Interview

The bioprocessing of stem cells: how to reach the clinic

Peter Zandstra speaks to Emily Culme-Seymour, Assistant Commissioning Editor

Peter Zandstra

Stem Cell Bioengineering at the Institute for Biomaterials & Biomedical Engineering, University of Toronto, ON, Canada
and
Centre for Commercialization of Regenerative Medicine, Toronto, ON, Canada
peter.zandstra@utoronto.ca

Peter Zandstra graduated with a Bachelor of Engineering degree from McGill University (QC, Canada) in the Department of Chemical Engineering, and obtained his PhD degree from the University of British Columbia (BC, USA) in the Department of Chemical Engineering and Biotechnology, under the supervision of Jamie Piret and Connie Eaves. He continued his research training as a Post Doctoral Fellow in the field of Bioengineering at the Massachusetts Institute of Technology (MA, USA; with Doug Lauffenburger) before being appointed to the University of Toronto (ON, USA) in 1999. He holds an academic appointment as a Professor at the University of Toronto's Institute of Biomaterials and Biomedical Engineering, and he is cross-appointed with the Departments of Chemical Engineering and Applied Chemistry, and the Donnelly Centre for Cellular and Biomolecular Research. Zandstra is a Canada Research Chair in Stem Cell Bioengineering and is a recipient of a number of awards and fellowships including the Premiers Research Excellence Award (2002), the Edgar William Richard Steacie Memorial Fellowship (2006), the John Simon Guggenheim Memorial Foundation Fellowship (2007) and the McLean Award (2009). Zandstra is a fellow of the American Institute for Medical and Biological Engineering and the American Association for the Advancement of Science. Zandstra currently serves as associate editor for several journals. In addition to his academic appointment, he serves as the Chief Scientific Officer for the Centre for Commercialization of Regenerative Medicine in Toronto (ON, Canada).

■ **What first brought you from the engineering & biotechnology disciplines to the area of stem cells?**

The area of stem cells is actually where I started in biotechnology. I completed an undergraduate degree in Chemical Engineering and Biotechnology, followed by a PhD in a biotechnology laboratory with Jamie Piret, a bioengineer, and Connie Eaves, a stem cell biologist. We were interested in understanding how cytokine–receptor interactions could be controlled to grow blood stem cells *in vitro*. So, during my PhD I was already working on both aspects of the science and was fully immersed in stem cell biology.

■ **What source & type of cells do you mainly work with?**

We work with both somatic cells, such as hematopoietic or blood stem cells, and pluripotent cells, from both mouse and human. Although I started working mainly with blood stem cells, we soon became very interested in using pluripotent cells, initially murine embryonic stem cells and later on other types of pluripotent cells, as model systems to try to understand how cells interpret signals in the environment. It has been very exciting to be able to move back and forth between these different stem cell systems, and to try to either compare what the rules are that are conserved between pluripotent cells and blood stem cells, or try to determine what unique aspects either has. Having both systems going in the laboratory is useful since they both have their strengths: blood stem cells are particularly useful in terms of immediate translation, yet have certain challenges in terms of their identity and their rarity, whereas pluripotent stem cells have advantages in terms of molecular level investigations, owing to both the ability to more easily propagate them and their relative homogeneity. It is nice to be able to move back and forth between the two systems!

Regenerative Medicine

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■ What do you feel has been the most exciting discovery to come out of your laboratory in the past year?

We are currently really excited about the role of feedback networks in cell fate control. Our interest is built upon observations over many years, wherein we have recognized that the development of cells and tissues, whether pluripotent cell derived, generated as a function of blood stem cell growth, are strongly influenced by intercellular 'conversations' or the interactions of secreted factors between different cell types. This so-called 'non-stem cell autonomous feedback signaling' is something that we are starting to both understand and control quite well. One particular example is a paper that was published last year in *Cell Stem Cell*, where we identified that different subsets of more mature blood cells (e.g., megakaryocytes vs monocytes) secrete either positive or negative feedback signals to the blood stem cells, to create environments that support either differentiation or self-renewal.

Extending these *in vitro* studies to the *in vivo* stem cell niche, we believe the niche is a local environment that is 'created' to help with the interpretation of feedback signals. It acts to protect or modify the signals stem cells receive from the global or systemic environment; it is likely that some of the signals get screened out while others get amplified. That relationship between the local and global environments is something that we are studying at the moment in a number of ways. This network and language that occurs within any developing tissue to control the relative proportions and levels of the cells within that tissue is something that is turning out to be very interesting, and certainly is also true in pluripotent cell differentiation and development. For example, the relationship between cardiac development and endoderm development has been recognized for some time now, but not well understood. Although there has been a lot of work done regarding intracellular signaling networks and genetic networks, relatively, there has not been that much progress in cell–cell interaction networks, and that is the area that we are really excited about.

■ How has the field of stem cell bioprocessing evolved with new technologies coming onto the scene & an increase in knowledge of the stem cell niche?

The field is certainly moving quickly in terms of a few different things. It has only been during the last 3–5 years that we have been able to start to grow pluripotent cells and most types of somatic cells in more defined media. Removing feeder cells, serum and other media components that are not well defined has really helped us to understand what the fundamental molecular needs and mechanisms are to support stem cell growth and differentiation. These can then be implemented in bioreactors or bioprocesses to try to mimic key environments. One of the goals of the field really should be to try to remove as much complexity and uncertainty from our manufacturing processes as we can.

■ In addition to your academic position, you serve as Chief Scientific Officer of the Centre for Commercialization of Regenerative Medicine in Toronto, Canada. What attracted you to this role & what do you hope the Centre for Commercialization of Regenerative Medicine will achieve in the forthcoming years?

