

Regenerative medicine: the emergence of an industry

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Over the last quarter of a century there has been an emergence of a tissue engineering industry, one that has now evolved into the broader area of regenerative medicine. There have been ‘ups and downs’ in this industry; however, it now appears to be on a track that may be described as ‘back to the future’. The latest data indicate that for 2007 the private sector activity in the world for this industry is approaching \$2.5 billion, with 167 companies/business units and more than 6000 employee full time equivalents. Although small compared with the medical device and also the pharmaceutical industries, these numbers are not insignificant. Thus, there is the indication that this industry, and the related technology, may still achieve its potential and address the needs of millions of patients worldwide, in particular those with needs that currently are unmet.

Keywords: tissue engineering; regenerative medicine; industry; cell-based technologies

1. INTRODUCTION

Regenerative medicine/tissue engineering can be defined as a rapidly growing interdisciplinary field involving the life, physical and engineering sciences and seeking to develop clinical therapies for the repair, maintenance, replacement and/or enhancement of biological function. Research that we now would describe as regenerative medicine has been going on for a long time. It has been driven, at least in part, by the biologic revolution. This revolution started with the advent of cell culture in the very early part of the twentieth century, and it continues to advance, seemingly at an ever accelerating pace.

The first reference to a more biological approach to the replacement of tissues and organs is the book published in 1938 entitled ‘The Culture of Organs’ written by Alexis Carrel, a renowned biomedical researcher, and Charles Lindberg of trans-Atlantic flight fame (Carrel & Lindberg 1938). This unique partnership has been described by David Friedman (2007). By the 1970s and 1980s research had begun to accelerate, and the term tissue engineering was ‘coined’ in 1987 at a committee meeting at the National Science Foundation in the USA. The first scientific meeting that was called tissue engineering was held in 1988 at Lake Tahoe, California (Skalak & Fox 1988). Since this first meeting the number of meetings has ‘proliferated,’ and with the emergence of stem cell technology, the world of tissue engineering has evolved into the broader area of regenerative medicine. This has all

happened over the last quarter of a century, and in this same time period a tissue engineering and subsequently regenerative medicine industry has emerged. It is this evolution in industrial activity, an industry that has gone through its share of ‘ups and downs,’ that is described in the next three sections.

2. THE ‘GO-GO’ YEARS

As the field moved into the early 1990s research in tissue engineering accelerated (Langer & Vacanti 1993; Nerem & Sambanis 1995) and a tissue engineering industry began to emerge. As can be seen in table 1, by 1994 there were \$246 million in private sector activity, 40+ companies/business units, and 1500+ employees working in these units (Lysaght 1995). It would be the skin substitute area, i.e. living skin replacements, that early on came to the market with several products. One of these was a product called the Integra Dermal Regeneration Template, manufactured by Integra Life Sciences and at that time marketed by Ethicon, a Johnson & Johnson business unit. This was first described in a publication in 1980s by Yannas & Burke (1980), also Burke *et al.* (1981) and reviewed by Yannas (1998). In 1996 it received approval by the food and drug administration (FDA) in the USA. There also were the products of advanced tissue sciences (Naughton 1999). These included Transcyte, approved by FDA in 1997, and Dermagraft, approved finally in 2001. Transcyte, though made with cells, was an acellular product, whereas Dermagraft was a dermal equivalent made from dermal fibroblasts derived from foreskin and seeded into a polymeric scaffold (Naughton *et al.* 1997). Organogenesis had a skin substitute called

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One contribution to a Theme Supplement ‘Translation and commercialization of regenerative medicines’.

Table 1. Regenerative medicine commercial activity (Lysaght 1995; Lysaght *et al.* 1998, 2008; Lysaght & Reyes 2001; Lysaght & Hazlehurst 2004).

	1994	1997	2000	2003	2007
total private sector activity (millions)	\$246	\$453	\$610	\$487	\$2400
no. business units	40	40	73	89	171
no. employee FTEs	1500	2380	3080	2610	6100

Appligraf that was based on the research of Bell *et al.* (1981). It was made with collagen and included both a dermal equivalent and an epidermis (Parentau 1999). These living skin replacements were made with allogeneic cells, and these proved to be immune acceptable.

There also was the approach of Genzyme that led to both Epicel for skin replacement and Carticel for cartilage replacement. Epicel was based on the pioneering research of Howard Green at Harvard (Rheinwald & Green 1977; Green 1991), while Carticel was based on an approach developed by Brittberg *et al.* (1994). In these the patient's own cells are taken, and Genzyme expands these to the number needed for either skin replacement (Epicel) or cartilage replacement (Carticel). Although an intriguing approach, there really was no product and thus Genzyme was in a service business.

