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Spotlight: François Mach, MD, FESC

Involved in Discovering the Crucial Role of Inflammation in Atherosclerosis and Working to Find Ways to Treat It

François Mach, head of the Cardiology Division, Geneva University Hospital, Geneva, Switzerland, and professor of cardiology, Geneva University Medical School, Geneva, talks to Jennifer Taylor, BSc, MSc, MPhil.

An article about inflammation and atherosclerosis by Peter Libby, MD, now chief of cardiology at the Brigham and Women's Hospital, Boston, Mass, sparked a research interest in François Mach, MD, FESC, now head of the Cardiology Division at Geneva University Hospital, Geneva, Switzerland. The article was published in 1992 in a relatively unknown journal called *Hospital Practice*, and Professor Mach remembers the title well: "Do Vascular Wall Cytokines Promote Atherogenesis?"[1] It led to a discussion with Thomas W. Smith, MD, the legendary chief of cardiology at the Brigham and Women's Hospital, who is famous for his work on digoxins and who died of cancer in 1997 at the age of 60.

Mach had the opportunity to meet Professor Smith to talk about these cytokines (which were quite unknown at the time) when Professor Smith was visiting Geneva soon after the publication of Professor Libby's article. He recalls, "T.W. Smith said, 'Clearly you have to come to Boston to visit Peter Libby and we will see'."

Just 1 year later, Professor Mach was able to meet Professors Smith and Libby in Boston. He says, "It all went very fast. One minute I was putting forward my project proposals and the next Professor Libby was offering to free up a space in his already very busy research laboratory for me to carry them out. All that was expected from me was to organise the funding for the research."

As a result, from 1995 to 1998, Mach was a research fellow in the Vascular Medicine and Atherosclerosis Unit, Department of Medicine, Division of Cardiovascular, at the Brigham and Women's Hospital in Boston. His salary was funded by the Swiss National Science Foundation but only after he was able to find local support for the first year. Geneva University Hospital agreed to pay for the first year.

A Multitude of Articles on Inflammatory Pathways in Atherosclerosis in Prestigious Journals

Everything began that summer in 1995 when Mach joined the Vascular Medicine and Atherosclerosis Unit at 221 Longwood Avenue. Professor Libby was chief of this strong unit. Although his work saw him flying all over the world, when Professor Libby was not travelling he was in the laboratory, providing support for his fellows. Now, 10 years later, Professor Libby continues to acknowledge his fellows' work in his talks. Professor Mach says, "Having been given the opportunity to work under Professor Libby's leadership has been the most rewarding and inspiring aspect of my career in research. When Professor Libby takes you under his wing it is not just for the restricted time spent in his lab, it is for life."

It was, however, a risky venture for Mach when he flew to Boston with his wife and 3 children, the youngest just 1

On other pages...

Teams 2009: Inflammation and Cardiovascular Disease, Cell-to-Cell Communication, and Heart Failure and Cardiomyocytes Research Groups, Cardiovascular Biology, Geneva University Medical School, Geneva, Switzerland
François Mach, MD, FESC, head of the Cardiology Division, Geneva University Hospital, Geneva, Switzerland, and professor of cardiology, Geneva University Medical School, Geneva, describes these 3 research groups: who leads them, their research interests and overall aims, what they have uncovered so far, and what they are working on at present.
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Professor Mach with colleagues in 1998. Left, from left to right, Masanori Aikawa, MD, PhD, Professor Libby, and Professor Mach. Right, from left to right, Professor Mach and Uwe Schönbeck, PhD. Photographs courtesy of Professor Mach.

year old. He had never done research before, he had never even worked in a laboratory; he just went with ideas. For that he will be forever grateful to Professor Libby who had the instinct to believe that some of his ideas might actually be worth pursuing and at any rate it was worth giving him a shot.

