

## Anthony Cerami Award in Translational Medicine

### A Journey in Science: Medical Scientist in Translation

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Real innovations in medicine and science are historic and singular; the stories behind each occurrence are precious. At *Molecular Medicine* we have established the Anthony Cerami Award in Translational Medicine to document and preserve these histories. The monographs recount the seminal events as told in the voice of the original investigators who provided the crucial early insight. These essays capture the essence of discovery, chronicling the birth of ideas that created new fields of research; and launched trajectories that persisted and ultimately influenced how disease is prevented, diagnosed and treated. In this volume, the Cerami Award Monograph is by Göran K Hansson, MD, PhD, Karolinska Institute. A visionary in the field of cardiovascular research, this is the story of Dr. Hansson's scientific journey.

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#### INTRODUCTION

My decision to go to medical school was based in equal parts on a desire to help people, a wish to have a meaningful job and the challenge to get into a program that was, at the time, the most coveted one in the Swedish university system. I had dreams of becoming a thoughtful psychiatrist, a decisive cardiologist or perhaps a doctor for the poor somewhere in a developing country. I made it to and through medical school, but I fulfilled none of these dreams. After a short time in internal medicine, the research bug had bitten me and I became a physician-scientist, with the emphasis gradually moving toward the latter part of the term.

I grew up in a small town in the province of Bohuslän on the Swedish North Sea coast. My dad ran the local newspaper of the town, and my mum was a nurse at its small hospital. The town of Lysekil was dominated by the sea surrounding it. Commercial fishing, herding canneries, and a factory producing boat engines were its main activities. In summer, the coast was invaded by tourists from the big cities—Stockholm, Göteborg and Oslo. When the sea warmed up, we went swimming, canoeing and sailing. Life was magical for a teenager—sailing in the day and partying at night. Winds from the big world brought new influences and new sounds, such as the Beatles, Bob Dylan,

world politics and student protests. The 1960s were an exciting time.

#### MEDICAL SCHOOL AND HOW TO SURVIVE IT

The curriculum in medical school started with anatomy. It was a nightmare. We were expected to memorize Latin names for hundreds of structures on bones—fossae, sulci, capita and so on. We were incessantly told that knowledge of all these anatomical details was absolutely necessary for any clinical doctor. When I started working as a clinician myself, I found this kind of descriptive anatomy completely useless. In real life, bones have tendons and muscles attached; they are not bare except in the cemetery.

One day, I saw a poster in the corridor outside the anatomy department. The neighboring department of histology invited students to an evening with information about medical research. We talked about it over a beer in the park when we were skipping another boring hour of anatomy, and decided to attend. That evening, we met other kinds of teachers. They were scientists and told us about

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**Figure 1.** Göran Hansson smashes some glassware while trying to isolate organelles. Caricature by student colleague Tom Björnheden, 1980; reproduced with permission from him.

medical problems that needed to be solved, pointing out methods for solving them. And they wanted us to join them in that endeavor. We immediately signed up.

Our first experiment was not a success. My classmate, Per Elias, and I joined a neurobiology project to analyze biochemical changes in the cerebellum after alcohol exposure. Our main finding was that the cerebellum is completely devoid of protein. Neurobiology was not ready for such a paradigm shift, and we decided to move to other fields.

In the laboratory of Sören Björkerud, I heard about cardiovascular disease, the major cause of death in our society. Sören was an enthusiastic teacher. It was fascinating to hear him explain how the cells of the blood vessels form a barrier to prevent cholesterol from accumulating and how that barrier could be damaged by the forces of blood pressure, leading to atherosclerosis and ultimately to myocardial infarction.

I was assigned to work with Göran Bondjers, a young physician-scientist

who had just finished his PhD in Sören's lab. Göran taught me how to dissect arteries, analyze cholesterol in tissues and label dividing cells with radioactive isotopes. I was learning the craft of science (Figure 1).

Life was intense. There were lectures and classes in physiology, pharmacology and pathology in the mornings and afternoons, work to do in the research lab in the evenings, and books to read at night. And there were a thousand things to protest against in endless demonstrations, ranging from the war in Vietnam to the new curricula in universities. My girlfriend (and future wife), Margareta, who was studying psychology, and I were busy all the time.

