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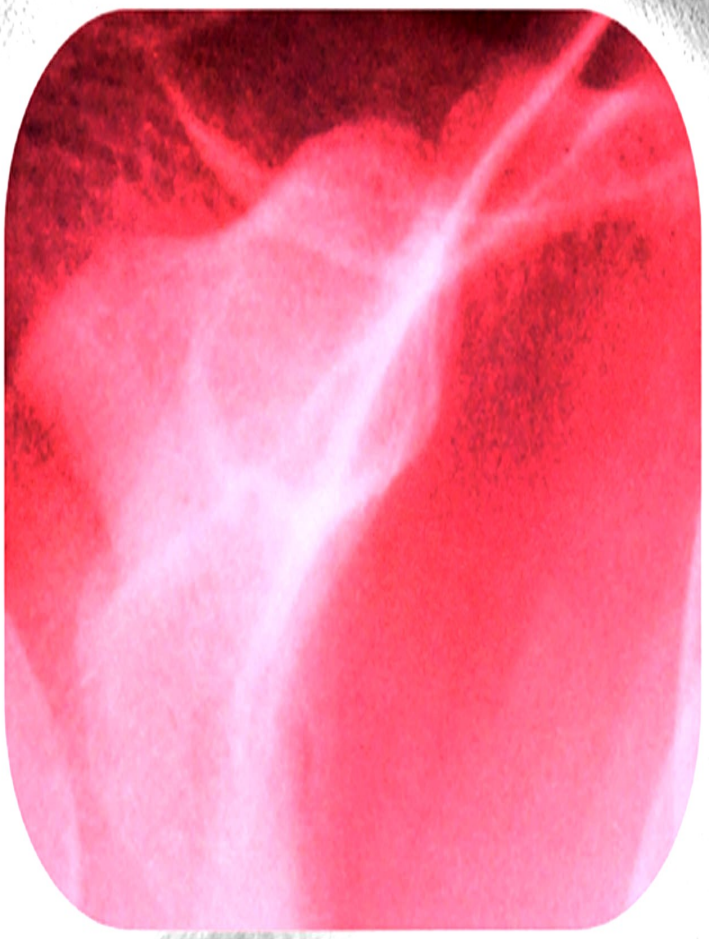

The Commercial Development of Cell Therapy – Lessons for the Future?

Survey of the Cell Therapy Industry and the Main Products in Use and Development
Part 1: Summary of findings

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Executive summary

1. Aims of the survey: Great hopes currently surround the emerging field of regenerative medicine and the use of cells as therapeutic agents. In particular, much attention had been paid to the potential of novel stem cell based therapies, following a number of major scientific breakthroughs and media reports of potential new cures. These therapies have become the focus of a new sector of the biotechnology industry, which faces a number of major challenges in translating the promise of these scientific advances into widely used medical products.

This report forms part of a workpackage within the EPSRC funded Remedi Grand Challenge that addresses the issue of understanding user needs in regenerative medicine. It summarises the findings of a survey of the cell therapy industry completed in January 2009 that set out to assess the current state of private sector activity, the prospects for the future of the industry and the main challenges it currently faces. In particular, it aimed to:

- Map the commercial development of cell based therapies within regenerative medicine and tissue engineering – the size, location and growth of the industry;
- Describe the main products on the market or in development, including the disease focus and the main cell types used;
- Chart the changing pattern of industrial collaborations in this area, and the extent to which the cell therapy sector is being integrated into the pharmaceutical and device industries.

2. Definitions: Careful definitions of tissue engineering, regenerative medicine and cell therapy were used to provide a sound basis for the industry survey. A key difference was drawn between *primary* (cell based) products and *secondary* products that provided structural components (matrices, scaffolds and biocompatible materials) to enable cell growth. Another important set of distinctions was made between: A) non-stem cell based *first generation* products and a *second generation* of products based on stem cell technology; and B) *autologous products* (based on a patient's own cells) and *allogeneic products* (based on cells from an unrelated donor). These categories proved a valuable way of segmenting and analysing the industry and its dynamics.

3. The size of the industry: The size of the cell therapy sector has increased significantly over the last five years and was composed of 138 primary firms and 49 secondary firms at the start of 2009. The survey also identified 177 cord blood banks. The latter were not profiled in detail as they are not directly involved in developing new therapies. The UK ranks in the top three countries in the world with 15 firms working in this area.

4. Sectoral composition: The sub-structure of the cell therapy industry has changed very substantially over the last five years and is now dominated by firms working on stem cells (71% of all primary firms). No new firms working on non-stem cell therapies have been founded since 2002. The shift to stem cells is also associated with a greater emphasis on allogeneic products across the industry.

5. Geography: The cell therapy industry is highly geographically concentrated. It is dominated by US firms, which together with German and UK companies account for ~75% of the primary industry. US firms are older and more mature. The European industry has lagged behind, but whilst it made good progress in narrowing the US lead in the late 1990s, growth in the EU has stalled in recent years. This is largely due to the shift to stem cell technology, which the US dominates and suggests further entrenchment of its competitive advantage over Europe.

6. Maturity and firm growth: The cell therapy sector is relatively well established compared to other parts of the biotechnology industry, as measured by age of firms, number of public companies and products on the market. Despite this, there is a very high level of turnover and commercial failure amongst primary firms. Furthermore, there are problems with company growth and the primary sector remains dominated by small companies. Both these features are largely due to problems getting access to finance. In contrast, there are a greater number of medium-sized secondary firms, reflecting their commercial success.

7. Disease focus: The most popular disease target worked on by firms was cardiovascular conditions. This was followed by classical tissue engineering applications in skin, bone and cartilage, and metabolic disorders. The only clinical areas that fell outside the broad field of tissue engineering were CNS diseases and blood/ immune disorders (including some haematological cancers). The latter mainly relates to the application of haematopoietic and cord blood stem cells, an area with a long pedigree stretching back to the 1980s. It therefore appears that the transition from tissue engineering to regenerative medicine that has been marked by the application of stem cell technology has not yet led to a dramatic shift in the diseases targeted by industry.

8. Cell type used: Over 50 firms are working on different types of adult stem cells, compared to ~20 firms working on hESCs and less than 15 on cord blood stem cells. This highlights the fact that most commercial activity is in the adult stem cell area and this is even more marked when looking at products in clinical development.

9. Products on the market: The cell therapy industry is unusual compared to other biotechnologies by having a relatively large number of companies with products on the market (48 out of 187). However, this is very unequally distributed: 30 of the 49 secondary firms have launched products, whereas only 18 of the 138 primary firms had marketed products. Of this latter group, only two stem cell firm have therapies for sale. Furthermore, all allogeneic products were launched by US firms, whilst all but one of the firms selling autologous products were European. A total of 97 products were identified by the survey, of which 88 were for skin, bone or cartilage. Most products were sold by small firms and the development time to market was 5-10 years.

10. Product sales: These were broken down by product type:

Autologous first generation (non-stem cell) products – The survey identified 17 autologous cell-based products (13 for cartilage repair; three for skin repair of burns and chronic wounds, and one for bone grafting). Sales of these products have been very limited, with only one product (Carticel) treating more than a 1,000 patients a year. There are a number of reasons for this including poor product specification, lack of clinical evidence of utility and the high cost of manufacturing.

Allogeneic first generation (non stem cell) products – Five allogeneic products were identified by the survey, of which four were for skin repair. These have generated significant sales and cell-based products for the active treatment of chronic skin wounds now have an established market. Organogenesis' Apligraf is currently used on ~35,000 patients a year and has been used on over 200,000 patients in total since 1998. However, it is unclear if this success can be extended to other therapeutic areas, as issues of transplant rejection from unmatched tissue donors are not a major issue with skin repair, but may be far more important for other indications.

Second generation (stem cell based) products - Only two product based on stem cell technology had been launched at the time of the survey. These have only been on the market for a few years and have limited sales of less than $20M a year. It would be premature to make a judgment about likely peak sales of these or other stem cell based therapies that might reach the market in the next few years.

Secondary products – In contrast to the relatively poor sales for primary products, the sales of a number of secondary products are significant totalling over $750M a year. Sales of the leading bone related secondary products were over $180M in 2007 and secondary skin products $300M. The most successful product in this category was Integra Dermal Regeneration Template.

Taken together, sales of primary products (containing cells) totalled no more that $100M a year. When combined with sales of secondary products (> $750M a year) and the cord blood banking industry (sales of ~$200M a year), this gives an industry total of over $1 billion a year.

11. Products in development: There were 120 primary products in clinical development at the time of the survey. 64 (53%) were either Pilots, Phase I or Phase I/II; 34 (28%) were in Phase II; and 22 (19%) were in Phase III. Of the primary products in clinical development 35% were non-stem cell based and 65% used stem cells. Trials of primary non-stem cell therapies (autologous and allogeneic) and secondary products were mainly for classical tissue engineering conditions (skin, bone and cartilage). However, there were a number of trials for cardiovascular disorders. The clinical development of stem cell therapies was slightly different, split between classical tissue engineering conditions (28 trials), cardiovascular disorders (30 trials) and diseases treated by haematopoietic stem cells (13 trials, mainly for cancer). Only three trials were for metabolic conditions and one for a CNS disorder). No clinical trial involved human embryonic stem cells had started by January 2009, but one had just received approval from the FDA.

12. Industry pipeline: Based on the number of different products in clinical development, it can be estimated that approximately 28 new products might reach the market in the next 5-10 years. Of these six might be for cardiovascular conditions, 16 for classical tissue engineering and six for other indications, mainly cancer. Whilst this is largely illustrative, it provides a sense of the scale of potential product launches and strongly suggests that therapies for the treatment of skin, bone and cartilage are most likely to reach the market in the medium term (1-5 years), with a number of cardiovascular products reaching the market in 5-10 years.

11. Industry collaborations – Collaboration between companies is a good index of industrial activity and alliances with large companies are important for the development and growth of small firms. There were a total of 411 cell therapy deals between 1987 and the end of 2008. The great majority of these were formed after 2000. A total of 56 (14%) deals involved first generation primary product firms, 236 (57%) deals involving second generation stem cell firms and technology, and 119 (29%) were with secondary product companies. There are significantly fewer alliances per firm/ year than in other parts of the biotechnology industry, with few sizeable alliances with large money transactions (>$10M) taking place.

12. Collaboration with large companies: One of the most important features of the pattern of collaborations was the lack of investment from large companies. In total large firms formed 99 alliances in cell therapy since the mid-1980s. Of these, 33 (33%) were with pharmaceutical and biotechnology companies, with only six biotechnology companies (Genzyme, Teva, Centocor, Amgen, Serono and Genentech) and three pharmaceutical companies (Novartis, Pfizer and Novo

Nordisk) making more than one deal in the whole industry since it was founded. However, there are some signs that this might be starting to change. In addition, ten large device companies have invested in the sector forming a total of 49 (50%) collaborations. More recently, a number of major reagent and equipment firms have also invested in the stem cell industry.

13. Reasons for lack of demand: The key issue determining poor sales is the lack of clinical uptake of cell therapy products and this is mainly related to difficulties establishing clinical utility and cost-effectiveness. Creating an appropriate evidence base is the key to addressing this deficit.

13. Conclusions: These findings point to a significant risk of market failure for a number of types of cell therapy. Whilst the sales of non-stem cell allogeneic and secondary therapies appear sufficient to sustain companies working in these areas, this is not the case for non-stem cell autologous and most stem cell based therapies. The historic high level of company failure in this sector looks set to continue, but with far fewer new firms taking their place. Unless this situation changes, the industry will contract and the progress needed to develop important cell therapies will be adversely affected.

Another key conclusion is that the barriers facing the industry are largely structural rather than technical. These include establishing closer collaboration with clinical end-users, the funding of clinical studies, greater regulatory certainty and clearer reimbursement policies. In addition, there is the need to develop enabling technologies that could lower manufacturing costs. None of the barriers have changed as a result of the shift to stem cell as the underlying technology in the sector, but each can be addressed by public policy.

A comprehensive package of policies therefore needs to be developed that address the risk of market failure and the structural barriers facing firms. These might include:

- Greater emphasis of public-private partnerships (PPPs) around particular therapies that are at risk of market failure, in which the costs and risks of development are shared in return for part of the profits/ royalties or lower cost access to products. PPPs are already being created in relation to hESCs and should be extended to other areas;
- Help with the credit available to small firms and greater public support for R&D costs;
- Much more direct financial support for clinical studies that will help develop the evidence base required to establish clinical utility and cost-effectiveness;
- Experiments with provisional reimbursement that would open-up access to the NHS whilst linking final market approval and the price paid for a product to clinical outcomes;
- Speeding-up the adoption of a clearly defined and well supported regulatory framework;
- Increased public funding for the development of enabling manufacturing technologies aimed at reducing the cost of cell therapies;

At the same time it is important that a more realistic set of expectations is adopted about the level of resourcing and length of time needed to realise the potential of cell therapy. The history of the field is one of incremental change and the slow build-up of the social, technical and clinical infrastructure required to develop products that offer significant improvement in patient care. As with many other novel biotechnologies, long-term success will depend on the public sector playing a major role in supporting private companies through the difficult early stages of the translation process.

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1. Introduction

Great hopes currently surround the emerging field of regenerative medicine and the use of cells as therapeutic agents. In particular, much attention had been paid to the potential of novel stem cell based therapies, following a number of major scientific breakthroughs and regular media reports of potential new cures. In addition to creating a new generation of treatments for some of the most important and intractable chronic conditions, the development of cell-based therapies also offers to help stimulate the growth of the biotechnology and biopharmaceutical industries. This could bring important economic benefits through both the creation of a large number of highly skilled jobs and significant export sales. Government policy has therefore identified stem cells and regenerative medicine as an important area of the UK 'knowledge economy'.

This study in part of a larger programme of work supported by the Engineering and Physical Sciences Research Council (EPSRC). The 'Regenerative Medicine - A New Industry' (remedi) Grand Challenge's main aim is to demonstrate how established bio-science can be transformed into profitable commercial practice and generate affordable therapies while developing the science of manufacture[1]. An important part of this programme is to understand the market for regenerative medicine products and a specific workpackage is dedicated to this with the following aims:

- Survey the regenerative medicine industry and identify the main products in use and development;
- Map commercial and academic collaborations with clinicians in UK regenerative medicine;
- Analyse the needs of clinical users in relation to regenerative medicine products;
- Assess the main factors shaping the adoption and acceptability of regenerative medicine products.

This report addresses the first of these aims, whilst the others are considered in a separate study[2]. Before setting out the objectives of the survey it is useful to provide some background information and definitions.

1.1 Tissue engineering and the birth of regenerative medicine

The development of regenerative medicine has to be set in the context of the prior history of tissue engineering (TE) which emerged in the 1990s as a multidisciplinary field that had roots in a broad range of disciplines within clinical medicine, engineering and science, such as cell biology, transplantation science, biomechanics and biomedical engineering. Tissue engineering was primarily motivated as an innovative solution to important problems within clinical medicine. For instance, it responds to a number of difficulties associated with transplantation such as the shortage of donors, immunological complications and poor compatibility between artificial substitutes and the human body[3]. In particular, tissue engineering promised:

[1] See http://wolftest.lboro.ac.uk/research/healthcare/remedigc/aims-objectives.html

[2] Rowley, E. and Martin, P (2009) Barriers to The Commercialisation and Utilisation of Regenerative Medicine In The UK. Nottingham; Institute for Science and Society.