The 3 years in Boston were not easy for Mach and his family. Mach worked very long hours and saw little of his family. He dropped the children off at school at 8 AM, went home at midnight, and returned to the laboratory during the night to oversee experiments. "But we were riding a wave," he says. The wave was the discovery that inflammation was a crucial player in atherosclerosis, and it was put together at Harvard Medical School in a few buildings located on Longwood Avenue. "Everything was there," says Mach. "All the people were there, all the chemicals were there, all the animals were there to build this wave and then surf on it."

When Mach went to Boston he had good ideas, but he maintains that "ideas are cheap; it is how you translate them into experiments and then put them down on paper that counts." He had never done basic science—never used a pipette, polymerase chain reaction, or centrifuge. He was lucky that in December 1995 a researcher named Uwe Schönbeck, PhD, came from Germany to take up his first postdoctoral post. Schönbeck liked Mach's ideas and proposed that the 2 work together as a European team. He taught Mach the scientific basics "from A to Z," and they spent a fruitful 3 years publishing articles in *Circulation* and *Nature*.

The wave of inflammation was raising its head but these were still risky projects. Nevertheless, Professor Libby kept the money flowing for antibodies and animals. "Peter had an excellent capacity to make good ideas fly," says Professor Mach. "We came up with the ideas and he was always there to push them, like a big motor."

At this stage another article proved influential. Mach's father, a microbiologist, was head of a research group that included a friend of Mach's who was completing a PhD and had published an article in *The Journal of Experimental Medicine*, so Mach looked at the article for interest. However, he could not understand it. Again out of interest, he checked the references, which led to another article, which proved crucial. It was from a rheumatology group at the Rockefeller University in New York about CD40 ligand and endothelial cells. No one in the cardiovascular field knew about CD40 ligand at that time and Mach wondered what a rheumatology group, which he would later compete with, could be doing with an adhesion molecule and endothelial cells. At the next lab meeting, instead of presenting data he gave a journal club on the article. "This is something that will fly," was Professor Libby's response, and he signed an open cheque. It led to nearly 2 years of work on CD40 ligand and its possible interaction in inflammation as a crucial player in atherosclerosis.

At the time, inflammation had not been related to atherosclerosis or cardiovascular disease but only to rheumatoid arthritis, multiple sclerosis and infectious disease. Professor Mach describes this time as "breaking a barrier between different fields of biology."

Since then thousands of articles have been published on CD40, CD40 ligands, monocytes, platelets and endothelial cells, and patents have been secured. Now, just 10 years after these discoveries, cardiologists are beginning to treat inflammation to reduce cardiovascular events after myocardial infarction, and even in primary prevention.

The work produced a multitude of articles on inflammatory pathways in *Circulation*, *Circulation Research*, *The Journal of Clinical Investigation*, *The Journal of Experimental Medicine,* and so on, but the master article was published in *Nature* in 1998.[2] Mach and his colleagues showed for the first time that by blocking an immunoinflammatory process in an animal model of atherosclerosis they could reduce the progression of the disease.

Showing That Treating Inflammation Reduces Atherosclerosis

The difficult thing about surfing on a wave is the inevitable return to land. For Mach, that meant going home to a small city called Geneva. His success with publishing articles meant that the Swiss National Science Foundation agreed to fund his salary—for 2 years initially but with the possibility of an extension—and gave him a grant to start his own research group. His task now was to prove that he could achieve similar successes at home, and he anticipated that this would be difficult. But again he broke barriers between the fields of biology in inflammation and atherosclerosis by being the first to demonstrate that statins,

Professor Mach likens being a good department head to being a good skipper. He experienced this as a crew member of the sailing boat UBS Switzerland, which won the Whitbread race around the world that took place in 4 steps of between 20 and 27 days each, between 1984 and 1985. The boat had 18 other crew members and Mach was a navigator and sailor and took a year out of his medical studies for the trip. They were the only boat to start and finish with the same crew. As Mach says, "That is probably how you make a good team." In most of the boats there were arguments and people quit, and Mach saw how important it was to choose the right people, a lesson he took to the laboratory. He says, "I am pretty convinced that what counts is that people enjoy work and then they work hard." Photograph courtesy of Professor Mach.

which were already on the market for their lipid-lowering effects, also had the capacity to be antiinflammatory and immunomodulators.[3] This discovery, made in a small laboratory in a building called La Tulipe in Geneva, opened up a completely new field of treatment.

