Pioneer in Cardiovascular Research: Sian Harding, BSc, PhD, FESC, FAHA, FISHR, FSB

Developing a New Stem Cell-Based In Vitro Model of the Human Ventricular Myocyte to “Give Us the Capability to Produce Data From a Genetically-Defined Human Cardiac Model in High-Throughput Ways, Matching the Output From ‘Omics’ Data at a Functional Cellular Level”

Sian Harding, professor of cardiac pharmacology at the National Heart and Lung Institute, a division of the Faculty of Medicine, Imperial College, London, England, and outgoing president of the International Society for Heart Research, talks to Judy Ozkan, BA.

Born the daughter of artists in the East End of London, England, and with an interest in astronomy and mathematics and a desire to be a scientist from an early age, Sian Harding, BSc PhD, FESC, FAHA, FISHR, FSB, professor of cardiac pharmacology at the National Heart and Lung Institute, a division of the Faculty of Medicine, Imperial College, London, and outgoing president of the International Society for Heart Research, has lived and worked in the English capital all her life. For many women in 1960s Britain, science was not seen as a viable career choice, but Professor Harding credits her single-sex secondary school with nurturing her interest in all things scientific. She recalls, “It was never a problem for me, although when I investigated undergraduate opportunities at various places, I found that Oxford and Cambridge had 5 times fewer places for women to study science.”

Putting aside her early plans to be an astronomer or a mathematician in favour of something more practical, Professor Harding was attracted to biological sciences, and says, “I was never attracted to a clinical career; it was always the investigative side that interested me.” Pharmacology seemed a good choice, and when she started her studies at King’s College, London, in 1974, she found she had an immediate affinity with the subject. Although university life, with its career structure and procedures, was rather mystifying, she enjoyed her undergraduate years. She then accepted the offer to stay in the pharmacology department and study for a PhD with supervisor John Halliday, MD, who was “great fun to work with.” From the outset, Professor Harding set her own research agenda, with a project on cardiac glycosides, partly inspired by her father-in-law, who had heart failure at that time.

“Fortunately He Liked the Idea, and We Started to Work on G-Protein–β Receptor Coupling Mechanisms”

One particular pharmacology lecturer would become a valued mentor. Ian Morton, MD, was a champion of women in science, and many of his mentees have gone on to forge high-profile careers in pharmacology. After completing her PhD in 1981, Professor Harding wanted to work in a research-oriented institution. “I knew someone who had gone to do postdoctoral work in the Cardiothoracic Institute at the National Heart Hospital, as it was then, and I liked the idea of working in a research-focused institute of this kind.” There was no job available, but buoyed up by having just had an article from her PhD published in...
“What Was Particularly Problematic Was Getting Most of the Tissue We Needed From Transplants. This Involved Getting Up in the Middle of the Night to Wait for the Operations, and I Worked Out That I Must Have Done That Several Hundred Times Over the Years”

During the 5 years with Professor Harris, new possibilities began to take shape. Professor Harding says, “In the course of my work on the β receptor and human heart failure, I thought it would be a good idea to use the real substrate itself—human myocardial tissue. We were attached to the National Heart Hospital in London at that time, and I knew it would be possible to get tissue from there.” Because they could only obtain small samples, she decided to try and make individual cardiomyocytes.

Professor Harris was not initially keen, but Professor Harding pushed ahead. “Luckily, he went on sabbatical, so I did it anyway, and it worked. When things work, people are quite happy for you to carry on. Peter was then extremely supportive of this work.”

Professor Harding and her colleagues began to make animal myocytes at first—a fairly unusual procedure at that time. Progress on producing human myocytes continued, but the yields were limited in the early days.

The next stage was to measure the contraction of individual cells. There was no commercial apparatus for doing this, so Professor Harding worked with a small firm to adapt a rat maze tracking system that could provide the speed necessary to follow the movement of the cell edges during contraction.

