SCIENCE|BUSINESS

REGENERATE THE FUTURE

SPECIAL REPORT

Experts debate the future of stem cells

What is the state of play in R&D funding for stem cell research?

What research should Horizon 2020 support?

Will restrictions on patenting hold back market entry?

How Europe Can Build on its Leading Position in Regenerative Medicine and Stem Cells

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The Health for All, Care for You Project

Health for All, Care for You is an ongoing multi-stakeholder investigation led by Science|Business analysing the future opportunities for – and barriers to – stratified, personalised, and next generation medical therapies in Europe. Launched in 2009, the project has led to collaborations between members of the US Congress and European Parliament, as well as multiple high-level working groups and peer review publications.

In terms of personalised medicine this has involved two major pieces of research. The first gauged opinions and sized up the barriers to implementation. The second study used real-life data to feed computer simulations of the impact that adopting personalised healthcare measures would have in breast cancer and cardiovascular disease. Some of the outcomes have been surprising, but they show the potential for reducing the cost per patient and promoting the sustainability of EU health systems.

Following on from this international overview of the current state of play in regenerative medicine, in 2013 Science|Business will launch an investigation into the potential impact of "big data" analytics on European healthcare systems. Ultimately, Health for All, Care for You is an ever-expanding warehouse of knowledge, outlining Europe's opportunities for innovation in healthcare.

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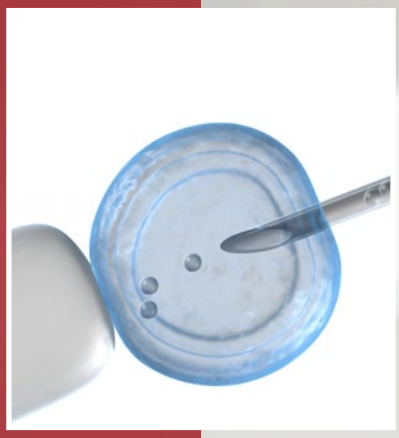
FOREWORD

Stem cells hold limitless promise for treating disease

Europe is currently a world leader in the fundamental science underpinning regenerative medicine and cell therapy, and in its therapeutic use and regulation.



Although this technology is still in its early stages, there is clear evidence of the transformational prospects it offers. To date, most evidence of the benefits comes from autologous treatments, in which cells or tissues are taken from a patient and processed in some way, before being administered back to the patient.

These autologous treatments are delivered at hospital-scale, with local processing on site. However, one autologous cell therapy, ChondroCelect, for treating damaged cartilage, has been approved by the European Medicines Agency, under the Advanced Therapies regulation – a recognition that the process for extracting, processing and administering cells can be done in a quality-controlled, repeatable manner.

While by using a patient's own cells autologous treatments avoid the risk of immune rejection, they are expensive to make and deliver. What's needed to open up the true medical potential are allogeneic therapies that are suitable for any patient.

This calls for alternative sources of cells. In particular, it calls for the development of techniques for reliably and repeatably differentiating and expanding them, both from human embryonic stem cells – with their ability to become any type of cell in the body – and from adult stem cells, which have a more limited repertoire.

Whatever the original source of the cells, new technology must be developed for manufacturing specialised cells – be they liver cells, brain cells, muscle cells – at scale. These advances are necessary not only to deliver on the therapeutic potential, but to make cell therapies commercially viable and affordable for Europe's healthcare systems.

The first off-the-shelf allogeneic stem cell therapy was approved by the regulator Health Canada in May 2012. The product, Prochymal, based on stem cells from healthy adult donors, is used to treat children with graft-versus-host disease (an acute immune reaction to a bone marrow transplant).

The approval is a breakthrough: it demonstrates there is a route to approving and commercialising therapies based on allogeneic stem cells.

So – there is much to play for in this fast-paced area of science.

Despite solid foundations in regenerative medicine, Europe is now at risk of losing its momentum, with challenges to the patentability of cell therapies based on human embryos and a debate over the funding of human embryonic stem cell research in the European Union's 2014-2020 R&D programme, Horizon 2020.

■ *continued on* ***page 4***

■ *continued from* ***page 3***

This report explores the science of stem cells, provides snapshots of the regulation and progress being made in a number of countries in Asia and elsewhere, and examines Europe's standing vis-à-vis the US.

It also presents the views of experts in the science, policy, regulation, funding, ethics, translation and commercialisation of regenerative medicines and stem cells brought together by Science|Business to assess what needs to be done to build on Europe's strong research and clinical base, weigh the possible consequences of limiting patentability and consider the impact of any change in the funding rules.

Their major conclusions:

1. Cutting human embryonic stem cell (hESC) research would damage regenerative medicine and cell therapy as a whole, holding back critical basic science, undermining collaborations that are central to this multidisciplinary field, sending the wrong message to investors – and damaging innovation in Europe.

2. Induced pluripotent stem cells derived by reprogramming adult cells are an important breakthrough and a potent new tool for drug discovery, disease research and studying pluripotency, but they are not suitable currently for use in cell therapies.

3. As the "gold standard" of pluripotency, hESC cells are needed as the reference for what is the normal pluripotent state, and for understanding the mechanisms that drive stem cells to become specialised cells.

4. The ruling of the Court of Justice of the European Union (CJEU) in November 2011 that cell therapies derived from human embryos are not patentable, will not block the commercialisation of products based on human embryonic stem cells. Germany's Federal Court of Justice (Bundesgerichtshof), which took the case to the CJEU, has now ruled that patents can be granted on products based on human embryonic stem cells as long as their development did not involve the destruction of an embryo. In any case products will be protected by the significant know-how that is involved in their development and by patents on surrounding technologies such as delivery systems and manufacturing processes. As a result there is no justification on the grounds of commercial potential for saying that hESC research should not be funded under Horizon 2020.

5. Although hESC research – which to date has received €107 million to fund 18 projects – represents a small proportion of the current EU R&D programme, Framework Programme 7, axing this funding would have a disproportionate effect, signalling that the EU was moving to a more restrictive regime just as the first clinical trial of a European-developed, hESC-based therapy gets under way.

In summary – cell therapy is a reality. But for the full advantages to be delivered, there must be evidence from properly regulated clinical trials of long-term benefits, allowing this new form of medicine to move from the hospital-scale, autologous model on which it operates today to a scaled-up, regulated European – and global – industry.

Nuala Moran, Managing Editor, Science|Business

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THE SCIENCE AND THE PRODUCTS
Regenerative medicine and stem cells

The term regenerative medicine has become a catch-all for a broad range of currently available and envisaged technologies and products that have the single unifying theme of enabling the body – in effect – to heal itself.

By Nuala Moran

Regenerative medicine products promise to provide both a step function increase in efficacy and – while not necessarily cures – to have long-lasting effects. Regenerative medicine offers the prospect of treatments for disorders that currently are untreatable, and encompasses the vision of being able to generate whole organs to replace ones that are diseased or damaged.

Products falling under the regenerative medicines banner range from:

- de-cellularised patches of pig tissue that are colonised by a patient's own cells and become completely integrated when used to repair damaged veins;
- tissue from human donors that is stripped of donor cells and then coated with cells from the recipient before it is transplanted;
- therapies that involve removing a patient's own cells, expanding and possibly differentiating them before re-injection;
- strategies for encouraging the body's own stem cells to differentiate in situ;
- off-the-shelf cell therapies derived from donor cells and suitable for use in any patient.

At the heart of ambitions for regenerative medicine is the stem cell, the body's own biological repair system with its ability to differentiate into many types of specialised cells.

Within the body a number of different types of so-called adult stem cells busy themselves with the processes of growth and repair – generating new blood cells, repairing torn muscles, producing new bone cells. But it should be noted that the term adult stem cell does not mean the cell comes from a mature human, rather, an adult stem cell is one that occupies a specific and specialised niche, as a blood stem cell or a bone stem cell, and so on.

The various types of stem cell can be seen in the glossary in Table 1, page 9.

This in-built repertoire of body maintenance, growth and repair mechanisms illustrates the potential of stem cells. It is this innate system that underpins one of the longest-established stem cell therapies – the use of bone marrow transplants to regenerate the immune system following chemotherapy for blood cancers.

Bone marrow is also the source of Prochymal, the first approved off-the-shelf allogeneic stem cell product in a western market. The product, which received marketing approval from the regulator Health Canada in May this year, consists of mesenchymal stem cells from the bone marrow of healthy adult donors. Prochymal was approved for treating graft-versus-host disease in children, but it is also in clinical trials in the treatment of Crohn's disease and diabetes.

The approval of Prochymal was seen as a defining moment for the field, illustrating that there is a pathway to commercialising stem cell products. Among the companies celebrating was the Australian stem cell specialist Mesoblast, which is currently planning a Phase III clinical trial of its own allogeneic

mesenchymal stem cell therapy Revascor, in the treatment of congestive heart failure. This will build on Phase II trials, in which there was sustained improvement in heart muscle function at six months in treated patients compared with progressive loss of heart function in controls.

Another company currently planning a Phase III test of a stem cell therapy in congestive heart failure is Cardio3 BioSciences of Mont-Saint-Guibert, Belgium. Its therapy involves taking stem cells from a patient's own bone marrow and re-programming them to heart cells. The cells are then injected back into the patient's heart through a minimally invasive procedure.

Culturing a patient's own cells takes time, and in some indications this may mean missing out on the optimal therapeutic window. To take a related example, in the case of a heart attack, the damage to the heart muscle happens just after the attack occurs. This points to the need for cell therapies to be developed for specific indications, to be available off-the-shelf and to be suitable for use in any patient.

Alongside development of therapies that involve administering cells derived from adult stem cells, another avenue of research is looking at ways to attract stem cells within the body to the site of an injury and then differentiate, thus initiating a natural repair process. One example involves coating stents used for cardiac bypass with antibodies, attracting stem cells that are involved in the formation of new blood vessels to help with the repair. In more preliminary research, scientists are looking to the epicardium, the outer layer of the wall of the heart, as a source of endogenous stem cells that could be prompted to initiate repair and regeneration after a heart attack.

Adult stem cells are a crucial source of cells for use in regenerative medicine, and the past decade has seen significant advances in the tools, techniques, manufacturing and delivery mechanisms needed to process, formulate and administer them. However, they cannot offer the same repertoire of different specialised cells as can be derived from embryos of less than 14 days. Up to this stage of embryonic development, all the cells are pluripotent and can potentially be differentiated into any kind of specialised cell.

hESCs are also fundamental to understanding the processes that prompt stem cells of any variety to maintain a steady state, or to differentiate into a particular cell type.

