Centre of Excellence: 
Charité Centre for Cardiovascular Medicine, 
Universitätsmedizin Berlin, Berlin, Germany

Showing That Novel Therapies Aimed at Virus Elimination Are Beneficial in Certain Cardiomyopathies

Heinz-Peter Schultheiss, MD, FESC, director of the Department of Cardiology and Pneumology, Charité Centre 11 for Cardiovascular Medicine, Charité Hospital, Campus Benjamin Franklin, Berlin, Germany, talks to Mark Nicholls.

The Charité is one of the oldest hospitals in Germany, tracing its history back more than 300 years to the early 1700s. In that time, it has changed, merged, and evolved into one of the largest university hospitals in Europe. The Centre for Cardiovascular Medicine is quite literally at its heart and continues to develop, evolve, and move forward. Its reputation for research and clinical care is widely acknowledged.

Charité Centre 11 for Cardiovascular Diseases is 1 of 17 Charité centres, each with its own subdivisions. It includes the departments of Vascular Surgery, Cardiovascular Surgery, and Cardiology and Pneumology, the latter of which is led by Professor Heinz-Peter Schultheiss, MD. Professor Schultheiss explains, “The Department [of Cardiology and Pneumology] provides the whole spectrum of cardiovascular diagnostics and therapies for major parts of the city of Berlin and also for patients from the surrounding areas of the city whenever highly specialised diagnostic or interventional procedures are required. In addition, patients with complex cardiovascular problems—in particular acute and chronic cardiomyopathies—from other parts of Germany are admitted to the centre.”

Complex interventions performed at Charité Centre 11 on the Campus Benjamin Franklin include transluminal approaches and advanced hybrid treatment strategies requiring cooperation between cardiologists and cardiovascular surgeons. Professor Schultheiss says, “Charité Centre 11 for Cardiovascular Medicine was founded several years ago to improve the coordination of the cardiovascular research activities within Berlin to achieve the most effective exploitation of the cardiovascular resources at the Charité and to keep it competitive at the international level.”

“Optimal Integration of All Relevant Clinical Disciplines”
Charité Centre 11 continues to build on the clinical and basic research of a number of high-ranking cardiovascular groups and is still moving towards its final form. Professor Schultheiss says, “One particular aim is the optimal integration of all relevant clinical disciplines at close distances. Another one is the continuous and close cooperation between clinical and basic researchers in a decidedly translational medicine setting.” Within the clinic, the different areas of expertise are served by 10 senior physicians with longstanding clinical and research experience in their...
Circulation: European Perspectives

Research Focused on Multiple Forms of Cardiomyopathy and Acute Coronary Syndromes

Experimental and translational research is conducted in various molecular biology, virology, and cell biology laboratories and animal facilities. Several local clinical and experimental research groups have close collaborations with national and international research partners. Professor Schultheiss says, “In the central fields of research, different topics are covered by physician-scientists who lead their own groups and organise their own funding and scientific direction. These groups interact, whenever appropriate, within the centre and with selected outside groups—both national and international—to achieve effectiveness and close integration within the international research community.”

The central fields of research in the clinic are the aetiology (genetic, environmental), molecular pathogenesis, differential diagnosis, and causal therapies for human cardiomyopathies. These clinical interests are supported by several experimental research groups, which conduct basic and translational research in the fields of cardiomyopathies and heart failure within the context of a transregional research network. Professor Schultheiss explains, “In these areas the clinic has made contributions to the research literature, including the discovery of a high prevalence of cardiotropic virus in the hearts of patients with idiopathic dilated cardiomyopathy, the first description that cardiotropic virus persistence is associated with an adverse clinical prognosis, and the finding that cardiac function and clinical status may be significantly improved by therapies that promote virus elimination. The clinic have participated in developing the current international guidelines for cardiomyopathies.”

Novel therapeutic approaches for the treatment of cardiomyopathies and heart failure are being developed, with research directed at new targets identified by genomic expression profiling of endomyocardial biopsies from patients with cardiomyopathies. Professor Schultheiss says, “This effort has led to increasing recognition of inflammatory processes in the myocardium as novel targets for molecular therapies.” Novel experimental strategies used by the translational research groups at the centre include antiviral (eg, recombinant “virus trap” proteins for virus elimination) and antiinflammatory gene therapies. Recently, one of the groups conducted the first successful treatment of heart failure in an animal model that was based on the local cardiac expression of a regulatory RNA (cardiac RNA interference therapy).

