History of regenerative medicine: looking backwards to move forwards

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If the song by the international popstar Sting is to be relied upon, 'History will teach us nothing'. At the risk of contradicting a one-time schoolteacher, I believe the reverse is true for regenerative medicine. In fact, I think we dismiss the past at our peril. In this review, I aim to trace the history of regenerative medicine to date. I will examine parallels with other areas of medicine and show how commercial, technical and socio/economic factors have influenced the pace and direction of the sector's evolution. I will discuss how, by learning from the past, those involved in regenerative medicine are reinventing their sector for the better. In conclusion, I will evaluate the current state of the industry, suggest what the future may hold and explain why I believe regenerative medicine is about to 'come of age'.

Keywords: Apligraf®, cell therapy, cloning and stem cells, ICX-PRO, ICX-RHY, ICX-SKN, ICX-TRC, integrated business model, regenerative medicine, tissue biology, tissue engineering, tissue rejection, whole-organ regeneration

future medicine

Nobody really knows how many cells there are in the body, but best estimates suggest there may be between 10 and 100 trillion. Despite its amazing complexity, the human body is very poor at repair and, unlike amphibians, which can grow a new limb in 70 days [1], our organ systems are in chronic and sometimes acute decline – either through disease, aging or trauma. As Yannas, one of the field's pioneers said: "The adult organism responds spontaneously to a severe injury by mounting a healing response that spares the organism but condemns the injured organ" [2]. The first clinical solution to this problem, organ transplantation, was, in effect, the first form of cell therapy. Work began in the 1950s, initially with identical twins, where success depended primarily on the skills of the surgeon as the host did not mount an immune response to the graft. It was only when the need for immunosuppression became understood and the relevant drugs became available that transplantation became more broadly applicable. As is commonly the case in many areas of technology and frequently illustrated in regenerative medicine, two or more interacting technological advances are needed to support the emergence of a completely new field.

Once the two technologies of surgical expertise and immunosuppresion were united, transplant medicine advanced rapidly, with the first kidney transplant in 1954 between identical twins [3], the first liver and lung transplants taking place in 1963 [4], pancreas transplant in 1966 [5], culminating in the first heart transplant in 1967 [6]. In all of these cases, mature, fully functional organs were transplanted. The next breakthrough occurred in 1968, with the first bone marrow transplant [7]. Here, the introduction of hemopoetic stem cells, rather than a fully functional organ, 'seeded' the reconstitution of all hemopoetic cells in the patient and a new bone marrow slowly developed. Despite these significant landmarks in transplant medicine and the undoubted impact it has made on many people's lives, the bottom line remains the same – there simply aren't enough organs to go around [8].

Tissue engineering emerges

While transplant medicine made rapid progress, cell biologists were reporting similarly important advances, although the clinical significance of these had yet to be identified. From initial research on cell and tissue culture back in the 1960s, where scientists were looking at ways of keeping pieces of tissue alive outside of the body, work progressed to cell biology, where different cell types were purified out of tissue samples to produce monolayer cultures of a single cell type. Once scientists were able to do this, and began to understand what different cell types made, the role of different metabolites and signals and how each cell behaved, tissue biology emerged. Researchers started to look at 'organotypic cultures', whereby two or more cell types were grown together and their interactions examined. From there, it was a short intellectual step to tissue engineering, a term introduced by YC Fung of the University of California, San Diego (CA, USA), in 1985 [9]. Definitions of

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tissue engineering vary. In 1993, Langer and Vacanti described it as '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 or a whole organ' [10]. MacArthur and Oreffo defined tissue engineering as 'understanding the principles of tissue growth, and applying this to produce functional replacement tissue for clinical use' [11].

Tissue engineering, subsequently identified as a subset of the overarching field of regenerative medicine, was in effect born in Massachusetts as a result of that serendipitous combination of circumstances that sometimes occurs in science. Much of the initial work in the field began in four independent laboratories at the Massachusetts Institute of Technology (MIT) in Cambridge (MA, USA), run respectively by Green, Bell, Yannas and Vacanti (who collaborated with Naughton out of the Hunter College School of Health Sciences, NY, USA) [12]. Each laboratory pursued a somewhat different strategy and each strategy eventually resulted in approved medical products that are available today. Concurrently, a short distance away across the Charles River at Harvard Medical School in Boston (MA, USA), WL Chick was working to develop a bioartificial pancreas [13]. His alternative approach, to encapsulate islet cells in order to isolate them from immune attack, led to a variety of biohybrid organ projects some of which are showing clinical promise (**Table 1**).

By 1993, the first major review publication on tissue engineering appeared in *Science* [10] and, in 1998, the US FDA granted its first approval for an allogeneic tissue engineered product in the form of Apligraf®, which was described originally as a living skin equivalent by Organogenesis, a company spawned by Eugene Bell's laboratory. The launch of Apligraf® followed the autologous burns treatment, Epicel® which originated from Green's laboratory and was, at first, unregulated by the FDA and treated as a tissue graft. Epicel® was originally commercialized by Biosurface Technology and later by Genzyme Biosurgery after its purchase of Green's company. These products were followed by Dermagraft® produced by Advanced Tissue Sciences (ATS) and commercialized through a joint venture with Smith and Nephew (ATS was renamed from Marrowtec, a company formed by Gail and Brian Naughton to develop bone marrow feeder cultures on 3D nylon meshes) [14]. Yannas' laboratory focused on the development of acellular scaffolds that would stimulate the patient's cells to repopulate and regenerate tissue. This led to the development of the collagen/glycosaminoglycan sponge covered with a silicone membrane called 'Integra Dermal Regeneration Template', which was approved in 2002 for the treatment of severe burns and commercialized by Integra Life Sciences. Although each of these therapies has been important in its own way, rather like monoclonal antibodies a decade earlier and genetic engineering a decade before that, initial product flow has been a small trickle rather than a mighty deluge.

In another parallel to monoclonal antibodies and genetic engineering, initial claims for tissue engineering were grossly oversimplified and overplayed. Fanciful stories, such as the suggestion that livers and other organs might be 'grown in a Petri dish' [15], were bandied about indiscriminately, resulting in unrealistic expectations and wild media hype. This peaked in 2000 when Time magazine named tissue engineers as 'The Hottest Job' for the future. By the end of that year, over 3000 people had elected to pursue this 'hottest' career option and annual R&D spending on tissue engineering was estimated at US$580 million [16]. There were 66 companies operating in the field and those that had gone public had a capital value of US$2.5 billion.

By this stage, the industry was starting to run into problems. The most serious of these was underperformance: the first products, although mostly approved by the regulators, just did not behave as originally intended once they entered the clinic. Apligraf broke down in the wound and merely acted as a wound stimulant rather than a living skin equivalent and, despite investment in excess of US$200 millions [16], work to develop a replacement pancreas never even delivered a functional large-animal prototype. To compound the agony, the challenges of commercial-scale manufacture were considerable. As if the scientific and operational challenges were not great enough, most tissue engineering companies were pursuing a biotechnology business model centered on out-licensing or partnering through joint ventures. In hindsight, this proved wholly inappropriate, since the products did not sell in sufficient volume in their approved applications to generate enough return to satisfy both partners, especially when the cost of goods in the suboptimized manufacturing systems was still extremely high.

