



# Regenerative Medicine

## The Industry Comes of Age

**C. Mason**

Regenerative Medicine Bioprocessing Unit, Advanced Centre for Biochemical Engineering, University College London, UK.

The regenerative medicine industry has moved into a new era in which commercialisation and not research is the number one priority. To achieve its new goal, much has had to change, including the introduction of expert business management, simpler but superior products and scalability of manufacture. Mass public and political support is supplying both long-term resources and the market demand to finally create a sustainable new health-care sector.

Image: iStockphoto

This article was first published in *Medical Device Technology*, March–April 2007.

### Important refocusing

With the arrival of 2007, the regenerative medicine industry has finally come of age. This is not because it is now approximately 21 years since the pioneers started their tissue engineering companies. Far more importantly, it is because the companies' focus has changed forever from being research establishments into commercial organisations. Today, the translation of regenerative medicine science, both cell therapies and tissue engineering, is the number one company objective. This shift heralds the start of a successful and sustainable global health-care sector. Today's industry is not a continuation of the exciting forays embarked on by a few pioneers, but a focused campaign with widespread public and political support. The hallmark of the pioneers was polymer scaffolds on which to grow whole organs and tissue on the laboratory bench at literally any price. By 2006, tissue engineering had largely been replaced by cell therapy. The focus has switched from whole organs grown in the laboratory at uneconomic cost to cell therapies where cells alone are surgically implanted to restore damaged and diseased organs: in vivo tissue engineering.<sup>1</sup> This dramatic refocusing occurred because of a number

of major factors, but principally: the high cost associated with growing whole organs for weeks or months in facilities operating according to good manufacturing practices (GMP), the complexity of bioprocessing solid organs, market opportunities, and stem cells.<sup>2,3</sup> The latter triggered the new wave of commercial activity encouraged by mass public support.

### Naming the change

When needing to distinguish eras, there is a requirement for pragmatic terminology. Historians have universally adopted a numbering system for this, for example, World War I and II, and Henry I–VIII. This logical approach has been adopted by the technology sector to indicate new versions of established software programmes (Windows 1.0, 2.0 and 3.0) and periods of commercialisation of the Internet (Web 1.0 and 2.0).<sup>4</sup> A similar nomenclature has been proposed to distinguish the two distinctly different periods of the regenerative medicine industry: Regenerative Medicine 1.0 spanning 1985–2002, and Regenerative Medicine 2.0 commencing in approximately 2006.<sup>1</sup> In keeping with the vogue of blending technology words, for example, picture element (pixel), electronic

mail (email) and iPod broadcast (podcast) and the fact that in everyday conversation regenerative medicine is frequently blended to “regenmed,” it seems sensible to adopt the terms RegenMed 1.0 and 2.0 when discussing the two separate periods in the history of the sector.

### RegenMed 1.0

From approximately 1975, scientists in the United States (US) started to research into better ways to restore human health by attempting to grow living tissues in the laboratory. Spurred on by initial research successes, the investment community became enticed. In 1985 the first of a number of tissue engineering companies were formed including Celox, Creative Biomolecules (now Curis, [www.curis.com](http://www.curis.com)) and Biohybrid Technologies.<sup>5,6</sup> The two leading pioneers, Organogenesis ([www.organogenesis.com](http://www.organogenesis.com), technology of Massachusetts Institute of Technology) and Marrow Tech (New York University technology, later to become Advanced Tissue Sciences, [www.advancedtissue.com](http://www.advancedtissue.com)) were formed shortly after in 1986 and 1987, respectively.<sup>6</sup> Fuelled by copious quantities of media hype, business angels, venture capitalists and the public via the NASDAQ and →

→ New York Stock Exchange enthusiastically invested. Speculation was rife that any day whole organs would be grown in the laboratory, leading to a multibillion-dollar gold rush. The industry continued to expand throughout the 1990s and reached its peak by early 2001. The sector consisted of more than 70 companies that employed approximately 3300 people and had a combined annual expenditure of more than US\$600 million. Total investment in tissue engineering had reached US\$3.5 billion and the 16 publicly listed companies reached a combined market capitalisation of US\$2.6 billion.<sup>7</sup> But all was far from well.

