk for rheumatism. However, Klareskog and his coworkers realised that the risk increases dramatically if smokers carry HLA risk genes. It increases even more if they also carry antibodies against citrullinated proteins. Klareskog's team has shown that smoking stimulates the formation of those proteins.

The researchers' systematic mapping has yielded a hypothesis that the most common form of rheumatoid arthritis can start in the lungs. Scientists now believe that citrullinated proteins may fit into the special pocket formed by certain HLA proteins. The disease can thus develop through the interplay between genetics and environment and can slumber in the body for years before awakening. This increased knowledge about the disease's causes hopefully will result in more refined treatments.

The Crafoord Prize Laureates in Polyarthritis 2013

PETER K. GREGERSEN,
THE FEINSTEIN INSTITUTE FOR MEDICAL RESEARCH, MANHASSET, NY, USA

U.S. citizen. Born 1950. MD 1976 from Columbia University, New York, NY, USA. Investigator at The Feinstein Institute for Medical Research, Manhasset, NY, USA.

PHOTO: GUSTAV MÅRTENSSON

LARS KLARESKOG,
KAROLINSKA INSTITUTET, STOCKHOLM, SWEDEN

Swedish citizen. Born 1945. MD 1974 from Uppsala University, Uppsala, Sweden. Professor at Karolinska Institutet, Stockholm, Sweden.

PHOTO: COLUMBIA UNIVERSITY MEDICAL CENTER

ROBERT J. WINCHESTER,
COLUMBIA UNIVERSITY, NEW YORK, NY, USA

U.S. citizen. Born 1937. MD 1963 from Cornell University, Ithaca, NY, USA. Professor at Columbia University, New York, NY, USA.

ABSTRACTS

Crafoord *Days* 2013

From HLA to the human genome: 30 years of chasing genes for rheumatoid arthritis

PETER K. GREGERSEN, CRAFOORD LAUREATE 2013
THE FEINSTEIN INSTITUTE FOR MEDICAL RESEARCH, MANHASSET, NY, USA

In the early 1980s, developments in the nascent field of molecular genetics and structural biology provided an exciting context for a young rheumatology fellow to employ the new tools of gene cloning to understand HLA associations with rheumatoid arthritis (RA). With the support of Robert Winchester and others, we were able to define a common sequence element among different HLA alleles, "the shared epitope", that was strongly associated with risk for RA (1). This observation catalyzed many theories; the most recent genetic analysis (2) supports the hypothesis that the HLA alleles containing the shared epitope act by selecting citrullinated peptides for presentation to the immune system. The work of Lars Klareskog and colleagues has now elegantly shown that these citullinated peptides may be induced in the lungs of smokers, thus linking smoking and the shared epitope in the anti-citrulline response. Thus, a thirty year old observation has now led to one of the most compelling demonstrations of how genetic and environmental factors can interact to cause an autoimmune disease. In the intervening years, it became apparent that many other genetic factors are also involved in RA. Lars Klareskog and I were privileged to lead a large international consortium to address this issue (3), with nearly 50 genes now known to be involved in risk for RA. Current work suggests that many of the common genetic variants act through rather subtle threshold effects on the immune response (4). This leads to a concept that part of the risk for autoimmunity involves quantitative alterations in "immune rheostats" that, along with HLA and environmental factors, put an individual at higher risk for tipping over into an autoimmune state. Over time this may lead to clinical disease and tissue damage. Establishing the details of these mechanisms will be a key to developing new approaches to diagnosis, prevention and therapy in the future.

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Genes, environment and immunity in the development of rheumatoid arthritis

LARS KLARESKOG, CRAFOORD LAUREATE 2013
KAROLINSKA INSTITUTET, STOCKHOLM, SWEDEN

To understand the origins and to influence the outcomes of rheumatoid arthritis (RA) is a challenge for the scientist, for the practicing physician and for the patient. As for many common and complex diseases, the origins and outcomes of RA are dependent on the combined influence from genes, environment and chance. How these factors work together has, however, been difficult to understand and, therefore, disease was for long been seen as a "fate" where it was not possible to influence its occurrence, although medications might help to improve its outcomes.

