Denise Hilfiker-Kleiner, PhD

A Training in Basic Science That Led to Elucidation of the Pathophysiological Mechanism of Postpartum Cardiomyopathy—“What I Want to Know Is What Identifies Somebody Who Is at Risk”

Denise Hilfiker-Kleiner, professor of molecular cardiology, Department of Cardiology and Angiology, Hannover Medical School, Hannover, Germany, talks to Jennifer Taylor, BSc, MSc, MPhil.

My dream as a scientist is to take a discovery at the basic science level and translate it directly into a clinical application,” says Denise Hilfiker-Kleiner, PhD, professor of molecular cardiology in the Department of Cardiology and Angiology, Hannover Medical School, Hannover, Germany. Her most important work so far came as such a discovery. Together with her husband, Andres Hilfiker, PhD, she elucidated a pathophysiological mechanism of peripartum cardiomyopathy (PPCM) using a mouse model—a finding that she believes they would not have made had their training not had roots in basic science.

A lucky coincidence brought the Hilfikers in contact with cardiologist Karen Sliwa, MD, PhD, FESC, DTM&H, professor and director of the Soweto Cardiovascular Research Unit in the Wits Department of Cardiology, Chris Hani Baragwanath Hospital, University of the Witwatersrand, Johannesburg, South Africa, a well-known expert on PPCM, who was very interested in their experimental findings. As a result of her subsequent involvement a translational study was soon underway, revealing major pathophysiological parallels between PPCM in patients and in the mouse model. After a small pilot trial and several healing attempts in patients with PPCM with the drug, bromocriptine, which is widely used in the clinic to stop lactation and had been successful in the mouse model, they are now performing controlled randomised trials on the efficacy of bromocriptine in PPCM patients in Germany and in South Africa. The work on PPCM won Professor Hilfiker-Kleiner 2 awards in 2007: the European Society of Cardiology’s Outstanding Achievement Award for the category “Cardiac Biology,” and the Sir Hans Krebs Preis.

“The Ideal Scenario for Research Translating Into Clinical Applications Would Entail Having 4 Sectors That Work in an Integrative Way”

As a developmental biologist, Professor Hilfiker-Kleiner says she approaches research in a completely different way from someone with clinical training. She says, “I think as a biologist you’re trained in looking in the microscope or looking at a plant, and from what you see you start to formulate your hypothesis.” The ideal scenario for research, says Professor Hilfiker-Kleiner, would entail having 4 sectors that work in an integrative way. First, the “basic, basic scientists”; second, scientists with some clinical understanding (her laboratory would fit into this category); third, physicians with a clinical background who also have some understanding of basic science; and finally, the trialists—
Among the First to Discover a Pathophysiological Transcriptional Regulation Mechanism

Hilfiker-Kleiner studied biology and then zoology at the University of Zurich, Switzerland. She had always wanted to be a scientist and she has had an interest in biology for as long as she can remember. In 1989 she began her PhD thesis at the University of Zurich’s Department of Classical and Molecular Genetics and Developmental Biology, and worked on the second half of her PhD at the Department of Biology, Emory University, Atlanta, Ga, completing it in 1994. The move to Emory arose when her husband received the offer of a postdoctoral post there. When he finished, they stayed on for an extra 2 years, until 1996—he as a senior researcher and she as a postdoctoral researcher.

While studying transcriptional regulation, Hilfiker-Kleiner and her husband were among the first to discover that histone modifying enzymes and subsequent chromatin alterations were key for transcriptional regulation in eukaryons. Transcriptional regulation was attracting much interest at that time, and they later took it into cardiology.

Professor John C Lucchesi, PhD, was one of Hilfiker-Kleiner’s mentors at Emory, and she liked his open-minded approach. She had come to him with completely new ideas that lay outside his particular area, and he immediately took an interest and began looking to see whether he could open any doors for her. It led to some connections with the Centers for Disease Control and Prevention. At the end of the 2-year extension, Hilfiker-Kleiner had the option of staying at Emory and continuing a career in basic science.