The RegenMed 1.0 companies were almost all focused on research and not on translation and commercialisation. As a result, few products reached the market and none were profitable.<sup>8</sup> The handful of products approved by the US Food and Drug Administration (FDA) were unable to demonstrate real clinical benefits that were in anyway proportional to their high price differential over conventional remedies. Furthermore, scaling up of production was an afterthought and resulted in a cottage industry approach that was incapable of meeting potential demand. By the end of 2002, a further US\$1 billion in investment had been exhausted and the bubble finally burst.<sup>8</sup> The leading companies folded, downsized or merged. Advanced Tissue Sciences and Organogenesis, which at their peak had a combined market capitalisation of more than US\$1.5 billion, filed for bankruptcy, Ortec ([www.ortecinternational.com](http://www.ortecinternational.com)) downsized considerably and Genzyme Tissue Repair merged with another Genzyme division to form Genzyme Biosurgery ([www.genzymebiosurgery.com](http://www.genzymebiosurgery.com)).<sup>7,9</sup> By December 2002, the combined market capitalisation for all the remaining stock market traded companies had collapsed from US\$2.6 billion in 2001 to US\$300 million. RegenMed 1.0 was over.

For the next three to four years,

times were turbulent with the main objective being company survival at all cost.<sup>10</sup> The few FDA-approved products were either off the market because of their manufacturer's financial difficulties or were not profitable. Worse still, all nine of the tissue-engineering products in the development pipeline at the end of 2002 failed to reach the market for regulatory reasons or were withdrawn on economic grounds by the companies.<sup>11</sup> It seemed that matters could not be worse.

### Supporters build the future

The shining light was stem cells or more importantly the promise of cures using stem cells. However, President George W. Bush put an end to US researchers using human embryonic stem cells (hESCs) lines by banning federal funding (principally from the National Institute of Health) for work on hESC lines made before 9.00 pm EDT on 9 August 2001.<sup>12</sup> At that time, it was believed that there were more than enough hESC lines to allow future research. It subsequently transpired that of the 60 lines believed to be in existence only 21 actually existed and all were contaminated.<sup>10</sup> Since 2001, stem-cell scientists have likened Bush's restrictions to sending soldiers to Iraq equipped with weapons from the World War II era.<sup>13</sup> As a direct response to this ban, a number of leading figures from all walks of life contributed to a campaign to side-step the federal funding restriction.<sup>14</sup> The focus was to support the Californian Proposition 71, "The California Stem Cell Research and Cures Bill."<sup>15</sup> The bill was to provide funding of up to US\$350 million per year for stem cell research for one decade. Supporters who made substantial financial donations included Sergey Brin (founder of Google), William Bowes (founder of Amgen), Bill Gates (founder of Microsoft) Robert Klein (Klein Financial Corporation), Pierre Omidyar (founder of eBay) and Jerry Zucker (billionaire industrialist).<sup>16</sup> Other leading figures firmly behind the campaign included Christopher

Reeve, Michael J. Fox and Nancy Reagan (wife of ex-President Reagan) and the Republican California State Governor, Arnold Schwarzenegger. On 2 November 2004, the bill was easily voted into law with 59% of voters (more than 7 million people) in agreement. Thus, a ban by President Bush effectively galvanised and swung public opinion and long-term public funding behind the regenerative medicine sector. After a number of years in the wilderness, RegenMed 2.0 was on the horizon.

### RegenMed 2.0

Today, the regenerative medicine industry is almost exclusively focused on translating science into commercial products, thus integrating the science into the health-care system.<sup>17</sup> The products in development are in general cell therapies, that is, therapies that can be surgically delivered to restore organs and tissues in vivo. Current targets include heart failure, spinal-cord injury, stroke and diabetes. It is no longer the aim to build a whole organ such as a complete living heart. This is an exciting concept, but with today's technology and funding, it is impossible to achieve. Instead, injecting cells around the damaged area of a heart potentially offers a far simpler and cost-effective solution. Hundreds of patients are being enrolled in various cardiac studies all round the world to test the merits of this approach.<sup>18</sup>

In 2006, StemCells Inc. ([www.stemcellinc.com](http://www.stemcellinc.com)) announced the commencement of the first clinical trial for a neurological disease using neural stem cells.<sup>19</sup> Although the initial target is Batten's Disease, which is a rare neurodegenerative disease, the principles learnt will later be used to address other neurological disorders such as multiple sclerosis, Alzheimer's Disease and spinal-cord injuries. All are potential "blockbuster" applications.

