



Regenerative Medicine 2.0



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'2006 heralded the era of Regenerative Medicine 2.0 (RegenMed 2.0), where the focus is almost exclusively on the translation of research into commercially successful products. A stark contrast to the period 1985–2002 when research goals almost totally predominated the fledgling industry.'

This editorial started life as an 'end of year report' style review of the stem cell and regenerative medicine sector. However, during its preparation it became very apparent that 2006 was not just a further 365 days in the gradual continuum from its origins in the laboratories at the Massachusetts Institute of Technology in the 1980s through to a mature industrial sector. 2006 was the year that regenerative medicine started to enter the next phase in its development into a successful and sustainable global healthcare industry. This editorial proposes that the regenerative medicine sector is not moving continuously in one direction from the tissue engineering pioneers through to the establishment of a new commercial sector, but that it is undergoing a similar disjointed journey to that of the World Wide Web. Does this quote from Tim O'Reilly, a leading web commentator and IT book publisher [101], sound familiar?

"The bursting of the dot-com bubble in the fall of 2001 marked a turning point for the web. Many people concluded that the web was overhyped, when in fact bubbles and consequent shakeouts appear to be a common feature of all technological revolutions.

Shakeouts typically mark the point at which an ascendant technology is ready to take its place at centre stage. The pretenders are given the bum's rush, the real success stories show their strength, and there begins to be an understanding of what separates one from the other."

Simply replace the words 'dot-com' and 'web' for tissue engineering and change the date to the fall of 2002 and the fit is spot on. As we all know, out of the chaos that ensued from the

bursting of the Internet bubble surfaced the second generation of Internet-based pioneers who continue to be far more successful than their predecessors. These companies include Google, YouTube, MySpace and Flickr with new innovative business models, products and services and, most importantly, a far greater sense of realism. Web 2.0 was born, with the '2.0' alluding to the version numbers that are commonly deployed by software houses to designate computer software upgrades. Likewise, after an equally stormy transition period, the second generation of regenerative medicine companies and products has arrived. 2006 heralded the era of Regenerative Medicine 2.0 (RegenMed 2.0), where the focus is almost exclusively on the translation of research into commercially successful products. A stark contrast to the period 1985–2002 when research goals almost totally predominated the fledgling industry.

Regenerative Medicine 1.0

At the close of 2006, are we still traveling hopefully down the same path as started by the tissue engineering pioneers some 20 or more years ago? From tissue engineering's origins in the laboratories of Bell, Burke, Green, Langer, Naughton, Vacanti and Yannis came, via the commercial sector, most of the US FDA-approved regenerative medicine products that we have today [1,2]. Throughout the 1990s, the media frenzy around the growing of whole human organs in the laboratory helped the pioneer companies to keep raising much-needed finance to fuel their cash-burning research budgets. In turn, the companies were desperately trying to keep pace with public expectations. Thus, a vicious circle was set up that was inevitably weighted against the companies. 2000 saw the peak of the first wave of regenerative medicine, with over 73 companies in operation employing a total of over 3000 workers and a combined annual research and development spend in excess of US\$580 million [3]. Media sensationalism was also running at an all-time high, including in May 2000, *Time* magazine naming tissue engineering as the number one hottest job for the future. The introduction ran [4]:

“Looking for a career change? A decade ago, who would have guessed that Web designer would be one of the hottest jobs of 2000? Here are some clues.

Number 1: TISSUE ENGINEERS – With man-made skin already on the market and artificial cartilage not far behind, 25 years from now scientists expect to be pulling a pancreas out of a Petri dish. Or trying, anyway. Researchers have successfully grown new intestines and bladders inside animals’ abdominal cavities, and work has begun on building liver, heart and kidney tissue.”

However, just like the World Wide Web at exactly the same period, all was far from perfect. Media hype and unrealistic expectations had merely papered over the growing cracks for both the Internet and the tissue engineering industrial sectors. Box 1 gives a list of the problems that both pioneering industries faced at the beginning of the 21st century.