But she says, “In many US states you have no social security and you can be fired from one day to the other and lose your health insurance and everything.”

“Sure Whether I Would Have Dared to Make This Move”

By chance Hilfiker-Kleiner and her family lived in the same apartment complex in Atlanta as a German couple who were doing postdoctoral research in cardiology in the Department of Medicine at Emory, and they became close friends. The couple, Bernhard and Elisabeth Schieffer, were from Professor Helmut Drexler’s group in Freiburg, Germany, and when they returned in 1995 they mentioned that Professor Drexler, who had become chief of medicine at the Department of Cardiology and Angiology at Hannover Medical School, was looking for scientists to set up a laboratory in molecular cardiology. Hence they moved to Hannover in 1997.

Professor Hilfiker-Kleiner started as a research assistant, and although she found it exciting to move into a new scientific area that seemed more practically oriented, the departure from basic science was tough. Most of her research had focused on Drosophila, the tiny flies used for research on genetic analysis. “If I had known how hard it would be, I’m not sure whether I would have dared to make this move,” she says. “You start completely from the beginning.” She spent the first 2 or 3 years keeping up with the literature to understand the new field while she and her husband were building up the laboratory. She feels indebted to Professor Drexler who proved inspirational and to many colleagues from the Department of Cardiology and Angiology who introduced her to clinical science. In addition, she is grateful to the European Society of Cardiology Working Group on Myocardial Function—of which she became vice chair last summer—for introducing her to researchers in her field with whom she could discuss findings she could not interpret. Hilfiker-Kleiner did not regard it as her field (or stop feeling like an outsider looking in) until 2001.

Having made it through the transition, she is reaping the rewards of combining her basic-science knowledge with clinical application, and she feels her work is making a difference. After just 3 to 4 years, the results from the mouse model of PPCM had made their way into the clinic, and a trial to confirm the findings has since begun.

But the transition between fields led to a setback in career progression. In 2002, Hilfiker-Kleiner became assistant professor in molecular cardiology, then professor in 2008. “I think I’m not that young anymore for the career stage that I achieved last year,” she says. “I had to raise 2 children besides doing all the work. This was only possible because my husband and I are always a team, and because my parents were stepping in and helped with the children, but still it’s something that makes it not so easy for you.”

In Switzerland and Germany, a person’s age can significantly affect the positions for which an institution will consider him or her. Professor Hilfiker-Kleiner thinks that equal chances for women in science can only be achieved if
they have a bit more time, “and not saying strictly if you’re 40 and you haven’t reached [a certain] kind of degree, forget it. I think if a woman has children it’s a wonderful thing, but you cannot work at the same speed as somebody who has no children. However, this doesn’t make you a worse scientist with a lower quality. I go home, and I still think about my projects. I think of them at night and all the time, which other people might not do. It’s part of myself, part of my personality.”

Professor Hilfiker-Kleiner’s commitment was evident when it seemed that she did not get a PhD position because she had a child. She says, “This was hard, and I had to fight to finally be able to enter a PhD programme. I was lucky because Professor Andres Duebendorfer gave me a chance to start my thesis as a part-time job, but most of the time I worked without payment, supported by my husband (who had a PhD position and was teaching) and by my parents.” The project proved successful and led to an article in a high-ranking journal.

Throughout her career, Professor Hilfiker-Kleiner has worked in partnership with her husband, a senior scientist at the Hannover Medical School, who also has a biology background. This provides the perfect mixture for them, she says, because they can understand perfectly each other’s joys and frustrations at work and their skills complement each other. Together they built up Hannover’s molecular cardiology laboratory and, a few years ago, Dr Andres Hilfiker moved to the Department of Cardiac Surgery where he works on tissue engineering. They still consider themselves a team and discuss their respective projects.