The work from me and my collaborators has aimed to understand the combined influence of genes and environment for onset and course of RA, with the hope that such understanding would both help to unravel the molecular mechanisms causing the disease, and provide individuals with tools to influence their "fate" by influencing their environment and life style.

Our work has evolved over many years from the initial recognition of the molecular structure of key molecules in the immune system, the class II transplantation, over studies on the role of these molecules in the inflamed joints of RA patients. Later work along the same line has investigated how environment might trigger immune reactions that are dependent on these transplantation antigens and how such immune reactions may contribute to arthritis. Key previous discoveries on which we have built our work were made by my co-laureates who recognized structures within the transplantations antigens that determine the risk for RA. Key features in our own studies have been work performed by rheumatologists all over Sweden who have collected information from large many RA patients concerning their disease course, life styles, environment and genes.

A major conclusion from our work is that development as well as course of RA depend on the combined influence of genes, in particular transplantation antigens, and environment/life style, in particular smoking. Our hope is that this information will enable individuals/patients to influence their "fate" by changing their own environment or life style, and scientists to change the "fates" of many using the new molecular insights in finding new ways to prevent and treat polyarthritis.

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Rheumatoid arthritis and autoimmunity: Good genes, elegant mechanisms, bad results

ROBERT J. WINCHESTER, CRAFOORD LAUREATE 2013
COLUMBIA UNIVERSITY, NEW YORK, NY, USA

HLA molecules enable T cells to function in the adaptive immune system by presenting peptides. Different HLA alleles confer different peptide-binding properties on the HLA molecules. Since each person's repertoire of T cells is selected on self-peptides bound to our HLA molecules, this forms both the basis of a unique immunological self and the potential to develop autoimmunity.

The line of research that led to finding that certain normal allelic forms of MHC molecules underlie the development of RA, began with studies on the mixed lymphocyte culture reaction. These led to identifying particular pregnancy sera that detected structures on B cells and monocytes that we now call HLA-DR molecules. The application of these pregnancy sera to the study of RA revealed that some allelic forms of the HLA-DR molecules, such as those designated as HLA-DR4 were significantly more common in RA, and more intriguingly, that some pregnancy sera identified structures or epitopes shared by many of those patients with RA who lacked DR4. However the association with DR4 could not be replicated in patients from East of the Bosporus, where RA was primarily associated with HLA-DR1.

So the questions arose of whether there was a shared molecular structure on HLA-DR molecules that could account for these findings? The answer was sought at the level of the DNA sequence with Dr Peter Gregersen, and colleagues. We found that each HLA-DR allele conferring RA susceptibility encoded a shared sequence motif of positively charged or neutral amino acids, designated the 'shared epitope', and this motif was replaced with negatively charged amino acids for HLA-DR alleles not associated with RA. The subsequent availability of the HLA-DR structures enabled visualizing that the shared epitope motif was an important pocket that bound amino acid side chains of an antigenic peptide, providing the molecular equivalent of Cinderella's glass slipper to search for the elusive peptide driving RA.

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Beyond anti-TNF therapy: can we get closer to a cure?

SIR MARC FELDMANN, THE KENNEDY INSTITUTE OF RHEUMATOLOGY, UNIVERSITY OF OXFORD, LONDON, UK

Over the past generation, the association of rheumatoid arthritis with the major histocompatibility complex, first to HLA-DR4 then to the 'shared epitope' helped propel research to understand its pathogenesis, and thus to uncover new approaches to treatment. This research has been highly successful, and over the past few years a number of the highly targeted therapies for rheumatoid arthritis have emerged, first anti-TNF which my colleague Ravinder Maini and I discovered, but subsequently anti-Interleukin-6 receptor antibody, both inhibiting important cytokine pathways. Then anti-CD20 targeting B lymphocytes and CTLA4-Ig inhibiting T cell antigen presenting cell interaction were approved. All of these are proteins, monoclonal antibody or antibody-like fusion proteins, and their success has helped propel a therapeutic revolution, such that now these very specific protein inhibitors dominate the lists of the world's best-selling pharmaceuticals.