The period spent working to isolate and characterise cardiomyocytes was one of the most enjoyable periods of Professor Harding’s career, but it was not without difficulty. She explains, “What was particularly problematic was getting most of the tissue we needed from transplants. This involved getting up in the middle of the night to wait for the operations, and I worked out that I must have done that several hundred times over the years. But I believe that if you want to study human diseases, you should work on human tissue.”

Although it was a painstaking process, the team was ready to publish its first article by 1989. It was the first of many articles on a rewarding and absorbing thread. Professor Harding says, “The cardiac myocyte experiments are particularly rewarding for the instantaneous data they produce and the biophysical studies they make possible. Our latest work with Julia Gorelik, PhD, has involved using a scanning ion conductance microscope to nonoptically image the topography of the surface of the cells and to identify where the β-receptor signalling is located.”

In 1988, the Cardiothoracic Institute moved to South Kensington, close to the Brompton Hospital, and Philip Poole-Wilson, MA, MD, FRCP, FESC, FACC, FMedSci unexpectedly in 2009, which Professor Harding says “was a great shock and sadness to all.” She adds, “I have been proud to give public obituaries for both these great men, who gave so much to cardiovascular science and to me personally.” She worked with Professor Poole-Wilson for 20 years, and describes him as “always there in the background and very supportive in a gentle way; to so many people he was an inspiring but modest man.” She also enjoyed collaborations on β blockers with the late Nobel Prize winner, Sir James Black.

The new head of the National Heart and Lung Institute is Michael Schneider, MD, PhD, who came from Baylor College of Medicine in Houston, TX, in 2008. Professor Harding describes him as “an invigorating presence” who has not only stimulated new ways of thinking about stem cell research and cardiac regeneration, but has also brought novel methodologies to London. Importantly, she feels, he has reinforced and strengthened the cardiovascular science base at Imperial at a time when the absence of people such as Professor Poole-Wilson was creating a real vulnerability.

“My Initial Thoughts Are That β Blockers Are Actually Harnessing and Activating a β-2 Pathway That Comes Into Action to Protect the Heart Against Excessive Adrenaline”

Professor Harding’s early expectations about a career in research have been fulfilled. She particularly enjoys the long-term development of intellectual threads, such as the β receptor. She explains, “Initially finding that β receptors were desensitised in human heart failure resulted in attempts to stimulate them. This was followed by the realisation that this strategy did more harm than good and drove forward heart failure. Professor Harris explained this phenomenon in an evolutionary context of short-term gain of heart function being directed towards emergency rescue after, for example, haemorrhage, and being paid for by long-term damage. The counterintuitive idea that β blockers would be beneficial then gained momentum. β-blocker therapy has gone from being absolutely forbidden in heart failure to being mandatory.”

“Now we have taken this one step further, by studying the distinction between the β-1 and β-2 adrenoceptors. My initial thoughts are that β blockers are actually harnessing and activating a β-2 pathway that comes into action to...
Professor Harding has also developed a new stem-cell based in vitro model of the human ventricular myocyte using cardiac myocytes derived from human embryonic stem cells or induced pluripotent cells. She explains, “I believe that these will give us the capability to produce data from a genetically defined human cardiac model in high-throughput ways, matching the output from “omics” data at a functional cellular level. It is clear that you cannot study one thing in isolation, but must consider integrated systems. If I was going into science now, I would stay with my mathematical background and move towards the bioinformatics side of systems biology.”

In addition to her own research, Professor Harding enjoys nurturing emerging talent. She finds PhD student training the most rewarding form of teaching, and has supervised 33 PhDs so far.

A Lead Investigator in a Trial to Use Gene Therapy to Restore Sarcoplasmic Reticulum Ca2+ ATPase (SERCA) Levels in Failing Human Hearts

Although Professor Harding has never worked abroad, she has strong international collaborations, particularly with the German labs of colleagues such as Ursula Ravens MD, PhD, head of the Department of Pharmacology and Toxicology at the University of Technology, Dresden, Germany (see http://circ.ahajournals.org/cgi/reprint/122/11/f61), and Thomas Eschenhagen, MD, director of the Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany. Professor Ravens spent a memorable sabbatical...
at the National Heart and Lung Institute in 1995, and made many lasting friendships.

