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News Feature

Nature Reports Stem Cells
Published online: 17 September 2009 | doi:10.1038/stemcells.2009.122

(Stem cell) banking crisis

Lucas Laursen[1]

Stem cell banking must expand to keep up with demand, say researchers

Like most stem cell biologists, **Helen Mardon** obtained her first cell lines from someone she knew. Later, when she needed more material, she chose to pay for a line from a commercial dealer. Eventually, the Oxford Stem Cell Institute co-director derived her own in-house human embryonic stem cell core from embryos donated by *in vitro* fertilization patients.


Derek Hei, US National Stem Cell Bank

Mardon could have gotten human embryonic stem cell (hESC) lines for the cost of delivery from the UK Stem Cell Bank (SCB), one of a handful of stem cells banks worldwide (See **A bank in England for stem cells**). Supported by government funds, the bank stores, distributes and provides ethical oversight of hESC lines in Britain free of charge to academic and commercial researchers. The samples they distribute are top notch: a half-dozen bench researchers screen their stocks to ensure banked lines are free from viral infections or mycoplasma contamination, and routine checks are also completed before lines are shipped. But for now, Mardon says, "going through the bank just adds a huge layer of paperwork and bureaucracy".

Due diligence

Some British researchers are using the bank. Lesley Young, chief supervising biologist of the UK SCB, declined to provide names of researchers who have received lines from the facility, citing confidentiality agreements. However, the SCB's 2008 annual report states that the facility received 124 requests for lines and sent 59 shipments to requestors.

"The UK Stem Cell Bank set one of the higher [quality control] standards," says **Chad Cowan** of Harvard University's Harvard Stem Cell Institute in Cambridge, Massachusetts. But British researchers pay a price: they only have access to 14 cell lines through the SCB. Young says that the bank's 3 full-time staffers are chipping away at an additional 20 or so hESC lines donated to the bank. Depending on how successfully they grow, each line can take 2–8 months of preparation before the bank can offer it to researchers.

The US National Stem Cell Bank, funded on a $16.1 million, 4-year contract from the National Institutes of Health (NIH) and administered by the WiCell Research Institute at the University of Wisconsin–Madison, distributes 19 of the 24 or so hESC lines that were eligible for US federal funding under former president George W. Bush and brokers distribution of some lines banked elsewhere. At Harvard, Cowan says, stem cell researchers have banked about 50–60 hESC lines and around 30 induced pluripotent stem (iPS) cells, of which 17 are currently available to outside researchers, pending material transfer agreements. This has been achieved using funds from the Harvard Stem Cell Institute, the Howard Hughes Medical Institute in Chevy Chase, Maryland, and other private sources. Preparation and shipping times are comparable to those for other banks (3–6 months to characterize and bank; 2 months to ship banked lines) at a cost of around $200,000 a year, Cowan estimates (**Table 1**).


Glyn Stacey, UK National Stem Cell Bank

Table 1: Banks and registries of pluripotent stem cell lines.
Other institutions that ship lines include Australian Stem Cell Centre (4 lines), Kyoto University Stem Cell Research Center (3 lines), University of Tokyo Stem Cell Resource Bank (composed of Public Cord Blood Banks, RIKEN cell bank and other research facilities), Massachusetts Human Stem Cell Bank (2 hESC lines shipping, 3 iPS cell lines planned)


Full table

If collaborators in the United Kingdom wish to use Harvard's lines, however, UK law requires that the researchers offer samples to the UK SCB so that an oversight committee can decide whether to bank the lines. This arrangement, coupled with growing amounts of stem cell research, threatens to flood the bank with deposits as researchers diversify existing hESC lines and introduce greater numbers of iPS cells. It's a burden, says Mardon. "Every time [we] genetically modify stem cells, we're supposed to inform the bank, and the idea is that we bank those cells with them."

Peter Andrews of the University of Sheffield, UK, where several of the UKSCB's lines were derived, agrees that banks will have a hard time keeping up with newly created lines, especially if they try to stick to the diligent UK model. "Once you've got a line you very quickly make sublines and variants, and the banks don't have capacity to take all these variants." The best banks can hope to do, he suggests, is "provide an archive of the originals".