And things were to get even busier. Margareta was pregnant, and we hadn't even finished our educations. Our son, Emil, was born the day I had my major exam in internal medicine. Axel followed 3 years later. Margareta switched from psychology to physiotherapy when it became obvious that job opportunities were dwindling in psychology. I continued in medical school and could even continue with part-time research, thanks to an understanding wife and a modest need for sleep.

### IMMUNITY IN BLOOD VESSELS?

Immunology immediately captivated me in medical school. I took immunology courses as part of my PhD program and learned about antibodies, vaccination and memory. I was fascinated by the fact that this powerful defense system was patrolling our bodies, next to the blood vessels where atherosclerosis developed. "How would the immune system react to a pathology that builds up in its immediate vicinity?" I asked myself. "Someone must know," I reasoned, and I went to the library and read all the textbooks and review papers I could find about cardiovascular pathology. Not a word was said about the immune system. I asked Göran Bondjers. His answer was "Go and find out."

I knocked on the door of the microbiology department, and they allowed me to

come and learn. The head of the department was the famous immunologist, Örjan Uchtermann, who had invented the immunodiffusion method for analyzing antigens. Much of the work in the department still dealt with the "Uchtermann technique," but they were also doing immunofluorescence microscopy. I stained normal rabbit arteries for immunoglobulins and complement factors and found nothing. But when I applied the same staining protocol to atherosclerotic arteries of fat-fed rabbits, there were tons of IgG and C3 in the lesions! Something was going on. There was an immune activity of some kind in the atherosclerotic lesion. For the first time, I had made a discovery.

### POSTDOCTORAL STUDY IN A MECCA OF VASCULAR BIOLOGY

I finished my PhD thesis, applied for a postdoctoral fellowship and contacted scientists at the University of Washington in Seattle, which was a Mecca for vascular biology and atherosclerosis research. I was overwhelmed with joy when I was awarded a Fogarty International Postdoctoral Fellowship from the U.S. National Institutes of Health and could move to Seattle with my little family.

Seattle was a fun city and the University of Washington was everything a research university should be. I worked with Steve Schwartz, an eccentric, exciting and intellectually brilliant scientist in the pathology department. Steve's passion was cell kinetics, and he could argue for hours about cell cycles and population dynamics in the endothelium. Next door was Earl Benditt, the former chairman of the department, who had proposed that atherosclerosis was a monoclonal population of smooth muscle cells. The new chairman, Russell Ross, had another theory—that atherosclerosis was caused by the platelet-derived growth factor, which was released when platelets aggregated at sites of arterial damage. Earl and Russell would never reach a consensus, but some kind of working relationship developed, with Earl being the king of vascular biology in Seattle and Russell in the rest of the world.

The young generation of cardiovascular scientists was a great crowd. Ron Heimark, a skillful biochemist, patiently taught me how to run SDS (sodium dodecyl sulfate) gels. Alec Clowes was a promising young vascular surgeon who did beautiful work on arterial restenosis, together with his wife Monica, and Alan Chait, a brilliant endocrinologist studying lipoprotein metabolism. I shared an office with an expatriate Brit, Michael Reidy, at the time of the Falklands war and was offered advice on military strategy every day.

Our family had a good time. We made lots of friends, some with whom we still keep in touch. Weekends were spent doing excursions into the fantastic nature surrounding Seattle, with the Olympic peninsula, the Cascade Range and the Pacific Ocean. In the summer of 1982, we drove down the Pacific coast, camping in Oregon and California and having a wonderful time. I came back to Sweden in 1983 as a full-fledged cell biologist. I knew how to grow endothelial cells and smooth muscle cells, how to analyze growth factors and how to assess cell proliferation.

### WHERE DO THE CELLS IN THE PLAQUE COME FROM?

At this time, the cellular composition of the atherosclerotic lesion was still unknown. It was a question everyone in the field was asking. While most pathologists thought of it as a smooth muscle lesion, histochemical data pointed to a contribution of macrophages. In the 1950s, John Poole and Howard Florey in Oxford had identified macrophagelike cells, possibly emanating from blood monocytes, accumulating in the artery wall of fat-fed rabbits. Twenty-five years later, Ross Gerrity in Cleveland described how monocytes entered the arterial intima of fat-fed swine, and Bob Wissler in Chicago detected macrophages in lesions of nonhuman primates. Russell Ross was setting up a heroic experiment, by using the new monoclonal antibody technology to make antibodies against homogenates of lesions and then identifying what these an-