[3] National Science Foundation (2004) The Emergence of Tissue Engineering as a Research Field. National Science Foundation. Arlington, VA. Available from http://www.nsf.gov/pubs/2004/nsf0450/start.htm

'… a more advanced approach in which organs or tissues can be repaired, replaced, or regenerated for more targeted solutions. This approach also responds to clinical needs that cannot be met by organ donation alone'[4].

By the late 1990s a number of cell therapies had been developed using the principles of tissue engineering, mainly targeting skin, bone and cartilage disorders (referred to as 'classical tissue engineering' in this report). At the same time the fist stem cell therapies were starting to be developed. In particular, the use of adult haematopoietic stem cells (HSCs) for the treatment of cancer started to enter routine clinical practice in the late 1990s[5]. However, it wasn't until the early 2000's following the discovery of human embryonic stem cells (hESCs) that the field of regenerative medicine started to emerge, stimulated by high expectations that stem cells held the potential to transform medicine. This led to a major upsurge in commercial interest in the cell therapy field and the creation of a large number of new firms dedicated to this area.

1.2 The chequered history of the commercial cell therapy

However, despite the clinical success that cell therapy started to enjoy in the area of HSC therapy, it proved a difficult area for industry. In the 1990s a number of cell therapy firms were established to commercialise HSC therapies and novel treatments for diabetes, and despite generating great interest from the pharmaceutical industry were ultimately unsuccessful[6]. Similarly, a number of small firms were established to work on the first generation of tissue engineered products. Previous studies by Lysaght and colleagues[7, 8] have traced the emergence and development of the commercial tissue engineering field, and have highlighted a number of issues for scientists, industry and policy makers. Commenting on a survey of the industry carried out in 2000 Lysaght and Reyes concluded positively that "*Tissue engineering remains a dynamic and growing private sector ...New technology, new ideas, and new firms continue to invigorate this very promising new therapy*."[9]. However, by 2004 Lysaght and Hazlehurst had found that the field had suffered a number of important set-backs, with poor sales from the first wave of products, disappointing results from clinical trials and cutbacks in investment[4].

More recently this picture has started to change, with evidence of renewed private sector interest in the broad area of cell therapy following the further development of stem cells. This shift has become associated with the idea of regenerative medicine, of which tissue engineering is now seen as a core element. In 2007 Mason observed that there had been an important shift in the field between 2002 and 2006, with a transition to what he has called Regenerative Medicine 2.0[10]. This is associated with a change in the industry's core technology (to stem cells), company focus (translation) and diseases targeted. Further empirical evidence for increasing commercial activity has recently been given by Lysaght et al's 2008 update in his longitudinal survey of the tissue

[4] World Technology Evaluation Centre. WTEC Panel Report on: Tissue Engineering Research. 2002. Available from http://www.wtec.org/loyola/te/final/

[5] Martin, P., Brown, N., and Turner, A. (2008) Capitalising hope: the commercial development of umbilical cord blood stem cell banking. *New Genetics and Society.* 27(2):127-143

[6] Martin, PA., Coveney, C., Kraft, A., Brown, N and Bath, P (2006) The commercial development of stem cell technology: lessons from the past, strategies for the future. *Regenerative Medicine 1(6): 801-807*

[7] Lysaght, M.J. and Reyes, J. (2001) The growth of tissue engineering. *Tissue Engineering*. 7: 485-493

[8] Lysaght, M.J. and Hazlehurst, A.L. (2004) Tissue engineering the end of the beginning. *Tissue Engineering*. 10(1/2): 309-320

[9] Lysaght, M.J. and Reyes, J. (2001) The growth of tissue engineering. *Tissue Engineering*. 7: 485-493. p490

[10] Mason, C. (2007) Regenerative Medicine 2.0. *Regenerative medicine* 2(1):11-18

engineering/ regenerative medicine industry[11], in which they conclude that the growth of sales, patients treated, product s in development and staff employed in the industry:

> *'…represents a remarkable recovery from the downturn in 2000-2002, at which time tissue engineering was in shambles because of disappointing product launches, failed regulatory trials, and the general investment pull back following the dot-com crash. Commercial success has resulted in large measure from identification of products that are achievable with available technology and under existing regulatory guidance. … The resilience of the field, as well as its current breadth and diversity, augurs well for the future of regenerative medicine.' (p305)*

This study was carried out at roughly the same time, but independently of Lysaght's work. In particular, it adopted a different approach that was more tightly focused and provided more detail about firm strategies and the technologies they are developing. Whilst it shares some of the same findings as Lysaght, it provides what we believe is a more nuanced account that leads to a rather different and more critical set of conclusions. These will be discussed at the end of the report.

1.3 Definitions and aims of the survey

Before describing the aims of the survey, it is important to highlight a few issues concerning the terms and definitions used. In general, there is a lack of any consensus on the definition of regenerative medicine, and to a lesser extend, tissue engineering. This makes it sometimes difficult to compare studies and reach common ground in discussions about overall trends. We have been careful to define the area of study in a way that enables some comparison with the work of Lysaght and others, whilst providing a tight technical focus. The terms we used are discussed at length in Appendix 1, where we present an operational definition of both tissue engineering and regenerative medicine. In contrast to some authors we deliberately excluded the development of a number of technologies which sometimes fall under the general rubric of regenerative medicine, most notably therapeutic proteins. Out focus is purely on therapies that either contain living cells (we term primary products) or provide an environment for the growth of cells (secondary products composed on scaffolds, gels and matrices); in doing so we adopt the broad term of 'cell therapy'.

The aim of the survey was to:

- Map the commercial development of primary and secondary cell based therapies within regenerative medicine and the subordinate field of tissue engineering – the size, location and growth of the industry;
- Describe the main products on the market or in development, including the disease focus and the main cell types used;
- Chart the changing pattern of industrial collaborations in this area, and the extent to which the cell therapy sector is being integrated into the pharmaceutical and device industries..

In doing so it provides a detailed overview of the global cell therapy industry at January 2009 and presents a picture of how this important set of technologies is being commercialised. The methods used for the survey are described in Appendix 2.

[11] Lysaght, M.J., Jaklenec, A., and Deweerd, E. (2008) Great Expectations: private sector activity in tissue engineering, regenerative medicine and stem cell therapeutics. *Tissue Engineering* 14(2) 305-315.

This report is divided into two parts: Part 1 summarises the main findings and conclusion of the study, whereas Part 2 presents the detailed data, charts and tables and a series of appendices. Where data tables and charts referred to in the summary are also contained in Part 2, they are referred to as Data Tables.

2. The structure of the cell therapy industry

2.1 The size of the industry

The survey involved a search[12] of over 700 biotechnology firms related to tissue engineering and regenerative medicine and 187 were identified as belonging to the cell therapy industry as defined in Appendix 1. Of these 138 were classified as primary cell therapy companies (i.e. working on therapies containing living cells), of which seven were UK firms – see Data Tables 4.6, 4.7 and 4.8. A further 49 were classified as secondary companies (i.e. working on scaffolds, matrices and biocompatible materials to support tissue repair) of which four were UK based – see Data Table 4.9. The survey also identified 177 cord blood banks (120 private; 57 public) that were not involved in the development of new cell based therapies. However, those private cord banks actively creating cell-based therapeutics were included in the main survey. It should also be noted that firms working on biopharmaceuticals, such as growth factors, were not included in the survey.

These findings mark a significant break with earlier surveys of the industry and suggest that its overall size has increased significantly in recent years. For example, Lysaght and Reyes profiled 73 tissue engineering companies in 2000[13]; Lysaght and Hazlehurst profiled 89 companies in 2002[14]; and Bock, Ibarreta and Rodriguez-Cerezo profiled 113 companies in 2003[15]. We deliberately adopted a definition that enabled a broad comparison with these studies in order to identify recent trends. However, it must be stressed that differences in analytical categories and the way they have been applied only makes it possible for very general comparisons between the data gathered by different authors.

In terms of the focus on different types of products, firms working on first generation non-stem cell based structural products (e.g. skin, bone and cartilage) made up 27% of the sector in 2008 and those focused on non-stem cell based metabolic products (e.g. liver and pancreas) 2%. Companies working on second generation stem cell based therapies comprised 71% of the industry. This compares with Lysaght's historic data that showed that cellular (i.e. stem cell based) firms composed 29% of the industry in 2000 and 47% in 2002; structural firms 58% in 2000 and 37% in 2002; and metabolic firms 12% in 2000 and 15% in 2002 (Lysaght and Hazlehurst, 2004). It therefore appears that the sub-structure of the cell therapy industry has changed very substantially since 2002 with a major shift to stem cell based therapies and a decline in the proportion of firms working on non-stem cell products. This broadly agrees with Lysaght's latest 2008 survey[16] and is supported by data on the founding of new firms (see Graph 4.2), which shows continuing growth in the number of new stem cell firms (24 since the start of 2002) and a

[12] See Appendix 2 for details of methodology and search and selection criteria.

[13] Lysaght, M.J. and Reyes, J. (2001) The growth of tissue engineering. *Tissue Engineering*. 7: 485-493

[14] Lysaght, M.J. and Hazlehurst, A.L. (2004) Tissue engineering the end of the beginning. *Tissue Engineering*. 10(1/2): 309-320

[15] Bock, A.K., Ibarreta, D., and Rodriguez-Cerezo, E. (2003) *Human tissue-engineered products - Today's markets and future prospects*. Seville; IPTS/ ESTO.

[16] Lysaght, M.J., Jaklenec, A., and Deweerd, E. (2008) Great Expectations: private sector activity in tissue engineering, regenerative medicine and stem cell therapeutics. *Tissue Engineering* 14(2) 305-315. Due to changes in the inclusion criteria we believe that no direct comparison can be made between this latest study and previous surveys.

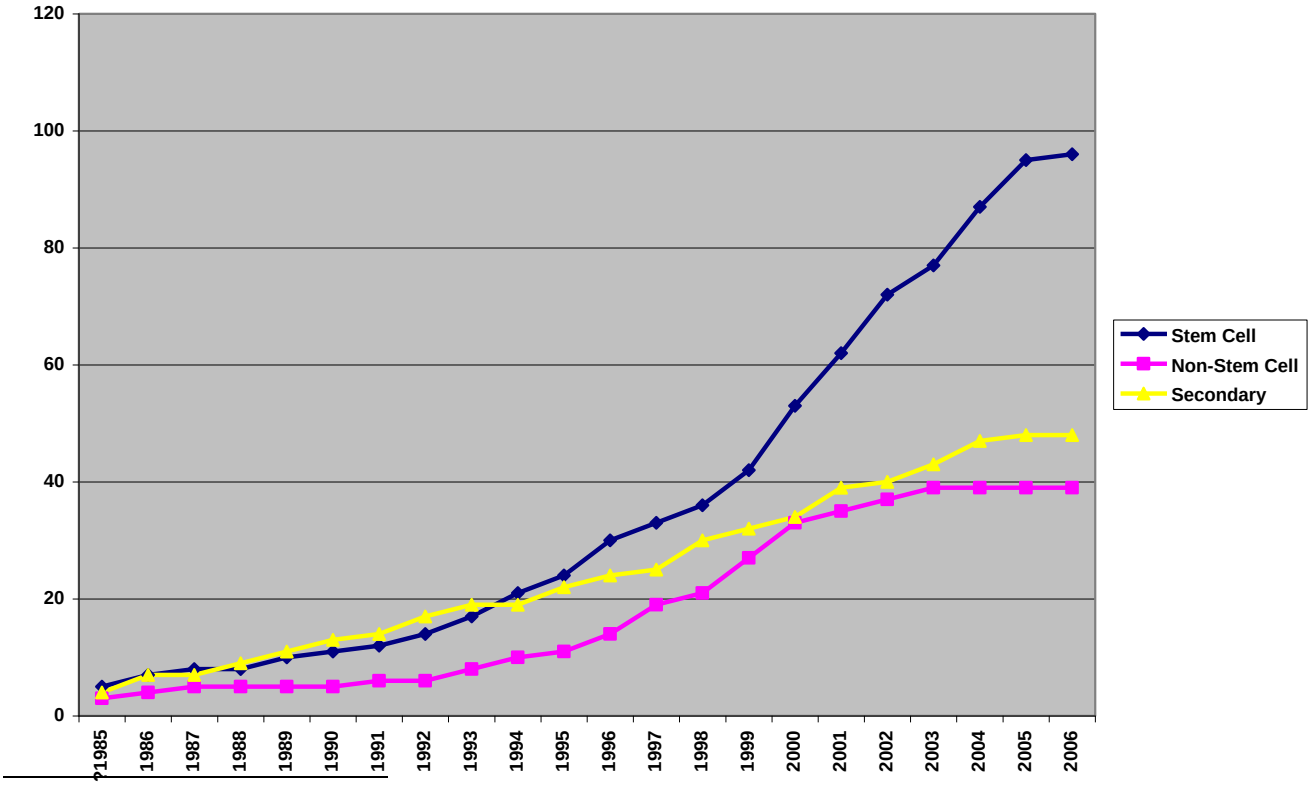
complete lack of new non-stem cell based firms (0 since 2002). This shift to stem cell based therapies is most marked in the area of metabolic products (liver and pancreas therapies), where only three non-stem cell therapies remain. However, it should be noted that there continues to be significant commercial interest in metabolic products, with one stem cell based firms (Ixion) dedicated to metabolic products and a further 35 working on metabolic disorders (mainly diabetes) as part of their product portfolio. Overall, the shift to a focus on stem cell technology as the basis for the future development of tissue engineering/ regenerative medicine identified in earlier surveys is now a dominant feature of the industry. The possible reasons for this are discussed below.

An analysis of the 40 non-stem cell based firms shows that 27 (68%) are based on autologous cell processing and a further 13 (32%) are working on allogeneic products. In contrast, 24 (22%) stem cell based firms are working on autologous products and 51 (47%) on allogeneic products (see Chart 4 below)[17]. It therefore appears that the shift to stem cell technology is also accompanied by greater emphasis on allogeneic products. This distinction is important and will be discussed in more detail later in this summary.

2.1.1 The age, size and location of firms

In terms of the age of firms, the cell therapy sector is relatively well established compared to other sub-sectors of the biotechnology industry, with the first US firms being created in the early 1980s. The growth of new firms focusing on stem cells started in the 1990s (see Graph 1) and accelerated after 1998, although a number of these firms probably started life as non-stem cell companies and subsequently changed their technology focus. Similarly, the growth in new firms working on non-stem cell therapies started in the mid 1990s, but came to a complete halt after 2002.

