

## The embryo grows up December 2008

*With the passage of the Human Fertilisation and Embryology Act 2008, the stem cell community is able to turn to more immediate challenges. Julian Hitchcock of Mills & Reeve, who is also a Director of the East of England Stem Cell Network, reviews a domain whose time has come.*

### Introduction

The new *Human Fertilisation and Embryology Act 2008*, which reforms the 1990 Act of the same name, changes the law on embryo research rather less than the fuss might suggest. True, research may now be licensed for purposes of increasing knowledge, not only of serious disease, but of other serious medical conditions; for example, neural trauma or tissue damage. True, applications may now be founded for the purpose of developing treatments for such conditions; for example, studies into how stem cells transform into particular tissues may lead to methods for repairing and regenerating tissue lost to disease or trauma. True, the Human Fertilisation and Embryology Authority (HFEA) may now grant licences when it is “desirable” to support such research; a purpose which would include the development of non-biological technologies. Licences to alter the genetic structure of cells forming part of an embryo will also become possible. These are all quietly significant advances, but the more controversial aspect, the legitimacy of creating embryos using both “animal” and “human” material, had already been accepted by the HFEA. No, the significance of the new Act is not the enlargement of the research franchise or the statutory tidying-up, but the fact that it could all have been so different. Precisely because these issues had to run the gauntlet of full-on Parliamentary debate, the 2008 Act provides the highest possible support for an area of immense economic importance: regenerative medicine.

### Embryonomics

One law never changes: things fall apart. Living longer is no answer: our aging bodies still wear out, surviving on a regime of pharmaceuticals and care. The cost, already vast, is spiralling and the ratio of economically productive to economically dependent members of society is being turned on its head. A technology which *cured*, rather than dosed, conditions such as Alzheimer’s, diabetes and blindness would, therefore, not only alleviate human suffering, but provide a solution of colossal economic significance to individuals, insurers and governments. Indeed, the state with the most valuable regen patent ownership on its patch could effectively tax all the others.

It's not all about embryos. Many stem cells live in adults, and are of considerable significance, as the recent example of the Bristol windpipe clearly shows. However, such "adult" cells lack the capacity of embryonically-derived cells to differentiate into *any* tissue type, for example, nerve cells. Such "pluripotency" puts a premium upon embryo patents, notably on a group of patents, owned by the Wisconsin Alumni Research Foundation, concerning techniques for isolating human embryonic stem cells and the cells themselves. WARF's claims are so broad that, in effect, it guards an embryonic stem cell gateway, collecting royalties from all those who can afford to enter. While WARF's US patents were recently certified as valid, following concerted opposition, the corresponding European application was rendered invalid last week by the Enlarged Board of Appeal . More significantly, however, the ruling expressly does not affect other stem cell patents in Europe. The many related applications to inventions that do not directly involve the destruction of embryos are unaffected and, having sat on EPO ice for some years, may now proceed in the direction of grant; an ironic shot in the arm if ever there was one.

There is, however, a more fundamental problem with stem cell patents: they are just too short. For all the headlines, the road to market for many therapies is harder and longer than that of any other medicinal product you care to think of. So long, in fact, that the original patents may have expired by the time anything is sold: hardly a reason to invest in research. Given the coincidence of economic benefit and investment need, voices within the stem cell community are calling for an international extension of term for therapeutic stem cell inventions. The embryo squad, of course, will be waiting to do battle.

### Beyond the embryo

Oddly, the entities that inspire so much debate are "embryos" more in law than biology. Their elevation, following the majority advice of the Warnock Committee, was based upon their inherent human merit; their chimp equivalents remaining with the blastocyst *hoi polloi*. The "embryos" from which stem cells are extracted are, therefore, little more than fertilised eggs, whose significance lies in their potential to change into different tissue types and which become useless if, before extraction, they actually do. If they could develop sufficiently to suffer (which they can't) they would be worthless. The prospect of making "embryos" using animal egg shells (to compensate for a shortage of human eggs) added a frisson of *Doctor Who* to the HFE debate, but the truth is fairly mundane.

Nevertheless, the "embryo problem" lingers on, leading some to pray that pluripotent cells might be derived from an alternative source. A year ago, in the midst of the House of Lords debate on the Bill, these prayers were answered by Shinya Yamanaka and James Thomson, using ordinary skin cells. Lord Alton and his allies, apparently unmoved by a subsequent report that entire human embryos could be made from skin, pounced on the announcement, proposing an amendment that would permit the use of embryos only where the use of such ethics-free cells was impossible.

Alton's amendment failed, but "iPS" cells are transforming the domain anyway, by providing a way to bypass WARF in areas such as drug testing and, possibly, in the clinic. If the requirement of cancer genes to induce pluripotency can be eliminated, companies like Izumibio, which seek dominance in iPS patents, are heading for the money. Some, however,

see Yamanaka as betokening a deeper shift; from cells to the factors which determine their fate. In the emerging patent landscape, inventions for producing pluripotent cells may wane before processes for transforming one specific cell type into another. Such epigenetic power may lie in relatively small molecules; the stock-in-trade of a business in desperate need of new products and imagination; the pharmaceutical industry. Indeed, on the very day that the new HFE Act became law, Pfizer launched a new regenerative medicine unit in Cambridge; a development of at least equal significance. Cambridge is home to the world's leading epigenetics company, CellCentric, and some of its foremost epigeneticists.

### From ethics to engineering

The drift toward regenerative reality will be brought home this month, with the coming into force of the European Advanced Therapies Regulation, under which tissue engineered products sitting in the gap between cell/tissue grafts and medical devices achieve medicinal product status. The classification of such products, insofar as there were any, has tended to exercise regulators across Europe, with some states treating them as devices and others as medicinal products. This was unlikely to enhance the prospects of a young industry with more than enough challenges to face, but the Regulation changes everything: by centralising (under the European Medicines Agency) the marketing authorisation of genetic-, cellular- and tissue engineered products, discounting fees, offering opinions on whether they fall within the requisite definition, providing scientific advice and support from a newly convened expert committee and to some extent exempting hospitals. The market scalability, which the Regulation promises, provides a singular boost to the development of increasingly complex products, from windpipes, bladders, joints and jaws to synthetic pancreases and regenerate lung, retina and heart tissue.

The ethical issues haven't gone away: the Regulation will be subordinate to national legislation prohibiting or restricting the use of human embryonic stem cells, or the sale, supply or use of medicinal products containing, consisting of or derived from them. Until advanced therapy products involve embryo-related cells, the European market should remain uniform. Thereafter, more sophisticated therapies, notably in relation to the nervous system, may only be available in states such as the UK.

By providing reassurance that moral issues are being handled responsibly, the 2008 Act allows a shift towards the practical, from ethics to engineering, with growing attention to good manufacturing practice and the need for closer transatlantic coordination on regulatory approval. The problems are mighty and our new laws are bound to date quickly. Nevertheless, the sense of progress is palpable.

**Julian Hitchcock**

**Senior Solicitor**

[julian.hitchcock@mills-reeve.com](mailto:julian.hitchcock@mills-reeve.com) +44 (0)1223 222545

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