

Review

The business of exploiting induced pluripotent stem cells

Catherine Prescott*

Biolatris Ltd, St John's Innovation Centre, Cowley Road, Cambridge CB4 0WS, UK

Induced pluripotent stem cells (iPS cells) can be exploited for both research and clinical applications. The first part of this review seeks to provide an understanding of the financial drivers and key elements of a successful business strategy that underpin a company focused on developing iPS-related products and services targeted at the research market. The latter part of the review highlights some of the reasons as to why the reprogramming of somatic cells is currently being used to develop cell-based models to screen for small molecules with drug-like properties rather than to develop cell-based regenerative medicines *per se*. The latter may be used to repair or replace a patient's damaged cells and thereby have the potential to 'cure' a disease and, in doing so, prevent or delay the onset of associated medical conditions. However, the cost of an expensive regenerative medicine and time to accrue any benefit linked to a decrease in co-morbidity expenditure may not outweigh the benefit for a healthcare community that has finite resources. The implications of this are discussed together with evidence that the UK National Institute for Health and Clinical Excellence (NICE) and the National Health Service (NHS) have established a precedent for a cost-sharing strategy with the pharmaceutical industry.

Keywords: regenerative medicine; stem cells; finance; health economics; business

1. INTRODUCTION

The business of exploiting induced pluripotent stem cells (iPS cells) embraces multiple facets including alignment of the technical, operational, commercial and financial strategies. For the purpose of this review, it is proposed that technical, financial and regulatory hurdles will be addressed, enabling the commercialization of iPS-related products and services for research and clinical applications. For example, the methods for reprogramming and differentiation of the cells will be assumed to be robust, reliable, efficient, cost effective and amenable to scale-up if required in large quantities for commercialization. It is also assumed that reprogramming methods will result in cells that are suitable for clinical applications, i.e. that they do not retain any exogenous genetic material and have the correct epigenetic profile. There are already several reports demonstrating that non-genetic approaches using RNA [1], proteins or small molecules [2] can be used to replace the original methods that relied on viral-based transfection of a series of genes, such as *Oct3/4*, *Sox2*, *c-Myc* and *Klf4* [3,4]. For the purpose of this review, it is also assumed that the technology and products are protected by robust intellectual property rights including the freedom to operate and that there is a favourable financial climate whereby investors are willing to invest in product development (for research and clinical applications) and service companies. Finally, it is also presumed that there is a recognition that the iPS technology can potentially be exploited for clinical and

research applications, including the generation of disease models, novel drug and target discovery, toxicity screening and for cell-based therapeutics. Further details are presented by other contributors to these proceedings and therefore will not be covered in this review.

The aim of this review is to address business-related aspects of both the research and therapeutic product markets. The first part draws on two case studies to provide a framework for an understanding of the financial drivers that underpin the business and investment strategy for a model iPS-based company focused on developing products and services targeted at the research market. The latter part of the review seeks to highlight some of the challenges facing the uptake and the adoption of iPS-derived products for therapeutic applications, namely manufacturing and reimbursement. General investment trends in the field have been reviewed elsewhere [5,6].

2. THE BUSINESS OF EXPLOITING INDUCED PLURIPOTENT STEM CELLS FOR RESEARCH APPLICATIONS

There are several business models deployed by companies that exploit the iPS-technology platform for research applications in order to supply products and services to the academic, public-research and life-science industry sectors. Companies such as Invitrogen Life-Technologies (www.invitrogen.com), Stemgent (www.stemgent.com), ReproCELL (www.reprocell.net), R&D Systems (www.rndsystems.com), Promega (www.promega.com), Miltenyi Biotec (www.miltenyibiotec.com) and STEMCELL Technologies (www.stemcell.com) supply reprogramming kits and reagents, iPS cell lines and media. Many of these companies also provide

*cprescott@biolatris.com

One contribution of 15 to a Discussion Meeting Issue 'What next for stem cell biology? The evolving biology of cell reprogramming'.

contract services, such as the development of bespoke screening systems for toxicity testing and drug discovery, optimization of reprogramming and culturing conditions, derivation of iPS and reporter cell lines and their characterization. For example, cellular dynamics international (CDI; www.cellulardynamics.com) supplies human iPS-derived cardiomyocytes for cardiotoxicity screening [7]; Stemgent and Fate Therapeutics had launched the Catalyst programme to enable fee-paying members to access iPS technology developed by Ding & Jaenisch [8].