The skin substitutes developed by Advanced Tissue Sciences and Organogenesis were approved by the FDA through the Center for Devices and Radiological Health (CDRH), where wound-healing products are regulated. Carticel, on the other hand, was approved by the FDA through the Center for Biologic Evaluation and Research (CBER), i.e. as a biologic. To the best of this author's knowledge, Epicel originally did not go through a regulatory approval process at the FDA as the approach was considered one where the cells were 'minimally manipulated'. Subsequently, however, Epicel was approved by the CBER.

By 1997 the total private sector activity had almost doubled to \$453 million, as shown in table 1. There were still approximately 40 companies and business units, but the number of employees working in these various units had increased to nearly 2400 (Lysaght *et al.* 1998). As also can be seen in table 1, by 2000 the total private sector activity had increased further to \$610 million (Lysaght & Reyes 2001). The number of business units also had increased, this to more than 70, and there were more than 3000 employees.

Another aspect of the 1990s was the emergence of stem cells and the morphing of tissue engineering into regenerative medicine. There was excitement about the potential of embryonic stem cells (Shamblott *et al.* 1998; Thomson *et al.* 1998) and the role of adult stem cells (Caplan & Bruder 2001), and the National Academies report (2001) discussed the future of stem cells and regenerative medicine. At this point, however, the activity was almost exclusively in the academic arena, with the commercialization of stem cell technology still to come. With all of this, the latter half of the

Table 2. Capital value of publicly traded regenerative medicine companies (Lysaght *et al.* 1998, 2008; Lysaght & Reyes 2001; Lysaght & Hazlehurst 2004).

year	1997	2000	2003	2007
value (billions)	\$1.7	\$2.6	\$0.3	\$4.7

1990s, leading into the turn of the century, can be viewed looking back as the 'go-go' years. There were great expectations, and the future appeared to be unlimited.

3. THE 'SOBERING' YEARS

The beginning of the twenty-first century, however, proved to be a different story. Whereas in the 1990s there not only had been a continued expansion in private sector activity but also a significant increase in research within the academic arena, by 2003 the data proved to be more 'sobering'. This led to the publication of an article by Lysaght & Hazlehurst (2004) entitled 'Tissue engineering: the end of the beginning'. This title was derived from the 1942 quote by Sir Winston Churchill during the middle of World War II where he said 'This is not the end. It is not even the beginning of the end. But it is perhaps the end of the beginning'. This proved to be true about the war, and it also proved to be true about the state of tissue engineering as we entered a new century.

Certainly the 2003 data, as shown in table 1, sent a 'sobering' message. Private sector activity had decreased 20 per cent to \$487 million (Lysaght & Hazlehurst 2004). Although there was an increase in business units to 89, the number of employees had decreased to 2600. This was not totally unreasonable in a stagnant economy; however, most 'sobering' was the plummeting of the capital value of publicly traded tissue engineering companies from \$2.6 billion in 2000 to \$310 million in 2003, as shown in table 2. This was a 90 per cent decrease.

What happened to the companies that had made the 1990s the 'go-go' years? For Advanced Tissue Sciences there were a variety of problems. One might argue that they had not realistically estimated the size of the market and the patient need. There were problems that were more of a business, management nature, and there were delays in reimbursement. The 'bottom line' was that the time from benchtop to product had just taken too long and in 2002 Advanced Tissue Sciences declared bankruptcy. Organogenesis had its own share of problems, and it also had to declare bankruptcy. And Carticel? Here it turned out that being in a service business as opposed to a product business proved to be a situation where it was difficult to get any kind of real return on investment.

There were some other interesting trends. One of these was tissue engineering becoming a worldwide activity. This was not only true of academic research, but also private sector activity. For the latter, whereas in 2000, 80 per cent of total private sector activity was in the USA, by 2003 this had decreased to 54 per cent.

Another interesting trend was the emergence of stem cell activity in the private sector. Thus, the downturn in private sector skin, cartilage and structural activity, with a loss of 1500 full time equivalents (FTEs), was at least in part countered by the addition of 300 employees in stem cell business units. This was due to a 42 per cent increase in stem cell companies and business units, and clearly the basic stem cell science of the 1990s had entered the world of commercialization.

4. BACK TO THE FUTURE

Just as the 2003 data provided 'sobering' news, the 2007 data reported by Lysaght *et al.* (2008) provided evidence that the field of tissue engineering and regenerative medicine had rebounded. In a real sense this field, which always exhibited great promise and potential, was now back to a future of 'great expectations' where the potential and promise might be able to be realized.

