European Perspectives

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Pioneer: Johannes Waltenberger, MD, FESC

Investigating Vascular Endothelial Growth Factors and Their Receptors to Find New Therapeutic Targets to Prevent and Treat Atherosclerosis and Inflammatory Vascular Diseases

Johannes Waltenberger, professor and chair, Internal Medicine, Cardiology and Vascular Medicine, director, Division of Cardiology, managing director, Department of Cardiovascular Medicine, University Hospital Münster, University of Münster, Münster, Germany, talks to Judy Ozkan, BA.

A fascination with blood vessels informed and inspired the early research of Johannes Waltenberger, MD, FESC, professor and chair, Internal Medicine, Cardiology and Vascular Medicine, director, Division of Cardiology, managing director, Department of Cardiovascular Medicine, University Hospital Münster, University of Münster, Münster, Germany, and took him to Sweden, the Netherlands, the United Kingdom, and the United States. His plan was to contribute to the biological basis of this field through integrating his investigations with his work as an interventional cardiologist. He says, "In 1990, I started out as a basic scientist to identify novel targets for the stimulation of (cardio)vascular repair. This task was successful, and we identified novel receptors for vascular endothelial growth factor, a molecule that was completely unknown to the cardiology community at that time. I have since devoted the past 20 years to finding out all relevant aspects of vascular endothelial growth factor function in the context of metabolic and cardiovascular risk factors. These studies led to novel mechanistic insight into endothelial, monocyte, and stem cell function; opened novel avenues for cellular diagnostic risk assessment; and opened novel strategies for the optimisation of (cardio) vascular repair.

"Previously, as a student, I was impressed by the potential that molecular and cellular biology could contribute to medicine and cardiology. The mid- to late 1980s were a fascinating period in that respect. While at medical school at the University of Heidelberg, I did elective studies in Glasgow, Scotland; London, England; Little Rock, AR; Boston University, Boston, MA; and Harvard Medical School, Cambridge, MA. I gained substantial insights into how clinical cardiology and cardiovascular research can happen and interact." During this time, Professor Waltenberger was inspired by Peter Sleight, FRCP (see http://circ.ahajournals.org/content/115/20/f97), Philip Poole-Wilson, FRCP, FMedSci (see http://circ.ahajournals.org/content/119/8/f43), and Jane Somerville, FRCP (see http:// circ.ahajournals.org/content/115/14/f61), in England; and Edgar Haber, MD, Peter Libby, MD, and Thomas Ryan, MD, in the United States. Wolfgang Kübler, MD (see http://circ.ahajournals.org/content/121/25/f145), former chair of cardiology at Heidelberg University and Professor Waltenberger's first chief was another important early influence. Professor Waltenberger recalls, "He [Professor Kübler] sharpened my view on combining clinical and research work with the mantra, 'What is the clinical relevance of your investigation?'

"I started out looking for ways to directly and specifically stimulate the growth and regeneration of the endothelium. The most attractive system appeared to be peptide growth factors and their receptors. Several of these receptors, including

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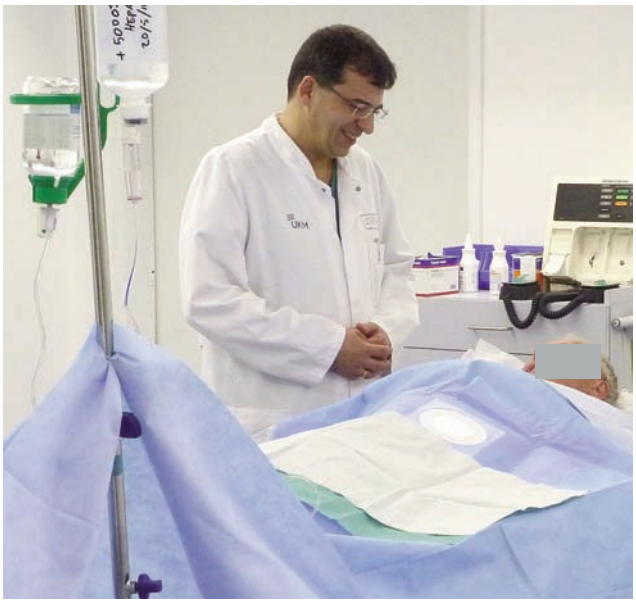
Supporting specific research projects in selected areas of emphasis that can be completed in predictable periods of time at universities and research institutes, primarily in Germany, with a special emphasis on junior researchers and also supporting international cooperation. **Page f29**





