Striving for improved understanding of stromal cells

Dr Mark Coles and Professors Jan de Boer and Burkhard Ludewig form part of an extensive multidisciplinary research team aiming to promote the study of stromal cell and immune system interactions. Below, they discuss their respective roles and what the project could unearth.

Could you begin by providing a brief summary of your backgrounds and what led to your interests relating to STROMA?

**JB:** I am a biologist and have been working a lot on cell biology and genetics, using genetic model systems like fruit flies and mice. About 13 years ago, I switched from basic to more applied sciences, so I am now working in the field of biomedical engineering. The objectives of my work are translating basic biological knowledge into new therapies for patients.

**BL:** I am an immunologist and currently act as head of the Medical Research Center and the Institute of Immunobiology at the Kantonsspital St Gallen, Switzerland. My research interests are focused on the interaction of viruses with the innate and adaptive immune system and potential autoimmune sequelae resulting from viral infections. Moreover, we have developed a strong interest in the role of stromal cells in defence against infections and in steering immune responses against cancer cells.

**MC:** I have been fascinated by immunology since being at Cornell University, USA; my coursework focused on microbiology and immunology. After completing my undergraduate research project on macrophage differentiation, I studied molecular and cellular immunology in David Raulet’s laboratory at the University of California, Berkeley, where I learned an immense amount about immune system development and function. This drove my fascination in understanding how immune responses work because, while on the surface immune systems seem complicated, underneath cells follow a set of simple rules.

**Dr Coles, how did you come to put the STROMA network together?**

I knew about the EU initiatives from the initial training networks; it was really a matter of bringing some of my colleagues together and working to establish a group of scientists with a collective interest in this area of expertise. Thus, we brought together a network of scientists from across Europe with key expertise in different areas of stromal cell biology and their interactions with immune cells. STROMA has involved a number of investigators and has been a fantastic opportunity to collaborate and drive world-leading science.

It was exciting bringing people together who had not worked with each other before. Indeed, it has led to some longlasting collaborations and has therefore proved inspirational. Collectively, STROMA participants can have a level of impact that individual scientists could not.

**What excites you most about the STROMA project and stromal research in general?**

**BL:** The project brings together leading experts in an exciting research field and provides a brilliant environment to train young researchers in stromal cell research. Our focus on viral immunology has been instrumental in training young scientists in infection biology. Moreover, the versatile mouse models generated in our lab serve as a key experimental approach in several joint projects within and outside the consortium.

**MC:** The project has been immense fun to help
lead. The groups of early stage researchers and early researchers have come together to collectively advance the field and help translate basic research from the lab into industry and the clinic. I view STROMA as the beginning of long-term collaborations that will advance our understanding of the immune system and translate these into new therapies and vaccines for human disease.

I think it is an area of immunology that has been very much underexploited and, as a consortium, we have been incredibly productive and successful in bringing this new field to the forefront. STROMA ran a stromal meeting in Cambridge a couple of years ago and I think this has helped galvanise excitement across the field of immunology.

You have adopted a holistic approach to discovery and application throughout the project. Why is this important?

**JB:** Every cell type can be defined by 25,000 different components, but which one acts for which process is unknown; entering into an unknown research area such as this, requires a broad look at the whole picture. A particular problem regarding this aspect of the project is that to do it manually is virtually impossible, so you have to automate it, which requires the use of computation and technology. But this is only one example – the high level of complexity involved requires the merging of different disciplines to fill knowledge gaps. Thus, involving experts from a wide range of fields enables us to achieve something collectively that would not be possible individually.

**BL:** I anticipate that defining the origins and functions of different stromal cells will provide critical knowledge to further elaborate diagnostic and therapeutic avenues for cancer, infections and autoimmune diseases.

**MC:** My laboratory group has worked on developing new approaches to immunological challenges through combining computational modelling and experimental approaches to quantitatively understand immune responses and translate into new therapies and biomarkers for human disease. The focus of these studies has been on immune microenvironments, the sites where immunity is generated and tissue pathology can occur. Although computational approaches are inherently ‘not correct’, they can be incredibly useful. In essence, what we’ve been doing is developing a methodology to tackle immunological problems using computers.

Stromal cells, whether in vivo, in vitro or in silico, are at the core of all the immunology we work on.

**JB:** One chief goal is to produce a medical device that can be used in patients. Another goal is to acquire a better understanding of the biology behind some of the phenomena we have observed. Finally, we would like to invest more into computational sciences to enable a better integration of that with experimental sciences – something wholly necessary to successfully analysing all the big data that is ongoing at the moment.

Lymph node stromal networks. Image kindly provided by Anne Thuery, Dr Mark Coles’ lab, University of York
Improving understanding of the immune system through interaction

December 2015 saw the conclusion of the **STROMA ITN** project – a programme involving eminent immunologists, several different companies, early career researchers and experienced researchers. The network has dramatically increased understanding of the role of stromal cells in immunity, and could lead to new therapies and vaccines for human disease.

**THE IMMUNE SYSTEM** is composed of a multitude of cells, proteins, tissues and organs that help an organism protect and defend itself from infectious microorganisms and the uncontrolled growth of tumour cells. In order for the immune system to function properly, it must be able to identify and distinguish pathogens and cancer cells from normal, healthy tissue, and do so through a variety of interactions between different types of specialised cells.

