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An Industry to Grow

By Clive Cookson

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As California wrestles with a horrendous budget deficit, the axe hangs over almost every area of state spending, from welfare to education. But there is one activity set for healthy growth: stem cell research.

Dozens of new laboratories are being fitted out and hundreds of scientists recruited. The California Institute of Regenerative Medicine - set up in 2004,when a referendum approved $3bn of state spending on the research - is moving ahead after delays caused by legal challenges and uncertainties over selling the state bonds that will fund it. About $1bn (€700m, £600m) has been committed in research grants and spending on labs and other infrastructure, according to Alan Trounson, CIRM president.

The Golden State provides the most striking example of a growing wave of public spending in the US and globally on stem cells, which many scientists see as the foundation of a new type of medicine in which failing or damaged body tissue will be replaced with fresh young cells. Held back for years by political opposition and lack of funding, stem cell research - which supporters say holds the key to curing diseases ranging from diabetes and heart failure to Parkinson's and spinal injury - is powering ahead.

Ironically, just as the controversial practice has slipped down the news agenda,it has been advancing scientifically at an unprecedented pace. Researchers are finding new ways to make stem cells and turn them into blood, brain, bone and other tissues.

On the political front the arrival of Barack Obama in the White House has changed the regulatory climate, as the new US president fulfils his campaign pledge to relax his predecessor George W. Bush's stringent restrictions on federal funding.

New rules are expected to open the way for the National Institutes of Health, the main US biomedical research agency, to pour hundreds of millions of dollars into stem cell projects - though the regulations may not be as liberal as some research advocates had hoped. “Federal funding for the most advanced embryonic stem cell research remains limited,” says Susan Solomon of the New York Stem Cell Foundation. “This reality makes it a moral imperative that states with funding systems continue to fund the work that the NIH is not able to support.”

New York's $600m scheme is the biggest after California's. There are also big efforts in Europe and Asia. The world is growing more permissive in the regulation of research involving human embryos, though a few countries maintain severe limitations for ethical or religious reasons. Funding from the private sector is set to improve, too. While all agree that spectacular cures may still lie decades in the future, pharmaceutical and biotechnology companies believe they are laying the foundations for what could become a huge industry.

Governments have mixed motives for funding stem cell research; the main two are to develop a high-technology economic base and to promote medical progress. The initiatives that set up the schemes in California and New York were led by high-profile patient advocates. “Our funding in New York focuses on finding cures through science rather than economic development,” says Ms. Solomon. “I think the economic development will follow excellent science.”

Even critics of lavish state funding believe it could pay off in the long run by creating a regenerative medicine industry. "A bidding war [for talent] between the states is not a good model for supporting American science because it encourages the balkanisation of research," says James Thomson of the University of Wisconsin, who first extracted stem cells from human embryos in 1998. "But, having said that, I think California will benefit enormously from the investment."

Dr. Trounson, formerly Australia's leading stem cell researcher, performs a delicate balancing act - between scientific rigour and patients' impatience. "Their need to have treatments available as soon as possible is very strong," he says. "I keep telling them that we are talking about a 10,12,15-year timescale." But, he adds, "They are a very important group of people for dealing with the politicians. Scientists don't carry the day as well as patient advocates."

When patients ask how long it will take to develop treatments,the answer is often confusing because stem cells - immature cells - come in various types that are at different stages of clinical development.

Everyone retains some stem cells throughout life to replenish dying tissues. "There are probably stem cells in all adult tissues, though we have not discovered them all yet," says Jonas Frisen of Sweden's Karolinska Institute. Bone marrow is particularly rich in stem cells - and some people argue that stem cell treatments, in the form of bone marrow transplants, have been carried out for decades.

But most people think of *embryonic* rather than adult cells when they think of stem cells. Unlike adult stem cells, which have limited potential, those derived from the early embryo are "pluripotent", with the ability in principle to generate any specialised tissue in the body. Actually getting embryonic stem cells to differentiate in this way is the biggest scientific challenge for the field.

The first clinical trial of embryonic stem cells, approved by the US Food and Drug Administration in January, is expected to start this summer. Geron, a Californian biotech company, plans to inject nerve cells derived from embryonic stem cells into patients paralysed by recent spinal cord injury.
To back up its case, Geron gave the FDA a 21,000-page submission describing 24 separate studies in which its product safely restored movement to rats and mice with spinal injury. Although a few experts feared that stem cell therapies would carry a risk of cancer, the data showed that this did not happen in the animals.

Some scientists worry that too much hype still surrounds embryonic stem cells. "The public and media interest is still amazing," says Pete Coffey of University College London. "There seems to be an idea that it is a miracle type of technology."

Professor Coffey is planning a clinical trial of a stem cell treatment for macular degeneration, an important cause of blindness, in partnership with Pfizer, the giant US drug company. "Remember that it is just over 10 years since the first embryonic stem cells were derived - and already the Geron trial is approved and we hope to have ours within two years," he says. "That is a remarkable timeline to go from zero to the clinic."