As of April 2010, CDI has raised a total of \$70 million since 2004 [9]. Substantial investment rounds were secured in 2008 following a merger of CDI's sister companies (\$18 million) and in 2010 when the company raised a further \$40.6 million. Stemgent was launched more recently (2007), raising \$14 million in a series A financing in 2009 [10], and is currently seeking up to \$10 million in a series B round of which \$5.6 million was secured in April 2010 [11]. Accordingly, it is not unreasonable to propose that an iPS-based company targeting the research market will need to raise in the order of \$50 million and undergo an exit event, probably via acquisition by a larger corporation, 5 years after the company was launched (see below). For simplicity, the premise is that all investors have equal rights in terms of asset distribution, that they have invested since day 1 and are willing to accept a twofold ($2\times$) return on their investment and that the company's employees own one-third of the company at the time of exit, i.e. at the point of sale, the investee company is worth \$150 million.

(a) What would the company have to achieve to reach a valuation of \$150 million?

The value of a products and service-based company is typically based on a 3 to 10 times multiple of the gross revenue generated by the company. Therefore, it is not unreasonable to assume that the company will be valued at five times its revenue and so under these circumstances the company must generate \$30 million in revenue to reach the \$150 million valuation. \$30 million in revenue equates to approximately 15–30% of the \$100–200 million estimated annual global market for stem cell-related research products [12]. In fact, reports of the size of the stem cell market vary enormously and the value of the iPS-based research market *per se* is unclear; however, the demand for iPS-related products is rapidly growing as evidenced by the increasing number of related peer-reviewed publications. This raises the question as to how a company is able to deliver to a competitive market.

(b) What are the key elements of a successful business strategy required to underpin the penetration of the induced pluripotent stem-based research market?

At least three key factors underpin a successful commercialization strategy: a pipeline of high-quality products, credible third party endorsement of the products and an effective sales and marketing strategy. Stemgent has formed a series of relationships with a number of the top academic researchers in the USA

and China in order to gain access to their cutting edge research. The company has also established collaborations with industry including Pfizer and Fate Therapeutics. The collaboration with Pfizer will enable certain compounds with pharmaceutical modes of action developed or discovered by Pfizer to be made available to the research community through Stemgent [13]. Stemgent has also formed a strategic partnership with Miltenyi Biotec for the co-development and marketing of stem cell research products [14]. Under the terms of the exclusive agreement, Miltenyi Biotec will be responsible for worldwide marketing and sales of Stemgent's existing stem cell product portfolio outside the USA, whereas Stemgent will continue to serve the US market. Accordingly, Stemgent has access to the global market without having to extend its own in-house sales and marketing force. CDI has also formed a series of collaborations with the pharmaceutical industry including sequential agreements with Roche, in order to test and validate their iPS-derived cardiomyocytes prior to market launch in December 2009 [7,15,16]. Such collaborations serve two purposes: (i) to ensure that the customers' criteria as to how the product should perform and be used are understood and met and (ii) the provision of a credible and independent product-endorsement. CDI also obtained a non-exclusive licensing agreement with iPS Academia Japan, Inc., for the seminal iPS cell patent portfolio arising out of the work of Dr Shinya Yamanaka [17].

From an investment perspective, a twofold return on an investment by year 5 would yield a respectable 15 per cent internal rate of return (IRR, a rate of return for an investment). The 5 year time horizon is not unreasonable: analysis of investment trends in biotechnology revealed that two out of three deals took 5 years or more to reach an exit and only 13 per cent of the deals resulted in $2-3\times$ return on the investment [18]. Furthermore, 44 per cent of the deals resulted in a complete or partial loss of an investment. Therefore, since venture capital funds manage a portfolio of investments, the portfolio will consist of a mix of successful and failed investments. The risk–reward profile of any single company must be viewed with the potential to return a sufficiently high IRR so as to compensate for the investments that fail. A 15 per cent IRR for an individual investment is good but arguably border-line in the context of a portfolio. A higher IRR could be achieved by either the company exiting at a point earlier than year 5 (for example, a 26% IRR could be obtained by exiting by year 3 with $2\times$ return on the investment) or by increasing the amount of revenue generated. Either strategy is a challenge given the rate at which technologies are being developed, the time required to translate such technologies into a commercially viable product and the level of competition.

