

New sources of sex cells

Within the next decade or so, it will become possible to derive sperm and eggs from skin cells. The ethical and technical hurdles need to be addressed with the scientific and therapeutic benefits in mind.

Earlier this month, the world had its first look at a pregnant man, a jarring reminder of how conventions in the way humans are created could shift. Just a week later, scientists, bioethicists, lawyers and journal editors convened in Hinxton, UK, to ponder how long it will be until sperm and eggs can be made entirely in a Petri dish from, say, skin cells induced to pluripotency. They asked questions such as how will these advances transform reproductive research and medicine? How might they change society? Is the bioethics community prepared?

These questions have acquired a sense of urgency, at least in Britain, where a government bill updating the 1990 Human Fertilisation and Embryology Act is working its way through the system. If passed by the House of Commons in its present form, the bill would allow basic research on human gametes derived *in vitro* but would not permit the use of such gametes for fertility treatment. Opponents may yet propose amendments designed to stop all embryo research — including the demonstration that *in-vitro*-derived gametes are normal by seeing whether they are capable of fertilization and further development. The Hinxton group's consensus statement, arrived at after three days of discussion, can be viewed at www.hinxtongroup.org/Consensus_HG08_FINAL.pdf.

The organizers scheduled the topic of pluripotent stem cell derived gametes (PSCDGs) two years ago. Since then, making induced pluripotent stem (iPS) cells has become relatively straightforward, but although the technique circumvents the ethical and technical problems associated with collecting human eggs and creating embryos, there are still serious ethical implications. Indeed, the facility with which iPS cells can be derived could make it easier to derive gametes from any person, living or dead.

The potential benefits of PSCDGs are impressive. They could reveal much about the mechanism of gamete development, with implications for treating infertility, certain cancers and genetic diseases, and for facilitating drug tests on gametes. Other potential applications present social and ethical challenges: germline genetic modification for the correction of disease mutations or for research; various

forms of biological enhancement; genetic screening of embryos for selection; and enabling same-sex couples to have their own genetic offspring.

The Hinxton group believes that eggs and sperm will be generated from pluripotent stem cells in 5–15 years, although it concedes this is something of a guess. Technically, a major sticking point is getting the developing gametes to undergo meiosis. Ethically, the problem is quality control: the only conclusive way to test that gametes are functional and can create a viable embryo is to go ahead and do so.

Once gametes can be made, the immediate question will be whether and how embryos derived from them can be created and studied. So iPS research will come full circle, and we will be faced again with the issue that has dogged us since the birth of Louise Brown, the first IVF baby in 1978. Is it moral to use human embryos for research or to create human life with the implicit intention of destroying it during an experiment?

Not conducting this research could cause harm: without it, a pregnancy using an embryo produced by PSCDGs would pose an unacceptable risk for both child and mother. If PSCDGs are to one day join the tools of assisted reproduction, functional tests must be developed to eliminate faulty gametes. Quality tests developed for IVF will be useful in this context and the methods should first be exhaustively assessed on animal models, including non-human primates.

Clearly, appropriate oversight of PSCDG research is needed, but much of the framework for doing so is already in place, in the form of committees for overseeing stem-cell research and institutional review boards for human experimental subjects. Nonetheless, 14 countries already prohibit or restrict PSCDG technology for genetic screening or germline genetic modification, some under penalty of imprisonment. Japan prohibits the creation of human PSCDGs altogether. Where stricter regulations are needed in many countries is on experimental fertility treatments involving human embryos carried out in clinics. But for any country considering legislation in this area, beware of impeding basic research and losing the benefits that could result. ■

The big ome

It's time to make the case for proteins.

The body's building blocks, 'cellular machinery': proteins are sometimes stuck with rather mundane labels. Certainly they sit in the scientific shadow of the genome sequence and the eulogies that inspires. So protein biologists face an uphill battle if they are to fire up the research community — and the world beyond — enough to buy into a Human Proteome Project.

The project is just getting past the back-of-the-envelope stage but, in essence, it would systematically catalogue all the proteins manufactured in the body: what they are, where they are and in what abundance (see page 920). A cancer biologist might reveal whether a rogue protein is overexpressed in the tumours she studies compared with levels from healthy tissue that are logged in the proteome register. A geneticist who traces Alzheimer's susceptibility to a region of code could consult the proteome to reveal which proteins are being manufactured from that region in the brain. We can expect this catalogue of proteins to eventually include the targets for almost all future drugs.

There are many obvious parallels with efforts to elucidate the

human genome. A human proteome would be a very expensive and ambitious undertaking and, by its nature, the full benefits cannot be spelt out beforehand. That's how it should be. The fun of the human genome is that spelling out the letters did little to decipher the code — there is so much more complexity than had ever been imagined. We can expect that the proteome will also reveal unexpected delights about the ways in which proteins rally together to perform a task or become tissue.