Thus Web 1.0 as it has since been referred, had the same intrinsic problems and flaws as the early tissue engineering sector. Because of these similarities, dare we do likewise and term this early period of regenerative medicine, RegenMed 1.0? Thus the research intensive RegenMed 1.0 (1985–2002) can then be clearly and easily distinguished from today’s translation-driven industry, RegenMed 2.0.

Regenerative Medicine 2.0

The term ‘Web 2.0’ was coined in 2004 in order to be able to easily distinguish the second generation of Internet offerings from the pioneers [102]. With currently over 160 million references on the web (Google search on 10/12/2006) the term would appear to have succeeded. Why the term ‘RegenMed 2.0’? Are we not on the same path that Bell and his fellow pioneering scientists started to tread two decades ago? Expressed in the familiar terms of Geoffrey Moore’s *Technology Adoption Life Cycle* [5], the industry had acquired a number of early adopters of the technology (>250,000 patients treated) and after a period trapped in the notorious chasm, is now just starting to climb out the other side into mainstream clinical practice [6]. The answer is that we are probably leaving the chasm by a totally different route to the one we predicted when we tumbled in. RegenMed 2.0 is demonstrating itself to be far more than just a linear progression from point A to B, but a definite step change. A step change that was essential to overcome the challenges that beset the original industry (Box 1).

The defining events for RegenMed 1.0 were not the scientific discoveries of the pioneers. They were, however, the formation of their commercial companies in the mid-1980s (including Advanced Tissue Sciences, BioHybrid, Celox, Creative Biomolecules, LifeCell, Marrow-Tech, Neomorphics and Organogenesis), the accompanying media hype, exuberance of extremely willing but naive investors and the eventual Filing under Chapter 11 of the US Bankruptcy Code by both the industry leaders Organogenesis and Advanced Tissue Sciences in the autumn of 2002 [1,7]. While Web 1.0 was about commerce, Web 2.0 is about people and their active participation [103]. The same is true for regenerative medicine; the pioneers were all about the science and research and little about translation into genuine products with benefits to both patients and shareholders. Whereas RegenMed 2.0 is almost exclusively focused on the pragmatic translation of great science into routine clinical practice. The defining events that helped shape RegenMed 2.0 include the cloning of Dolly the sheep, Jamie Thomson’s derivation of human embryonic stem cells (hESCs), UK Stem Cell Initiative, Proposition 71 and the California Institute for Regenerative Medicine (CIRM). Thus bringing, for the first time ever, new science and technology, massive public awareness and support, political debate at the highest level and substantial long-term financial commitment to the sector.

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Today we live in a participation age [8]. Thus the ‘architecture of participation’ has evolved for regenerative medicine. No longer is it just the enthusiastic scientists and their financial backers pushing the sector, with the mistaken belief that building a better ‘mouse trap’ will have everyone, cash in hand, beating a path to their door. The essential pull factor in the push–pull equation had arrived largely because of the potential promise of hESCs.

Box 1. Common problems that were associated with the demise of both the early Internet entrepreneurs (Web 1.0) and the tissue-engineering pioneers (RegenMed 1.0).

- Lack of successful business models
- Offerings with poor performance
- Large gaps in scientific and technical knowledge
- Shortage of experienced people ('Gray-hairs')
- High cash-burn rates and, as a result, non-cost-effective products and services
- Lack of scalability
- Totally unrealistic expectations and nonsustainability
- Frustrated investors with return on investment either very slow or nonexistent
- Lack of an 'architecture of participation'
- Lack of industry standards which hampered collaboration