3. THE BUSINESS OF EXPLOITING INDUCED PLURIPOTENT STEM CELLS FOR CLINICAL APPLICATIONS

Turning now to exploiting iPS cells for therapeutic applications, once again for the purpose of this

review, it is assumed that the range of potential products and applications is understood including the use of iPS cells to develop disease models for target and drug discovery and for toxicity screening, as well as for cell-based therapeutics. It is also assumed that the intellectual property rights including freedom to operate are secure and that these may cover methods for reprogramming, differentiation, cell-selection, -purification, -amplification and the route of administration. Finally, it is also assumed that the regulatory path is well defined and that the clinical trial data are considered by the regulators to demonstrate safety and efficacy.

The two leading companies that are exploiting iPS-technologies for therapeutic applications are iPierian (www.ipierian.com) and Fate Therapeutics (www.fate-therapeutics.com). Both companies are undertaking a similar strategy in that they are reprogramming somatic cells to develop cell-based models to screen for small molecules with drug-like properties. The difference between the two companies is that iPierian is using cellular reprogramming and differentiation technologies to advance the understanding of human diseases for which there are poor *in vivo* and *in vitro* models (and limited treatments to date) in order to find new molecular targets and develop proprietary therapeutics for its own pipeline to treat specific diseases. The company is currently focused on three neurological disorders, namely Parkinson's disease, spinal muscular atrophy and amyotrophic lateral sclerosis. By contrast, Fate Therapeutics is developing an understanding of the pathways that specifically activate and modulate adult stem cells and iPS-technology to screen for stem cell modulators (SCMs), described as small molecules and biologics that modulate cell fate *in vivo* (i.e. by activating a patient's resident population of adult stem cells) to repair and regenerate tissues. iPierian was formed in 2009 following a merger between iZUMI and Pierian and the company has raised approximately \$60 million in venture funds [19,20]. Fate Therapeutics was established in 2007 and has raised approximately \$47 million in venture capital [21].

It is notable that neither company is promoting the exploitation of iPS-technologies to develop cell-based therapeutics. The cost to develop cell-based therapeutics means that their use as personalized therapeutics will probably be prohibitively expensive for general use (see below) and face significant regulatory hurdles. However, the economy of scale could be applied if iPS-technologies underpin the development of biobanks that contain 'ready-to-use' cells with close immunological matches to a population. Studies have estimated that as few as 150 cell lines would be sufficient to provide close immunological matches for the UK population [22] and just 50 lines would be sufficient to represent 90 per cent of the Japanese population [23]. The key issue remains as to whether the cell-based therapeutics can be manufactured at a sufficiently low price such that they will be eligible for reimbursement by the health insurers.

The cost to derive three iPS cell lines in a dedicated academic facility using the current transfection method is estimated to be approximately \$15 000 (B. Reeve 2010, personal communication). Although

these costs are anticipated to decrease as methods improve (including the development of non-genetic approaches to reprogramming), the current costs are for research-grade lines and do not include teratoma formation analysis. The costs will probably increase when cell lines are derived for clinical applications. i.e. under good manufacturing practice (GMP) conditions which, like human embryonic stem cell lines, will require strict testing and monitoring systems to be in place [24].

4. THE IMPORTANCE OF THE MANUFACTURING PROCESS

Relative to traditional approaches (chemical and biologic), cell-based products will be expensive to manufacture. The precise manufacturing costs will reflect multiple parameters including the complexity of the manufacturing protocol, scale and the efficiency of yield. For example, the generation of iPS-derived insulin-secreting islet-like cells is reported to require the addition of Activin A, epidermal growth factor, basic fibroblast growth factor, Noggin and insulin-like growth factor II [25]. Each of these supplements must be manufactured to meet the quality standards set by the regulators for their use in the manufacturing of advanced biologicals, thereby further increasing the manufacturing cost of a cell-based therapeutic.