The path to discovering anti-TNF therapy for which Maini and I received the Crafoord Prize in 2000 will be reviewed, as will the current state of knowledge and therapy today. While it is so much better than a generation ago, we are still some distance from the ultimate goal of a cure. How can we get closer to a cure? Understanding more of the pathogenesis and aspects of aetiology, as contributed by this year's Laureates will help. Our current approach to getting closer to a cure will be described; there are many clues that need to be followed up.

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Genetic and environmental contributions to human autoimmune disease

DAVID A. HAFLER, YALE SCHOOL OF MEDICINE, NEW HAVEN, CT, USA

Genome-wide association studies have identified numerous genetic associations between common SNPs and risk of autoimmune diseases, some of which are shared between diseases. Along with clinical evidence, this suggests that some genetic risk factors with their biologic effects may be shared across diseases. We evaluate the extent of this sharing for 107 immune disease-risk SNPs in seven diseases and have developed a novel statistic for *C*ross *P*henotype *M*eta-*A*nalysis which detects association of a SNP to multiple, but not necessarily all, phenotypes. We find evidence that 47/107 (44 %) immune-mediated disease risk SNPs are associated to multiple – but not all – immune-mediated diseases (SNP-wise $P_{CPMA} < 0.01$). Distinct groups of interacting proteins are encoded near SNPs that predispose to the same subsets of diseases; we propose these as the mechanistic basis of shared disease risk. We have begun efforts to identify the biologic effects of disease causing SNPs at non-coding regions of the genome where it has been difficult to assign function to DNA sequence and to compare these effects across different autoimmune diseases. We use fine-mapping genetic data to identify causal mutations and integrate these data with chromatin maps of ten defined human CD4+ T-cell populations and 56 additional cell-types. These investigations identified risk variants disrupting the enhancers of distinct cell types among the different autoimmune diseases.

Finally, autoimmune disease results from untoward interactions between genetics and the environment. We recently showed that increased salt (NaCl) concentrations found locally under physiological conditions *in vivo* dramatically boost the induction of Th17 cells mediated by SGK1. The Th17 cells generated under high-salt display a highly pathogenic and stable phenotype characterized by the up-regulation of the pro-inflammatory cytokines GM-CSF, TNFα and IL-2. Mice fed with a high-salt diet develop a more severe form of EAE, in line with augmented central nervous system infiltrating and peripherally induced antigen specific Th17 cells. It was of interest to observe that RNA array analysis of genes induced by NaCl were markedly enhanced among GWAS hits. Identifying specific sites where a single, non-coding nucleotide variant is responsible for disease risk may pinpoint specific disruptions of consensus transcription factor binding sites that ultimately define disease risk as related to environmental factors.

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Gut reactions: Immune pathways in the intestine in health and disease

FIONA POWRIE, UNIVERSITY OF OXFORD, UK

The gastrointestinal (GI) tract is home to a large number and vast array of bacteria that play an important role in nutrition, immune system development and host defense. It is now apparent that a breakdown in this mutualistic relationship between the host immune response and its microbial residents may underlie not only inflammatory bowel disease but other chronic inflammatory diseases including inflammatory joint disease. Studies in model systems indicate that intestinal homeostasis is an active process involving a delicate balance between effector and immune suppressive pathways. The cytokine IL-23 plays a pivotal role in orchestrating intestinal inflammation and several genes in the IL-23/Th17 pathway confer risk to IBD. We have recently shown that IL-23 acts directly on T cells to promote pathological Th17 type responses at the expense of immune suppressive regulatory T cells. Inflammatory Th17 responses are characterised by dysregulated myeloid responses and GM-CSF-driven extra-medullary hematopoiesis in tissues. In addition IL-23 drives a novel population of RORγt-dependent innate lymphoid cells (ILC) that mediate colitis through the production of Th17 associated cytokines. In this presentation I will discuss the multiple pathways through which IL-23 promotes tissue inflammatory responses in some cases leading to tumorigenesis.