Graph 1: Cumulative growth of new cell therapy firms by year founded and by type[18]



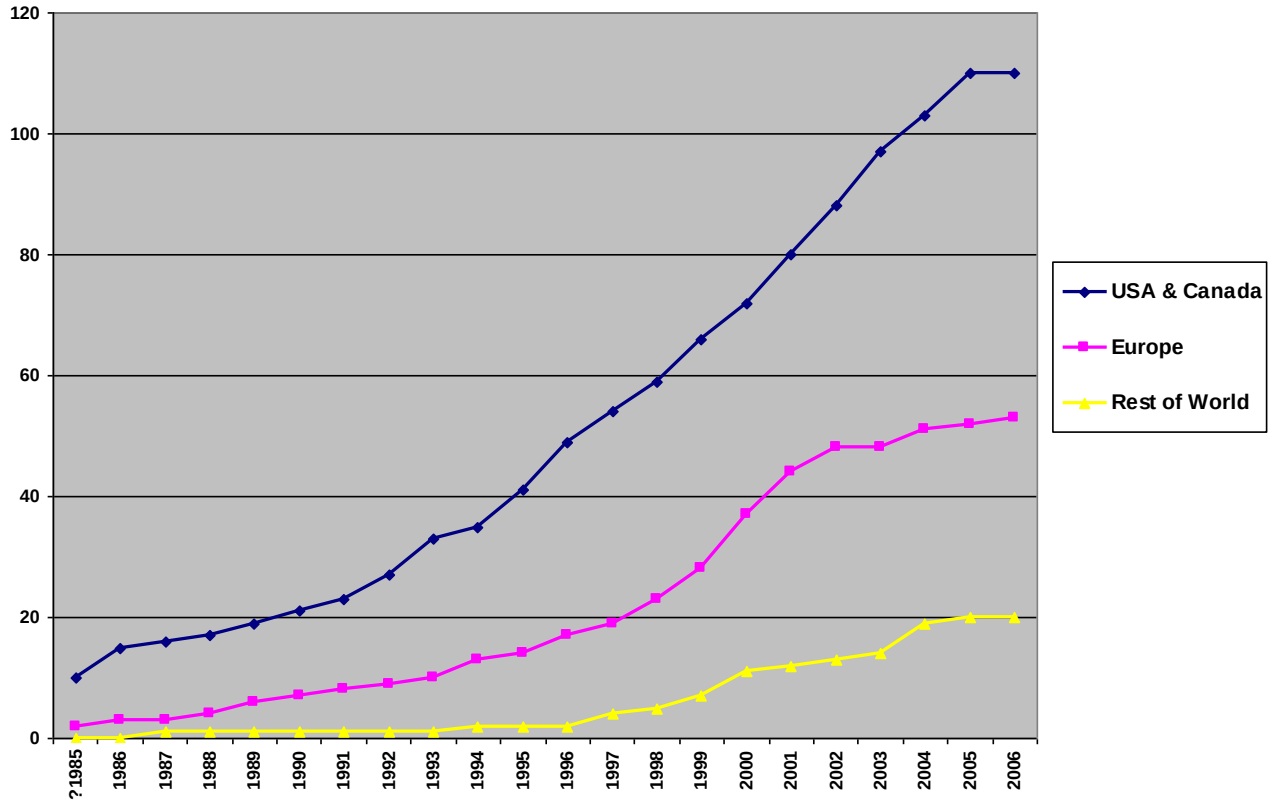
[17] In addition there are a number of firms that are classified as 'other' and work on stem cell related technology.

[18] Same as Data Graph 4.2

Between the mid-1980s and the present, there has been a steady growth in the creation of new US firms (see Graph 2). In contrast, the first European firms were founded in the late 1980s and the industry only started to grow rapidly in the mid 1990s. This mirrors the more general expansion of the European biotechnology industry during this period, and represents a 5-7 year time lag between Europe and North America. However, this growth in Europe seems to have stalled after 2000/01.

It is important to note that Graphs 1 and 2 only describes the number of new firms founded in each year and not the cumulative total number of companies. This latter figure depends on also knowing the number of firms that ceased to belong to the sector in any year and is difficult to estimate. A comparison of the companies listed in Lysaght's research indicates that only seven (out of 73 i.e. ~10%) companies from his 2000 survey and 14 (out of 89 i.e. ~15%) companies from his 2002 survey were included in this study. Further analysis indicates that a large number of companies identified in these previous surveys had either ceased trading or stopped working on cell therapy products, suggesting a high level of company turn-over and major problems sustaining commercially viable businesses in this area.

Graph 2: Cumulative growth of new cell therapy firms by location and year founded[19]



The relative maturity of the cell therapy industry is also reflected in the fact that 30% of primary and over 50% of secondary firms are listed on public markets. Floatation is normally only possible if a company has been established for a number of years and has products on the market or in late

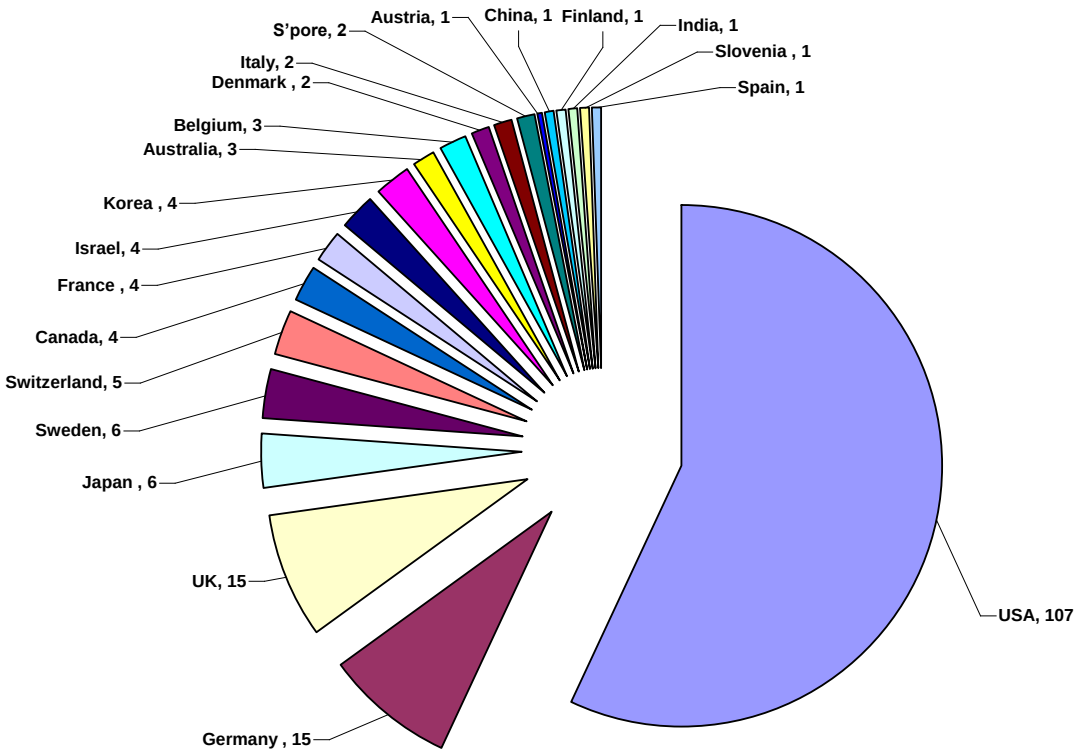
[19] Same as Data Graph 4.1

stage development. It is an important step, as if gives firms easier access to capital, and is a feature of an established sector.

However, one of the most notable features of the cell therapy sector is the lack of company growth. Given that many firms have been in existence for 10-15 years and have successfully created new products (see below), it is surprising that nearly 85% (117/138) of primary firms are small (i.e. with less than 100 staff). Only 10 firms (out of 138) have between 100-500 employees and there were 11 large companies (out of 138) with more than 500 staff identified as being actively involved in the development of cell-based products. This industry structure probably reflects a lack of resources from relatively low product sales and limited support from large pharmaceutical and healthcare companies – see below for details. In contrast, the profile of companies working on secondary products (scaffolds, matrices etc.) was different with around 65% of firms being small, 25% medium sized and roughly 10% large. The greater number of larger companies reflects both the presence of large integrated device and medical supply companies (BD Biosciences, Biomet, Integra, Q-Med and Zimmer) and particularly the growth of medium sized specialist firms (Artes Medical, Celltrix, Cryolife, Fidia, Interpore, IsoTis, Kuros, LifeCell, OrthoVita, Osteotech, Regeneration Technolgies and Tissue Sciences Laboratories) working on synthetic bone grafts and collagen matrices. The existence of significant product sales in these areas is a key factor explaining this marked difference in industry structure and suggests long-term viability for secondary companies.

In terms of geographical location, primary TE companies were based in 20 countries around the globe, with 80 (59%) of the total based in North America, 37 (27%) in Europe and the remaining 18 (14%) based elsewhere in the world. There was a similar distribution of secondary firms.

Chart 3: Breakdown of cell therapy firms by country[20]

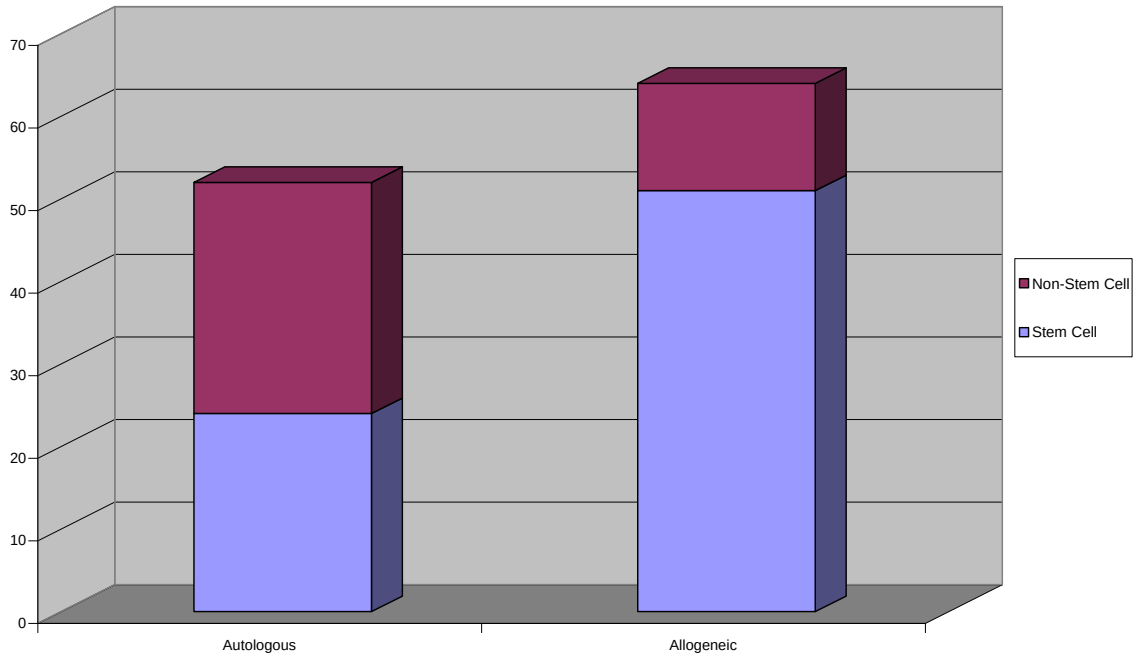


[20] Same as Data Chart 4.4

The countries with the most primary and secondary tissue engineering firms were the US with 107 (57%), the UK with 15 (8%), and Germany with 15 (8%) of the total number of companies (see Chart 3). Together these three countries accounted for nearly 75% of the global industry, reflecting a high level of geographical clustering. The most striking feature of a more detailed analysis of the geographical distribution of primary firms by sub-sector is the dominance of American firms (59 or 60%) and the small number of German firms (6 or 6%) working on stem cells. A similar picture is present for first generation (non-stem cell based) firms working on both allogeneic structural and metabolic products, where there are 10 US firms out of a total of 13. In contrast, there are similar numbers of US (9/27 – 33%) and German firms (7 or 26% of total) working on first generation autologous products.

It therefore appears that there is a marked international pattern of specialisation, with the US dominating second generation (stem cell) and first generation allogeneic technology, and Europe, especially Germany, playing a more important role in creating first generation autologous therapies. This has significant implications when placed in the context of the shift from first to second generation products and suggests further entrenchment of US dominance of the global cell therapy industry.

Chart 4: Primary cell therapy firms by autologous/ allogeneic distinction[21]



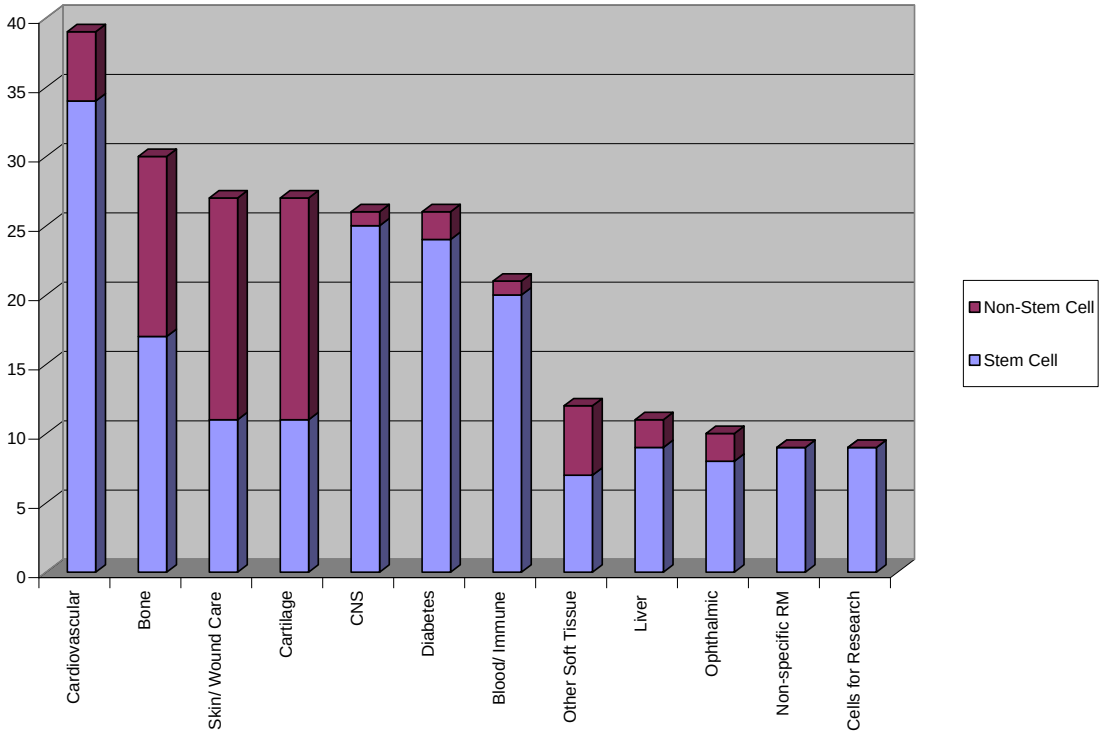
2.1.2 Firm technology and disease focus

A major division within the industry is between primary firms developing autologous and allogeneic products. Chart 4 provides an indication of the split within the industry and shows that slightly more firms are developing allogeneic than autologous products. However, there are marked differences between first generation and second generation products, with nearly twice as

[21] Same as Data Chart 4.6

many non-stem cell firms working on autologous products compared to stem cell companies[22]. In therefore appears that there is also a general shift from autologous to allogeneic products given the increasing dominance of stem cell technology.

