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# The Use of a Hydrogel Matrix as a Cellular Delivery Vehicle in Future Cell-Based Therapies: Biological and Non-Biological Considerations

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## 1. Introduction

Cell therapy is defined as the minimally-invasive delivery of therapeutic cells into a human host to repair damaged or diseased tissue(s). Its long-term goal is to reduce the current expense of 1% of US GDP on organ replacement therapies (Lysaght, et al., 2008). Hematopoietic stem cell transplants are the most popular cell therapy and have been crucial in treating a variety of hematological diseases (Cutler and Antin, 2001; Horowitz, 2004). For novel cellular therapies (i.e. using non-hematopoietic cells directed against non-hematological diseases), the numbers fall off precipitously. Of these, only cell-based cartilage repair is the only novel cell therapy so far used with significant frequency (Martin, et al., 2010). Since this therapy additionally requires the expansion of and the use of autologous chondrocytes, this data suggests a crucial bottleneck for a wide variety of novel cellular therapies will be both in producing enough rare cells for therapeutic effect as well as for obviating immunologic concerns.

The emergence of stem cell biology has reshaped the cell therapy and tissue engineering landscape because the quantity and breadth of therapeutic cell has been dramatically expanded. Stem cells are typically derived from embryos or adult tissues and have two abilities: to self-renew (i.e. one stem cell can divide and make more stem cells) and to differentiate into specialized cells. These characteristics allow stem cells to be used to produce large quantities of a wide variety of cell types, including rare or difficult to harvest cell types (Takahashi, et al., 2007; Thomson, et al., 1998; Yu, et al., 2007). The therapeutic value of these cells can be captured by either using them to directly produce new tissue (Keirstead, et al., 1999) or as a source of bioactive agents such as cytokines and growth factors inducing host cells and tissues to regenerate themselves (Caplan and Dennis, 2006). In addition, a wide variety of stem cells can be harvested or derived from adult tissues such as bone marrow, adipose tissue, or cord blood (Ingram, et al., 2004; Lennon and Caplan, 2006; Zuk, et al., 2001). Adult stems can potentially lower the hurdle of immunologic incompatibility due to either their autologous nature or immunomodulatory effects (Caplan and Dennis, 2006).

While stem cells obviate the shortcomings of using a patient's differentiated cells, the rate-limiting step in successful cell therapy is not only the number of transplanted cells but their survival rate post-transplantation. In short, the transplanted stem cells need help to stay

alive long enough for their therapeutic effect to be seen. The majority of stem and progenitor cells in the transplanted bolus die shortly after transplantation (Bliss, et al., 2007; Snyder, et al., 2010; Terrovitis, et al., 2008; Zhong, et al., 2010). In some cases, more than 95% of transplanted stem cells die within two weeks of transplantation (Snyder, et al., 2010; Terrovitis, et al., 2008; Zhong, et al., 2010). Since tissues contain cells encapsulated in a carbohydrate and protein-rich extracellular matrix (ECM), one approach to significantly improve stem cell survival is to include a biomaterial carrier that acts as an ECM mimic upon *in vivo* delivery. These carriers have been prepared from synthetic or naturally sourced polymers and provide an adhesion surface which not only localizes cells but also provides a template for new tissue formation (Mooney and Vandenburgh, 2008).

While there are excellent review articles describing the design criteria for clinically useful matrices (Lutolf and Hubbell, 2005; Prestwich, 2008), this chapter focuses on their translation to the clinic—that is, the development of these matrices as FDA-approved injectable cell carriers, or cellular delivery vehicles, and how both biological as well as non-biological considerations (i.e. physician requirements, intellectual property, regulatory, manufacturing) must be satisfied before the biomaterial can reach the medical marketplace. In the first part, we present an overview of some of the basic biomaterials which have the potential to be developed as FDA-approved cellular delivery vehicles. Next, a more in-depth discussion of these biological and non-biological considerations follows. Finally, we describe one matrix, HyStem®, and its potential use in three areas: stroke, cartilage repair, and gene therapy.

## 2. Injectable matrices for stem cell therapies

### 2.1 Lessons from Hematopoietic Stem Cell Transplantation—the first stem cell therapy

The first stem cell therapy developed was hematopoietic stem cell transplantation (HSCT) reported in 1968 (Bach, et al., 1968; Gatti, et al., 1968) and is used to treat a variety of hematological malignancies (Cutler and Antin, 2001). It is also by far the most popular: there are in excess of 45,000 HSCTs performed annually worldwide (Horowitz, 2004). While there is still much research to do to understand the entire mechanism of how HSCT works, a review of HSCT is informative since many lessons can be learned and applied to novel non-hematological stem cell therapies.

HSCT can be summarized as follows: HSCT typically begins with the harvest of either bone marrow or the leukocyte fraction of peripheral blood either autologously or allogeneically from an immunologically (or human leukocyte antigen (HLA)) matched donor. The therapeutic fraction of these cells are the CD34<sup>+</sup> (early hematopoietic cell marker) cells and contains both multipotent hematopoietic stem cells (CD34<sup>+</sup>/CD38<sup>-</sup>) (Cutler and Antin, 2001) and more mature hematopoietic precursor cells (Duran-Struuck and Dysko, 2009). A minimum of  $2 \times 10^6$  CD34<sup>+</sup> cells are required per kg recipient body weight, or 300 million cells per 150 kg adult (Cutler and Antin, 2001; Mavroudis, et al., 1996). Importantly, the mixture of the young pluripotent and more mature hematopoietic stem cells is crucial since the older cells act as escorts to provide temporary immunological restoration and host survival while the younger cells engraft and generate mature cells to replace the former (Duran-Struuck and Dysko, 2009).

After harvest from the donor, these cells are then transplanted intravenously into a recipient who may require prior myeloablation of the host bone marrow. Myeloablative treatment

destroys the host hematopoietic cellular population while leaving many aspects of the hematopoietic niche intact (Dominici, et al., 2009; Duran-Struuck and Dysko, 2009; Slayton, et al., 2007). The niche includes cells such as osteoblasts and mesenchymal stromal cells to which the HSCs attach to as well as communicate with via soluble and insoluble signals (Scadden, 2006; Taichman, 2005). While HSCs find the bone marrow randomly (Cui, et al., 1999), a significant number of cells travel to the marrow where engraftment occurs 2-4 weeks post-transplantation (Cutler and Antin, 2001).

From this example, it can be inferred that the key steps in successful stem cell engraftment include 1) cellular and sample integrity, 2) cellular travel to and anchoring within the niche (homing and lodgment) (Cui, et al., 1999; Lam and Adams, 2010), 3) niche remodeling (Sands and Mooney, 2007), 4) cellular proliferation and differentiation (engraftment) (Cutler and Antin, 2001), and 5) an appropriate space and nourishment to do so (Scadden, 2006). HSCT only requires a 2-4 week post-transplantation time period for engraftment since the transplanted cells and the host cell niche are ready to be merged. The transplanted cells are a mixture of gently-processed cells and they only require less than two days for bone marrow localization after IV administration (Cui, et al., 1999). Once in the bone marrow, the cells should lodge efficiently since the irradiated bone marrow niche mostly retains its native matrix structure and supporting cells (Dominici, et al., 2009; Slayton, et al., 2007) with little remodeling required. In HSCT, both space and access to blood supply is present for the cells since bone has significant open regions for the cells in its interior and is highly vascularized (Gentry-Steele and Bramblett, 1988).