Other companies are also committed to enter the arena, including the Geron Corporation (Menlo Park, California, USA, [www.geron.com](http://www.geron.com)),

which plans to start the world's first human embryonic stem cell derived therapy for spinal-cord injury in 2007. By choosing a condition that has an incidence of approximately 11 000 new patients per year, the company believes that scaling up manufacture to meet this demand is not an issue. For future blockbusters, scale-up development programmes are already under way.<sup>20</sup> ReNeuron (Guildford, UK, [www.reneuron.com](http://www.reneuron.com)) has filed its Investigational New Drug application with FDA to commence its Phase 1 clinical trial for stroke.<sup>21</sup> There are currently no treatments to restore permanently lost neurological function. The annual health and social costs of caring for disabled stroke patients is estimated to be in excess of £5 billion (approximately €7.4 billion) in the United Kingdom (UK); stroke patients occupy 25% of long-term hospital beds. In the US, the annual direct and indirect costs of stroke are estimated to be US\$50 billion. Already ReNeuron is addressing the issues of scale-up by collaborating with two contract manufacturing organisations (CMOs).

CMOs represent one of the fastest growing sectors within the regenerative medicine industry in the US and UK. Possessing a vast wealth of knowledge from bioprocessing mammalian cells to produce biopharmaceutical products, these organisations also possess much of the GMP resources required to switch to cell therapy production. The leaders include Angel Biotechnology (Cramlington, UK, [www.angelbio.com](http://www.angelbio.com)), BioReliance (Scotland, UK, [www.bioreliance.com](http://www.bioreliance.com)), Cambrex (Walkersville, Maryland, USA, [www.cambrex.com](http://www.cambrex.com)), Cognate BioServices (Baltimore, Maryland, USA, [www.cognatebioservices.com](http://www.cognatebioservices.com)) and Progenitor Cell Therapy (Hackensack, New Jersey, USA, [www.progenitorcell.com](http://www.progenitorcell.com)).<sup>22</sup> Using a CMO has the benefit of freeing company resources to concentrate on sales and marketing. This is a massive departure from RegenMed 1.0 when the companies attempted at great expense to be totally self-sufficient. For example,

Advanced Tissue Science produced its own culture media and also possessed vast electricity generating capacity in the event of a possible long-term power failure.<sup>22</sup> Another related development is the beginning of industrial standards, which will help facilitate collaborations and outsourcing within the industry.<sup>23</sup>

From the above it is clear that the technology push is strong, and unlike for RegenMed 1.0, the market pull is equally forceful. The mass public and political support has created a demand for products that is unparalleled in the history of regenerative medicine. No longer is the industry an overly confident and enthusiastic collection of start-up companies trying to individually push products into an indifferent market. Proposition 71 clearly states in its purpose and intent to, "Improve the California health-care system and reduce the long-term health care cost burden on California through the development of therapies that treat diseases and injuries with the ultimate goal to cure them" and "Benefit the California economy by creating projects, jobs and therapies that will generate millions of dollars in new tax revenues in our state."<sup>15</sup> Research alone will not meet these goals; translation is now number one on the agenda.