“We Are Contacted Almost Daily by Physicians or by Patients Who Have the Disease”

Professor Hilfiker-Kleiner’s major research now focuses on refining the translational aspects of PPCM. The work has received important funding from the Leducq Foundation, 1 of 2 principal research foundations that have supported her work in Hannover, the other being the Deutsche Forschungsgemeinschaft. A key aspect to the work involves a registry (both nationwide and international) that she is setting up of patients with PPCM. She says, “We are contacted almost daily by physicians or by patients who have the disease or who would like to have information on the disease.” People from about 10 different countries have been in touch, and 60 patients have been added to the registry. Cardiologists who want more information can email Professor Hilfiker-Kleiner at hilfiker.denise@mh-hannover.de.

A second important aspect involves the collaboration with Professor Sliwa. This has enabled a faster translational approach to PPCM because the disease has a higher incidence rate in South Africa. A controlled trial on patients with the acute form of the disease is being carried out, and the results should be presented soon. It has proved a fruitful collaboration, with patient outcomes fed back to the laboratory. In 2008, it was observed that inflammation in patients seemed to be responsible for particularly poor outcomes, so they returned to the mouse models to see how they could explain the inflammatory link.4

In Europe, PPCM remains a relatively rare disease and patients have quite different aetiologies. Professor Hilfiker-Kleiner thinks that they will need at least 100 to 200 cases in Europe before they can extract meaningful data, but patterns are beginning to appear. Her ultimate aim is to develop a blood test for every woman who has given birth to a baby that identifies who is at risk of PPCM and who is not.

As a scientist through and through, Professor Hilfiker-Kleiner says: “What I really want to know is what identifies somebody who is at risk. Maybe for me it’s less important that I have a large number of articles published every year than that I really understand a mechanism and can organise it within a certain pathophysiological background.”

References


Jennifer Taylor is a freelance medical journalist.
Spotlight: Marc van Bilsen, PhD

“By Learning About How Metabolism Is Regulated, Both at the Biochemical and at the Gene level—at the Transcriptional Level—We Might Find New Targets for the Treatment of Cardiac Failure”

Marc van Bilsen, associate professor of molecular physiology, Department of Physiology, Cardiovascular Research Institute Maastricht, Maastricht University, the Netherlands, talks to Jennifer Taylor BSc, MSc, MPhil.

In 1990, Marc van Bilsen, PhD—now associate professor of molecular physiology in the Department of Physiology, Cardiovascular Research Institute Maastricht (CARIM), Maastricht University, the Netherlands—had recently finished his doctorate and was searching for a position at a foreign institute. He wanted to work with Ken Chien, MD, PhD, director of Massachusetts General Hospital Cardiovascular Research Centre, Department of Cell Biology, Harvard Medical School Stem Cell Institute, Cambridge, Mass, who at the time was in Dallas, Tex. They shared the same interest—membrane damage during cardiac ischaemia and reperfusion. And a visit to Dallas revealed the laboratory’s willingness to welcome van Bilsen, though Professor Chien was moving to San Diego, Calif, and changing his area of research. “He had done a sabbatical on molecular biology and was asked to start a laboratory on molecular cardiology in San Diego,” explains Professor van Bilsen, who also made the career shift.

Molecular cardiology had not existed for long at that point, with just a few groups in the United States and hardly any in Europe: van Bilsen and his colleagues felt as though they were working at the frontiers of science. And it resulted in the most enjoyable time in his career.

“You need the fertile soil of basic research for translational research to be able to flourish,” Professor van Bilsen says. Here he is shown in the laboratory with Chantal Munts. Photograph courtesy of Professor van Bilsen.

“To Get a Prestigious Grant Later on, It’s Close to Mandatory to Have Experience Abroad”

Van Bilsen’s career started at the University of Leiden, Leiden, the Netherlands, when he switched from ecology to cellular biology. He liked “the real science” of cellular biology. He moved to the Department of Physiology in the Faculty of Medicine at Maastricht University to pursue PhD studies in 1983. He says, “I was hired because of my experience with ultrastructural techniques, but when I moved here I hardly touched an electron microscope.” His colleagues had intended to carry out ultrastructural analysis of cellular membranes after ischaemia reperfusion damage, but they opted for biochemical techniques instead and looked at the degradation of membrane phospholipids as the cause of irreversible cardiomyocyte damage. The studies showed an association between reperfusion damage and enhanced degradation of membrane lipids.

