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Spotlight: Axel Pries, MD, PhD, FESC

"Arteriogenesis Is the Most Potent Biological Process for Fighting Myocardial Underperfusion Due to Arterial Occlusion"

Axel Pries, head of the Institute for Physiology at Charité, Berlin, Germany, General Secretary of the European Society for Microcirculation, and chair of the Council on Basic Cardiovascular Science of the European Society of Cardiology, talks to Mark Nicholls.

As a leading expert in vascular biology and microcirculation, Axel Pries, MD, PhD, FESC, head of the Institute for Physiology at Charité, Berlin, Germany, General Secretary of the European Society for Microcirculation, and chair of the Council on Basic Cardiovascular Science of the European Society of Cardiology, is continually working with colleagues and collaborators to generate research that could lead to new therapeutic strategies. With key research interests that include rheology, vascular adaptation, endothelial cell biology, and tumour microcirculation, he is endeavouring to translate microcirculatory concepts to the clinical setting.

Professor Pries' interest in cardiovascular science was shaped at an early stage of his medical training as a result of discussions on key issues of the microcirculation with his mentor, Professor Peter Gaehtgens, MD, PhD, at the Physiological Institute, University of Cologne, Cologne, Germany. Further inspiration was provided by the early research of physiologists such as Otto Frank and Ernest Starling, whose work resulted in the Frank–Starling law of the heart and the "fascinating strong link between mechanical, molecular, cellular, and physiological mechanisms." He adds, "Also, the cardiovascular field field has a lot of visual aspects and the microcirculation is beautiful to look at."

Professor Pries explains, "I started in physiology because I wanted to understand the mechanisms behind the many facts you have to learn as a medical student. At that

Professor Pries with his most important and inspirational colleague, Professor Timothy W. Secomb, PhD, from the Department of Physiology at the University of Arizona, Tucson, Ariz, at the first Frontiers in Cardiovascular Biology *meeting in 2010. They have been collaborating since the early 1980s. Professor Pries says, "I know him from my postdoctoral stage in Cologne. He is a gifted mathematician with the determination to apply his knowledge to problems of biological significance. We have established a fruitful exchange with both of us using a mutual set of tools, approaches, and knowledge. I stay with him in Tucson usually 1 month every year. This is the most productive time of the year for me in scientific terms." Photograph courtesy of Professor Pries.*

On other pages...

Young Investigator Spotlight: Radoslaw Debiec, MD
Polish-born and trained Dr Debiec, a PhD student at the Department of Cardiovascular Sciences, University of Leicester, Leicester, England, won the Young Investigator Award for Population Sciences at the 2010 European Society of Cardiology Congress in Stockholm, Sweden. For his PhD he is investigating the genetic control of the urotensin II signalling pathway in the predisposition to hypertension and its renal complications.
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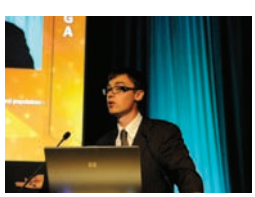

Photographs from the Frontiers in Cardiovascular Biology *meeting in 2010 in Berlin, Germany. Professor Pries says, "Over the years, I have found it relevant and rewarding to maintain and develop mechanisms of exchange, discussion, and support for younger colleagues. The work for the Council on Basic Cardiovascular Science has allowed us to bring together scientists from different European societies and working groups within the European Society of Cardiology. A recent result was the first* Frontiers in Cardiovascular Biology *meeting in 2010 in Berlin. These meetings provide a forum for exchange in the entire field of cardiovascular basic (and translational) science in a relaxed atmosphere with a strong focus on the needs of our younger colleagues."* Left, *Professor Pries organising the first* Frontiers in Cardiovascular Biology *meeting with European Society of Cardiology staff. He comments, "This kind of work is taking quite a bit of my time, but it is necessary for the field and worthwhile."* Right, *In the anatomy lecture room at the first* Frontiers in Cardiovascular Biology *meeting 2010 in Berlin. Professor Pries says, "The setting was academic to maintain the scientific atmosphere and keep prices low for younger colleagues." Photographs courtesy of Gina Pries.*

time in the 1970s, the development of molecular biology was still in its infancy, and physiology provided explanations for many observations in healthy and ill organisms."

Professor Pries recalls, "In the following years, I was fascinated by the intimate link of biology, physics, and mathematics ruling the 'microcirculatory' world. I became intrigued by the fact, which is very obvious on the small microcirculatory scale, that vessels are plastic and remodel on different timescales in response to their environment. However, in an adaptive system, the endpoint of adaptation is only determined by the local conditions and adaptive rules. There is no guarantee of the 'proper' result, or even of stability, if the rules are not right. There is no blueprint to check and correct the results. An example for the vascular system is the overenlargement of short arteriovenous connections, leading to shunting of blood away from the parenchymal tissue and maldistribution of flow in tumours."[1]

Born in Cologne in 1954, Professor Pries trained at the University of Cologne Medical School from 1973 to 1980, and he went on to hold a number of positions at the Department of Physiology at the Free University Berlin, becoming an associate professor in 1995 and joining the Institute of Anaesthesiology, German Heart Institute Berlin, from 1997 to 1998. He became a full professor in the Department of Physiology at the Free University Berlin in a liaison with the German Heart Institute Berlin, which financed the professorship. He says, "The opportunity to work with Professor Hermann Kruppe (MD, PhD), of the German Heart Institute Berlin, was important for me in that I was able to create a group of my own and to start independent research, and we still work together." Professor Pries and Professor Kuppe have cooperated since 1995, generating a research environment to translate microcirculatory concepts to the clinical setting and to support younger scientists entering the area.