It was the derivation of the first stable, replicating hESC line by James Thomson at the University of Wisconsin in 1998 that prompted the rapid proliferation of hESC research. But it also sparked ethical and political controversy, leading to bans on research in some countries and strict oversight in others.

The controversy has held things back, deterring scientists from researching hESCs, limiting grant funding and discouraging private investors. Layered on top have been the difficulties of convincing regulators that hESC-based products can safely be tested in humans.

Despite these hurdles hESCs have finally progressed into clinical development, and the first patient in the first hESC trial to be held in Europe left Moorfields Eye Hospital in London in January 2012 after being treated for macular degeneration as part of a Phase I study being staged by the US company Advanced Cell Technology (ACT) Inc.

Soon to be joining ACT in testing retinal pigment epithelial cells derived from hESCs in a European trial is Pfizer's Neusentis stem cell research unit in Cambridge, which will be staging the trial in collaboration with scientists at University College London.

Although the ACT study is designed to demonstrate safety, the company has published initial clinical data on the US arm of the trial showing tantalising early signs of efficacy. The data appeared in *The Lancet* in January 2012, in what was the first report in a peer-reviewed journal of the clinical use of hESC-derived cells for any purpose.

The two patients whose progress was reported in *The Lancet* had shown

A CEO's View

For Silviu Itescu, CEO of the Australian cell therapy company Mesoblast, the approval by Health Canada of Prochymal, an allogeneic, off-the-shelf stem cell-based therapy, in May 2012, is a breakthrough for cell therapy as a whole.

As the first such product to be approved in a western, regulated environment Prochymal has created a clear precedent. "The allogeneic path appears to provide regulators with a reasonably comfortable way of regulating vis-à-vis other biologics, in particular autologous cell therapies, which have variation from patient to patient," Itescu says.

Different cell types in different indications will have to be approved case-by-case, but there should be no barriers in terms of the intrinsic allogeneic nature of such products.

On conducting the European clinical trials of Mesoblast's allogeneic cell therapy Revascor for treating heart failure, Itescu says he has been happy with the European Medicines Agency's oversight. But it is still very bureaucratic getting approvals for clinical trials nation by nation in Europe. "The lack of homogeneity makes it difficult to perform clinical trials, it's much slower than the US," he says.

an improvement in their vision in the four months after being treated with the retinal pigment epithelial cells in July 2011. The improvement in vision came along with an apparently clean safety profile, with no sign of tissue formation outside the retina or any immune rejection at up to four months post-treatment.

The ACT news was very welcome, coming soon after another US regenerative medicine pioneer, Geron, stopped recruitment in its ground-breaking Phase I trial of hESC-derived cells in treating acute spinal injury trial in November 2011. It took Geron 15 years to move from early research to getting permission from the FDA for the trial. The company withdrew from stem cell research blaming the funding environment, not the science.

While in the ACT trial data reported in *The Lancet* there was evidence from imaging that the transplanted cells survived and continued to persist, it is not necessarily the case that cells administered as therapies act as replacements for naturally occurring counterparts. Other trials suggest any positive impacts are not due to engraftment of cells that have been administered – since there is no evidence that they remain in situ – but rather to so-called paracrine effects resulting from growth factors that implanted cells generate. In other words, the delivered cells disappear, and the cells that make up any new tissue are host-derived.

This highlights the need for greater insights into the basic biology of how cell therapies work. The invention of induced pluripotent stem (iPS) cells is proving to be very important here. By removing ethical constraints iPS cells have opened up new avenues of research into the mechanisms of pluripotency.

However, there are fundamental differences between iPS cells and hESC cells which mean the former cannot substitute for the latter – either as a source of cells for therapy or in research.

Reprogramming an adult cell to an iPS cell involves the addition of DNA and as a result, iPS cells would not be a suitable basis for therapies. In addition, there is evidence of fundamental differences between the biology of iPS cells and hESCs, which means they are not equivalent as research tools either.

One example is that the genes in iPS cells derived from patients with Fragile X, an inherited form of mental retardation, behave differently from the genes in hESCs derived from embryos affected by Fragile X.

These differences underline the need to keep supporting research in hESCs – not only because of their potential to differentiate into any type of cell in the body, but also because they are the gold standard for understanding the biology of pluripotency.

Table 1: Glossary with definitions and abbreviations for stem cells and regenerative medicine

Term	Abbreviation	Definition
Regenerative medicine	RM	Reconstruction of functionally impaired, diseased or injured tissue by activation of endogenous repair systems or by implantation of exogenous cells or combination products.
Tissue engineering		An interdisciplinary field that applies the principles of engineering and life sciences toward the development of biological substitutes that restore, maintain, or improve tissue function.
Stem cell	SC	A cell that can continuously produce unaltered daughters and also has the ability to produce daughter cells that have different, more restricted properties.
Embryonic stem cell	ESC	Pluripotent SC lines derived from early embryos before formation of the tissue germ layers.
Foetal stem cell	Foetal SC	Found in blood from the umbilical cord, in the placenta or isolated from aborted foetus.
Adult stem cell	Adult SC	May be derived from umbilical cord blood or adult tissues, among which bone marrow and fat are mostly used.
Tissue stem cell		A cell derived from, or resident in, a foetal or adult tissue, with potency mostly limited to that tissue. These cells sustain turnover and repair throughout life in some tissues.
Induced pluripotent stem cell	iPS cell	An adult somatic cell which is reprogrammed to become pluripotent and behave like ESCs typically, by inducing a "forced" expression of certain genes (including the master transcriptional regulators Oct-4 and Sox2).
Mesenchymal stem cell	MSC	An adult multipotent cell derived from a well-characterised population that can form fat cells, cartilage, bone, tendon and ligaments, muscle cells, skin cells and even nerve cells.

Source: ESF Science Policy Briefing 38 on Human Stem Cell Research and Regenerative Medicine – A European Perspective on Scientific, Ethical and Legal Issues, page 3. European Science Foundation, May 2010.

THE VIEW FROM EUROPE

Delivering on the vision of regenerative medicine and stem cells

The EU must continue to support human embryonic stem cell research if it is maintain Europe's lead in regenerative medicine. The upcoming Irish Presidency will face calls to recognise the importance of this research and resist any pressure for a ban on funding in Horizon 2020

The European Parliament in Brussels. Image: EP

By Cormac Sheridan

John Gurdon's share of the 2012 Nobel Prize in Physiology or Medicine with Shinya Yamanaka is a timely reminder of Europe's deep roots in the biological science underlying stem cell research.

Gurdon's recognition comes fully 50 years after his classic 1962 nuclear transfer experiment, which demonstrated that the nucleus of a fully differentiated cell from the intestine of a tadpole remains "totipotent", capable of generating a complete organism.

Europe is still at the forefront of stem cell research, with international leaders such as Hans Schöler and Oliver Brüstle in Germany; Hans Clevers in the Netherlands; Elena Cattaneo in Italy; Petr Dvorak in the Czech Republic; and Austin Smith and Ian Wilmut in the UK. But Gurdon's Nobel prize comes at a time of real anxiety for European stem cell scientists, as the political debates that will determine the overall European Union budget for the 2014–2020 period, as well as the budget for the European Commission's Horizon 2020 programme, start to heat up. Four members of the 754-member European Parliament are threatening a legal challenge to Horizon 2020 if it continues support for human embryonic stem cell (hESC) research. "It is a real concern that they won't allow human embryonic stem cell research," says Christine Mummery, Professor of Developmental Biology at Leiden University Medical Centre.

Patent ruling

The four MEPs, Peter Liese (EPP, Germany), Miroslav Mikolasik (EPP, Slovakia), Gerald Häfner (Greens-EFA, Germany) and Konrad Szymanski (ECR, Poland) and other opponents of hESC research have been energised by the controversial October 2011 ruling of the Court of Justice of the European Union (CJEU), which holds that any innovations derived from hESC research are unpatentable.

These opponents are now seeking to tear up the rules under which hESC research has been conducted in Europe for the past decade. The European Commission's Directorate for Research & Innovation is keen to maintain the status quo, a compromise originally hammered out during the Sixth Framework Programme (FP6) and carried forward to Framework Programme 7 (FP7). This requires researchers to follow the national rules governing hESC research in their respective countries, which takes account of the contrasting attitudes to the research across the EU's 27 member states.

Ireland, the home country of the Commissioner for Research & Innovation,

Máire Geoghegan-Quinn, will have a key role in the political debate on the future of stem cell research, as it will hold the EU Presidency for the first six months of 2013, during which many of the finer details of Horizon 2020 will be thrashed out.

Ireland is one of Europe's laggards in engaging with hESC research – it has yet to pass legislation on the issue, and summarily disbanded the Irish Bioethics Council in 2009 after the council published a report calling for the introduction of a liberal regime. "Ireland is now important to the future of all European research for the next ten years at least," says Stephen Sullivan, chief scientific officer of the Irish Stem Cell Foundation. "My fear is that officials from Ireland won't have a full appreciation of the issues that European stem cell research is facing."

In general, the position of most countries on hESC research has not shifted greatly during the lifetime of FP7 – national laws, where they exist, were laid down earlier (see Table, page 12). According to data from the European Commission-funded site eurostemcell.org, eleven EU member states permit the derivation of hESC lines from embryos generated during in vitro fertilisation procedures that either are unsuitable for or are not needed for implantation.

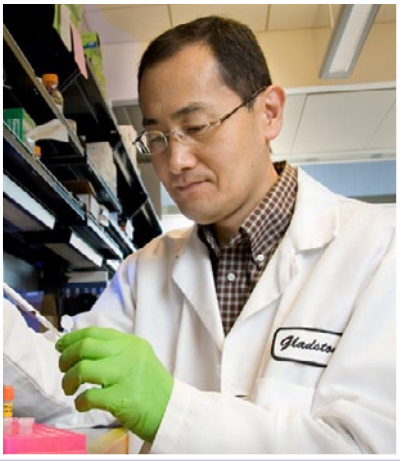
Generation of cell lines

Three of these countries, Belgium, Sweden and the UK, also permit, in limited circumstances, the generation of cell lines from embryos created by somatic cell nuclear transfer. This is essentially the same technique pioneered 50 years earlier by Gurdon and involves inserting the nucleus of an adult cell into an egg cell and then stimulating it to start dividing.

