

STEM CELL patent trends

Stem cell therapies hold great promise for future medical treatment, but in order to realise their potential there must be sufficient investment, private or public, in the technology. A key aspect of obtaining investment in any biotechnology field is the availability of patent protection; conversely, the filing patterns of those companies and other entities which are filing patent applications can give valuable information on the state of the industry.

**By Dr Gareth
Williams**

One significant aspect of stem cell technologies is the ethical controversy surrounding their use. In particular, the use and derivation of human embryonic stem cells (hES cells) provokes considerable ethical debate over the technology. This ethical debate has spilled over into the legal arena, as some jurisdictions have limited the scope of available patent protection for hES-related inventions. Furthermore, although the ethical issues are directed toward the use and derivation of hES cells, commercially there may be some impact on investment and take up of other stem cell technologies, such as that using adult stem cells.

The current legal position on patentability of hES-related inventions differs around the world. The two main jurisdictions are the United States and Europe. The position in the United States is relatively simple: the US Patent and Trademark Office (USPTO) has a current policy against granting patents to inventions which would cover human embryos or human/non-human chimeric embryos. The patenting of humans *per se* is also not permitted. Beyond this, however, “anything under the sun that is made by man” may be patented, subject of course to the other legal require-

ments of the US patent system, such as novelty, non-obviousness and utility. For example, US Patent 6,200,806, issued to Thomson, includes the following claim:

“A purified preparation of pluripotent human embryonic stem cells which (i) will proliferate in an *in vitro* culture for over one year, (ii) maintains a karyotype in which the chromosomes are euploid and not altered through prolonged culture, (iii) maintains the potential to differentiate to derivatives of endoderm, mesoderm, and ectoderm tissues throughout the culture, and (iv) is inhibited from differentiation when cultured on a fibroblast feeder layer.”

Note that this claim specifically encompasses any human ES cells having the appropriate characteristics. The same patent also includes claims to methods of obtaining such cells, based on deriving the cells from a human blastocyst.

Similarly, US patents have been granted to Thomson for primate ES cells, and to human ES cells which are not limited to pluripotent cells. Other inventors have obtained patents to various multipotent stem cell lines; to methods of deriving, maintaining, or differentiating stem cells; or to therapeutic methods involving such stem cells.

That this last question may be significant is shown by the recent grant of a European patent (EP1040185, to Brüstle) covering an ES cell composition; the claims as granted include a proviso that the ES cells are not obtained by a method which involves the destruction of human embryos. Since the examiner on this case apparently felt no need to delay issuance pending the Enlarged Board decision, this suggests that it is at least possible that hES cell patents will eventually be held patentable in Europe in some form.

Clarity in the legal position is not helped by the interaction between the EPO and the national patent offices. The various EU countries were required to implement the Biotech Directive in their national law, but there is a wide divergence in how this has been done. For example, although UK law includes the same wording as the law governing the EPO, the UK patent office at the moment interprets the law differently, considering that pluripotent hES cells are patentable under the Directive; there is no legal requirement for the UK Patent Office to fall into line with the EPO, so there may well be a lack of clarity for some time to come. Another example comes from Italy, where the Biotech Directive has been implemented, but with the relevant national law saying not only that uses of human embryos are unpatentable, but also that uses of hES cells or processes for obtaining such cells are considered unpatentable.

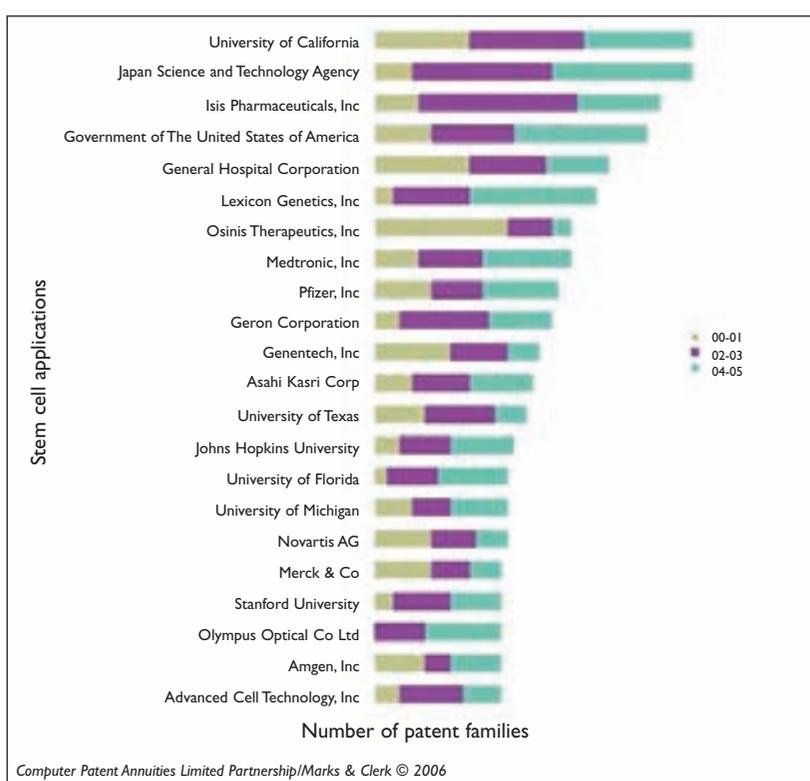
It is clear that there is great uncertainty across Europe as to what is patentable, and this uncertainty can be expected to have an effect on industry investment. What is needed is clarity in the law, regardless of whether the final ruling is for or against patenting of hES cells.