Professor Mach's time in Boston had been about relating inflammation to atherosclerosis. The next 5 years in Geneva focused on trying to prove that treating inflammation could reduce atherosclerosis. In 2004, Professor Mach and his group were the first to demonstrate in vitro how statins have a direct antiinflammatory effect by reducing C-reactive protein released by human liver cells.[4] They described the entire mechanism, all the basic biology, of how clinical concentrations of statins reduce the production and secretion of C-reactive protein. Today, these antiinflammatory properties of statins are begging to be considered for therapeutic uses.

In 2005, Professor Mach's team published a famous *Nature* article that showed how treating mice prone to atherosclerosis with a very low dose of cannabis could lower the progression of atherosclerosis.[5] Again, barriers were being broken between fields. The decision to pursue investigations on the possible antiinflammatory effects of endocannabinoids in the clinical setting was prompted by the discovery of a famous French artist's account on how she claimed to have kept the symptoms of rheumatoid arthritis and pulmonary fibrosis under control by regular absorption of cannabis. Professor Mach searched the literature to find out what was known about marijuana and cannabis. The endocannabinoid system was well known in psychiatry and neurology and the receptor for the endocannabinoids had been described in the brain. But there were other receptors in inflammatory cells, on circulating leukocytes. He hypothesised that acting on the endocannabinoid system via marijuana could have antiinflammatory effects, and that if this could decrease symptoms in a purely inflammatory disease such as rheumatoid arthritis, it might also lower the progression of atherosclerosis. The article completed the circle started when he had been first author on the 1998 *Nature* paper with Professor Libby.

Having shown that drugs can reduce inflammation and cardiovascular events, Professor Mach is confident that the future will see drugs developed specifically for this purpose. It is well known how to treat cardiovascular risk factors such as diabetes mellitus, hypertension, and hyperlipidaemia, but 30% to 40% of patients do not have these risk factors and may have inflammation. For them the key to treating their atherosclerosis will be treating the inflammation, so the future lies in discovering a drug that treats vascular inflammation without producing side effects.

Professor Mach's research in cardiology was recognised in 2000 when he was awarded the Swiss Society of Cardiology Prize. In 2007, he won the Professor Max Cloëtta Prize, a prestigious national award for scientific and clinical contributions to medicine.

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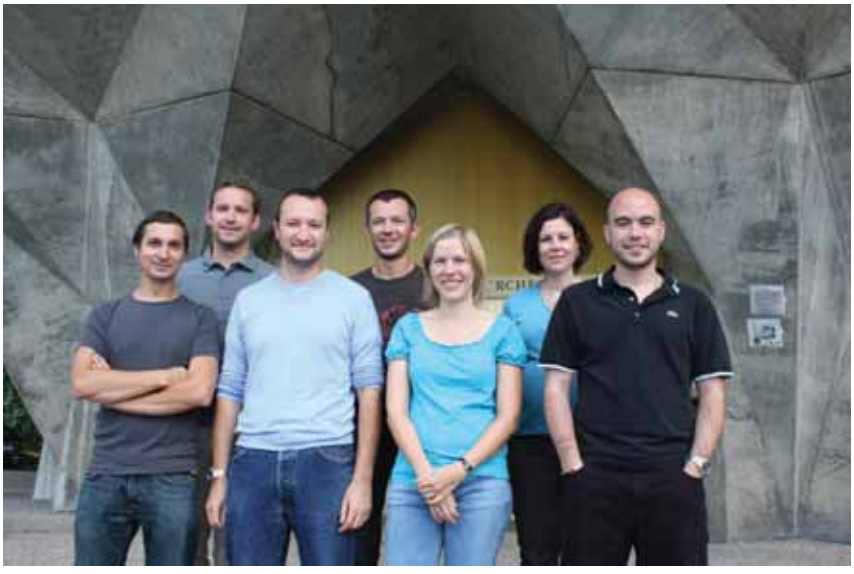
Teams 2009: Inflammation and Cardiovascular Disease, Cell-to-Cell Communication, and Heart Failure and Cardiomyocytes Research Groups, Cardiovascular Biology, Geneva University Medical School, Geneva, Switzerland