Table 1. Cell-based regenerative medicine companies with approved clinical products or products in clinical trial

Company	Website	Product	Status	Notes
Aastrom Bioscience	www.aastrom.com	Tissue-repair cells	Phase II	Expanded autologous bone marrow cells for the treatment of long bone fracture, jaw bone reconstruction and spinal fusion
		Tissue-repair cells	Phase I	Expanded autologous bone marrow cells for the treatment of diabetic limb ischemia
Advanced Biohealing	www.advanced.biohealing.com	Dermagraft®	Approved in the USA	Cultured allogeneic fibroblasts on a biodegradable mesh for the treatment of diabetic ulcers
		Transcyte®	Approved in the USA and UK	Devitalized, cultured allogeneic fibroblasts on a nylon membrane coated with silicone membrane
		Celaderm™		Cultured growth-arrested allogeneic keratinocytes for the treatment of partial thickness burns
Amcyte	www.amcyte.com		Phase I/II Canada	Microencapsulated allogeneic islet cells for the treatment of Type I diabetes
Arteriocyte Inc.	www.arteriocyte.com		Phase I	Bone marrow stem cells to treat chronic ischemia
Bio Tissue Technologies	www.biotissue-tec.com	Bioseed-C	Approved in Germany	Autologous chondrocytes for articular cartilage defects in the knee
		Bioseed-oral bone	Approved in Germany	Spherical chips of autologous osteogenic cells in vicryl mesh
		MelanoSeed®	Approved in Germany and Netherlands	Autologous cultured pigmented cells for the treatment of vitiligo
Bioheart Inc.	www.bioheart.com	Myocell™	Phase II/III Europe	Cultured autologous skeletal muscle myoblasts for the treatment of myocardial infarction and congestive heart failure
			Phase I USA	
Cambrex	www.cambrex.com	Permaderm™		Cultured autologous keratinocytes with cultured allogeneic fibroblasts on a collagen matrix
Cartilage Regeneration Systems	www.arsartho.com	CaReS	Approved in Germany	Autologous chondrocytes in collagen matrix for articular cartilage defects in the knee
CellTran	www.celltran.co.uk	Myskin™	Approved in the UK	Cultured autologous keratinocytes on plasma-treated silicone membrane for the treatment of burns, ulcers and nonhealing wounds
Clinical Cell Culture	www.clinicalcellculture.com	Cellspray®		Cultured autologous keratinocyte cell suspension spray
Co-don	www.codon.de	Co.don chondrotransplant	Approved in Germany	Cell suspension of autologous chondrocytes for the treatment of articular cartilage defects in the knee
		Co.don chondrosphere	Approved in Germany	
		Co.don chondrotransplant disc	Approved in Germany	
Fidia Advanced Biopolymers	www.fidiapharma.it	Hyalograft®		Autologous chondrocytes on a hyaluronic acid-derived matrix for the treatment of cartilage defects
		Hyalograft 3D		Autologous fibroblasts on a hyaluronic acid-derived matrix for the treatment of deep dermal lesions, nonhealing ulcers and deep burns

Table 1. Cell-based regenerative medicine companies with approved clinical products or products in clinical trial (cont.).

Company	Website	Product	Status	Notes
Fidia Advanced Biopolymers		Laserskin® autograft in Europe VivoDerm™ in US		Autologous keratinocyes cultured on a hyaluronic acid support
Genzyme Biosurgery	www.carticel.com	Carticel®	Approved in the USA	Cell suspension of autologous chondrocytes for the treatment of articular cartilage defects in the knee
		Epicel™	Approved in the USA	Sheet of autologous keratinocytes for the treatment of burns
		MACI®	Approved in Europe Australia	Autologous chonrocytes on a collagen membrane for knee cartilage defects
Healthpoint	www.healthpoint.com	Epidex™		Cultured autologous keratinocyte for recalcitrant leg ulcers
		Acudresss		Cultured autologous keratinocytes grown on a fibrin substrate
		Allox™	Phase II	Keratinocytes, fibroblasts and fibrin in a spray
Intercytex	www.intercytex.com	ICX-PRO	Phase III trial in USA, Canada and UK	Cultured allogeneic fibroblasts in a fibrin gel for the treatment of venous stasis ulcers
		ICX-TRC	Phase II trial in the UK	Cultured autologous dermal papilla cells for the treatment of male pattern baldness
		ICX-SKN	Due to enter Phase I in 2006	Cultured allogeneic fibroblasts in cell-synthesized collagen extracellular matrix for use as skin replacement
		ICX-RHY	Approved for use in UK	Cultured autologous fibroblasts for dermal rejuvenation
Interface Biotech	www.aci.dk	Cartilink-2	Approved in Denmark and Spain	Cell suspension of autologous chondrocytes for the treatment of articular cartilage defects in the knee
Invitrix Inc.	www.invitrx.com	Invitra™	Approved in the USA	Fibroblasts on a collagen/vicryl sheet with added keratinocytes
Isolagen	www.isolagen.com	Autologous cellular system (ACS)	Phase III in the USA Approved in the UK	Cultured autologous fibroblasts for dermal rejuvenation
Laboratoire Genevrier	www.laboratoires-genevrier.com	Epibase®		Cultured autologous keratinocyte sheet for burns and reconstructive surgery
Neurotech SA	www.neurotech.fr	NT-501		Intraocular polymer implant containing retinal epithelial cells genetically modified to secrete ciliary neurotrophic factor
Novocell	www.novocell.com		Phase I/II	Microencapsulated allogeneic islet cells for the treatment of Type I diabetes
Opexa		Tovaxin™	Phase IIb USA	Cultured autologous irradiated T cells for treatment of multiple sclerosis
Organogenesis	www.organogenesis.com	Apligraf®	Approved in the USA and Canada	Allogeneic bilayered skin substitute for the treatment of venous stasis and diabetic ulcers
Ortec	www.ortecinternational.com	Orcel®	Approved in the USA	Porous collagen sponge containing allogeneic fibroblasts and overlain with allogeneic keratinocytes for the treatment of epidermolysis Bullosa

Table 1. Cell-based regenerative medicine companies with approved clinical products or products in clinical trial (cont.).