Germany does not permit the derivation of hESC lines, but it does allow work on imported lines generated before 1 May 2007. The country remains one of Europe's powerhouses in stem cell research, although

Japan

An already positive environment for stem cell research in Japan has been hugely invigorated by the award of the Nobel Prize in Physiology or Medicine to Shinya Yamanaka for his discovery that it is possible to reprogramme adult skin cells to a pluripotent state, and subsequently differentiate them to specialised types of cell.



Shinya Yamanaka. Image: University of California, San Francisco (UCSF)

At the beginning of November, the Japanese Science Ministry published a ten-year road map for regenerative medicine, setting out objectives for the application and commercialisation of induced pluripotent stem (iPS) cells. One of the first moves will be the establishment of a national iPS stem cell bank, a plan that mirrors the European Union Innovative Medicines Initiative's outline proposal to set up an iPS cell bank for use by academics and industry across Europe.

Yamanaka's award has given him influence with the government. After the Nobellist called for more support for translation and commercialisation activities at a meeting of the country's Council for Science and Technology Policy in November, prime minister Yoshihiko Noda instructed ministries and agencies to promote the application of iPS cells and promised to put safety standards in place governing their use, according to the newspaper *Asahi Shimbun*.

Safety standards are needed because although iPS cells provide an important tool for studying pluripotency and are powerful cellular models of disease, they are – as yet – unsuitable for use in human therapies. Indeed, some of the shine was taken off Japan's Nobel glory in October when Hisashi Moriguchi, a researcher at Tokyo University, was forced to retract a claim that he had successfully treated six patients who were suffering from heart failure, by reprogramming their liver cells to iPS cells, differentiating them to cardiac cells and injecting the cells to restore damaged heart muscle.

Although Japan allowed human embryonic stem cell research from 2001 onwards, it was difficult to get the necessary licences, and the law was updated in 2009 after lobbying by researchers. In common with other countries with a liberal regime, hESCs can be derived from embryos up to 14 days old generated by in vitro fertilisation that are either unsuitable, or not needed, for implantation. Therapeutic cloning, in which the nucleus of an adult cell is implanted in a human egg, is also permitted under licence. In both cases donor consent is required and payment is not allowed.

Table 2: EU clinical trials – selected cell therapies in development in Europe

Company	Programme	Mechanism	Indication	Status
TiGenix	ChondroCelect	Autologous	Cartilage repair	Approved
TiGenix	Cx601	Allogeneic	Fistulas in Crohn's disease	Phase III
TiGenix	Cx611	Allogeneic	Rheumatoid arthritis	Phase IIa
Bone Therapeutics	Preob	Autologous	Osteonecrosis (hip bone disorder)	Phase III
Cardio3 Biosciences	C3BS-CQR	Autologous	Congestive heart failure	Phase III
ReNeuron	ReN001	Allogeneic (neural cells derived from foetal tissue)	Stroke	Phase I
Advanced Cell Technology	Retinal pigment epithelial cells	Allogeneic (derived from human embryonic stem cells	Macular degeneration	Phase I
Pfizer	Retinal pigment epithelial cells	Allogeneic (derived from human embryonic stem cells)	Macular degeneration	Preclinical
TxCell	Ovasave	Autologous	Crohn's disease	Phase IIb
Mesoblast	Revascor	Allogeneic	Heart attack, congestive heart failure	Phase II
Cell Medica	Cytovir CMV	Allogeneic	Prevention of cytomegalovirus infection after bone marrow transplant	Phase II

its strengths in the field have been overshadowed by controversies, foremost among them being Greenpeace's legal challenge to patents on neural precursor cells, which Oliver Brüstle, of the University of Bonn Medical Centre, derived from hESCs.

The German Supreme Court sought legal clarification from the CJEU last year, and after hearing further legal arguments in November 2012 provided a final decision on 27 November. This says products that involve the destruction of an embryo cannot be patented, but that products based on human embryonic stem cells can be patented if their derivation does not involve the destruction of an embryo, leaving scope for patent grants in the field. The German Federal Court of Justice said the patent owned by Brüstle can remain in force. Crucially, the Court was satisfied that a general disclaimer excluding the destruction of human embryos would render inventions relating to human embryonic stem cells patentable.

Paul Chapman, Partner at the London patent lawyers Marks & Clerk said, "This is good news for bio-medical researchers worldwide. Those who want to protect inventions relating to human embryonic stem cells in Europe now have a glimmer of hope following the disappointment of last year's European decision."
"According to the German Federal Court, because stem cells do not have by themselves the capability to initiate the process of developing into a human being, they cannot be treated as human embryos per se. This means that, save when stem cells are harvested by destroying human embryos, cells derived from human embryonic stem cells can be patented," Chapman said.

Embryonic stem research remains essential

If Europe is to remain internationally competitive in stem cell research, continued support for hESC research is necessary. Although Shinya Yamanaka's development in 2006 of a simple technique to induce pluripotency in adult somatic cells has shifted the focus of stem cell research considerably, hESC research remains essential at this point in the field's development. "We still need human embryonic stem cells as a benchmark," Mummery says.

That scientific reality is reflected in funding for stem cell research under FP7. Between 2007 and 2011, 55 research projects involving

South Korea

South Korea's liberal laws on hESC research, which include allowing the use of therapeutic cloning techniques to generate human embryos as a source of cells for use in therapy, propelled the country to global stem cell fame when, in 2005, scientist Woo-suk Hwang published papers in the peer-reviewed journal *Science* describing how he had generated eleven patient-specific stem cell lines by transferring the nucleii of cells from patients into eggs donated by women for use in research.

The subsequent exposure of these claims as fraud caused embarrassment for the scientific establishment in South Korea and led to new legislation being passed in 2008, which among other measures, provides greater protection for women when donating eggs. However, the law continues to allow somatic cell nuclear transfer – or therapeutic cloning; the technique used to generate Dolly the Sheep, and which Hwang claimed to have used to generate human embryos as the source of the eleven cell lines. This permitted for research into diseases that currently are untreatable.

Although Hwang's deceit was perceived to be a national disgrace at the time, stem cell research in South Korea has bounced back. In the past two years the government has singled it out as an area that has strategic importance in its overall life sciences strategy, and has committed €68 million in funding for 2013.

The country has also taken a lead in commercialising stem cell therapies, with three companies receiving regulatory approval from the Korea Food and Drug Administration to market stem cell therapies. These are HeartCelligram for treating the after effects of heart attack; Cartistem, a treatment for damaged cartilage and Cupistem, for treating anal fistulas.

Seoul

some aspect of stem cells received €338 million; 18 of these involved hESCs and received €107 million. Final figures for 2012 are not yet available, but foremost among the new clutch of projects is StemBANCC, an ambitious €52 million initiative, led by Zam Cader at Oxford University.

Funded under the pharmaceutical industry-backed Innovative Medicines Initiative, StemBANCC will recruit some 500 patients and healthy volunteers, from whom it will generate over 1,500 human induced pluripotent stem (iPS) cell lines for use as probes in drug discovery and drug toxicology research. "Genomic studies of disease have got a bit stuck," Mummery says. "iPS cells can exhibit phenotypes that allow comparisons between diseased and healthy cells."

Basic stem cell biology

Large-scale EU-funded stem cell collaborations of this kind represent a kind of "champions league" for stem cell researchers in Europe. They complement national initiatives, which, inevitably, vary in scale and focus. Philanthropic funding has been an important source of cash for some of them. DanStem, the Danish Centre for Stem Cell Research, established in Copenhagen in 2011, received a ten-year DKK350 million (€47 million) grant from the Novo Nordisk Foundation, for example. The centre is focused on basic stem cell biology, but it also has ambitions to translate its findings into new approaches to cancer and diabetes therapy.

Software entrepreneur Dietmar Hopp, a stalwart supporter of Germany's commercial biotechnology sector, has also backed his country's stem cell research efforts. In October, his foundation announced that it was doubling its support for the Heidelberg Institute for Stem Cell Technology and Experimental Medicine (HI-STEM), bringing its total commitment to €15 million.

HI-STEM, which the Dietmar Hopp Foundation jointly established in 2008 with the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ), is focused on the detailed study of cancer stem cells and has ambitions to develop therapies, particularly for patients with late-stage cancer.

■ *continued on* ***page 16***

Table 3: Country by country view of legislation in Europe

Country	Reproductive cloning prevented by national law	Research authorised by national law on				Prohibition of human embryonic stem cell (hESC) research	No specific legislation regarding hESC research	Ministry or official body in charge
		Stem cells*	Human embryos		Aborted foetuses			
			Procurement of stem cells from super-numerary embryos	Creation of human embryos for research purposes**				
Austria [1,2]	●	●						Federal Chancellery
Belgium	●		●	●				Public Health & Research (W) Justice & Health (F)
Bulgaria [3,4]	●						●	Health
Croatia [3,4]							●	N/A
Cyprus [3,4]	●						●	Independent Body
Czech Republic [3,4]	●		●					Health
Denmark [3]	●		●					Science Technology and Innovation
Estonia [3,4]	●		●					Social Affairs
Finland	●		●		●			Social Affairs and Health
France	●		●		●			Health
Germany	●	●						Federal Ministry of Health
Greece [3,4]	●		●					Development and Health
Hungary [3,4]	●		●		●			Health
Iceland [3,4]	●		●					Health and Social Security
Ireland		●						Department of Health and Children
Italy	●	●			●			Health
Lithuania [1,3,4]						●		Health
Luxembourg [6]							●	Health
The Netherlands	●		●		●			Health, Welfare and Sports
Norway [3]	●		●		●			Health and Care Services
Poland [1]						●		Health and Social Affairs & National Education and Science
Portugal [3,4]	●		●					Health
Romania [3,4]	●						●	Health
Slovakia [1,3,4]	●				●	●		Health
Slovenia [3,4,7]	●		●		●			Health
Spain [3,4]	●		●		●			Health & Science and Innovation
Sweden [8]	●		●	●	●			Health and Social Affairs & Education
Switzerland [3,4]	●		●					Federal Office of Public Health
Turkey [3,9]	●						●	Health
United Kingdom	●		●	●	●			Department of Health