These interactions occur within particular organs, such as lymph nodes or the spleen, that contain a ‘superstructure’ to provide physical support for the tissue and a place where immune cells are able to interact and respond to pathogens. This superstructure is made up of specialised fibroblasts called stromal cells that form a 3D cellular meshwork, enabling interactions that mediate immune responses and provide long-term protection against particular infections. Thus, stromal cells can be seen as the basic infrastructure of the immune system.

**THE PROS AND CONS OF STROMAL CELLS**

Stromal cells are known to play an essential role in guiding specific immune responses by producing chemokines (signalling proteins secreted by cells), to attract lymphocytes and cytokines to bring the right cell into the right place at the right time. In this way, stromal cells are vital for the formation of specialised structures that support adequate responses of the immune system.

However, in addition to providing beneficial immune responses, it is known that stromal cells can drive the onset of pathological diseases. For instance, they can interact with tumour cells to play a major role in the growth and progression of cancers, and help regulate the formation of tertiary lymphoid tissue to drive autoimmune diseases. Although researchers are aware of the benefits and pitfalls associated with stromal cells, very little is understood about these processes.

Thus, it is extremely important for researchers to deepen understanding of stromal cells and their interactions in health and disease, as they provide fascinating potential as a therapeutic target to increase the efficacy of immune responses, and prevent and treat a range of disease pathologies.

**INVESTIGATING IMMUNE CELL INTERACTIONS**

In recognition of this, a multidisciplinary team established a project called STROMA ITN. Funded through the EU Seventh Framework Programme (FP7), the project began in January 2012, ran until the end of December 2015 and brought together world-leading experts from both academia and industry across Europe to address some of the key scientific questions in the niche – but emerging – field of stromal cell research.

Dr Mark Coles of the Centre for Immunology and Infection at the University of York played a fundamental part in establishing the STROMA network, with the dual purpose of ensuring that Europe retained its global leadership in the field of stromal cell research, whilst translating the research findings on immune cell interactions into novel products and technologies for European industry. “The STROMA network was initiated to bring together a network of scientists from across Europe with key expertise in different areas of immune interactions,” explains Coles. “It involved a number of investigators and has been an exciting opportunity to collaborate and drive world-leading science; even now it is considered really young in the field of immunology, but we have managed to get a group of researchers together who are passionate about it and want to develop centres of excellence in this particular area.”

**INVOLVING INTERNATIONAL IMMUNOLOGISTS**

The network recruited 14 early stage researchers (ESRs) and three experienced researchers (ERs) from a variety of countries – including Portugal, India, Italy, Poland, Taiwan, Belarus, Croatia, France, Uruguay, Germany, Spain and the Netherlands – and provided extensive research training to benefit the individuals involved, the project itself and the future of stromal cell research.

The training comprised an intensive week-long course at the University of York, UK, and the Kantonsspital St Gallen, Switzerland, but also involved industrial partners, such as MedImmune, ProBioGen and Miltenyi Biotec. These partners hosted ESRs as part of secondments lasting between one and four weeks. In addition to gaining an insight into how scientific research can translate into industrial applications, the ESRs were able to
THWARTING PARTICULAR PATHOGENS
The nature of the project meant there were several separate research foci happening at any one time, although one main focus was on responding to the need for developing novel methods to increase the efficacy of vaccines. Coles headed a group that focused on understanding how adjuvants work. Adjuvants are substances added to vaccines to increase the body’s immune response to them and have been used for over a century.

However, certain vaccines have proven ineffective, as they demonstrate a particular bias towards a certain type of immune response unsuited to these pathogens. Thus, scientists have developed next generation adjuvants. While more effective, the way they work is still not fully understood, prompting Coles’ group to focus their efforts on these newer agents. “We hope to make these adjuvants even better through focusing on the stromal part of the cellular network, rather than focusing on the dendritic cells as people have done in the past,” explains Coles. “We have developed new understandings and novel concepts to improve vaccination approaches to drive rapid protective immune responses. Indeed, through the STROMA ITN project, we have discovered a new mechanism to regulate the type and timing of the immune response.”

Although the project was officially completed in December 2015, the bonds it formed between immunologists who collaborated throughout the duration are sure to continue, encouraging ongoing research into stromal cells. That the programme has also afforded the ESRs the opportunity to present their work to the highest level possible.

To ensure effective collaboration throughout the duration of the four-year project, the network held one project meeting each year, where the ESRs and EEs were given the opportunity to present their findings and receive feedback regarding the progress they had made. Beginning with an introductory session in Rennes, France, in September 2012, a larger meeting was subsequently held in Cambridge, UK, in October 2013, where the senior researchers imparted their insight, advice and expertise to the ESRs and EEs. The third meeting took place in 2014 in Lisbon, Portugal, where group and individual work was showcased. The final meeting, which was held in Strasbourg, France, in October 2015, afforded the ESRs the opportunity to present their work to the highest level possible.

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STROMA ITN
OBJECTIVE
To promote the study of stromal cell and immune system interactions during stroma development and function in health and disease.

KEY COLLABORATORS
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STROMA is a Marie Curie Initial Training Network funded under FP7 that began in January 2012 and ran until the end of December 2015. The aim is to promote the study of stromal cell and immune system interactions during stroma development and function in health and disease. The Network brought together world-leading experts from academia and industry in Europe to address the key scientific questions in this emerging field. It sought to ensure that Europe retains global leadership in this field and translates basic research on stromal cell and immune cell interactions into novel products and technologies for European industry.

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