Company	Website	Product	Status	Notes
Ortec		Orcel®	Phase III trial in the US	Porous collagen sponge containing allogeneic fibroblasts and overlain with allogeneic keratinocytes for the treatment of venous leg ulcers
Osiris Therapeutics	www.osiristx.com	Chondrogen™	Phase I/II	Cultured allogeneic bone marrow mesenchymal stem cells suspended in hyaluronic acid for meniscal regeneration
		Prochymal™	Phase II	Cultured allogeneic bone marrow mesenchymal stem cells for the treatment of graft-versus-host disease
		Prochymal™	Phase II	Cultured allogeneic bone marrow mesenchymal stem cells for the treatment of Crohn's disease
		Provacel™	Phase I	Cultured allogeneic bone marrow mesenchymal stem cells for the treatment of myocardial infarction
ProNeuron	www.proneuron.com	Procord spinal cord injury treatment	Phase II in USA and Israel	Activated autologous macrophages for treatment of patients with spinal cord injury
RenaMed Biologics	www.nephrosthera peutics.com	RBI-01	Completed Phase II in the USA	Physiologically active human renal epithelial cells in hollow fiber cartridge for the treatment of acute renal failure
ReNeuron	www.reneuron.com	ReN001	About to enter Phase I	Genetically stable neural stem cell lines for the treatment of stroke
Stem Cells Inc.	www.stemcellsincs	HuCNS-SC	Phase I	Cultured human fetal neural stem cells
Tengion	www.tengion.com	Neo-bladder	Completed Phase II in US	Cultured autologous bladder cells on a biodegradable matrix
TETEC AG	www.bioregio-stern.de/en/node/331	Novocart®	Approved in Germany	Autologous chondrocytes
		Novocart®	Approved in Germany	NOVOCART 3D and a combination of autologous cartilage cells and a biphasic, 3D, collagen-based matrix
		Novocart®	Approved in Germany	3D autologous cell preparation for the biological reconstruction of partially-damaged intervertebral discs
Tigenix	www.tigenix.com	ChondroCelect™	Phase III Europe	Autologous chondrocytes for cartilage regeneration in the knee
Vesta Therapeutics	www.vestatherapeutics.com		Phase I	Cultured allogeneic hepatocytes for the treatment of end stage liver disease
Vital Therapeutics	www.vitaltherapies.com	ELAD®	Phase III in China	Immortalized allogeneic human hepatocytes for the treatment of liver failure
XCELLentis	www.xcellentis.com	Autoderm		Cultured autologous keratinocytes for burns and chronic skin wounds
		CryoCeal®		Allogeneic cultured keratinocyte sheet for the treatment of burns and chronic wounds

At this point, 10 years of scientific overclaim and media hype conspired with the early commercial teething troubles to exact a large penalty from the struggling industry. During the early years of tissue engineering, private money flooded in, responding to the highly publicized 'dream ticket'. Meanwhile, federal research lagged behind as governments tried to evaluate the current status, real potential and genuine timeframes of research before they committed money. In his 2001 report, Michael Lysaght estimated that, between 1990 and 2000, US$3.5 billion was invested worldwide in tissue engineering and that 90% of this was private sector finance. Such imbalance in funding had a profound impact on the direction of research and the timeframe under which results had to be delivered. Investors are

always looking for a significant and preferably early return on the risks taken in providing early-stage funds.

As the new millennium dawned, the sector was in trouble. In the absence of commercially successful products or profitable outlicensing deals, tissue engineering companies struggled to make money and their overdependence on private investment became a real problem. The investor community tired of its new baby, turned its back on the sector and, without substantial federally sponsored work, the bubble burst. In the autumn of 2002, the two pioneering corporations in the sector, Organogenesis and ATS, each valued at their peak at approximately US$1 billion, both went into Chapter 11 within a month of each other.

The 2004 industry review by Lysaght and Hazlehurst neatly quantifies the extent of this decline. Between 2000 and 2002, activity in the sector fell by 50% and 800 full-time employees were lost. Furthermore, the capital value of publicly traded tissue engineering corporations dropped by almost 90%, from US$2.5 billion at the end of 2000 to $300 million by the end of 2002. Lysaught and Hazlehurst concluded that, like many breakthrough medical technologies, "tissue engineering was having difficulty making the transition from a development stage industry to one with successful product portfolio".

Tissue engineering & regenerative medicine

In hindsight, the dramatic decline of the tissue engineering industry was inevitable, as it lacked a foundation of genuine scientific and commercial understanding. Similar to the early aeronautical engineers who simply copied the shape of bird wings, strapped them on and stepped into the abyss, failure was inevitable. During the early days, most tissue engineers were blindly copying the biological structures they wanted to replicate, rather than trying to understand how they originally formed. Tissue engineering needed more developmental biology and less engineering.

Developmental biology first entered the story through yet another Massachusetts-based company, Ontogeny Inc, founded in 1994 after the discovery of a group of genes, known as hedgehog genes, which play a crucial role in guiding the development and growth of an embryo. Leaders of five laboratories at the forefront of developmental biology joined Ontogeny's scientific advisory board, under Doug Melton, a cellular and molecular biologist at Harvard University (MA, USA). Ontogeny later merged with two other Boston companies, Creative Biomolecules Inc. and Reprogenesis Inc. to form Curis Inc. in 2000. The latter is still looking to commercialize molecular factors to stimulate the regeneration of new tissues or organs.

The late 1990s were also marked by two high-profile discoveries in the field of developmental biology that heralded a resurgence of interest and belief in the field: Dolly the sheep was cloned in Roslin, Scotland [17] and the first human embryonic stem cells were simultaneously isolated in Wisconsin, USA [18] and Johns Hopkins [19]. While the tissue engineering sector continued to languish early in the new millennium, stem cell research became the latest 'hot job'. The 2004 industry review by Lysaght and Hazlehurst reported a 42% upturn in stem cell firms between 2000 and 2002 and a gain of more than 300 employees, contrasting sharply with the downturn in tissue engineering alluded to earlier.

In a pattern redolent of tissue engineering, cloning and stem cell therapy rapidly became the subjects of over-hype and media extrapolation, despite cautionary comments from luminaries, such as Lord Robert Winston, who warned that the potential benefits of embryonic stem cell research had probably been oversold [101]. Although the original tissue engineering groups were not immediately working with stem cells, it was obvious that the two technologies were related in some way and, amidst the largely unhelpful background media noise, the term regenerative medicine was first coined, probably by William Heseltine, Chairman and CEO of Human Genome Sciences (Rockville, MD, USA) who used it to describe 'the broad range of disciplines adopted by companies working towards a common goal of replacing or repairing damaged or diseased tissue'. Thus, tissue engineering, stem cell therapy, regenerative factors, specific acellular scaffolds and therapeutic cloning united under a single umbrella term of regenerative medicine, encompassing companies such as Organogenesis and the UK-based Intercytex, those that use differentiated cells, those working with acellular matrices, such as Integra, regenerative factors, such as Curis Inc or the new stem cells companies, such as Geron, Reneuron and Stem Cell Sciences (**Figure 1**).

As well as sharing a common name, scientists involved in cellular aspects of regenerative medicine all use cells that are ultimately derived from the blastocyst, although some take fetal cells and others, such as Intercytex, work from postnatal