### Production and automation

The production of large amounts of living human cellular material for therapy is at least one order of magnitude more difficult than that for biopharmaceutical applications. Therefore, intellectual property, skills and systems associated with bioprocessing will be of central importance. The California Institute of Regenerative Medicine ([www.cirm.ca.gov](http://www.cirm.ca.gov)) initiative (set up by Proposition 71 to invest the US\$3 billion) intends to commit US\$60 million to bioprocess engineering and automation. CIRM may also commit substantial funds to GMP and cell-banking facilities to a maximum of US\$107 million.<sup>22</sup> Furthermore, companies are not only focused on basic sound manufacture,

but are also beginning to seriously consider automation of their production. Two options are being adopted:

- pragmatic automating of part of an existing manufacturing process to improve efficiency; for example, Organogenesis and the production of its lead product, Apligraf,<sup>2</sup>

- starting to automate during the early phase of product development; for example, Advanced Cell Technology (ACT, Alameda, California, USA) has a robotic roller bottle cell culture programme in its 10 000 ft<sup>2</sup> (929 m<sup>2</sup>) GMP manufacturing facility; this programme is aimed at checking the suitability of newly produced cell lines for mass production before any significant preclinical studies are performed.<sup>1</sup>

### Winning management

The leaders of the RegenMed 2.0 companies are significantly different from the pioneers. No longer are they made up of great visionary scientists, but are instead seasoned businessmen focused on building great companies. A good example is William Caldwell, Chairman and Chief Executive Officer of ACT. Caldwell has more than 30 year's experience ranging from emerging technology companies, public companies and corporate restructuring. These core competencies ideally complement those of Dr Michael West, President and Chief Scientific Officer of ACT, who is widely regarded as one of the leaders and creators of the field of stem cells and regenerative medicine having founded Geron and ACT. Likewise other companies in the new industry have similarly experienced management, including Organogenesis, which is headed up by Geoff MacKay (ex Novartis), and Tengion (King of Prussia, Pennsylvania, USA, [www.tengion.com](http://www.tengion.com)), which is led by a senior management team all originally from leading positions in big pharmaceutical companies. In 2006, an important milestone for the industry was reached, under its new management, Organogenesis became the world's first profitable regenerative medicine company.<sup>11</sup>

### → The future challenge

Will RegenMed 2.0 out perform RegenMed 1.0 in the same way that Web 2.0 with Flickr, Google, MySpace and YouTube have already far outshone their predecessors? Both industries have undergone a major step change and upgrades in their respective technologies since their investor bubbles burst so spectacularly in 2001/2. However, far more importantly for their long-term success is interaction and active participation with all the stake-holders. Both industries now have a strong base of public support, which is willing to invest and eager for new products.<sup>1</sup> To date, more than 250 000 patients have been treated with regenerative medicine products. This is a good start, but it is only a start. To quote from Proposition 71, "Millions of children and adults suffer from devastating diseases or injuries that are currently incurable, including cancer, diabetes, heart disease, Alzheimer's, Parkinson's, spinal cord injuries, blindness, Lou Gehrig's disease, HIV/AIDS, mental health disorders, multiple sclerosis, Huntington's disease, and more than 70 other diseases and injuries. Recently medical science has discovered a new way to attack chronic diseases and injuries. The cure and treatment of these diseases can potentially be accomplished through the use of new regenerative medical therapies ...".<sup>15</sup> Happy 21st birthday Regenerative Medicine, you've got a lot to live up to! [mdt](#)

