A powerhouse of biomedical cardiovascular specialties is being orchestrated in London, England, to make regenerative therapy of the damaged heart at least as effective as pharmacological remodelling within 5 years. The conductor is Michael D. Schneider MD, FMedSci, head of Cardiovascular Science, National Heart and Lung Institute, British Heart Foundation (BHF) Simon Marks Chair of Regenerative Cardiology, and director, British Heart Foundation Centre of Research Excellence, Imperial College London, Faculty of Medicine, Imperial Centre for Translational and Experimental Medicine, London, England, talks to Barry Shurlock MA, PhD.

The Discovery of Cardiac Stem Cells in Adult Myocardium Has Unlocked Novel Strategies for Regenerative Therapy of the Damaged Heart

Michael D. Schneider, MD, FMedSci, head of Cardiovascular Science, National Heart and Lung Institute, British Heart Foundation Simon Marks Chair of Regenerative Cardiology, and director, British Heart Foundation Centre of Research Excellence, Imperial College London, Faculty of Medicine, Imperial Centre for Translational and Experimental Medicine, London, England, talks to Barry Shurlock MA, PhD.

“IT WAS CATASTROPHIC. WE LOST 700 CAGES OF MICE, AND KEY PROJECTS HAD TO BE ABANDONED”

Few weather events can be said to have played a part in groundbreaking medical research, but one that did was Allison, the major US tropical storm that wandered its way up from the Gulf of Mexico in June 2001. Despite never reaching hurricane force, it impacted massively on the states of Texas and Louisiana. In places as much as 40 inches (1 metre) of rain fell. Downtown Houston, TX, was particularly badly affected, with extensive flooding that made thousands of people homeless and destroyed many buildings, including some on university and medical campuses.

One of those who watched on helplessly, knowing that years of painstaking research had been decimated, was Professor Schneider. In the previous year, he had been appointed to the MD Anderson Foundation Chair at Baylor College of Medicine, Houston, 7 years after arriving in Houston as an assistant professor. During this time, he had led teams of researchers investigating the molecular biology and cell biology of the heart, with an emphasis on the mechanisms that control the growth and development of cardiomyocytes. Much of his experimental work depended on hundreds of unique transgenic animals kept in an underground vivarium on the Baylor campus in the city. As he watched pictures of canoes being paddled down familiar streets and learned that the animal house was flooded chest-high, he realised that his research was about to suffer an enormous setback.

Recalling the storm, he says, “I was in the poetically appropriate place to see videos of the flood as I was on holiday in Italy, en route to Venice with my wife and sons. It was catastrophic. We lost 700 cages of mice, and key projects had to be abandoned. Power was lost to all freezers for days. It was very, very sad. We had put a lot of emphasis in our research on creating complex genetic models of cardiac growth, including double and triple knockouts of cardiac cell cycle regulators. Some projects survived, many did not. The lab staff took all the precautions they could, but countless reagents were lost, and the major vivarium was not restored for months. With the assistance of the National Institutes of Health (NIH), we got back on track over the following 2 years and now the vivarium there is as watertight as a submarine.

“But it was not all bad. There was a necessity to refocus our research, abandon some projects we were fond of,
and concentrate on other questions to regain time. If joking, I say we discovered cardiac stem cells instead.”

Four years later, in mid-spring 2007, Professor Schneider decided to move from Houston to London. It was not his first taste of the British Isles. That was in 1974, when he had spent 3 months learning “traditional bedside skills” under the tutelage of Desmond Julian, MD, in the Department of Clinical Cardiology at the University of Edinburgh School of Medicine, Edinburgh, Scotland, home of the founding physicians of Dr Schneider’s alma mater, the University of Pennsylvania School of Medicine, Philadelphia, PA. For someone who had fuelled a career by many successful grant applications, his immediate response to accepting the London appointment was predictable: that afternoon he started writing an application to the British Heart Foundation, which would eventually fund a Centre for Research Excellence at Imperial College London to the tune of £9 million.