"What Counts is That People Enjoy Work and Then They Work Hard"

François Mach, MD, FESC, head of the Cardiology Division, Geneva University Hospital, Geneva, Switzerland, and professor of cardiology, Geneva University Medical School, Geneva, describes the research groups to Jennifer Taylor, BSc, MSc, MPhil.

Professor Mach heads up Cardiovascular Biology, Geneva University Medical School, Geneva, Switzerland, which encompasses 3 research groups: Inflammation and Cardiovascular Disease; Cell-to-Cell Communication; and Heart Failure and Cardiomyocytes. As head of cardiology, he is in charge of all 3 groups, but his own work is focused on the latter and he believes in letting the groups have independence. He says, "I learned from Peter Libby [MD, now chief of cardiology at the Brigham and Women's Hospital, Boston, Mass] that you sometimes have to let others fly, and fly means their own grants, their own articles. I am no longer listed on the articles from the Heart Failure and Cardiomyocytes group. This is not my field. I am just there to help them have space, to enjoy coming to work every day, and if possible to have good grants. But they need to fly alone. That is how they can be successful."



Team 2009. The Inflammation and Cardiovascular Disease Research Group, Cardiovascular Biology, Geneva University Medical School, Geneva, Switzerland From left to right, Vincent Braunersreuther, PhD student; Graziano Pelli, technician; Fabrizio Montecucco, MD, PhD student; Sébestien Lenglet, PhD, assistant; Sabine Steffens, PhD, maitre assistante; Fabienne Burger, technician; Filippo Molica, PhD student. Photograph courtesy of Professor Mach.

Inflammation and Cardiovascular Disease Research Group

The group leaders of the Inflammation and Cardiovascular Disease Research Group are Sabine Steffens, PhD, maitre assistante at the University of Geneva, and Fabrizio Montecucco, MD, at the University of Geneva. Dr Steffens' primary research interest is the role of the endocannabinoid system in atherosclerosis, whereas Dr Montecucco's main interest is the inflammatory response in acute myocardial infarction and atherosclerosis.[1–3]

Investigating the Role of the Endocannabinoid System

Evidence suggests that endocannabinoid signalling plays a critical role in the pathogenesis of atherosclerosis and its clinical manifestations. The system is composed of the 2 known receptors CB1 and CB2, their endogenous ligands (endocannabinoids), and enzymes for ligand biosynthesis and inactivation. Rimonabant was the first CB1 antagonist under investigation in clinical trials. Despite its recent withdrawal from the market (mainly for the slight increase in adverse psychiatric events), CB1 receptor antagonism could represent a promising therapeutic strategy to reduce obesity. It also improved other cardiometabolic parameters including high-density lipoprotein and triglyceride levels, and glycaemic control.

CB2 receptors may also play a prominent role in atherosclerosis. Using an experimental mouse model of atherosclerosis, Dr Steffens' group recently demonstrated that oral administration of low-dose delta-9-tetrahydrocannabinol inhibited plaque development, an effect that could be reversed by the CB2 antagonist SR144528.

The aim of the research is to discover the precise role of the endocannabinoid system and to test a potential therapeutic benefit of pharmacological intervention.

