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A Human Stem Cell Project?

Advances in the study of embryonic and adult stem cells offer opportunities to boost research on both cell types towards clinical applications. But funding and coordination at national levels will be required to make the most effective progress.

This issue of *Nature* contains two significant papers on stem cells, prompting an assessment of the scientific and political terrains ahead and of some of the hurdles that must be overcome to bring stem-cell therapies to the clinic. One paper, by Catherine Verfaillie and colleagues (see page 41), describes a kind of adult stem cell that may turn out to be as versatile as embryonic stem (ES) cells. The other, by Ron McKay and colleagues (see page 50), shows that mouse ES cells can generate neurons effectively to relieve symptoms of Parkinson's disease in a rat model.

Opponents of ES-cell research are already heralding Verfaillie's adult stem cells (called multipotent adult progenitor cells, or MAPCs) as proof that work on human ES cells is no longer needed. Appropriately, the message from the stem-cell research community has been a resounding call for more research on both adult and ES cells in animal models of human diseases. It is far too early in the game to discount ES cells that can perform as powerfully as those studied by McKay and other researchers. And it is clear that thorough functional characterization of engrafted MAPCs needs to be carried out before it can be said that these cells have the same kind of clinical potential as ES cells.

Stem-cell researchers have already greeted both reports with cautious optimism, but they note that it will be years before human therapies emerge from this and other stem-cell research, and cite gene therapy as an object lesson in the dangers of promising too much, too soon. Verfaillie's findings have been rumoured for over a year, but her results are so remarkable that they await confirmation by many other labs to gain true acceptance. If confirmed, there will need to be a coordinated effort to train researchers to use MAPCs, derive new cell lines, and make them widely available to the scientific community. Interest in the cells will be intense, and the burden of training and distribution should not fall on Verfaillie's modestly scaled academic lab.

A coordinated endeavour

Likewise, to realize the potential of human ES cells, coordinated efforts should be made to standardize techniques and practices for growing and differentiating cells, from all available sources. This will be necessary to determine which ones perform best for different applications, and to develop ways to scale up production and provide a uniform, highly characterized source of human ES cells for primate studies, which will now be needed to confirm the rodent experiments. Putting in place such a cohesive research infrastructure could also provide a transparent and regulated framework so that the derivation of new human ES-cell lines can be conducted according to approved procedures and ethical guidelines.

The research community widely acknowledges that the creation of new ES-cell lines will be necessary to obtain cells with optimal growth and differentiation, and this will no doubt be the case for MAPCs as well. In countries such as Israel, Singapore and Britain, where researchers are permitted to derive ES-cell lines from few-day-old embryos generated by *in vitro* fertilization, deriving new cell lines is a priority.

However, since President George W. Bush's ruling on 9 August 2001, US researchers with federal funding must make do with the 64 ES-cell lines that existed before that date. In fact, the reality seems much more restrictive, as scientists have complained that only a few of these lines are actually available. Moreover, the available lines are said to be difficult to cultivate, and in some cases carry hefty price tags or heavy intellectual-property entanglements.

An example of the kind of analysis that would hasten the progress of work on embryonic and adult stem cells is demonstrated by labs in Israel. Researchers there are painstakingly comparing the characteristics of cells sent to them from around the world, albeit with only a handful of human ES-cell lines at present. This type of effort must be carried out on a much greater scale for both ES cells and MAPCs, if further studies confirm their clinical promise.

Growth funds

The US National Institutes of Health (NIH) has made some movement in this direction, by providing $1 million in grants for establishing courses on human ES cells (see http://grants1.nih.gov/grants/guide/pa-files/PA-02-054.html). It has also provided $3.5 million to enhance resource infrastructure at two companies and two universities that between them possess 17 human ES-cell lines that meet Bush's criteria. The grants are meant to promote the expansion, testing, quality assurance and distribution of human ES-cell lines (see http://www.nih.gov/news/pr/apr2002/od-26.htm).

ES cells and MAPCs represent tools for defining the molecular basis of pluripotency (the ability to form most or all tissues or cells of an organism), as well as the molecular cues that steer these 'blank' cells to different developmental fates. Scientists must now explore how ES cells and MAPCs are alike and how they differ, by growing and analysing them side by side. This should ideally be done at facilities that have demonstrated expertise in working with both cell types, something that doesn't exist at this time. Will the observed differences between MAPCs and ES cells prove to be fundamental to their developmental potential? What other differences will emerge? For example, it seems that MAPCs are good at forming liver cells, but not cardiac cells, which ES cells form easily in culture. Undifferentiated ES cells form tumours when injected into animals — will it be possible to remove potentially contaminating ES cells from differentiated cell populations? Only by making these studies comprehensive and carrying them out under highly standardized and reproducible conditions will meaningful conclusions emerge. In this way, we can discover the appropriate practices, protocols and high-quality cell sources for clinical trials.

Several stem-cell institutes have been initiated worldwide, albeit all on a relatively small scale compared with, for example, the heavily funded and highly coordinated enterprise to sequence the human genome. The $3.5 million the NIH has earmarked for infrastructure grants seems absurdly small, especially when weighed against the extraordinary promise of stem cells to deliver therapies for many human diseases in a relatively short time. Researchers estimate that it will be about a decade before stem cells can be used to treat human diseases, but by applying the lessons in teamwork and leadership learned from other big-science endeavours, this time line might be accelerated. Perhaps it's time to start thinking about a Human Stem Cell Project. ■