In January 2011, Professor Waltenberger was appointed chair of Internal Medicine, Cardiology and Vascular Medicine, and managing director of the Department of Cardiovascular Medicine at Münster University. In addition to day-to-day organisation of the department, his main responsibilities are direction of the Division of Cardiology, including its programme on interventional cardiology, its heart failure programme involving an active heart transplant programme, an intensive care programme for the whole Department of Medicine, a programme on vascular biology and a programme on cardiovascular imaging. He says, "Besides the Division of Cardiology, we have other specialised sections in the Department focusing on adult congenital heart disease, electrophysiology, vascular medicine, and the genetics of heart disease." Professor Waltenberger's main interest remains interventional cardiology and translational vascular science, from molecular mechanisms related to vascular cell function to risk prediction and risk reduction in patients with heart disease. Photo courtesy of Professor Waltenberger.

insulin receptor and the receptor for platelet-derived growth factor, had been cloned in that period, and the best place to carry out this research was the Ludwig Institute for Cancer Research, Uppsala, Sweden, where I started as a postdoctoral scientist in 1990.

"In the search for solid basic science training as the foundation for my career, I chose the European way. It was rather unusual in my generation because most young physician scientists of the 1980s went almost exclusively to labs in the United States. I had had experience in the United States, so I was keen to strengthen the European roots of my scientific career in Sweden with a network of international collaborators available there. This research period in Uppsala was a great opportunity both scientifically and socially, and I appreciate the continuous friendship of many of my Scandinavian colleagues. Carl-Henrik Heldin, MD, PhD, from the Ludwig Institute of Cancer Research became an important scientific mentor, whose humane approach to science was as valuable as it was ethical and rational. Over 3 years in the early 1990s, Dr Heldin taught me how to judge findings, explore hypotheses, organise research, and fill the gap between a fundamental and relevant question and its mechanistic explanation with honesty and modesty. One of his pearls of wisdom was to judge a scientist only at the end of his or her career because long-term achievements define a successful scientist." Dr Heldin's scientific ideal continues to guide Professor Waltenberger today. Lars Ryden, MD, PhD (see http://circ.ahajournals.org/content/118/10/f55) at the Karolinska Institute, Stockholm, Sweden, was also influential. Professor Waltenberger says of him, "I greatly appreciate both his analytical view and long-term vision."

Two other scientists have influenced Professor Waltenberger's way of thinking: Werner Risau, PhD, from the Max Planck Institute for Physiological and Clinical Research, Bad Nauheim, Germany, and Judah Folkman of Harvard Medical School. Professor Waltenberger says, "Werner [who died in 1998 at the age of 44 years] taught me that listening carefully to a student, which was me at that time, is an extremely important task for a professor, and that vision and ideas can often be more important than seniority or previous achievements. Judah taught me that real breakthroughs require courageous advocates and proper timing."

"If We Succeed In Manipulating Cellular Functionality, We May Be Able to Create Novel Therapeutic Perspectives for the Prevention and Treatment of Atherosclerotic and Inflammatory Vascular Diseases"

In 1993, Professor Waltenberger returned to Germany to Ulm to continue his clinical training in internal medicine and cardiology and to set up his own lab. He says, "We applied novel knowledge of vascular biology to clinically relevant issues, namely, the impact of cardiovascular risk factors on endothelial and vascular cell function and the elucidation of the underlying molecular mechanisms. This topic turned out to be of significant interest, especially when there was a great interest in vascular gene therapy in the late 1990s and cell therapy during the past decade." Over the past decade, the team has moved with Professor Waltenberger from Germany to Maastricht, the Netherlands, and back again, presenting some logistic challenges for all concerned.