* Prohibiting the procurement of stem cells from supernumerary embryos but allowing the import and use of stem cell lines.
** SCNT is not considered in this table: Belgium, Sweden, UK, Spain and Portugal allow SCNT by law, while Finland and the Czech Republic neither prohibit nor allow it by law.
1. Countries that voted against the Council Decision on hESC research during FP7 (www.consilium.europa.eu/ueDocs/cms_Data/docs/pressData/en/intm/90654.pdf)
2. AT: The Austrian Bioethics Commission published an opinion on 16 March 2009 which recommends allowing hESC derivation from supernumerary IVF embryos.
3. Countries who have signed and ratified the 1997 Convention of the Council of Europe on Human Rights and Biomedicine CETS 164 (http://conventions.coe.int/Treaty/Commun/ChercheSig.asp?NT=164&CM=8&DF=4/16/2009&CL=ENG)
4. Countries who have ratified the 1998 Protocol on the Prohibition of Cloning in Human Beings CETS 168 (http://conventions.coe.int/Treaty/en/Treaties/Html/168.htm)

Specific national committee(s)	Competences of the committee members	Committee website(s)
Bioethics Commission	Medical experts (reproductive medicine, gynaecology, psychiatry, oncology, pathology), legal experts, sociologists and experts in philosophy, theology and microbiology.	www.bka.gv.at/DesktopDefault.aspx?TabID=3575&Alias=english
Advisory Committee on Bioethics [5]	Biologists, ethicists, lawyers, philosophers, physicians and theologians.	https://portal.health.fgov.be/portal/page?_pageid=56,512676&_dad=portal&_schema=PORTAL
Central Ethical Committee [5]	Medical doctors, pharmacist, pharmacologist and laywer.	Not available
N/A	N/A	N/A
National Bioethics Committee	Biologist, geneticist, medical doctor, psychologist and sociologist.	www.bioethics.gov.cy
(a) Bioethical Commission of the R & D Council and (b) Ethical Committee of the Ministry of Health [5]	Bioethicist, biologist, biotechnologist, ethicists, geneticist, immunologist, medical scientist, molecular biologists, philosophers, physiologist, sociologist and theologian.	www.vyzkum.cz/FrontClanek.aspx?idsekce=15908
Council of Ethics [5]	Bishop, former politician, journalist, lawyer, lay persons, scientists, teacher, theologian and vicar.	www.etiskraad.dk/sw293.asp
Council on Bioethics	Ethicists, lawyers, medical doctors and ministry representatives.	http://eetika.ut.struktuur.ee/260565
Sub-committee on Medical Research Ethics of the National Advisory Board on Health Care Ethics [5]	Ethicists, medical doctors, lawyers and lay persons.	www.etene.org/e/index.shtml
Biomedicine Agency [5]	Lay persons, philosophers, theologians, scientists and medical doctors.	www.agence-biomedecine.fr
(a) German National Ethics Council (Deutscher Ethikrat) and (b) Central Ethics Commission for Stem Cell Research [5]	(a) Scientists, politicians, lawyers, lay persons, philosophers, medical experts, bishop and theologians and (b) biologists, ethicists, medical experts and theologians.	www.nationalerethikrat.de www.rki.de/cln_049/nn_216782/EN/Content/Institute/DepartmentsUnits/StemCell/StemCell__node.html?__nnn=true
National Bioethics Commission	Lawyers, philosophers, scientists and theologians.	www.bioethics.gr/index.php?category_id=3
Health and Scientific Council/National Scientific and Ethical Committees [5]	Bioethicist, biologist, geneticist, lawyer, lay person, medical doctors, nurse and priest.	www.ett.hu (in Hungarian only)
National Bioethics Committee	Lawyers, medical doctors, philosophers, scientists and theologians.	www.visindasidanefnd.is
Irish Council for Bioethics [5]	Ethicists, lawyers, scientists, philosophers and physicians.	www.bioethics.ie/
National Bioethics Committee [5]	Ethicists, lawyers, medical doctors, scientists, pharmacologists and patient representative.	www.palazzochigi.it/bioetica/eng
Bioethics Committee	Ethicist, geneticist, lawyer, medical doctors, philosophers, psychologists, psychiatrist and priest.	http://bioetika.sam.lt/index.php?-1876243809
(a) National Consultative Bioethics Commission for Health and Life Sciences and (b) Committee for Research Ethics (Ministry of Health)	Government representative (Social Security), lawyers, medical doctors, social workers, teachers and theologians.	www.cne.public.lu/
Central Committee on Research Involving Human Subjects [5]	Ethicists, medical doctors, nurses, scientists and pharmacologists.	www.ccmo-online.nl
National Committee for Medical and Health Research Ethics [5]	Ethicists, lawyer, lay persons, pharmacist, philosopher and psychologist.	www.etikkom.no/In-English/
N/A	N/A	N/A
(a) National Committee for Reproductive Medicine and (b) National Council of Ethics for the Life Sciences [5]	(a) Biologists and medical doctors and (b) geneticists, legal experts, medical doctors, philosophers and theologians.	www.cnecv.gov.pt/cnecv/en/
Bioethics Commission of Health and Family	N/A	N/A
National Ethics Committee	Geneticist, medical doctor, ministry representative (Health), priest, sociologist and theologian.	www.health.gov.sk
(a) National Committee for Medically Assisted Reproduction and (b) National Medical Ethics Committee	(a) Ethicist, lawyer, medical doctor, ombudsman representative and psychologist and (b) ethicist, lay person, lawyer, physicians, psychologist, sociologist and theologian.	Not available
(a) National Commission on Human Reproduction and (b) Observatory of Law and Ethics	Scientists, lawyers, psychologists and government representatives (Health).	Not available
National Council on Medical Ethics	Ethicists, lawyer, medical doctors, politicians and ministry representative (Health and Social Affairs).	www.smer.se
National Advisory Commission on Biomedical Ethics [5]	Ethicists, lawyers, lay persons, medical doctors and scientists.	www.swissethics.ch www.bag.admin.ch/nek-cne/
Ethics Council [5]	Medical doctors, a pharmacist, and ministry representatives (Health).	Not available
(a) Human Fertilisation and Embryology Authority and (b) Human Genetics Commission [5]	Ethicists, journalist, lawyers, lay person, medical doctors and scientists.	www.hfea.gov.uk www.hgc.gov.uk

5. Apart from national committee(s), whether existing or not, there are local and/or regional ethical committees.
6. LU: A new law is under preparation. Opinion against human reproductive cloning has been given in 2004. Opinion for the authorisation of research on stem cells obtained from supernumerary embryos and of creation of embryos for therapeutic purposes has been given in 2003.
7. SI: Research on supernumerary embryos from IVF procedures (and thus the procurement of hESC) is allowed with zygotes or embryos until 14 days of development.
8. SE: Tissue from aborted fetuses may be used for medical purposes only.
9. TK: hESC research has been suspended at all levels by the Turkish Ministry of Health and legislation regarding hESC research is under preparation.

Source: ESF Science Policy Briefing 38 on Human Stem Cell Research and Regenerative Medicine – A European Perspective on Scientific, Ethical and Legal Issues, Annex 1. European Science Foundation, May 2010.

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Industrialising production of stem cell therapies

Industrialisation initiatives, which will move cell and stem cell therapies from academic laboratories into full-scale manufacturing environments, are also getting under way. CellforCure is leading a French consortium that is investing €80 million in a facility at Les Ulis, near Paris. It will initially take on five clinical stage programmes, which consortium members are developing. A similar UK initiative, the Cell Therapy Catapult Centre, is being developed at Guy's Hospital in London.

Translating stem cell science into clinically useful therapies remains an early stage effort, and many companies across Europe are struggling to raise the necessary finance. "We have a very good academic base," says Michael Hunt, CEO of Guildford, UK-based stem cell therapy developer ReNeuron plc. "We just don't seem to be very good at translating that into commercial businesses."

Nevertheless, one company, TiGenix, has gained approval for a cell therapy, and several others are conducting clinical trials. For stem cell therapy to deliver on its enormous promise will require continuing investment at all stages of research, from the academic lab through to the clinic. The future shape of Europe's participation in much of this will be determined in the coming months.

Cormac Sheridan has covered the European and global biotechnology industry for the past 15 years, during which time he has been a correspondent for BioWorld and a regular contributor to Nature Biotechnology and many other international publications.

Singapore

Stem cell research is at the heart of Singapore's ambitions to become a leading biomedical research hub in Asia. Building on a liberal – but regulated – regime allowing somatic cell nuclear transfer or therapeutic cloning and research on hESCs, the island state has attracted a number of leading stem cell researchers from overseas. Perhaps the most high-profile example is the head of the Singapore Stem Cell Consortium, Alan Colman, one of the scientists involved in the birth of Dolly the sheep, the first mammal cloned by nuclear transfer.

Alan Colman. Image: Singapore Stem Cell Consortium

The Singapore Stem Cell Consortium, based in Singapore's biomedical research institute Biopolis, focuses on the translation of stem cells into clinical trials. This effort builds on basic research carried out at the Institute of Medical Biology, where there are groups specialising in how to control the differentiation of stem cells, stem cell models of disease (research that is also led by Colman) and in understanding the gene expression networks underlying the maintenance and differentiation of stem cells.

Meanwhile, scientists at the Mechanobiology Institute of Singapore are investigating how mechanical forces influence stem cell fate. These studies are intended to inform the development of combinations of scaffolds, growth factors and stem cells for use in tissue engineering and regenerative medicine.

Colman was also chief scientific officer and later CEO of Singapore's flagship stem cell company, ES Cell International, between 2002 and 2007. The company was the first in world to develop a clinical grade human embryonic stem cell line and offer it for sale. Under Colman's direction it was also developing a pancreatic islet cell therapy for diabetes. However, this early attempt at commercialisation was not successful, and ES Cell International – in which the Singapore government held a 44 per cent stake – was sold to the US company Biotime in April 2010.

EXPERTS DEBATE
What Europe must do to maintain its lead in regenerative medicine

Europe is currently a world leader in therapeutic applications of regenerative medicine. It has seen companies spin out from universities and approved products reach the market. Science|Business brought together experts to discuss how to build on these foundations.

Participants at the 18 October event at the British Embassy in Brussels

By Nuala Moran

Regenerative medicine is one of the most promising fields of medical research, offering the prospect of disease reversal. Europe is currently a world leader in the therapeutic applications of a swathe of technologies that fall under the regenerative medicines banner, ranging from patches of decellularised pig tissue for use in repairing veins to patient-specific cell therapies for repairing damaged knee cartilage, and human embryonic stem cell-based treatments for degenerative eye diseases.

