Genetic determinants of heart disease

Given that your background is in biochemistry, what prompted you to study the molecular mechanisms of heart development and function?

Initially, I was interested in understanding the transcription of genes in brain cells. How genes are regulated in the cell, what would turn them on and what would shut them off. As I was doing this work, however, colleagues of mine who had discovered a new hormone in the heart asked me if I would collaborate with them.

I accepted, and started reading about the heart; I was fascinated because people thought it was a simple pump, and no one expected it to have hormones. The cells of the heart are quite different to other cells in the body in that they don’t regenerate, or become cancerous. I was intrigued by these cells, and I helped isolate the gene for this hormone, which I then showed was actually synthesised and produced in the heart.

This led me to start looking at how the heart regulates its own genetic programme. One thing led to another and I identified a protein was key to turning on this gene, and that protein turned out to be very important for heart development. Before I knew it, I was working on heart development – and I’ve been doing this for the last 15 years.

Could you provide an insight into the collaborations you are involved in?

This is an important point to emphasise. We’re not doing all of this ourselves in our lab; we have established multiple national and international collaborations. These involve human geneticists, clinicians, cardiologists and experts in blood pressure regulation. We would like to share our basic discoveries and measure them against the human reality in the genes and hormones of patients.

On the other hand, we also collaborate with basic scientists who work in complementary fields and use complementary models that present different advantages. Some are working with zebra fish, others with frogs. You can conduct genetics research much faster with these models. Others are undertaking experiments with large animals and are more into pharmacology. And we have an important collaboration with medicinal chemists. We have been doing lots of exciting things recently!

When compared with the studies of other researchers, what is unique about your work?

This is a highly competitive area, so we are not the only ones working on this. What’s unique about us is that, first of all, we have developed animal models that are completely new over the years. This allows us to look at doing longitudinal experiments that you cannot conduct in humans. Using these models, we can tweak one gene at a time and look at what has gone wrong, observe what happens and see if we can fix the problem, or even reverse it.

How does your laboratory combine state-of-the-art genomic approaches with molecular genetics in animals to explore the circuits of heart development?

Once again, what’s really important to highlight is the collaborative nature of the work. You need to reach out to different stakeholders. As an example, in terms of the valve investigations, we’re part of a large international consortium called BavCon. This brings together people from Italy, France, England, the US, Canada and Japan. It’s really global and there’s a wide range of expertise. A good example of how this happens was when we recently found another gene that we activated in mice. Immediately, we reached out to the consortium and asked if they had witnessed mutations in this gene in their work. Sometimes we get the answer within a week, other times it can take a bit longer, but it leads you to the next investigation and tells you that what you’re doing here has an impact on human health.

What direction will your lab pursue in the future?

Before the molecule we’re interested in becomes a drug, there are a lot of things that need to be done in terms of preclinical testing in the lab – to really understand the mechanism of action. At the same time, we’re continuing our work with congenital heart disease. On that front, we’re going to be focused on valve disease, particularly a condition called bicuspid aortic valve. This is a very prevalent disease, and affects at least 1 per cent of the population.
Congenital cardiac defects

Molecular cardiologists at the University of Ottawa’s Faculty of Medicine in Canada have been conducting original work into the genetic basis of congenital heart defects – information that could lead to better care for these often undiagnosed diseases.

HEART DEFECTS MAKE up the largest class of birth defects in the world, and they frequently go undetected until it is too late – which is why they are also the number one cause of death in children under a year old. Following the early stages of development, heart defects often become very difficult to catch; many of them produce few symptoms and of themselves. However, these defects are also prominent causes of cardiovascular disease in later life. Cardiovascular disease, along with cancer, is the biggest cause of death worldwide, and it is difficult to determine how much of this tremendous burden might be traced back to heart defects that are simply never identified.