The move from Ulm to Maastricht in 2003 was planned for 6 months in advance when Professor Waltenberger was appointed professor of cardiology and invasive cardiology at Maastricht University and principal investigator at the Cardiovascular Research Institute Maastricht. During this time, Professor Waltenberger continued to integrate his basic scientific line into the clinical arena with numerous external cooperations. This scientific period was fruitful. Basic research work was complemented by high-profile clinical studies in the cath lab, including a first-in-man myocardial infarction study to test the concept of pacing-induced postconditioning in the clinical setting.[1] The concept was developed by Frits W. Prinzen, PhD, at Maastricht University, and the work represented true translational cardiology.

Although ≈4 team members made the move from Germany to the Netherlands, it was necessary to rebuild the group in Maastricht. The move was challenging in terms of organisational requirements and funding structures. A minor

Professor Waltenberger with his basic, clinical, and translational molecular biology lab team, including Evangelia Pardali, PhD, Nynke van den Akker, PhD, Rinesh Godfrey, PhD, Tobias Weis, MD, Wisam Iraqi, MD, Dieter Fischer, MD, and Hans-Jörg Hippe, MD. Professor Waltenberger suggests that a shared vision, a sense for excellence, and personal trust are the requirements for a successful team. Photograph courtesy of Professor Waltenberger.

issue was the policy in the Netherlands of only accepting medical qualifications from European Union countries. This caused problems for those researchers who wished to move but whose qualifications were not recognised in the Netherlands even if they obtained a Dutch passport.

When Professor Waltenberger returned to Germany and the University of Münster in January 2011 as chair of the Division of Cardiology and managing director of the Department of Cardiovascular Medicine, some former team members were keen to be re-enrolled. Evangelia Pardali, PhD, a key researcher in the basic science lab group, moved back to Germany. The group is now up and running, but it has not yet reached "cruising altitude," and Professor Waltenberger is looking to recruit 1 or 2 talented research and clinical scientists to create a better integrated group on vascular development.

The lab's focus is the role of growth factors and cell function in vascular development and repair. Among the team's most important achievements are the identification and characterisation of novel targets for stimulating vascular repair and vascular growth. The team identified and characterised 2 vascular endothelial growth factor receptors, identified their functional role in vascular endothelium in health and disease, and elucidated their roles in atherosclerosis and cancer to some extent. This research has come to fruition over the past decade, with results published in *Circulation*, *Nature Medicine*, and the *Journal of Biological Chemistry*.[2–6]

The team is currently identifying and characterising mechanisms of risk factor-related growth factor resistance to better assess the functionality and integrity of the vascular system. These efforts may lead to the introduction of novel diagnostic tests. Professor Waltenberger says, "If we succeed in manipulating cellular functionality, we may be able to create novel therapeutic perspectives for the prevention and treatment of atherosclerotic and inflammatory vascular diseases."

Important external collaborators include Frank-Dietmar Boehmer, PhD, of the University of Jena, Jena, Germany; Mark Post, PhD, Professor Prinzen, and Hugo ten Cate, MD, PhD, of Maastricht University; Lena Claesson-Welch, PhD, of Uppsala University; Peter ten Dijke, PhD, of Leiden University, Leiden, the Netherlands; Peter Carmeliet, MD, PhD (see http://circ.ahajournals.org/content/122/1/f1), of the University of Leuven, Leuven, Belgium; Gerard Pasterkamp, MD, PhD (see http://circ.ahajournals.org/content/118/18/f103) of the University of Utrecht, Utrecht, the Netherlands; Masabumi Shibuya, MD, PhD, of the University of Tokyo, Tokyo, Japan; Alexander Levitzki, PhD, of the Hebrew University, Jerusalem, Israel; Hans Schoeler, PhD, Lydia Sorokin, PhD, Otmar Schober, MD, PhD, and Michael Schäfers, MD, of the University of Münster; Charles Lapière, MD, PhD, of the University of Liège, Liège, Belgium; and Juleen Zierath, PhD, and Kenneth Caidahl, MD, PhD, of the Karolinska Institute.