Commenting on the move, he says, “It was quite a change, but it was not intended to be a vote on the US system versus the UK system. Many of my friends were less surprised that I was going to London than they had been [in 1984] when I moved from the East Coast to Texas. However, before I accepted the London job, I wanted to be sure that there was a reasonable likelihood of achieving something significant. Houston was a terrific city in terms of its impact on my early career, and it was a great place to have brought up kids. Baylor has many strengths, including world-leading molecular genetics, but it is a free-standing medical school without several of the other basic sciences found in a university. Here, at Imperial College London, there is a special opportunity to bring the cardiovascular sciences together from what had been separate ‘silos’ that did not interact as they might. What impressed me was the quality of the colleagues and the strategic direction of travel. In medicine today, there is an opportunity to transform the subject with the quantitative sciences, and here we have them all around—chemistry, bioengineering, systems biology, biophysics [etc].”

“I was approached to fill the position of [the late] Philip Poole-Wilson [MD, FMedSci] (see http://circ.ahajournals.org/content/119/8/f43) a much-beloved heart failure researcher and BHF chair, who was retiring. It was ironic that earlier, at a Japanese heart failure meeting, Philip and I had been twinned as the opposite poles of cardiovascular research, with him having strengths in clinical studies and pathophysiology and I in molecular biology. Over the period of 1 year, the job description evolved towards much broader and strategic responsibility for cardiovascular science, which was an irresistible offer.”

Five years after moving to London, Professor Schneider has just moved into a purpose-built research facility on the campus of the world-renowned Hammersmith Hospital, the Imperial Centre for Translational and Experimental Medicine. As well as providing 3600 m² of floor space across 3 storeys for cardiovascular science and a floor for Medical Research Council investigators in cardiovascular genomics, the centre houses the Wellcome Trust-funded Clinical Research Facility for all medical specialities and Imperial’s Cancer Research UK Centre. It is so new that Professor Schneider and his staff have only just figured out how to work the phones. A major advantage of the new building emphasised by Professor Schneider is that it is next to the UK Medical Research Council Clinical Sciences Centre, a nexus of cutting-edge research in epigenetics, stem cell biology, metabolism, imaging, and other essential disciplines.

Historically, the significance of the new building is that, for the first time, it brings together the cardiovascular scientists from a wide variety of disciplines, who had been scattered over 5 London campuses of Imperial College. This geographical dispersion is a legacy of the creation 15 years ago of the Imperial College Faculty of Medicine from constituent medical centres, each with an
international reputation in its own right. As well as the Hammersmith Hospital, home to the Royal Postgraduate Medical School, these include institutes or schools at the Royal Brompton Hospital, Harefield Hospital, and St. Mary’s Hospital, the birthplace of antibiotics.

“I Didn’t Want to Spend My Time Ticking Boxes on the Diagnostic and Therapeutic Menu. I Wanted to ‘Rewrite the Menu’”

Professor Schneider is the son of a dentist and was brought up in Philadelphia, PA. After school he spent 3 years reading history and science at Harvard College, Cambridge, MA, before returning to Philadelphia for his MD at the University of Pennsylvania School of Medicine. After further clinical training at Duke University Medical Center (Durham, NC), he spent almost his entire career as a scientific investigator, far from the daily routine of clinical cardiology. He says, “I was always interested in the scientific aspects of medicine from an early age. Possibly the predilection for cardiovascular research is in part a matter of chance that came from spending several summers in my teens in a cardiac surgery lab. My clinical mentors at Penn were fantastic, with every case considered at the bedside like a Sherlock Holmes mystery. But, although the academic banner in cardiology and paediatric cardiology was held aloft there, something was missing. I felt that there was not enough basic science—in fact, at the time, it was not the style in most US cardiology programmes to train physicians in contemporary molecular methods.

“However, I had the immense good fortune while at Duke to learn from the example of Bob Lefkowitz [MD], a Howard Hughes investigator and one of my attending physicians when an intern. It was a eureka moment in my career. There was a high level of scientific innovation at Duke, and it gave me lots of inspiration. But I needed bench training, and I subsequently had the good fortune to be offered a position at the NIH in Bethesda, MD.”