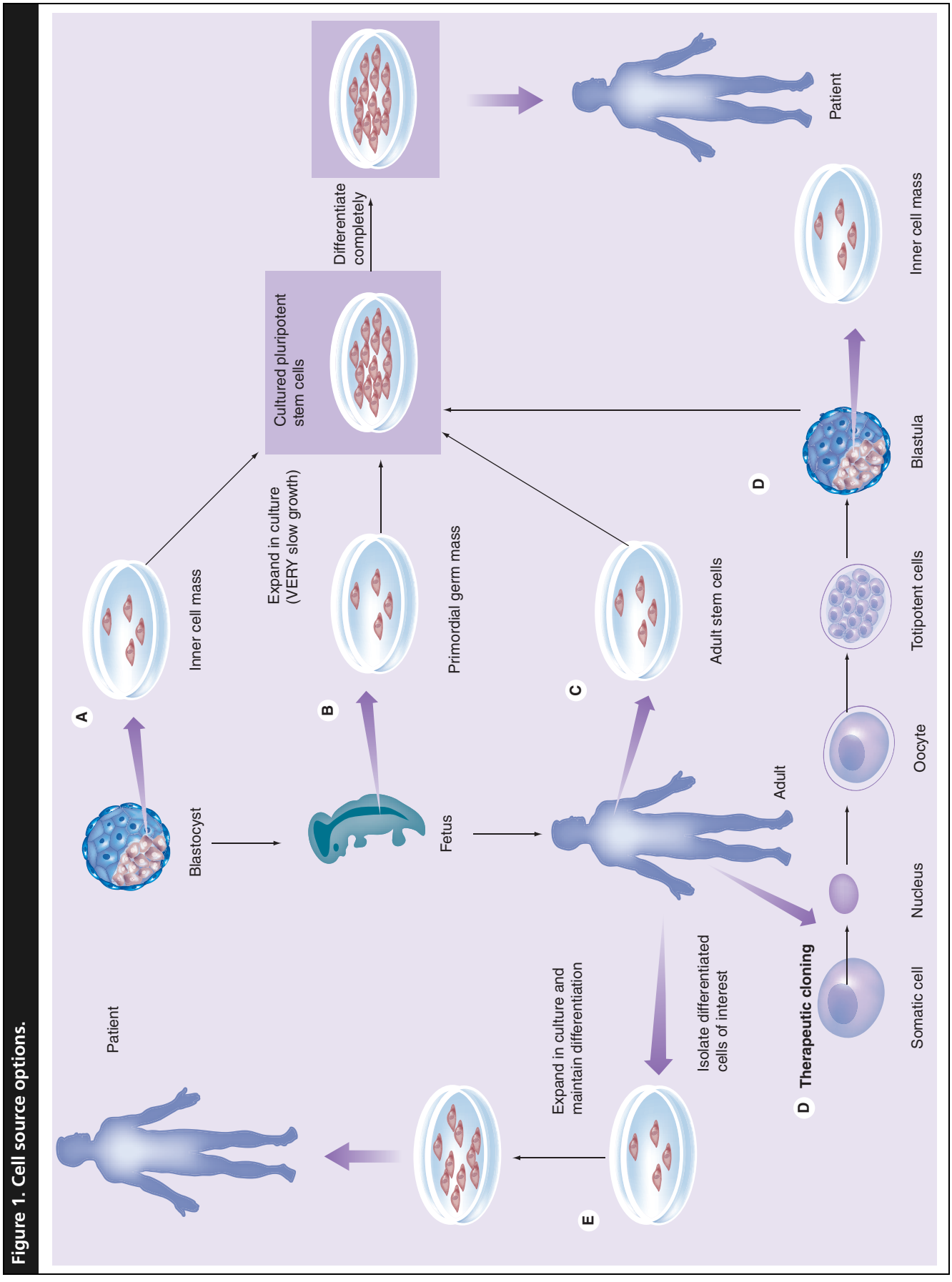


Figure 1. Cell source options.

cells (**Figure 2**). However, irrespective of their starting material, groups involved in regenerative medicine must undertake five key steps: the first, procurement of the original tissue, has founded the emerging field of whole-cell bioprocessing. This in itself has evolved from the bioprocessing industry, which has successfully developed industrial-scale processes to produce and isolate the products of cells in culture. By contrast, in whole-cell bioprocessing, it is the cells themselves that are the product [20]. Once procurement has been achieved, all regenerative medicine groups pursue four further steps: isolation of the cells of interest, expansion of these cells in culture, assembly of the cells in a delivery or maturation system and transport/application of the product to the clinic and, ultimately, the patient. It sounds simple but in reality, each stage is complex and a huge effort is required to get all five elements right, no matter where the original cells come from.

Gaining regulatory approval represents yet another rapidly evolving challenge, because, currently, there is no consistent framework for regenerative products (**Figure 3**). Product classification varies enormously, with Apligraf being classified as a medical device in the USA, a medicinal product in Germany and being unregulated in the UK. Novartis, which initially distributed Apligraf for Organogenesis, was not able to gain approval for the product anywhere outside the USA, despite the fact that it has been used there to treat over 100,000 patients. Gaining worldwide approval is tortuous and time consuming and even large companies, with dedicated regulatory affairs departments, have found the existing product approval environment too challenging. Dermagraft® and Transcyte® (formed from human dermal fibroblast on a larger sheet of biodegradable matrix than that of Dermagraft, in which the cells were killed by repeated freeze thaw cycles prior to shipping) were distributed originally by Smith and Nephew but, despite having been available for sale in the USA for many years, gaining European and Japanese approval proved impossible. In October 2005, Smith and Nephew decided to cut its losses and announced it would exit the therapeutic area, although, according to its CEO Sir Christopher O'Donnell, its lead product, Dermagraft worked 'very well'. O'Donnell attributed the decision to the fact that the 'regulatory frameworks...are not sufficiently well defined'. It subsequently sold Dermagraft and Transcyte to Advanced Biohealing, a small, private US biotechnology company that will manufacture the product and set up its own sales and distribution channels to service the US market.

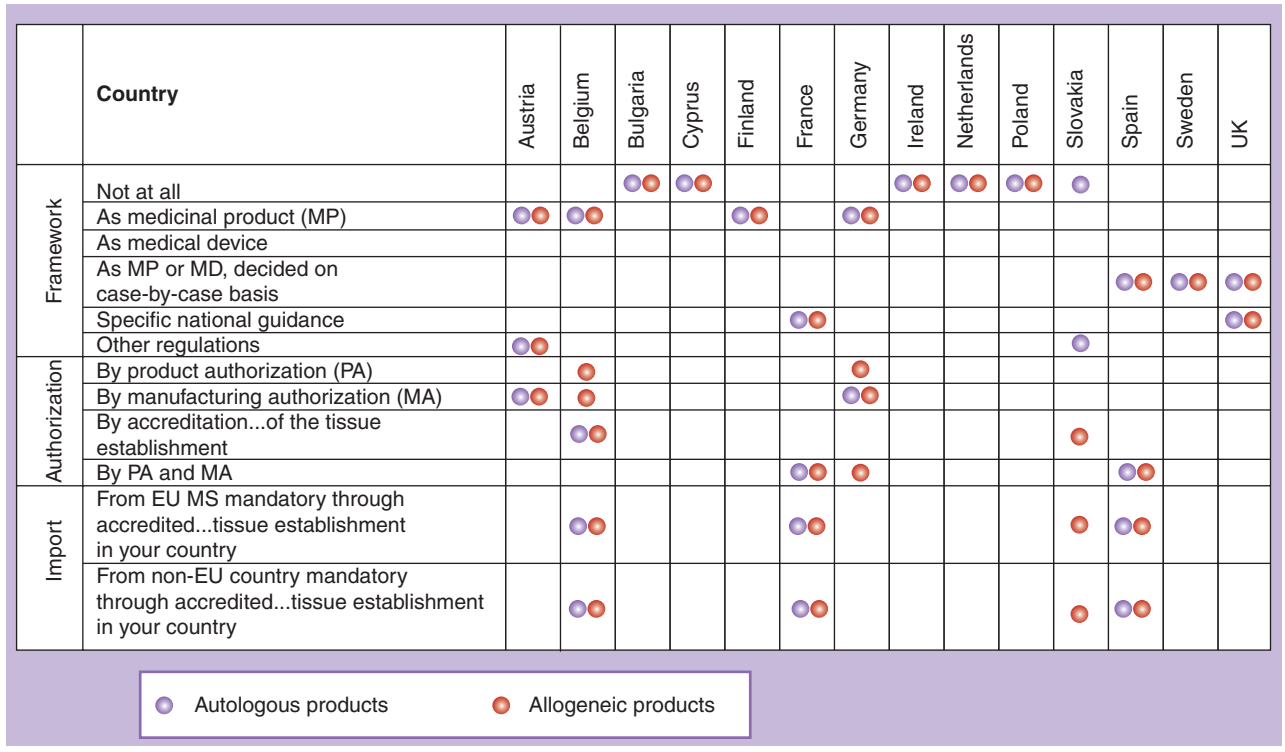
To be fair, the regulatory authorities in Europe are now trying to bridge the gap and the European Commission has declared its intention to provide an appropriate legislative framework by 2007. This should include a 'grandfather clause', giving companies with products already on the market a number of 'grace' years in which to comply. Reassuringly, the regulators have been doing their homework, working with the industry and trying to understand the unique dynamics of regenerative therapies. For example, the Medicines and Healthcare products Regulatory Agency (MHRA) recently gave an overview of tissue engineered/regenerative medicine products, where it recognized that a characteristic of this field is 'the gradual emergence of efficacy'. This is an extremely important feature of regenerative medicine and reflects the fact that the products are intended to interact with cells and tissues of the patient and the way in which the product is applied, or subsequently cared for, could have a huge impact on the ultimate efficacy of that product. Hopefully, the final regulatory framework will be flexible enough to accommodate this fact.