Another area of intense work at the centre focuses on the acute coronary syndromes and emergency medicine in general.5,6 This work includes a number of clinical trials to optimise the treatment of acute coronary syndromes. Those clinical studies are also supported by basic research groups, particularly in the fields of thrombosis and haemostasis.

Professor Schultheiss emphasises that a careful balance exists between clinical care and research, which takes into account the basic workload for physician-scientists who are involved in major clinical and/or basic research projects. “The balance for individuals is adjusted as required. The overall balance is determined by the requirement for optimal clinical care for all patients versus the need to further translational research at the highest possible level in the long-term interest of the patients.” he says.

Professor Schultheiss feels that some of the most exciting research developments at Charité Centre 11 have taken place over the past 5 years. He highlights the discovery of a high prevalence of cardiotropic virus persistence in certain cardiomyopathies and the finding that clinical benefit can be derived using therapies aimed at virus elimination. He says, “The discovery would not have been possible without the development and extensive clinical evaluation of new differential diagnostic procedures based on endomyocardial biopsies and the demonstration in very large patient cohorts of the safety of the biopsy procedure as performed at our centre.”

Charité provides the basic funding for the centre, with extensive additional funding for clinical and basic research from Deutsche Forschungsgemeinschaft, Bundesministerium
Für Forschung und Technologie, charitable foundations, and numerous other sources.

Professor Schultheiss says it is important to establish close and long-term cooperation between clinical workers and experimental scientists on clearly defined clinical problems, and to address these in parallel from a patient-based perspective—with full access to data and clinical samples from large patient groups—and by the use of relevant animal models. “Close communication between these areas will significantly promote progress in both fields and, most importantly, also give a fair chance to recognise truly novel issues,” he explains.

“The Next Decade Will Be Devoted to Further Elucidation of Molecular Pathomechanisms”

Future plans for the Department of Cardiology include intensifying efforts in the “translation of recent experimental therapeutic approaches to the clinical setting.” Professor Schultheiss reports that approaches with promising results in animal models include recombinant proteins for virus elimination in viral cardiomyopathy, RNA interference for the treatment of heart failure, and gene- and protein-based approaches for the therapeutic modulation of inflammatory processes in the myocardium. The centre will seek closer cooperation with industry by requiring highly sophisticated production and test facilities before new tools can be applied in patients. He says, “The next decade will be devoted to further elucidation of molecular pathomechanisms in viral, inflammatory, and genetic cardiomyopathies, and of heart failure in general. As in the past, insights from these studies should provide the foundations for a better understanding of the clinical problems of our most severely ill patients, both for those with acquired and those with primarily genetic pathogenesis. Many questions are unanswered and need to be urgently addressed.”

Another goal is to overcome difficulties in assessing the prognosis—and optimal handling—of patients with heart failure of various origins. He says, “We will try to establish novel diagnostic tools for prognosis assessment (eg, endomyocardial biopsy-based gene and microRNA profiling) and to systematically evaluate these new methods in sufficiently large patient cohorts.”

References


Mark Nicholls is a freelance medical journalist.
Spotlight: John J.P. Kastelein, MD, PhD

“This Will Be About Making the Databases Large Enough so we Find the Few Diamonds That We Need”

John J.P. Kastelein, professor of medicine, chair of the Department of Vascular Medicine, and strategic chair of Genetics of Cardiovascular Disease at the Academic Medical Centre, University of Amsterdam, the Netherlands, talks to Jennifer Taylor, BSc, MSc, MPhil.

Setting up the first Lipid Research Clinic in the Netherlands has fed the research work of John J.P. Kastelein, MD, PhD, professor of medicine, chair of the Department of Vascular Medicine, and strategic chair of Genetics of Cardiovascular Disease at the Academic Medical Centre, University of Amsterdam, the Netherlands.

A Life-Changing Experience in Canada
The idea sprang from a 2-year break in Canada, which became a determining point in Professor Kastelein’s career. He had completed his medical degree in Amsterdam in 1980 and was “a little bit fed up with the Netherlands. Training to become an internist was in my view quite a boring experience with very little exposure to science at the time,” he says. He had saved enough money to live for 2 years without a salary, and he decided to interrupt his training to go to the University of British Columbia, Vancouver, Canada, from 1986 to 1988 where he was taught by Professor Michael Hayden, MD. “[He] completely changed my outlook on life and science,” says Professor Kastelein.