Chart 5: Cell therapy firms by disease focus[23]



Data was also collected on the disease focus of firms (see Chart 5), which shows that the most popular category was cardiovascular diseases, a historically important target for tissue engineering. In addition, three of the four main diseases groups worked on were classical tissue engineering targets (bone, skin and cartilage), with metabolic disorders (diabetes and liver) also well represented. The only clinical areas that fell outside the broad field of tissue engineering (see definitions in Appendix 1) were CNS diseases and blood/ immune disorders (including some haematological cancers). The latter mainly relates to the application of haematopoietic and cord blood stem cells, an area with a long pedigree stretching back to the 1980s and given new commercial life by the growth in cord blood banking[24]. It therefore appears that the transition from tissue engineering to regenerative medicine that has been marked by the application of stem cell technology has not led to a dramatic shift in the diseases targeted by industry. With the notably exception of CNS disorders, these remain concentrated on well established clinical areas. However, in all disease areas outside classical tissue engineering (skin, bone, cartilage), stem cells now constitute the overwhelming mode of therapy.

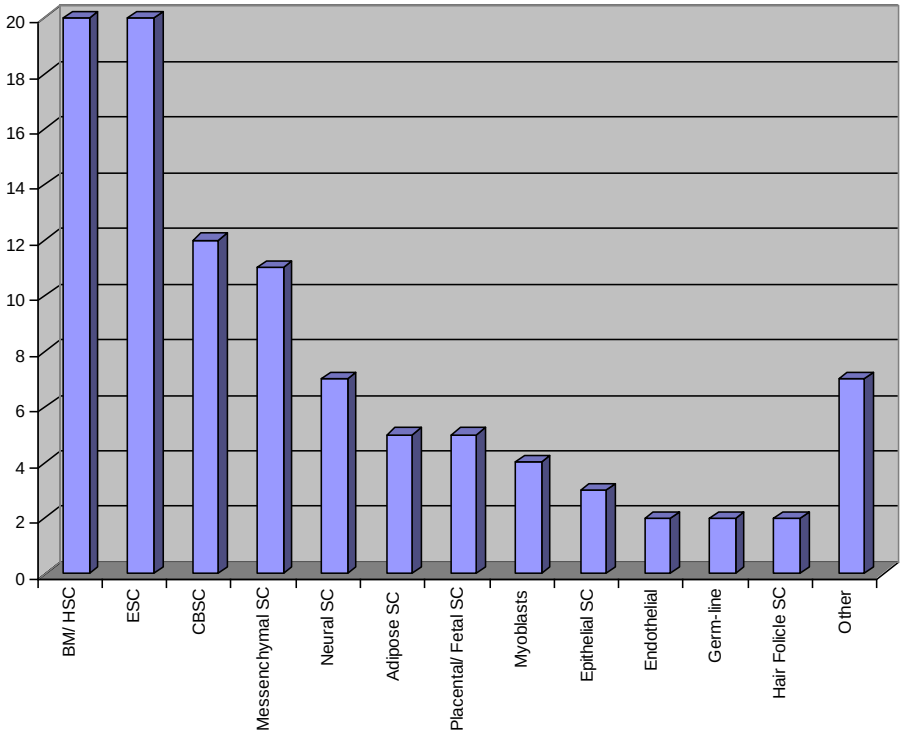
[22] Note that the numbers in the table do not add up to the total number of stem cell firms, as a small number work on both autologous and allogeneic, and others that work on enabling technology, such as cell lines and equipment rather than therapies . See Data Table 4.6 in data appendix for details.

[23] Same as Data Chart 4.5

[24] See Martin, PA., Coveney, C., Kraft, A., Brown, N and Bath, P (2006) The commercial development of stem cell technology: lessons from the past, strategies for the future. *Regenerative Medicine 1(6): 801-807;* Martin, P., Brown, N., and Turner, A. (2008) Capitalising hope: the commercial development of umbilical cord blood stem cell banking. *New Genetics and Society.* 27(2):127-143

The therapeutic focus of the industry is reflected in the main stem cell types being used by companies (see Chart 6). Whilst the high number of firms with an interest in hESCs is unsurprising, it is striking that adult haematopoietic and mesenchymal stem cells and cord blood stem cells are well represented. Taken as a whole, over 50 firms are working on different types of adult stem cells, compared to ~20 firms working on hESCs and less than 15 on cord blood stem cells. This highlights the fact that most commercial activity is in the adult stem cell area; this is even more marked when products in clinical development are examined (see below).

Chart 6: Primary stem cell firms by cell type[25]



3. Products, technology and sales

3.1 Cell therapy products

The cell therapy industry is unusual compared to other biotechnologies in the fact that a relatively large number of companies have products on the market (48 out of 187)[26]. However, this is very unequally distributed across different segments of the industry – 30 (60%) of the 49 secondary firms have launched products, whereas only 18 (13%) of the 138 primary firms had marketed products. Of this latter groups, 12 (45%) of the 27 autologous and four (40%) of the 10 allogeneic first generation structural firms had launched products, whereas no first generation metabolic firm and only two (2%) second generation stem cell firms (Osiris and Euroderm Biotech) had marketed products. This can largely be understood in terms of the time to market, with non-stem cell firms being generally founded significantly earlier that stem cell companies. The main focus of early firms working on tissue engineering was on autologous cell therapies for skin and cartilage

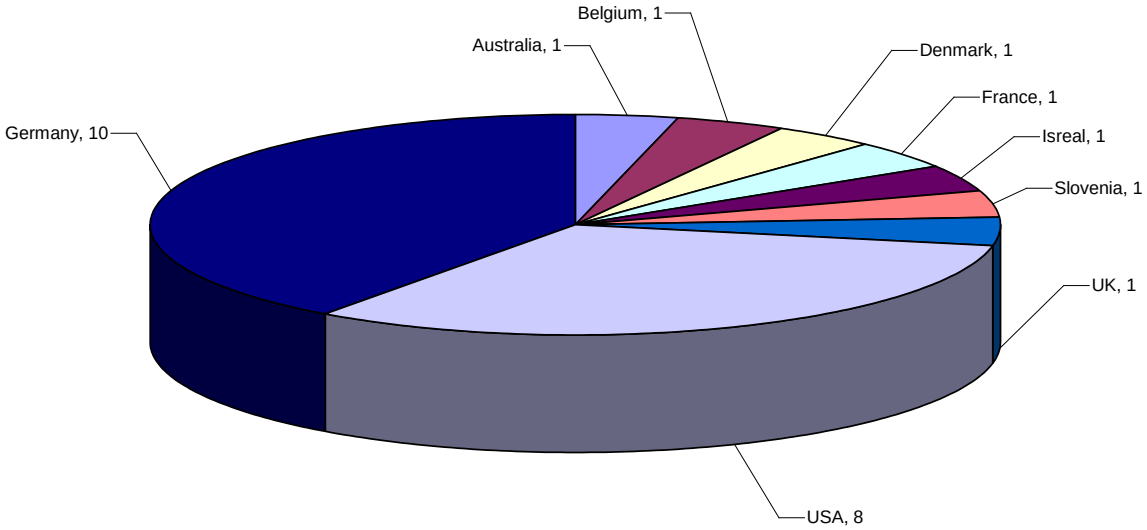
[25] Same as Data Chart 4.7

[26] For example, in the field of drug discovery and development, the majority of small firms only ever take products into early clinical development (Phase I or II) and only a handful ever sell drugs themselves. The product development process typically takes 10-15 years and most products are outlicensed to large companies at an early stage.

and the lack of any metabolic products reflects the great difficulties that have faced innovators trying to create substitutes for the liver and pancreas.

Nearly all firms with primary products on the market (15 out of 18) are small companies. The exceptions to this were Genzyme Biosurgery (a large US company established in 1981) Organogenesis (a medium sized US firm founded in 1986) and TiGenix (a medium sized Belgian firm founded in 2000). The majority of small enterprises with marketed primary products were created between 1993 and 2000, with most founded in the four years between 1997 and 2000. Only two firms created after 2000, Advanced Biohealing and Euroderm Biotech, had a product on the market. In the case of Advanced Biohealing their main product (Dermagraft) was acquired from Smith and Nephew and had been developed in the 1990s. This strongly suggests that the time required to get primary cell therapy products to market is roughly 5-10 years. This is significantly less than that needed for conventional drug therapies (10-15 years).

Chart 7: Breakdown of primary cell therapy products on market by geographical location[27]



The geographical location of the firms with products on the market is shown in Chart 7. A striking feature of the pattern of marketed products is that all allogeneic products, including the only stem cell therapy of this sort, were launched by US firms. In contrast, all but one of the 14 firms selling autologous products were based in Europe, with Genzyme Biosurgery being the only American company. Possible reasons for this are discussed below.

3.1.1 Products on the market

There were 97 cell-based products that had reached the global market place at the time of the survey – see Table 8 for summary. Of these, 22 were non-stem cell primary products and two second generation stem cell based primary product. In addition, there were 73 secondary products (matrices, gels, scaffolds bone substitutes etc).

[27] Same as Data Chart 2.7

Table 8: Summary of products on the market by type and application area

Application area	Primary – cell based		Secondary	TOTAL
	1st generation (non-stem cell)	2nd Generation (stem cell)	Matrices, scaffolds, gels	
Cartilage	13		2	15
Skin	7	1	20	28
Bone	1	1	32	34
Bone (dental)			11	11
Ophthalmic	1		3	4
Aesthetic			1	1
Other			4	4
TOTAL	**22**	**2**	**73**	**97**

With respect to product sales, it is notable that there is very little publicly available data on primary cell therapy products identified in the survey. Although publicly traded companies disclose their total sales, few of these were broken down by product type. Considerable effort was made to contact firms with products on the market to get sales figures, but many companies were very reluctant to disclose this information. Based on previous experience, it seems likely that the main reason for this was lack of product sales. The data that was available was gathered from a number of sources (company documents, and reports, statutory filings, direct contact with firms and previous studies) and has been compiled into a composite table (Table 2.3) giving sales for a number of products by different years. These data will be discussed in detail in the next section, which describes the main groups of cell therapy products. It is notable that significantly greater sales data was available for secondary products.

3.1.2 First generation (non-stem cell based) primary products

A) Autologous structural products (for cartilage, skin, bone etc)

By January 2009 there were 17 autologous cell therapies on the market – 13 for cartilage repair in joints (using chondrocytes), three for skin repair of chronic wounds and burns (using epidermal cells) and one bone graft (using cambrium cells). These were manufactured by 12 different companies, 11 of which were from Europe (seven from Germany, one from the UK), and only one from the USA (Genzyme Biosurgery).

The only available sales data on a number of autologous products (Bioseed, and Cartilink) was several years old, and each had rather small volumes. In this context, the lack of contemporary sales figures suggests that there has been little change in recent years. Three products (Epicel, Co.don Chondrotransplant and CaReS) had more up-to-date sales data, indicating a small market of roughly 50-200 hundred patients treated each year. In contrast, only one autologous product, Carticel, appeared to have significant sales each year.

Nearly all the autologous primary products targeting cartilage repair, including Co.don Chondrotransplant, CaReS and Carticel, were based on autologous chondrocyte transplantation (ACT) for traumatic knee joint injury. ACT is a labour intensive process that involves culturing cells for several weeks and is difficult to carry out at scale. In 2003 ITPS estimated that between 3-5,000 ACT procedures were undertaken each year, with global sales of these products being no more

than Euro 40 Million a year (~$53M)[28]. The majority of this was probably accounted for by Genzyme's Carticel, the first cell therapy product to gain FDA approval (in 1997), which had sales of $20M in 2002. However, the sales for Carticel were no more than $34M in 2007, with a total of 14,000 patients treated by March the same year, suggesting that there has not been a significant expansion of this market in the last five years. This is in contrast to previous market estimates that were in the range of several billion US$ a year[29].

The autologous skin products, targeting burns and chronic wounds, that were included in the survey had even smaller sales. Genzymes's Epicel for skin burns only appears to be used 50-70 times each year, whilst CellSpray had total sales of 1,500 units by 2003 and has recently been withdrawn from the market. No sales data was available for either MySkin or Epibase, but these are unlikely to be significant.

The problem of generating significant sales for autologous cell based primary products has led to the withdrawal of a number of these from the market in the past few years. For example, the skin products Epidex (produced by Modex) and CellActive Skin (IsoTis) and the cartilage products previously manufactured by IsoTis and Verigen, all appear to have stopped being available by 2008. At the time of writing, CellSpray and CellSpray XP had been recently taken off the market and their manufacturer, Clinical Cell Culture, was in financial difficulty.

In summary, it appears that overall sales of first generation products based on autologous cell therapies have been very disappointing, with low volumes and little growth. This has led to a number of commercial failures.

[28] Bock, A.K., Ibarreta, D., and Rodriguez-Cerezo, E. (2003) Human tissue-engineered products - Today's markets and future prospects. Seville; IPTS/ ESTO.
[29] Ibid.

Table 9: Sales and Application Data on Skin and Cartilage Products (2000-2008)[30]

Product	Company	2008	2007	2006	2005	2004	2003	2002	2001	2000
Skin										
Apligraf (Allogeneic)	Organogenesis		200,000 patient applications of Apligraf since 1998 ~$60M p.a.	~35,000 patients a year 170,000 since 1998a					20,000 patients since 1998[b]	€12M[c, d]
Dermagraft (Allogeneic)	Advanced BioHealing (Smith & Nephew)				Δ	€4.4M[c]	€11M			
Epicel	Genzyme		>1,000 treated since by Oct 07	700 treated in total since 1987					75 patients treated in total[c]	
Cartilage										
BioSeedC	Biotissue Technologies AG							€0.5M[c]		
Carticel	Genzyme	14,000 patients treated by Mar 08	$34.7M[e]	$28.0M	$27.4M			$20M	$18.4M	
Cartilink 1/ 2	Interface Biotech									4,000 patients treated 1995-2000[c]
Co.don Chondrotransplant	Co.don		1,350 patients treated since 1996						€1M[c] 350 transplanted	€0.6M[c] 210 transplanted
CaReS	Arthro Kinetics		2.7M	€1.3M. 1,000 patients treated since 2002						

All products are autologous unless otherwise stated. Data from company web sites and public documents unless otherwise stated. All sales in $,000 and worldwide unless otherwise
stated. a. Correspondence with Organogenesis; b. Pollack A. (2001) Another Stem Cell Debate; Ethics Aside, A Good Business Model Remains Elusive *New York Times* (28.07.2001) c. Hüsing B, Bührlen B; Gaisser S. (2003) *Human Tissue Engineered Products – Today's Markets and Future Prospects. Annex of the Final Report for*

[30] Same as Data Table 2.3

Research: Germany; d. Wood, F.M. Clinical Potential of autologous epithelial suspension. Wounds. Jan. 15(1): 16-22, 2003; e. Genzyme 2008 10-K (Exhibit 13 F-24). Figures are for all Genzyme Biosurgery's products in this area, including Carticel and Epicel; Δ Smith & Nephew sold Dermagraft (and Transcyte) to Advanced Biohealing, June 2006.

B) Allogeneic structural products (for cartilage, skin, bone etc)

Five allogeneic products were described in the survey; four for skin indications (chronic wounds and burns) and one for ophthalmic indications (repair of the cornea). These were manufactured by four firms, all of which were based in the USA.

In contrast to the situation with autologous products, there have been significant sales of some allogeneic first generation products. In particular, cell-based products that are designed for the active treatment of chronic skin wounds now have an established market. Organogenesis' Apligraf is currently used on ~35,000 patients a year and has been used on over 200,000 patients in total since 1998. Advanced Biohealing's Dermagraft is also claimed to have significant sales, although exact figures are not available.

