Spotlight: Ursula Ravens, MD, PhD, FESC, FAHA

“Until We Understand How to Prevent Arrhythmias and the Associated Morbidity and Mortality, There Will Be a Need to Study Electrophysiology and the Associated Pharmacology”

Ursula Ravens, professor of pharmacology and toxicology and head of the Department of Pharmacology and Toxicology, Technical University of Dresden, Dresden, Germany, talks to Judy Ozkan, BA.

In a research career that spans 5 decades, Ursula Ravens, MD, PhD, FESC, FAHA, professor of pharmacology and toxicology and head of the Department of Pharmacology and Toxicology, Technical University of Dresden, Dresden, Germany, has published >250 articles, including many important articles on ion channels and beta-adrenoceptors in the heart and stem cells. She suggests, however, that her most important article is her first article,1 which has been cited >100 times and resulted from her thesis, which won the “Best Medical Thesis of the Year” prize at her medical school (Albert-Ludwigs University of Freiburg, Freiburg, Germany) in 1968. Professor Ravens recalls, “I was thrilled to achieve a simultaneous recording of length, force, and membrane potential. We found that stretching the myocardium depolarised the cells and induced pacemaker action potentials. Upon release of stretch, the muscle became quiescent again, and electrical stimulation evoked normal ventricular action potentials.”

Despite being intrigued by calcium antagonism and being taught by the late Albrecht Fleckenstein, MD, professor of physiology, later known as the “father of calcium antagonism,” Professor Ravens (née Theophile) chose stretch-induced automaticity in isolated cardiac tissue from the Rhesus monkey for her thesis because the supervisor, the late Raimund Kaufmann, MD, who ran the electrophysiology lab, was an inspirational teacher who enthused his students so that they felt they were working at the forefront of science. Professor Ravens says he was instrumental in her decision to do research before specialising in a clinical discipline. She comments, “I was very happy in the early days in Freiburg because I thoroughly enjoyed electrophysiological experiments. I was fascinated to see how one could measure a biological parameter and establish a functional relationship between, say, stretch and pacemaker activity. It was great to be an accepted member of the team.”

Eventually We Were Very Proud of Our Articles on Human Cardiomyocytes and Reporting Heterogeneity of Transient Outward Currents Within the Ventricular Wall and Differences Between Atria and Ventricles

After final exams in Freiburg in 1969 and a year of internship in Berlin, Germany, Dr Ravens moved to the University of Kiel, Kiel, Germany, where her then boyfriend had a post in internal medicine. She achieved registration as a physician in 1970 and joined the group of Heinz Lüllmann, MD, professor of pharmacology. He was known for his work on cardiovascular drugs and calcium, and Dr Ravens’ first project was on the structure and activity relationships of digitalis glycosides. She says, “We wanted to know whether electrophysiological and contractile effects could be disassociated to arrive at drugs with preserved inotropic effects but less proarrhythmogenic potential.” During her 15 years at the University of Kiel, Dr Ravens published a number of important articles on the...
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projects with generous funding for staff and facilities. She moved to Dresden. The move offered her the chance to pursue multiple lines of research and continue her work on human cardiomyocytes, her extensive knowledge, and heart failure. She recalls, “Sian’s dedication to the study of human cardiomyocytes, her extensive knowledge, her brilliant interpretations of experimental results, her perfect time management, and her subtle humour—the list could be extended endlessly—impressed me and has led to a lifelong friendship.”

In 1997, Professor Ravens took up her current post in Dresden. The move offered her the chance to pursue multiple projects with generous funding for staff and facilities. She regrets that recent economic constraints are now limiting the scope and extent of her team’s work. Much of her work then focused on electrical remodeling in chronic atrial fibrillation with description of $I_{Kur}$ and constitutively active $I_{K,AC}$, as putative new drug targets for treating atrial fibrillation. At Dresden, Professor Ravens has also built up a group researching stem cells with the eventual aim of differentiating cardiomyocytes from adult (human) progenitor cells of various sources. She says, however, “Our major problem was that we could never to any appreciable extent reproduce in-vitro cell differentiation into a cardiomyocyte-like cell that had been published by so many others! Nevertheless we have published a few articles on the topic in regenerative medicine.”

In 2000, Professor Ravens became involved in the modernisation of the medical curriculum in collaboration with the Harvard Medical School Association. “He [Dr Kaumann] Is a Fine Example of How Simple Experimental Methods Like Measuring Force of Contraction in Isolated Atrial Muscle Strips Are Still Useful for Resolving Pharmacological Problems If the Results Are Interpreted by a Brilliant Mind”

Many other teachers, colleagues, and collaborators have inspired Professor Ravens. In 1968, she received a scholarship from the German Academic Exchange Service to work in the lab of the legendary German-American cardiologist Richard Bing, MD, at Wayne State University, Detroit, Mich. Professor Bing, who celebrated his 100th birthday in 2009, had just established the $^{84}$Rb method to measure coronary perfusion in dogs and humans. Professor Ravens recalls, “He regularly took us on his rounds in the downtown receiving hospital, and he seemed to have perfected the balance and combination of experimental and clinical medicine.”