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Structural mechanisms for peptide repertoire selection by HLA-DM

KAI W. WUCHERPFENNIG, DANA-FARBER CANCER INSTITUTE AND HARVARD MEDICAL SCHOOL, BOSTON, MA, USA

MHC class II genes are associated with susceptibility to many human autoimmune diseases, including rheumatoid arthritis. A critical question in the field concerns the mechanisms controlling selection of the peptide repertoire presented to CD4 T cells. HLA-DM catalyzes dissociation of the invariant chain derived CLIP peptide, stabilizes empty MHC class II molecules and promotes selection of the highest-affinity ligands for presentation to T cells. The structural mechanisms for HLA-DM catalyzed peptide selection were difficult to determine because the HLA-DM – MHC class II complex could not be crystallized for many years. We identified a short-lived intermediate of MHC class II molecules that is susceptible to HLA-DM: we found that a HLA-DM susceptible state is created by dissociation of the N-terminus from the MHC class II groove (Anders et al, 2011). We crystallized the complex using a HLA-DM sensitive conformer in which an N-terminally truncated peptide was covalently linked in the groove (Pos et al, 2012). The structure shows an unexpected mechanism by which HLA-DM stabilizes the empty MHC class II binding site: two hydrophobic MHC class II residues move into the highly hydrophobic P1 pocket, preventing aggregation. Thus, only part of the groove is initially accessible to incoming peptides. Peptides need to compete with these MHC class II residues for access to the P1 pocket, and this energetic barrier favors presentation of the highest-affinity ligands. The structure also explains why peptide binding induces HLA-DM dissociation: insertion of a hydrophobic peptide residue into the P1 pocket reverses the conformational changes required for HLA-DM binding. Low-affinity peptides are relevant in several animal models of autoimmunity, and inefficient removal of such peptides has been implicated in autoimmune diseases (Schulze and Wucherpfennig, 2012). The general principles may also be relevant for peptide selection by MHC class I proteins.

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PROGRAMMES

Crafoord *Days* 2013

Overview programme Crafoord *Days* 2013

Thursday 2 May

PRIZE AWARD CEREMONY 16:20–17:15

In the presence of Their Majesties the King and Queen of Sweden

THE BEIJER HALL
THE ROYAL SWEDISH ACADEMY OF SCIENCES
LILLA FRESCATIVÄGEN 4A, STOCKHOLM

Friday 3 May

INTERNATIONAL PRIZE SYMPOSIUM IN POLYARTHRITIS 08:45–17:10
INCLUDING CRAFOORD PRIZE LECTURES BY THE LAUREATES

NOBEL FORUM, KAROLINSKA INSTITUTET
NOBELS VÄG 1, STOCKHOLM

Detailed programme

INTERNATIONAL PRIZE SYMPOSIUM IN POLYARTHRITIS INCLUDING CRAFOORD PRIZE LECTURES BY THE LAUREATES

From genes and environment to pathogenetic mechanisms and treatment of autoimmune diseases

08:45–17:10

NOBEL FORUM,
KAROLINSKA INSTITUTET
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THE SYMPOSIUM IS FREE OF CHARGE AND OPEN TO THE PUBLIC

Friday 3 May

08:45	Registration & coffee	
09:15	Opening address	*Staffan Normark*, Permanent Secretary of the Royal Swedish Academy of Sciences
09:30	*Rheumatoid arthritis and autoimmunity: Good genes, elegant mechanisms, bad results*	**CRAFOORD LAUREATE 2013** **ROBERT J. WINCHESTER**, Columbia University, New York, NY, USA
10:20	*From HLA to the human genome: 30 years of chasing genes for rheumatoid arthritis*	**CRAFOORD LAUREATE 2013** **PETER K. GREGERSEN**, The Feinstein Institute for Medical Research, Manhasset, NY, USA
11:10	*Genes, environment and immunity in the development of rheumatoid arthritis*	**CRAFOORD LAUREATE 2013** **LARS KLARESKOG**, Karolinska Institutet, Stockholm, Sweden
12:00	Lunch	(Included for registered participants)
13:20	*Genetic and environmental contributions to human autoimmune disease*	*David A. Hafler*, Yale School of Medicine, New Haven, CT, USA
14:10	*Gut reactions: Immune pathways in the intestine in health and disease*	*Fiona Powrie*, University of Oxford, UK
15:00	Break with refreshments	
15:30	*Structural mechanisms for peptide repertoire selection by HLA-DM*	*Kai W. Wucherpfennig*, Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA, USA
16:20	*Beyond anti-TNF therapy: can we get closer to a cure?*	*Sir Marc Feldmann*, Kennedy Institute of Rheumatology, University of Oxford, London, UK
17.10	End of the symposium	