However, in this context it is worth noting that both Apligraf and Dermagraft have had long and sometimes difficult histories. Organogenesis has previously had major financial difficulties and sales of Apligraf have only taken off in the last few years. Dermagraft was acquired by Advanced Biohealing from Smith and Nephew (who had previously acquired it from Advanced Tissue Sciences), and the peak sales of this product when it was marketed by Smith and Nephew appear to have been no more than Euro 11M a year. Advance Biohealing claim that they exceeded the previous maximum sales generated by Smith and Nephew in 2008.

In summary, allogeneic cell-based skin products finally appear to be generating commercially attractive sales. However, it is unclear if this success can be extended to other therapeutic areas, as issues of transplant rejection from unmatched tissue donors are not a major issue with skin repair, but may be far more important for other indications.

C) Metabolic products

There were no metabolic products on the market by September 2008. This reflects the long history of disappointment in attempting to develop cellular replacement therapies for liver and pancreas going back to the 1980s. Increasingly the focus has shifted to stem cell based therapy for these indications.

Table 10: Sales of Secondary Products[32]

Company	Products	2007 Sales
Bone		
Biomet	Calcibon, Calcibon, Granules, Colloss, Endobon, Collapat II	$ 22 M
IsoTis	Accell Range, DynaGraft II, OrthoBlast II, OsSatura	$ 40 M
Orthovita	Vitoss, Vitagel, Cortoss	$ 45 M
Osteotech	Grafton & Xpanse Range	$ 57 M
Regeneration Technologies	Sterling Biological Matrix & Conventional Allografts	$ 17 M
Skin		
Integra Life Sciences	Integra Dermal Regeneration Template	$166 M
Cook Biotech	SIS family of products	$240 M*
LifeCell	AlloDerm, Cymetra, Repliform, Graft Jacket	$132 M
Other Soft Tissue Repair		
Q-med	Duralane, Deflux, Zuidex	$ 37 M
TOTAL		$756 M

All data from company web sites and public documents, *except for SIS family which is from Lysaght 2008. All sales in $M and worldwide.

[32] Same as Data Table 2.5

3.1.3 Second generation (stem cell based) primary products

Only two second generation product based on stem cell technology had been launched at the time of the survey. The first was a 3D scaffold containing allogeneic mesenchymal stem cells for bone grafting, produced by the US firm NuVasive (developed by Osiris Therapeutics). This had 2006 sales of $8 million and was growing rapidly, with projected sales of $15M for 2008. The second was an autologous skin therapy for treating chronic wounds, for which no sales data was available. At present it would be premature to make a judgment about likely peak sales of these or other stem cell based therapies that might reach the market in the next few years.

It is also worth noting that a number of stem cell companies are generating revenue by selling stem cell lines as reagents. Data on this income is limited, but is summarised below in Table 11:

Table 11: Summary of reagent sales by selected stem cell companies

Lifeline Cell Technology	Reagents sales are "modest" - 10-K 2008
ReNeuron	£27,000 in 2008, generated from licensing stem cell lines for non-therapeutic uses (to Millipore) - 2008 annual report
Stem Cell Sciences	£121,000 for six months ended June 08 generated from stem cell services - 2008 interim report.
Vitro Diagnostics Inc	$9,000 in 2007, $1,600 in 2006 generated from cell lines and media for research uses - 2007 annual report.

3.1.4 Secondary products

There were 73 secondary products on the market at the time of the survey, which were manufactured by a range of firms distributed across several countries. In particular, US, German, and UK companies were all strongly represented. The largest group was for bone repair with 32 products and a further 11 were in the closely related dental market. These were nearly all bone substitute materials or temporary biodegradable scaffolds designed to promote bone healing for orthopaedic indications. The next largest group was focused on skin applications (20 products) and these were nearly all matrices and membranes used to support natural skin repair after surgery or injury. In addition there were three ophthalmic products, two cartilage products, one aesthetic product (for the treatment of wrinkles) and four other products for various soft tissue applications.

In contrast to the relatively poor sales for primary products, the sales of a number of secondary products are significant (see Table 10) totalling over $750M a year. Sales of the leading bone related secondary products were over $180M in 2007 and secondary skin products $300M. The most successful product in this category was Integra Dermal Regeneration Template.

4. Products in development

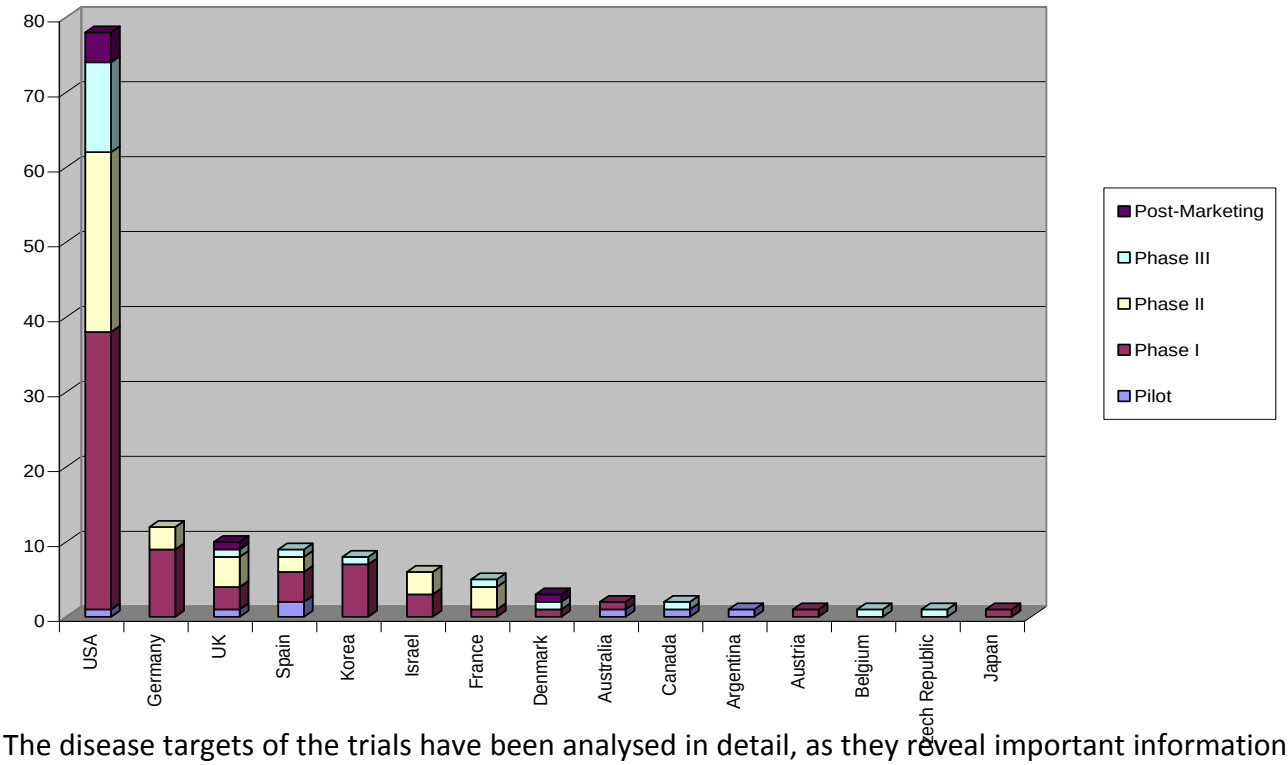
There were 120 primary products in clinical development at the time of the survey. As shown in Data Chart 3.10, 64 (53%) were either Pilots, Phase I or Phase I/II; 34 (28%) were in Phase II; and 22 (19%) were in Phase III. In addition, there were four post-marketing studies (Phase IV). There were also 16 secondary products in clinical development (2 of unknown status). Of the primary products in clinical development 42 (35%) were non-stem cell based: 21 (18%) were autologous non-stem cell structural products, 17 (14%) were allogeneic non-stem cell structural products and

4 (3%) were non-stem cell metabolic products. In addition, there were 78 (65%) stem cell based products in clinical development; of these 44 were autologous and 34 were allogeneic. So stem cell products now make up two-thirds of the industry pipeline.

This pattern broadly reflects the structure of the industry described above, but with autologous non-stem cell products slightly over-represented and stem cell therapies in general slightly under-represented. This is probably due to the relatively immaturity of the stem cell sector compared to classical tissue engineering. Within the stem cell sector, autologous trials were over-represented compared to the profile of firms, this probably reflects the lack of any clinical development of embryonic stem cells which are the focus of a significant number of companies[33].

The geographical distribution of trials is shown in Graph 12 and indicates that 78 (56%) were being conducted in the USA, 42 (30%) in the EU and 20 (14%) in the rest of the world. This is broadly in line with the geographical location of the industry as a whole.

Graph 12: Products in Clinical Development by Country[34]



The disease targets of the trials have been analysed in detail, as they reveal important information about the types of products that may reach the market (see Table 13). Trials of non-stem cell based autologous products are mainly targeting 'classical' indications for skin, bone and cartilage (15 out of 21 trials; one bone, four cartilage, and four skin/wound, six other soft tissue), with a number focusing on new indications (hair loss, wrinkles, facial rejuvenation, damage to the vocal cords). In addition, a minority targeted cardiovascular conditions (heart failure, coronary bypass, A-V shunt in dialysis). This marks a shift away from the disease indications that have been the historical focus of autologous cell therapy, with greater emphasis on cardiovascular and cosmetic applications.

[33] In January 2009 Geron received FDA approval for the first commercially sponsored trial using hESCs. However, it was not included in this study as it has not formally started and falls outside the study period.
[34] Same as Data Graph 3.5

Similarly, the majority (14 out of 17) of non-stem cell allogeneic trials are targeting 'classical' tissue engineering indications (12 skin and 2 cartilage), with only one trial using dermal fibroblasts for facial rejuvenation. The large number of skin trials is probably due to the commercial success of allogeneic products in this area. The other three allogeneic trials were for cardiovascular conditions. Furthermore, three of the non-stem cell metabolic trials were focussed on liver disease and one on diabetes. The focus of secondary trials is also similar, exclusively targeting classical tissue engineering applications in soft tissues, skin/ wounds, bone and cartilage (knee injuries, wounds, fistula, hernia, spinal injury, bone repair, breast reconstruction, varicose veins).

In contrast, the trials of stem cell based products are more mixed, and target both classical tissue engineering conditions (28/78: spinal fusion, knee injury, bone repair, dental bone grafts, osteoporosis, osteonecrosis, fistulas, Crohn's disease, diabetic foot ulcers, muscular dystrophy and sinus, breast and bladder reconstruction.) as well as a number of cardiovascular related conditions (30/78: limb ischemia, cardiovascular and coronary artery disease, Angina, myocardial infarction and heart failure) and other well established haematopoietic stem cell therapy indications (13/78: haematological malignancies, other cancers and GvHD). Only three stem cell trials targeted metabolic disorders and only one was for a CNS disorder (Neuronal Ceroid Lipofuscinosis). As with autologous first generation trials, the focus on cardiovascular disorders marks an important change in direction for the cell therapy industry with a move away from bone, skin and cartilage.

Table 13: Disease focus of all clinical trials

All trials	**Stem Cell**		**Non-Stem Cell**		**Secondary**	**Total**
	Auto	**Allo**	**Auto**	**Allo**		
Cardiovascular	22	8	6	3		**39**
Classical TE						
Cartilage	1	3	4	2	2	**12**
Bone	9	3	1		4	**17**
Skin/Wound Care	3	2	4	12	6	**27**
Other Soft Tissue	5	2	6		2	**15**
Metabolic						
Diabetes	1	2		1		**4**
Liver				3		**3**
Other						
CNS		1				**1**
Blood/Immune		4				**4**
Cancer	3	6				**9**
Other		3				**3**
TOTAL	**44**	**34**	**21**	**21**	**14**	**134**

In summary, the majority (71 trials = 53%) of clinical activity is still focused on classical tissue engineering applications in cartilage, bone, skin and other soft tissues, although there is an increasing emphasis on cosmetic indications. These are evenly split between stem cell and non-stem cell based products, reflecting the change in the industries underlying technology. Furthermore, the growing importance of cord blood stem cells has formed the basis for trials focused on haematological disorders and cancer; these are well established clinical targets and whilst representing a broadening of the industry's activity, this does not mark a significant new departure. In addition, a small number of trials (7 = 5%) continue the long-tradition of work on

metabolic disorders. However, the most important finding is the large amount of clinical activity that now takes place on cardiovascular disorders; the majority of which uses stem cells. This is a major shift and represents the most promising area for future commercial development. In contrast, it is surprising that there is only one trial for a CNS disorder, suggesting that it may be many years before cell therapy is used routinely in this area[35].

4.1 Industry pipeline

A detailed analysis was undertaken of the clinical trials broken down by phase of trial to make some assessment of the number and type of products most likely to reach the market in the next decade. Human Phase I trials are the first step in the clinical development process. They aim to test safety and clinical proof of principle in a small group of patients, with a success rate of 70-80%[36]. Phase II trials aim to establish the efficacy of a new intervention in a larger group of patients and have a success rate of 35-60% (Ibid.). Finally, Phase III trials aim to test both safety and efficacy in a large number of patients; success rates are between 25-60% (Ibid.). If a therapy is successful in Phase III this normally forms the basis for marketing approval. As described above, it appears that the clinical development process for cell based therapies takes 5-10 years, but it is unclear how many of the products already on the market have been through each of these stages of development.

The data on the 72 Phase I trials of cell based therapies (see Data Tables 3.7) shows that there are a significant number (26 = 36%) of cardiovascular products in development. These are mainly stem cell based (19/26) and autologous (17/26). In addition, there are still a large number of trials (34 = 47%) for classical tissue engineering, suggesting that there is still significant commercial interest in these therapeutic areas. These are split almost evenly between autologous and allogeneic. The profile of the 34 Phase II trials is similar (see Data Tables 3.8) with 11 (=32%) cardiovascular trials, but the great majority (9) are autologous. In addition, there were 16 (=47%) trials for classical tissue engineering indications. However, it was only in the 28 Phase III trials (see Data Tables 3.9) that this profile changed, with just two (7%) cardiovascular trials (both autologous) and 21 (75%) trials for classical indications. This data can be used to make a very broad estimate of the size and focus of the industry product pipeline over the next 10 years.

If the success rate of Phase I is assumed to be 70%, Phase II 50% and Phase III 40%[37], then roughly 10 products currently in Phase I, seven products in Phase II and 11 in Phase III might be expected to reach the market (i.e. a total of 28 products). Of these six might be for cardiovascular conditions, 16 for classical tissue engineering and six for other indications, mainly cancer. Whilst this is largely illustrative, it strongly suggests that therapies for the treatment of skin, bone and cartilage are most likely to reach the market in the medium term (1-5 years), with a number of cardiovascular products reaching the market in 5-10 years.

A summary of the products currently in Phase III is given in Table 14. This shows that of these 28 late-stage trials, only six were for non-classical indications (shown in bold). Of these, two were based on cord blood stem cells and were alternatives to established haematopoietic stem cell therapies, with limited commercial potential; three used bone marrow derived stem cells for major disease indications and one was targeting heart disease. These four products have considerable commercial potential. Furthermore, of the classical products in development, most are for indications already covered by products on the market, but two cosmetic products (shown in bold italics) are genuinely novel and if successful could also have large markets. It therefore

[35] Geron will start a trial of hESC therapy for spinal cord injury in the first half of 2009

[36] http://bmartinmd.com/2008/03/clinical-trial-phases-what-are.html

[37] These seem reasonably generous estimates based on the literature.