At NIH, Professor Schneider trained with the late Marshall W. Nirenberg, PhD, who was head of the Section of Biochemical Genetics of the National Heart, Lung, and Blood Institute. Dr Nirenberg was a biochemist who set out to follow up the work of Crick and Watson and others on DNA, and in 1968 he was jointly awarded the Nobel Prize for Medicine or Physiology for cracking the genetic code (determining the codons that direct protein synthesis). Much later, he became interested in developmental biology and was a strong advocate of embryonic stem cell techniques. Dr Nirenberg also had the distinction of being the first US government employee to win a Nobel Prize. In an interview in 1987 with the New York Times, he extolled the virtue of the place where he had carried out the work. He is quoted as saying, “The salary here is relatively low, but the advantage to NIH is that you can use the time completely for research, without the distraction of teaching or committee work.”

Similar advantages were available at NIH to Professor Schneider, who had the opportunity to acquire the skills and insights that come from a sustained period carrying out experiments in the lab. He says, “I learnt a lot there from Marshall Nirenberg’s developmental biology and also from Bob [Robert S.] Adelstein’s [MD] work on contractile proteins and their regulation. I also worked in the cardiology research clinic at NIH, which mainly studied hereditary cardiomyopathies. Overall, my time at NIH positioned me well to develop an independent lab at Baylor.”

For much of his first decade at Baylor College of Medicine, Professor Schneider taught on the wards for 2 months of the year but ultimately stepped away from direct clinical involvement. He is aware that there is a wide range of opinions on the best mix of science and clinical
experience for cardiology (or any other specialty), but has clear views, at least as applied to himself. He says, “My feeling is that it is difficult to do both scientific research and clinical work at a globally competitive level. I do like patient care, and I miss the day-to-day satisfaction of dealing with patients and their families. But, I didn’t want to spend my time ticking boxes on the diagnostic and therapeutic menu. I wanted to ‘rewrite the menu.’”

Looking back to the time in 1984 when he was recruited to Baylor, he recalls that cardiology had not then embraced the new opportunities being offered by molecular biology. He says, “I had the good fortune to be recruited by Bob [Robert] Roberts, PhD, who [2 years before] had gone from Washington University [St. Louis, MO] to Baylor as head of cardiology. He was one of those pioneers in bringing molecular biology into the cardiovascular divisions, where it had not previously been. At the time, there was a lack of application of fundamental science to the problems of the heart, while it was routine in a number of other specialties, such as immunology, neuroscience, haematology, endocrinology, and cancer. A couple of years after my move, the American Heart Association decided to fund a number of training programmes in molecular biology of the cardiovascular system, and happily Baylor was one of them.”

“IT WAS A TRUE SURPRISE IN 2003, ALONG WITH SIMILAR FINDINGS BY PIERO ANVERSA, MD, WHEN WE REPORTED THE DISCOVERY THAT THE ADULT HEART INDEED CONTAINS DORMANT OR LATENT STEM CELLS”

One of main areas of interest for Professor Schneider and his coworkers was the molecular regulation of cardiac muscle growth. A key question has always been how the workload of the heart gets translated into sustained effects on the structure and molecular composition of its muscle. They have therefore directed their attention to signal transduction in the growth and hypertrophy of the heart, and to mechanisms for the loss of myocyte proliferation after birth.

A transformative breakthrough occurred in 2003. Professor Schneider explains, “Unlike the early heart, adult myocytes grow only by cell enlargement, and no stem cell pool had ever been identified, akin to the satellite cells that regenerate skeletal muscle. It was therefore a true surprise in 2003, along with similar findings by Piero Anversa, MD, when we reported the discovery that the adult heart indeed contains dormant or latent stem cells.” We were puzzled [as to] why they were there, and how they contributed because in the adult mammalian heart, unlike the axolotl or zebrafish, there is little restorative growth. If stem cells are there, expressing many of the necessary heart-forming transcription factors, much of the usual apparatus for cardiac muscle creation, why don’t these stem cells differentiate? In other words, why are the target genes not switched on?”