Following market authorization of those products clinically proved to be safe and efficacious, health insurers then determine whether the product is eligible for reimbursement. A positive response is evidently required to enable a product to successfully enter the market. However, if the response is negative because the product is too expensive, then the manufacturing process must be redesigned in order to reduce the cost of goods (COGs) sold to a level that is affordable to the health insurers [26]. If the new manufacturing process changes the original product specification then the regulators will consider that this is a new product and therefore require testing in clinical trials. Consequently, the product-developer faces a significant loss both financially and in terms of time. This is particularly a sensitive issue for products that are both expensive to manufacture and for which the specification is arguably less easy to control than, for example, the synthesis of a chemical. Accordingly, the reimbursement question should be addressed as early on in the development of the product as possible so as to minimize the risk of failing at the last hurdle. McAteer & Lilford [27] developed the 'headroom method' to facilitate this type of early assessment based on whether a technology would be cost effective if it works as well as hoped and at what cost would the new therapy be cost effective. The first part of the assessment involves making optimistic assumptions about the incremental effectiveness of the proposed treatment relative to the best alternative and the latter part determines the maximal potential cost of the new treatment, including development costs.

Accepting the premise that iPS-derived cell-based therapeutics will be expensive relative to conventional therapeutics, they may be relegated to a last line of resort when all other available treatments have been

tried and shown to fail. However, this would effectively narrow the market size and therefore potentially undermine the commercial viability of the product. Therefore in order to command a premium price, the product must demonstrate superior efficacy relative to an alternative treatment or target an indication for which there is no existing treatment.

5. HOW SHOULD A REGENERATIVE MEDICINE BE VALUED?

Regenerative medicines undertake a fundamentally different approach to treatment, aiming to repair or replace diseased or damaged cells or tissues. Many regenerative medicines in development are targeting chronic diseases, which have a significant and increasing impact on the economic burden on healthcare. For example, within the UK, the National Health Service (NHS) is reported to spend approximately 10 per cent of its annual budget on treating diabetes and its associated complications [28]. Similarly in the USA, it is reported that \$1 in every \$10 healthcare dollars is attributed to diabetes and costs (in 2007) have risen by 32 per cent since 2002 [29]. Chronic diseases are also linked to one or more associated medical conditions. For example, adults with diabetes have a two- to fourfold increase in the risk of stroke and heart disease, and 75 per cent of adults have increased blood pressure. Diabetes is also the leading cause of blindness and kidney failure and accounts for more than 60 per cent of non-traumatic lower-limb amputations. In the USA, the indirect costs of treating medical conditions associated with diabetes were approximately twice the direct costs of treating diabetes (\$58 billion versus \$27 billion, respectively).

If regenerative medicines effectively ‘cure’ the patient of the disease or at least better manage the underlying cause of the disease by repairing or replacing the diseased or damaged cells, then the approach should also diminish or delay the onset of the associated medical conditions. Therefore, should the value of the regenerative medicine not only take into account the direct treatment costs but also the savings made by not having to treat (or at least delay) the associated medical conditions (‘indirect’ costs)? In principle, yes—however, there are several issues that need to be considered including the need to provide evidence for such claims and the time period over which the benefit of the indirect cost savings are accrued. For example, clinical trials may have to be conducted over a longer period of time and measure not only the clinical endpoints for the target indication but also those for the associated medical conditions. Increasing time and complexity of measurements will increase the clinical trial costs, which may become prohibitively expensive for cash-strapped regenerative medicine companies. A second consideration relates to the cost of the treatment relative to the time needed to recover the benefit. In many countries, health insurance is a competitive industry and the customers will select what is determined to be the best value option. Therefore, if a health insurer pays the high upfront costs for an expensive treatment and the client then elects to move to another health

insurer, the first health insurer is unlikely to have been able to benefit from the overall cost benefit that is accrued over a longer period of time.

The economic burden of chronic diseases extends beyond that of healthcare expenditure alone. The Milken Institute report that the loss of economic output owing to chronic diseases is approximately five times more than healthcare expenditure [30]. The loss of economic output is owing to a decline in worker productivity, absenteeism and a loss of productive capacity owing to early mortality. Therefore, should the economic value of regenerative medicines also take into account the potential to decrease the loss of economic output? Demonstrating such an economic benefit would clearly be an enormous challenge, if not impossible. However, a positive outcome would be in the interest of both the public and private sectors and not just the healthcare providers and insurers.