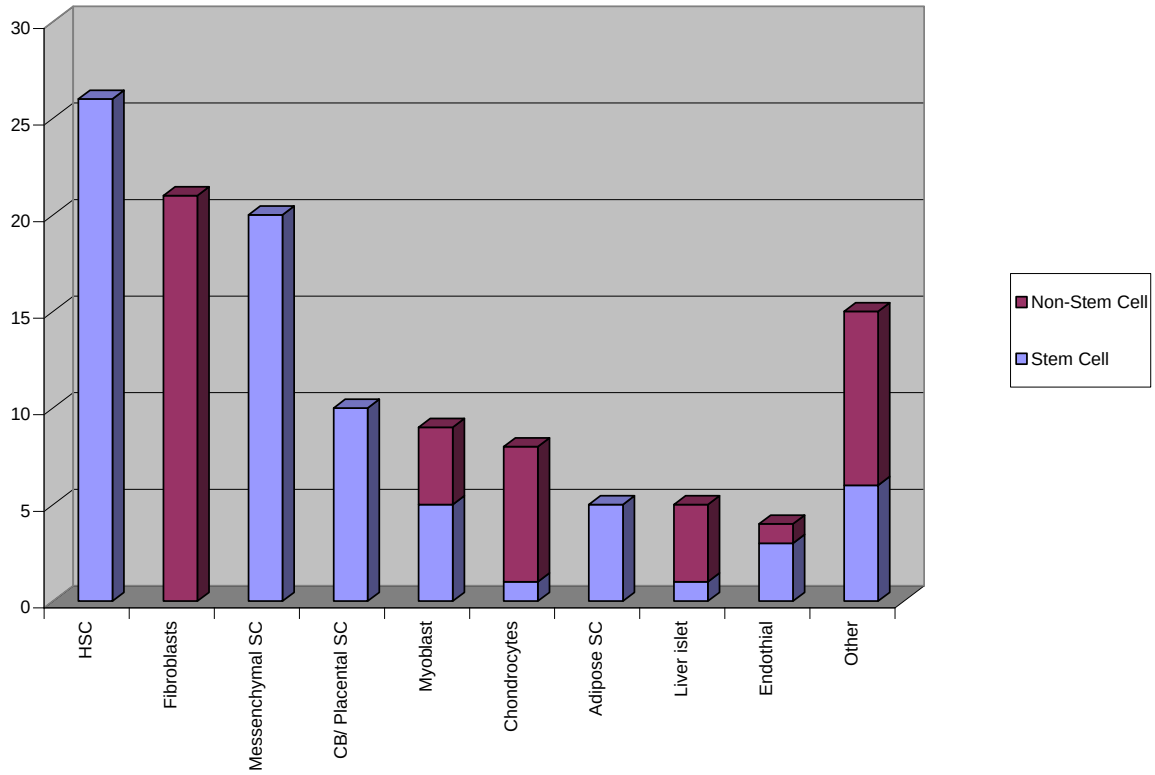
appears that the majority of products in late stage development aim to improve on established first generation products or expand the market for these. Only a minority are aimed at new indications with large potential markets.

Table 14: Summary of products in Phase II/III and Phase III trials

Company	Product	Disease Focus
Stem Cell (7)		
Aastrom	Autologous Tissue Repair Cells	Osteonecrosis (2 trials)
Aldagen	Allogeneic cord blood stem cells	**Rare inherited metabolic disorders**
Cellerix	Autologous adipose-derived stem cells	Wound care - Fistulas
Gamida	Allogeneic cord blood stem cells	**Hematologic malignancies**
Miltenyi Biotec	Autologous bone marrow derived SCs	**Coronary artery disease**
Osiris	Allogeneic messenchymal stem cells	**Crohn's disease**
Osiris	Allogeneic messenchymal stem cells	**GvHD (2 trials)**
Non-Stem Cell (13)		
Bioheart	Autologous myoblasts	**Cardiac heart failure**
Cellerix	Autologous keratinocytes	Epidermolysis Bullosa (skin wounds)
Forticell	Orcel Matrix – allogeneic	Skin ulcers
Genevrier	Dermagen Matrix - allogeneic	Skin ulcers
Genzyme	Autologous chondrocytes	Cartilage defects
Isolagen	Autologous Fibroblasts	***Acne scarring***
Isolagen	Autologous Fibroblasts	***Wrinkles***
Intercytex	Allogeneic Fibroblasts	Wound care
Organogenesis	Autologous palatal tissue	Oral tissue repair
Organogenesis	Apligraf - allogeneic	Epidermolysis Bullosa (skin wounds)
ReGen Biologics	Collagen meniscus implant - allogeneic	Knee injury
SEWON	Autologous osteoblasts	Bone fractures
TiGenix	Autologous Chondrocytes	Cartilage defects
Secondary (6)		
Biosyntec	BST-DermOn - Bioactive Dressing	Ulcers
Biosyntec	BST- CarGel	Knee injuries
Cook Biotech	Surgisis Repair Graft	Hernia
Integra	DuraGen Plus Matrix	Spinal injuries
LifeCell	LTM - LifeCell Tissue Matrix	Hernia
Orthovita	Cortoss Filler	Spinal fractures

Finally, data on the main cell types used in clinical trials was analysed (see Graph 15). This has a number of important features, most notably that no commercial trial based on human embryonic stem cells (hESCs) had commenced by the end of 2008, although Geron will start a trial of this sort in 2009 after gaining approval from the FDA This is surprising given the high level of investment and expectation that has led many to see the stem cell field as synonymous with hESCs. In addition, the great majority of trials are based on bone marrow or cord blood derived stem cells. This reflects the much longer history of work on HSCs and the recent growth of interest in cord blood as a source of potentially pluripotent stem cells.

Graph 15: Breakdown of Primary Products in Clinical Development by Cell Type[38]



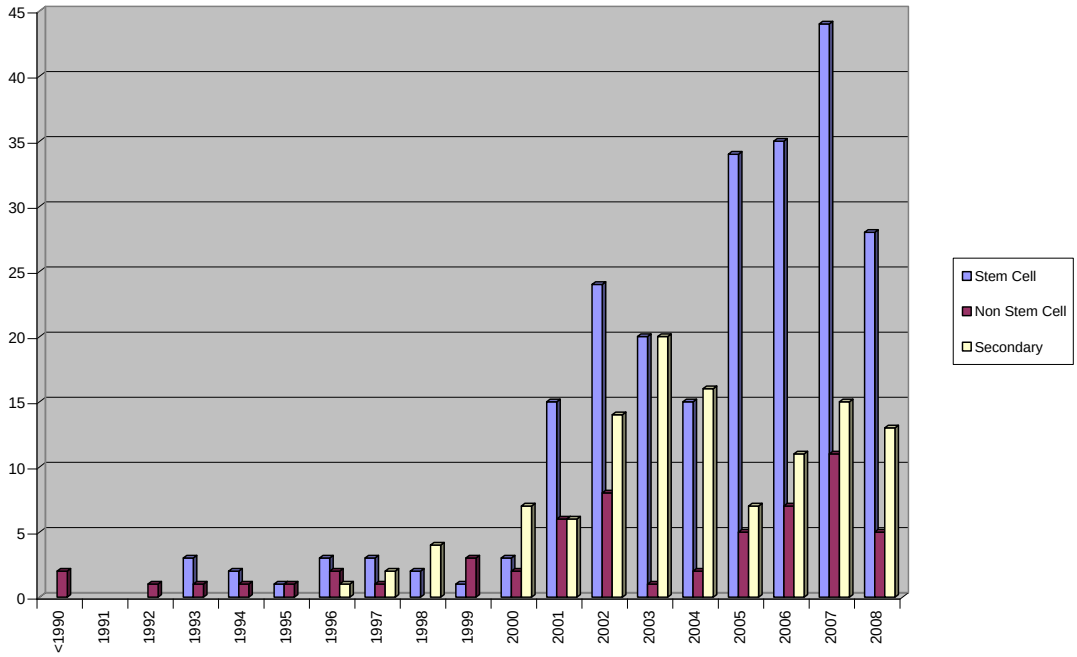
5. Industry collaboration

An important part of the survey was to examine the pattern of industry networking. This provides an index of corporate activity and, in particular, collaborations with large companies give smaller firms access to finance and the complementary assets required for late stage product development and marketing. In many ways alliances can be seen as forms of market transaction involving the exchange of knowledge and resources. There were a total of 411 cell therapy deals identified by the research between 1987 and the end of 2008. The great majority of these were formed after 2000, with only 10 formed before 1995. A total of 56 (14%) deals involved first generation primary product firms, 236 (57%) deals involving second generation stem cell firms and technology, and 119 (29%) were with secondary product companies (see Graph 16).

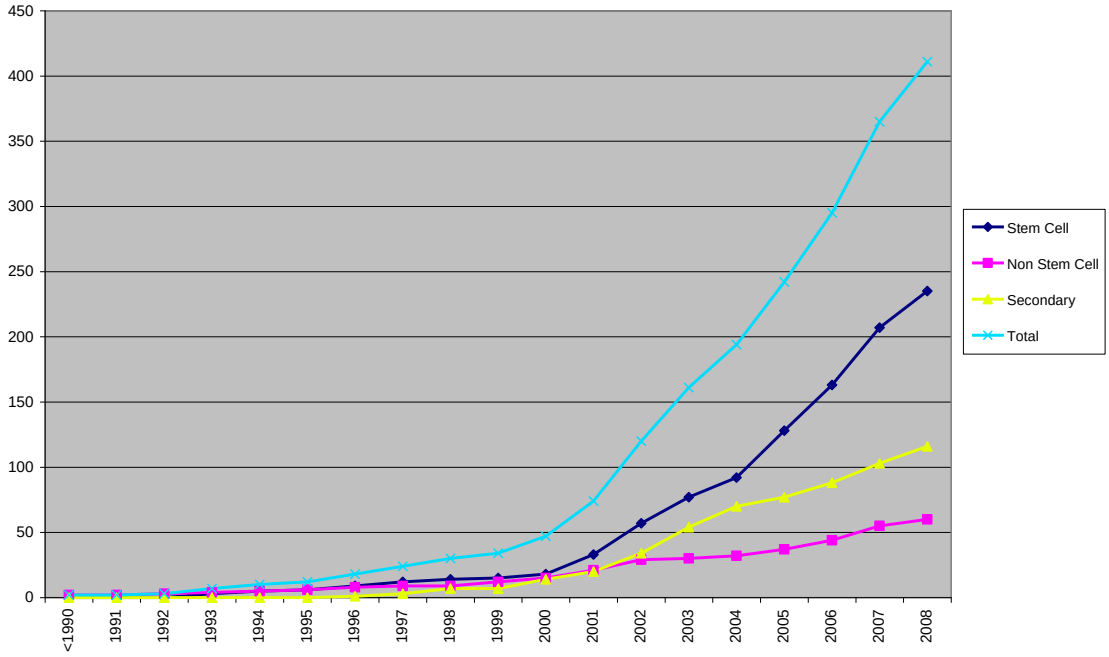
Most networking in the cell therapy sector was between primary companies or with firms outside of the cell therapy industry, and there were also a small number of alliances between primary and secondary firms. Several features mark the pattern of collaboration in this industry; firstly, there are significantly fewer alliances per firm/ year than in other parts of the biotechnology industry. This suggests a relative lack of commercial activity and investment, particularly from large companies (see below). Secondly, there are few sizeable alliances with large money transactions

[38] Same as Data Graph 3.15

***Graph 16: New company alliances by year*[39]**



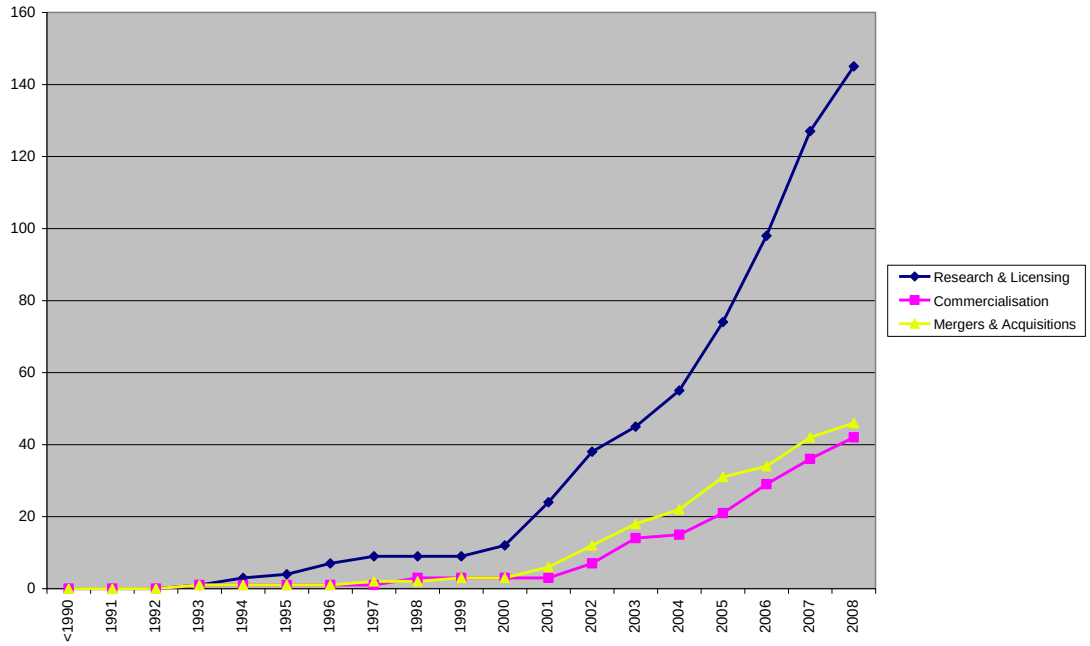
***Graph 17: Cumulative Growth of Cell Therapy Company Alliances*[40]**



The collaborations formed by companies were divided into three broad groups: a) research and licensing – concerned with the creation and exchange of new knowledge; b) commercialisation, including manufacturing, distribution, marketing etc; c) mergers and acquisitions.