## 2.2 Challenges for novel stem cell-based therapies

Unlike HSCT, novel stem cell therapies face a more difficult road primarily because neither the stem cell nor its host microenvironment has been prepared in advance of their arrival in their new home. Since stem cells have little function outside of their niche (Scadden, 2006), they must construct their own among their other duties under transplantation duress. Initially, the stem/progenitor cells are extracted from its self-synthesized ECM either from a solid tissue organ or from the surface of a tissue culture plastic plate. Cellular integrity is the first obstacle these cells face. Since harsh enzymatic methods such as trypsinization are typically used, integrins required for cellular attachment are cleaved and need to be resynthesized by the cell (Harrison and Rae, 1997; Wu, et al., 2005). The next major obstacles are lodgment and niche remodeling. While the cells are then injected adjacent to the host target tissue of interest, they have few surface receptors to attach to the surrounding ECM. If the target tissue is diseased or damaged, its niche may also need significant remodeling. For example, the tissue ECM may have significant scar tissue with dramatically different mechanical properties and function from those of the native target tissue (Laflamme, et al., 2007; Martens, et al., 2009; Reilly and Engler, 2009; Scadden, 2006). Altered microenvironment compliance could provide more resistance to remodeling by affecting the desired stem cell differentiation path (Engler, et al., 2006). The final obstacle is the inadequate conditions for engraftment since there is no pre-established vasculature present to nourish the transplanted cells (Martens, et al., 2009). In some cases, there will be little or no space for the cells to divide into since the target tissue has no cavity (Darabi, et al., 2009; Laflamme, et al., 2007; Terrovitis, et al., 2008). It is no surprise that most transplanted cells die within 24 hours of transplantation (Bliss, et al., 2007; Guerette, et al., 1997; Snyder, et al., 2010; Suzuki, et al., 2004; Tate, et al., 2009; Terrovitis, et al., 2008; Zhong, et al., 2010).

## 2.3 The hydrogel cell delivery matrix

A solution is to borrow principles from the field of Tissue Engineering by providing a temporary, more native niche for the cells until they can synthesize their own. Tissue engineering is the *ex vivo* cultivation of cells on polymeric scaffolds in order to generate tissues or organs for transplantation (Kaihara and Vacanti, 1999). The use of degradable polymer scaffolds is crucial since it provides an initial remodelable substrate for the cells, provides space for the cells to reorganize into more complicated tissues, and potentially can be designed to provide an initial template to guide subsequent structure formation (Kaihara and Vacanti, 1999). Hydrogels made from naturally occurring biopolymers are one kind of degradable scaffold that has four key characteristics: first, their high water content simulates the microenvironment for soft tissues and allows for transfer of gases, small molecules, and proteins (Tibbitt and Anseth, 2009). Second, the starting biopolymers frequently have chemically-available side groups which can be functionalized for altering its mechanical properties, degradation time, and cellular adhesion surfaces (Serban and Prestwich, 2008; Tibbitt and Anseth, 2009). Third, they can be constructed to encourage neovascularization for the cells (Cai, et al., 2005; Liu, et al., 2007; Phelps, et al., 2010). Finally, they are injectable when in liquid form, fulfilling the minimal invasive surgery criterion favored by physicians (Miles, et al., 2004).

### 2.3.1 Types of hydrogels currently available

While there are currently no hydrogel matrices FDA-approved for use specifically for stem cell therapies, there are a number of biomaterials to choose from with varying degrees of regulatory and manufacturing hurdles (Table 1). These include those that 1) have been recently developed in academic laboratories, 2) are commercially available for research use only and whose regulatory status can be extended for human clinical use (e.g. HyStem-C, MT-3D Q-gel, RGD-alginate, etc), or 3) are in fact FDA-approved for acellular indications and would need to be extended for stem cell delivery indications (e.g. Fibrin glue), (Figure 1, Table 1).

All of these matrices roughly fall into one of three classifications: natural, synthetic, or semi-synthetic (Fig. 1). While natural matrices are typically well-tolerated by the host and cells due to their mimicking the natural ECM in terms of backbone and microstructure, they generally suffer from lot-to-lot variability, high degradation rates, and poor tunability (Tibbitt and Anseth, 2009). In addition, their complexity and poor definition can portend difficult manufacture pursuant to current Good Manufacturing Practices (cGMPs) required for clinical application. For example, Matrigel is arguably the most popular hydrogel matrix used in preclinical studies since it is in fact a native ECM with a variety of matricellular proteins and growth factors. Despite these benefits, Matrigel will likely never be placed in humans due to regulatory and manufacturing concerns. In particular, its mouse tumor origin and ill-defined, variable composition are problematic with nearly two-thousand unique proteins present (Hughes, et al., 2010; Nagaoka, et al., 2010).

Synthetic matrices are the opposite: while very reproducible, tunable, and amenable to more facile regulatory and manufacturing protocols, they generally require engineering to provide both cellular attachment sites and degradation rates comparable to those for native ECMs (Tibbitt and Anseth, 2009). Semi-synthetic matrices share characteristics of both classes and can be constructed either by modifying purified natural biopolymers such as HA or Alginate (Alsberg, et al., 2001; Darr and Calabro, 2009; Zheng Shu, et al., 2004) or by



engineering synthetic polymers with integrin and/or growth factor binding sites and degradation signals to more closely mimic the natural ECM (Raeber, et al., 2005; Tibbitt and Anseth, 2009).

Name	Base Biopolymer	Crosslinker	Cell Attachment sites	References
<i>Natural</i>				
Matrigel™ (BD Biosciences)	Laminin and Collagen IV	None	Yes	(Kleinman and Martin, 2005)
Purecol ® (Advanced BioMatrix)	Collagen I	None	Yes	(Beckman, et al., 2008)
Tisseel ® (Baxter)	Fibrin	Glutamyl/lysine covalent bonds	FN	(Ahmed, et al., 2008)
Alginate (FMC Biopolymer)	Alginic acid	Calcium	none	(Alsberg, et al., 2001)
<i>Semi-Synthetic</i>				
HyStem-C (Glycosan BioSystems)	Thiolated HA	PEGDA	Thiolated gelatin	(Zheng Shu, et al., 2004)
RGD-alginate (FMC Biopolymer)	Alginic acid	Calcium	RGD	(Alsberg, et al., 2001)
Corgel ™ (Lifecore)	Tyraminated HA	Dityramine covalent bond	none	(Darr and Calabro, 2009)
<i>Synthetic</i>				
Puramatrix ™ (BD Biosciences)	(RADA) <sub>16</sub>	None	RAD	(Semino, 2008)
PEGDA (Glycosan BioSystems)	PEGDA	Covalent bond	none	(Moon, et al., 2009)
MT-3D (Qgel)	PEGDA	Di-cysteine containing peptide	RGD	(Raeber, et al., 2005)

Table 1. Commonly-used commercially available injectable hydrogel matrices. Abbreviations: PEGDA, polyethylene glycol diacrylate; HA, hyaluronic acid; FN, fibronectin; RADA, arginine-alanine-aspartate-alanine tetrapeptide; RGD, arginine-glycine-aspartate tripeptide. Suppliers are shown in parentheses below product name

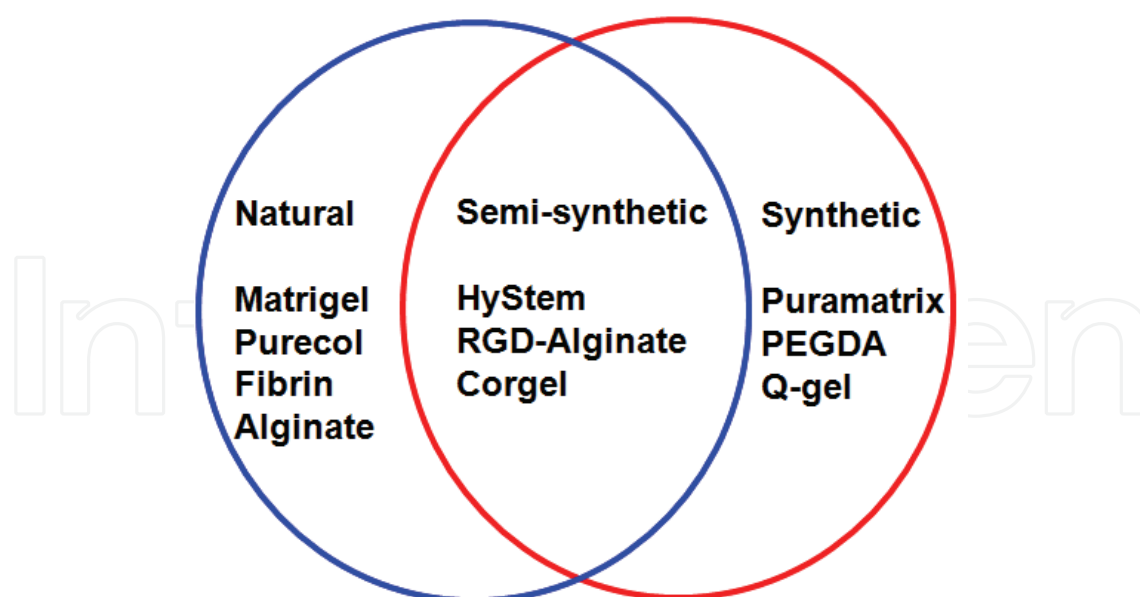


Fig. 1. Different types of hydrogel matrices

A common misconception is that a variety of FDA-approved hydrogel matrices are simple to transfer from its approved indication to one involving stem cell delivery. One case in point is natural biopolymer-derived dermal fillers which are currently approved for use as acellular space fillers in cosmetic indications. Examples include collagen-based Zyplast® and HA-based Juvederm® and Restylane® (Newman, 2009). Many of these biomaterials, however, are pre-crosslinked within prefilled syringes and preclude the addition and homogenous distribution of cells prior to injection. In addition, these HA-based biomaterials have no cellular attachment sites, causing cellular apoptosis or anoikis.

