Cells respond to their structural surrounding and within nanostructures exhibit unique proliferative and differentiation properties. The application of nanotechnologies to the field of regenerative medicine offers the potential to direct cell fate, target the delivery of cells and reduce immune rejection (via encapsulation), thereby supporting the development of regenerative medicines. The overall objective of any therapy is the delivery of the product not just into the clinic but also to patients on a routine basis. Such a goal typically requires a commercial vehicle and substantial levels of investment in scientific, clinical, regulatory and business expertise, resources, time and funding. Therefore, this paper focuses on some of the challenges facing this emerging industry, including investment by the venture capital community.

**Keywords:** regenerative nanomedicines; nanotechnology; investment

1. **INTRODUCTION**

Nanotechnology as defined by the US National Nanotechnology Initiative (US NNI 2010) is ‘...understanding and control of matter at dimensions between approximately 1 and 100 nanometers, where unique phenomena enable novel applications...’. Nanoscale materials (nanomaterials) can have chemical, physical or biological properties that differ from their larger counterparts and these properties can be exploited to influence cell attachment, proliferation and differentiation (Oh et al. 2009). The understanding of how these properties influence cell fate and their application to develop the next generation of therapeutics that serve to repair, replace or stimulate the repair of target cells and tissues is known as regenerative nanomedicine. For example, nanomaterials developed to mimic extracellular matrices that promote cell adhesion are being used to develop scaffolds for a range of applications including the skin, bone, cornea and nervous system (Smith et al. 2009). Bioactive scaffolds that include surface modifications are being developed to immobilize cells, drugs and proteins such as cytokines, thereby providing cells with developmental cues within a controlled niche environment (Zhang et al. 2007). Nanopatterning technologies are also being developed and used in combination with the bioactive scaffolds to facilitate the control of adhesive motifs on the cell–scaffold interface (Schmidt & Healy 2009). This combination enables control of the nanooarchitecture of bioactive domains such as their orientation, density and the presentation of ligands with multi-valent properties. Furthermore, superparamagnetic iron oxide nanoparticles are being developed to track the migration of transplanted cells (Wu et al. 2008).

Evidently, the application of nanomaterials to tissue engineering and cell therapy has the potential to underpin a wide array of regenerative medicine products and technologies and arguably represent the type of ‘disruptive technology’ sought by venture capitalists (VCs). However, within the life science arena, not all disruptive technologies make compelling investments as the route to market may be ill-defined; therefore, neither the required level of funding is known nor how the value of the investment will be realized. Accordingly, what are the key factors that influence the decision of an investor to invest in an emerging and disruptive technology such as ‘regenerative nanomedicine’? To answer this question it is necessary to understand how venture capital works.

2. **HOW DOES VENTURE CAPITAL WORK?**

A venture capital fund is a pooled collection of investments made by institutional investors and wealthy individuals (collectively known as ‘limited partners’). A fund is managed by a specialist team (VCs) that has deep sector knowledge and expertise encompassing science, technology and business. The funds are managed and invested with complete discretion by the VC subject to a agreed mandate in terms of the industry sector, geographical location, stage (i.e. seed, early...
stage, expansion or late stage) and duration of the fund (typically 10 years). The VC has the single objective to maximize shareholder value for the limited partners. Success of the fund is dependent on the overall performance of the portfolio of investments, and a successful track record enables a VC to raise additional funds. Typically an investment portfolio will comprise both successful and unsuccessful companies, and therefore, the VC must undertake high risks to generate the high returns required to compensate for the underperforming investee companies. However, to mitigate the high risk, VCs adopt a managed risk approach by tranching investments against agreed milestones that enhance the value of the company. This means that VC cannot afford to invest in low-value opportunities (i.e. those with a restricted market size) as the VC would not be able to generate a sufficient return on the investment to compensate for the underperforming investee companies within the portfolio.