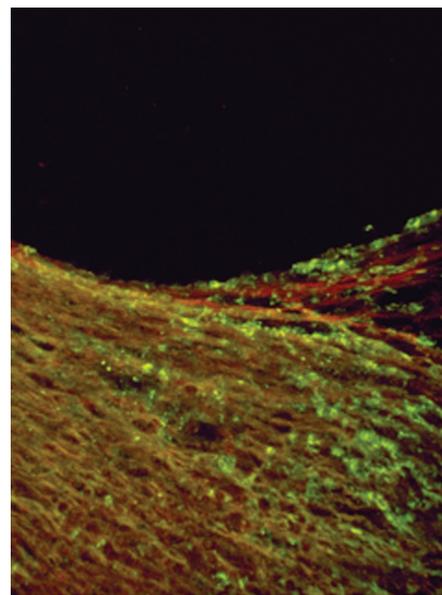
tibodies recognized to characterize the features of the cells forming the lesion. I thought I had a better idea and started testing it as soon as I came back to Göteborg.

My idea was to use well-characterized antibodies to known cell types, apply them to human atherosclerotic lesions and find out if they stained any of the cells. From the immunology literature, I knew about the T- and B-cell-specific antibodies, later to be known by their CD numbers, and my friend Giulio Gabbiani in Geneva sent us antibodies to smooth muscle cell components. But where could we find human arteries? Autopsy material was probably too degraded, so we needed surgical material.

My clinical training helped solve the problem. As part of my 21-month internship at Sahlgrenska University Hospital in Göteborg, I worked for 4 months in vascular surgery. I was a lousy surgeon, but I learned a lot and had a good time. The chief vascular surgeon, Jan Holm, recommended me to use endarterectomy material from the carotid artery. Even better, Jan offered to provide carotid endarterectomies for our studies. We struck up a collaboration that lasted throughout my years in Göteborg and led to a great friendship as well as an exciting scientific endeavor. We were joined by an MD/PhD student, Lena Jonasson, now professor of cardiology at Linköping University. Always enthusiastic, Lena prepared the surgical specimens, cut the sections and did the immunostaining. When I came back to the lab in the evening after a day in the clinic, we looked at the results in the fluorescent microscope together.

### INFLAMMATION LEAVES HLA TRACKS

The expected suspects were there, but we were also in for some surprises. Vascular smooth muscle and endothelial cells did not account for more than about half of all cells in the lesions. Suspecting that the rest might be macrophages, we applied an antibody that was supposed to stain macrophages, OKIa1. But the results were astonishing. This antibody



**Figure 2.** HLA-DR expression in the human atherosclerotic plaque. HLA-DR protein (green) is expressed by most cells in the atherosclerotic plaque (right side) but not in the normal artery adjacent to it (left side). This fluorescent micrograph of a section from a human endarterectomy sample led us to propose that atherosclerosis is an inflammatory disease driven by a local immune reaction. Reproduced from (42): Hansson GK; Jonasson L. The discovery of cellular immunity in the atherosclerotic plaque. *Arterioscler. Thromb. Vasc. Biol.* 2009;29(11):1714-7.

Also, see (1):

Expression of class II transplantation antigen on vascular smooth muscle cells in human atherosclerosis. L Jonasson, J Holm, O Skalli, G Gabbiani, G K Hansson  
Published in Volume 76, Issue 1  
*J Clin Invest.* 1985; 76(1):125-131 doi:10.1172/JCI111934

stained the majority of cells in the plaque (Figure 2) (1).

When looking into the details, we found that this antibody recognized HLA-DR, a major histocompatibility complex (MHC) protein that presents antigen to CD4<sup>+</sup> T cells. HLA-DR was expressed not only by macrophages but also by a significant proportion of the smooth muscle cells as well as some endothelial cells. Therefore, OKIa1 was not a macrophage marker but a marker of antigen-presenting capacity. But how did

HLA-DR end up on smooth muscle cells? We could never detect it in normal arteries, only in atherosclerotic plaques. It was already known that interferon- $\gamma$ , a proinflammatory cytokine produced by activated T cells, could induce HLA-DR on certain target cells. But T cells, the key activators and regulators of adaptive immunity, were not supposed to be involved in atherosclerosis. We were, therefore, both surprised and excited when we found that about 10% of all cells in human plaques were positive for the T-cell marker OKT3 (recognizing CD3 protein). And when we stimulated smooth muscle cells in culture with interferon- $\gamma$ , they started to express HLA-DR.