## 2.4 Matrix choice

Even though there is a wide variety of hydrogel matrices to choose from, there is still doubt as to whether a delivery vehicle is even needed and if so, how one might choose the best matrix for an application. For many researchers and physicians, the widespread death of stem cells after transplantation is thought to be unavoidable and provides the rationale for implanting a massive number of cells. The hope is that enough cells survive post-transplantation for there to be a therapeutic effect. For those who see value in including a matrix carrier, its selection is usually an afterthought. For some, the choice is made out of convenience due to collaboration with a bioengineer in the same institution. For others, it is made from a scan of the literature or from collaborator recommendations. Without considering their therapeutic stem cell microenvironment after transplantation, the range of options, and requirements for translation, all matrices appear comparable. However, there are at least three distinct lenses through which a researcher or physician must peer to decide on the best matrix for the therapeutic stem cell and indication. These viewpoints provide the basis for three sets of criteria that a matrix must fulfill.

### 2.4.1 Biological criteria for the researcher

From a researcher's perspective, the matrix choice will be driven by maintaining consistency with a) the therapeutic stem cell mode of action b) the properties of the ECM from both the transplanted cell and the target tissue. There are two primary modes of action for a

therapeutic stem cell after transplantation: *direct*, or transplanted cell engraftment into the host tissue and *indirect*, or secretion of trophic bioactive factors which induce host tissue repair (Caplan and Dennis, 2006). The former requires the matrix to be degradable in concert with the remodeling and cell proliferation of the transplanted cells (Mooney and Vandenburgh, 2008). Alternatively, the latter requires a release of soluble factors as well as a longer-term protective environment from the host immune system (Luca, et al., 2007; Penolazzi, et al., 2010). Since alginate and PEGDA degrade very slowly (Liao, et al., 2008; Shikanov, et al., 2009), they are well suited for the latter indication. Indeed, both have already been used for non-stem cell based therapeutics; for example encapsulating pancreatic beta cells or islets in alginate or PEGDA prior to transplantation promotes cellular immunoprotection and survival for these cells and extends the window of insulin production (Lin and Anseth, 2009; Wilson and Chaikof, 2008).

Matrix choice is also dependent on the properties of the therapeutic cell ECM since it can provide cues for proper cellular function. In particular, the matrix biopolymer backbone is an essential property to consider since it can contain a great deal of biological information crucial to the cell type. For example, HA has a dual role in cellular biology: it plays a key structural role in the ECM through its interaction with members of the lectican family of proteoglycans while affecting cellular signaling important for development (Camenisch, et al., 2000; Ruoslahti, 1996). In cartilage, HA interacts with the lectican aggrecan which stabilizes the cartilage ECM (Aszodi, et al., 2006; Fraser, et al., 1997; Knudson and Knudson, 1993; Laurent and Fraser, 1992). In addition, HA also interacts with the chondrocyte CD44 receptor to induce genes involved in matrix degradation (Schmitz I et al., 2010). Hence, the use of an HA-based scaffold for implanting chondrogenic cells to heal osteochondral cartilage defects is logical and has in fact been shown to be effective for *in vitro* chondrocyte culture and for animal models of cartilage injury (Chung and Burdick, 2009; Liu, et al., 2006; Toh, et al., 2010). In cardiac development, HA interacts with another lectican, versican, in the cardiac ECM while playing a crucial signaling role in endothelial cell migration and transformation (Camenisch, et al., 2000). Successful use of HA-based hydrogels in the study of cardiac development logically follows (Young and Engler, 2010). Importantly, since all lecticans including neurocan and brevican are also expressed in the nervous system (Yamaguchi, 2000), HA plays a crucial role in the brain extracellular matrix and can provide an excellent substrate for neural tissue engineering (Zhong, et al., 2010).

Matrix choice also depends on the target cell ECM since its matrix compliance and cellular attachment sites present provide differentiation cues for the cells (Engler, et al., 2006; Flaim, et al., 2005; Soen, et al., 2006). With respect to ECM compliance, stem cells are like chameleons—they assess their current substrate compliance and figure out which cells they need to differentiate into so that the compliance of their new ECM matches. For example, a matrix stiffness of less than 1 kPa induces mesenchymal stem cells to become neural-like ((Engler, et al., 2006); Fig. 2), suggesting softer hydrogels are more appropriate for CNS applications (Zhong, et al., 2010). For this reason, it is important to use a matrix whose compliance matches that of the target tissue/cell ECM. A comparison of different matrix compliances is shown in Figure 2. Like matrix stiffness, the appropriate mixture of polypeptide sequences representing cellular attachment sites will likely need to be matched to the cell type and application. While there are hydrogels engineered to contain the RGD peptide for cellular attachment (Alsberg et al., 2001; Raeber et al., 2005), this peptide will likely not be sufficient for each application to maximize differentiation down an specific path (Flaim et al., 2005; Soen et al., 2006).



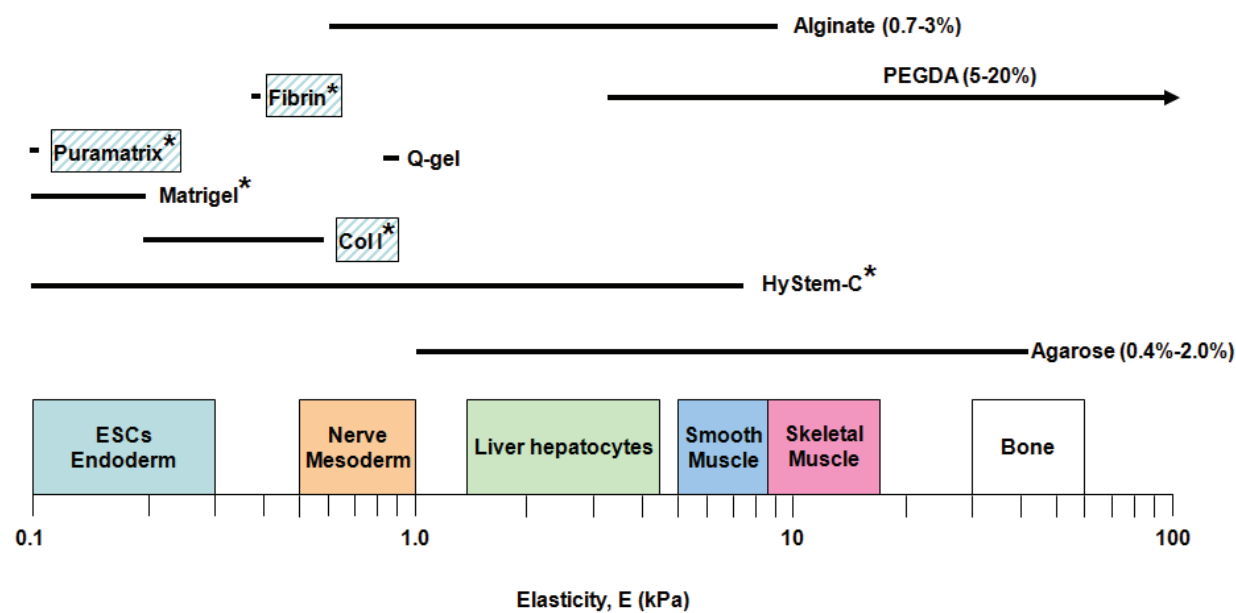


Fig. 2. Elasticities of tissues and of commercially available hydrogel matrices. The Young’s modulus of various vertebrate tissues (colored boxes (Reilly and Engler, 2009); ESCs, embryonic stem cells) compared to the ranges attainable with various hydrogel matrices (solid lines; alginate (West, et al., 2007), PEGDA (Patel, et al., 2005), Fibrin (Weisel, 2004), Q-gel (Raeber, et al., 2005), all remaining hydrogels (Doty, 2011)). Hatched boxes indicate which matrices are fibrillar. Asterisk (\*) indicates which matrices have basic cellular attachment sites