These uncertainties can be expected to impact on future patent filing strategies; however, the current filing data is a good indicator of growth and innovation in the industry. In order to investigate this, we conducted a search for stem cell related patents and published applications from the period 2000 to 2005. Around 300-400 granted patents were issued in each of these years, with the number steadily increasing each year. The search covered patents worldwide, although the results made it immediately apparent that the USPTO grants by far the greatest number of patents in this area each year: generally around 85% of stem cell patents are granted by the USPTO, with the remaining patents being split between the EPO, Australia and the rest of the world. The dominance of US patents in this field may reflect a number of factors; primarily the US is the largest potential market for the technology, so companies are likely to file US patents in preference

to less important markets. The grant figures may also reflect in part the relative speed with which US patents are examined and granted, particularly when compared with the EPO. This view is supported by the number of patent applications published each year; the total for this is consistently around three times the number of granted patents for each year, although the US represents only around a third of this number. Thus, significant numbers of patent applications are being published outside the US which have not yet matured into granted patents; partly because the scope of available protection is narrower outside the US, and partly due to longer prosecution times. This delay in prosecution can be advantageous to the industry, as it allows more time to develop the product before the final scope of the patent is fixed.

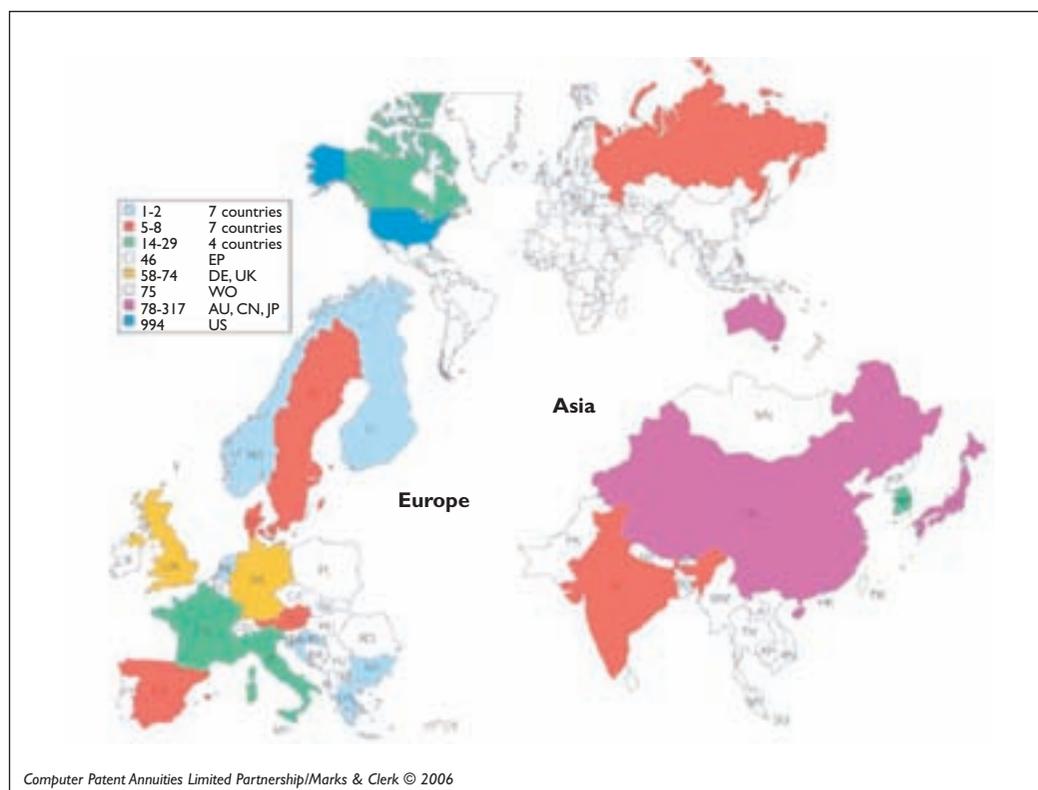
In addition to the numbers of granted patents, it is instructive to look at the number and distribution of priority filings. Typically an applicant will file a first application in one country (often, but not always, their home country), and only later will file elsewhere based on the initial filing. Thus the priority data can give an indication of the location of key research or of key companies in the field; caution must be taken, however, as many non-US applicants will first file in the US for commercial reasons. **Figure 1** gives the filing data; again the US has by far the greatest number

