Childrens Hospital Boston

Straight talk with… George Daley

In 2008, the method of taking skin cells from people suffering from disease and transforming them into embryonic-like stem cells was heralded as the 'breakthrough of the year' by publications such as *Time* magazine. Two years on, so-called induced pluripotent stem (iPS) cells are just beginning to shed new light on disease biology. From day one of this burgeoning area of study, stem cell pioneer George Daley of Children's Hospital in Boston, who developed the first library of disease-specific iPS cells lines, has remained involved in this fast-paced field. Ahead of the June annual meeting of the International Society for Stem Cell Research (ISSCR) in San Francisco, **Elie Dolgin** spoke to Daley about when and how reprogrammed stem cells will deliver.

Had you been working on cellular reprogramming before Kyoto University's Shinya Yamanaka reported the first mouse iPS cells in 2006?

Yes, I'd been thinking about reprogramming since the late 1990s, when I started to consider using embryonic stem cells to make customized cell therapies. That initially took the strategy of using cloning, though we never made human nuclear transfer effective. Then, in 2004, I wrote a grant proposing a facsimile of the Yamanaka experiments but using spermatogonial stem cells and germ-lineage pluripotency as a vehicle for affecting reprogramming. Once Yamanaka solved the problem, I turned around virtually my entire program to take advantage of that breakthrough. So, I've been thinking about generating customized stem cells for well over a decade.

How is your lab using the two dozen or so disease-specific iPS cell lines that you've made?

For our interest in bone marrow failure, we're starting by recapitulating and gaining confidence that these cell lines actually reflect disease phenotypes. In the case of Shwachman-Diamond syndrome, for instance, that they reflect granulocytes defects; or in the case of Fanconi anemia, red cell defects. There's a whole variety of these [disease-specific iPS cell lines] that we're just documenting the deficiencies in.

Will it be easy to use iPS cells to study complex diseases of unknown genetic causes, such as Alzheimer's and schizophrenia?

That's an area of modeling that is going to be one of the more challenging. There's no doubt, particularly for complex diseases that are more than monogenic, that there's a very elaborate interplay between the way the genotype plays out and the way the environment affects the cells. It may be that for certain diseases with a strong environmental component, we won't see the recapitulation. So most research groups are starting with well-defined, single-gene disorders where you have a reasonable sense of what the cell type being influenced by the disease process is.

Several studies have hinted that iPS cells are not as versatile as embryonic stem cells. Will this limit the utility of the former?

I'm taking a little bit of a wait-and-see approach with some of these papers, because I think some are contaminated by the fact that the cell lines they're working with are incompletely reprogrammed. We're still learning how to make a true *bona fide* iPS cell in many contexts, and the technology is evolving. There's no reason in my mind to think that we're not going to have iPS cells that function as well as embryonic stem cells, but it may be that there are fundamental limitations in the reprogrammed cells.

What's the next step after validating these cells' utility as disease models?

Once you have a cellular phenotype, then you can use these as templates for drug screens. This has been established by proof of principle, but there's at least one company that I'm actually involved in, [South San Francisco–based] iPierian, that's doing this on a grand scale for finding new drugs, although we still need to validate that. This company is going to succeed based on being able to prove to the community that these iPS lines are a novel substrate for discovering new drugs. And the early data that I know from the company is very promising in that regard.

Why haven't we seen many new insights from disease-specific iPS cell lines?

You can't hold the field to too high a standard. It's only been two years, and a lot of this stuff is in the pipeline. As with any new technology, the initial wave of infatuation finds a bit more reality, and we ultimately come back to a more sober sense of what the relative advantages and limitations are. The first wave of papers that you're going to see will be proof-of-principle experiments that, in a sense, validate our preconceptions. And then, from the basis of established knowledge, you generate new insights. I certainly hope and I anticipate seeing over the next three to five years an even greater exploitation of that platform to not only give us new insights into disease but, I would hope, also generate new drugs.

What are the main hurdles to iPS-based cellular therapies?

The first and major challenge to making cell therapies work is to understand how to direct the differentiation of a specific cell type that is amenable to transplantation, engraftment and survival. Then, once you get actual protocols that are effective *in vitro*, then you have all these safety issues, all of the concerns about genomic and epigenetic integrity of cell lines that have been kept in culture for months, and the attendant safety and toxicity questions when you start putting cellular products of a completely novel nature into patients. I've written widely about this, and I continue to find this a very challenging road ahead, but there are many people working in earnest to try and solve these problems.