Since 2002, Professor Pries has been head of the Institute of Physiology, 1 of 3 physiological institutes of the Charité, Berlin, where his tasks involve organisation, teaching, research, and working for national and international scientific organisations, such as the European Society of Cardiology. He is responsible for ≈20 employees, and is involved in the restructuring process underway at the Charité, including planning for a new preclinical research facility. He also teaches physiology to students at Charite. He has no clinical commitments, and senses the loss of this aspect of medical life at times because he considers treating patients as "highly rewarding." However, the freedom and thrill of science are strong compensations, and he remains extremely interested in translational research, hoping that discoveries and developments will eventually have an impact on patient wellbeing.

"We Recently Showed That Specific Pulsatile Flow Patterns Are Crucial for Arterial Development"

Professor Pries' main areas of research are modelling of vascular adaptation, the endothelial surface, endothelial cell biology, and the microcirculation in tumours and clinically.

With a few researchers in his institute focusing on each of these areas, his major contribution is in modelling, where he conducts a large part of the development in cooperation with Professor Secomb and younger researchers.

Areas of particular interest for Professor Pries are vascular adaptation, arteriogenesis, and angiogenesis. He says, "A main concept here is the fact that the number of vessels or overall volume, alone, does not guarantee effectiveness of vascular networks. Adequate function of terminal vascular beds depends critically on the exact adjustment of vessel diameters by adaptive processes. Relative to research on angiogenesis, adaptive reactions (angioadaptation) are somewhat neglected under terms such as 'maturation' or 'remodelling.' This situation may be involved in some of the disappointments with therapeutic approaches in the area. Angioadaptation is also closely linked to the natural possibility of the recent vascular system to develop collaterals from smaller existing vessels. This arteriogenesis is the most potent biological process for fighting so-called myocardial underperfusion due to arterial occlusion, but gets surprisingly little attention in vascular biology. In this context, we recently showed that specific pulsatile flow patterns are crucial for arterial development."[2]

Professor Pries with colleagues at an international microcirculation/oxygen transport conference in Japan. From left to right, back row: Makoto Suematsu, Roland Pittman, Axel Pries, Ryon Bateman; front row: Naoharu Takano, Christopher Ellis. Professor Pries says, "There are things in science beyond science: good company, longstanding friends, and, sometimes, a beer in a nice setting." Photograph courtesy of Professor Pries.

"The Endothelium in Vivo Is Covered by a Thick, Fragile, Gel-Like Layer, Which, Among Other Effects, Influences Flow Resistance, Inflammation, and Permeability"

Professor Pries describes his research on endothelial surface and endothelial cell biology as follows:[3] "A major focus is investigation of the so-called 'endothelial surface layer' or 'glycocalyx.' A number of studies have shown that the endothelium in vivo is covered by a thick (≈0.5 μm), fragile, gel-like layer, which, among other effects, influences flow resistance, inflammation, and permeability. We have shown that this layer is compromised by artificial infusion fluids, and there are data that show that conditions such as diabetes mellitus or hypertension also have a negative effect. The layer's fragile nature has made it difficult to thoroughly investigate its composition and involvement in vascular pathophysiology. However, its functional and pathological importance makes its study crucial to understanding endothelial biology in cardiovascular medicine."

In addition, working with the German Heart Institute Berlin, Professor Pries' team is endeavouring to improve the measurement options for microcirculatory phenomena in humans. Professor Pries has also conducted a significant amount of research on tumour microcirculation.

Professor Pries points to a number of articles that have been among the most enjoyable to work on and are his most important. He says, "It is difficult to select articles based on the 'fun factor,' because a main incentive in science is the enduring pleasure in exploring new territory and the freedom to do so driven by your own concepts and thoughts." Professor Pries is also aware that at times a lot of energy and persistence can and has to be used in discovering "less beaten" paths, which may at times end in a "dead end street" in the pursuit of scientific breakthroughs. He adds, "If you look at it from the other end, one great pleasure of research is to see a concept resulting in a decent article, which hopefully is helpful for others in developing science and medicine."

Professor Pries reflects on a 1981 article[4] describing model studies on phase separation at a capillary orifice as particularly rewarding. He says, "This was my first 'own' work, and the smell and feel of science were still new. Being naive and not knowing much about all possible problems, and with all my time at my hands, I could experiment and explore new territory. I tell my younger colleagues to cherish the time before administration catches up with them."