Figure 2



Business

Figure 1



In Europe, the legal position is very different. European patents are granted by the European Patent Office (EPO), while applicants also have the option to pursue national patents directly through national patent offices. There is a specific prohibition on the EPO granting patents for inventions “the exploitation or publication of which are contrary to order public or morality”; it is therefore a normal part of EPO patent prosecution for the office to consider ethical and moral issues. Some guidance on these issues was given by the so-called Biotech Directive (Directive 98/44/EC), a piece of EU legislation which among other things set out the availability of patent protection in various biotechnology fields. The Directive states that the following, among others, will be considered unpatentable:

“(a) processes for cloning human beings; (b) processes for modifying the germ line genetic identity of human beings; (c) uses of human embryos for industrial or commercial purposes.”

Further, “the human body, at the various stages of its formation and development ...cannot constitute [a] patentable [invention]”.

There is however a current debate as to how widely these exclusions should be interpreted. The debate is centred about the European equivalent of the Thomson patent mentioned above; after a

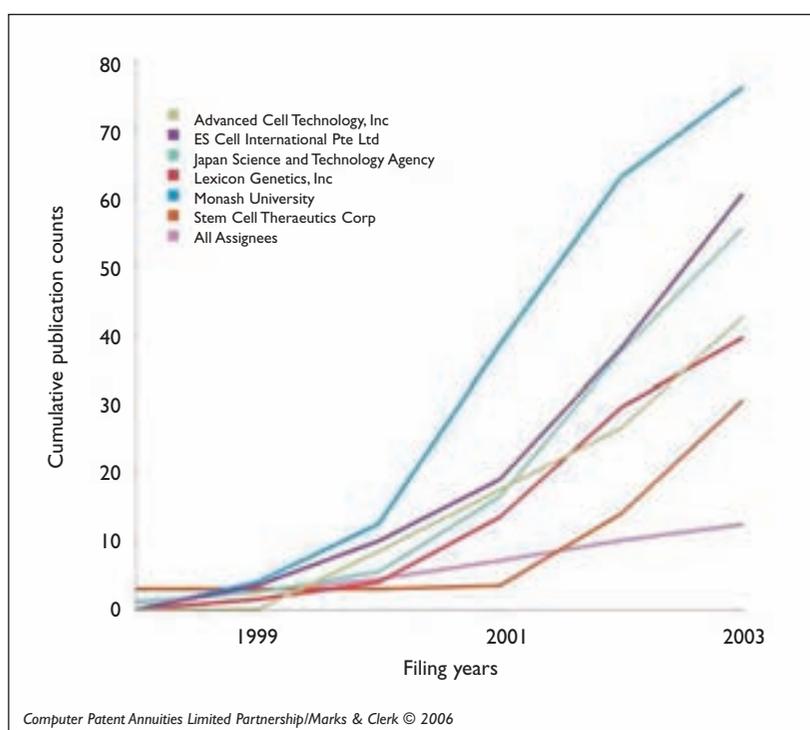
lengthy examination process, the patent application was rejected in Europe on the grounds that the invention required the destruction of human embryos, and as such the exploitation of the invention would be contrary to morality. The applicant appealed, and the Appeal Board referred the decision upwards to the Enlarged Board of Appeal of the EPO, the body which rules on interpretation of the law. The case is currently pending, and a decision could take some time, leaving applicants in a state of uncertainty over whether a particular invention is patentable; it cannot help the industry that applicants will have no choice but to file an application in Europe without knowing whether the invention is patentable.

The Enlarged Board has been asked to consider various questions, including whether the exclusion from patentability of uses of human embryos “forbid[s] the patenting of claims directed to products which ...could be prepared exclusively by a method which necessarily involved the destruction of the human embryos from which the said products are derived, if the said method is not part of the claims?” The questions also consider the further point as to whether it is of relevance that after the application was filed, alternative methods for generating the cell lines which do not involve destruction of human embryos became available.

of priority filings, although Asia-Pacific countries such as China, Japan and Australia all have high levels of activity. Filings in Europe are split between national patent offices (primarily UK and Germany) and the EPO itself; interestingly Europe as a whole shows activity generally comparable to that of China. Canada shows far lower activity than would be expected from its significance in stem cell research; it is probable that Canadian companies will first file in the US rather than Canada.