Europe has also put in place a science-based regulatory pathway for clinical development, manufacturing and approval of these complex products. Now the first European clinical trial involving a human embryonic stem cell (hESC) line is under way at sites in London and Aberdeen, where cells developed by the US company Advanced Cell Technology Inc are being tested in the treatment of Stargardt's macular dystrophy, a cause of blindness.

The first European-developed therapy based on hESCs is due to enter the clinic in 2013. The product, which has been developed in a collaboration between Pfizer Inc and University College London, is a treatment for age-related macular degeneration, a cause of sight loss and blindness.

However, attempts to force through cuts to embryonic stem cell funding in the European Union's (EU) next five-year R&D programme Horizon 2020, coupled with the Brüstle ruling on 24 October 2011 by the Court of Justice of the European Union that an invention involving the destruction of a human embryo cannot be patented, have been perceived as a threats to progress – not only in treatments based on embryonic and foetal cells – but in regenerative medicine as a whole.

On 18 October 2012 Science|Business brought together business, politicians, research funders, patients' representatives and scientists to debate the challenges that exist for Europe to maintain its lead in the field and translate excellent publicly funded science into marketed products – providing significant health benefits and delivering on the commercial potential of regenerative medicine.

Welcoming delegates to the meeting at the British Embassy in Brussels, the UK Ambassador to Belgium, Jonathan Brenton noted that the award of this year's Nobel Prize in Physiology or Medicine to John Gurdon, for the discovery in 1962 that the specialisation of cells is reversible, and to Shinya Yamanaka for demonstrating in 2006 that adult skin cells can be reprogrammed to pluripotent cells with the potential to develop into any cell type, has put the spotlight on the therapeutic promise of stem cells.

Ambassador Brenton said this is an appropriate time to have an "honest and searching debate" as discussions on the exact shape of the Horizon 2020 R&D programme move towards a conclusion. Not only is there huge potential in terms of the medical applications, there is a growing

commercial opportunity, with the cell therapy market forecast to reach €5 billion in 2014, and the prospect of further growth as more products are developed and come into use.

This debate should focus on what kind of legislative framework Europe needs to unlock the medical and commercial potential, and what level of research funding is required to maintain Europe's lead, Ambassador Brenton said.

Maintaining the 'triple-lock'

Some EU member states and anti-abortion Members of the European Parliament (MEPs) are lobbying for the existing restrictive rules on funding embryonic stem cell research in the current Framework Programme 7 (FP7) to be further tightened in its successor, the proposed €80 billion Horizon 2020 programme, which currently is under consideration by the European Parliament.

EU Research Commissioner Máire Geoghegan-Quinn has made it clear she intends to resist any change, noting that a great deal of time and effort was spent sorting out the existing "triple-lock" agreement negotiated for FP7. The triple-lock states that any EU-funded embryonic stem cell research must conform with the laws of the country in which it is undertaken; that the research is subject to ethical review; and that EU money cannot be used for the derivation of new human embryonic stem cell lines, or any research involving the destruction of human embryos.

The European Council supports retaining the triple-lock agreement in Horizon 2020.

Arnd Hoeveler, DG Research and Innovation

The view from the Commission

The Commission's approach to regenerative medicine research in Horizon 2020 is based on its assessment that this is a high-value technology that will deliver life-changing treatments.

However, a huge barrier – in the shape of the lengthy development timelines – lies in the way of realising this potential. An analysis of the advanced therapies clinical trials coming before the European Medicines Agency shows they are mostly sponsored by academics and SMEs, indicating the need for public sector support.

The Commission wants to support more clinical trials in Horizon 2020 to take products through from preclinical development to proof of principle in humans, providing showcases for the technology and examples of the therapeutic power.

At the same time it is necessary to put the focus on medical need and expand the range of therapies that are being developed. "We need to get cell therapies to more patients and build up safety and efficacy data," said Arnd Hoeveler, Head of Unit for Advanced Therapies and Systems Medicines, DG Research and Innovation.

Horizon 2020 contains proposals for new funding schemes and instruments for SMEs. The intention is to give small high-tech companies access to support for each stage of development, from the exploratory phase, to clinical trials, scale-up and commercialisation. While the European Union will not directly finance commercialisation activities, it intends to make it easier to access finance, for example, through loan guarantees and risk-sharing mechanisms, so that SMEs will be able to take their products through to market.

The EU has the regulatory framework in place to underpin this, Hoeveler noted, in the shape of the European Medicines Agency's Committee for Advanced Therapies, which has built up considerable skills and expertise since coming into operation in 2007. To date, two advanced therapy products have been approved: ChondroCelect, a cell therapy derived from a patient's own cells, for treating damaged knee cartilage; and Glybera, a gene therapy for treating a rare metabolic disorder.

In addition, the Commission has just put forward two regulatory proposals, the regulation on clinical trials, which aims to make it easier to set up clinical trials, and new regulations for medical devices and diagnostics. This is relevant for the new sector because regenerative medicine is not a single, standalone technology, but draws on a range of tools and devices in a complex evolving regulatory framework. "The interlink between different areas is extremely important," Hoeveler said.

Marina Yannakoudakis, a UK MEP representing London, told delegates at the Science|Business meeting that this is an area where Europe "should not attempt to devise a one-size-fits-all policy". Instead, the subsidiarity principle operating in FP7 should be maintained: where permitted by member state legislation it should continue to be possible to get funding in Horizon 2020 for stem cell research. "Horizon 2020 should fund the best stem cell science, but it cannot, and it should not, seek harmonisation," Yannakoudakis said.

This is also the position of the ITRE (Industry, Research and Energy) Committee in the European Parliament, noted another MEP, Amelia Andersdotter. The issue of funding embryonic stem cell research "has not been particularly controversial", with ITRE more or less supporting the status quo in FP7.

Sweden's Pirate Party, of which Andersdotter is a member, also supports maintaining the status quo in FP7. However, the Green group of MEPs, to which the Pirate Party belongs, is of the opinion that European Union money should not be used for research that would be illegal in some member states.

Those member states that allow embryonic stem cell research will continue to fund the work through national R&D budgets. The Green group of MEPs believes in a time of austerity it is better to support research that everyone has in common, rather than research that is carried out in some countries and not others, Andersdotter said.

Regenerative medicine: a high-value technology

The European Commission's approach to funding regenerative medicine research in Horizon 2020 is based on the assessment that this is potentially a high-value technology that will deliver life-changing treatments. "It is a new paradigm for medicine," said Arnd Hoeveler, Head of Unit for Advanced Therapies and Systems Medicine, DG Research and Innovation.

However, a huge barrier – in the shape of lengthy development timelines – lies in the way of moving the new technology from the bench to the bedside, manufacturing the product and meeting the requirements of the regulators. An analysis of the advanced therapy medicinal products coming before the European Medicines Agency shows they are mostly sponsored by academics, charities and SME start-ups. Few larger and better-financed companies are involved in the field. "In other words there is a need for public sector support if the promise of the new technology is to be realised," Hoeveler said.

Such support will allow Europe to capitalise on its high knowledge base and experience, which in part has been built up by the €338 million the Commission has put into regenerative medicine and stem cell research projects over the past five years. The Commission wants to support more clinical trials to take products through from preclinical development to proof of principle in humans, providing showcases for the technology – and concrete examples of its therapeutic power. However, with the wide diversity of technologies being developed, the range of potential therapeutic targets and the lack of tried and tested business models, this is no easy task.

The view from big pharma

Pharmaceutical companies will only invest in regenerative medicine and cell therapy if there is a supportive ecosystem. This includes appropriate and consistent legislation, regulation and product definitions.

Theo Meert, Janssen Pharmaceutica

It also requires a body of publicly funded research that is open for industry to draw on. If academics cannot get funding for human embryonic stem cell research in Horizon 2020, a gap will open up in European expertise, believes Theo Meert, Senior Director External Innovation in Neurosciences, Janssen Pharmaceutica.

Clinical development will require the cooperation of patients, and it is critical to ensure there is an appropriate system of informed consent.

In addition, there must to be an accredited quality control system in place to guarantee consistency in cell therapy products. The basic research needed to underpin this system is pre-competitive, and could be carried out in publicly funded centres that bring academics, clinicians and industry together, Meert said.

Amelia Andersdotter, Member of the European Parliament

Life-saving therapeutic power

The therapeutic power, the huge unmet medical demand, and the difficulties involved in scaling-up and commercialising regenerative medicines are highlighted by the inspiring research of Suchitra Sumitran-Holgersson, Professor of Transplant Biology at Gothenburg University.

Sumitran-Holgersson has developed a technique for removing all the cells from a vein taken from a deceased donor and repopulating it with a patient's own endothelial and smooth muscle cells, obtained by differentiating stem cells obtained from the bone marrow of the recipient. In the case of a 10-year old girl who had an obstruction of the portal vein feeding blood between the intestines and the liver, the graft immediately provided a functional blood supply. And because the donor's cells were replaced with her own, there is no need for the girl to take drugs to suppress her immune system.

The publicity that was attracted when details of the case were published in the medical journal *The Lancet* on 14 June 2012 drew thousands of emails and enquiries from around the world, convincing Sumitran-Holgersson there is a widespread need for this type of regenerative medicine. "My request is, could the EU help me to get this therapy to the rest of the world? How can I build the infrastructure and get the therapy out there?" she asked.

Intellectual property protection

As Sumitran-Holgersson acknowledged, there are many hurdles to be overcome in scaling up the vein replacement technique, not least of which are the ethical aspects surrounding the commercialisation of donor tissue.

Such ethical issues overhang the question of whether a commercial regenerative medicine product can get the intellectual property protection needed to attract investment. In general, patents are less important in regenerative medicine than in conventional drugs because products such as cell therapies involve huge amounts of know-how and cannot readily be copied. However, intellectual property protection is very important to investors, and small companies are unlikely to get funded to start out on the long path to market unless they have patents.

The Court of Justice of the European Union ruling in the Brüstle case was upsetting for scientists working with embryonic stem cells, who found that approved and regulated research was nonetheless deemed to be unethical. The judgement also set alarm bells ringing that there could be a flight of research and scientists from Europe.

The Court of Justice of the European Union made the ruling after the German Federal Court of Justice asked it for clarification on the legal definition of an embryo. A year later, on 27 November 2012 (and after the Science|Business meeting covered in this report), the German Court ruled that products based on embryonic stem cells are not patentable if obtaining the cells involved destruction of an embryo. However, patents will be allowed – including Brüstle's contested patent – if hESCs are obtained in ways that do not involve the destruction of an embryo. Legal experts are digesting the implications, but this certainly leaves some scope for patents to be granted on cell therapies based on hESCs.