Commenting on the findings, which are one of the highlights of his research career, Professor Schneider says, “The real driver was a body of work we had done in the years immediately beforehand. This was on the ‘anti-ageing’ enzyme telomerase. We had shown by genetic engineering in mice that telomerase reverse transcriptase has the ability to sustain heart muscle proliferation, but normally is silenced in the heart after birth. Using a protein called stem cell antigen-1, we were able to purify a subpopulation of persistently telomerase-expressing cells that had more than one foot on the road to becoming cardiomyocytes and were significantly different from stem cells that might have come from the bone marrow or bloodstream.”

Two recent clinical trials, led by Roberto Bolli, MD, and Eduardo Marban, MD, PhD, suggest that human heart repair after myocardial infarction can be improved using adult cardiac stem cells grown from biopsies, expanded, and delivered by catheter, a transition from bench research to clinical application that Professor Schneider finds gratifying, though many challenges remain. Other approaches are underway with the alternative strategy of activating dormant stem cells in situ.

“WITHIN ANOTHER 5 YEARS, THE EFFICACY OF CELL THERAPY WILL BE WELL PROVEN, AT LEAST AT THE LEVEL OF MANY DRUGS PRESENTLY GIVEN AFTER MYOCARDIAL INFARCTION”

Much of the impetus in regenerative medicine in recent years has come from Japan, from where Professor Schneider recruited many of his trainees over the years. These include the lead author in his article reporting the discovery of dormant stem cells in the heart,1 Hidemasa Oh MD, PhD, who is now head of the Department of Regenerative Medicine at the Centre for Innovative Clinical Medicine at Okayama University, Okayama, Japan. Another was Motoaki Sano, MD, PhD, who holds joint positions at the Department of Regenerative Medicine and Advanced Cardiac Therapeutics, Keio University, Tokyo, Japan, and Precursory Research for Embryonic Science and Technology Organisation (PRESTO), an arm of the Japan Science and Technology Agency, based in Saitama, Japan. Sano is the lead author for key articles from Professor Schneider’s group that showed that activation of an atypical cyclin-dependent protein kinase, Cdk9, represses an important metabolic factor, peroxisome proliferator-activator receptor gamma coactivator, leading to heart failure in cardiac hypertrophy.2,3

The list of trainees who have passed through Professor Schneider’s lab includes many who have gone on to distinguished careers, including W. Robb MacLellan MD, who holds the Robert A. Bruce Chair of Medicine and heads the Cardiology Division at the University of Washington, Seattle, WA. Professor MacLellan was lead author for a key article on the mechanism that blocks cardiac muscle cell proliferation in the adult myocardium based on an animal model with heart-specific deletion of the tumour suppressor Rb plus germline deletion of its relative, p130.4

Professor Schneider’s heart-specific Cre “deleter” line created for that study is regarded as an important tool for a genetic dissection of cardiac biology and is used in >80 institutions worldwide. Thomas Brand, PhD, is another ex-trainee who originally worked with Professor Schneider.
on mutations of the transforming growth factor-β receptor. In 2009, he moved from the University of Würzburg, Würzburg, Germany, to join Professor Schneider at the National Heart and Lung Institute.

Among the many awards that Professor Schneider has received, he is particularly proud of the Distinguished Alumnus Award of 2010 from the Duke Medical Alumni Association. He says, “I enjoyed my time at Duke University Medical Center, and have fond memories of Bob Lefkowitz and the enormous inspiration he gave me. It was the crucible of my training experience, and I still have many close professional colleagues who date from that time. I was also pleased to receive the Distinguished Achievement Award of the American Heart Association Council on Basic Cardiovascular Sciences in 2007.”

In addition, Professor Schneider was the US coordinator for a Leducq Foundation Transatlantic Network of Excellence on cardiac regeneration, led in Europe by Stefanie Dimmel, PhD (see http://circ.ahajournals.org/content/120/17/f97) at the University of Frankfurt, Frankfurt, Germany, and he is the recipient of an Advanced Investigator Grant from the European Research Council, awarded to the top scientists in Europe.