While in Detroit, Professor Ravens met her husband, Kurt-Günther Ravens, MD, a research fellow from Germany, who later was head of the Department of Internal Medicine in a large community hospital in Hanover, Germany, until he retired in 2004. They have 1 daughter, Kathrin, who studied civil engineering and married a fellow civil engineer. Professor Ravens says, “She declared that she would never study medicine because she did not want her father
and mother to always know better.” The occasional need to spend time away from her family when her daughter was young was particularly difficult for Professor Ravens, who is grateful for her husband’s ongoing help and support. In 1985, for example, Professor Ravens commuted between the family home in Hanover and Essen University.

Other inspirational figures for Professor Ravens include Johanna Janke, MD, in the Department of Physiology, who was the first woman at Freiburg University to do her habilitation qualification in physiology. Professor Ravens recalls that Dr Janke’s lectures on muscle physiology were presented like a crime story, leaving the audience hungry for the next discovery.

Gerrit Isenberg, MD, was also important. She explains, “He taught me the single-cell voltage clamp technique in the early 1980s and how to measure cell shortening. I invited myself to his lab in the Department of Physiology chaired by Wolfgang Trautwein MD, in Homburg, Saarland, Germany. I used to take the night train to arrive early Monday morning and travel back on Friday evening. After 1 week in Homburg, I analysed the countless paper tracings for a few weeks at home before I returned to Homburg for another week of day and night experimentation until we had enough data for our first publication on the ATX II-induced inhibition of sodium channel inactivation. I enjoyed the freedom of all-day work without any family duties. Gerrit was a strict but generous teacher and still is a good friend.”

Alberto Kaumann, MD, PhD, Department of Physiology, Development and Neuroscience, University of Cambridge, Cambridge, England, is also a notable influence. Professor Ravens says he is a “treasure trove of knowledge on the pharmacology of cardiac adrenoceptors and serotonin receptors.” She says, “I have had the pleasure of hosting him at regular intervals ever since I moved to Dresden. He is one of the few senior scientists who regularly performs his own experiments and he has worked with some of the most excellent scientists in cardiovascular pharmacology. He is a fine example of how simple experimental methods, like measuring force of contraction in isolated atrial muscle strips, are still useful for resolving pharmacological problems if the results are interpreted by a brilliant mind. I share with him what he calls the ‘libido’ for science and music. Science and piano playing, especially Bach, are his life-long obsessions.”

Professor Ravens is active on the editorial boards of a number of pharmacological and cardiovascular journals, and chaired the European Working Group on Cardiac Cellular Electrophysiology from 1996 to 1998. She has also been active on the steering panel of the German Cardiac Society. In 1991 she was made an honorary professor of cardiology of the Military Postgraduate Medical School in Beijing, China, and in 2001, she was elected to the Leopoldina Academy of Sciences (the German “National Academy of Sciences”). She was recently given a Doctor Honoris Causa of Szeged University, Szeged, Hungary. She advises her students and fellows to work hard and “enjoy the beauty of a successful experiment.”

Now nearing retirement, Professor Ravens is winding down projects but would like to see some success with her team’s work relating to stem cells and regenerative medicine before she leaves. She says, “I find it hard to imagine a life without work, and yet there are so many other aspects I would like to catch up with, such as reading and travelling. Last, but not least, I would love to be a grandmother.” Professor Ravens’ many interests outside work include gardening, classical music, theatre, and opera, and she enjoys cooking, especially Chinese food. Given more time, she says she would have liked to develop new technology. Imaging, electron microscopy, lipid membranes, and molecular motors have always fascinated her.

For the future, Professor Ravens says, “Until we understand how to prevent arrhythmias and the associated morbidity and mortality, there will be a need to study electrophysiology and the associated pharmacology.”

References

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Team 2010: Professor Ursula Ravens’ Research Group, University of Technology, Dresden, Germany

“Although the Long-Awaited Breakthrough Has Not Yet Been Reached, Lab Life Is Pretty Exciting These Days”

Ursula Ravens, MD, PhD, FESC, FAHA, professor of pharmacology and toxicology and head of the Department of Pharmacology and Toxicology, Technical University of Dresden, Dresden, Germany, describes the team to Judy Ozkan, BA.

For a team to work, Ursula Ravens, MD, PhD, FESC, FAHA, professor of pharmacology and toxicology and head of the Department of Pharmacology and Toxicology, Technical University of Dresden, Dresden, Germany, says, “There must be trust among team members. Fostering an environment of enquiry, encouragement and support is the best way to get good results from a team. The great thing about teamwork is the inspiration that can come during discussion of the work.”

Although Professor Ravens suggests that electrophysiologists are usually “lone fighters” and do not usually work as part of a team, she says that their work does need to be complemented with insights from specialist colleagues.