Demonstrating That a CB2-Selective Agonist Has a Cardioprotective Effect During Myocardial Ischaemia

One aspect of Dr Montecucco's work has been to investigate antiinflammatory and antichemokine treatments in a mouse model of acute myocardial infarction. He is also studying antichemokine treatments in postischaemic left-ventricle dysfunction in wild-type mice in the left coronary permanent ligation model using magnetic resonance imaging. This project is being performed in collaboration with the radiology group of Professor Jean-Paul Vallée, MD, PhD, at Geneva University Hospital.

Dr Montecucco has investigated the possible cardioprotective effect of selective CB2 cannabinoid receptor activation during ischaemia in collaboration with Graziano Pelli, Vincent Braunersreuther, Dr Lenglet, Fabienne Burger, and Dr Steffens in C57BL/6 mice. He recently showed that cannabinoid agonists modulate integrin, chemokine receptor expression and chemotaxis on human neutrophils and monocytes. At present, he is testing leukocyte adhesion to different substrates to assess the functional modulation of these antiinflammatory agents.

In collaboration with Professor Bernard Hirschel, MD, Dr Montecucco investigated the cardiovascular risk in patients with human immunodeficiency virus infection in a randomised clinical study of interruption of antiretroviral therapy. A new collaboration with Professor Franco Dallegri, MD, has started to investigate the inflammatory mediators in human atherosclerotic instability. These projects on humans and animals are all focused on plaque instability and the risk of acute myocardial infarction.

Cell-to-Cell Communication Research Group

The primary research interest of Brenda Kwak, PhD, professor adjoint at the University of Geneva, Geneva, Switzerland and group leader of the Cell-to-Cell Communication Research Group is cell-to-cell communication in cardiovascular disease.[4–6] It is becoming clear that connexins (Cxs), proteins that form gap junctions allowing for direct intercellular communication, play important roles during atherogenesis. Professor Kwak's group recently showed that progression of atherosclerosis is reduced in mice with genetically reduced Cx43. In addition, these atheroma contained fewer inflammatory cells and had thicker fibrous caps with more smooth muscle cells, a plaque composition that is associated with stable atherosclerotic lesions in humans. In contrast to the proatherogenic role of Cx43, Cx37 appeared atheroprotective. The group has demonstrated in a mouse model that Cx37 hemichannels control initiation of atherosclerotic lesion development by inhibiting autocrine ATP-dependent regulation of monocyte adhesion.

Professor Kwak's current research is looking into a role for Cxs in complications of atherosclerotic disease, such as plaque rupture and thrombosis. A genetic polymorphism in the human Cx37 gene has been associated with increased risk for atherosclerosis and myocardial infarction in various populations, including in Switzerland. A second research goal is to determine how the polymorphism in the human Cx37 gene affects molecular interactions and regulation of Cx37 channels, hence providing a basis for the association between the genetic polymorphism and cardiovascular risk.

Heart Failure and Cardiomyocytes Research Group

The group leaders of the Heart Failure and Cardiomyocytes Research Group are René Lerch, MD, associate professor at the University of Geneva, and Christoph Montessuit, PhD, biologist at the University of Geneva. The primary research interest of Professor Lerch is the cellular and molecular regulation of myocardial energy metabolism whereas that of Dr Montessuit is the expression of the insulin-regulated glucose transporter (GLUT4) (found in adipose tissues and striated muscle) and insulin resistance in cardiomyocytes and ATP-dependent potassium channels in heart failure.[7–9]

Investigating the Relationship Between Modification of Substrate Metabolism and Myocardial Damage in Heart Disease

In many forms of heart disease, including repeat ischaemia, hypertrophy, and heart failure, there is a shift from fatty acids to glucose, resembling a return to a fetal pattern of energy metabolism. Professor Lerch's research focuses on the assessment of the cellular and molecular mechanisms underlying altered substrate preference and the consequences for cardiomyocyte phenotype and survival.