The time was ripe for proposing a hypothesis:

1. T cells are recruited to atherosclerotic lesions.
2. They are activated by an (unknown) antigen.
3. When activated, these T cells produce the cytokine interferon- $\gamma$  that activates macrophages and smooth muscle cells.
4. Cytokine-activated cells express immune/inflammatory genes including HLA-DR.
5. Inflammation promotes atherosclerosis.

We thought this was important enough to justify publication in *Nature*. Unfortunately, the editors of that revered journal did not agree with us, and the manuscript came back by return mail. We had more success with the *Journal of Clinical Investigation*, although their reviewers demanded one control experiment after another, delaying the publication for more than a year. They also forced us to tone down our conclusions and hypothesis; therefore, the paper that came out in July 1985 was not as exciting as the first version of the manuscript (1).

A follow-up paper was written, in which we provided a map of the cell populations in the plaque. It was a straightforward, descriptive paper that was published in *Arteriosclerosis, Thrombosis, and Vascular Biology* [ATVB] in March 1986 (2). Because the paper did not contain the immunopatho-

logical concepts and proposals of the paper published in the *Journal of Clinical Investigation*, it was more appealing to the cardiovascular community. Our findings were soon confirmed by the Ross team and by several other groups. The 1986 paper was considered “unpublishable” by many of our colleagues, but it has now been cited nearly a thousand times. Descriptive data are helpful; we need maps to orient ourselves in an unknown terrain.

Some key questions that needed to be addressed were: what was the specificity of the cellular immune response in atherosclerosis, and which were the vascular effects of the immune effector response? How important were the inflammatory effects of interferon- $\gamma$  and other cytokines in atherosclerosis?

#### CHASING IMMUNE SPECIFICITY

To determine the immunologic specificity of T cells resident in atherosclerotic lesions, we needed to clone them. This step was not a trivial exercise, and we needed to learn from a master. I had followed the work of Marc Feldmann in London on the autoimmune specificity of Graves’ disease and was impressed, both by the technology and the biology. Hence, I wrote to Marc and asked if we could visit his lab to learn T-cell cloning. He kindly invited me and PhD student Sten Stemme to come to his lab, then at the Charing Cross Sunley Research Institute in West London.

Sten and I went to London in the winter of 1990 to spend a couple of weeks in Marc’s lab learning human T-cell cloning. This was at the time when Marc and his colleagues made the groundbreaking discovery of the role of tumor necrosis factor in rheumatoid arthritis, which led to a revolution in rheumatology. We returned to Göteborg, inspired by the spirit at the Institute and equipped with knowhow on how to clone T cells.

Obtaining arterial T cells from patient samples was not a trivial problem. After a year of methodological development, Sten had produced enough clones, from surgical specimens of four patients, to start an antigen challenge. I assumed

that all humans would be tolerant to native low-density lipoprotein (LDL) and hypothesized that oxidation would break tolerance. Therefore, we exposed our T-cell clones to oxidized LDL, in the presence of antigen-presenting monocytes. Some of the T cells reacted and started to divide; this response was blunted when anti-HLA-DR antibodies were present in the cultures. The interpretation was obvious: oxidized LDL was taken up by antigen-presenting monocytes, fragments of LDL protein were bound to HLA-DR and the LDL-HLA-DR complex was exposed to T cells. T cells carrying TCR antigen receptors that could bind this complex were activated and mounted an immune response. Our paper presenting these findings was published in *Proceedings of National Academy of Sciences of the United States of America* in 1995 (3).

When we revisited this problem later on using the more refined tools of T-cell hybridomas, we confirmed that LDL acts as an autoantigen but also found, to our surprise, that T cells recognize native rather than oxidized LDL epitopes (4). Indeed, heavy oxidation makes LDL unrecognizable by T cells. Mild oxidation may increase scavenger receptor-mediated uptake of LDL into antigen-presenting cells, whereas heavy oxidation destroys the T-cell epitopes. We proposed that a window of mild oxidation permits both uptake and recognition and therefore can cause autoimmune reactions to LDL (5).

#### PHYSICIAN OR SCIENTIST?

At this stage, it became necessary to reconsider my career plans. I had gone into medicine with the goal of becoming a clinician, with an aim to practice internal medicine or cardiology. Medical research was a way to get there and to be able to do it better. But with the discovery of the atherosclerosis-associated immune response, I found myself in the midst of an extremely exciting research project that promised to provide new insights into the pathogenesis of a major lethal disease, and perhaps even offer new therapeutic opportunities. I realized that I did not

have the capacity to simultaneously lead this line of research, take good care of severely ill patients and be a good father to my children. I had to make a choice.