While not a property of the cell or target tissue, a final criterion from a practical standpoint to consider is the use of potentially noxious crosslinking mechanisms since both the reagents used and/or the conditions to catalyze gelation can cause aberrant cell behavior or cell death. For example, UV light is used to photoinitiate radical chain polymerization of macromolecules functionalized with vinyl groups (e.g. PEGDA, HA methacrylate). Cytotoxicity must be evaluated in the presence of specific photoinitiator concentrations and UV light intensities (Bryant and Anseth, 2006). An additional example is the use of calcium as a crosslinking agent for alginate-based hydrogels. While alginate has been successfully used for culturing a variety of cell types (Alsberg, et al., 2001; Xu, et al., 2006), calcium has also been shown to reduce cellular viability in Sertoli cells with extended exposure during encapsulation (Luca, et al., 2007).

2.4.2 Physician criteria

For a doctor to adopt a new technology, it must satisfy the needs of all stakeholders involved in a patient’s care. These include the surgeon transplanting the cells, the assisting nurse who prepares the hydrogel and cell mixture, the patient, and the payer. While all stakeholders have a vested interest in the hydrogel matrix improving cellular survival, arguably the most important are the physician and assisting nurse who find convenience of use crucial (Reiner, 2009). Critical variables affecting convenience include speed of hydrogel dissolution in clinically relevant buffers (e.g. lactated ringer’s solution), number of vials required to reconstitute the hydrogel, and speed of gelation of the hydrogel/cell mixture prior to injection. Of these, speed of gelation may be the most important since too fast of

gelation precludes facile injection of the hydrogel/cell mixture. Too slow of gelation may not properly localize the incorporated cells since they may either settle to the bottom of the injected bolus, the bolus may begin to disperse, or the very motion of an organ may cause the bolus to ooze out (Martens, et al., 2009). A comparison of the different matrices' gelation times are shown in Table 2

Fast (< 5 min)	Medium (10-20 min)	Slow (60+ min)
Corgel Fibrin PEGDA Alginate RGD-alginate	Matrigel HyStem-C Q-gel	Purecol Puramatrix

Table 2. Gelation times of hydrogel matrices

2.4.3 Non-biological criteria

2.4.3.1 Introduction

While the first two sets of criteria have focused on the science behind cell delivery vehicles, this third set of criteria is a dramatic departure representing key concerns surrounding the development of any human therapeutic. That is, the question must be answered: can it be made profitably and in compliance with regulatory standards? With the increasing levels of research activity in stem cell therapy and tissue engineering, it is expected that many novel stem cell delivery vehicles in addition to different injectable hydrogels will emerge. Indeed, there are already numerous reports in the medical literature of the use of a wide variety of matrices and scaffolds with stem cells and range from synthetic polymers (James, et al., 2011), cell extracts (Rajasingh, et al., 2008), to de-cellularized tissues such as small intestinal mucosa, urinary bladder basement membrane and mucosa, skin, heart, and fat (Badylak and Gilbert, 2008; Flynn, 2010). Nevertheless, all of them must overcome the last and perhaps the most difficult hurdle: commercialization and regulatory approval for human use.

Commercialization is the conversion of a technology into a profitable product and this is usually done by a for-profit institution. Its financial support and guidance are required to fund and navigate an efficient path to the clinic and then to the marketplace. The first step in this process is typically the licensing of the technology's rights from the academic medical institution (Poltorak and Lemer, 2004). However, the majority of these matrices and scaffolds will never be licensed since they cannot be patented or be made profitably. From an intellectual property standpoint, the lack of commercial viability for these materials typically arises from the absence new or novel intellectual property that can be protected by patent. Without patent protection, the ability to maintain a competitive advantage in the marketplace is absent and hence the potential to make a highly profitable product is compromised. If the technology survives IP landscape scrutiny, the cost in manufacture must be significantly less than the price acceptable to the marketplace. In general, there is a high manufacturing cost for biomaterials derived from animal or human sources (including costs for both raw materials and for cGMP manufacture especially in the beginning when low volumes of materials are prepared (Thompson, 2006)). Finally, the path to regulatory approval can be expensive and treacherous.

Successful translation of basic research in tissue engineering and regenerative medicine to clinical applications demands a thorough understanding of a number of regulatory issues for the therapeutic cell as well as the delivery matrix or scaffold. The remainder of this section will focus on describing the regulatory approval path for combination stem cell/matrix products as well as general considerations surrounding cGMP manufacturing.

#### 2.4.3.2 Regulatory

Since a matrix will be combined with the stem cell, two distinct centers within the FDA share the regulatory responsibilities. Cell-based products are regulated by the Center for Biologics Evaluation and Research (CBER) (FDA, 1997). Therapeutic products consisting of stem or progenitor cells delivered to the body in a matrix or implanted in a scaffold however are considered combination products where the matrix or scaffold is a medical device and the cells the new therapeutic agent. CBER will request consultation from the Center for Devices and Regulatory Health (CDRH) for guidance in device approval issues. CBER's final approval will be for a specific delivery matrix and cell type for a clearly defined indication. As a result there is no pathway, at this time, for approval of a matrix or scaffold as a medical device for general cell delivery for stem cell therapy applications.

From the cellular standpoint, the regulatory path for somatic cells and tissues and for stem cells is similar since the former serves as the basis for the latter. Since 1993, the FDA has been developing guidelines and regulatory pathways to regulate the development, manufacture and distribution of somatic cell therapy products. Over the last decade these guidelines have been broadened to include stem and progenitor cell therapeutic products. These guidelines are designed to ensure that such products meet defined safety requirements and have the identity, strength, quality and purity characteristics as those represented to the FDA. In addition, the FDA has recently mandated that any procedure in which human cells manipulated for clinical use are subject to federal manufacturing standards and oversight (18 21 C.F.R. § 1271.3(d) (2009); see 42 U.S.C. § 264). Specifically, Part 1271 of Chapter 21 of the Code of Federal Register unifies the registration and listing system for establishments that manufacture human cells, tissues, and cellular and tissue-based products (HCT/Ps) and establishes current good tissue practices, and other relevant procedures. These regulations, known as the Good Tissue Practice (GTP) requirements, encompass the minimal manipulation of cells for clinical use; i.e. for processes that do not alter the biologic characteristics of the cells (21 CFR Parts 16, 1270, 1271). For procedures in which the biologic nature of the cells is altered to affect a clinical outcome, termed "more than minimal manipulation," Part 211 pharmaceutical cGMP will apply, as well as relevant aspects of Parts 210, 600 and 1271. In addition to these base requirements, any stem-cell-based product that contains cells or tissues that "are highly processed, are used for other than their normal function, are combined with non-tissue components, or are used for metabolic purposes would also be subject to the Public Health Safety Act, Section 351, which regulates the licensing of biologic products and requires the submission of an investigational new drug application (IND) to the FDA before studies involving humans can begin. (21 C.F.R. Part 312 (2009); (Carpenter, et al., 2009))

From the matrix standpoint, its regulatory path depends on which medical device classification it is assigned within the FDA. If the device has not been previously approved

or cleared for its intended use, detailed device information must be included in the investigational new drug (IND) submission for a Center for Devices and Radiological Health (CDRH) consult review. It is also recommended that a Device Master File (DMF) be submitted to CDRH (a DMF provides confidential information surrounding manufacture and can be referenced by a sponsor in support of an IND application (FDA, 2011; Read and Khuu, 2009)). In applications where the matrix and cells are used topically, such as wound healing, the delivery matrix is usually classified as a class II medical device. However, when the cells are injected or *implanted* within the body in a matrix to promote attachment and proliferation of the therapeutic cells, these delivery vehicles are classified as class III medical devices (21 CFR, 860.93; 21 U.S.C., 360c (c)(2)(C)). The scope of the information required in a DMF varies only slightly between class II and class III medical devices with the class II devices requiring less biocompatibility testing. For class III, permanently implanted or resorbable, medical devices, biocompatibility of the device alone is assessed through the prescribed *in vitro* and *in vivo* animal testing asset set forth in the ISO-10993 guides. These tests encompass cytotoxicity, sensitization, irritation, acute and chronic systemic toxicity, genotoxicity, and long term implant with histopathology.