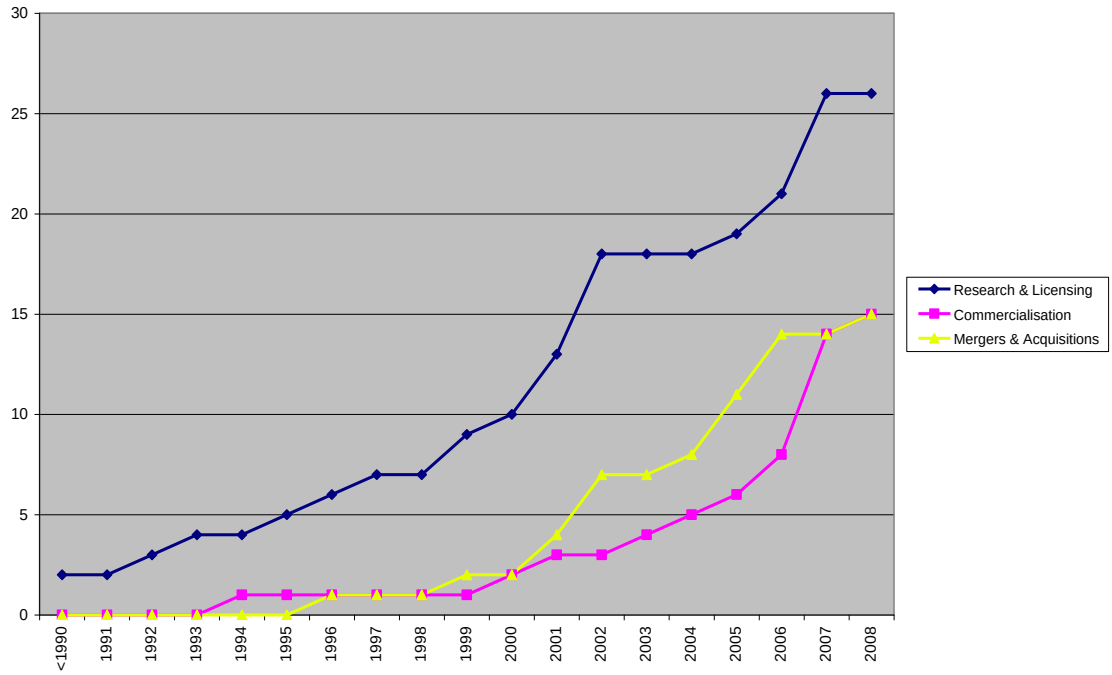
[39] Same as Data Graph 5.1
[40] Same as Data Graph 5.2

Graph 18: Alliance Focus of Stem Cell Companies (Cumulative[41])



When the pattern of collaborations is broken down by type of firms, some important divisions within the sector emerge. Graph 18 details the alliances formed by stem cell firms. It shows that the overwhelming focus of activity was on research and licensing. This is a feature of an early stage technology where the creation and exchange of new knowledge is the main activity.

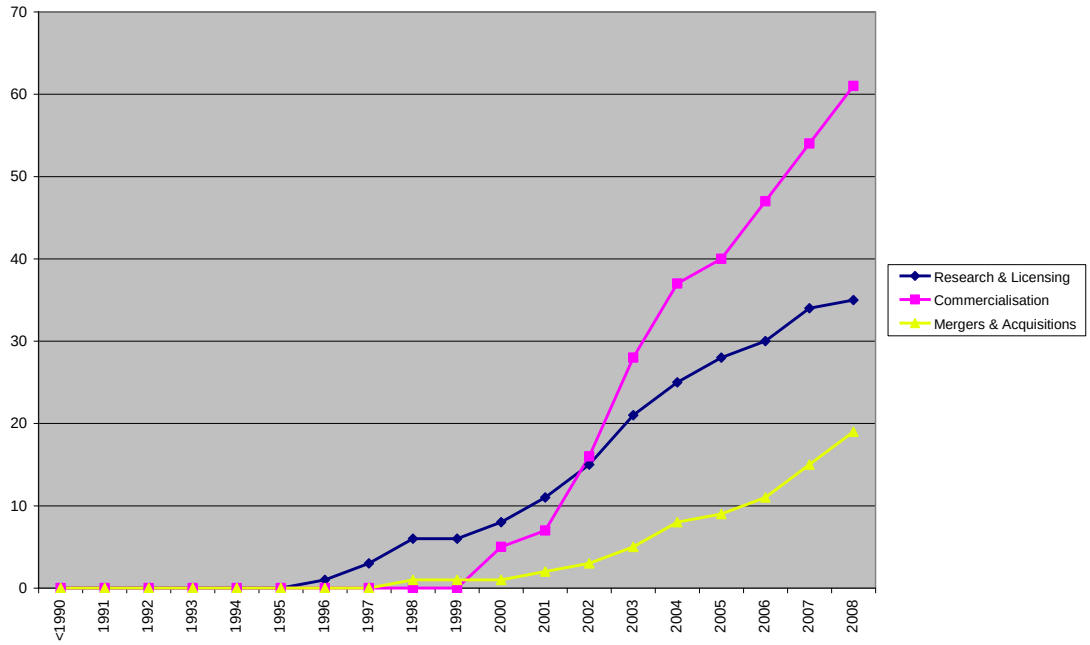
Graph 19: Alliance Focus of Non-Stem Cell Companies (Cumulative)[42]



[41] Same as Data Graph 5.3
[42] Same as Data Graph 5.4

In contrast, a much smaller number of collaborations were formed by non-stem cell companies (Graph 19); just over 25 research and licensing deals in total compared to over 140 in the stem cell field, with less than 10 since 2001. However, there was a much higher proportion of both commercialisation collaborations, reflecting the existence of marketed products, as well as mergers and acquisitions. The latter reflecting the problem of commercial sustainability.

Graph 20: Alliance Focus of Secondary Companies (Cumulative)[43]



The pattern with secondary companies (Graph 20) was different again, with relatively large numbers of commercialisation deals. This is probably a sign of the fact that these firms had a large number of commercially successful products that needed manufacturing and distributing. Their commercial sustainability best explains the relatively low level of mergers and acquisitions, although the low research and licensing intensity is harder to understand.

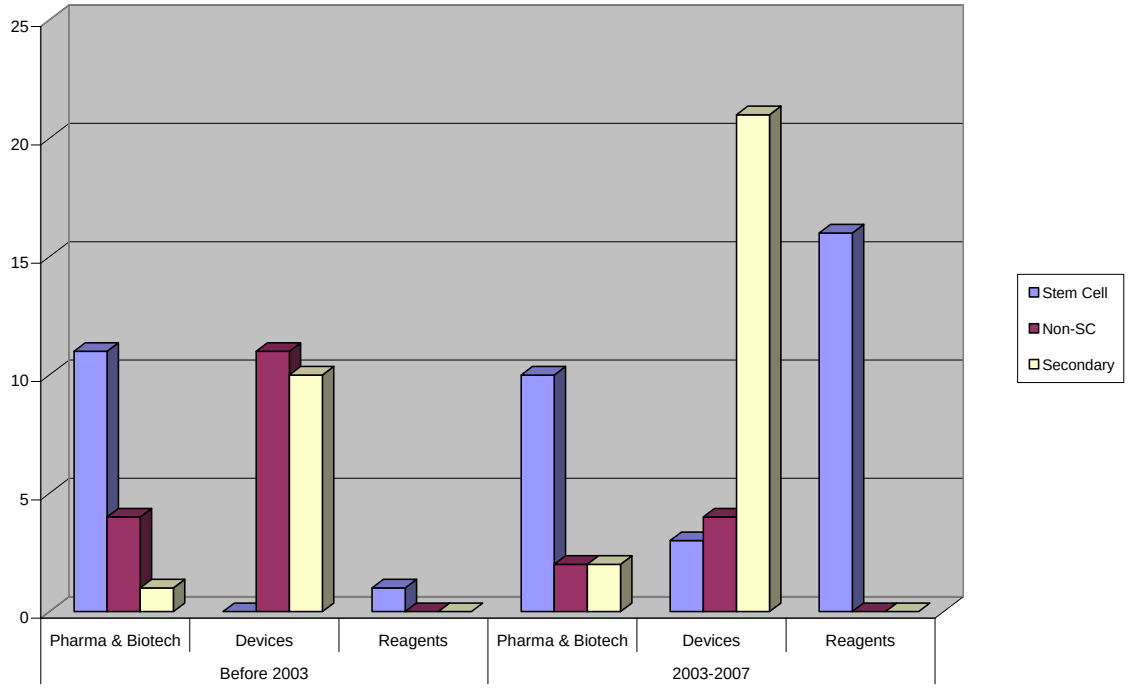
Perhaps the most important feature of the pattern of industrial collaborations is the lack of investment from large companies (see Data Table 5.6 for details). In total large firms formed 99 alliances in cell therapy since the mid-1980s. Of these, 33 (33%) were with pharmaceutical and biotechnology companies, with only six biotechnology companies (Genzyme, Teva, Centocor, Amgen, Serono and Genentech) and three pharmaceutical companies (Novartis, Pfizer and Novo Nordisk) making more than one deal in the whole industry since it was founded. This compares with genomics, where a single large pharmaceutical company may have formed 50-100 alliances since 1990[44]. Furthermore, only four of these companies (Genzyme, Novo Nordisk, Pfizer and Teva) have formed more than one alliance since 2003.

In addition, ten large device companies have invested in the sector forming a total of 49 (50%) collaborations, with Biomet, Smith & Nephew, Integra and Baxter being the most active. More recently, a number of major reagent and equipment firms have also invested in the stem cell

[43] Same as Data Graph 5.5
[44] Reference to genomics data

industry, creating 17 (17%) collaborations. Data Table 5.6 and Graph 21 show the changing pattern of alliances before and after 2003.

Graph 21: Number of large company alliances in different periods[45]



What is most striking about the trends in the industry as a whole are: a) the fairly stable level of pharma company investment in stem cells and a decline in non-stem cell technologies; b) the decline in the investment of device companies in non-stem cell technology and a dramatic increase in their investment in secondary products; and c) a massive growth of reagents companies investing in stem cell firms. This is further evidence of the move away from non-stem cell technologies. It also highlights the increased attractiveness of secondary companies for device manufacturers, which they have technological synergies with, as they start to generate greater sales. Almost all these deals are about commercialisation or acquisition. However, the pattern with stem cells firms is harder to interpret, with the main growth being the licensing of stem cell lines to reagents and equipment companies such as Invitrogen and Corning. Pharmaceutical and biotechnology companies appear to be watching and waiting as stem cell technology matures, although the recent announcement by Pfizer of major strategic investment in regenerative medicine and its formation of two collaboration in the second half of 2008 may mark an important turning point for the industry.

[45] Same as Data Graph 5.7

6. Summary and conclusions

This survey has presented a detailed analysis of the contemporary development of cell therapy. By paying attention to the technical aspects of the activities of firms it has allowed a much more nuanced analysis of the different technological options being developed and the short to medium term prospects for each of these. This is important, as it is likely that different forms of cell therapy will encounter different problems in the translational journey and policy will need to be sensitive to these if it is to be successful.

A number of important conclusions can be drawn from the data summarised above. Firstly, there have been a series of positive developments in the cell therapy sector.

6.1 A dynamic industry with increasing commercial success

There continues to be a high and increasing level of commercial activity in the cell therapy area, which has grown very significantly since 2002; it now involves nearly 200 firms developing primary or secondary cell therapies, plus another 180 banking cord blood. The rapid growth of cord banking is an important recent development and may allow greater integration in the future between the supply of cells and the development of new therapies. A small number of cell therapy companies are now well established and have been in existence for over 20 years. Furthermore, the industry is unusual in having a relatively large number of products on the market, many created by small firms. This success demonstrates that the cell therapy industry has been commercially focused, and the resources and time required to get a product to market have been significantly less than for conventional biopharmaceuticals.

In particular, there have been two main areas of success. Firstly, after many years of development and commercial set-backs, a number of non-stem cell allogeneic products for the treatment of skin disorders (most notably Apligraf) are now generating large sales and this area looks set to expand, with a number of new products in late stage clinical development. Furthermore, the growing importance of cosmetic indications for skin based cell therapies offers an important area of expansion for the industry. Secondly, firms working on secondary cell therapy products (gels, scaffolds and matrices) are starting to enjoy considerable commercial success, with a number generating large revenues. The total sales for the secondary sub-sector was over $750M in 2007 and appeared to be growing steadily. Secondary firms were also entering into commercial collaborations with larger device companies to help with manufacturing, distributions, and sales. There is every reason to believe that this success will continue. In addition, hope is also provided by the fact that the first commercial products based on stem cells are now starting to reach the market[46].

Previously we have estimated that the cord blood banking sector generates annual revenues of approximately $200M a year[47]. When this is combined with estimated sales for primary cell therapy products, which are in the range $50-100M a year, the total cell therapy industry currently has sales of over $1 billion a year[48].

[46] Although it should be remembered that a number of stem cell therapies developed with in the public sector are already in routine use, most notably HSCs for the treatment of cancer.

[47] Martin, P., Brown, N., and Turner, A. (2008) Capitalising hope: the commercial development of umbilical cord blood stem cell banking. *New Genetics and Society.* 27(2):127-143

[48] Lysaght et al (2008) estimated the market for tissue engineering, regenerative medicine and stem cell therapeutics to be ~$1.3 billion in 2007. The difference with the estimate given here is largely accounted for by their inclusion of

Going forwards there continues to be signs of success in developing proof of concept for stem cell based therapies, as demonstrated by the steady number of products reaching late stage clinical trials. There are a large number (120) of products in development – two thirds based on stem cells - including 22 products in Phase III. As a consequence, it is reasonable to expect a significant flow of new cell-based products reaching the market over the next decade.

6.2 The transition from tissue engineering to regenerative medicine

One of the most important features of the cell therapy sector over the last five years has been a major shift to stem cells as the core underlying technology of the industry. This confirms the findings of Lysaght's recent study[49] and gives empirical weight to Mason's[50] argument that there has been an important transition in the industry associated with the emergence of regenerative medicine. Stem cell firms now constitute over 70% of this sector and the long-term decline in non-stem cell technologies is demonstrated by the fact that no new firms of this sort have been created and only a handful of alliances formed since 2002. The shift to stem cells is also associated with a greater emphasis on allogeneic products in terms of company technology strategies, with a decline in the commercial interest in autologous therapies. However, this has yet to translate into the pattern of clinical trials, with the industry pipeline as a whole still weighted towards autologous products. This almost certainly reflects the lack of clinical development of human embryonic stem cell products.

The data on company strategies and clinical trials shows that adult stem cells are the dominant technology, with cord blood stem cells increasingly used. At present no commercially sponsored trial of hESCs has commenced, but one will start in early 2009. This strongly suggests the fact that their routine use in the clinic may be at least a decade away. However, it may be the public sector research system that takes the lead in the hESC area, as a number of other non-commercial trials are due to start in the next few years.

Unsurprisingly, given a development time lag of 5-10 years, all primary (cell based) and secondary products that have so far reached the market are for classical tissue engineering indications – skin, bone, cartilage and other soft tissue. Furthermore, despite the increasing dominance of stem cell technology, this has not resulted in a major change in the disease focus of the industry. The main therapeutic targets remain those associated with the tissue engineering tradition, although the growing interest in cardiovascular and cosmetic indications is an important shift. This is particularly true for non-stem cell therapies and secondary products. The main clinical areas that lie outside tissue engineering are those associated with the use of haematopoietic and cord blood stem cells (haematological diseases, including cancer) and the use of other stem cells for the treatment of CNS disorders. However, there has been very little clinical progress to date with the latter.

In terms of the industry pipeline, based on current clinical activity it can be estimated that roughly 30 new products may reach the market in the next 5-10 years. Of these, the majority are likely to be for classical tissue engineering indications, with a smaller number focused on cardiovascular conditions. Whilst it is possible that a stem cell based therapy for classical tissue engineering applications could bring about a breakthrough in sales, this seems unlikely for reasons discussed

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products based on bone morphogenic protein (BMP), which have considerable sales. Therapeutic proteins were explicitly excluded from this study.

[49] Lysaght,M.J., Jaklenec, A. and Deweerd, E. (2008) Great expectations: private sector activity in tissue engineering regenerative medicine, and stem cell therapeutics. *Tissue Engineering* 14(2):305-315

[50] Mason, C. (2007) Regenerative Medicine 2.0. *Regenerative medicine* 2(1):11-18

below. Only a minority (<10) of the products describe in the survey have large new potential markets beyond those already served by existing products and it is difficult to assess where a breakthrough product is most likely to arise.