Products that work

In his State of the Union address in January 1971, President Nixon declared his famous "War on Cancer", which, at the time, was the second greatest cause of death in the USA. Over 30 years later, despite the many billions spent on research, the 'cause' of cancer is still unknown and a cure remains elusive. Some people believe that the war is, at best, stalled and, at worst, lost, since cancer now threatens to become the leading cause of death. However, there have been incredible advances and, presently, approximately half of all cancer patients can expect to live for 5 years or more after diagnosis. Cancer, if not cured, is slowly being controlled.

Similarly, the field of regenerative medicine has not found methods to grow intact organs, nor yet developed cell-based methods to treat diseases such as Type I diabetes or Parkinson's disease. However, the various strategies of cellular or biohybrid tissues and organs that trace their origins back to those laboratories in Massachusetts continue to progress steadily and provide the technology that has, to date, helped over a 100,000 people.

Figure 2. Current regulatory status for tissue engineered products.



The first generation of cell-based regenerative medicine companies were pioneers in a revolutionary new area. There was no established frame of reference for producing living human products and this meant that there was a steep learning curve involving a great many lessons. One of the most important of these was the multitude of factors that determine the efficacy, medical uptake and commercial success of these unique products. Price, cost of goods, ease and frequency of use, functionality, shelf life, packaging and post-implant therapy all impinge on the performance and success of regenerative medicine products. Such commercial, operational and logistic criteria were not always 'front of mind' for the university scientists working on the technology that underpinned the first therapies. As a result, many of the initial products failed to address the multiplicity of factors needed for full commercial success.

Intercytex has benefited greatly from the pioneering work carried out by its predecessors in the 1980s and 1990s. From the very outset, they were determined to develop easily used and stored products with the lowest risk, while maximizing the possible upsides.

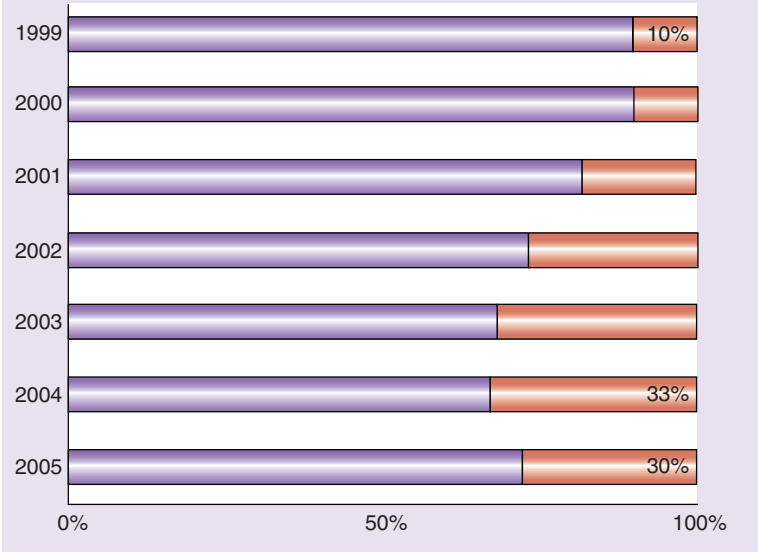
Intercytex decided to concentrate on products directed towards the skin and, today, that is its exclusive therapeutic focus. There are several reasons behind this thinking, not least the fact that skin is relatively low risk (e.g., compared with a heart or liver), it is the organ currently best suited to regenerative therapies and the one in which the many novel issues related to regenerative medicine products (e.g., manufacture, storage and delivery) are most clearly defined. In hindsight, it was possibly a very lucky accident that the four MIT laboratories that pioneered tissue engineering all developed initial products directed towards the skin.

Intercytex has four products in development and each illustrates how the company applied the learning of its predecessors to develop a range of products in development.

IXC-PRO

IXC-PRO is an allogeneic human dermal fibroblast construct for chronic wound healing. The first generation of approved tissue engineered products all demonstrated the benefits of living cell therapy for the treatment of both chronic wounds (Apligraf and Dermagraft) and burns (Transcyte and Epicel). However, although they

Figure 3. Percentage of overall funding.



were originally intended to act as tissue engineered 'skin equivalents', it soon became apparent that, once in humans, they did not live up to this expectation. In fact, they functioned by the degradation of the support scaffold and release of cells and factors into the wound environment. In this context, they made slow and small initial sales that illuminated the critical issues of price, reimbursement and ease of use in terms of adoption. They also demonstrated that by far the larger market for these products was in chronic wounds, rather than burns.

With these valuable lessons in mind, ICX-PRO was designed from the outset to be the most cost-effective and easiest to use cell-based regenerative medicine product for the treatment of chronic wounds, and the product is now in Phase III clinical evaluation. ICX-PRO takes 1 day to manufacture, is delivered in an easy-to-use package and can be stored for 21 days in a simple refrigerator. This contrasts sharply with its predecessors, which were intended to be tissue replacements and required a 3–4 week manufacturing cycle to enable the cells to produce the 3D tissue constructs. Furthermore, the first generation of companies chose to either ship the cells warm and metabolically active or cryopreserved and in stasis. Both of these strategies raised problems, some of which were completely unexpected. Shipping a product warm means that the cells are using up the media provided and, therefore, there is a limit to how long they can survive without a media change, resulting in a short shelf life. Apligraf began with a 5-day shelf life, which caused considerable logistical problems. This has been increased to 10 days by the simple expedient of shipping at a lower starting temperature in a container that is more able to maintain the narrow temperature range required [102]. Conversely, Dermagraft and Orcel® are cryopreserved and therefore have a much longer shelf life. However, the complexity of the thawing procedure and the need for the end user to have cryostorage facilities close to the patient have proven a barrier to its uptake.