For example, more than 59% of voters were in favor of Proposition 71, the 'California Stem Cell Research and Cures Initiative'. This initiative makes the conducting of stem cell research a state constitutional right. It authorizes the sale of bonds in order to allocate US\$3 billion over a period of 10 years to stem cell research and facilities. Although the funds can be deployed to finance all types of stem cell research, it gives priority to hESC research. In addition to large-scale public support, over 70 patient advocacy groups plus the State Governor, Arnold Schwarzenegger, were also firmly behind the initiative. Stem cells for the curing of human diseases is now firmly on the political agenda. For example, Proposition 71 aims, through the funding of stem cell activities, to 'Benefit the California economy by creating projects, jobs, and therapies that will generate millions of dollars in new tax revenues in our state' and 'Advance the biotech industry in California to world leadership, as an economic engine for California's future' [9]. However, this political and public support is not just limited to California but also in a number of US states including Connecticut, Maryland, New Jersey and New York and throughout much of the Western World, including the UK via the UK Stem Cell Initiative [10]. It is important to note that it is not 'stem cells the science' that has got the public backing but the promise that they potentially hold for healthcare. This is best illustrated by the title of Proposition 71, 'California Stem Cell Research and Cures Initiative' and its intentions including to 'Improve the California healthcare system and reduce the long-term healthcare cost burden on California through the development of therapies that treat

diseases and injuries with the ultimate goal to cure them' [9]. RegenMed 1.0 had little or none of this public and political mass buy-in and therefore the critical pull factor was almost totally absent. Getting everyone to participate as early as possible is vital for a new technology to succeed. Web 2.0 has flourished because of its phenomenal success with MySpace, YouTube and Flickr websites where everyone can post their own pictures, videos and music thus making them available to the entire web. Public participation is continuing to grow. For example, many more US states are continuing to join the California Proposition 71 bandwagon and are in the process of actively planning how to commit their tax payers' dollars to regenerative medicine activities both in the hope of creating new and better therapies but also to create companies, jobs and the potential to establish locally embedded regenerative medicine healthcare centers that could attract large volumes of extremely profitable medical tourism. No US state economy wants to miss out on this financial opportunity.

Transition from RegenMed 1.0 to 2.0

Just as Web 2.0 is very different to Web 1.0 with, for example, Google replacing AltaVista, iTunes replacing mp3.com, Wikipedia replacing Britannica online and personal websites evolving into blogs, the list is endless. So too has the regenerative medicine sector changed, for example, stem cells have largely displaced somatic cells, the term 'tissue engineering' has been replaced by 'cell therapy' or 'regenerative medicine' and, most importantly, basic science hype is being replaced by translation. The above changes further helped to get the public on board. Stem cells provide exciting front page news stories; however, at the same time, they offer an improvement in scalability and flexibility to companies on a par with the transformation of the web from 56 Kb telephone dial-up modems to high-speed Gb broadband. In 2006, the term 'tissue engineering' sounds too unfriendly to patients to be part of the modern healthcare vocabulary with its patient-centered values. Are patients really interested in the methodology or the benefits? On the other hand, the terms 'cell therapy' and 'regenerative medicine' blend nicely with today's healthcare environment and patient expectations. Finally, while science and science fiction excite the public in the short term, people's long-term financial commitment to a

'dream' can only be sustained by successfully translating the science into social benefits, that is, clinical therapies that either perform significantly better than their earlier counterparts or produce a real cost benefit.

Healthcare economics are now driving industry to produce cures rather than therapies [11]. As the industry moves forward as RegenMed 2.0 this translation phase is starting to take center stage. For example, companies are now not only focused on manufacture but are beginning to consider automation of their production [12]. Two routes are being followed, either the pragmatic automating of part of an existing manufacturing process in order to improve efficiency, such as Organogenesis (Canton, MA, USA) and the production of their flagship product Apligraf®; or even starting to automate during the very early phase of product development, such as Advanced Cell Technology (Alameda, CA, USA) and their robotic roller bottle program [13]. This program is aimed at checking the suitability of newly produced cell lines for mass production before any significant preclinical studies are performed [104].

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Linear progression or step change?