Venture funds typically have a 10 year lifespan, must be fully committed within 5 years (meaning no new investments after this period) and ‘exited’ within 10 years. In order to realize (exit) the fund (i.e. return the investment and profit-assuming success to the limited partners), the portfolio companies must undergo an exit event: either an Initial Public Offering (IPO) or a trade sale (acquisition by another company). A third and less desirable option is to close down a company. The stage of the fund cycle has a direct impact on any investment decision. A new fund means that there is an extended period of time during which to develop a disruptive technology to a point that is of recognized value (this often equates to what is considered to be a ‘de-risked’ stage; see below). A fund reaching the stage at which it must be fully committed will seek to invest in a company that can reach a clear exit point within the remaining 5 years of the fund.

3. INVESTMENT TRENDS IN NANOTECHNOLOGY

In 2007, venture capital firms invested $702 million in nanotechnology start-ups across 61 deals (Lux Research Inc. 2008). Most investment activity was focused on the application of nanotechnology to sectors other than the life sciences and healthcare sector (figure 1). However, nanomedical start-ups proved to be the most successful, generating 77 per cent of the returns despite attracting only 27 per cent of the investment capital. Healthcare and life sciences companies accounted for 65 per cent (equivalent to $1.65 billion) of the total $2.57 billion valuation of nanotech start-ups at IPO. Moreover, the revenue multiples at IPO were an order higher for the healthcare sector. These results probably underpinned the subsequent investment trend observed in 2009 whereby there was a 42 per cent increase in activity in the healthcare and life sciences sector when overall investment activity in nanotechnology fell 42 per cent relative to 2008 activity (ObservatoryNano 2010).

Within the life sciences industry sector, VC funding has been primarily focused on those companies that apply nanotechnologies to ‘conventional’ therapeutics (i.e. drugs as either chemicals or biologics) to increase or extend their application; for example, targeted drug delivery systems (BioDelivery Sciences International, CytImmune Sciences Inc., NanoBioMagnetics Inc., Nanobiotix, Nanotherapeutics Inc.), diagnostics (Nanosphere Inc., Oxonica Ltd) and medical imaging systems (Life Technologies Inc.—Qdots). These products and applications have a relatively well-defined route to commercialization (subject to the regulatory hurdles facing nanotechnologies per se; see below). By contrast, the route to market for cell-based products (regenerative medicines) is relatively unproven, characteristic of an emerging industry. This in turn has an impact on the decision by VCs to invest in regenerative nanomedicines. Why?

As mentioned earlier, investee companies must undergo a successful exit event (trade sale or IPO) in order to leverage a return on the investment. Exiting via a trade sale typically results in a higher valuation than at IPO and the sale usually represents ‘cash in hand’ (Behnke & Hütleneschmidt 2007). By contrast, a usual condition of an IPO is that the existing investors are not permitted to sell their shares until after an agreed period of time (the ‘lock-up’ period is typically 6–12 months), during which the share value may decrease. Furthermore, over the past 3 years there has been a significant decrease in the number of companies being able to exit via IPO (figure 2). Therefore, the
due diligence that a VC will conduct leading to an investment decision will include an assessment of the potential for the company to exit via a trade sale and an understanding of what milestones the company must achieve in order to trigger the exit event. The milestones must be aligned with the needs of the ‘buyer’, i.e. the larger corporations. Accordingly, companies that are applying nanotechnologies aligned with accepted pharmaceutical practices (drug delivery, imaging, diagnostics) can be more readily assessed, adopted and integrated into the existing product pipelines. However, for truly disruptive and emerging technologies such as regenerative medicines, their adoption and integration are less straightforward and, at best, the number of options to form partnerships will be narrow.