A path to the patients

If concerns about patenting have been overdone, it is also the case that Europe has a better system of

■ *continued on* ***page 22***

Katherine Littler, Wellcome Trust

The view from Europe's largest research charity

As the largest charitable funder of research in Europe (and the second largest in the world), the Wellcome Trust takes an active interest in ensuring that the regulatory environment fosters the translation of the science that it funds.

In regenerative medicine and cell therapy the regulatory system needs to provide:

1. Certainty – without this people will not invest
2. Clarity – researchers are happy to respect the rules if they are clear. This sounds straightforward, but can be difficult to achieve, said Katherine Littler, Policy Adviser, Wellcome Trust.
3. Proportionality – there is a need to weigh any risks against the public benefits
4. Streamlined rules – if regulations are too complicated or time-consuming to follow, companies and investors will go to other regions of the world that have both the expertise and appropriate but flexible regulatory frameworks
5. Harmonisation – while upholding the principle of subsidiarity, harmonised rules and standards are key in underpinning research and promoting translation.

Littler believes that individual governments need to be made more aware not only of the potential health benefits of regenerative medicines, but also of the economic returns. At the same time, it is important not to over-promise and to be realistic about time frames.

■ *continued from* ***page 20***

regulation for cell therapies than many give it credit for. As head of TiGenix NV, the only company to date to have had a cell therapy approved by the European Medicine Agency's Committee for Advanced Therapies, Gil Beyen has a particular insight into the regulatory pathway. While not without its problems, he said, "Europe has done a lot: we have the regulation in place, which is the basis for defining products and setting out the route to making products available to patients. If well implemented now, it can be the basis for giving Europe a strong competitive position in the fast-growing field of advanced therapies." The requirements are onerous, but the existence of a science-based regulatory framework allowed TiGenix, as a spin-out from KU Leuven, to put a development plan in place and to raise a total of more than €100 million in venture capital and on the public market. In October 2009 the company was granted approval for ChondroCelect, a treatment for injured knee cartilage which involves taking healthy cartilage cells from the patient, expanding them in the lab and administering them into the damaged area.

Aligning regulatory requirements

Early pioneers of stem cell therapy, including TiGenix and the UK company ReNeuron plc – which is developing a cell therapy treatment for the after effects of stroke based on neuronal cells that were originally derived from foetal cells – have found themselves caught between the divergent requirements of the FDA and the EMA. However, Janice Soreth, Deputy Director of the FDA Europe Office and Liaison to the European Medicines Agency, said that on the back of regular meetings of experts from the two agencies, along with representatives of the national competent authorities from member states, there is now much more communication and cooperation with a view to more alignment. "The bottom line is that there is a great deal of collaboration between the [FDA and EMA] and member states under the umbrella confidentiality arrangements of the two agencies," Soreth said.

As a result, more companies are taking parallel scientific advice from the EMA and FDA when designing studies and applying for permission to carry them out. These moves to align the regulatory pathways draw on the research base in cell therapies. "The aim of this joint approach is to reduce the regulatory overhead, while at the same time ensuring that the science drives the process, in the best interests of the public we serve," Soreth told the meeting.

Regulatory framework attracts investment

In 2008 when Pfizer Inc became one of the first big pharmaceutical companies to move into cell therapies, it chose to establish a research unit – now called Neusentis – in Europe because of the strong regulatory framework and positive public attitude to stem cell research,

The view from the European pharmaceutical industry

Magda Chlebus, European Federation of Pharmaceutical Industries and Associations

Over the past decade there has been a massive flight of pharmaceutical R&D from Europe to Asia and the US. The factors that prompted this shift now threaten to undermine the investment that member states and the European Union have made in regenerative medicine and cell therapies, Chlebus said.

To start with, there is a lack of consistency in EU policies. Then there is over-regulation. "The EU generates an enormous number of laws that impact the research environment, and scientists don't react until it is too late," said Magda Chlebus, Director Science Policy, European Federation of Pharmaceutical Industries and Associations.

This is compounded by over-use of the precautionary principle and by a lack of communication and education about human embryonic stem cells and their potential. "People need to understand there are certain things you can't do without human embryonic stem cells," Chlebus said. "We need to make clear what Europe would be missing out on."

Suchitra Sumitran-Holgersson, Professor of Transplantation Biology, University of Gothenburg

Ruth McKernan, Chief Scientific Officer, Neusentis, Pfizer

Ruth McKernan, Chief Scientific Officer of Neusentis, told delegates.

In April 2009 Pfizer signed an agreement to work with Professor Peter Coffey of University College London to translate his research in differentiating human embryonic stem cells to form retinal pigmented epithelial (RPE) cells into a treatment for age-related macular degeneration. The condition leads to the loss of RPE cells and is a leading cause of blindness.

University College and Pfizer have worked together on the production of RPE cells, the safety studies needed to underpin the clinical trial, and partnering with regulators. Clinical trials are due to start next year. "After several years of research, we are excited to get our retinal epithelial cells into patients," McKernan said.

"The collaboration with Peter Coffey is an important one for us," McKernan said. Pfizer collaborates extensively with academic researchers in many areas and has over 200 research agreements in Europe. One challenging area for life sciences at the moment is starting new companies. "It is important to encourage spin-outs and support new biotech companies. Many great ideas come from them," McKernan said. To build a sustainable regenerative medicine sector, Europe needs to complete all the links in the chain from basic research to market. In particular it is critical to support university spin-outs and SMEs that can take academic research and push it through to clinical proof of principle. Public support is needed for these very early steps on the path to commercialisation.

There are a couple of role models in member states. One is CellforCure, a consortium of French biotechnology companies and academic centres that has a €30 million contribution from the government innovation agency OSEO towards the construction of an €80 million pharmaceutical-grade facility for the production of cell therapy products. This will allow companies to move away from their current dependence on university or hospital-based production facilities. The facility, based in Les Ulis, on the southwestern suburbs of Paris, will initially take on the production of cells for five clinical-stage products that members of the consortium are developing. A second example is the UK's Cell Therapy Catapult Centre, which in common with CellforCure has been set up to provide the missing pieces in the commercialisation jigsaw, by providing SMEs with help in scaling up, repeatability, quality control, quality assurance, developing manufacturing processes, establishing supply chains, and so on.

The CEO of the Cell Therapy Catapult Centre, Keith Thompson, told the meeting the aim is to address unmet medical need and provide demonstrations of the potential of stem cells to improve health and wealth. "We don't have all the answers for cell therapies as yet, but we do have the collective will to get the field going and I'm confident we will help bring an array of therapies to market over time," Thompson said.

In support of this, Thompson cited some small-scale – but highly effective – examples of existing cell therapies, including a diabetic patient who was able to stop administering insulin within two weeks of a pancreatic islet cell transplant, and the use of autologous corneal epithelial stem cell transplants to repair injuries to the cornea.

These examples hint at the imminent clinical and commercial potential of stem cells, and underline the importance of maintaining a

consistent approach and providing clarity on stem cell research, both for SMEs and academics, in Horizon 2020. "We don't want to see any particular cell type excluded, that would limit the potential benefits for patients," said Thompson.

Basic research is still needed

The discovery of induced pluripotent stem cells makes it possible to turn an adult (somatic) differentiated cell, for example, a skin cell, back into a pluripotent cell. While these are embryonic stem cell-like, this feat of re-programming requires the addition of DNA, making induced pluripotent stem cells unsuitable as the starting point for cell therapies.

Similarly, while induced pluripotent stem cells are important in opening out research into the mechanisms behind pluripotency and are providing powerful new tools for drug discovery, they cannot fully substitute for human embryonic stem cells in the basic research that is still needed to support the development of commercial products. Translating the promise of stem cells is not a one-way street: as stem cell therapies make progress in development, clinicians are feeding back data from trials to prompt further – focused – research into the basic biology of stem cells. Human embryonic stem cells are crucial here, since they represent the "gold standard" pluripotent cells. Clinicians need access to basic research as they see how treatments play out in the clinic, so they can rationally improve a therapy.
It also clear that greater understanding of how stem cells give rise to regeneration and repair would help in applying them to treat disease.

In summary, induced pluripotent stem cells represent an important breakthrough, offering a powerful means of studying the biology of

The view from a translational expert

Thirty years ago monoclonal antibodies were a laboratory curiosity, now they represent one of the most therapeutically useful and commercially successful classes of drugs. "The conversations I'm having now about commercialising cell therapies are the same as those I was having about monoclonal antibodies at the start of my career," said Keith Thompson, Cell Therapy Catapult Centre, UK.

In common with CellforCure in France, the Cell Therapy Catapult Centre has been set up to fill in the missing pieces in scale-up, repeatability, manufacturing, establishing supply chains, and so on, that are needed to commercialise cell therapies. "We don't have all the answers as yet, but we do have the collective will to get the field going, and I'm confident we will bring an array of therapies to market over time," said Thompson.

A number of early, experimental treatments hint at what is at possible: a diabetic who received a pancreatic islet cell transplant was able to stop administering insulin within two weeks; autologous transplants of corneal epithelial stem cells are routinely used to repair injured corneas.

Meanwhile, a research project that aims to generate red blood cells from embryonic stem cells and scale up to an approved manufacturing process is making good progress.

The aim of the Cell Therapy Catapult Centre is to provide further demonstrations of how stem cells can address unmet medical need, improving health and creating a resilient commercial sector.

To achieve this, four elements must move forward in parallel, Thompson said:

1. Advancing the fundamental science
2. Moving products into clinical trials
3. Addressing manufacturing and supply chain issues, bringing down the cost of goods, and working on mechanisms and devices for administering therapies
4. Developing business models

The Cell Therapy Catapult Centre has government funding of £10 million per annum over five years, to be matched by funding from collaboration partners. It will use this to:

1. Provide people and laboratories to take on projects and get them into clinical trials and de-risk them to the point where it will be possible to attract further investment
2. Work on manufacturing issues in collaboration with industry, providing businesses with access to intellectual property and regulatory expertise
3. Set up a contract research service
4. Compile and maintain a database of clinical activity in the field

The objective is to "create the climate which will draw in major investment that will be required by big pharma to commercialise cell therapies," Thompson concluded.