ICX-SKN

As aforementioned, the first-generation products, such as Apligraf and Dermagraft, were originally referred to as 'living skin equivalents' and, although they did not function in this way, they illustrated the need for a skin replacement that is able to withstand the harsh environment of a human skin wound and integrate with the surrounding, undamaged skin to provide an immediate and long-lasting cover. The response of these products in actual human wounds indicated that it was the extracellular matrix component itself that was undermining performance. For this reason, ICX-SKN is being developed with the emphasis on the stability of the collagenous matrix itself. The product comprises allogeneic human dermal fibroblasts in a strong, stable matrix of collagen that is produced and assembled by the cells themselves. It can be produced with or without an overlay of human keratinocytes and is designed to integrate and persist in an acute wound, yet still turnover and provide permanent and immediate repair. Again, the issues of manufacture, shipping, storage and application have been uppermost in the minds of the scientists and engineers who have designed the prototype product. From the outset, it was apparent that it would need considerable *in vitro* maturation in order for the cells to lay down their matrix. As aforementioned, long manufacturing times that result in products with short shelf lives present logistical issues. To minimize this, the process has been designed with 'stops', whereby a product can be stockpiled and then processing continued as needed. The final step, when the cells are 'committed' to make a product that is distributed, is less than 1 week and, therefore, product output can be better matched to the need.

ICX-TRC

Both ICX-PRO and ICX-SKN are promising therapies because, although there are alternative treatments available, these are unsatisfactory, in

short supply or impractical in some cases. However, regenerative medicine will probably only really come of age when it delivers a product that answers a significant and wholly unmet medical need. One good candidate for this is the use of autologous dermal papillae cells to regenerate hair. ICX-TRC is based on a 40-year-old finding that dermal papillae cells are able to induce surrounding epidermal cells to form entirely new hair structures [21]. Although the biological basis of the therapy has been known for many years, it could not be translated into a commercial treatment because, until the work of Yoshizato and colleagues in 1996 [22], there was no way to expand these dermal papillae cells to a commercial degree and maintain their inductive potential. Even with this technology, the cells cannot be expanded directly in culture to a sufficient level needed for an allogeneic therapy. Allogeneic therapies will always be easier to produce than autologous equivalents where each patient's samples need to be treated independently; however, the high costs associated with the current hair transplant procedures ($3–10/hair transplanted) make this application commercially viable as an autologous therapy.

ICX-TRC might not be the most dramatic or lifesaving therapeutic application of regenerative medicine, but it is a strong starting point, inasmuch as there really isn't an alternative. Current hair transplants simply relocate a finite number of hair follicles around the head, whereas this treatment will multiply the number of hairs. Furthermore, ICX-TRC is applied to the surface of the body and is therefore easy to observe and monitor. It is also a relatively safe tissue on which to start, enabling the industry to gain key learning to indicate how such therapies may work for other organ systems. It will also shed light on the prospects for implanting cells that interact with the body's cells *in situ* to produce small 'combination' organs, ones that are formed from cells of the implant and those provided by the patient at the site of implant.

ICX-RHY

The logistics of producing an autologous cell therapy 'to order' are significantly higher than those faced by an allogeneic therapy and, ultimately, this will be reflected in the cost to produce such a therapy. Allogeneic therapies will always be cheaper to produce, assuming that there is a technologically feasible way to proceed and there are no immunological, regulatory or cell scale-up issues. Autologous fibroblasts have been shown to 'rejuvenate' dermis in aged or scarred tissue, probably by altering the balance of cells to extracellular matrix and therefore increasing the turnover of the matrix and deposition of new material. ICX-RHY is designed to achieve this by using a very highly concentrated suspension of allogeneic human dermal fibroblasts, thereby overcoming the need to harvest patient biopsies, wait for the cells to be expanded and suffer the cost of such a manufacturing system. Moreover, ICX-RHY has a shelf life that will greatly ease the logistical hurdles of transporting concentrated cell suspensions, where the typical shelf life is a matter of hours.

The aspects of design that Intercytex has applied when developing its first four products demonstrate some of the issues that need to be addressed, in addition to the 'classic' R&D questions. Issues, such as cost, ease of use, functionality, shelf-life and manufacture, are key to the success of regenerative medicine products. The adoption of an appropriate business model that answers these multiple and sector-distinct parameters, is also fundamental to the industry's future.

Business model that works

The very first biotechnology companies, such as Amgen, Genentech and Biogen, adopted a fully integrated approach to business, developing, manufacturing and selling biological products themselves. They were able to follow this model very successfully by selling new treatments for the 'low-hanging fruits' (i.e., poorly treated ailments) that generated billions of dollars in revenue. However, the set up and running costs of such an approach are very high and such a model proved inappropriate for the smaller, second-generation biotechnology firms that were developing products for smaller but still significant markets. This group adopted a different business model, based on finding larger partners who would carry out the expensive late-stage clinical development, sales and marketing, while the biotechnology company was rewarded by a royalty income and milestone payments. This model was pursued by some of the early tissue engineering companies who adopted it on the basis that their products would generate similar sales to their biotechnology cousins. There was also considerable investor pressure to secure 'product validating' sales and marketing deals. In this context, Organogenesis signed a licensing agreement with Novartis for Apligraf and Advanced Tissue Sciences set up a joint venture with Smith and Nephew to commercialize Dermagraft and Transcyte. However,

Genzyme, a larger company that had more resources thanks to its established portfolio of nonregenerative medicine products, followed a more integrated approach and bought Howard Green's pioneering regenerative medicine company Biosurface Technology. Thanks to its greater critical mass, Genzyme was able to produce and sell Epicel to treat burns and Carticel® for arthritis 'in-house'.

The attractions of the 'royalty model' is that the marketing partner, with its larger resources of money and personnel, is often better suited to carry out the very expensive later-stage clinical trials, set up the equally expensive marketing channels and build the hugely capital intensive manufacturing facility. Moreover, the new product can be added to the already established portfolio being marketed by the company's preexisting sales force. However, the disadvantages for the development partner are that often they only gain a relatively small proportion of the ultimate sales of the product. They are also disconnected from the sales force and unable to influence or motivate it. Furthermore, it has been found that selling regenerative medicine products requires a very different approach to selling a drug. In fact, it has more similarities to selling an implantable medical device, whereby the salesman must be very well informed technically about the product. The salesman must also be able to interact directly and credibly with surgeons and other medical practitioners, as the application of the product to the patient has a fundamental influence on its subsequent efficacy.

At the time Intercytex was founded in 1999, it was becoming apparent that the dynamics of product development, manufacture and use of cell-based regenerative medicine products were quite distinct compared with those of nonliving biological products made by biotechnology companies. The approved regenerative medicine therapies (Apligraf, Dermagraft, Transcyte, Epicel and Carticel) had each been developed in under 9 years, during which time they were evaluated in approximately 200–300 patients. The Ernst & Young LLP Biotechnology Industry Report (Convergence 2000) clearly contrasts this with the 16-year development timeframes involving 1000–5000 patients typical of the drug discovery process operated by biotechnology companies. Another distinction is that regenerative products are designed for single use or possibly a handful of applications, rather than the chronic, repeated or lifetime dosing typical of many pharmaceuticals. Hindsight also underlines the fact that typical annual unit sales of regenerative medicine products have been less than 100,000, with each item costing approximately US$1000. Furthermore, the relatively small number of units needed and their short shelf life means that current products are produced 'just in time' rather than stockpiled, so manufacturing facilities can be small scale and relatively low cost compared with traditional drug producers. Moreover, as demand for a product increases, this can be accommodated by 'scale-out' of the process rather than scale-up, which again minimizes the capital expenditure required; although it does limit the savings on cost of goods that can be made as an economy of scale.