"The Major Lesson I Have Learned Is That the Set of Circumstances and Rules Comes as a Package, Which Makes It Almost Impossible to Compare Single Aspects in Different Systems With Each Other Unless One Knows Why Things Are the Way They Are"

Professor Waltenberger's first-hand experience of training and working abroad has given him a unique view of how things are done in other countries. He explains, "Health systems and the organisation of the scientific community follow quite different rules in different countries. I have experience of the systems in Germany, the Netherlands, and Sweden. The bottom line is that there are different rules and different 'games.' Although the final outputs are rather comparable (ie, treating patients and producing scientific deliverables), one needs to respect the different rules and adopt accordingly. The major lesson I have learned is that the set of circumstances and rules comes as a package, which makes it almost impossible to compare single aspects in different systems with each other unless one knows why things are the way they are. And there are always good reasons that things are the way they are. In my personal experience, it takes several years to fully appreciate all different aspects and to make use of this knowledge."

Professor Waltenberger plays an active role in the European Society of Cardiology. He says, "The European Society of Cardiology has facilitated a number of ideas, and I fully supported it, even in the early 1990s, where the number of basic science-interested delegates was rather limited at annual meetings. It was right to build on this idea and its success over recent years has proven this was right. I was especially glad that I was elected as a councillor to

Professor Waltenberger with his daughter (right), who is following in her father's footsteps by studying medicine in Heidelberg, and his son (left), who is finishing high school with a view to becoming a physician. The most important influence in Professor Waltenberger's life has been his wife of 23 years, Marion Waltenberger, a master of arts in German literature and theology. He says, "Marion has followed and supported my work at each stage. We got to know each other at a summer school on Europe in 1985, and we decided to make this a programme for our common lives. Europe is so rich in cultural diversity, but it still combines strong common convictions. Exploring this fascinating cultural heritage is a continuously rewarding experience for both of us." The couple has lived >3 years in Uppsala, >10 years in Ulm, Germany, and ≈8 years in Maastricht, and in 2011, they moved to Münster. Marion is now preparing for her second career in psychological counselling. Professor Waltenberger was the first in his family to embark on a career in medicine. He says, "My relatives were farmers, craftsmen, and engineers; nevertheless, many of them shared a pioneering spirit, combined with the endeavour to serve their communities and environments." Professor Waltenberger enjoys family life, sports, and flying model aircraft. He is also a keen trumpet player and is currently looking for an orchestra and/or ensemble in Münster. Photograph courtesy of Professor Waltenberger.

the European Society of Cardiology Board in 2008." Professor Waltenberger is currently a member of the European Society of Cardiology Congress Programme Committee and secretary for the Council on Basic Cardiovascular Science.

During his career, Professor Waltenberger has received a number of awards, including the Oskar-Lapp-Award of the German Cardiac Society in 1994, the Young Investigator Award of the European Vascular Biology Association in 1995, the Merckle Research Award in 1996, the Eberhard-Betz-Award of the German Society for Atherosclerosis Research and the Heinz-Meise-Award of the German Heart Foundation in 1997, the Prevention Award of the German Heart Aid in 1998, the Science Award of the City of Ulm in 1999, the Heisenberg Award of the German Research Council in 2000, the Franz-Loogen-Award in 2001, and the Silver Medal of the European Society of Cardiology in recognition of his service as a councillor on the European Society of Cardiology Board.

Professor Waltenberger believes that there is an optimal time for the role of clinician, academic, and researcher to come to the fore in the course of a career. "I could imagine being a full-time clinician again, and I have worked as a full-time scientist, albeit 20 years ago, and I still have great friends in both worlds. In isolation, I would miss the other roles, and I am glad that academic medicine offers the chance to combine these roles in an integrated fashion. I regard teaching as an intrinsic aspect of any professional activity of excellence. Being a professional, I have to take care about the next generation; moreover, teaching offers the chance to reflect on the priorities of one's own academic and professional concepts. The past 25 years have been characterised by a tremendous development of medicine in general and cardiology in particular. I am glad that I could actively follow this development and that I was able to contribute a small part."

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