Anna-Greta and Holger Crafoord

HOLGER AND ANNA-GRETA CRAFOORD

Holger Crafoord (1908–1982) was prominent in Swedish industry and commerce. He began his career with AB Åkerlund & Rausing and devoted a larger part of his working life to this company. In 1964, Holger Crafoord founded Gambro AB in Lund, Sweden, where the technique of manufacturing the artificial kidney was developed. This remarkable dialyser soon became world famous. Since then, a series of medical instruments has been introduced on the world market by Gambro.

In 1980, Holger Crafoord founded the Crafoord Foundation, which annually contributes greatly to the Anna-Greta and Holger Crafoord Fund.

Holger Crafoord became an honorary doctor of economics in 1972 and in 1976 an honorary doctor of medicine at the University of Lund.

Anna-Greta Crafoord (1914–1994) took, as Holger Crafoord's wife, part in the development of Gambro AB. Through generous donations and a strong commitment in the society around her, she contributed to the scientific and cultural life. In 1986 she founded the Anna-Greta Crafoord foundation for rheumatological research and in 1987 Anna-Greta Crafoord became an honorary doctor of medicine at the University of Lund.

Over the years, the Crafoords have furthered both science and culture in many ways and it is noteworthy that research in the natural sciences has received an important measure of support from the Anna-Greta and Holger Crafoord Fund.

THE ROYAL SWEDISH ACADEMY OF SCIENCES founded in 1739, is an independent, non-governmental organisation whose aim is to promote the sciences and strengthen their influence in society. Traditionally, the Academy takes a special responsibility for the natural sciences and mathematics, but in its work it strives to increase exchanges between different disciplines.

The activities of the Academy are aimed mainly at:

- *spreading knowledge of discoveries and problems in current research*
- *providing support for young researchers*
- *rewarding outstanding contributions in research*
- *stimulating interest in mathematics and the natural sciences in schools*
- *spreading scientific and popular-scientific information in various forms*
- *offering unique research environments*
- *maintaining contact with foreign academies, learned societies and other international scientific organizations*
- *representing the sciences in society*
- *carrying out independent analyses and evaluations, based on scientific grounds, of issues of importance for society*

The Academy has about 450 Swedish members and 175 foreign members. The Swedish members are active within Classes and Committees. They initiate investigations, responses to government proposals, conferences and seminars. Once a month the Academy holds a General Meeting and in connection with this a public lecture. (Visit http://kva.se for the programme.) The Academy´s own institutes offer unique research environments for botany, ecological economics, the history of science, mathematics and other subjects. Besides the prominent Crafoord Prize, the Academy awards annually a number of prizes, the best known of which are the Nobel Prizes in Physics and Chemistry and the Sveriges Riksbank Prize in Economic Sciences in Memory of Alfred Nobel. Other important prizes are the Söderberg Prize and the Göran Gustafsson Prizes. The latter are awarded to outstanding young researchers and are a unique combination of a personal prize and a research grant. The Academy also supports researchers who have been researching actively for five to ten years after taking their doctorate by providing a salary for five years through the support of external foundations. Through its various Committees the Academy also works for the development of a society based on scientific grounds. Great interest is paid to educational issues and a major school development program, NTA (Natural Sciences and Technology for All), is organized in collaboration with the Royal Swedish Academy of Engineering Sciences.

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