The first collaboration with Professor Secomb resulted in a 1990 *Circulation Research* article analysing blood flow in the microcirculation by bringing together experimental data with computer modelling.[5] Other important articles established a set of adaptation "rules" explaining the experimentally found vascular patterns of vessel diameters and wall thickness throughout microvascular networks.[6,7]

A piece of collaborative research that Professor Pries believes has had the most impact on his work and the way

Professor Pries with his wife Gina, at the first Frontiers in Cardiovascular Biology *meeting 2010 in Berlin. Gina is a photographer and physiotherapist. They have 2 daughters, Cara and Nicole, and have lived in Berlin since 1982. Professor Pries says, "Without continuous support and a safe haven, the demanding scientific life is not sustainable." Away from medicine, Professor Pries enjoys woodwork and woodturning, black and white photography, and playing the piano. Photograph courtesy of Professor Raffaele de Caterina.*

he thinks examined the design principles of vascular beds.[8] He explains, "This was the starting point for our approach to address angioadaptation. The idea to do so came from the experimental finding that shear stress was related to intravascular pressure, irrespective of vessel type, and declined by about 1 order of magnitude from the arterial to the venous end of the microvascular networks. This work was related to our appreciation of the fundamental difference between a 'blueprint' approach and the investigation of adaptive systems. We were asking ourselves what the local biological mechanisms could be to establish this overall pattern in the absence of a blueprint. The idea was that local vascular adaptation rules should be at the heart of the phenomenon."

"There Is a Need to Better Understand the Complexity Underlying Pathophysiological Events and to Develop Corresponding Treatment Concepts"

Professor Pries enjoys his research, and is happiest when he has the feeling "that something completely new is starting to surface during the work." He has won a number of awards, including the 1980 Thesis Award, Hochhausstiftung, Medical Faculty, University of Cologne; the Abbott Microcirculation Award, European Society for Microcirculation in 1986; and the International Society for Clinical Haemorheology and Laboratoire L. Lafon Haemorheology-Microcirculation Award in 1995 for his work on the article "Resistance to Blood Flow in Microvessels *in Vivo*."[9]

Professor Pries advises young people wanting a career in medicine and cardiology to look for the right environment to work in at an early stage, whether that is in science or cardiology. He says, "When I started, I thought just being interested and working hard would be good enough, but if you really want to be involved in something that is of value and have a chance to make a career, then you have to look for good teachers and advisors who are successful in their own research, and willing to share their knowledge with the next generation. Whatever you do, you have to love it, and if you feel that it is not right for you, look around for something else." As for his own future, Professor Pries aims to continue working at the "forefront of scientific endeavour" and following up the work of recent articles on tumour microcirculation and the endothelial surface layer.

For future developments in cardiovascular science, Professor Pries is anxious for authorities to continue to fund less orthodox and recognised areas of research as well as mainstream projects. He explains, "Really groundbreaking developments normally come from an area where you do not expect them. In my own field of work, I believe in the future we will have to recognise complexity in a deeper sense than we did. In the past, we have tended to neglect complexity and simplify things. There is a need to better understand the complexity underlying pathophysiological events and to develop more complex treatment concepts." Professor Pries also believes cardiology will have to adapt to a more patient-specific approach that takes into account the way patients differ from each other.

References

1. Pries AR, Höpfner M, le Noble F, Dewhirst MW, Secomb TW. The shunt problem: control of functional shunting in normal and tumour vasculature. *Nat Rev Cancer*. 2010;10:587–593.
2. Buschmann I, Pries A, Styp-Rekowska B, Hillmeister P, Loufrani L, Henrion D, Shi Y, Duelsner A, Hoefer I, Gatzke N, Wang H, Lehmann K, Ulm L, Ritter Z, Hauff P, Hlushchuk R, Djonov V, van Veen T, le Noble F. Pulsatile shear and Gja5 modulate arterial identity and remodelling events during flow-driven arteriogenesis. *Development*. 2010;137:2187–2196.
3. Pries AR, Kuebler WM. Normal endothelium. *Handb Exp Pharmacol*. 2006;176:1–40.
4. Pries AR, Albrecht KH, Gaehtgens P. Model studies on phase separation at a capillary orifice. *Biorheology*. 1981;18:355–367.
5. Pries AR, Secomb TW, Gaehtgens P, Gross JF. Blood flow in microvascular networks: experiments and simulation. *Circ Res*. 1990;67:826–834.
6. Pries AR, Secomb TW, Gaehtgens P. Structural adaptation and stability of microvascular networks: theory and simulations. *Am J Physiol*. 1998;275:H349–H360.
7. Pries AR, Reglin B, Secomb TW. Remodeling of blood vessels: responses of diameter and wall thickness to hemodynamic and metabolic stimuli. *Hypertension*. 2005;46:726–731.
8. Pries AR, Secomb TW, Gaehtgens P. Design principles of vascular beds. *Circ Res*. 1995;77:1017–1023.
9. Pries AR, Secomb TW, Gessner T, Sperandio MB, Gross JF, Gaehtgens P. Resistance to blood flow in microvessels *in vivo*. *Circ Res*. 1994;75:904–915.

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