These unique dynamics led Intercytex to adopt an integrated business model from the outset, which is best suited to the current dynamics of the regenerative medicine market and existing product ranges. With this model, the company can concentrate on gaining rapid approval of therapies that have commercial potential, rather than looking for early licensing partners to survive. A key outcome of the financial dynamics alluded to earlier, is that a turnover of US$30 million is initially sufficient to sustain R&D, the small-scale manufacture and niche sales force required to support a company that can then grow by increasing sales and bringing other products to market. On that basis, the industry can afford to target smaller markets that are neglected by the traditional pharmaceutical and biotechnology sectors. However, the high cost of cell-based products makes it inappropriate to aim for markets where illness is adequately treated by established methods or where the price threshold is set too low.

Other companies, such as the newly reformed Organogenesis, are also adopting this integrated approach. In its first incarnation, the marketing deal Organogenesis struck with Novartis meant it received a small (and as it turned out, insufficient) royalty on Apligraf sales. After it filed for Chapter 11, Organogenesis was reorganized with support from business angels. Presently, it operates an independent, fully integrated business model whereby it undertakes its own research, manufacture and sales. Apligraf, which is now positioned as a wound stimulant, is estimated to turn over a respectable $45 million in 2006 and these sales have been growing steadily at approximately 50% per year. Thus, Organogenesis now has a positive cash flow and is currently the most successful regenerative medicine company. The

current group of approved regenerative medicine products are not directed towards 'blockbuster markets' (defined as a product with annual sales in excess of $1 billon) and instead have annual sales in the US$20–50 million range. However, the reason there has been such a sustained academic, media and public interest in regenerative medicine products is that they have the theoretical potential to address enormous medical markets, such as cardiovascular disease, brain and spinal cord disease and damage, or organ and metabolic diseases, such as end-stage renal disease or diabetes. Each of these areas currently costs the healthcare industry many billions of dollars annually to treat, and existing 'state-of-the-art' therapy is often severely lacking. As regenerative medicine companies develop and commercialize cell-based technologies, including stem cell therapies, that are focused towards these 'blockbuster' markets, the early integrated companies will be in an excellent position to exploit these technological breakthroughs, due to their infrastructure and skill base.

The integrated approach is also paying dividends in the short term and, as companies begin to make money by delivering products that live up to expectations, venture capital companies are returning to the regenerative medicine arena. The numbers of dollars invested per year in stem cells/regenerative medicine has now surpassed the first peak in 2000. This is a significant achievement since biotechnology investments in 2000 were huge, but declined considerably when the dot com bubble burst, impacting on all areas of high technology (**Figure 3**).

At present, 90% of investment in regenerative medicine remains private, but there are signs that public funding is on the up and the UK Department of Trade and Industry (DTI) made £10 million in grants available for regenerative medicine businesses in 2006, its largest ever funding for biological science. The outlook is also more favorable in the USA, where public funding, particularly of stem cell work, has been bogged down by ethical questions and legal challenges. In California, Governor Arnold Schwarzenegger recently overcame objections to Proposition 71 and, as a result, US$3 billion of California State money has been released to provide stem cell researchers with US$295 million a year for the next 10 years, although, to date, the California Stem Cell initiative has spent only approximately US$10m dollars and has yet to fund any outside research.

The industry is also making progress opposite those critical issues of manufacturing and distribution, again by recognizing that cell-based products are distinct from traditional drugs and require a different approach suited to the unique product needs. Cell-based regenerative medicine products have short shelf lives and they cannot be 'campaign' manufactured, whereby a manufacturing facility is used to produce large batches of different products at different times. Thus, the industry has had to rethink the established pharmaceutical manufacturing ethos that focuses on economies of scale. Instead, the companies continuously make small batches of product, meaning issues such as maintaining quality control, establishing efficient transport, storage and delivery mechanisms become critical and must be given priority attention and investment. Once manufactured, the hurdles of shipping a sensitive living product that has a short shelf life with a narrow temperature range efficiently and economically have been, and continue to be, considerable.

Although there are still exciting challenges ahead, in terms of manufacturing, shipping, reimbursement and regulatory issues, some of these are being resolved and the overall outlook for our sector is increasingly positive. In this more supportive environment, those of us involved in regenerative medicine are at liberty to focus more time on increasing our scientific understanding and there is plenty to be done in this regard.

Key scientific hurdles

In terms of R&D, preventing tissue rejection remains a significant challenge and one that scientists are approaching from two angles. The first is to try and make products less immunogenic, while the second is to make the patient more graft tolerant. It is generally believed that the latter is more achievable, not least owing to the tremendous advances in transplant medicine. In fact, as pointed out at the start of this review, organ transplant and whole-blood infusions are really sophisticated versions of cell therapy and work already undertaken to screen, ship and store organs and whole blood is very relevant to regenerative medicine.

Many questions must be answered before regenerative medicine therapies can replace organ transplants. However, this still remains a goal, at least in the eyes of the public, and considerable research and money is being directed towards meeting that objective.

In 1998, the Living Implants From Engineering initiative was established with the stated aim of 'building a functioning human heart within 10 years'. At that time, the founder, Michael Sefton from the University of Toronto, Canada, said the vision was to raise billions of dollars from a global research project and claimed that "we'll be able to pop out a damaged heart and replace it as easily as you would replace a carburetor in a car" [103]. On the basis of such claims, the initiative created a lot of media interest and resulted in headlines such as 'tissue engineered organs a heart beat away'. With the passage of time, Sefton has agreed that the deadline on the original goal was naive; however, although the technical ability to build an entirely new heart may never be achieved, several groups around the world are working on developing parts of the heart. Producing coronary arteries, heart valves, septal repair and replacement patches of cardiac muscle appears to be much more realistic and reachable.

There was also considerable media interest in 2006 when a paper by Atala and colleagues, entitled 'Tissue-engineered autologous bladders for patients needing cystoplasty' appeared in the *Lancet* [23] and commentators indicated that this represented the 'world's first artificially grown organ' [104]. Although this work was very significant and followed patients for up to 5 years, the implants were sections of bladder and not intact organs, the ureters draining the kidneys and the sphincter muscles at the base of the bladder were still the patients' originals, the grafts were not innervated and, although they did function to some extent and the spina-bifida patients received benefit from the treatment, they did not become completely continent. The reality is that the scale and number of technical and commercial hurdles that must be overcome before we can deliver a full-sized, functional organ, such as a kidney or heart, are considerable. In this context, the provision of 'new' organs to replace transplants is beyond the realms of the possible – both now and for the foreseeable future.

Whereas the media talk concerning tissue engineered hearts and livers, in actuality, the industry is producing tissue and organ progenitors that will either increase or support the functionality of pre-existing tissues and organs or else induce new organ structures to form *in situ* (**Table 2**).