Our community, and indeed many communities across the world, is very good at creating new discoveries; however, those discoveries have trouble getting out of the laboratory, being taken up by industry and, ultimately, implemented in a way that can help people and help progress our field. In Toronto and in Ontario, this was particularly true: while we have excelled in fundamental stem cells and regenerative medicine discoveries, and have participated in helping to launch the careers of really good students and postdoctorates, a local (or even Canadian) receptor industry community to hire these people, was underdeveloped. Therefore, one motivation for the Centre for Commercialization of Regenerative Medicine (CCRM) was to attract and create industry to Toronto, Ontario and Canada in order to seed such a receptor community for the scientists emerging from our research facilities. There is also the additional benefit that the technologies

that the trainees are involved in developing now have a more defined path from discovery to commercialization and translation.

That initial goal is in progress and now we are broadening our vision – we have established an industry consortium and a local receptor vehicle for technologies. CCRM can now participate more fully in actually taking the best technologies, whether they are from Ontario or from other places in the world, and bringing them together to create solutions that any one technology alone would not be able to do. By being able to bundle technologies into common themes, to participate with industry in technology validation and development, and by guiding the emergence of technologies into companies, we hope to be able to accelerate their uptake by the market, and ultimately help them to achieve the true global impact that they can have.

■ **In 2011, Osiris's product Prochymal® was given marketing approval from Health Canada & was the first stem cell product to be approved for a systemic indication. In your view, does Canada have a conducive environment towards translating science from the laboratory bench to the clinic & how does CCRM fit within this landscape?**

CCRM is designed to try to make that environment more appealing to companies. We all face certain challenges in terms of helping good technologies become good products, and indeed that is part of the role of a translational research center.

In terms of the environment in Canada, Health Canada and the approval agencies are certainly very open to cell therapies and new types of regenerative approaches; however, they also do not have a huge amount of experience in this. This is an area where we are all learning and there is enthusiasm to try to find solutions that are both safe and effective. Another important component of progression in our field is having a clinical community that is both willing and able to implement these therapies. Here, there is an opportunity to use the more centralized health system to successfully track patients and therapies across Ontario, and ultimately Canada.

■ **You have spoken about the key role of collaboration in your work. Why do you think collaboration is so important in this field?**

In my work we are driven to find specific solutions to what, hopefully, are important problems. For example, we want to learn how to generate and formulate cardiac cells into a system for high-throughput screening, or we want to learn how to grow blood stem cells of certain quality and quantity. These are clearly defined problems, and what we are really open to are the different solutions to achieving results. In one case it might mean that we need to understand the network biology of feedback secreted factors, and in another case we might have to microfabricate specific types of engineered devices to formulate cells into. These are very different skills, and skills that different groups are much better at than us. Being driven by the problem as opposed to always being tied to a specific type of solution has really allowed us to make some progress, while also introducing more people to the exciting field of regenerative medicine.

One of the fantastic things about regenerative medicine in general is that it requires the contribution from many different types of investigators in order to be successful. The strength of networks such as CCRM and the Canadian Stem Cell Network is that they can serve as a catalyst for focusing efforts on particular potentially high-impact problems.

■ **The Canadian Stem Cell Network has a strong reputation in facilitating such a collaborative environment, both within Canada & internationally. How have you experienced working with the Network?**

The Canadian Stem Cell Network is in its last 3 years of its final funding cycle, but it has been absolutely transformative in terms of its impact on Canadian stem cell and regenerative medicine research. It has created a very tight-knit collaborative community across the country, which was certainly not present before in the same manner.

I have been involved with the Canadian Stem Cell Network for the last 13 years – it

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basically started the year that I got my principle investigator position. I have grown up in it and I am now a member of their Research Management Committee. It is interesting to think about why it has been so successful. Part of its success is that the network has brought groups together on certain projects where different skill sets can contribute, and another part of it is fiscal support where there is enough money to achieve something, but not enough that it can be done without innovative collaboration. It has allowed the formation of a network where students interact with each other and really drive projects and collaborations, as well as working within the network of principle investigators themselves. It has been a really successful experiment and it is very important for us to now think about how to continue to support this ecosystem after the funding is completed.

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One way that we are continuing the Network's activities is through the annual Till & McCulloch Meetings, which are now partnered with the CCRM. We have an exciting meeting in Banff, Canada, coming up in October 2013. While we definitely want to ensure that there are a number of exciting projects within the network that CCRM will help to bring over the finish line, it would be a mistake for Canada to focus solely on translational aspects, since the discovery pipeline that the Canadian Stem Cell Network (and other stem cell funding programs in Canada) represents is vital in order to continue the long-term process of solving regenerative medicine problems that should impact the health of people worldwide.

■ **Where do you see your research being focused in 5–10 years?**

We are now becoming very interested in how to take what we are learning about these feedback networks and the interactions in the stem cell niche that we are modeling and recreating *in vitro*, and actually target them *in vivo*. Can we change the balance of signaling by delivering specific molecules or specific molecular signals to cells *in vivo*, and thus never have to take the cell out of the body? That would result in more of a regenerative biological-type therapy than a cell therapy. While not feasible for all therapeutic options, this type of approach could be useful for some disease types, and thus is an area that we are thinking about quite carefully.

Disclaimer

The opinions expressed in this interview are those of the interviewee and do not necessarily reflect the views of Future Medicine Ltd. E Culme-Seymour is Assistant Commissioning Editor for Regenerative Medicine and is also an investigator on the BRITS project funded by the Technology Strategy Board under their Regenerative Medicine program: Value Systems and Business Modelling.

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P Zandstra is employed by the University of Toronto, and is a consultant for the Centre for Commercialization of Regenerative Medicine. P Zandstra has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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