6. A CURE AT ANY COST?

If it assumed that regenerative medicines cure the patient, does this automatically mean that the product will be reimbursed no matter how much the treatment will cost? Like any organization, healthcare providers and health insurers have finite resources and therefore consideration must be given to the economic burden of providing treatment to all patients with the disease. Accordingly, the prevalence (how commonly a disease occurs within a population) and incidence (rate of occurrence of new cases of the diseases) of a disease must be considered. If the available resources are insufficient to support the provision of a particular therapy to all patients that require it, then the aim must be to achieve a practical allocation of finite resources and maximize the overall health of the population. In other words, an expensive treatment, no matter how effective, could put a health insurer at risk of bankruptcy and, therefore, the health insurer must consider either rejecting the therapy, limiting its use or seek to offset some of the burden of cost. There is precedent for a risk-sharing approach including a developer agreeing to pay for some of the treatment costs, the reimbursement of non-responders and a combination of both approaches. For example, the National Institute for Health and Clinical Excellence (NICE) and the NHS have an agreement with Novartis to pay for the first 14 treatments with ranibizumab (Lucentis) for wet acute macular degeneration (AMD) and Novartis will pay for any subsequent injections [31]. Similarly NICE/NHS has an agreement with Celgene whereby the company will pay for any treatment with lenalidomide (Revlimid) for multiple myeloma after the first 2 years [32]. Janssen-Cilag has agreed to reimburse the NHS for multiple myeloma patients that fail to respond to bortezomib (Velcade) [33]. Pfizer agreed a 5 per cent price cut and six weeks of free treatment with sunitinib (Sutent) in patients with gastrointestinal stromal tumours and that the company would also reimburse the NHS for non-responders [34]. These examples may not be direct comparators of regenerative medicines in terms of their cost-profile, however they do provide evidence of

creative strategies that could be used as a basis to negotiate for the reimbursement of expensive regenerative medicines.

7. FUTURE PROSPECTS

Cellular reprogramming and differentiation technologies are primarily being exploited to advance our understanding of human diseases for which there are poor *in vivo* and *in vitro* models. This will lead to the identification of new molecular targets and proprietary therapeutics to treat specific diseases as well as drugs that stimulate a patients' resident population of stem cells to repair damaged cells. The approach using soluble factors (chemicals and biologics) rather than cell-based therapeutics as regenerative medicines has several advantages including providing a bridge to the pharmaceutical industry that has considerable experience in the development and commercialization of conventional drugs [6,35]. Furthermore, the self-administration of traditional therapeutics facilitates their rapid uptake relative to cell-based products that will, for the foreseeable future, probably be administered by a specialist in a clinical setting. For example, Apligraf was the first bio-engineered cell-based product to receive FDA approval indicated for the treatment of venous leg ulcers and diabetic foot ulcers and is delivered in a specialist wound care setting (www.apligraf.com).

Soluble factors can be protected by patent-claims relating to their precise composition (composition of matter patents), whereas cell-based products are primarily subject to process patent claims relating to the methods by which the cells are derived and cultured. Process patents are vulnerable as they can often be circumvented following modification of the described processes.

However, the apparent advantages of a soluble factor approach must be considered in the light of the key question of whether a soluble factor will be as effective as a cell-based therapeutic that secretes a plethora of cytokines and growth factors with paracrine activities that contribute to the repair and regeneration process [36]. Furthermore, if a combination of soluble factors is required to mimic the regenerative properties of a cell-based therapy, then this would likely significantly increase the complexity, time and the cost of successfully completing the clinical trial process.

Cell-based therapies may either act transiently to repair or regenerate damaged tissue or become engrafted to replace damaged tissue (cell replacement therapy). For either approach, the time required to manufacture the cells and the development of technologies that extend the currently limited shelf-life of 'ready-to-use' cells will be critical in determining their application in an acute or chronic setting. Increasing the efficiency of non-genetic approaches to generate iPS cell lines with the correct epigenetic profile would permit the generation of biobanks containing 'ready-to-use' cells with close immunological matches to a population [22,23]. By increasing the number of patients that could be treated by any single iPS cell line, this would decrease the cost of treatment per patient and thereby make the product

more affordable than a personalized medicine. However, a perfect immunological match would be optimal for a cell replacement therapy when treating a long-term chronic disease.

