Protective and pathological clots

Dr Nigel Mackman directs the UNC McAllister Heart Institute. In an engaging interview, he describes some of the seminal findings he has made in his 25-year career through explorations of the role of tissue factor in blood clotting in health and disease

You are Director of the UNC McAllister Heart Institute, occupy a range of editorial positions, act as a member of numerous committees, provide mentoring and conduct research. How do you prioritise and manage your time effectively?

My number one priority is my lab and science. This involves working with my students and postdocs, writing papers and grants. My next priority is the McAllister Heart Institute. Much of this work is supporting my faculty. After that, I work on my associate editor responsibilities for *Arteriosclerosis, Thrombosis, and Vascular Biology* (ATVB) and the *Journal of Clinical Investigation* and my chair duties for the ATVB Council of the American Heart Association.

I am very passionate about science and it is fun to be involved in many things – only occasionally is there too much work to do.

What was it that inspired you to study tissue factor?

My scientific career started at the University of Leicester, studying bacterial pathogenesis. My project was to clone the haemolysin gene from a plasmid in pathogenic *Escherichia coli*. I successfully cloned the gene and found that it was secreted via a novel C-terminal sequence. I also showed that this novel sequence could direct the secretion of other proteins from *E. coli*, which was interesting to industry because they used the bacterium to produce different recombinant proteins.

For my second postdoc position, I decided to change direction and work on a mammalian system. My PhD supervisor Professor Barry Holland suggested that monocytes were an interesting cell and that I should consider working on them. I arrived at the Scripps Research Institute in La Jolla looking for a job and Professor Tom Edgington gave me a position. When I arrived I had no project, but Professor Jim Morrissey knew I was a molecular biologist, so one day he asked if I would like to clone the tissue factor (TF) gene. As they say, the rest is history. This has formed the basis of my research for the last 25 years. So the answer to what inspired me to study TF is, being in the right place at the right time.

Can you elucidate the overall goal of your current research?

My goal is to better understand the factors that regulate the blood clotting cascade in health and disease. Most people assume that there is one blood clotting cascade. However, we now know that there are many different triggers that can lead to a clot, which is very important if we are going to use the right drug to prevent clots forming. I work at a basic level with human blood and mouse models, and am also a consultant for pharmaceutical companies that are developing new, safer anticoagulant drugs.

What is the link between cancer and venous thrombosis?

TF is the major physiological activator of blood coagulation. Tumours express high levels of TF and release small membrane fragments into the blood that contain TF. We are working on a hypothesis that in some cancer patients, circulating tumour-derived TF-positive microvesicles bind to the walls of large veins and/or cells and trigger the formation of a clot.

Your lab has recently generated mouse models expressing different levels of TF. Have these models provided insights into the role of TF in haemostasis and thrombosis?

We made a mouse model that had very low levels of TF and found that these mice bled in certain tissues – such as the lung and heart – which normally express high levels of TF. We used this information to propose that some tissues use TF as the main pathway to prevent excessive bleeding, whereas other tissues with low TF – such as skeletal muscle and joints – are more dependent on another pathway, called the intrinsic pathway.

Finally, can you highlight your proudest achievement to date?

I was very proud to be elected as the 2010 chair of the Hemostasis Gordon Research Conference. However, my proudest achievement is my appointment as the Director of the UNC McAllister Heart Institute. I moved to the University of North Carolina at Chapel Hill in 2007 because I wanted to take a leadership position rather than simply run a research laboratory. I was delighted to be selected as the new Director to lead an outstanding faculty studying cardiovascular disease.