And yet there was a certain intellectual allure about 'cracking' the human genome that, on the face of it, is lacking from cataloguing all the proteins. And although the human genome is finite, the proteome is almost boundless, because each of the body's proteins may be present in different forms and different amounts in each tissue — and even in precisely the same cell from one moment to the next. That very complexity, however, should inspire, not dissuade.

Proteomic analyses have also been viewed with some scepticism, in part because many studies involving mass-spectrometry profiling have proved difficult to reproduce. And the field has so far largely failed to deliver the disease-tracking biomarkers on which these early efforts were sold. There are few examples of clear, clinically proven benefits. Starting out with this kind of reputation will make

a Human Proteome Project particularly hard to sell.

The Human Proteome Organisation (HUPO) has taken some praiseworthy steps towards resolving these issues with, for example, a project to show that different labs can now produce identical results from the same sample. With the rapid evolution of proteomic techniques, the field's reputation and utility is likely to pick up. But HUPO — and the proteomics community — still has a lot to prove and a successful Human Proteome Project is its chance to prove it. It needs to consult widely to devise a strategy that has strong community backing. It will also need to demonstrate that the knowledge stemming from this project will transform the research landscape in the same way that the genome sequence has done.

Failing these, either the project will die or HUPO could risk being left on the sidelines as organizations with money to spend make the decisions about how proteomics should be done.

Times have changed since the Human Genome Project — proposals for mega-biology projects are rather more common and money scarcer. HUPO, and all biologists who love proteins, should articulate clearly and loudly the benefits of sinking US\$1 billion into protein biology. It will take much work to get due recognition for the 'cell's work-horses'. ■

Superconductors *redux*

Yet another surprise has been uncovered in the complex oxides.

With the discovery of a new class of high-temperature superconductors by researchers in Japan (see page 922), history seems to be repeating itself. In 1986, Georg Bednorz and Alex Müller of IBM's Zurich research laboratories discovered that a complex oxide of barium, lanthanum and copper became superconducting at 35 K. This sparked an orgy of research that led to the discovery of a related compound (yttrium barium copper oxide) with a superconducting transition temperature of 90 K: high enough to be attained with relatively cheap liquid-nitrogen cooling. It also won Bednorz and Müller a Nobel prize just a year later.

The excitement stemmed from the prospect of exploiting low-cost superconductivity for loss-free electrical transmission, magnetic levitation and other dazzling applications. In superconductors, currents flow essentially without electrical resistance, the source of energy loss through heating. Before 1986, most superconductors were metals and alloys, with generally paltry transition temperatures that no one had managed to push above 23 K.

Now Hideo Hosono of the Tokyo Institute of Technology and his colleagues have shown that another complex oxide, containing lanthanum, iron, arsenic and a little fluorine, will superconduct at 43 K when squeezed by around 40,000 atmospheres pressure: a higher temperature than anything bar the copper oxides (see H. Takahashi *et al.* advance online publication: doi:10.1038/nature06972). Like them, the new material has a sandwich structure of alternate conducting and insulating layers. And like them, doping (replacing some oxygen with fluorine) injects electrons into the conducting

layer that contribute to the supercurrent.

The copper-oxide materials have found some uses, but nothing to match the expectations heaped on them in the late 1980s — levitating trains and so forth. It has proved hard to fashion these brittle materials into wires and progress is slow. So cynics might grumble that the new breakthrough will merely renew the same unfulfilled promises.

But the new compound already offers more. For one thing, it reveals how much remains to be discovered about complex solid-state compounds. The combinatorial possibilities for four or more elements are so vast that we have barely scratched the surface, despite efforts to automate the search. And as before, the discovery followed from sound chemical intuition. Bednorz and Müller were led to the copper oxides from the apparently unpromising strontium titanium oxide, a superconductor at a mere 0.3 K, by reasoning what kind of crystal chemistry might boost the requisite interactions between electrons. Hosono and his colleagues similarly picked a systematic path from their initial discovery, in 2006, of superconductivity at about 4 K in a related material, a temperature so low that it attracted little interest. They raised this to 26 K by the start of 2008, and rightly figured that squeezing would take it further.

Most crucially, the 'iron oxypnictides' show that high-temperature conductivity is not the sole preserve of copper oxides. As in that case, superconductivity in the new materials seems to be related to magnetic behaviour. But quite how this works has remained a mystery. With an entirely new family of compounds to play with, the mechanism might be persuaded to start giving up some secrets. With a theory to hand, 'designer superconductors' with much higher transition temperatures might not look like a fool's quest. There could be another Nobel prize in that. For now, it is enough that the oxypnictides have set the community buzzing in a way that recalls the last heyday of superconductors two decades ago. ■