This is a difficult question to answer unless one looks at all the important factors with respect to the regenerative medicine industry both before the collapse of the first wave of the industry in 2002 and the emergence of a new, wiser, stem cell-influenced industry with broad public and political participation by the close of 2006. Table 1 compares the predominant features of the two periods from the commercial perspective. The question is whether the transition from RegenMed 1.0 to 2.0 is just a simple progression with a brief pause, a chasm or closed window of opportunity, due to financial and commercial difficulties following the slightly earlier dot.com crash, compounded by the slow uptake of products by healthcare providers and

patients, or did the paradigm significantly change? Looking at the two distinct sets of features, it quickly becomes apparent that in only a few instances a clear progression can be observed, however, for the majority, a definite step change has occurred.

The obvious features that support the notion of a progression that can be observed in Table 1 include the emerging from bankruptcy of the two leading pioneer companies. Organogenesis was restructured under the leadership of Geoff MacKay (ex Novartis) and is today one of the world's first profitable regenerative medicine companies with an annual revenue of over US\$40 million and continuing to climb. The workforce numbers are also returning to the pre-2002 level, with 220 employees producing and marketing over 2000 pieces of Apligraf a month. To date, the company has treated in excess of 150,000 patients with Apligraf [14]. Interestingly, the very first line of Geoff MacKay's CEO message on the company website is, 'Tissue regeneration has come of age' [105]. Likewise, Advanced Tissue Sciences (La Jolla, CA, USA) is being turned around, first by Smith & Nephew (London, UK) and now as part of Advanced BioHealing (New York, NY, USA). Production of their lead product Dermagraft® is expected to recommence in 2007 [15].

The step changes in Table 1 are far more numerous and widespread and stem from a few highly significant influences. The most important influence was the arrival of hESCs into the public awareness. Initially, the public and politicians debated the ethical issues; however, when Christopher Reeve, Michael J Fox and Nancy Reagan (wife of ex-President Ronald Reagan) all became passionately involved, suddenly it was 'show time'. Robert Klein, the great public champion of stem cells, further raised the bar by initiating and promoting Proposition 71. Klein is now Chair of the Independent Citizens' Oversight Committee, which is responsible for governing the CIRM, while still vigorously promoting stem cells and their benefits to patients both in the USA and internationally. To quote a leading venture capitalist in the sector, Greg Bonfiglio (Proteus Venture Partners, Portola Valley, CA, USA), "Everyone in the industry owes Bob Klein a big thank you" [16]. President George W Bush also made his significant contribution to the progress of the sector by first putting stem cells firmly on the political stage and secondly using

Table 1. Regenerative medicine industrial periods.

Category	Regenerative Medicine 1.0	Regenerative Medicine 2.0	Ref.
Approximate period	1985–2002	2005–	
Major company focus	Research	Translation into products Integrating the science into the healthcare system	
Dominant terms	Tissue engineering	Regenerative medicine, cell therapy, stem cells, therapeutic cloning	
Modus operandi	<i>In vitro</i> tissue engineering involving 3D scaffolds	<i>In vivo</i> tissue and organ regeneration	
Geographical location	USA	Global, including Australia, Canada, Japan, South Korea, Singapore and UK	
Leading companies	Advanced Tissue Sciences, Genzyme Biosurgery, Organogenesis, Ortec	Advanced BioHealing, Advanced Cell Technology, Genzyme Biosurgery, Geron, Intercytex, ReNeuron, StemCell, Stem Cell Sciences, Tengion, ViaCell	
Cumulative revenue	US\$100–150 million by December 2002	US\$300–400 million by December 2006	[16,20]
Number of companies	Peak: 90+ (2000)	150+ (USA, Europe and Asia – 2006)	[19]
Business model	Grandiose ideas 'Build a better mouse trap' Technology push Biotech model and selling product as biopharmaceuticals Run by founding scientists Poor commercial orientation Few experienced people	Technology push coupled with market pull Fully integrated approach focusing on the uniqueness of the products [1] Run by professional managers often ex big Pharma or IT Many experienced people including management and production staff	
Organisations	Tissue Engineering Society (TESI), European Tissue Engineering Society (ETES), BRITE Net – British Tissue Engineering Network	Tissue Engineering & Regenerative Medicine International Society (TERMIS), International Society for Stem Cell Research (ISSCR), California Institute for Regenerative Medicine (CIRM), UK National Stem Cell Network (UKNSCN)	
Funding	Venture capital Big Pharma US stock markets mainly NASDAQ NASA	Public finance including BBSRC, CIRM, DTI, MRC and NIH Philanthropists Military 'dual-use' products (DARPA and Project BioShield)	[21]
Public buy-in	Low	High	
Political issue	No	Yes – significant issue, especially in the USA	
Institutes of Regenerative Medicine and Centres of Excellence	Few	Many, including, Georgia Tech/Emory Center for the Engineering of Living Tissues, McGowan Institute for Regenerative Medicine and Wake Forest Institute for Regenerative Medicine	[20]
Manufacturing	Cottage industry requiring 'green-fingered staff' Lack of scalability Low volume Cost of goods – high Drive to have every aspect of production in house Bioprocessing often ignored Small amount of GMP facilities	Translation at the forefront Interest in automation and robotics Awareness to reduce cost of goods Contract manufacturing organizations becoming popular Bioprocessing important GMP facilities growing more common	[22,23]