Most experts say that, even if the Geron trial gives spectacular results from the start, embryonic stem cell therapies are at least a decade from widespread commercial application. Dr Thomson,who pioneered the field, says 20 years is more realistic.

One further complication over the past two years has been the discovery and rapid refinement of "induced pluripotent" stem cells. Human iPS cells were first produced in 2007 by Japanese and US

scientists including Dr Thomson. They appear to behave just like embryonic stem cells but are produced directly from skin or other specialised adult cells.

The production of iPS cells would have seemed like bio-alchemy until recently. The scientist takes some adult cells, adds three or four genes or proteins, and as if by magic the cells are reprogrammed back in time to an embryonic state.

The ethical advantage of making pluripotent stem cells without involving an actual embryo is obvious. Those with religious objections to embryo research have hailed iPS cells as an answer to their prayers.

But scientists are more interested in the practical advantage of iPS technology. It is a far simpler way to make stem cells that are genetically identical to the patient, as is sometimes necessary to prevent immune rejection, than the "therapeutic cloning" technique that was the previous focus of scientific attention. This involves making an early embryo by transferring the nucleus of an adult cell into an egg whose own genetic material has been removed, and then culturing stem cells from the embryo.
Many experts feel the advent of iPS cells makes therapeutic cloning redundant. The latter requires too many fresh human eggs, its critics say,and the use of animal instead of human eggs as a source remains unproved. Some, such as Stephen Minger, director of the Stem Cell Biology Laboratory at King's College London, want to pursue therapeutic cloning research in parallel with work on iPS cells but Professor Minger accepts this is a minority view.

However, every scientist working on iPS cells insists research on conventional embryonic stem cells,derived from surplus embryos after in vitro fertilisation treatment,must continue. Human iPS cells are so new that much more research is needed to understand their properties and how they differ from their predecessors. "We are still working with embryonic stem cells,because we understand them well, and are comparing them with iPS cells," says Dr Thomson.

While iPS cells may be even further from commercialisation than embryonic stem cells as direct therapy for patients, there are more immediate applications for pluripotent cells in research and development. They can be turned into specialist cells for assessing the safety and efficacy of new drugs. And cultures of iPS cells derived from patients promise to be an invaluable tool for studying the biochemistry of particular diseases and for developing treatments.
But even these more immediate applications will not benefit patients for many years. Anyone who takes a long- term view of public spending should congratulate California for investing scarce state funds in a field where any pay-offs - whether monetary or medical - lie so far in the future.

Wary investors follow governments and charities into the laboratory

Governments and, to a lesser extent, medical charities have been the main funders of stem cell research because the big commercial pay-offs lie so far ahead. But the private sector is moving into the field.

Among large pharmaceutical groups, GlaxoSmithKline led the way last year with a $25m (€18m,£15m) collaboration with the Harvard Stem Cell Institute. Then Pfizer set up a $100m programme, Pfizer Regenerative Medicine.

A host of small biotechnology companies is already working with stem cells. But Steven Burrill, the California-based biotech investment banker, says venture capital funds are wary because of risks involved in technology, regulation, future reimbursement for treatments and intellectual property - for example, there is a minefield of overlapping patent claims.

“We like stem cell technology and we [Burrill & Company] have looked at many stem cell companies but have not invested in any of them,” says Mr Burrill.

The leading quoted stem cell company, Geron of California, estimates it has spent $200m developing embryonic stem cells - including $45m on a spinal injury treatment about to start clinical trials. The share price,below $2 last year, has been trading in the $6-$7 range. In the UK, ReNeuron is using neural stem cells, derived from a foetal brain,as a treatment for stroke.

Among companies focusing on adult stem cells, Osiris Therapeutics has the most advanced product; it expects to submit Prochymal,derived from bone marrow cells,for US marketing approval this year to treat rejection of transplants. Others with adult stem cell products in trials include Aastrom Biosciences, Cytori Therapeutics and StemCells Inc.

Companies such as these, which transplant living cells directly into patients,are the most visible. But many others are taking an indirect approach, developing drugs that activate the body's own stem cells to repair damaged or diseased tissues. They include Fate Therapeutics of the US and Epistem of the UK.

Two companies are exploiting the recent observation that new neurons can grow in some regions of the adult brain. Braincells Inc of the US aims to develop a new generation of antidepressants by stimulating the growth of the patient's neural stem cells. NeuroNova of Sweden is targeting Parkinson's and motor neuron disease.

A further group of companies is developing stem cells as tools for the pharmaceutical industry to test drugs. Cellular Dynamics International, co-founded by the stem cell pioneer James Thomson, is selling heart cells for this purpose.

Taking all applications of stem cells together, Mr. Burrill estimates about 100 companies worldwide are active in the field.