In addition to the demonstration of biocompatibility for the matrix alone as described above, the interaction of the therapeutic cells and their delivery matrix or scaffold must also be characterized for safety and toxicology. Such studies should demonstrate that the matrix or scaffold does not alter the function of the cells in such a way as to raise safety and toxicity concerns. In addition to a thorough characterization of the delivery matrix and its interaction with the therapeutic cells, CBER will request complete documentation on the source and manufacture of the cells, dosing studies, and clear evidence of efficacy. While cell specific issues are beyond the scope of this discussion, they are a major part of any IND submission.

#### 2.4.3.3 cGMP manufacturing

Of equal importance to biocompatibility, safety, and toxicity, is the requirement for manufacture and testing of these cell delivery devices with appropriate quality assurance and quality control to meet FDA standards. To this end, manufacturing and testing in compliance with current Good Manufacturing Practices (cGMP) regulations following validated production and analytical testing protocols is required. What is cGMP? While this is the subject of a book chapter onto itself, at its heart it is a quality system which pervades every step of the product and process development. Validation is a critical part of cGMP manufacture and provides the basis for a program which provides documents assuring both proper systems functioning and final product which meets required specifications. It requires analytical methods development and validation, as well as production of engineering batches, process validation batches, and clinical trial material (Beckloff, 2008). Proper validation specifically for manufacturing procedures and analytical testing protocols for the Chemistry, Manufacturing, and Controls section of a DMF is arguably the major commitment of time and money in cGMP manufacture and should be addressed early the device development strategy.

As a final note, a question that frequently arises is: when a supplier claims their products are “cGMP quality”, what does this mean? Suppliers of matrices or scaffolds for basic research often represent their products as being made in a cGMP compliant facility. Does this mean that their products are “cGMP quality”? Such statements should be viewed with caution.



As with other industries where quality is crucial, a rigorous audit from an independent regulatory body is required to assure an institution is in substantial compliance with the quality system that the institution follows. Hence, until such time as the FDA has inspected a manufacturing facility and issued a Form 483 listing inspectional observations in response to a specific IND application, there can be no assurance that the manufacture of the device is indeed in substantial compliance with cGMP requirements.

### 3. HyStem applications in stem cell therapy

While a number of hydrogel matrices will substantially fulfill the criteria described, those matrices which are customizable have a distinct advantage since all stem cells are not created equal. To maximize its utility across a wide range of stem cells and indications, a hydrogel matrix whose composition can be easily modified by the end user is an important feature. The HyStem hydrogel platform is well suited for cell delivery of numerous stem cells since it not only mimics a variety of microenvironments with its basic HA formulation (*vida supra*), but it can be easily adapted to add functionality. The HyStem family of HA-based hydrogels are based on crosslinking HA, gelatin, and heparin with PEGDA using Michael addition chemistry (Zheng Shu, et al., 2004). These three components are modified with thiol groups and used as modules to make three different HA-based hydrogels: HyStem® (thiolated HA), HyStem-C (same as HyStem plus thiolated gelatin for cellular attachment), HyStem-HP (same as HyStem-C plus thiolated heparin for slow growth factor release) (Serban and Prestwich, 2008). Each component is thiolated using EDC/NHS chemistry followed by crosslinking at physiological pH and temperatures via Michael addition using the acrylate groups in PEGDA (Zheng Shu, et al., 2004). Importantly, HyStem's formulation can be further customized by covalent introduction of a variety of molecules compatible with HyStem's thiol-based chemistry. For example, molecules such as cellular attachment peptides with an acrylate or a free cysteine thiol group can be covalently crosslinked into the matrix (Zheng Shu, et al., 2004). In addition, matrix compliance can be modulated by the concentration PEGDA used (Hanjaya-Putra, et al., 2010; Vanderhooft, et al., 2009). Below we highlight three of the newest stem cell applications using HyStem technology.

#### 3.1 Stroke

Stroke is highly prevalent with 550,000 hospitalizations and 150,000 deaths annually in the US alone (Taylor, et al., 1996). While current treatments do little to recover lost function due to cerebral damage, direct implantation of neural stem or progenitors into the infarct cavity may be effective in repair and eventual recovery (Zhong, et al., 2010). The challenge in this approach is that stem and progenitor cells die *en masse* shortly after transplantation (Bliss, et al., 2007). A solution is to deliver the therapeutic cells in an HA-based cellular delivery vehicle. HA provides a biomimic of the brain microenvironment since HA is abundant in the brain ECM (Fraser, et al., 1997; Ruoslahti, 1996), shares brain mechanical properties (Hou et al., 2005) and is conducive to neural growth (Wei, et al., 2007).

HyStem-HP hydrogel was recently used to deliver neural progenitors into an brain infarct cavity (Zhong, et al., 2010). One week after infarct transplantation in HyStem-HP hydrogel, cellular survival of mouse neural progenitor cells doubled, cell distribution was highly localized, and activated microglia/macrophages were excluded from access to the cells



(Zhong, et al., 2010). Importantly, HyStem-HP's use is congruent with current stroke therapy procedures since it can be administered via a catheter or cannula through a burr hole using computed tomographic (CT) guidance (Montes, et al., 2000).

### 3.2 Cartilage repair

Degenerative joint diseases affect approximately 20% of the adult population and cost nearly US \$30 Billion dollars annually to treat (CDC, 2007; Grayson, et al., 2008). Two current treatments involving transplantation of autologous cartilage from other parts of the joint (mosaicplasty) or transplantation of expanded chondrocytes (Carticel) are non-ideal solutions since the transplanted tissue poorly integrates while causing damage to the donor area of joint (Grayson, et al., 2008). One solution is the transplantation of hESC-derived chondrocyte progenitor cells since the large quantities of the cells can be produced. In addition, they have the ability to fully differentiate into chondrocytes which induces cartilage ECM synthesis and hence better integration (Toh, et al., 2010). The delivery of these cells benefit from a hyaluronic acid based matrix since HA plays a key structural and biological role in cartilage ECM (*vida supra*).

Recently two successful approaches using HyStem-C have been reported: the first uses autologous bone-marrow derived mesenchymal stem cells which are injected and localized with HyStem-C in an full-thickness osteochondral defect in rabbits (Liu, et al., 2006); the second, while not an injectable therapy, also uses HyStem-C and serves to show its utility (hESC-derived chondrogenic cells are precultured in HyStem-C before implantation in rats (Toh, et al., 2010)). In both cases, healing was rapid and significant: In 4-6 weeks, a new smooth regenerated cartilage surface begins to form; by 8-12 weeks, smooth, hyaline-like cartilage has completely filled the defect with excellent integration (Liu, et al., 2006; Toh, et al., 2010). Importantly, the regenerated tissue abundantly expresses Collagen type II and proteoglycans indicative of hyaline cartilage (Toh, et al., 2010).

### 3.3 Stem cells as therapeutic carriers

Neural stem cells (NSCs), mesenchymal stem cells (MSCs), and endothelial progenitor cells can be used to selectively target and eradicate invasive and inoperable cancers because they migrate towards cancerous cells and can be engineered to overexpress and secrete therapeutic payloads. These therapeutics include apoptosis-inducing proteins (Sasportas, et al., 2009), suicide proteins such as cytosine deaminase in the presence of 5-fluorocytosine (Aboody, et al., 2006), and specific monoclonal antibodies (Dudek, 2010; Frank, et al., 2010). In addition to minimizing side effects due to systemic chemotherapy treatments and their side effects, this approach obviates the need to contend with crossing the blood-brain barrier for CNS applications and repeated treatments of potentially unstable proteins (Frank, et al., 2010; Roth, et al., 2008). Much like stem cells used for tissue regeneration, these engineered stem cells benefit greatly from extended survival time with encapsulation in a matrix since the temporal window of therapeutic treatment is extended.