BBSRC: Biotechnology and Biological Sciences Research Council; DARPA: Defense Advanced Research Projects Agency; DTI: Department of Trade and Industry; GMP: Good Management Practices; MRC: Medical Research Council; NASA: National Aeronautics and Space Administration; NASDAQ: National Association of Securities Dealers Automated Quotations, NIH: National Institutes of Health.

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Category	Regenerative Medicine 1.0	Regenerative Medicine 2.0	Ref.
Shipping and distribution	Fresh products with short shelf lives, high level of product wastage [24]	Move towards cryopreservation and long shelf lives, wastage reduced plus potential for centralised production	[22,23]
Industry standards	None	Beginning to emerge	[25,26, 27]
Product – unique selling points	No clear advantage over conventional approaches	Drive towards better developed product which deliver real benefits	
Main cell types deployed	Fibroblasts Epithelial cells (keratinocytes) Chondrocytes Allogeneic > autologous	Somatic cells Adult stem cells Embryonic stem cells Allogeneic > autologous	
Disease targets	Non-mission critical applications Chronic wounds Burns Sporting cartilage injuries	Chronic wounds Sporting cartilage injuries Moving into mission critical applications Bladder replacement Neurological disorders Spinal cord injury Heart failure	
Cumulative number of patients treated	100,000 (2000)	250,000+ (2006)	
Third world markets	Not considered	Considered as key areas for many regenerative medicine products	[28]
Bioaesthetics or aesthetic medicine	Not considered	Entering mainstream thinking as potential for early revenue generation, e.g., Isolagen	
Tools	A few products aimed at cosmetic and corrosivity testing, e.g., SkinEthic (L'Oreal)	Major drive towards tools for drug discovery and development plus toxicology	
Granted patents per year (global)	341 (2002)	357 (2005)	[29]
Scientific publications to date	19,652 (December 2002)	30,722 (December 2006)	[106]

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the presidential veto in order to block legislation that would have allowed expansion of federal funding in the area of hESC research. This action triggered State Governor, Arnold Schwarzenegger on the very next day to release a US\$150 million state loan to CIRM to initiate their funding activities. Thus, on 19th July 2006, the Bush starting pistol was unwittingly fired and California was quickly away from the blocks. In the future, stem cells will continue to be near the top of the political agenda. Political proponents include Congresswoman Nancy Pelosi (Speaker-designate of the House

of Representatives) who is quoted as putting stem cells at number three in her top six list of future initiatives.

Public opinion is likewise firmly behind the sector. Opinion polls in both the UK and USA repeatedly show that in excess of 60% of those surveyed support stem cell research. With the downturn in popularity of the Republican Party in the recent US midterm elections, optimism for stem cells has been further fuelled. For example, with the political heat reducing, stem cell-based companies have been showing a gradual gain in their share price as public confidence

in the sector rises. Even non-stem cell-based regenerative medicine companies have enjoyed the bystander effect.