Figure 2 shows those companies and other entities who have filed the greatest number of stem cell patent families (rather than individual patents) over the 2000-05 period. Given the restricted timescale, it is noticeable that some significant patent filers do not appear on this list – for example, WARF which holds the rights to the Thomson patents. Given industry concerns about investing in stem cell technology, it is not surprising that universities and public bodies dominate the list, although a number of specialist stem cell companies are present. This data confirms the findings of the UK Stem Cell Initiative Report (Report and Recommendations of the UK Stem Cell Initiative, November 2005), which highlighted several patents considered to be ‘influential’; of 16 patents, seven were held by research institutes, universities, or other non-profit entities. Future patent filings are likely to be more heavily dominated by public bodies in view of the current rush to establish publicly-funded stem cell institutes or other bodies around the world. At least until investors feel more confident that stem cell technology will provide the returns they seek, we can expect public funding to play a significant role; this has led to concerns in the US, where a Congressional delegation studying stem cell science in the UK warned that the lack of federal funds for such research in the US means that the US is falling behind in the field.

Having said that, however, many private companies are making great progress in commercialising stem cell technology, with encouraging results which can only encourage private investors. For example, Athersys is currently investigating use of its MultiStem™ technology (a non-ES cell technology) primarily for cardiovascular conditions, and “intends to file an IND (Investigational New Drug application) in the cardiovascular area in 2007”. The company is also partnering with a number of big pharma companies to exploit the technology. Stem Cell Therapeutics of Canada is currently planning Phase II clinical trials of its test compound NTx(TM)-265, intended to promote growth of neuronal stem cells in patients for treatment of neu-



rodegenerative conditions; the company has also recently been granted a number of US patents.

Figure 3

Other companies to watch can be seen in Figure 3, which shows the fastest growing patent portfolios in the stem cell area. The graph shows those companies which are filing more applications than the overall industry average (as determined from our data set). Several of the emerging players also appear on the list of top patent applicants, while others, although growing rapidly have not yet built a large enough patent estate to appear on the list. The companies shown in this Figure represent a wide range of technologies and companies. ES Cell International is a Singapore company focused on human embryonic stem cell technology, with patent filings directed to cell lines themselves, and growth, maintenance and differentiation of hES cells. Japan Science and Technology Agency is a governmental body; while Monash University is an Australian research institute. Lexicon Genetics is a US company which holds the rights to technology relating to transgenic mouse knockout ES cell lines. Among other partnerships, Lexicon, has received a \$35 million contract from the Texas Enterprise Fund to develop a knockout mouse ES cell library for the Texas Institute of Genomic Medicine. Stem Cell Therapeutics has already been mentioned, while Advanced Cell Technology, whose technology is intended to produce pluripotent cell lines compatible with patients, has recently relocated its

Business

headquarters from Massachusetts to California; an early indication that California's stance on stem cell research is achieving results.

In conclusion, the stem cell area is very active, with a prominent role being played by government and public bodies. This role is likely to increase in the near future as national and state governments rush to set up various stem cell institutes and other research centres of excellence; however, there is concern that the US in particular may lose its lead in the technology due to the federal restrictions on funding. These concerns must equally apply to other countries with a policy against human embryo research. Private investment appears nervous of the returns to be made from the technology; however, encouraging results coming from private companies at present, particularly in non-ES cell related technologies, should help to calm investors' nerves and promote the use of stem cell technology. Consideration of individual companies and specific patents shows that, at least for now, non-ES technology is likely to provide best returns for direct patient treatment, while ES technologies are more likely to be limited to roles in animal cloning and generation of transgenic lines, at least for the short term.

DDW

Dr Gareth Williams is a European Patent Attorney, and a partner in the biotechnology group at Marks & Clerk, a leading firm of patent and trade mark attorneys. He is a co-author of the Marks & Clerk Biotechnology Report, and has written and spoken extensively on a range of biotechnology-related patent issues.

ADVERTISEMENT INDEX

Akubio Ltd	38	Chemicon	64	Molecular Devices Corporation	13,15,37
American Laboratory Association	75	CISBIO International SA	4	NextGen Sciences Ltd	21
BD Biosciences	31	DeltaDOT	53	PerkinElmer Life Sciences	43,70
Beckman Coulter, Inc	48	ForteBio, Inc	59	ProQinase GmbH	6
Bentham Science Publishers Ltd	IBC	Gene Logic, Inc	IFC-3	Society of Biomolecular Sciences	47
BioDot, Inc	77	Genetix Ltd	44	Thermo Electron Corporation	22,OBC
Caliper Life Sciences, Inc	63	Greiner Bio-One GmbH	16	TTP Labtech	41
Cellomics, Inc	33	Invitrogen Corporation	24,56		