As shown in the final column of table 1, total private section activity by 2007 had soared to \$2.4 billion. As of mid 2007, there were a total of 167 companies/business units in the private sector that could be characterized as being in tissue engineering and regenerative medicine. Of these, approximately 50 were offering products and services and generally being profitable, and there were over 3000 employees in these business units. In addition, there were 110 companies in the development stage with 55 products that were in FDA-level clinical trials. Taking all of this together, the number of employees engaged in this field in the private sector had risen to more than 6000. Even more of an indication of a rebound is that the capital value of publicly traded companies had gone from \$300 million in 2003 to \$4.7 billion in 2007. This is shown in table 2 and represented quite a remarkable change.

Of the \$2.4 billion in private sector activity in 2007, more than half of this was in the sale of products, a total in excess of \$1.3 billion. Of this more than half was the Medtronic INFUSE, a recombinant bone morphogenic protein product. Although clearly highly successful and having a mode of action that involved cells *in vivo*, it was not a cellular product.

Other contributors to the \$1.3 billion in sales in 2007 were the living cell skin replacements and cartilage. For the former, organogenesis had come out of bankruptcy and was beginning to make a quarterly product. As far as Advanced Tissue Sciences, it never came out of bankruptcy; however, its products had been taken over by a new company, Advanced BioHealing, and thus Transcyte and Dermagraft were back on the market. Genzyme continued to market Epicel and Carticel. All of this thus added up to \$90 million in 2007.

Another contributor to the \$1.3 billion in sales was what was called regenerative biomaterials by Lysaght *et al.* (2008). This totalled \$240 million, and an important part of this was small intestine submucosa, what is called SIS, an extracellular matrix product derived from the pig (Badylak *et al.* 1999; Lindberg & Badylak 2001). Depuy, a J&J Company, had the orthopaedic rights, and their product called Restore was approved

Table 3. Private sector stem cell activity 2007 (Lysaght *et al.* 2008).

	no. of business units	employee FTEs	dollar volume (millions)
preclinical activity	41	744	\$230
clinical trial stage activity	25	687	\$277
commercial	25	1391	\$273
total	91	2822	\$780

in late 1990 by FDA through the 510 K process. Cook Biotech had the rights for other applications of SIS, and following the lead of Depuy also were able to get FDA approval using the 510 K process. The most successful Cook Biotech products have been their ventral, hiatal and inguinal hernia designs, their chronic wound matrix, and their fistula plug (M. Hiles 2010, personal communication). Since 2000 more than one million patients have been treated with Cook Biotech products; however, as Cook is a privately held company, no sales data are available.

Finally, there was another contributor to the 2007 data on sales. This was the area of cord stem cells, and the private banking of these cells exceeded \$270 million in sales. Since this is not a product, however, and since Medtronic's INFUSE and the SIS sold by J&J's Depuy business unit and by Cook Biotech are all acellular, for 2007 the actual sales of cell-based products has been estimated to be in the range of \$100 to 200 million (Mason & Manzotti 2010). This is somewhere on the order of 10–15% of the \$1.3 billion in total 2007 sales.

There were other aspects of the 2007 data reported by Lysaght and his co-authors that were of interest. One of these was that, of those companies working on cell-based products, 63 per cent were pursuing an allogeneic cell strategy and 37 per cent an autologous cell strategy. For the breakdown in development stage private sector activity, the total of \$864 million was divided by the authors into four separate categories: interactive biomaterials, \$84 million; cells and biomaterials, \$218 million; stem cells, \$507 million; and other, \$55 million. These numbers indicate that in 2007 it was the stem cell area clearly drawing the greatest private sector funding in this development stage category.

If the stem cell numbers are examined in more detail, then a more complete picture for 2007 is provided. These data are presented in table 3 (Lysaght *et al.* 2008). As may be seen, there were more than 2800 employee FTEs engaged in private sector stem cell activity. This is almost half of the total for 2007. Of these stem cell FTEs, however, approximately half are in the commercial arena which as noted earlier is the banking of cord stem cells. The other half were involved in pre-clinical/clinical trial stage activities. Furthermore, there were 91 companies involved in the stem cell area with 66 being in the preclinical/clinical stage. Of the total, 61 per cent were focused on adult stem cells, 12 per cent embryonic stem cells, and 27 per cent on cord blood stem cells.

The emergence of private sector stem cell activities also has been examined in a more recent report (Young 2010). In this, the market for stem cell products is forecast through 2020, starting with data from 2005. In 2007, the same year of the most recent Lysaght data, the Robin Young report indicates total revenues of \$34 million. By 2010, i.e. this year, the report forecasts total annual revenues of approximately \$145 million and by 2020 nearly \$8 billion.