6.3 Major challenges to the commercial development of cell therapies

Despite real signs of progress and a number of important longer-term shifts in its underlying focus, the cell therapy industry still faces a number of major challenges in translating the promise of scientific breakthroughs into clinically and commercially successful products. These can be described as follows:

a) Problems of commercial viability and sustainability
The cell therapy industry is marked by a very high level of company turnover, with the great majority of firms working in the sector in 2002 having ceased trading or changed focus. This points to major problems of sustainability, mainly caused by lack of finance from limited sales, where they exist, and the absence of investment from large pharmaceutical or device companies. In addition, there are significant problems with sustaining company growth where firms manage to survive. One consequence of both these factors is a sector dominated by small young companies, which currently lack the resources to easily bring products successfully to market. A number of stem cell companies are attempting to generate revenues from selling cell lines as reagents, and these have resulted in a growing number of collaborations with large reagent and equipment companies. So far these have only generated very modest returns.

b) Poor sales and limited prospects for some forms of cell therapy
One of the most important factors influencing the structure of the sector is the lack of product sales, despite a significant number of therapies reaching the market. This is particularly true for primary, cell-based products, although this varies by technological option:

Non stem cell autologous products – have had very limited sales despite a large number of products reaching the market, and a high proportion of these have been withdrawn, causing a significant number of companies to cease trading. Despite high expectations for indications such as autologous chondrocyte transplantation, the commercial potential of this area has not been realised and sales are probably an order of magnitude short of what would be required to have a sustainable sub-sector. The main reasons for this appears to be a lack of clinical uptake/ demand (see discussion below) and high manufacturing costs. It therefore seems that in future this type of therapy will be developed either by the public sector or not at all.

Non stem cell allogeneic products – despite allogeneic skin products starting to enjoy important commercial success, it seems that further expansion of this type of therapy into other clinical areas may prove slow, as major problems with transplant rejection have still to be overcome.

Stem cell based products – the launch of the first commercial stem cell products offers real hope for the future. However, early products on the market and in development appear to have a very similar clinical profile to existing non-stem cell based products and target similar clinical indications. A key question is whether the move to stem cells is going to help overcome the problems that existing products have faced, such as lack of clinical demand, high manufacturing costs etc? It is premature to make a clear judgement on this, but it seems unlikely in the short term at least, as these problems are structural in nature and are unlikely to be solved by a change in underlying technology (see discussion of clinical demand and manufacturing below).

It is also worth noting the lack of any real progress in the metabolic area (e.g. diabetes and liver disease). There are few dedicated firms, only a small number of clinical trials and a long history of disappointment stretching back 30 years. In the long term this may be one of the most important areas of cell therapy, but considerable scientific and technical progress will be required to enable this. For the foreseeable future this is likely to be led by the public sector.
In contrast, as mentioned above, the prospects for secondary products (gels, matrices and scaffolds) appear good, but there are some signs of market saturation in terms of the sheer number of very similar products that have been launched and the limited number of clinical trials outside established indications and disease areas.

c) Lack of investment from large companies
Industry collaboration, especially, with large companies, is one of the main ways in which small biotechnology firms are financed and get access to the complementary assets (expertise in late stage product development, regulatory affairs, sales and marketing) required to bring products successfully to market. The cell therapy industry has a relatively low level of networking compared to other parts of the biotechnology industry. In particular, there have been very few in the non-stem area, but more involving stem cells and secondary firms This points to a general lack of commercial activity, partly as a result of the very high level of company turn-over, and lack of financially important products. Most activity in the stem cells area was research and licensing, reflecting its early stage of development, whereas partnering was focused on manufacturing and distribution around established products in relation to secondary firms.

The most important feature of the pattern of collaborations was the lack of investment in cell therapy by large companies. Over the last decade major pharmaceutical companies have invested at a low background rate, with this only starting to change in the second half of 2008 with increasing signs of commitment to the technology (a total of five alliances in 2008 compared to five in the previous three years). In contrast, there has been growing investment from large device companies in secondary firms, reflecting the move to commercial viability. There has also been significant collaboration between stem cell and reagents companies, although these have not generated significant revenues to date.

There are probably three main reasons for the lack of investment by large pharmaceutical companies in cell therapy. Firstly, whilst there is a long-standing and important biologicals tradition in the pharmaceutical industry (e.g. vaccines, therapeutic proteins and more recently, monoclonal antibodies) the dominant technology and product paradigm is based on the mass production of highly standardised small molecule drugs using organic chemistry. Cell therapy is, in contrast, radically different, being based on much more personalised products for smaller niche markets that are difficult to manufacture and involve living cells. These differences pose multiple challenges for integration into existing businesses. Secondly, there was an important wave of large pharmaceutical company investment in the commercial development of haematopoietic stem cells in the 1990s (see Martin *et al*, 2006[51] for details of this). However, this proved to be disappointing largely due to lack of scientific and technical progress, and large companies disinvested by the late 1990s. Thirdly, the slow pace of adoption of marketed cell therapy products and the lack of significant sales for primary products has not proved sufficiently attractive to an industry based on blockbuster products with sales of over $1 billion a year. Once it can be demonstrated that a cell-based therapy has a real market measured in hundreds of millions of dollars a year, this situation is likely to change.

[51] Martin, PA., Coveney, C., Kraft, A., Brown, N and Bath, P (2006) The commercial development of stem cell technology: lessons from the past, strategies for the future. *Regenerative Medicine 1(6): 801-807*

d) The relative position of the EU and UK

It is clear from both the data on the total number of firms and the creation of new firms that the EU is lagging significantly behind the US. However, the industry is highly concentrated and whilst the US dominates overall, the UK and Germany have a significant number of cell therapy firms. Of more concern is the fact that the US has a much greater number working on stem cells and first generation allogeneic products compared to Europe; with the latter specialising in autologous therapies. Given the current lack of significant commercial potential in autologous therapies, this casts some doubt over the future of the European industry.

6.4 Why the lack of clinical demand/ uptake?

Perhaps the most important challenge facing the stem cell industry is establishing a significant market for its products based on clinical demand. Doctors and health services have been offered a range of cell therapy products over the last decade, but they have not generally used them in sufficient quantity to provide a commercially attractive return. In another part of this research project we have interviewed a range of academics, company managers and clinicians to try to establish the reasons for this limited demand. The results of this study have been published separately (Barriers Report)[52] and provide a detailed exploration of the key factors influencing clinical uptake. These can be summarised as follows:

Problems establishing clinical utility in practice – the main reason for lack of uptake is that many cell therapy products have limited or unknown clinical utility in practice. For a clinician to use a cell therapy routinely it needs to meet a number of criteria, including be shown to be efficacious, easy to use, fit into established services and patterns of care, be cost-effective and better than currently available alternatives;

Poor product specification – one of the reasons for lack of utility is due to poor product specification and design. A number of first generation cell therapy products were developed without significant input from clinical end-users. As a consequence, they were difficult to integrate into routine practice. Other related issues include problems with the storage and short shelf-life of autologous products and the long lead time in clinicians receiving products;

High cost of therapy – cell based products are often more expensive than existing alternatives due to high cost of manufacturing and distribution;

Lack of a clinical evidence base – one of the most important factor determining clinical uptake is the amount of evidence demonstrating cost-effectiveness and positive clinical outcomes. Whilst this is slowly being accumulated, a lack of evidence has made it hard to overcome other factors. A major constraint on establishing the required evidence base is a lack of private or public funding for appropriate studies. Companies have little incentive to fund research of this sort if sales are only likely to be modest.

6.5 Other important issues

Although not covered in this study, a series of other issues affecting commercialisation were highlighted in the interviews with company managers, academics and clinicians (see Barriers Report for full details). These included:

[52] Rowley, E. and Martin, P (2009) Barriers to The Commercialisation and Utilisation of Regenerative Medicine In The UK. Nottingham; Institute for Science and Society.

Regulatory uncertainty – this made it difficult to attract investment and increasing the risk and cost of the product approval process;

Difficulties with reimbursement – this was particularly seen to be an issue in public health systems, such as the NHS, which have historically been slow adopters of novel biotechnologies. The need to develop a suitable evidence base was seen to be the best way of addressing this problem;

Manufacturing costs – at present most cell therapies are manufactured in a labour intensive fashion that is at best only partially automated. The costs of producing cell-based products, particularly autologous therapies, are therefore high and this is a significant factor influencing cost-effectiveness compared to alternative interventions.

6.6 Conclusion – realising the potential of cell therapy

This study has highlighted a number of major findings, which can be summarised as follows:

- Cell therapy is now established as an important branch of medicine;
- The cell therapy industry is dynamic and starting to enjoy considerable commercial success with annual sales of over $1 billion;
- The medium term prospects are positive with a large number of products in clinical development which have real long-term potential for public health benefit;
- The sector has undergone an important transition in the last 5-7 years, moving from tissue engineering targeting skin, cartilage and bone to regenerative medicine based on a wide range of stem cell therapies;
- However, the shift to stem cells has yet to translate into new products that lie outside established markets. This is likely to happen in the next 5-10 years, with a series of therapies for cardiovascular conditions, cancer and cosmetic indications in the pipeline;
- Despite this considerable progress, the industry still faces a number of important challenges, including: problems of commercial viability and company growth, poor sales and lack of investment from large companies;
- The key issue determining poor sales is the lack of clinical uptake of cell therapy products and this is mainly related to difficulties establishing clinical utility and cost-effectiveness. Creating an appropriate evidence base is the key to addressing this deficit.

The risk of market failure

These findings point to a significant risk of market failure for a number of types of cell therapy. Whilst the sales of non-stem cell allogeneic and secondary therapies appear sufficient to sustain companies working in these areas, this is not the case for non-stem cell autologous and most stem cell based therapies. At present, firms working on these therapies have few sales and little funding from large companies and will face major problems surviving the downturn in biotech financing associated with the credit crunch. The historic high level of company failure in this sector looks set to continue, but with far fewer new firms taking their place. Unless this situation changes, the industry will contract and the progress needed to develop important cell therapies will be adversely affected. There are some signs that large pharmaceutical companies are starting to invest more heavily in this area, but it is too early to tell if this will be sufficient to meet the funding needs of the sector.

Another key conclusion is that the obstacles facing the industry are largely structural rather than technical. Although effective therapies that demonstrate positive health outcomes need to be

developed, the key barriers facing firms relate to important aspects of the translation process. These include establishing closer collaboration with clinical end-users, the funding of clinical studies, greater regulatory certainty and clearer reimbursement policies. In addition, there is the need to develop enabling technologies that could lower manufacturing costs. None of the barriers have changed as a result of the shift to stem cell as the underlying technology in the sector, but each can be addressed by public policy.

A comprehensive package of policies therefore needs to be developed that address the risk of market failure and the structural barriers facing firms. A series of recommendations to achieve this are outlined in the companion report to this study (the Barriers Report), some of which are also highlighted here, along with recommendations specifically aimed at the problems faced by industry.

Addressing the risk of market failure

The very serious risk of market failure described above for some groups of firms developing particular cell therapies can only be addressed by public sector intervention. This might be achieved through the creation of public-private partnerships (PPPs) in which the costs and risks of development are shared in return for part of the profits/ royalties or lower cost access to products when they reach the market. PPPs have already being created in Scotland to facilitate the production of hESCs and should be extended to other areas.

> ***Recommendation 1*: New forms of public-private partnerships should be established in the field of autologous and adult stem cell based therapies that are at risk of market failure, with the aim of progressing these technologies towards clinical adoption.**

Supporting SMEs

In the current financial climate small innovative firms that are leading the development of cell therapy are highly vulnerable due to the lack of financing and credit. The UK has an internationally competitive position in this area, but this could be lost if a significant number of small firms ceased trading or were acquired by foreign companies. It is therefore essential to maintain the existing industrial base.

> ***Recommendation 2:* Government should intervene to co-ordinate an emergency package of financial support for UK cell therapy firms in financial difficulty, including affordable credit, tax breaks and greater public support for R&D costs.**

Bridging the development funding gap

The Barriers Report highlights the difficulties firms have in gaining adequate funding in order to progress the clinical development of new products. In particular; the current funding model for the translation of basic regenerative medicine science is not operating efficiently. There is a gap in eligibility for funding between academic grants and being able to 'tap the market' or attract VC investment. Greater levels of research funding are therefore required for translational work that will help create a clinical evidence base related to safety, efficacy, utility and cost-effectiveness, and for the manufacturing of products.

> ***Recommendation 3:* Greater public funding should be made available to support the clinical and product development stages of the translation process. To achieve this, novel**

forms of public-private partnership and risk/ benefit sharing mechanisms should be experimented with.

Building manufacturing capabilities

A major area of concern, which has been fully explored in other parts of the remedi programme, is the need to develop improved methods to manufacture stem cell therapies. Currently, most products are developed using low throughput manufacturing techniques due to the very high cost of scale production. Furthermore, there is a lack of either private or public funding to develop new platform technologies that would allow low cost manufacturing. Until this is possible regenerative medicine products are likely to remain expensive to produce for both clinical testing and patient care. This will significantly hamper commercialisation. At present there are few signs that the small firms that dominate the cell therapy industry have the resources to do this and this represents another aspect of market failure.

***Recommendation 4*: A new publicly funded national bioprocessing centre or capability should be established that aims to create a series of technology platforms for the low cost scale manufacturing of cell and tissue therapies. Such an initiative should involve close collaboration between industry, basic scientists, engineers and clinicians.**

Reducing regulatory uncertainty

One significant barrier to the commercialisation of regenerative medicine and the lack of products on the market is the uncertain regulatory environment that has been charged with sanctioning products as efficacious and safe for use. Until recently there was no centralised European system for the regulation of regenerative therapies, with manufacturers facing disparities in the evidence required and approval process in different countries. This situation was unsurprisingly viewed unfavourably, and deemed prohibitively expensive to operate in. This situation has improved with the adoption of the Advanced Therapeutic Medicinal Products (ATMP) regulations governing tissue engineered and cell therapy products in the European Union and this may enable costs and lead times involved in bringing a product to market to be reduced. However, there are still concerns that companies may be penalised for being 'ground-breakers' and among the first to work within the new regulatory regime, and that applications may be delayed whilst regulators got up to speed or they may be asked to provide further data, all of which would have a costly impact. In this respect, a major issue is the relatively low level of staff and resourcing available within regulatory agencies to support product approval.

***Recommendation 5:* Regulatory agencies, including EMEA and the MHRA, should give regenerative medicine a much higher priority, with improved resourcing and clear points of contact in this area to help streamline the workings on the ATMP regulations and ensure reduced cost of compliance and time to market.**

Creating realistic expectations

Finally, it is important that a more realistic set of expectations about the level of resourcing and length of time needed to realise the potential of cell therapy is adopted. The history of the field is one of incremental change and the slow build-up of the social, technical and clinical infrastructure required to develop products that offer significant improvement in patient care. As with many other novel biotechnologies, long-term success will depend on the public sector playing a major role in supporting private companies through the difficult early stages of the translation process.

Recommendation 6: **The scientific, clinical, industrial, media and policy communities involved in regenerative medicine need to take care to ensure they present more realistic expectations about the future prospects of the field. This is essential to maintain public support.**