A patient I met as a resident in internal medicine helped me solve the problem. He was 40 years old and had been admitted with a major stroke. I saw him when he came to the medicine ward and found that the stroke had had a disastrous effect. A computed tomography scan showed a large ischemic lesion in the left hemisphere. At this time, no active therapy was available for ischemic stroke. We had nothing to offer this young patient with a devastating cerebrovascular condition.

We requested that the patient be transferred to intensive care and neurorehabilitation. But the neurologist found the brain damage too large for meaningful rehabilitation and said “no.” I was upset and tried to argue for my patient, but to no avail. The patient’s wife and their two young daughters came to visit and left crying. The prognosis was poor, and the man was likely to remain in need of hospital care for the rest of his life, with persistent paralysis and aphasia. The best they could hope for was that the man would die soon.

Meeting this patient made me realize the limitations of clinical medicine. As a physician, you can do a lot for your patient—but not more than the tools of medicine available at the time allow. As a clinician, your hands are tied by the limitations of medicine. As a physician-scientist, you can help stretch those limitations.

This experience made it easier for me to make the decision to focus on science. I switched residency, from internal medicine and cardiology to laboratory medicine. This turned out to be an ideal compromise. I could focus on research and development while maintaining contacts with clinical medicine through the laboratory service. My eccentric boss, Professor Sven Lindstedt, put it bluntly: “The task of the residents is to do research and develop new methods that we can apply in diagnostics. Don’t run

around in the routine lab disturbing the staff.”

Once the decision was made, it was easy to move on. Lots of excitement lay ahead. Equipped with cell culture systems, human tissue specimens and animal models, and learning the concepts and technologies of molecular biology, we were ready to make discoveries.

### **IMMUNOSUPPRESSANTS, INFLAMMATION, AND THE PROBLEM OF BEING TOO EARLY**

Encouraged by Per Peterson, then in Uppsala and later at Scripps, we tested the effect of an immunosuppressant drug, cyclosporin A, on arterial injury. The effect was striking—postinjury lesions in rat arteries were reduced by about 80% (6). I immediately saw the possibility to use immunosuppressants to prevent restenosis after vascular procedures. With the new stenting technique to maintain patency of arteries after intervention, it might even be possible to coat stents with cyclosporin as a slow-release preparation to eliminate restenosis altogether.

Unfortunately, the pharmaceutical industry was not as excited as I. At Sandoz (now Novartis), which produced cyclosporin, no one wanted to see me. I got an invitation to Hoffmann-La Roche, but they all shook their heads, thinking I was a crazy immunologist who thought I could cure heart disease with cyclosporin! We had to give up the project. A few years later, Andrew Marks and his colleagues in New York discovered a similar effect of another immunosuppressant, rapamycin/sirolimus (7), and were more successful in convincing industry. The sirolimus-coated stent is now a multimillion dollar industry.

Our hypothesis that atherosclerosis is an inflammatory disease was met with immense skepticism, although we and others made several findings that supported this notion. Michael Gimbrone, Peter Libby, Jordan Pober and their colleagues in Boston demonstrated, in cell culture systems and transplant models, that vascular cells are important targets

for immune cytokines and that their response includes expression molecules that promote recruitment of immune cells to lesions (8–10). Our own work showed, for the first time, local production of a proinflammatory cytokine, interferon- $\gamma$ , in the atherosclerotic lesion (11). Georg Wick and Qingbo Xu in Innsbruck identified heat shock protein-65–reactive T cells in atherosclerotic lesions of hypercholesterolemic rabbits (12). Our first review papers started to create some interest in the topic among cardiovascular scientists (13,14). However, all these findings were not sufficient to convince our colleagues that any other molecules than cholesterol and the platelet-derived growth factor were worth investigating.

At best, cardiovascular conferences had a session on inflammation on the last day of the meeting, when everybody was leaving town. The two speakers in the session were usually my friend Peter Libby and I. Peter chaired when I talked about the cellular immunology of atherosclerotic lesions, and then it was my turn to chair while he spoke about cytokine signaling in vascular cells. The rest of the audience consisted of a few energetic postdoctoral scientists who had not yet left the conference.