Roger Hajjar, MD, PhD, of the Mount Sinai Medical Centre in New York, NY, has also been an important collaborator for many years. Their first project arose when he visited London in the late 1990s, when he told Professor Harding that he was looking for someone to carry out adenoviral transfection of human ventricular myocytes for the first time. Professor Harding suggested that Federica Del Monte, a newly qualified PhD student who had expertise working with both human myocytes and animal models, should go to Dr Hajjar’s lab. She says, “After much exchange of people between laboratories, and Kerry Davia and Hardeep Ranu also spending periods with Roger at University of Massachusetts Medical School, Boston, MA, we worked out a way of doing the adenoviral transfection. Federica’s work in the United States on transfection of the human myocytes with SERCA, her initial animal work, and then a great deal of large animal work by Roger, led to a clinical trial now in progress.”

Professor Harding is a lead investigator of a UK branch of this trial to use gene therapy to restore SERCA levels in failing human hearts.

Outside the lab, in addition to her work with the Nuffield Council on Bioethics, Professor Harding is the outgoing president of the International Society for Heart Research, and she helped set up the International Society for Heart Research World Meeting in Kyoto, Japan, in 2010. As a member of the Council on Basic Cardiovascular Science of the European Society of Cardiology, she was also involved in organising the Frontiers in Cardiovascular Biology in Berlin, Germany, in 2010. She is looking forward to the next meeting, which takes place closer to home at Imperial College, London in 2012.

“If You Come Along With an Interesting Idea, Generally People Will Take Notice”

Professor Harding is sure that she could not have carried out her work without the support of her husband, Ray, who travelled with her and her daughter to international meetings. His work as a telecommunications designer also gave the Harding household a huge advantage. She says, “Our connectivity was always fantastic, and I was able to send files to work and access the US National Institutes of Health library database when I was on maternity leave, long before the World Wide Web was in use.”

Professor Harding’s enthusiasm for science may have rubbed off on her daughter, Elizabeth, a psychology undergraduate at University College London, London. At the age of 3, Elizabeth was carrying out experiments alongside her mother, and accompanied her to international meetings. Without having been able to do this, Professor Harding believes it would have been impossible to fulfil all her work commitments. Having a preschool child at international meetings also provided her with a new perspective on her colleagues. She says, “Elizabeth looked on scientists with a bemused eye: marvelling at their inability to put their badges on straight and their capacity for clearing a buffet table in seconds.”

Professor Harding’s working life has not followed the same path as other senior scientists. She says, “If asked for advice, I would say, ‘Don’t do what I did,’ because it is clear now that I have not done the right things in terms of where I published or by staying in one place. But if I cannot be a good example, at least I can be a useful warning.”

Professor Harding is also sanguine about having discovered the importance of nitric oxide and not having pursued that line of research before it took off. She says, “Mine was the first group to demonstrate that nitric oxide was important in the cardiac myocyte, with experiments by Adrian Brady, FRCP, FAHA (now a consultant in Glasgow, Scotland), but I did not follow it up because the effects were not very evident in the failing human myocytes. Now, of course, it has become a huge field.”

However, Professor Harding has always been determined to follow her own path, and advises others to drive their career without waiting for others to define their plans. She explains, “I have always had a project in mind that I wanted to do, and I always wanted to influence the work that I did. If you come along with an interesting idea, generally people will take notice of you. I can never understand why people say that they want to be independent and never do anything about it. Just be independent.”

References


Judy Ozkan is a freelance medical journalist.
Team 2011: The Cardiomyocyte Pharmacology Research Group at the National Heart and Lung Institute, Imperial College, London, England


Sian Harding, BSc PhD, FESC, FAHA, FISHR, FSB, professor of cardiac pharmacology at the National Heart and Lung Institute, a division of the Faculty of Medicine, Imperial College, London, England, describes the Cardiomyocyte Pharmacology Research Group and its work to Judy Ozkan, BA.