The pharmaceutical industry has been reticent to engage with the cell-based regenerative medicine industry with only a limited number of notable deals being secured. For example in 2008 Genzyme partnered with Osiris Therapeutics to develop and commercialize Prochymal and Chondrogen (mesenchymal stem cell products) (Osiris Therapeutics Press Release 2008). The deal included a $130 million upfront payment by Genzyme plus additional milestone and royalty payments. In 2009, Athersys and Pfizer entered into an agreement to develop and commercialize MultiStem for the treatment of inflammatory bowel disease (IBD). Under the terms of the agreement, Athersys received an upfront payment of $6 million and would be eligible to receive up to $105 million in milestone payments and tiered royalty payments on worldwide commercial sales of MultiStem IBD products (Athersys Press Release 2009). There have also been several corporate investments including the Roche and Novartis Venture Funds that invested in Cellerix S. A. (Cellerix Press Release 2007, 2009), a company focused on the development of adult stem cell-derived therapies; Johnson and Johnson Development Capital (JJDC) led the $25 million series C investment into Novocell (now ViaCyte, Inc.) (Novocell Press Release 2007), invested in several rounds in Tengion, Inc. including a $21 million series C round in 2008 (Tengion Press Release 2008) and Pfizer invested $3 million in EyeCyte in 2008 (Pfizer Press Release 2008). These examples illustrate that there is activity; however, the deals are few and far between. As a consequence, the trade sale options for a regenerative medicine company are limited and therefore arguably high risk.

Investment decisions are based on questions relating to what problem a technology is trying to solve, whether a product can be made, what the product will be worth, whether anyone will buy the product and how much investment will be required over what period of time to reach a viable exit. Investors therefore consider technologies that will gain market acceptance rather than the business opportunity that the technology platform creates. Accordingly, investors will review the potential of regenerative medicine products rather than nanotechnology as a platform per se.

Therefore, a key question is why are the large corporations reticent to fully engage in the regenerative medicine sector? There are a myriad of potential reasons; however, one major reason probably relates to regulatory issues that are complex and evolving both for regenerative medicines as well as for the use of nanomaterials.

4. EMERGING TECHNOLOGIES AND THE REGULATORS

In August 2006, the US Food and Drug Administration (FDA 2007) established a Nanotechnology Task Force with the remit to determine the ‘regulatory approaches that encourage the continued development of innovative, safe, and effective FDA-regulated products that use nanotechnology materials’. The resulting Nanotechnology Task Force Report (FDA 2007) recommended that the FDA consider the development of nanotechnology guidance for manufacturers and researchers and that, because of the emerging and uncertain nature of nanotechnology and the potential for multiple medical applications, there was a requirement for transparent, consistent and predictable regulatory pathways. The special properties of nanoscale materials may pose different safety issues from their larger or smaller counterparts and there is uncertainty with respect to knowledge about them and how their safety should be tested. Nanomedicines are relatively new and inevitably, therefore, the regulatory route is unpredictable. This in turn leads to uncertainty regarding the cost and time that will be required to successfully gain market approval for the nanomedicine. Such financial uncertainty would be equivalent to writing a blank cheque in order to develop the product: this is not an approach adopted by the venture capital community (see below).

It is interesting to note that the European Medicines Agency (EMA) will organize the ‘First International Workshop on Nanomedicine’ in September 2010 with ‘the objective to have a discussion on identified issues and emerging science aspects, which may provide directions for future developments and regulatory considerations for nanomedicines’ (EMA 2010).

The regulatory pathways for advanced therapeutic medicinal products, which include cell-based products derived from differentiated stem cells, are also complex.
and evolving, as illustrated by the interaction between Geron and the FDA. Geron invested $45 million and compiled 21,000 pages of documentation to support an investigational new drug (IND) application to enter the clinic with the world’s first human embryonic stem cell-derived therapy (GRNOPC1) for spinal cord injury (Tom Okarma, CEO Geron, 2010, personal communication). The FDA subsequently placed the IND on hold (Geron Press Release 2008) for approximately 10 months prior to granting permission for GRNOPC1 to enter the clinic in January 2009 (Geron Press Release 2009a). The trial was suspended in August 2009 owing to evidence of non-proliferative cysts in animal studies conducted in parallel with the clinical trial (Geron Press Release 2009b). Geron and the FDA subsequently reached an agreement as to what data would be required to re-initiate the clinical trial, anticipated towards the end of 2010 (Geron Press Release 2009c).