Once we determine the minimum unit needed for success, either as organ supports or organ inducers, the next question is: how should they be produced? At present, there are two schools of thought: the first centers on creating the material 'in a dish' and introducing it in an immediately functional state in a manner similar to that used by Atala's group; while the second is to rely more on developing an organ in the patient and implant material with no immediate functionality or structure. Although this is only feasible when some immediate functionality is not required, a number of groups are reporting success with this approach. In addition to ICX-PRO from Intercytex, the fledgeling British company Odontis recently published research on its work to develop new teeth *in situ* [105], which they believe will enter the clinic in 3 years. In terms of larger organs, substantial work is underway to address pancreatic disease and diabetes [24] and there is even very encouraging work to support the function of the human body's most complicated organ, the brain. For example, the British company Reneuron is about to commence clinical trials in stroke patients [106], where its therapy has shown some restoration of cognitive and motor functions.

Stem cell companies are also making significant headway; although we are still a long way from understanding how stem cells can be persuaded to create new organs. There have, however, been some successes in terms of developing organ precursors that can be seeded into the body where full

Table 2. 2006: Key regenerative medicine products.

Company	Target organ	Mode of action	Status
Organogenesis	Skin	Allogeneic fibroblast and keratinocytes in organotypic construct. Stimulates wound healing in chronic wounds	Approved in USA
Reneuron	Brain		Phase I
Intercytex	Hair	Injected suspension of autologous follicle cells regenerate hair	Phase II
ES Cell International	Heart	Allogeneic cells injected into vasculature	
Plureon	Bladder	Autologous bladder cells seeded onto collagen scaffold	

development can occur [107]. As with those groups using differentiated cells, stem cell companies are employing developmental biology rather than engineering in their quest for progress. Despite the gains made, we must be wary of overexpectation and Genzyme's recent decision to stop the development of its regenerative heart function MAGnesium In Coronay arteries (MAGIC) study [108] due to its link with arrhythmia, is a compelling reminder of how much we have to learn.

A bright future

Turning to the future of regenerative medicine, despite the hesitant beginnings, research problems and corporate failures, I believe that our industry is about to come of age. The legislative position is becoming clearer and hopefully simpler. Genuinely innovative products that deliver on their promises are nearing the market and regenerative medicine companies are starting to mature and succeed by adopting business models that recognize the uniqueness of regenerative medicine and the place and utility of this technology in the whole field of healthcare. There is still media hype and scientific overclaim, but it is tempered by pragmatic comment and a healthy cynicism from some quarters and, crazy headlines aside, media coverage has been generally helpful in fostering public interest and debate. The hurdles involved in commercializing living medical products have proved to be higher and more difficult to surmount than the pioneers ever imagined. However, one by one, they are slowly and inexorably being crossed. The process from 'bench to bedside' for regenerative medicine has had to be achieved step by painful step. Currently, after a long gestation, the scene is set for it to follow the basic evolutionary paradigm of other emerging areas of medicine, whereby well founded research advances can be commercialized by professional and experienced companies that are sufficiently funded and products are able to follow an established regulatory route to the market.

It is important to remember that medicine has been here before. When the biotechnology industry began in the early 1970s, it was founded on the technical promise of recombinant DNA technology. The early pioneers of the sector took some time in developing appropriate business plans and focusing their efforts. For example, when Genentech was created in 1976, it was touted as a panacea for agriculture, the environment, energy, industrial chemicals and human health. Amgen's original business plan in 1980 included human therapeutics, human diagnostics, animal healthcare and speciality chemicals, while Genzyme's 1981 plan sought to use biotechnology across a diverse set of applications and gain short-term revenue from the sale of reagents for research and enzyme diagnostics. Genetic engineering in the 1970s and monoclonal antibodies in the 1980s suffered from early hype and overexpectation, coupled with initial resistance and skepticism from big pharma. Both sectors were beset by early teething problems relating to product efficacy, regulation, manufacture and finding an appropriate business model, which caused virtual industry collapse followed by a slow but definite recovery. In fact, it took 11 years from the first invention of monoclonal antibodies [25] to the first product (Orthoclone; Ortho-Bio/J&J) being launched [110], and it was not until 8 years later that a second monoclonal antibody (ReoPro from Centocor Inc) reached the market. Thereafter, a couple more emerged in the following 3 years. It appears from the progress made to date that this pattern of slow, gradual uptake will be mirrored in our sector.

Today, despite the slow development and adoption, biologics and monoclonal antibodies are an important and integral part of the medical landscape and I believe that, by the end of the next decade, the same will be true of regenerative medicine. That success, when it arrives, will be gratifying for investors, governments, companies and academics. But, most importantly of all, it will be of huge benefit to patients. Because – hype, hubris and hyperbole aside – regenerative medicine will make a real and positive difference to people's lives and I believe that this will happen before I hang up my white coat for good.

Executive summary

Parallels from other areas of medicine

- As with transplant medicine, regenerative medicine required two or more interacting technological advances before a completely new area of medicine could be born.
- Similar to genetic engineering in the 1970s and monoclonal antibodies in the 1980s, early hype and overexpectation resulted in a surge of interest followed by failure and cynicism.
- Similarly, initial product flow is a slow trickle.

Executive summary

Tissue engineering 1990–2000: reasons for failure

- Initial work focused on trying to copy, rather than understand, the regenerative processes, resulting in poor product performance and/or low scientific achievement.
- Gross overclaims by scientists led to excess media hype and unrealistic expectations.
- The adoption of inappropriate business models, based on those employed by biotechnology companies, resulted in low profitability.
- There was an overdependence on private financing, which requires a rapid return.
- A complex and/or unformulated regulative framework made product approval slow and difficult.
- There were difficulties scaling up to commercial manufacture and addressing issues, such as distribution, storage and shelf life.

Integrated business model

- Clinical trials for regenerative therapies involve fewer patients, take less time and are, therefore, less costly compared with conventional pharmaceuticals.
- Lower development costs, leading to smaller markets, and small in-house sales teams are commercially attractive.
- Products must be made 'just in time', not stockpiled, so manufacturing can be small scale and of lower cost.
- Products are one-use or few-use and, therefore, must be relatively expensive.
- Many regenerative medicine companies can be sustained on a relatively small turnover and do not need to depend on early out-licensing deals.
- A fully integrated business model, whereby development, manufacture and sales can be undertaken in-house, is feasible and proving successful.

Hurdles remain

- One of the key remaining scientific hurdles is graft rejection, which can be addressed by reducing product immunogenicity or making the patient more graft tolerant.
- In terms of replacement organs, new organs could be made outside the body or grown within the body, the latter being more achievable.
- Creating entirely new organs remains challenging, although replacement hair, skin, teeth and pancreatic Islets may be achieved in the next 10 years.
- The kidney is likely to be the first major organ to be created outside the body, since it is small, the commercial imperative is high and some success has already been achieved.

Poised for success?

- Cell therapies showing promise include those to address brain and spinal cord injury/degeneration and functional restoration in cardiac, liver and knee-joint tissues.
- Current development pipelines comprise therapies that are understood, perform and address genuinely unmet needs.
- The legislative position is being simplified and new European regulation to encompass the unique nature of regenerative products is expected in 2007.
- Private backing has returned and public funding is increasing, especially in the USA and UK.
- Regenerative medicine can be viewed as 10 years behind monoclonal antibodies, in terms of its place in modern medicine.

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