In a recent study,  $10^6$  MSCs were genetically modified to overexpress a recombinant bispecific antibody (MSC<sup>dAb</sup>) and injected subcutaneously within Extracel-X® in mice (Extracel-X is based on HyStem technology and specifically designed for mouse tumor xenografts). MSC<sup>dAb</sup> implanted with Extracel-X survive at least 12 days longer, secrete up to 145 ng antibody/ml plasma over 42 days, and halts HCT-116 tumor xenograft growth (Compte, et al., 2009). In theory, this approach can be extended to improving tissue repair

and regeneration since stem cells can be engineered to express a variety of growth factors and/or signaling molecules to encourage orthopedic tissue repair for example (Hoffmann, et al., 2006; Sheyn, et al., 2008).

#### 4. The future of cell delivery vehicles

While the discussion so far has focused on hydrogels as injectable vehicles congruent with minimally invasive surgery, it would be arrogant and limiting to assert that hydrogel matrices are the only type and form of matrix that can be used. In fact, a number of biomaterials can be incorporated into these procedures and offer significant advantages over traditional scaffolds and *in vitro* established structures (Burg and Boland, 2003; Ochi, et al., 2004; Thornton, et al., 2004). One area where additional biomaterial options will play a significant role is in minimizing stem cell manipulation prior to implantation. Cellular manipulation is proportional to the extent to which cells have been changed *ex vivo*. In addition, cell expansion and encapsulation constitute more than minimal manipulation (Hellman and Smith, 2006). The level of cellular manipulation is becoming more heavily scrutinized and can influence the practicability of implementing a proposed cell-based therapy. Currently, the FDA guidelines regulate "highly processed" more stringently than "minimally manipulated bone marrow", so it is advantageous to reduce processing of cellular components (Burger, 2003; Halme and Kessler, 2006). Cell delivery vehicles that can address both requirements for minimally invasive surgical techniques and reduction of cellular manipulation will clearly play a significant role in future of cell based therapies.

Researchers have investigated both synthetic and natural biomaterials that can be adapted to relevant surgical techniques. Few, however, minimize cellular manipulation. Thornton et al, reported a macroporous alginate hydrogel that can be temporarily deformed for delivery through a small catheter and then expanded *in situ* to their original physical dimensions, these types of materials are also known as shape-memorizing or defining scaffolds (Thornton, et al., 2004). While these can be utilized in minimally invasive techniques they are unable to fill irregularly shaped defects and do not address the biological requirements of numerous stem cells. Elisseff et al, have developed photopolymerizable synthetic polymers that can be injected as a monomer solution and then cured using transdermal ultra-violet light (Elisseff, et al., 1999). These concepts allow for catheter deliver and irregular defects but again do not address the biological needs of cells nor the issue of reducing cell manipulation. Finally, numerous types of microcarriers have been proposed as potential cell delivery vehicles. These small spheres on the order of 10-500  $\mu\text{m}$  are often used to encapsulate cells as with alginate, or are highly porous structures that provide high surface area to attach cells, as with PLGA microcarriers. Burg and Boland have reported a composite system that combines an injectable gel delivery vehicle with polymeric microspheres for additional support and cell attachment sites (Burg and Boland, 2003). While novel, this idea misses a crucial benefit of microcarriers role in cell therapy - the ability to reduce cellular processing by expansion on the microcarriers themselves followed by minimally invasive delivery to targeted sites.

A microcarrier culture system that doubles as an expansion substrate and delivery vehicle for human MSCs (hMSC) would be ideal. This concept permits seamless expansion and transplantation of cells for therapy. Besides substantially decreasing the need for tissue culture space (compared with traditional 2D tissue culture plastic expansion) and the

possibility of contamination risks (no need for enzymatic passaging), a biologically relevant microcarrier would provide the requisite scaffold to improve a cell's survivability and localization post-transplantation.

There are a wide variety of microcarriers commercially available such as polystyrene-based MicroHex (Nunc) and Plastic Plus (SoloHill) which is compatible with hMSC, however few are biodegradable and even fewer can provide the biological cell requirements. Commercially available biodegradable microcarriers are suboptimal as delivery vehicles for hMSC as their compositions are not physiologically relevant for this stem cell type. Poly(D,L-lactic-co-glycolic acid) (PLGA) and poly (L)-lactic acid (PLLA) microcarriers do not provide a supportive microenvironment after implantation and they degrade to the acidic by-products, lactic acid and glycolic acid. Cultispher microcarriers (Percell Biolytica AB) - crosslinked, porous porcine gelatin microcarriers - have limited utility for regenerative medicine applications using hMSC. Neither collagen nor gelatin bind to the abundant hMSC CD44 (hyaluronic acid, HA) receptors required for function and the introduction of animal-derived components can lead to additional FDA regulations.

A solution is to prepare microcarriers from a physiologically relevant biomaterial for stem cells which can serve as both as an expansion substrate and delivery vehicle. This dual functionality is advantageous as it can reduce the cellular manipulation by eliminating enzymatic treatments to recover cells and can then be delivered either alone or within additional gel via minimally invasive catheter techniques. HyStem-based microcarriers have been recently produced using reverse emulsion techniques, i.e. water in oil polymerization methods (Figure 3). Unlike Cultispher microcarriers, HyStem offers users control over composition and matrix elasticity for ease in customizing future microcarriers. A variety of growth factors, cellular attachment domains, or peptides may be added to customize its formulation (Serban and Prestwich, 2008; Ventura, et al., 2004). In addition, matrix elasticity is easily modulated (Vanderhooft, et al., 2009) and is likely to be of paramount importance for applications involving hMSC transplantation (Engler, et al., 2006).

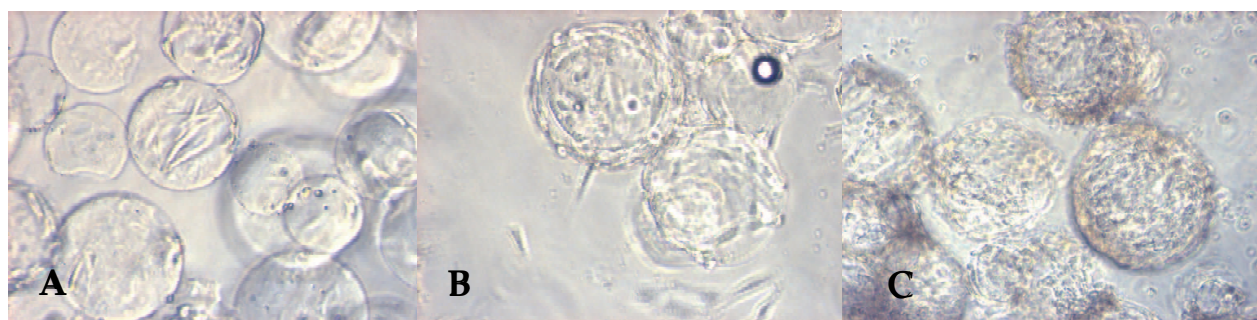


Fig. 3. Mouse fibroblast cells (NIH 3T3 line) seeded on HyStem microcarriers at day 1 (A), 4 (B), and 6(C)

## 5. Conclusion

In summary, a cellular delivery matrix in regenerative medicine extends the survival of the transplanted cells so that their chances of remodeling their microenvironment or delivering

a meaningful therapeutic payload are significantly enhanced. In the context of tissue repair, the use of degradable polymer scaffolds is crucial since it provides a tractable substrate for cells to remodel while providing space and a temporary home. For cell delivery matrices to be useful, however, they must also satisfy non-biological related concerns: From the physician's point of view, injectability and ease of use are of paramount importance. From the commercial point of view, it must be patentable and its surrounding patent landscape must also be favorable (i.e. the intellectual property (IP) has to be novel, non-obvious, and useful as well as unencumbered by potential blocking IP). The market must also be substantial, and the product has to have a significant profit margin in part due to economical manufacture (i.e. raw materials and cGMP costs are low) and the marketplace's acceptance of a fair price.

As a final thought, while there is a great deal of academic excitement and publication activity surrounding the development of ever-increasingly complex cellular delivery matrices that can replicate a new aspect of a stem cell niche (Engler, et al., 2006; Phillips, et al., 2008; Reilly and Engler, 2009; Stern, et al., 2009; Wosnick and Shoichet, 2008), the question is: after a point, when is more complexity in a cellular delivery vehicle too much? The resulting products may become highly unique and patentable from an IP standpoint but from a manufacturing point of view, as the number of components or complexity in manufacturing process increases, manufacturing cost may increase dramatically and block its commercialization. More importantly, from the developmental point of view, do we really need to recreate what nature does by adding every last detail of intricacy into an ECM for a stem cell whose residence time in a developmental intermediate state may be fleeting and only require the intricacy for a moment in time? (Sands and Mooney, 2007).