Demand will no doubt drive the resolution of the challenges facing the development and manufacturing of *affordable* regenerative medicines, including soluble factors and iPS cell-based approaches.

The author would like to acknowledge the contribution of the Technology Strategy Board 'Regenmed programme—Value Consortium' grant that in part supported this work.

REFERENCES

- 1 Warren, L. *et al.* 2010 Highly efficient reprogramming to pluripotency and directed differentiation of human cells with synthetic modified mRNA. *Cell Stem Cell* **7**, 618–630. (doi:10.1016/j.stem.2010.08.012)
- 2 Zhou, H. *et al.* 2010 Generation of induced pluripotent stem cells using recombinant proteins. *Cell Stem Cell* **4**, 381–384. (doi:10.1016/j.stem.2009.04.005)
- 3 Junying Yu, J. 2007 Induced pluripotent stem cell lines derived from human somatic cells. *Science* **318**, 1917–1920. (doi:10.1126/science.1151526)
- 4 Takahashi, K. & Yamanaka, S. 2006 Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. *Cell* **126**, 663–676. (doi:10.1016/j.cell.2006.07.024)
- 5 Benjamin, R. 2010 Public investment models: coming out of the closet and going public! In *The delivery of regenerative medicines and their impact on healthcare* (eds C. Prescott & D. J. Polak), pp. 67–84. Boca Raton, FL: CRC Press.
- 6 Prescott, C. 2010 Investing in regenerative medicine: what drives the private investor? In *The delivery of regenerative medicines and their impact on healthcare* (eds C. Prescott & J. M. Polak), pp. 59–66. Boca Raton, FL: CRC Press.
- 7 CDI Press Release. 2009 *Cellular dynamics announces commercial launch of icell™ cardiomyocytes for drug candidate toxicity screening*. See http://www.cellulardynamics.com/news/pr/2009_12_16.html.
- 8 Stemgent Press Release. 2009 *Fate Therapeutics and Stemgent launch Calatyst: a unique industry program for first access to the most advanced pluripotent stem cell technology*. See <http://www.prnewswire.com/news-releases/fate-therapeutics-and-stemgent-launch-catalyst-a-unique-industry-program-for-first-access-to-the-most-advanced-induced-pluripotent-stem-cell-technology-61965147.html>.
- 9 Biospace. 2010 *Cellular dynamics international raises \$40.6 million to revolutionize pharma drug research with industrial manufacture of human heart and other cells*. See http://www.biospace.com/news_story.aspx?NewsEntityId=178082.
- 10 Reuters. 2009 *Stem cell researcher Stemgent raises \$14 M*. See <http://www.reuters.com/article/idUSTRE52F30320090316>.
- 11 SEC Filing. 2010 *Filer ID Number 0001429173*. See http://www.sec.gov/Archives/edgar/data/1429173/000114036110020792/xslFormDX01/primary_doc.xml.
- 12 McBride, R. 2008 *Stem cell firms shift from treatments to tools*. See <http://www.masshightech.com/stories/2008/06/02/weekly10-Stem-cell-firms-shift-from-treatments-to-tools.html>.
- 13 Stemgent Press Release. 2010 *Stemgent And Pfizer Announce Collaboration*. See <http://www.reuters.com/article/2010/04/15/idUS215300+15-Apr-2010+BW20100415>.
- 14 Stemgent Press Release. 2010 *Stemgent and Miltenyi Biotec announce strategic partnership*. See http://www.miltenyibiotec.com/en/Stem_cell_News.aspx.