### References

1. C. Mason, "Regenerative Medicine 2.0," *Regenerative Medicine* 2, 1, 11–18 (2007).
2. C. Mason and M. Hoare, "Regenerative Medicine Bioprocessing: Building a Conceptual Framework Based on Early Studies," *Tissue Engineering*, February 2007.
3. C. Mason and M. Hoare, "Regenerative Medicine Bioprocessing: The Need to Learn From the Experience of Other Fields," *Regenerative Medicine* 1, 5, 615–623 (2006).
4. T. O'Reilly, "What Is Web 2.0? Design Patterns and Business Models for the Next Generation of Software," (2005), [www.oreillynet.com/pub/a/oreilly/tim/news/2005/09/30/what-is-web-20.html](http://www.oreillynet.com/pub/a/oreilly/tim/news/2005/09/30/what-is-web-20.html) (Retrieved on 31/12/2006).
5. P. Kemp, "History of Regenerative Medicine: Looking Backwards to Move Forwards," *Regenerative Medicine* 1, 5, 653–669 (2006).
6. J. Viola, B. Lal and O. Grad, "The Emergence of Tissue Engineering as a Research Field," The National Science Foundation, Arlington, Virginia, USA, (2003), [www.nsf.gov/pubs/2004/nsf0450/start.htm](http://www.nsf.gov/pubs/2004/nsf0450/start.htm)
7. M.J. Lysaght and J. Reyes "The Growth of Tissue Engineering," *Tissue Engineering*, 7, 483–495 (2001).
8. M.J. Lysaght, Personal communication 19 December 2006.
9. M.J. Lysaght and A. Hazelhurst. "Tissue Engineering: The End of the Beginning," *Tissue Engineering* 10, 309–320 (2004).
10. W.M. Caldwell IV "Commercialising Human Stem Cell Technology" at Commercialisation of Tissue Engineering & Cell Therapy, Marcus Evans Conference, London, December 2006.
11. M.J. Lysaght, "Tissue Engineering: Great Expectation," at London Regenerative Medicine Network event, London, December 2006.
12. G.W. Bush, White House speech, (2001), [www.whitehouse.gov/news/releases/2001/08/20010809-2.html](http://www.whitehouse.gov/news/releases/2001/08/20010809-2.html)
13. T. Somers, "Prop. 71 Opens Tap for Stem-Cell Studies," *San Diego Union-Tribune* 8 October 2004, [www.signonsandiego.com/uniontrib/20041008/news\\_1n8stemcell.html](http://www.signonsandiego.com/uniontrib/20041008/news_1n8stemcell.html)
14. T. Somers, "Stem Cell Research No Dream for California," *San Diego Union-Tribune*, 19 December 2006, [www.signonsandiego.com/news/business/biotech/20061219-9999-lz1n19stem.html](http://www.signonsandiego.com/news/business/biotech/20061219-9999-lz1n19stem.html)
15. Proposition 71 The California Stem Cell and Cures Act (2004), [www.cirm.ca.gov/prop71/pdf/prop71.pdf](http://www.cirm.ca.gov/prop71/pdf/prop71.pdf)
16. S. Usdin, "Prop 71. Promises to Keep," Centre for Genetics and Society 8 November 2004, [www.genetics-and-society.org/resources/items/20041108\\_biocentury\\_usdin.html](http://www.genetics-and-society.org/resources/items/20041108_biocentury_usdin.html)
17. G. MacKay, "Analysing the Path For the Reimbursement of Cell Therapies in the USA at Commercialisation of Tissue Engineering & Cell Therapy," Marcus Evans Conference, London, December 2006.
18. R.S. Schwartz, "The Politics and Promise of Stem-Cell Research," *New England Journal of Medicine* 355, 12, 1189–1191 (2006).
19. Press release "StemCells, Inc. Announces First Human Neural Stem Cell Transplant," (2006), [www.stemcellsinc.com/news/061115.html](http://www.stemcellsinc.com/news/061115.html)
20. A. Davies, "Development of Human Embryonic Stem Cell Technology for Human Therapeutic Application," at London Regenerative Medicine Network event, London, December 2006.
21. Press release, "ReNeuron Announces Filing IND Application to the FDA for ReN001," (2006), [www.reneuron.com/news\\_\\_events/news/document\\_113\\_237.php](http://www.reneuron.com/news__events/news/document_113_237.php)
22. "Advanced Cell and Tissue Therapy - A Mission to the USA," DTI Global Watch Mission Report, (2006), [www.oti.globalwatchonline.com/online\\_pdfs/36718MR.pdf](http://www.oti.globalwatchonline.com/online_pdfs/36718MR.pdf)
23. PAS 83: Guidance on Codes of Practice, Standardised Methods and Regulations For Cell-Based Therapeutics, From Basic Research to Clinical Application, DTI in Collaboration With the British Standards Institution (2006), <http://eshop.bsi-global.com/ProductListing.aspx?cat=PAS+83>.

### Chris Mason MBBS, PhD, FRCS

Regenerative Medicine Bioprocessing Unit, Advanced Centre for Biochemical Engineering, University College London, Roberts Building, Torrington Place, London WC1E 7JE, UK, tel. +44 20 7679 0140, e-mail: [chris.mason@ucl.ac.uk](mailto:chris.mason@ucl.ac.uk)

**This article was first published in *Medical Device Technology*, 18, 2, March–April 2007.**