Professor Ravens’ main areas of interest are electrical remodeling in cardiac disease, cardiovascular pharmacology receptor theory, inverse agonism, the functional role of cardiac ion channels and their pharmacological modulation, the regenerative potential of stem cells in the cardiovascular system, and species differences in the pharmacological modulation of detrusor muscle function. She highlights her team’s main achievements as drug actions in human myocardium in health and disease,1,2 contributions to cardiac electrophysiology and remodeling in atrial fibrillation,3–5 and getting down to earth again from the hype of cardiac differentiation of stem cells.6–8 New developments have been the reorientation of the Department of Pharmacology towards cardiovascular diseases and the beginning of work with human atrial tissue, as well as digging into the remodeling processes during atrial fibrillation.

Professor Ravens’ lab is always open to friends and visitors such as Alberto Kaumann, MD, PhD, from Cambridge, England, “who roams labs all over the world.” The Dresden team also enjoys collaborations with colleagues in England, Canada, Hungary, Italy, and Denmark, and offers research opportunities to young scientists from other countries. Its expertise in human atrial cardiomyocytes has attracted numerous scientists including Cristina Moreno, MD, from Spain (from the lab of Carmen Valenzuela, PhD); Maura Greiser, MD, from the Netherlands (from the lab of Ulrich Schotten, MD, PhD); Norbert Iost, PhD, and Peter Kovacs, MD, PhD, from Hungary (from the lab of Andras Varro, MD, PhD); and Reza Waikili, MD, from Germany (from the lab of Stefan Kääb, MD, PhD). In exchange, Susanne Radicke spent 2 years at the University of Piedmont, Novara, Italy, learning site-directed mutagenesis on ion channels before moving to the University of Leipzig, Leipzig, Germany.

A Wide Range of Experience and Expertise in Cardiac Cellular Electrophysiology and Pharmacology

Professor Wettwer, shown above, is the most senior member of Professor Ravens’ team. Dobromir Dobrev, MD, PhD, professor of pharmacology and a medical doctor, is another
senior member of the team, but will leave in 2010 to build up his own division of experimental cardiology at Mannheim University, Mannheim, Germany. He started training in neuropharmacology with Professor Ravens’ predecessor at Dresden but turned to cardiovascular topics, specifically atrial fibrillation, under her supervision. He has constructed an extensive network of worldwide collaborations and introduced some biochemical techniques to the group. Professor Ravens says, “He has a very successful publications record, as highlighted by his recent invited review in *Lancet*,¹⁰ and is an all-round gifted pharmacology teacher.”

Torsten Christ, MD, PhD, is a clinician specialising in internal medicine and teaches the postgraduate habilitation qualification in pharmacology. He joined Professor Ravens’ group in 1999 because he was looking for a place to do research on stimulating autoantibodies against beta-adrenoceptors, which are found in some patients with dilated cardiomyopathy. Professor Ravens comments, “His good clinical connections are instrumental to obtaining complete patient data sets. He has a strong interest in cardiac excitation–contraction coupling and is brilliant at practical experiments.”

Niels Voigt, MD, PhD, and Birgit Eichhorn, PhD, are postdocs. Professor Ravens says, “Niels will follow Professor Dobrev to Mannheim. He worked in the atrial fibrillation group, visited Stanley Nattel’s [MD, PhD] lab in Montreal, Canada, for a productive research summer, and collaborated with David Eisner [MD, PhD] and Andrew Trafford [BVSc, CertVA, PhD] in Manchester, England, on calcium transients in human atrial cardiomyocytes. Birgit was the smooth muscle specialist of the group but got excited about medical genetics and has moved on to work in a large community hospital in Dresden. For the next academic year we are hoping to attract a medical postdoc for our atrial fibrillation programme.” Ukrainian PhD student Nadiia Rozmaritsa is working on interactions between nitric oxide and human atrial calcium handling proteins.

Professor Ravens continues, “Working very hard in the area of regenerative medicine is Claire Poulet, from France, who is about to finish her PhD on the cardiogenic potential of skeletal muscle-derived stem cells. She has demonstrated how these cells possess both skeletal muscle and cardiac properties. She is also convinced that immunohistochemistry does not provide stringent proof of cardiomyocytes, but that you need electrical and mechanical function as well. Stephanie Protze has found that adipose tissue-derived stem cells develop to express a lot of cardiac markers but still do not provide ‘beating’ cardiomyocytes. She has started a huge programme on direct reprogramming of adult cells with a combination of several cardiac transcription factors. Last but not least, Lu Liang, from China, wants to find out whether regular stretching and electrical stimulation will sufficiently simulate a ‘cardiac niche’ to cause differential changes in stem cells. These students work along a similar theme—how can progenitor or any other cells be pushed towards myocardial differentiation? Although the long-awaited breakthrough has not yet been reached, lab life is pretty exciting these days.”


Judy Ozkan is a freelance medical journalist.