And demand will only increase. Researchers are making both iPS cell lines and hESC lines with specific disease mutations, and Harvard University, the University of Toronto, Kyoto University in Japan and other institutions have set up facilities to make, maintain and share lines — which defeats the purpose of a centralized, authoritative archive.

Eventually, researchers hope to bring some of the better-characterized lines to the clinic. The UK SCB hopes to produce clinical-grade lines and distribute them at a cost. This July, the Waisman Clinical Biomanufacturing Facility in Madison, Wisconsin, announced that it had produced a clinical-grade version of one hESC line. However, as precursors to potentially lucrative therapies, the rights to distribute and profit from such lines will be highly contested. In fall 2007, for example, the Singapore-based company ES Cell International announced that it had produced six current good manufacturing process (cGMP) lines, but it has yet to distribute them, reportedly because of disputes with the Wisconsin Alumni Research Foundation, which holds key intellectual property. Bruce Davidson, general manager of ES Cell International, said via email that his company planned to distribute research grade ES cell lines after drawing up an appropriate distribution agreement and that doing so did not require reaching an agreement with WARF. He did not comment on distributing the clinical-grade lines.

In any case, laboratory researchers aren't currently using that many different hESC lines. **Christopher Scott** of Stanford University in California and colleagues have found that the majority of hESC line requests and publications centre on a few well-known lines. He suggests that a well-documented and streamlined stem cell banking system could encourage researchers to characterize a more diverse set of stem cell lines and raise their quality. But researchers are more likely to keep using what they know rather than taking a chance on new lines. "There's a fair amount of superstition," says Scott. "If collaborators say [a line] works well, you naturally pick the lines that seem to be working best."

Surplus starting material (garbage in, garbage out)

Even without all these complications, stem cell banks have plenty to do just to maintain and ship the cell lines for which they are already responsible. The care and feeding of hESCs is a complex process that remains poorly understood. **Derek Hei**, principal investigator of the US National Stem Cell Bank as well as head of the Waisman Clinical Biomanufacturing Facility, says that hESC lines from the same source often show significant differences in behaviour — some grow uncontrollably, for instance, whereas others die prematurely.

"We don't really know why they differ [so much]," Hei says. Mycoplasmic contamination of the cells is a common culprit, and repeated cycles of cell division may be corrupting the behaviour of some cell lines despite their reputed immortality. And then there's the variation among researchers and their techniques. "There are always subtle differences with how they made their [embryonic fibroblasts] or prepared their media [that] can contribute to differences in behaviours," Hei says.

A surprising number of books have been published declaring protocols for maintaining stem cell lines, Harvard's Cowan says. But among bench scientists there is "still no generalized consensus". Instead, he says, "everybody's got their own special recipe, [and] almost anyone would acknowledge that we're learning something every day."

"People should realize right from the start the amount of effort that's involved in these kinds of activities," says Glyn Stacey, director of the UK SCB. For example, the purest growth media is expensive, and many labs compromise by using medium that suits their purposes but may not suit those of other labs. Other lines may have contamination from animal cells that exclude them from being used in human therapeutic applications. This means that the SCB often has to clean up an accessioned line for more general uses. In addition, Stacey adds, improvements each year in growth media and other culture conditions mean the banks must consider whether to re-bank some lines.

Bookkeeping

Besides tracking and shipping cell lines, banks provide an archive that permits researchers to keep track of each cell generation's quirks. Hei says that by closely tracking the behaviour of each line and its growth medium, the banks could offer useful information that provides continuity from one study to the next. Such work is unlikely to occur outside a banking facility, he says.

Cowan calls an easy-to-use hESC line registry low-hanging fruit for the stem cell community. For researchers seeking to work with stem cell lines, "part of the problem is just finding [the lines]", he notes. His recommendation to a Massachusetts inquiry on the best stem cell investment the state could make was to create a centralized registry with the histories of each existing stem cell line and where they can be obtained. That currently takes the form of the International Stem Cell Initiative's registry, hosted by the University of Massachusetts in Worcester, though it and other groups are currently considering a joint portal.