In the mid-1990s, all this changed. Vascular biologists, cardiologists and even immunologists were getting interested in vascular immunology and its role in atherosclerosis. The clinical and epidemiological findings of Atilio Maseri, Mark Pepys and Paul Ridker changed the tide. Maseri and Pepys discovered that interleukin-6 and its downstream product, C-reactive protein (CRP), are elevated in patients with unstable coronary disease (15,16). Ridker, when interrogating large population cohorts, demonstrated that modest CRP elevations predict future coronary events in healthy middle-aged individuals (17). But CRP does not cause the disease, since pure CRP preparations failed to elicit any atherogenic effects. Therefore, the lesion in the artery wall must “leak” inflammatory mediators such as IL-6, which induces CRP when reaching the liver.

## NEW OPPORTUNITIES AT THE KAROLINSKA INSTITUTE

In December 1994, I was appointed to a new chair in cardiovascular research at the Karolinska Institute in Stockholm. I now had a chance to build up a larger research team, set up new technology and embark on long-term projects. It was a golden opportunity, and I was excited to start working in Stockholm. For the first 2 years, I worked very hard in Stockholm Monday through Friday and spent weekends in our home in Göteborg. Two years later, when our youngest son had finished gymnasium (“high school,” in US terms), we sold our apartment in Göteborg and moved to Stockholm. Although Margareta in particular missed Göteborg, Stockholm is a great city that we enjoy living in, a beauty on the water, with a rich history and a great cultural life.

I decided to set up two new technologies. The first one was obvious: to establish a genetic mouse model for atherosclerosis. Because all possible immunological reagents were available and many molecules and genes were identified in the mouse, I was convinced that such a model would make it possible to dissect the immunopathogenesis of atherosclerosis to an extent that was unthinkable when using other species such as rabbits or rats. A golden era for experimental atherosclerosis dawned when Nobuyo Maeda and Jan Breslow knocked out the *apoe* gene in mice, and the Dallas team of Mike Brown, Joe Goldstein and Joachim Herz made an *ldlr*<sup>-/-</sup> mouse (18–20). We set up an *apoe*<sup>-/-</sup> colony at the Karolinska Institute, characterized its cellular pathology and went on to test the effect of immunomodulation on atherosclerosis.

My second initiative was to team up with the clinicians. In Göteborg, I had had fruitful collaborations with the vascular surgeons, and it was natural for me to establish a similar relationship with Jesper Swedenborg, Ulf Hedin and their colleagues at Karolinska Hospital. We set up a pipeline between the cardiovascular surgery theater and our lab in the Center for Molecular Medicine to obtain fresh

human specimens. It has emerged into the BiKE (Biobank of Karolinska Endarterectomy) biobank with tissue, RNA, DNA, sera, disease history and follow-up, and, I believe, the world’s largest global transcriptome database of human atherosclerosis (21). Collaboration with heart surgeons, cardiologists and rheumatologists has also helped us translate findings between experimental models and human disease.

## AN ATHEROPROTECTIVE IMMUNE RESPONSE

Two brilliant young postdoctoral scientists, Antonino (Tony) Nicoletti and Giuseppina (Pina) Caligiuri, both now in Paris, had joined the team and led the work on immunomodulation. Tony and I were thrilled when we saw that intravenous immunoglobulin treatment inhibited disease progression (22). This and a parallel study by Francois Mach and Peter Libby showing a similar effect when blocking the immune costimulatory factor CD40L (23) were the first studies to demonstrate a therapeutic effect of immunotherapy on atherosclerosis.

Pina performed another exciting experiment. She splenectomized mice with the thought that removal of a major immune organ might affect atherosclerosis. The effect was remarkable—lesions of splenectomized *apoe*<sup>-/-</sup> mice were twice as large as those in intact *apoe*<sup>-/-</sup> controls (24). By transfer experiments, we could show protective effects of T cells, but even more so of B cells. The immune response apparently contained an atheroprotective component that resides with a population of B cells in the spleen.