One strategy for designing an optimal stem cell delivery vehicle is to mimic what nature does during early embryonic development---simply provide a simple, malleable substrate that the embryonic cells can tailor according to their needs. An embryonic cell is in a constant tug-o-war with its surroundings where the cell is exerting a specific force on the ECM or neighboring cell via its acto-myosin cytoskeleton (Ingber, 2006). However, the embryonic organs in which these cells reside likely decide what that specific tension will be based on its physical demands at each of its developmental stage (Mammoto and Ingber, 2010). It is these developmental cues which likely drive the trajectory of the ECM remodeling and cellular differentiation. As an example, let's examine the embryo heart development: initially the embryo is highly compliant ( $< 10$  Pa) into which mesoderm cells penetrate (Reilly and Engler, 2009). There is an eight-fold increase in the developing heart tissue stiffness (Young and Engler, 2010), suggesting that its ECM is constantly being remodeled. In the end, the fully differentiated heart has a stiffness of 10 kPa which provides enough stiffness and stability to allow myocardial cells to generate enough traction to contract against for normal heart beating. In essence, the cells and the ECM are co-developing. Since a variety of stem cells are derived from embryos at various stages, the possibility exists that a simple hydrogel which the stem cells like and can remodel is all that is needed, leaving the building of complexity to nature.

## 6. Acknowledgements

We thank Dr. Mariluz Henshaw for critical reading of the manuscript.



## 7. References

- Aboody, K.S., Najbauer, J., Schmidt, N.O., Yang, W., Wu, J.K., Zhuge, Y., Przylecki, W., Carroll, R., Black, P.M. and Perides, G., (2006). Targeting of melanoma brain metastases using engineered neural stem/progenitor cells. *Neuro Oncol*, 8 (2):119-126.
- Ahmed, T.A., Dare, E.V. and Hincke, M., (2008). Fibrin: A Versatile Scaffold for Tissue Engineering Applications. *Tissue Eng Part B Rev*.
- Alsberg, E., Anderson, K.W., Albeiruti, A., Franceschi, R.T. and Mooney, D.J., (2001). Cell-interactive alginate hydrogels for bone tissue engineering. *J Dent Res*, 80 (11):2025-2029.
- Aszodi, A., Legate, K.R., Nakchbandi, I. and Fassler, R., (2006). What mouse mutants teach us about extracellular matrix function. *Annu Rev Cell Dev Biol*, 22:591-621.
- Bach, F.H., Albertini, R.J., Joo, P., Anderson, J.L. and Bortin, M.M., (1968). Bone-marrow transplantation in a patient with the Wiskott-Aldrich syndrome. *Lancet*, 2 (7583):1364-1366.
- Badylak, S.F. and Gilbert, T.W., (2008). Immune response to biologic scaffold materials. *Semin Immunol*, 20 (2):109-116.
- Beckloff, M. (ed), (2008). *Validation and Contract Manufacturing*. New York, NY: Informa Healthcare USA.
- Beckman, M., Shields, K. and Diegelmann, R. (eds), (2008). *Collagen*: Informa Healthcare USA.
- Bliss, T., Guzman, R., Daadi, M. and Steinberg, G.K., (2007). Cell transplantation therapy for stroke. *Stroke*, 38 (2 Suppl):817-826.
- Bryant, S. and Anseth, K.S. (eds), (2006). *Photopolymerization of Hydrogel Scaffolds*. Boca Raton, FL: CRC Press.
- Burg, K.J. and Boland, T., (2003). Minimally invasive tissue engineering composites and cell printing. *IEEE Eng Med Biol Mag*, 22 (5):84-91.
- Burger, S.R., (2003). Current regulatory issues in cell and tissue therapy. *Cytotherapy*, 5 (4):289-298.
- Cai, S., Liu, Y., Zheng Shu, X. and Prestwich, G.D., (2005). Injectable glycosaminoglycan hydrogels for controlled release of human basic fibroblast growth factor. *Biomaterials*, 26 (30):6054-6067.
- Camenisch, T.D., Spicer, A.P., Brehm-Gibson, T., Biesterfeldt, J., Augustine, M.L., Calabro, A., Jr., Kubalak, S., Klewer, S.E. and McDonald, J.A., (2000). Disruption of hyaluronan synthase-2 abrogates normal cardiac morphogenesis and hyaluronan-mediated transformation of epithelium to mesenchyme. *J Clin Invest*, 106 (3):349-360.
- Caplan, A.I. and Dennis, J.E., (2006). Mesenchymal stem cells as trophic mediators. *J Cell Biochem*, 98 (5):1076-1084.
- Carpenter, M.K., Frey-Vasconcells, J. and Rao, M.S., (2009). Developing safe therapies from human pluripotent stem cells. *Nat Biotechnol*, 27 (7):606-613.
- CDC, (2007). Targeting Arthritis: Reducing Disability for Nearly 19 Million Americans. In: *Prevention, C.f.D.C.a.* (ed): US Department of Health and Human Services.
- Chung, C. and Burdick, J.A., (2009). Influence of three-dimensional hyaluronic acid microenvironments on mesenchymal stem cell chondrogenesis. *Tissue Eng Part A*, 15 (2):243-254.



- Compte, M., Cuesta, A.M., Sanchez-Martin, D., Alonso-Camino, V., Vicario, J.L., Sanz, L. and Alvarez-Vallina, L., (2009). Tumor immunotherapy using gene-modified human mesenchymal stem cells loaded into synthetic extracellular matrix scaffolds. *Stem Cells*, 27 (3):753-760.
- Cui, J., Wahl, R.L., Shen, T., Fisher, S.J., Recker, E., Ginsburg, D. and Long, M.W., (1999). Bone marrow cell trafficking following intravenous administration. *Br J Haematol*, 107 (4):895-902.
- Cutler, C. and Antin, J.H., (2001). Peripheral blood stem cells for allogeneic transplantation: a review. *Stem Cells*, 19 (2):108-117.
- Darabi, R., Baik, J., Clee, M., Kyba, M., Tupler, R. and Perlingeiro, R.C., (2009). Engraftment of embryonic stem cell-derived myogenic progenitors in a dominant model of muscular dystrophy. *Exp Neurol*, 220 (1):212-216.
- Darr, A. and Calabro, A., (2009). Synthesis and characterization of tyramine-based hyaluronan hydrogels. *J Mater Sci Mater Med*, 20 (1):33-44.
- Dominici, M., Rasini, V., Bussolari, R., Chen, X., Hofmann, T.J., Spano, C., Bernabei, D., Veronesi, E., Bertoni, F., Paolucci, P., Conte, P. and Horwitz, E.M., (2009). Restoration and reversible expansion of the osteoblastic hematopoietic stem cell niche after marrow radioablation. *Blood*, 114 (11):2333-2343.
- Doty, N., (2011). Rheological Properties of Extracellular Matrices. Glycosan BioSystems.
- Dudek, A.Z., (2010). Endothelial lineage cell as a vehicle for systemic delivery of cancer gene therapy. *Transl Res*, 156 (3):136-146.
- Duran-Struuck, R. and Dysko, R.C., (2009). Principles of bone marrow transplantation (BMT): providing optimal veterinary and husbandry care to irradiated mice in BMT studies. *J Am Assoc Lab Anim Sci*, 48 (1):11-22.
- Elisseeff, J., Anseth, K., Sims, D., McIntosh, W., Randolph, M. and Langer, R., (1999). Transdermal photopolymerization for minimally invasive implantation. *Proc Natl Acad Sci U S A*, 96 (6):3104-3107.
- Engler, A.J., Sen, S., Sweeney, H.L. and Discher, D.E., (2006). Matrix elasticity directs stem cell lineage specification. *Cell*, 126 (4):677-689.
- FDA, (1997). 'Proposed Approach to Regulation of Cellular and Tissue-Based Products. Food and Drug Administration.
- FDA, (2011). Guidance Compliance Regulatory Information. Food and Drug Administration.
- Flaim, C.J., Chien, S. and Bhatia, S.N., (2005). 'An extracellular matrix microarray for probing cellular differentiation. *Nat Methods*, 2 (2):119-125.
- Flynn, L.E., (2010). The use of decellularized adipose tissue to provide an inductive microenvironment for the adipogenic differentiation of human adipose-derived stem cells. *Biomaterials*, 31 (17):4715-4724.
- Frank, R.T., Najbauer, J. and Aboody, K.S., (2010). Concise review: stem cells as an emerging platform for antibody therapy of cancer. *Stem Cells*, 28 (11):2084-2087.
- Fraser, J.R., Laurent, T.C. and Laurent, U.B., (1997). Hyaluronan: its nature, distribution, functions and turnover. *J Intern Med*, 242 (1):27-33.
- Gatti, R.A., Meuwissen, H.J., Allen, H.D., Hong, R. and Good, R.A., (1968). Immunological reconstitution of sex-linked lymphopenic immunological deficiency. *Lancet*, 2 (7583):1366-1369.