Ethical arbitrage

Information about a cell line's ethical history can be just as important as its biological history. When donors sign an informed consent form, they initiate a cascade of paperwork that grows longer every time their cells or the descendants of their cells change hands.

Work that is permissible or fundable varies from location to location depending on the sometimes obscure details of the donation. Mismatches between the consent obtained at the time an embryo was donated and the language used today can prevent scientists in some jurisdictions from using certain older lines. Other jurisdictions accept cells with fewer ethical restrictions. Such inconsistent ethical practices create what Stanford's Scott calls "ethical arbitrage" among users of stem cell lines, in which rules favour certain transactions over others.

"The ethical landscape is terrifically uneven", says Scott. It hands advantages to jurisdictions that require less rigorous ethical oversight and makes it difficult for researchers to exchange lines for collaborations.

"Anybody who takes a little bit of time to do banking immediately finds themselves drawn into what can be a fairly large and treacherous ethical landscape, and there's not much guidance," agrees Cowan, who, like many researchers, had hoped that the revised NIH guidelines released in July 2009 would offer a predictable, practical way for researchers to share their work with one another. (The NIH plans to create a new registry of ethically acceptable hESC lines pending a review process that has not yet been revealed.)

But reaching a consensus on the best way to obtain, store and distribute hESCs will inevitably result in compromises, Cowan says. Stem cell banks need to keep up with ever-changing biological standards, slow shifts in ethical values and the proliferation of pluripotent cell lines. "To have this one uniform set of ethics at the highest possible standard, to have this one uniform mechanism by which cells are grown, frozen, tested — that's the best," says Cowan. "It just may never come to that."

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A national treasure in three temporary trailers

The UK Stem Cell Bank (SCB) is a relatively recent addition to the imposing campus of the National Institute of Biological Standards and Control (NIBSC), located north of London. Since 1975, the NIBSC has been home to laboratories that ensure the quality of vaccines and other health-related biological references used by researchers and clinics. Visitors must pose for a security photo outside the main entrance before penetrating the barbed wire fence that rings the red brick complex and its parking lot.


Glyn Stacey, UK National Stem Cell Bank

"Our visitors are always less impressed when they see how small our offices actually are," says Lesley Young, the bank's chief supervising biologist, as she leads the way up a flight of stairs and into one of three temporary trailers which jointly house the SCB.

The UK Medical Research Council and the Biotechnology and Biological Sciences Research Council established the SCB in 2003 to provide quality control for human embryonic stem cell (hESC) research in Britain. Other cell banks, both public and private, existed already, but hESCs have proven particularly vexing for researchers to keep track of.

"Sometimes we've had people complain that we sent them cells that weren't viable," says SCB director Glyn Stacey, "and then we found they didn't get them from us." The scientific and technical staff at the bank have developed enough experience with hESC culturing that they often provide advice and training to newcomers to stem cell research. Young often accompanies shipments to train researchers in the methods used at the SCB.

Young shares an office with a handful of colleagues and a brand-new video screen–equipped microscope. One window of the office trailer reveals the doors of three sterile mini-laboratories, or 'clean rooms' in the attached trailer, and the other provides a glimpse through some trees towards the new building the bank will occupy sometime next year, when construction is complete. The newer facility should have five clean rooms and additional, larger freezers to store banked lines, plus an off-site location, just in case samples at the main facility are destroyed.

Expansion in space and staff should help the bank keep up with demand, along with planned staff hiring. A website upgrade is also in the works, which the bank has told users should trim wait times for steering committee decisions from weeks to days in some cases.

Still, even with greater technical capacity, the bank plans to grow judiciously. "We're not a stamp collection. We're not trying to get everything," says Stacey.

What the bank can do to speed things up for researchers, Stacey says, is improve coordination with its international counterparts. "There's every sign that's going to happen through the ISCF [International Stem Cell Foundation]," he says. New nonbinding guidelines, to appear in a forthcoming issue of *Stem Cells Reviews and Reports*, should, he says, help make ICSF members behave "a little like the World Health Organization for stem cells".

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