THE UNDERLYING CAUSE
Despite these impacts, little is known about the causative factors that trigger the initiation and progression of congenital heart defects. To some extent, they are the product of genes – a root that explains their status as congenital diseases that may affect several members of the same family. But there is an environmental contribution to the development of heart defects as well; not everyone with the malfunctioning genes will suffer from the condition. To make matters worse, the activity of these genes is not always evident. Tiny alterations – so small that they are subclinical and cannot be detected by doctors – in how cells are programmed actually have an impact on the development of disease states.

One research team is doing its utmost to get to the bottom of this difficult problem. Professor Mona Nemer is Vice President of Research at the University of Ottawa’s Faculty of Medicine and Professor of Biochemistry. During the course of her career, she has been responsible for a number of exciting discoveries in the field of cardiology. Today, her research focuses on discerning the key determinants of congenital heart defects of every kind, with a view to exploiting them in therapies and interventions. “Understanding how things should run normally will help us see what is going wrong later on, and find therapeutic and prevent ways of fixing the problem,” she says.

MORE THAN A PUMP
Nemer’s pioneering work in the field of molecular cardiology began some decades ago, at a time when the heart was generally considered to be nothing more than a muscular pump for driving blood around the body. Along with her colleagues, however, she discovered that the heart actually secretes its own endogenous hormones that travel out into the body and influence the behaviour of other...
organ; together, they identified and isolated the gene that produces pronatriuretin, a hormone precursor responsible for the peptides atrial natriuretic factor and cardiodilatin. This revelation was exciting in itself, but the researchers subsequently found an equally interesting but more practically valuable characteristic of these hormones: their concentration rises during the early stages of heart failure.

Today, high concentrations of these hormones in plasma remain among the best biomarkers of heart stress and heart failure; clinical tests to measure them are available on the market, and make a welcome alternative to imaging techniques. But there is more to be done, and Nemer has continued to work in this field over the intervening years, investigating the molecular characteristics of heart cells both in their healthy and diseased states. In particular, the research may lead to early diagnosis systems for subclinical congenital heart defects, allowing for better awareness, monitoring and care. There is also the potential that drugs could be developed to replace the products of the defective genes – just as insulin can be given to patients who are type 1 diabetic.

**GATA TRANSCRIPTION FACTORS**

In the 1990s, Nemer developed an interest in the GATA transcription factors – primarily GATA4 and GATA6, two proteins that regulate a number of genes in heart cells, and which are important to the organ’s function and development. “To have the heart functioning properly, you need to coordinate a lot of things – energy balance, hormone secretion, response to calcium, environmental stresses and so on,” Nemer explains – and by controlling the activation of a wide range of genes, the GATA transcription factors affect this coordination. Unfortunately, because of their broad role, mutations in the genes that code for GATA transcription factors are associated with a wide variety of congenital heart defects including valve diseases, holes between chambers and defects in electrical conduction.

Two early studies, published in 1997 and 2001, looked at the relationships and interactions. GATA4 has with Nkx2-5 and Rho-like GTPases, respectively, in the development and maintenance of the heart. In the first, the researchers revealed that GATA4 and Nkx2-5 – another transcription factor – are mutual cofactors, and assist one another in their roles. In the second, it was reported that GATA4 has a role in reorganising the sarcomeres, the contractile units that make up the heart, through its influence on RhoA – a relationship that influences oncogenic remodelling. Nemer has often collaborated with oncologists as part of her work, and, indeed, the cells of the heart are particularly interesting from this point of view since they are not susceptible to cancer.

**GATA4 AND CELL DEATH PREVENTION**

The most important discoveries made by the researchers, however, came more recently. According to studies published by the group from 2004 onwards, GATA4 plays a role in the development of the heart – and then, once the organ is mature, takes control of apoptosis, or programmed cell death. “We found that GATA4 is very important when it comes to keeping the cells of the heart alive, preventing them from being killed by genotoxic stress or by particular chemotherapy – which is known to lead to heart failure through damage,” Nemer says. Based on this revelation, the team began to investigate the role of GATA proteins in drug-induced heart failure, subsequently designing novel molecules to prevent it. The results have been encouraging so far, and research is ongoing. The group has filed three patents recently, and the outlook for the future is bright.