Professor van Bilsen then went to San Diego and learned molecular biology techniques, applying them to cardiology research. Funding came from a North Atlantic Treaty Organisation Science Fellowship Award for scientists in the Netherlands to spend a year in the United States. He also had a California Affiliate Fellowship Award from the American Heart Association. So, together, he had funding to spend 2 years in Professor Chien’s laboratory. The work revolved around the cardiac-specific expression of genes, and they used myosin light chain-2, a contractile protein gene, as the gene of interest.

The decision to work abroad had a specific aim. “It works 2 ways,” van Bilsen says. “Of course, it’s very refreshing to have an experience in another, preferably foreign, laboratory. But to get a prestigious grant later on, it’s close to mandatory to have experience abroad for at least 1 year.” At the time, the United States and the United Kingdom represented the countries of choice.

“We Came to [Work Out] the Mechanism as to How Fatty Acids Are Able to Regulate Gene Expression”

On van Bilsen’s return to Maastricht in 1992 as a postdoctoral fellow at CARIM, he had to decide what he would do next. “We came to the concept that fatty acids are not only oxidisable substrates for the heart but also signalling molecules that are able to regulate gene expression,” he says. The dual role, a new idea at the time, would become a major component of his career. His group represented one of the first groups to show that fatty acids regulate gene expression in cardiomyocytes.

The first important article started with a “disaster experiment,” recalls Professor van Bilsen. The team was studying fatty acid oxidation by isolated cardiomyocytes, and when they added saturated fatty acids to the culture medium, all of the cells died. He says, “It turned out that saturated fatty acids induce apoptosis of cardiomyocytes.” It’s unique for saturated fatty acids because unsaturated fatty acids are...
perfectly tolerated by the cardiomyocytes.” The second article showed that fatty acids can induce many genes involved in fatty acid metabolism and transport at the level of transcriptional regulation.3

The experience abroad not only produced a fruitful new area of research but also helped spawn a string of prestigious grants. The Royal Netherlands Academy of Arts and Sciences appointed van Bilsen as a senior investigator in 1993 for 5 years. He did the work at CARIM, continuing to explore the concept his team had developed that substrates act as modulators of cardiac gene expression. When the grant terminated in 1998, he became assistant professor and then associate professor of physiology in the Faculty of Medicine at Maastricht University. At that point, the teaching responsibilities kicked in. That translated into spending 30% of his time teaching physiology to medical students and represented a burden early on; but now with PhD students and postdoctoral researchers to take over the laboratory work, Professor van Bilsen has time to prepare and enjoy lectures.

Professor van Bilsen received another prestigious 5-year grant in 1999 when he became an Established Investigator of the Netherlands Heart Foundation. Both grants gave him the luxuries of finance and people to pursue his concept, with the added bonus of flexibility. “You can change your plans without having to write 3 pages with arguments [about] why you did it,” he explains. And as the recipient of these grants, he received the Edmond Hustinx Prize for Science in 1999, which Maastricht University awards to 1 scientist each year. He has also received funding on a number of occasions from the Netherlands Organisation for Scientific Research.

And as a result of the research, Professor van Bilsen says, “We came to [work out] the mechanism as to how fatty acids are able to regulate gene expression. Fatty acids act as a ligand for these nuclear receptors, which are called peroxisome proliferator-activated receptors (PPARs).4 From that time on, our research really focused for a large part on these nuclear receptors—how they work, how they are regulated, and what their role is in cardiac disease.”

“During Cardiac Hypertrophy and Cardiac Failure, There Is a Switch in Substrate Metabolism”

CARIM organises its research into 3 themes5: theme I—Thrombosis and Haemostasis; theme II—Cardiac Function and Failure; and theme III—Vascular Biology. In 1999, Professor van Bilsen became a principal investigator in theme II. Since 2007, he has also served as coleader of the subtheme Cardiac Failure.