One of the breakthroughs of this first decade of the twenty-first century has been the ability to apparently reprogram somatic cells into pluripotent cells, what are called induced pluripotent stem cells, i.e. iPS cells. As exciting as this has the potential to be, there are still many issues and questions to be resolved (Yamanaka 2009). Thus, the impact of this on the commercialization of regenerative medicine is still very much unknown.

5. CONCLUDING DISCUSSION

Over the last two decades the industry associated with tissue engineering and regenerative medicine has continued to evolve. Although still somewhat fledging in nature, particularly when compared with the medical device and pharmaceutical industries, it has become a 'credible new sector' as stated in the recent publication by Mason & Manzotti (2010). They estimate that for regenerative medicine cell therapies there have been a minimum of 675 000 therapeutic units manufactured, 323 000 patients treated, and an annual market of \$100–200 million. This is for cell-based therapies, and if one adds in acellular products like Medtronic's INFUSE and the various applications of SIS, the numbers are much larger.

There thus continues to be great expectations for the future. As noted earlier, the 'go-go' years was 'fuelled' at least in part by media hype. Examples include the September 1999 ABC Good Morning report (Gillian 1999) identifying tissue engineering and genetic medicine 'as the greatest scientific achievement of the twentieth century'. Both of these still have to prove themselves. Then in 2000 the business journal Barrons in an article entitled 'Spare Body Parts' forecasted a \$100 billion plus industry (Palmer 2000) and Time magazine in its May 22 issue had tissue engineering at the top of its list of the hottest new jobs for the twenty-first century. With this kind of hype, the 'sobering' beginning of this decade may have had at least one positive effect in introducing some needed reality into the assessment of the field of tissue engineering and regenerative medicine and into forecasts of the potential growth of this field and the associated industry.

The 2007 data taken together with the Robin Young forecasts for the stem cell sector of industrial activity suggest an upturn and one that will continue as we move further into this twenty-first century. Not only does Robin Young forecast a continuing increase in stem cell private sector activity, it also predicts for 2020 which areas will have the greatest application of stem cells. At the top of the list is the orthopaedic area followed by neural repair, the cardiovascular area, inflammatory applications and diabetes.

In yet another forecast of the future, A. Amed 2010 (private communication) indicates that there are currently more than 175 products in the regenerative medicine pipeline. This is in addition to 28 products already out there with most of these addressing skin and orthopaedic applications. Of the 175+ products under development, within the pipeline they range from the research and development stage to phase-3 clinical trials. Furthermore, of this total more than 125 are what would be called cell-based products.

As we near the end of the first decade of this twenty-first century, it thus does appear, that a brighter future is appearing. Although there is a long way still to go for this industry to become one of the major ones, there remains strong potential and this is supported by the recent upturn and the progress documented in recent reports. A strong industry is essential if the wide variety of patient needs are to be addressed, including what might be called the transplantation crisis, i.e. the discrepancy between the need for donor organs and the number available (Nerem 2005). This is because it is only through the commercialization of the technology needed for regenerative medicine that these therapies will be available in the widest way possible, not only at select academic medical centres but in the broader array of hospitals serving patients all over the world.

Successful commercialization ultimately requires regulatory and reimbursement approval, and in regard to the former, although the FDA is making progress in the regulation of cell-based therapies, a very much altered system is needed for the regenerative medicine products of the twenty-first century. Regulatory agencies thus must develop the necessary and appropriate processes for regulating the delivery of safe and effective clinical therapies based on advances in regenerative medicine. As far as third party reimbursement, this is another critical issue. Third party payers must provide the reimbursement necessary to sustain promising approaches and reward regenerative medicine therapies that have the potential to significantly affect healthcare. With this there must be physician acceptance of these new treatment and therapeutic strategies.

Finally, it should be remembered that the commercialization of biotech historically has a long time constant. An example of this is the monoclonal antibody industry which has taken decades to mature and reach profitability. Thus, the 'ups and downs' of the tissue engineering and regenerative medicine should not have been unexpected. As already noted, a brighter future is now appearing, and with the ever accelerating advances in the science and technology, regenerative medicine has the potential to truly live up to the promise of delivering therapies for diseases, injuries and disorders where currently patients have no options. To be all that it can be, however, will require the existence of a vibrant regenerative medicine industry.

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South Korea. Much of the data used in this article came from the series of publications by Dr Michael Lysaght and his co-workers. R.M.N. thus is indebted to Dr Lysaght and his team, and in a real sense, it is a tribute to Dr Michael J. Lysaght who passed away in November 2009. There are many legacies of Michael Lysaght as he contributed in so many ways to the field of tissue engineering and regenerative medicine, but one of his legacies is the data he assembled with his team which not only resulted in the series of publications, but provide a documentation of historic value to the field as it moves on into the future.

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