While I was busy setting up my new lab in Stockholm, the labs of Joe Witztum and Jan Nilsson published some very exciting findings. They reported that immunization of fat-fed rabbits with oxidized LDL reduced rather than increased atherosclerosis (25,26). Our spleen cell findings identified a mechanism for this protection (24), and I set up the goal to develop a vaccine against atherosclerosis. Later on, the discovery that regulatory T cells inhibit atherosclerosis added im-

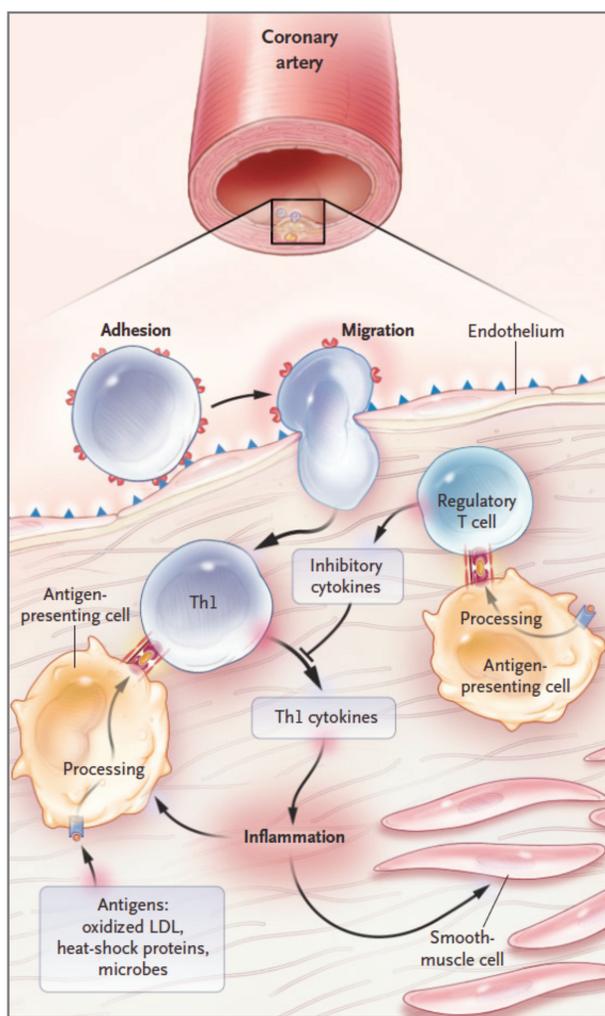
portantly to our understanding of atheroprotective immunity (27,28).

More than 15 years later and thanks to the work in several labs, we have learned a lot about the autoimmune response to LDL and the atheroprotective effector mechanisms it triggers (Figure 3). And although we still do not have a vaccine or an immunotherapy on the market, we have come a long way toward that goal.

## VASCULAR INFLAMMATION GETS HOT

Two major themes had emerged in our lab: the adaptive immunity of atherosclerosis and the vascular biology of inflammation. While a T cell-focused team studies the autoimmune properties of LDL, the mechanisms of its presentation as antigen and the effects of immunization on disease, a second team in the lab works on the vascular biology of immune inflammation.

The second line of work got a kickstart when Yong-jian Geng joined us as a PhD student in 1990. His cDNA cloning of rat iNOS (NOS2) (29,30) brought us into the core of molecular biology technology, and I learned that a research project is an excellent way of establishing a new technique. When Yong-jian moved to the United States, Zhong-qun Yan continued the vascular biology research and expanded into innate immunity (31,32). Zhong-qun moved with me to Stockholm, and we continue to collaborate, 20 years later. At the Karolinska Institute, Guro Valen joined us as a postdoctoral fellow, learned vascular biology and taught us heart physiology (33). After her postdoc, she set up her own lab in the physiology department and later moved to Oslo to take up a professorship in physiology. Another postdoctoral scientist, Gabrielle Paulsson-Berne (34), is now our lab manager as well as an expert in molecular biology. A gifted physician-scientist, Magnus Bäck, introduced us to eicosanoid biology and leukotriene signaling (35). He now runs his own research program on vascular inflammation at our center, while also serving as



**Figure 3.** Counterbalancing forces of adaptive immunity in the atherosclerotic plaque: proinflammatory Th1 cells and atheroprotective Treg cells, as proposed in a review article (43). We have since learned that native rather than oxidized LDL serves as a T-cell antigen. Reproduced from (43):

Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. *N. Engl. J. Med.* 2005;352(16):1685–95. Copyright © 2005 Massachusetts Medical Society. Reprinted with permission.

a consultant in cardiology at Karolinska University Hospital.