The group has observed in small rodent models that transient ischaemia and myocardial infarction elicit profound changes in the expression pattern of regulatory genes of glucose and fatty acid metabolism in the surviving myocardium. A switch occurs in the glucose transporter isoforms from insulin-sensitive GLUT4 to constitutively expressed GLUT1 and there is a downregulation of most

Team 2009. The Cell-to-Cell Communication Research Group, Cardiovascular Biology, Geneva University Medical School, Geneva, Switzerland. From left to right, Laurent Burnier, PhD, assistant; Brenda R.. Kwak, PhD, associate professor; Sandrine Morel, PhD, maitre assistante; Katia Galan, technician; Alexandra Chassot, technician; Esther Sutter, technician; Anna Pfenniger, MD, assistant. Photograph courtesy of Professor Mach.

Team 2009. The Heart Failure and Cardiomyocytes Research Group, Cardiovascular Biology, Geneva University Medical School, Geneva, Switzerland. From left to right, Christophe Montessuit, PhD, biologist; Irene Papageorgiou, technician; Corinne Pellieux, PhD, biologist; Mohamed Asrih, PhD student. Not in the photo: René Lerch, MD, associate professor. Photograph courtesy of Professor Mach.

proteins of the fatty acid oxidation pathway. The changes become most pronounced at the onset of heart failure.

Professor Lerch's research aims to assess the effects of growth factors and cytokines involved in hypertrophy and heart failure on the expression of regulatory genes of metabolic regulation, define signalling pathways mediating altered gene expression, investigate a potential causal relationship between alteration of the morphologic and metabolic phenotype of cardiomyocytes with particular emphasis on the role of peroxisome proliferator-activated receptors and retinoic acid receptors, and determine the involvement of altered metabolic regulation in the progression from compensated hypertrophy to heart failure.

Experimental models include isolated adult and neonatal rat cardiomyocytes, isolated perfused rodent hearts, and small animal models of cardiac remodeling induced by experimental infarction or targeted overexpression of angiotensinogen in the heart. The goal is to define the relationship between modification of substrate metabolism and myocardial damage in heart disease.

Therapeutic Strategies for the Prevention of Arrhythmias

Insulin stimulates the transport of glucose by inducing the translocation of the glucose transporter GLUT4 from intracellular stores to the cell surface. Metabolic stress also stimulates translocation of GLUT4, thereby allowing cardiomyocytes to withstand situations of transient ischaemia and improving recovery at reperfusion. Observations in hypertensive rats and cardiac patients have suggested that myocardial hypertrophy is associated with insulin resistance (failure of insulin to stimulate the transport of glucose) of cardiomyocytes. Adult rat cardiomyocytes in primary culture replicate several features of heart pathological hypertrophy in vivo, including insulin resistance and reduced GLUT4 expression. Dr Montessuit is using this model to identify signals related to cardiomyocyte hypertrophy and differentiation that control the expression of GLUT4 and delineate the mechanisms that govern the translocation of GLUT4 in response to insulin or metabolic stress.

Dr Montessuit is also investigating the direct influence of drugs used for the systemic treatment of insulin resistance on myocardial glucose metabolism. Almost half of patients with postinfarction heart failure die of sudden arrhythmias, and the susceptibility to arrhythmia is explained by heterogeneous prolongation of the action potential within the surviving myocardium. In a low-energy situation, open ATP-dependent potassium channels (KATP) shorten the action potential and reduce the triggered calcium transient, thereby limiting energy consumption. The physiological and pharmacological properties of KATP channels depend on their molecular composition. Using an in vivo model of postinfarction heart failure, Dr Montessuit is studying the alteration in composition of KATP channels and how it impacts on KATP physiology, duration of the action potentials, and calcium handling. Isolated cardiomyocytes in vitro are used to investigate the molecular mechanisms that lead to altered KATP subunit expression in heart failure and to further explore the electrophysiological repercussions of these changes.

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