An evolving regulatory landscape and increasingly stringent regulatory demands result in an uncertain regulatory path that has both unknown cost and time implications. Such uncertainties have a potentially negative impact on any organization (VC or co-development partner) that is considering committing financial resources to develop the product. VCs are willing to take risks but these must be managed to moderate the high risk (see above): ‘uncertainty’ is difficult to manage. Co-development partners evidently prefer to manage risk by waiting until some of the challenges have been de-risked. For example, Genzyme Corp. formed a partnership with Osiris Therapeutics when Prochymal and Chondrogen were already in late stage development (Osiris Therapeutics Press Release 2008). Athersys’ Multistem product had reached phase I when the agreement with Pfizer to co-develop Multistem for IBD was announced (although the phase I trials were not targeting IBD; Athersys Press Release 2009).

Other challenges facing regenerative nanomedicines relate to whether these products can be manufactured and assembled cost-effectively and at scale. Cell-based regenerative medicines will be expensive to manufacture relative to conventional therapeutics (chemicals or biologics) and therefore must command a premium price. For example, cell-based products and media supplements such as growth factors and cytokines, like biologics, must be produced under good manufacturing practice (GMP) conditions. However, unlike biologics, which are products in their own right, as a media supplement they contribute to the cost of the manufacturing process and therefore increase the overall cost of the cell-based product. Consequently, to justify such expensive cell-based products they must demonstrate superior efficacy or at best be relegated to being used as a last line of resort once other less expensive products have been tried and shown to fail. At worst, the regenerative medicine may fail to be reimbursed and therefore not reach the market.

Investors will typically carry out extensive due diligence of intellectual property (IP) assets to access whether a prospective investee company has a secure patent position including the freedom to practise their invention (freedom to operate). The IP landscape for the regenerative medicine sector is complex to navigate, reflecting a rapidly increasing number of patents filed and a large number of patents that have an impact across all aspects of regenerative medicine including cell isolation, expansion, differentiation and routes of administration to the patient. Furthermore, there are dominating patents with broad claims, such as the three WARF patents (Wisconsin Alumni Research Foundation patents: US Patent 7029913, US Patent 5843780 and US Patent 6200806), that restrict the exploitation of human embryonic stem cells (Rabin 2005). A commercial licence can be obtained; however, for an early stage company, the licence fee may represent a significant proportion of the initial investment round and therefore is unattractive to the investor.

The rapid and apparently concomitant emergence of the induced pluripotent stem cell (iPSC) methodologies has led to a series of patents filed (Webb 2009). Such rapid advances in the iPSC field are a good illustration of yet another dilemma facing the investor in terms of ‘which horse to back?’ and ‘how relevant will the existing IP be relative to the new advances in technology?’. The broad IP issues (complex landscape, dominating patents and rapidly evolving technologies) are not unique to the regenerative medicine field; however, together with the uncertainties related to the regulatory route for regenerative nanomedicines and the lack of an obvious exit route for investors, these serve to compound the challenges facing the sector.

5. CONCLUSION

The successful track record of VCs investing in nanomedicine has underpinned their continued appetite to invest in the healthcare and life sciences at a time when investment in nanotechnology applied to other sectors has sharply declined (ObservatoryNano 2010). However, investee companies are developing products that are aligned with those developed by the pharmaceutical industry, thereby enhancing the probability of their adoption and successful route to market.

There is no doubt that the application of nanotechnology to regenerative medicine may offer enormous benefits including the potential to control cell fate, generate advanced scaffolds for cell delivery and modulate the immune response to implanted cells. However, there are multiple challenges beyond those posed by the research alone, including how such products should be regulated and whether they can be manufactured at scale cost-effectively to ensure that they are eligible for reimbursement. It is anticipated that these challenges may be resolved over time and, in doing so, this should bring clarity regarding their route to market. Increasing clarity serves to de-risk a venture and will therefore be key to attracting substantial levels of commitment by investors and the pharmaceutical and biotechnology industry.

REFERENCES

Athersys Press Release. 2009 Athersys enters into global agreement with Pfizer to develop and market multi-Stem(R) for the treatment of inflammatory bowel