Our studies of adaptive immunity were facilitated immensely by the availability of gene-targeted mouse models. A succession of fellows including Xingha Zhou, Anna-Karin Robertson, Ariane Sultan, Daniel Johansson, Roland Klingenberg, Norbert Gerdes, Andreas Hermansson, Daniel Ketelhuth, Anna Lundberg, Olga Ovchinnikova, Daniela Strodthoff, Anton Gisterå and others addressed these aspects, by using

crossbreeding and transplantation techniques. Their work identified immune responses that promote vascular inflammation and atherosclerosis, but also other responses that inhibit lesion development, modulate lipoprotein metabolism and cause plaque stabilization (4,28,36–39).

After decades of controversy, it is time to reconcile the views of atherosclerosis as a metabolic disturbance or a response to injury. Atherosclerosis is a chronic inflammatory disease caused by an im-

mune response to LDL accumulation in the artery wall.

### NEW OPPORTUNITIES AND NEW EXCITEMENT

At the moment, we have an exciting set of scientific questions, a great panel of techniques to address them and a superb team to solve the problems. We have been able to translate many of our findings to human pathology and some to clinical development. With the exception of the coated stents, vascular immunology has not reached clinical therapy, but we remain hopeful that it will do so in the years to come. Ongoing clinical trials on interleukin-1 $\beta$  blockade and methotrexate-based immunosuppression should be informative, as should clinical studies of vaccination. Translational medicine is a slow but exciting process!

To be a medical scientist is stimulating not only because of the intellectual challenges you are facing, but also because of the discoveries you may make. Our workplace is global; we address similar problems and methods wherever we are located and we can easily cross borders created by language, culture or politics. Our apprentice system called the postdoctoral fellowship creates unique opportunities to live in another country and get to know another culture. I get a kick every morning when I come to work and meet my colleagues from Asia, Europe and the Americas (Figure 4).

The position at the interface between basic life science and clinical medicine is very special. You learn from both sides and appreciate all the various kinds of expertise that are needed for a translational research project, from biochemistry to surgery. I have had the privilege of working together with a series of outstanding basic and clinical scientists at the Karolinska's Center for Molecular Medicine. My lab neighbors include the surgeon and cell biologist Ulf Hedin, the cardiologist/geneticist Anders Hamsten, the rheumatologists/immunologists Lars Klareskog and Marie Wahren-Herlenius, the neurologist/immunologist



**Figure 4.** Hansson Lab 2014. Upper row: Anton Gisterå, Zhong-qun Yan, Daniel Ketelhuth, Andres Laguna Fernandez, Reiner Mailer, Roland Baumgartner, André Strodthoff, Marcelo Petri, Stephen Malin, Martin Berg. Middle row: John Pirault, Olga Ovchinnikova, Miguel Caoracedo, Sophie Xintong Jiang, Monica Centa, Linda Haglund, Katrin Habir, Gabrielle Paulsson-Berne, Konstantinos Polyzos. Lower row: Glykeria Karadimou, Maria Klement, Teodora Andonova, Göran Hansson, Ann Hellström, Anneli Olsson.

Tomas Olsson and the virologist Cecilia Söderberg-Nauclér, to mention a few. Our research network Center of Excellence for Research on Inflammation and Cardiovascular disease (CERIC) gives all of us access to unique biobanks and animal models of several inflammatory diseases, including atherosclerosis, multiple sclerosis and rheumatoid arthritis (40). Our biochemistry partners Jesper Haeggström, Thomas Renné and Rikard Holmdahl add expertise in fundamental sciences to our network. With support from the Linnaeus program of the Swedish Research Council, our vision for a translational research center in inflammation and cardiovascular disease has finally become a reality.

Scientific journals, conferences and organizations provide opportunities to extend our networks and to get insights

into many aspects of science. I have had the very special privilege of serving on the Nobel Committee for Physiology or Medicine for 15 years (41). By forcing me to learn about many different areas of life science and medicine, my work with the Nobel Prize is a continuing scientific education and a wonderful source of excitement and intellectual stimulation.

Science is a very large part of life for any scientist, and particularly so in translational medicine, since you try to bridge between two very dynamic areas: molecular life science and clinical medicine. It is, nevertheless, important to find time for other activities. Family life has always been a source of joy for me, as has music. I was introduced to classical music as an aspiring pianist with limited talent in my teens, and it has remained

with me since then, as an island of escape and a sheer pleasure. It remains a challenge to be a reasonably complete human being, but you must never stop trying.

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## DISCLOSURE

I have no competing interests as defined by *Molecular Medicine*, or other interests that might be perceived to influence the results and discussion reported in this paper.

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