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Delivery, retention and engraftment of progenitor cells in cell therapy

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In a recent issue of *Science Translational Medicine*, a multidisciplinary group of thought leaders in the field of biomaterial research and development contributed to a collection of opinion pieces highlighting the unique challenges and opportunities involved in translating biomaterials for use in humans.[1] These "Insider Views" were provided by experts from the industry, nonprofit, academic, clinical, intellectual property, venture capital, and regulatory sectors. They highlighted the potential bottlenecks that can occur in the biomaterial product development path, from uncertainty about the studies needed for regulatory approval to the risk associated with developing and commercializing an innovative biomaterial. These insider insights conveyed the message that translating regenerative medicine and cell therapy technologies to the clinic resembles a disorienting rollercoaster ride. To keep biomaterial development and approval on track, innovators need to negotiate the twists and turns associated with seven requirements of all product stakeholders: clinical need, intellectual property protection, preclinical validation, regulatory pathway, business and financial strategies, product design, clinical trial, and reimbursement. A recent TERMIS survey profiled the perceptions of 37 institutional investors regarding the numerous hurdles.[2] Successfully translating biomaterial technology into a product that truly benefits patients requires a balance of innovation and practicality. Although innovative technology is the starting point, it is the execution by a company to create and market a simple and effective medical product that determines whether a novel biomaterial reaches the clinic.

We are bombarded weekly with press releases about how stem cell therapies will soon change our lives. For example, headlines in *Genetic Engineering and Biotechnology News* tout "Accelerating R&D of Cell-Based Therapies" (October 1, 2012), "Cellular Therapy Wave Finally Cresting" (November 1, 2012), "Regen Med Nears the Market" (November 15, 2012), "Technologies Evolving for Cellular Therapies" (January 15, 2013), and "10 Most Significant Events in Cell Therapy in 2012" (March 15, 2013). Indeed, real progress is being made as "Cardiac stem cell therapies inch toward clinical litmus test" (*Nature Biotechnology*, January 2013). Reviewing the past year, Fisher and Mauck recount significant events in 2012 in tissue engineering and regenerative medicine.[3] In a State of the Art Review, Pashuck and Stevens summarize the tremendous potential for regenerative biomaterial therapies in light of the major scientific, regulatory and business hurdles that must be navigated to reach the market place.[4]

This themed issue was conceived to place a human face on these difficult issues by focusing on the efforts of seven translational research groups to mature, deliver and retain therapeutic cells at sites in need of clinical repair or regeneration. These research teams have in common the use of a clinical-grade injectable hyaluronan (HA)-based semi-synthetic extracellular matrix known as HyStem5 combined with progenitor cells, and the goal of each team is to realize the promise of treatment of human patients in the clinic. Let's start at the top, figuratively and literally. The first two papers describe injection of therapeutic cells into the brain. Moshayedi and Carmichael (http://dx.doi.org/10.4161/biom.23863) describe the use of HA hydrogels with neural stem cells for tissue reconstruction after acute ischemic stroke. Retention of cells in an anti-inflammatory matrix that supports cell growth and proliferation improves outcomes. In a very different context, Shah (http://dx.doi.org/10.4161/biom.24278) presents the use of HA hydrogels for encapsulation of therapeutically engineered cells into a post-resection cavity in the brain following removal of malignant glioblastoma multiforme. The third paper by Gaston and Thibeault (http://dx.doi.org/10.4161/biom.23799) summarizes the many uses of HA hydrogels for prevention and repair of injury to the human vocal folds.

In the fourth paper we get to the heart of the matter. Smith, Marban and Marban (http://dx.doi.org/10.4161/biom.2449) describe the use of cardiosphere-derived cells (CDCs), which have already used successfully in two clinical trials by intracoronary infusion in buffer. They describe how injection of CDCs encapsulated in the HA-gelatin HyStem-C after a myocardial infarct in a preclinical model enhances cell retention and engraftment, increases angiogenesis, adds cardiac muscle mass, and improves cardiac outcome relative to infusion of the CDCs alone. In the fifth paper, delivery of endothelial progenitor cells (EPCs) embedded in HA-gelatin hydrogels also serves as a treatment for acute kidney injury. Ratliff and Goligorsky (http://dx.doi.org/10.4161/biom.2449) summarize their preclinical studies in which gel-encapsulated EPCs can be delivered into the kidney capsule, or by slow release from EPC-gel constructs placed in the ear pinnae with a small amount of hyaluronidase. In both cases, increased kidney function, angiogenesis, and engraftment are observed.

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The final two papers draw attention to other important uses of HA-gelatin matrices. Compte, Nuñez-Prado, Sanz and Vallina (http://dx.doi.org/10.4161/biom.23897) draw attention to the concept of immunotherapeutic organoids as a new approach to cancer treatment. Echoing the use of engineered cells in the brain by Shah, this team highlights the practical importance of living cell factories capable of secretion of recombinant antibodies in vivo, an effect uniquely attributable to long-lived engineered mesenchymal stems cells delivered subcutaneously in an HA-gelatin hydrogel matrix. Finally, Sternberg, Janus and West (http://dx.doi.org/10.4161/biom.24496)introduce the concept of monoclonal embryonic progenitor (hEP) cells, which are clonally expanded human embryonic stem cells at an intermediate stage of differentiation. Combining these PureCell lines with the HA-gelatin hydrogel leads to HyStem-4D bead arrays, in which the hydrogel serves in expansion and differentiation in the dimension of time as well as three spatial dimensions.

It has been a pleasure working with the authors and editors to develop this themed issue. These stories of translational research embody the translational imperative: embrace complexity, engineer versatility, but deliver simplicity.[5]

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