Keith Thompson, Cell Therapy Catapult Centre, UK

pluripotency and of disease, and providing a tool for drug discovery. But they cannot replace human embryonic stem cells.

The need to continue basic research was one reason why UK medical research funding bodies reacted with alarm to the reopening of the political battle over human embryonic stem cell funding. In a joint statement sent to MEPs in June 2012, the Medical Research Council, the Wellcome Trust, the Association of Medical Research Charities (representing charities that fund over £1 billion of research each year) and other research groups, said it is important to maintain funding for all avenues of stem cell research. Any move to make human embryonic stem cells ineligible for Horizon 2020 grants would risk holding back progress across the entire field.

While the amount of funding for human embryonic stem cell research in Horizon 2020 would be only a small portion of the overall budget, axing it would have a disproportionate impact, Katherine Littler, Policy Adviser at the Wellcome Trust, told delegates. This is because of the high level of international collaboration: 40 per cent of stem cell research funded by the Wellcome Trust involves researchers outside the UK.

"If there's a negative funding environment, it will send out a negative message about the field; it will be more difficult to get funding for any type of stem cell research, and more difficult to form collaborations," Littler said.

Supporting cross-sector and transnational research

While it is obviously important to respect the principle of subsidiarity, it is also important to improve the environment for regenerative medicine and cell therapies from a pan-European perspective, said Magda Chlebus, Director of Science Policy at the industry body, the European Federation of Pharmaceutical Industries and Associations (EFPIA). Members of EFPIA include some of the biggest investors in private sector R&D in Europe. They want to continue to do research in Europe, and to do this research in international and cross-sectoral collaborations.

As things stand, member states that favour a more restrictive approach have a disproportionate influence on the European research environment as a whole. "We want to attract research to Europe, but taking a restrictive attitude is killing off the tools," Chlebus told the meeting.

Moral asymmetry

One of Europe's leading patient advocates, Alastair Kent, Director of Genetic Alliance UK, believes it is "time to get off the back foot" and highlight that the moral high ground does not automatically belong to opponents of human embryonic stem cell research. "They are putting greater importance on embryos than on doing something to benefit patients with life-threatening diseases," Kent said. The embryos that are the source of embryonic stem cells have been generated through in vitro fertilisation and are not suitable, or are not needed, for implantation, and would be disposed of. Refusing to fund embryonic stem cell research "is like saying people with Parkinson's disease or Alzheimer's disease are less important than a group of cells," said Kent.

For Kent, there is no doubt that cell therapies will fill unmet medical needs. "The only way to scale up these treatments, guarantee their quality and make them available to any patient that needs them is through commercialisation," he said.

Clear and unambiguous vision

There is also a risk that withdrawing from stem cell research – and so slowing commercialisation of products – will lead to an increase in rogue clinics offering unlicensed treatments. Patients are desperate and often willing to try anything. Advice and education from national health bodies, medical charities or patients' groups is not credible unless there is a clear and unambiguous vision of how and when approved therapies will become available.

It is essential to continue to carry out research with human embryonic stem cells, but the focus on this is obscuring progress that is being made with other cell therapies. "This is confusing the debate and does not leave room for discussion about other types of stem cells and cell therapies," said Emmanuelle Rial-Sebbag, Permanent Researcher in Biolaw and Bioethics, Inserm.
The best way to shift opinion and open out discussion is to showcase the progress that is being made, believes Rob Janssen, Secretary General of the Alliance for Advanced Therapies, a group launched in March 2012 to promote the development of these products and attract the financial, scientific, political and regulatory support required to create a thriving sector. From a corporate perspective, a prime requirement is predictability at the national as well as the European level. "Without this, investors won't invest," Janssen said.

Theo Meert, Senior Director, External Innovation in Neurosciences, Janssen Pharmaceutica, agreed. If pharmaceutical companies are to invest in the commercialisation of regenerative medicine and cell therapy products there must be a supportive ecosystem. This encompasses appropriate and consistent legislation, regulation, and product definition. "It also requires a body of publicly funded research that is open for industry to draw on," Meert said. If academics cannot get funding for certain types of basic research in Horizon 2020, a gap will open up in European expertise.

THE VIEW FROM THE US

Stem cell therapy steps up a gear with first approval and improved political climate

Positive clinical data, increases in federal funding and the first regulatory approval in North America of a manufactured stem cell-based product mean momentum is building in the US. With the re-election of President Obama, this is likely to continue

The US Capitol building in Washington, D.C.

By Peter Winter

When US President Barack Obama came into office in 2009 he made good on his promise to overturn President George W. Bush's executive order that – with the exception of a handful of existing stem cell lines – prohibited federal funding of human embryonic stem cell (hESC) research.

This easing of restrictions on hESC research was expected to engender enough confidence to attract investors into the space and encourage pharmaceutical and biotech companies to build robust product pipelines based on stem cell therapies. However, a tougher regulatory climate for biopharmaceuticals in general and a protracted legal challenge to the relaxing of rules on hESCs have served to keep both big pharma companies and venture capitalists on the sidelines to date.

Nevertheless, there has been progress, particularly at the research end of the development spectrum. Three-and-a-half years on, stem cells are no longer high on the political agenda as they once were. This speaks to the generally positive public acceptance of stem cell research in the US.

A Research!America poll of likely voters in the presidential election, conducted in August 2012, found that 61 per cent were in favour of expanding funding for hESC research.

Looking back over his first term in office Obama can point to some major gains. These include funding increases for the stem cell initiatives of the National Institutes of Health (NIH), and greater investor interest in the wider field of regenerative medicine including the use of adult stem cells and induced pluripotent stem (iPS) cells.

However, it hasn't all been smooth sailing. Although after protracted forethought, the US Food and Drug Administration (FDA) gave the green light for the Californian biotech Geron to begin the very first human clinical trial of a human embryonic stem cell-derived therapy in January 2009, the trial has not been without its problems.

The Phase I trial, treating patients with acute spinal cord injury, was hit with an FDA clinical hold, causing significant delays to its initiation in 2010. A year later, after 15 years' effort, the Geron washed its hands of the programme, blaming its withdrawal from the stem cell space on capital scarcity and uncertain economic conditions. The decision wiped out a leading player in hESC translation and commercialisation. However, the regenerative medicine sector has been able to recover and is beginning to blossom. (See Public Markets section). And the prime movers in the Geron trial are now attempting to revive it.

Table 4: Market capitalisation of stem cell companies (US$ M)

Company	Symbol	Mkt Cap 30/12/11	Mkt Cap 31/10/12
Aastrom Biosciences	ASTM	77.51	61.33
Athersys	ATHX	51.43	29.43
BioTime	BTX	287.60	188.60
Neuralstem	CUR	65.96	61.20
Cytori Therapeutics	CYTX	129.16	216.64
International Stem Cell	ISCO	34.90	21.81
Thermogenesis	KOOL	11.73	14.87
Neostem	NBS	78.29	102.85
Opexa Therapeutics	OPXA	21.44	15.67
Osiris Therapeutics	OSIR	175.80	345.03
Pluristem Therapeutic	PSTI	138.07	198.51
StemCells	STEM	24.94	62.04
Verastem	VSTM	235.66	168.73
Total		1332.48	1486.70

Research funding robust

Federal funding for all forms of stem cell research has increased over the past four years (see Table 4). However, the NIH funding component for hESC has been dogged by litigation for the past three years. In Sherley v. Sebelius, researchers James Sherley and Theresa Deisher, who worked with adult stem cells, claimed the NIH guidelines violated the Dickey-Wicker Amendment, which prohibits the use of federal funds for research in which human embryos are destroyed or discarded. This overhang was not finally removed until August 2012, when a three-judge panel from the US Court of Appeals for the District of Columbia Circuit unanimously upheld the NIH 2009 guidelines that permit funding of hESC research.

Through its Common Fund the NIH has established the Center for Regenerative Medicine (NIH CRM) to support this field, with the goal of accelerating the translation of stem cell-based clinical therapies.

State funding filling the void

With stem cell research in general not attracting a significant amount of venture funding, the California Institute of Regenerative Medicine (CIRM), which was established in 2004 with $3 billion for stem cell research at California universities and research institutions, has begun to fill the void left by traditional venture capital firms. To date CIRM has allocated $150 million in funding to help move promising stem cell-based therapies from the bench into clinical trials.

"We are a lot closer to having promising therapies ready for clinical trials, so it makes sense that we step up our engagement with industry to help fund those trials and move those therapies closer to approval by the FDA," says Duane Roth, vice chair of the governing board of CIRM.

CIRM's funding for translational research is good news for biotech companies, providing them with a source of funds in a field where it remains challenging to raise private capital.

Three biotech companies have been funded so far under CIRM's Strategic Partnership Awards initiative. A grant of $10.1 million was awarded to ViaCyte Inc. to continue preclinical research and initiate clinical testing of an embryonic stem cell-based therapy for patients with insulin-dependent diabetes.

Meanwhile, Bluebird Bio Inc will use a $9.3 million grant to support a Phase I/II

study to evaluate the safety and efficacy of LentiGlobin, the company's programme for the treatment of the inherited blood disorder beta-thalassemia, which will be initiated in the US in 2013.

StemCells Inc has been awarded up to $20 million to fund preclinical development of its product consisting of purified human neural stem cells for treating Alzheimer's disease, with the goal of filing for permission to carry out a clinical trial. In July, CIRM approved a separate award to the company for up to $20 million to fund preclinical development of a cell therapy for spinal cord injury. The aim is that this funding will enable the company to advance the product to the point where it is ready for clinical trials.

Public markets

It has been a good year for stem cell companies on the public markets, with the 13 publicly listed stem cell companies showing an average increase in share price of 11.6 per cent in the year to date. (See Table 4)

This boost came from a regulatory approval and positive clinical trials results. It was a big breakthrough for the field as a whole when the Canadian regulator Health Canada approved Prochymal, Osiris Therapeutics Inc's allogeneic stem cell treatment for graft-versus-host disease (GvHD) in children. The decision marked the world's first regulatory approval of a manufactured stem cell product and the first therapy approved for GvHD – a devastating complication of bone marrow transplantation that kills up to 80 per cent of children affected, many within just weeks of diagnosis. The company's stock value has almost doubled in the course of this year.

Meanwhile, Newark, California-based StemCells Inc has seen its shares rise 148 per cent in the year to date. In addition to its CIRM grants, the company recently reported clinical and preclinical data demonstrating the therapeutic potential of a cell therapy for treating myelination disorders.