- 15 CDI Press Release. 2008 *Cellular dynamics international and roche palo alto enter agreement to screen drug compounds for cardiotoxicity*. See http://www.cellulardynamics.com/news/pr/2008_03_05.html.
- 16 CDI Press Release. 2009 *Cellular dynamics international and roche expand existing cardiotoxicity screening agreement*. See http://www.cellulardynamics.com/news/pr/2009_07_01.html.
- 17 CDI Press Release. 2010 *Cellular dynamics partners with iPS academia Japan, Inc. to in-license seminal iPS cell patent portfolio*. See http://www.cellulardynamics.com/news/pr/2010_05_07.html.
- 18 Cockburn, I. & Lerner, J. 2009 The cost of capital for early stage biotechnology ventures. See <http://www.slideshare.net/NVCA/the-cost-of-capital-for-early-stage-bio-technology-ventures>.
- 19 iPierian Press Release. 2009 *iZumi Bio and Pierian Merge to form iPierian to advance cellular reprogramming*. See <http://www.ipierian.com/news-events/press-releases/2009/iZumi-Bio-and-Pierian-Merge-to-form-iPierian-to-Advance-Cellular-Reprogramming-93/>.
- 20 iPierian Press Release. 2010 *iPierian announces second close of \$28 million series B financing*. See <http://www.ipierian.com/news-events/press-releases/2010/iPierian-Announces-Second-Close-of-28-million-Series-B-Financing-323/>.
- 21 Fate Therapeutics Press Release. 2009 *Fate Therapeutics Closes \$30 Million Series B Financing*. See <http://www.fate-therapeutics.com/news-press-releases.php>.
- 22 Taylor, C. J., Bolton, E. M., Pocock, S., Sharples, L. D., Pedersen, R. A. & Bradley, J. A. 2005 Banking on human embryonic stem cells: estimating the number of donor cell lines needed for HLA matching. *Lancet* **366**, 2019–2025.
- 23 Nakatsuji, N., Nakajima, F. & Tokunaga, K. 2008 HLA-haplotype banking and iPS cells. *Nat. Biotechnol.* **26**, 739–740. (doi:10.1038/nbt0708-739)
- 24 Unger, C., Skottman, H., Blomberg, P., Dilber, M. S. & Hovatta, O. 2008 Good manufacturing practice and clinical grade human embryonic stem cell lines. *Hum. Mol. Genet.* **17**, 48–53. (doi:10.1093/hmg/ddn079)
- 25 Tateishi, K., He, J., Taranova, O., Liang, G., D'Alessio, A. C. & Zhang, Y. 2008 Generation of insulin-secreting islet-like clusters from human skin fibroblasts. *J. Biol. Chem.* **283**, 31601. (doi:10.1074/jbc.M806597200)
- 26 Placzek, M. R. *et al.* 2009 Stem cell bioprocessing: fundamentals and principles. *J. R. Soc. Interface* **6**, 209–232. (doi:10.1098/rsif.2008.0442)
- 27 McAteer, H. & Lilford, R. 2008 The use of health economics in the early evaluation of regenerative medicine applications. *Eur. Cells Mater.* **16**, 5.
- 28 Diabetes UK Report. 2008 *Diabetes. Beware the silent Assassin*. See www.diabetes.org.uk/Documents/./Silent_assassin_press_report.pdf.
- 29 American Diabetes Association. 2007 *Diabetes statistics*. See <http://www.diabetes.org/diabetes-basics/diabetes-statistics/>.
- 30 DeVol, R. & Bedroussian, A. 2007 An unhealthy America: the economic burden of chronic disease—charting a new course to save lives and increase productivity and economic growth. Milken Institute. See <http://www.milkeninstitute.org/publications/publications.taf?function=detail&ID+38801018&cat=resrep>.
- 31 NICE Guidance. 2008 *Ranibizumab and pegaptanib for the treatment of age-related macular degeneration*. See <http://guidance.nice.org.uk/TA155>.
- 32 NICE Guidance. 2009 *Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy*. See <http://guidance.nice.org.uk/TA171>.
- 33 NICE Guidance. 2007 *Bortezomib monotherapy for relapsed multiple myeloma*. See <http://guidance.nice.org.uk/TA129>.
- 34 NICE Guidance. 2009 *Sunitinib for the treatment of gastrointestinal stromal tumours*. See <http://guidance.nice.org.uk/TA179>.
- 35 Prescott, C. 2008 The promise of stem cells: a venture capital perspective. In *Advances in tissue engineering* (eds J. M. Polak, A. Mantalaris & S. Harding), pp. 491–500. London, UK: Imperial College Press.
- 36 Gnecci, M., Zhang, Z., Ni, A. & Dzaou, V. J. 2008 Paracrine mechanisms in adult stem cell signaling and therapy. *Circ. Res.* **103**, 1204–1219. (doi:10.1161/CIRCRESAHA.108.176826)