Overall, gaining mass public support has had a number of significant effects including providing the much needed market pull, thus matching the technology push for healthcare products as well as ensuring adequate quantities of long-term private and public investment in the sector.

The other big shift from pre-2002 is the focus of the companies. Prior to 2002, the science and research was the top priority and funding was almost exclusively from the private sector. Today the reverse is true. In 2006, the approach is nearer to the biotechnology research and development model, with the research and scientific discoveries being made by academia funded by public money (excluding hESCs in the USA). For example, many of the new players in the field have substantial academic research effort behind them, including, for example, Tengion (King of Prussia, PA, USA), who have Professor Anthony Atala and his substantial team of researchers at the Wake Forest Institute of Regenerative Medicine to deliver the basic science [17]. This frees the companies and their finances to invest in translation of the science into commercial products. This switch can be observed throughout the industry. For example, William Caldwell, Chairman and CEO of Advanced Cell Technology (ACT) has publicly stated that ‘ACT is not a research company but a development company. This change occurred when the company floated in 2005’ [18]. Likewise, Organogenesis, by concentrating exclusively on product development and manufacture since its restructuring, has managed to successfully obtain the, ‘ability to mass-produce and distribute living technology reliably, timely and conveniently to medical clinics around the world’ [105].

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Finally one other significant change from 2002 is the commercial targets for *in vitro*-produced

cells and tissues. In 2002, virtually everyone was tissue engineering for eventual clinical application. Today, the targets include not only clinical products but also aesthetic medicine (bioaesthetics), drug discovery and development as well as toxicology studies.

Aesthetic medicine may at first sound rather trivial, that is, the deployment of cell-based products for cosmetic applications. However, it represents a very significant market opportunity for regenerative medicine companies since it leverages their existing core competencies. In addition, it has the benefit of offering faster times to market compared with regular clinical applications since the regulatory and reimbursement issues are simpler. Leading companies in this sector include Intercytex (Manchester, UK), Isologen (Exton, PA, USA) and Organogenesis. Aesthetic medicine products potentially offer companies early revenue streams, which can be then used to fund the more costly development of clinical products, which have far longer time scales prior to generating revenues. The tools areas of drug discovery and development including toxicology are also significant opportunities for the industry. For example, many industry experts believe that this may be the route that finally brings big Pharma to the hESC table especially as the political heat in Washington is now significantly cooling. The other appeal is that the technology offers a potential alternative to animal testing, which is both expensive, unreliable and is against the tide of public opinion. The topic of toxicology studies deploying stem cells was firmly put on both the UK political and big Pharma agendas when Sir John Pattison in the UK Stem Cell Initiative Report in 2005 put amongst the recommendations, ‘The UK Government should establish a public–private partnership to develop predictive toxicology tools from stem cell lines’ [10].

Conclusion

The all important concept of public buy-in or ‘architecture of participation’ as the Web 2.0 opinion leaders prefer to say, has produced a new and dynamic stem cell and regenerative medicine industry. This mass public commitment arose as a direct result of the hESC debate and hESCs’ potential to cure a great number of diseases that today have no satisfactory treatments let alone cures. Furthermore, being immortal and pluripotent, stem cells form the possible basis for scalable production and there-

fore favorable cost of goods, thus offering a possible solution for the formation of successful and sustainable commercial companies [11]. Stem cells are the catalyst for regenerative medicine in the same way that the invention and the rapid universal adoption of broadband catalyzed and enabled the Internet, which facilitated the emergence of Web 2.0. In the words of the legendary tissue engineering and stem cell industry commentator, Professor Michael Lysaght (Brown University), “Stem cells are the new 900 pound gorilla in the field”[19].

With the assistance of this ‘gorilla’ the regenerative medicine industry has been able to perform a step change from its old research-orientated, cottage-industry past (RegenMed 1.0) to its new position as a shining example of a 21st century, translation-focused, healthcare enterprise with both strong public and political support.

Was 2006 the year that finally saw the regenerative medicine industry climb out of the chasm with its firmly shut window of opportunity and herald the arrival of RegenMed 2.0? Only time will tell!

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