Pluristem Therapeutics Inc's stock value also has jumped 44 per cent, on the strength of reporting a single case study in which a patient with aplastic bone marrow who received an intramuscular injection of its PLacental eXpanded cells under compassionate use saw an improvement. The company was also able to successfully complete a public offering which netted about US$30 million.

Brazil

There has been a strategic approach to stem cell research and regenerative medicine in Brazil since the turn of the century, with backing for basic research, clinical trials and stem cell banking. This has fostered the development of a strong stem cell community in the country.

However, protracted legal challenges mean that the regulatory framework has lagged behind, and from the first draft of the law in 2003, it was not until 2008 that hESC research was sanctioned. Following this, Lygia da Veiga Pereira, a scientist at the University of São Paulo, became the first to generate an hESC cell line in Brazil.

Since 2003, the government has invested €201.8 million in 2,694 research projects. It has also supported the formation of eight Cell Technology Centres, which together form the Brazilian Network of Cellular Therapy. These include the National Laboratory of Embryonic Stem Cell Research in Rio de Janeiro, which is working to scale up production of human stem cells. The lab was also the first in the country to generate iPS cells.

Another leading institute in Brazil is NECEL – the Centre for Cellular and Molecular Therapy at the University of São Paulo, set up in 2004 with a brief to work on the mechanism controlling cell proliferation and differentiation and collaborate with clinicians to translate this through to therapies.

There has been progress in the clinic too, as exemplified by a Phase I/II trial currently in progress at the University of São Paulo, assessing the safety and efficacy of mesenchymal stem cells in treating Type I diabetes. Other trials at the university are testing bone marrow cells in treating the eye diseases, diabetic retinopathy, age-related macular degeneration and retinitis pigmentosa.

Positive clinical trials will begin to encourage investment

While still in their early stages of development – and with clinical trials having only involved a limited number of patients – reports to date have been very promising, and provide further validation for encouraging investment in stem cell therapeutics. For example, data from a human embryonic stem cell trial conducted by Advanced Cell Technology and published in medical journal *The Lancet* showed that two patients with Stargardt's disease, a degenerative eye condition, had regained some vision.

In addition, positive early data from a spinal cord injury trial involving StemCells' neural stem cells indicated that two patients with no feeling below the site of injury were able to regain sensation, while in another study from the company, patients with a rare myelination disorder were able to create myelin, an advance that holds promise for treating multiple sclerosis and cerebral palsy.

This scientific progress has helped breath a new sense of optimism into the US stem cell sector. The Fiscal Cliff apart, it seems likely this momentum will continue now Obama has secured a second term.

REFERENCE

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Australia

Australian stem cell research is getting back on track after the demise of the Australian Stem Cell Centre (ASCC) in June 2011. The centre was set up to great fanfare in 2002, with funding of AU$100 million (€80 million) from the government. Backing of AU$11.4 million from the State of Victoria ensured ASCC was located in Victoria, at Monash University.

ASCC was founded by Alan Trounson, a pioneer of stem cell science who discovered that human embryonic stem cells can be differentiated to neural cells. As a well-endowed and early mover in the field, the centre also attracted scientific luminaries from abroad, most notably, Stephen Livesey, founder of the US regenerative medicine company LifeCells, who joined as the ASCC's chief scientific officer.

The palpable energy of the ASCC's early years was reinforced by Australia's liberal regime for research. From 2002 onwards the law has allowed scientists to apply for licences to generate human embryonic stem cells from IVF embryos that are not required for infertility treatment. In 2006 the legislation was extended to allow therapeutic cloning by somatic cell nuclear transfer. A government review of the law concluded last year, saying there should be no changes in the current regulatory framework.

That review was published on 7 July 2011, just one week after the ASCC's funding came to an end and the centre began to wind down. Trounson had departed some time earlier, becoming President of the California Institute for Regenerative Medicine in January 2008. By this time Livesey was CEO of the ASCC, but his tenure ended in July 2008, when he left following a difference of opinion with the ASCC's board.

As the ASCC was winding down, a new government-backed research initiative was getting off the ground, in the shape of Stem Cells Australia. This consortium of universities and research institutes, led by Martin Pera at Melbourne University, was awarded AS$21 million (€16.8 million) at its inception, and is now the main dedicated stem cell research organisation in the country. It is focusing its efforts on four areas: pluripotency and reprogramming; cardiac regeneration and repair; natural regeneration and repair; and haematopoiesis (blood and bone marrow stem cells).

Alongside Stem Cells Australia are a number of dedicated centres, including the Sydney Centre for Developmental and Regenerative Medicine, the Australian Centre for Tissue Regeneration, the National Centre for Adult Stem Cell Research and the Australian Regenerative Medicine Institute.

Table 5: NIH stem cell research funding, FY 2002–FY 2011 (US$ M)

Year	Human Stem Cells		Non-Human Stem Cells	
	Embryonic	Non-Embryonic	Embryonic	Non-Embryonic
2002	$10.1	$170.9	$71.5	$134.1
2003	$20.3	$190.7	$113.5	$192.1
2004	$24.3	$203.2	$89.3	$235.7
2005	$39.6	$199.4	$97.1	$273.2
2006	$37.8	$206.1	$110.4	$288.7
2007	$42.1	$203.5	$105.9	$305.9
2008	$88.1	$297.2	$149.7	$497.4
2009 (Non-ARRA*)	$119.9	$339.3	$148.1	$550.2
2009 (ARRA)	$22.7	$57.9	$29.1	$88.1
2010 (Non-ARRA)	$125.5	$340.8	$175.3	$569.6
2010 (ARRA)	$39.7	$73.6	$19.6	$74.2
2011	$123.0	$394.6	$164.6	$619.9

**ARRA American Recovery and Reinvestment Act*

Table 6: US clinical trials

Phase I			
COMPANY	PRODUCT	INDICATION	NOTES
Advanced Cell Technology Inc. (Marlborough, Mass.)	Human embryonic stem cell-derived retinal pigment epithelial cells (hESCs)	Stargardt's macular dystrophy	Treated the 4th patient in Phase I/II trial
	hESCs	Dry, age-related macular degeneration	Treated its fourth patient in a Phase I/II trial
America Stem Cell Inc. (San Antonio, Tex.)	ASC-101	Increase the efficiency of engraftment in transplantation of cord blood-derived stem cells	
BrainStorm Cell Therapeutics Inc. (New York)	NurOwn	Amyotrophic lateral sclerosis	
Neuralstem Inc. (Rockville, Md.)	NSI-566 Spinal cord neural stem cells	Amyotrophic lateral sclerosis	Completed a Phase I trial
StemCells Inc.(Newark, Calif.)	Purified human neural stem cells (HuCNS-SC)	Pelizaeus-Merzbacher disease	
	HuCNS-SC	Spinal cord injury	Phase I/II data showed it was well tolerated
Phase II			
Osiris Therapeutics Inc. (Columbia, Md.)	Prochymal adult mesenchymal stem cells	Type I diabetes	
Aastrom Biosciences Inc. (Ann Arbor, Mich.)	Ixmyelocel-T stem cell therapy	Ixmyelocel-T stem cell therapy	
AlloCure Inc. (Burlington, Mass.)	AC607 Mesenchymal stem cell therapy	Acute kidney injury	
Athersys Inc. (Cleveland, Ohio)	MultiStem adult stem cell therapy	Ischaemic stroke	
Phase III			
Aastrom Biosciences Inc. (Ann Arbor, Mich.)	Ixmyelocel-T stem cell therapy	Critical limb ischaemia	

Source: BioWorld Snapshot (www.bioworld.com), company press releases

China

China's permissive embryonic stem cell policy allows for the extraction of cells from embryos and the use of therapeutic cloning, in line with liberal regimes in other countries, including the UK and Sweden. By 2002 scientists had derived the first hESC lines to originate in China, and by 2010 more than two dozen hESC lines had been established in the country.*

Stem cell research and regenerative medicines is one of the key programmes of the Chinese Academy of Sciences. This is built around four main research centres, in Beijing, Shanghai, Guangzhou and Kunming, with 17 satellite centres elsewhere. Money has also come from regional government and municipalities. As a result of this investment, China has moved up the league table, to become the fifth largest publisher of stem cell research in peer-reviewed journals in 2010 (see reference).

China is also striking up international collaborations in stem cell research. For example, in January 2012 the National Natural Science Foundation of China and the UK's Medical Research Council launched the China-UK Stem cell partnership development initiative to support 10–12 long-term research projects focused on basic and preclinical research of relevance to the longer term-development of therapies for human disease.

In common with its push in other areas of science, China has made a concerted effort to attract Chinese nationals back from overseas. As one indication of the impact this has made, in 2003, Hui Sheng, a researcher at Shanghai Medical University, published data showing she had generated human stem cell lines from embryos produced by inserting the nucleus of an adult human cell into an enucleated rabbit egg. Before this world first in Shanghai, she had spent more than 15 years working at the US National Institutes of Health.

Research in China has been dominated by adult, rather than embryonic stem cell research, and there has been a big push to translate this research to the clinic. One result is that the country has become an international centre for so-called stem cell tourism, with patients being attracted both from abroad and within China to have stem cell treatments for a wide range of conditions, ranging from autism to epilepsy, cerebral palsy, Parkinson's disease, multiple sclerosis and traumatic brain injury.

Chinese regulators have been criticised for ineffective supervision and oversight of clinics administering these therapies. The International Stem Cell Society (ISCS), a not-for-profit organisation that promotes the safe and ethical use of stem cells, has campaigned against stem cell tourism in China and elsewhere, saying desperately ill patients are travelling thousands of miles for stem cell therapies few – if any – of which are based on sound preclinical data published in peer-reviewed journals.

At the beginning of 2012, the Health Ministry in China started a crackdown, ordering an immediate halt to the administration of unapproved stem cell products and putting a six-month hold on applications to carry out clinical trials. (It should be noted that in the US the Food and Drug Administration has been on a similar crusade to control the use of unregulated stem cell therapies.)

Researchers in China see proper regulation and oversight as critical to ensuring that the significant investments the country is making in stem cell research are translated through to regulated, approved products. In response to the Chinese Health Ministry's announcement of the crackdown on unregulated therapies in January, Hongkui Deng, a researcher at Peking University and a member of the ISCS, called on the government to create an appropriate regulatory framework.

*www.futuremedicine.com/doi/pdf/10.2217/rme.09.78

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