“A Very International Setup”

Describing the team, Professor Harding says, “It is a very international setup, and people tend to arrive from many different countries.” Postdoctoral researchers in the group are Gabor Foldes, Mirna Chahine, Fabian Gonzalez Jara, and Mark Bannister, and current PhD students are Helen Paur, Max Mioulane, Andre Chow, Markus Sikkel, Ljudmilla Kolker, Evie Maifoshie, Dan Reed, and Peter Wright. Among the lab staff, Professor Harding says, “Peter O’Gara has been my cardiomyocyte technician for more than 20 years. He is the person who teaches everyone to isolate cardiac myocytes and generally holds the lab together.”
Important Collaborations With Colleagues at Imperial College and Harefield Hospital

In addition to the core team, Professor Harding has important collaborations with close colleagues at Imperial College, and many of the core posts are held jointly with them.

Senior lecturer Julia Gorelik, PhD, a biophysicist currently engaged in developing new imaging methods for receptor tracking on cardiomyocytes, designed the system for imaging β-receptor signalling.1

Alex Lyon, MD, PhD, Walport Clinical Lecturer in Cardiology at the National Heart and Lung Institute, was one of Professor Harding’s PhD students, but now has his own group. He shares common interests on the effects of sarcoplasmic reticulum Ca2+ ATPase (SERCA2a) on cardiomyocytes and on the β receptors in stress cardiomyopathy.2

At Harefield Hospital, Middlesex, England, Cesare Terracciano, MD, PhD (see http://circ.ahajournals.org/cgi/reprint/121/24/f139), is a long-time collaborator with a major interest in human tissue from patients with heart failure and the left ventricular assist device.3

Nadire Ali is a senior research fellow who brought the embryonic stem cell technology to the National Heart and Lung Institute, and now runs that group.4

When looking for students for postdocs, Professor Harding says it is aptitude that counts. She explains, “Quite often, I look for someone who is dynamic and intelligent rather than looking for a particular skill. Having said that, there are a dearth of people who can handle embryonic stem cells and cardiomyocyte differentiation, but that may be because few people are working on that in the United Kingdom. In the future, I am looking for a systems biologist or mathematician to interpret the kind of data I am getting out of the human embryonic stem cells and the large data sets from that and other projects that would benefit from some kind of mathematical analysis.”

The team has 3 main research foci. The first is gene therapy of heart failure, in particular to shadow the SERCA gene therapy trials with animal models to interpret the results and improve the vector strategy. She considers the team’s role in the development of SERCA as a potential gene therapy target as one of their finest achievements.5

The second is the β receptor and its role in the protection of the heart, particularly its role in stress cardiomyopathy. The understanding of the β-2 receptor as a protective receptor in different circumstances and the role of β blockers to harness this is another breakthrough of which the team is proud.6

The third area is how to use stem cell-derived myocytes as a model, particularly in terms of harnessing the power of individual genotypes. The development of a new in vitro model of the stem cell-derived myocyte is a big step forward that Professor Harding says “will help to overcome the many problems that we have had with the adult myocytes over the years.”7 A longer-term goal is the use of stem cell-derived cardiac myocytes for therapy.

Professor Harding explains, “One thing I am interested in is the possibility that the recruitment of patients with implanted left ventricular assist devices to clinical trials can help us understand whether and how novel therapies are working. At the moment, in our UK clinical trial, we are going to use gene therapy on patients who already have an implanted left ventricular assist device. These patients have some myocardium removed when the pump is implanted, and are ultimately destined to have a heart transplant. The left ventricular assist device will protect them if anything goes wrong, and in some cases we will be able to compare the pretreatment tissue sample with the explanted heart and understand whether we achieved our objectives in terms of viral transfection and alteration of SERCA2a levels. This information is valuable, and I can see that it could also work well for understanding cell therapy to know whether the implanted cells have integrated and developed.”

References

Contact details for Professor Harding: Sian E. Harding, 4th Floor Flowers Building, NHLI, Imperial College, South Kensington, London SW7 2AZ, E-mail: sian.harding@imperial.ac.uk Tel: +44 207 594 3009

Judy Ozkan 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.