Regenerative medicine has elicited huge expectations among scientists, clinicians, and the potential public beneficiaries, with corresponding resources currently being invested by major research funders worldwide. Indeed, in the UK, the Research Councils and Technology Strategy Board have just launched a comprehensive strategy for regenerative medicine. Pharmacological means to assist the mechanical performance of the damaged heart have long been a reality, but there are now encouraging signs of enhancing cardiac regeneration and repair. For his part, Professor Schneider offers a prediction: “Within another 5 years, the efficacy of cell therapy will be well proven, at least at the level of many drugs presently given after myocardial infarction. Longer term, the goal is to have products that are more effective and persistent than the current suspensions of naked stem cells, which do not stably engraft, perhaps involving microencapsulation, cell scaffolds, gels, or more complex tissue-engineered constructions, along with means to activate the dormant stem cells in vivo or ex vivo.”

References

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Supporting Postgraduate and PhD Studies at German Universities

Roland Klingenberg, MD, interventional and research fellow, Department of Cardiology, University Hospital Zürich, Zürich, Switzerland, talks to Jennifer Taylor, BSc, MSc, MPhil.

A Friedrich Naumann Foundation scholarship (see http://www.en.freiheit.org) provided substantial support for Roland Klingenberg, MD, interventional and research fellow, Department of Cardiology, University Hospital Zürich, Zürich, Switzerland, during his medical studies at the University of Freiburg, Freiburg, Germany, from 1996 to 2000. Scholarships are awarded to postgraduate students at German universities on the basis of grades, recommendations from academic teachers, and active social commitment. Embracing this concept of equal opportunity for all based on achievement, during his studies in Freiburg, Dr Klingenberg developed a set of objective and independent criteria for selecting candidates for an international exchange programme. He was co-chair of a local student group that established an exchange programme for medical students to facilitate mutual insights into medical education and bring back new ideas. “Following this concept throughout my professional life, I have had the privilege to learn cardiovascular medicine from great teachers,” says Dr Klingenberg.

Initially at the University of Tübingen, Tübingen, Germany, for preclinical studies and then at the University of Freiburg, Dr Klingenberg was fascinated by inflammation and its involvement in common diseases. For his dissertation, he conducted a basic research project on retroviral gene therapy in experimental cancer research with Professor Bernd Groner, PhD. He decided on a career in cardiovascular medicine in the final year of his medical studies after spending 8 months in clinical service at the Baylor College of Medicine, Texas Heart Institute, Houston, TX, and the Moffitt Cancer Center, Tampa, FL. He says, “I enjoyed the evidence-based approach in cardiovascular medicine using data from large clinical trials.”

Back in Germany, Dr Klingenberg started a residency in internal medicine and cardiology with Professor Wolfgang Kübler, MD, and then Professor Hugo A. Katus, MD, at the University Hospital Heidelberg, Heidelberg, Germany. Continuing his interest in inflammation alongside his clinical duties, his research focused on vascular inflammation and heart failure/heart transplantation, which earned him the Michel Mirowski Award 2005 from the German Cardiac Society. He then joined the Experimental Cardiovascular Research group of Professor Göran K. Hansson, MD, at Karolinska Hospital in Stockholm, Sweden, in late 2005 as a postdoctoral fellow with funding from the German Research Foundation to investigate the mechanisms of anti-inflammatory therapies in experimental atherosclerosis with a special focus on adaptive immunity.

After 2 years in the lab, Dr Klingenberg started seeing patients again. With the aim of translating experimental anti-inflammatory therapies into the clinics and completing his residency in cardiology, he joined the Department of Cardiology (Professor Thomas F. Lüscher, MD) at University Hospital Zürich in 2008, where he is a senior investigator with a team of students and study nurses responsible for the identification and prospective evaluation of novel inflammatory biomarkers as potential surrogates for anti-inflammatory therapies. Reaching a milestone in his career, Dr Klingenberg currently directs a clinical trial with Professor Lüscher on the effects of everolimus in patients with acute coronary syndromes (CLEVER-ACS, NCT01529554). Dr Klingenberg says, “Building on a network of excellent scientists and physicians, I hope to implement and share my expertise in translational medicine for the benefit of patients.”

References

Jennifer Taylor is a freelance medical journalist.