**Stem cell detective work: How George Daley uncovers iPS cells’ secrets**

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George Daley (File photo)

Immediately after last month’s ISSCR meeting, George Daley travelled to the University of Toronto where he had been invited to be an external reviewer on a PhD thesis defense. While there, Daley spoke to a packed audience interested in what he had to say about cell differentiation.

In Boston just days earlier, Daley explained that [iPS-derived blood-forming cells can produce early embryonic components](http://cirmresearch.blogspot.ca/2013/06/isscr-it-takes-neighborhood-to-get-cell.html) of the blood system, like hemoglobin, not the adult forms required from a mature clinical product, which foreshadowed his Toronto lecture on how his group can detect limitations in cell differentiation protocols that leave cells a few steps away from their intended identity.

When not playing the role of External Thesis Examiner, Daley is a detective when it comes to iPS cells, seeking truth amongst nuances of stem cell biology. He leads a group of nearly twenty at Children’s Hospital in Boston whose collective goal is to try and coax iPS cells towards becoming useful cells that could be used to regenerate crucial systems within patients and solve liver and blood diseases.

His interest in the subject reaches back to Daley’s years as a graduate student with David Baltimore, where he routinely differentiated embryonic stem cells into blood cells *in vitro*, believing that someday it would be possible to regenerate a fully functional hematopoietic system.

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Yet, while bone marrow transplants are recognized as the best clinical path for curing certain malignancies in the blood system, Daley claims that they’re usually – and wrongly – portrayed as easy. The reality is that bone marrow transplants are far from perfect, he claims, and not low risk solutions at all, referring to them as “heroic interventions, plagued by problems of toxicity.”

He believes that understanding how to perfect the process of creating transplantable cells from iPS cells is critical. “If we could make bone marrow transplants routinely autologous, we could eliminate immunological toxicity.” said Daley. “It’s still my hope to get there one day.”

The lecture hall in Toronto heard him speak at length on the need for reliable methods to induce pluripotency and differentiation in cells. Current methods leave a lot of variability between cells descended from similar progenitors, an observation perhaps obvious to those up-to-date in this field, but this wasn’t the case until recently.

Part of the problem comes from the wide variety of techniques used in the field.

“There are now a dozen different ways of making iPS cells,” said Daley, “but most of these have made way for non-integrating methods [that don’t alter genomic DNA], which are safer.” Revealing his preference, Daley explained that [episome-based protocols](http://www.lifetechnologies.com/ca/en/home/communities-social/blog/blogs/generating-virus-free-and-integration-free-induced-pluripotent-stem-cells-ipscs.html) have become the dominant technique used by his group.

The other part of the problem seems to have developed from the scientific community as a whole.

In an interesting historical anecdote, Daley hinted that the changing demands of publishers and peer reviewers in past years influenced opinions and the questions being investigated by cell biologists researching iPS cells.

“In the early years (2006-2008), it was necessary for us to get into high impact journals and we had to argue that iPS and ES cells were identical,” said Daley. After a few years of demonstrating the cells’ equivalency, the field had shifted 180 degrees, he said, explaining that, “In 2009-2011 we had to argue there were interesting differences between the two.”

In hindsight, the first several years of iPS work delayed recognition of their diversity, and it’s only now that the knowledge to control their variability is blossoming.

Daley shared examples from current work from a collaboration with [Jim Collins](http://www.bu.edu/abl/index.html) at Boston University, where activity within genetic pathways emblematic of different cell types can be scored and tracked.

Using their method, called CellNet, Daley showed that pathway activation and deactivation can be monitored in differentiation experiments converting mouse embryonic fibroblasts to induced hepatocytes (iHep), and that the cells, previously considered to be terminally differentiated hepatocytes, expressed posterior gut genes like Cdx2.

Exploiting this data, the group was able to repeat the differentiation experiment and showed that additional inhibition of activity within the Cdx2 signalling module produced improved iHep performance in terms of albumin and urea production.

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In essence, the CellNet approach can be used to determine how to improve cell differentiation protocols by revealing incomplete conversion of cells.  The work should be published shortly, said Daley.

As to why cells resist complete conversion, Daley explained that some epigenetic memory still exists when differentiated cells are made pluripotent again.

“Cellular memory” is an even greater problem when transdifferentiation is studied, where cells of one type are converted directly to another without going through an embryonic state.

“We still don’t know if transdifferentiated cells get close enough to the target cells,” he said, explaining that differentiation strongly depends on transcriptional factor combinations and cellular history. “We’re not going to be able to pattern normal cells unless we follow the normal developmental path followed within the embryo.”

Closing his talk, Daley walked through a number of practical problems and opportunities in stem cell research, mostly linked to methods of cell manipulation.

Daley claimed that one of the largest practical obstacles in regenerative medicine translation appears to be lack of clinical grade commoditized reagents, with a clear need for cGMP-compliant kits in embryonic stem cell research.

He also predicted that single cell genomics is going to influence stem cell research in a big way very soon, and the technology to do so is becoming more available with single-cell genomics centres opening in [Singapore](http://www.fluidigm.com/april-12-2013.html), at the [Sanger Institute](https://www.sanger.ac.uk/about/press/2013/130412.html), and at the [Broad](http://www.fluidigm.com/may82012.html).

Concerning clinical translation of stem cells, Daley sounded very optimistic. “I predict that in 2-3 years we’ll see clinical trials with iPS cells, maybe even sooner”, he mused. Perhaps not coincidentally, just ten days after Daley spoke in Toronto, Japan‘s Health Ministry announced preliminary approval for [clinical research using iPS cells to treat retinal degeneration](http://online.wsj.com/article/SB10001424127887323689204578571363010820642.html). Daley[seemed upbeat about this work](http://www.nature.com/news/stem-cells-cruise-to-clinic-1.12511) getting the go ahead when interviewed by *Nature* in March.

Other trials could possibly be to replace dopaminergic neurons devastated by Parkinson’s disease, but given the breadth of work he’s led and the news from Japan, I can’t help but think that Daley was much more aware of the timeliness of stem cell clinical trials than he was letting on. With researchers like Daley in the field, the next few years should be very exciting indeed.