Professor van Bilsen’s main research interest today involves the concept that during cardiac hypertrophy and cardiac failure, a switch occurs in substrate metabolism as the diseased heart starts to use less fatty acids and more glucose. But researchers have not yet determined whether this represents a detrimental or beneficial change. In other words, is it an adaptive or maladaptive process?

“We started out thinking that it was a maladaptive process,” says Professor van Bilsen. “But research from our group and also from other groups tends to suggest that it might be an adaptive response because if you further stimulate glucose uptake, the function of the heart tends to improve rather than to deteriorate.”6 They are examining the question in rat models of hypertrophy and infarction and in transgenic mouse models, primarily looking at the mechanism that causes this shift in metabolism. They believe that the PPARs may prove very important. He says, “We examined the role of these nuclear receptors in the cardiac muscle, and we showed that of the 3 isoforms that exist, PPAR α and PPAR δ are particularly important; PPAR γ appears to be less significant in the regulation of this process.”

Participants of one of the first cardiac metabolism meetings, which was held in Houston, Tex, in 1999. Professor van Bilsen sees his role in helping to put cardiac metabolism back on the map as his most important research contribution. He says, “In the 1970s and 1980s, cardiac metabolism was hot, but it was based purely on biochemical research. I think we managed to revitalise this topic by also including molecular aspects, in terms of transcriptional regulation.” Photograph courtesy of Professor Heinrich Taegtmeyer, MD, DPhil.
“We Have Managed to Revitalise the Topic of Cardiac Metabolism by Including Molecular Aspects”

Finding ways to improve cardiac metabolism may delay progression toward heart failure. Professor van Bilsen says, “I think every cardiologist would agree that the metabolism is crucial—the generation of energy to sustain contraction. It’s crucial for the normal functioning of the heart, so it’s logical that, when there are disturbances in metabolism, you will get cardiac dysfunction. So, that’s what happens during cardiac failure. The idea is that by learning about how metabolism is regulated, both at the biochemical and at the gene level—at the transcriptional level—we might find new targets for treatment of cardiac failure.”

Another evolving area of heart failure research involves multidisease and the metabolic syndrome. Professor van Bilsen’s group is trying to develop models of the metabolic syndrome that mimic the multidisease often seen in the elderly. He says, “There’s a large group of patients who develop heart failure that also have insulin resistance or type 2 diabetes, and I think that this is an area of research that’s going to be very fruitful in the coming years. It’s interesting to know what the impact is of insulin resistance on the heart. And, vice versa, if cardiac disease gives rise to, for instance, insulin resistance by itself.”

“Never Forget the Word Function When Doing Research”

“I think that in every institute, there has to be a good mix of basic research, translational research, and purely clinical research. You need the fertile soil of basic research for translational research to be able to flourish,” says Professor van Bilsen. He has found the trendy component of research annoying at times. He recalls with dismay the period when microarray research seemed fashionable and people conducted studies using a scattergun approach and says, “I think every good research has to be based on a hypothesis-driven approach and on conceptual thinking, and not purely on screening and looking for what’s popping up.” During another period, molecular biology seemed so fashionable that people did not receive sufficient training in old-fashioned integrative physiology. He says, “People were studying interesting mechanisms, but they didn’t know how to examine what the functional implications were of these changes in, for instance, gene expression or gene regulation. Molecular biologists can lose themselves in studying a gene and how it’s being regulated, but of course you always have to have some feeling about the relevance of a gene, how it works, and what it does.”

He adds, “Never forget the word function when doing research. Even if you are trained as a molecular biologist, you have to master physiological and pathophysiological concepts. I think it’s only then that you will learn how to apply science and how to address the correct and relevant questions.”

References

Jennifer Taylor is a freelance medical journalist.

The opinions expressed in Circulation: European Perspectives in Cardiology are not necessarily those of the editors or of the American Heart Association.
European Perspectives

Circulation. 2009;119:f61-f66
doi: 10.1161/CIRCULATIONAHA.109.192195
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/119/11/f61.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/