Professor Hayden trained in South Africa, “which at that time was a country that trained great physicians,” and had a lot of exposure to science at Harvard University, Cambridge, Mass. He ended up in Vancouver, and Professor Kastelein was one of his first pupils. It meant he could “spend a lot of his very large brain” training Professor Kastelein in lipiddology, epidemiological thinking, and molecular biology, a combination that proved fortuitous later on in Professor Kastelein’s career.

The choice of the University of British Columbia had been partly cultural and partly scientific. “The Dutch owe a lot to the Canadians because they liberated us in the Second World War.”

Evidence-based medicine was becoming more popular, and David Sackett, MD, one of its pioneers, was based at McMaster University in Hamilton, Ontario, so that would have been an obvious choice. However, one of the clinicians with whom Kastelein had trained in the Netherlands, Harry Buller, MD, PhD, who is now his cochair in the department, had already trained there.

“I didn’t want to copy exactly what he was doing so I went 1000 miles west,” says Professor Kastelein. “I had never been there; I just knew by reputation that a number of individuals there worked in the field of what we now call vascular medicine.”

On his return to the Netherlands, Kastelein rapidly completed his training as a board-certified internist and then set out to do what he wanted to do, which was to start a lipid clinic at the University of Amsterdam and study the molecular basis of dyslipidaemia and coronary artery disease.

A Family Database Containing the DNA and Biomaterial of More Than 5000 Patients Facilitates an “Extreme Genetics Approach”
The Lipid Research Clinic has now been transformed into a tertiary referral centre that is part of the Department of Vascular Medicine. The clinic sees more than 5000 patients each year. Professor Kastelein brought back plans for a North American–style clinic, which was a novel concept for the Netherlands in 1988.

Professor Kastelein says, “I worked in a lipid clinic in St. Paul’s Hospital, Vancouver, which is a university training hospital, so I had seen with my own eyes how you could organise this and how fertile this was in terms of the science—both the basic science as well as the clinical science.”

The time was right for such a venture. In 1985, Brown and Goldstein, 2 internists from Dallas, Tex, had received the Nobel Prize for elucidating the molecular basis of familial hypercholesterolaemia. In 1988, the first statin was registered in the Netherlands. Two things were coming together at the same time: People began to think beyond measuring lipids towards genes and gene mutations, and, for the first time, drugs were available that could make a difference. Professor Kastelein says, “You realise that there are a large number of other disorders in lipoprotein metabolism that are all associated with premature coronary disease—and there were at that time multiple novel modalities in development—this suddenly exploded into an extremely fertile field.” But he adds, “In order to participate in that success, you needed the patients—to find novel genes, to find novel mutations in known genes and to be able to participate in clinical trials with novel drugs. And therefore I took the approach of starting with the patients first. So I set up a tertiary referral clinic, and patients are still referred from all over the country.”

The team began to see and treat many patients with dyslipidaemias and extremely pronounced coronary disease, and it discovered severe underdiagnosis and undertreatment...
of these disorders. Therefore, Professor Kastelein began discussions with the Ministry of Health in the Netherlands, which in 1995 allocated him a €30 million grant to find and treat all of the individuals with genetic high cholesterol in the Netherlands.

Since its inception, around 16,000 patients with familial hypercholesterolemia have been diagnosed and treated. The project is now being copied in the United Kingdom and Norway, and discussions are underway in Spain and elsewhere.

Professor Kastelein now holds a family database that contains the DNA and biomaterial of more than 5000 patients with hereditary disorders of lipoprotein metabolism, which is used in much of his collaborative work. The database has facilitated the “extreme genetics” approach that underlies his work and that was developed in Vancouver with Professor Hayden. The concept is that genetics—rather than environment—is primarily at work at the extremes in the distribution of a biological trait.

Using the concept in practice requires very large databases. “You can’t do it with 100 people,” says Professor Kastelein. “You need thousands of people to find a few diamonds that are mostly genetically determined. Those you use to pinpoint genes of interest, and then, very often, those genes are also relevant for the entire population. So you learn a lot about biology and biological pathways by using what we call the ‘extreme genetics approach’.”

This approach was used to reveal the molecular basis for extremely low–high-density lipoprotein (HDL) cholesterol. In the 1990s, the gene for ATP-binding cassette A1 (ABCA1), was cloned; this was completely knocked out in patients with almost no HDL.1 It also proved to be an important regulator of reverse cholesterol transport for everybody.

“To Begin and Run a Discovery Company, You Need a Lot More Than Just Academic Enthusiasm”

Professor Kastelein returned to Vancouver between 1997 and 1998 for a visiting professorship at the Centre for Molecular Medicine and Therapeutics at the University of British Columbia. He was “extremely happy” there. He was free from clinical and bureaucratic responsibilities—it was science the whole day, writing articles, sitting in research meetings, preparing lectures, and working with research technicians and clinicians.

During this time, he was one of the cofounders of a discovery company, which is based in Vancouver. The company was founded initially on the extreme genetics approach but has now been transformed into a full-fledged pharmaceutical company that is involved in high-throughput screening and preclinical and clinical drug development. Still a private company, it is active in a number of fields, including iron metabolism, energy metabolism, and pain, and it has partnerships with many large pharmaceutical companies. “Developing that company was very instructive,” says Professor Kastelein. “It taught me that to begin and run a discovery company you need a lot more than just academic enthusiasm.”

The experience proved useful when he returned to Amsterdam and became the cofounder of a gene therapy company, which is now listed on Euronext. The company was based on the concept of gene replacement in hereditary lipoprotein disorders.

It is unusual for cardiologists to set up companies, admits Professor Kastelein, and it is because of the environment at the Academic Medical Centre in Amsterdam that he has been allowed to do it. He believes that looking at the other side of the fence has enhanced his scientific abilities. “Normally of course, you’re only on the academic receiving end, and now I am forced to think how to translate a scientific idea into clinical reality. That is something entirely different,” he says.

Rather than just accepting a novel therapy from a biotech company and testing it in patients, it requires starting with the patient, trying to find the gene, understanding the protein, attempting to find a therapy, optimising it, and so on. “It’s a very complicated and sometimes painful process that requires an enormous amount of endurance and stamina,” says Professor Kastelein.

He would recommend this process to other cardiologists, and discussions are ongoing in the European Community about the benefits of such companies given that scientists’ good ideas often disappear. Many of the good universities across Europe now have patent offices, and the trend of trying to convert patents and ideas into companies is increasing. “Of course, the current climate makes it even harder than it already was because it’s very
Involved With the Trial That Led to the “Lower Is Better” Hypothesis for Low-Density Lipoprotein Cholesterol

Although the large patient databases were crucial to deploying the extreme genetics approach to look for novel genes and novel mutations, having access to large numbers of patients also made it possible to do clinical trials, which have formed the second stage in Professor Kastelein’s career. He has been on a number of executive and steering committees for trials on dyslipidaemia, including the Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) trial, the Treating to New Targets (TNT) study, the Vascular ACAT (acyl-coenzyme A: cholesterol acyltransferase) Inhibition Treatment Effects (CAPTIVATE), the Effect of Combination Ezetimibe and High-Dose Simvastatin Versus Simvastatin Alone on the Atherosclerotic Process in Patients with Heterozygous Familial Hypercholesterolemia (ENHANCE) trial, the Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events (ILLUMINATE) trial, the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER), and the Rating Atherosclerotic Disease Change by Imaging With A New CETP (cholesteryl ester transfer protein) Inhibitor (RADIANCE) trial.

Professor Kastelein’s favourite clinical study so far is a small imaging study, not an end-point study, called the Antioxidant Supplementation in Atherosclerosis Prevention (ASAP) study. He says, “We showed for the first time that 80 mg of atorvastatin—the highest dose of a potent statin—was better in reducing carotid intima-media thickness progression than a moderate dose of a moderate statin.” It was the first surrogate marker study to announce the so-called “lower is better” hypothesis for low-density lipoprotein cholesterol, and it became the starting point for many of Professor Kastelein’s imaging studies and morbidity and mortality trials. By lowering low-density lipoprotein further and further, science has been able to demonstrate that, when coronary disease is present, lower low-density lipoprotein is better.

For Professor Kastelein, becoming an established investigator with the Netherlands Heart Foundation in 2000 was an important career step. “To become an established investigator is like a sure path for a full professorship,” he says.

His ambition for the next 5 years is to find and clone novel genes in HDL metabolism. “There are still a number of disorders that I see in the clinic that I don’t understand, and there must be novel genes and proteins that we have not discovered yet,” he says. “The Dutch like to explore, as you know from our history in the 17th century, and maybe it’s in my genes, but that’s something I really aspire to. I would love to find and understand some of the disorders we see frequently here.” Are there any clues yet? “No,” he says, “and so this will be about making the databases large enough so we find the few diamonds that we need, as we did in our search for the low-HDL gene in the late 1990s.”

References

Jennifer Taylor is a freelance medical journalist.
European Perspectives

Circulation. 2009;119:f79-f84
doi: 10.1161/CIRCULATIONAHA.109.192198

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2009 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circ.ahajournals.org/content/119/14/f79.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/