- Gentry-Steele, D. and Bramblett, C., (1988). *The Anatomy and Biology of the Human Skeleton*. College Station, TX: Texas A&M Univ Press.
- Grayson, W.L., Chao, P.H., Marolt, D., Kaplan, D.L. and Vunjak-Novakovic, G., (2008). Engineering custom-designed osteochondral tissue grafts. *Trends Biotechnol*, 26 (4):181-189.
- Guerette, B., Skuk, D., Celestin, F., Huard, C., Tardif, F., Asselin, I., Roy, B., Goulet, M., Roy, R., Entman, M. and Tremblay, J.P., (1997). Prevention by anti-LFA-1 of acute myoblast death following transplantation. *J Immunol*, 159 (5):2522-2531.
- Halme, D.G. and Kessler, D.A., (2006). FDA regulation of stem-cell-based therapies. *N Engl J Med*, 355 (16):1730-1735.
- Hanjaya-Putra, D., Yee, J., Ceci, D., Truitt, R., Yee, D. and Gerecht, S., (2010). Vascular endothelial growth factor and substrate mechanics regulate in vitro tubulogenesis of endothelial progenitor cells. *J Cell Mol Med*, 14 (10):2436-2447.
- Harrison, M. and Rae, I., (1997). *General Techniques of Cell Culture*. New York, NY: Cambridge University Press.
- Hellman, K. and Smith, D. (eds), (2006). *The Regulation of Engineered Tissues: Emerging Approaches*. Boca Raton, FL: CRC Press.
- Hoffmann, A., Pelled, G., Turgeman, G., Eberle, P., Zilberman, Y., Shinar, H., Keinan-Adamsky, K., Winkel, A., Shahab, S., Navon, G., Gross, G. and Gazit, D., (2006). Neotendon formation induced by manipulation of the Smad8 signalling pathway in mesenchymal stem cells. *J Clin Invest*, 116 (4):940-952.
- Horowitz, M. (ed), (2004). *Thomas's Hematopoietic cell transplantation*. Malden, MA: Blackwell Publishing Inc.
- Hughes, C.S., Postovit, L.M. and Lajoie, G.A., (2010). Matrigel: a complex protein mixture required for optimal growth of cell culture. *Proteomics*, 10 (9):1886-1890.
- Ingber, D.E., (2006). Mechanical control of tissue morphogenesis during embryological development. *Int J Dev Biol*, 50 (2-3):255-266.
- Ingram, D.A., Mead, L.E., Tanaka, H., Meade, V., Fenoglio, A., Mortell, K., Pollok, K., Ferkowicz, M.J., Gilley, D. and Yoder, M.C., (2004). Identification of a novel hierarchy of endothelial progenitor cells using human peripheral and umbilical cord blood. *Blood*, 104 (9):2752-2760.
- James, R., Kumbar, S.G., Laurencin, C.T., Balian, G. and Chhabra, A.B., (2011). Tendon tissue engineering: adipose-derived stem cell and GDF-5 mediated regeneration using electrospun matrix systems. *Biomed Mater*, 6 (2):025011.
- Kaihara, S. and Vacanti, J.P., (1999). Tissue engineering: toward new solutions for transplantation and reconstructive surgery. *Arch Surg*, 134 (11):1184-1188.
- Keirstead, H.S., Ben-Hur, T., Rogister, B., O'Leary, M.T., Dubois-Dalcq, M. and Blakemore, W.F., (1999). Polysialylated neural cell adhesion molecule-positive CNS precursors generate both oligodendrocytes and Schwann cells to remyelinate the CNS after transplantation. *J Neurosci*, 19 (17):7529-7536.
- Kleinman, H.K. and Martin, G.R., (2005). Matrigel: basement membrane matrix with biological activity. *Semin Cancer Biol*, 15 (5):378-386.
- Knudson, C.B. and Knudson, W., (1993). Hyaluronan-binding proteins in development, tissue homeostasis, and disease. *FASEB J*, 7 (13):1233-1241.
- Laflamme, M.A., Chen, K.Y., Naumova, A.V., Muskheli, V., Fugate, J.A., Dupras, S.K., Reinecke, H., Xu, C., Hassanipour, M., Police, S., O'Sullivan, C., Collins, L., Chen,

- Y., Minami, E., Gill, E.A., Ueno, S., Yuan, C., Gold, J. and Murry, C.E., (2007). Cardiomyocytes derived from human embryonic stem cells in pro-survival factors enhance function of infarcted rat hearts. *Nat Biotechnol*, 25 (9):1015-1024.
- Lam, B.S. and Adams, G.B., (2010). Hematopoietic stem cell lodgment in the adult bone marrow stem cell niche. *Int J Lab Hematol*, 32 (6 Pt 2):551-558.
- Laurent, T.C. and Fraser, J.R., (1992). Hyaluronan. *FASEB J*, 6 (7):2397-2404.
- Lennon, D.P. and Caplan, A.I., (2006). Isolation of human marrow-derived mesenchymal stem cells. *Exp Hematol*, 34 (11):1604-1605.
- Liao, H., Munoz-Pinto, D., Qu, X., Hou, Y., Grunlan, M.A. and Hahn, M.S., (2008). 'Influence of hydrogel mechanical properties and mesh size on vocal fold fibroblast extracellular matrix production and phenotype'. *Acta Biomater*, 4 (5):1161-1171.
- Lin, C.C. and Anseth, K.S., (2009). Glucagon-like peptide-1 functionalized PEG hydrogels promote survival and function of encapsulated pancreatic beta-cells. *Biomacromolecules*, 10 (9):2460-2467.
- Liu, Y., Shu, X.Z. and Prestwich, G.D., (2006). Osteochondral defect repair with autologous bone marrow-derived mesenchymal stem cells in an injectable, in situ, cross-linked synthetic extracellular matrix. *Tissue Eng*, 12 (12):3405-3416.
- Liu, Y., Shu, X.Z. and Prestwich, G.D., (2007). Tumor engineering: orthotopic cancer models in mice using cell-loaded, injectable, cross-linked hyaluronan-derived hydrogels. *Tissue Eng*, 13 (5):1091-1101.
- Luca, G., Calvitti, M., Nastruzzi, C., Bilancetti, L., Becchetti, E., Angeletti, G., Mancuso, F. and Calafiore, R., (2007). Encapsulation, in vitro characterization, and in vivo biocompatibility of Sertoli cells in alginate-based microcapsules. *Tissue Eng*, 13 (3):641-648.
- Lutolf, M.P. and Hubbell, J.A., (2005). Synthetic biomaterials as instructive extracellular microenvironments for morphogenesis in tissue engineering. *Nat Biotechnol*, 23 (1):47-55.
- Lysaght, M.J., Jaklenec, A. and Deweerdt, E., (2008). Great expectations: private sector activity in tissue engineering, regenerative medicine, and stem cell therapeutics. *Tissue Eng Part A*, 14 (2):305-315.
- Mammoto, T. and Ingber, D.E., (2010). Mechanical control of tissue and organ development. *Development*, 137 (9):1407-1420.
- Martens, T.P., Godier, A.F., Parks, J.J., Wan, L.Q., Koeckert, M.S., Eng, G.M., Hudson, B.I., Sherman, W. and Vunjak-Novakovic, G., (2009). Percutaneous cell delivery into the heart using hydrogels polymerizing in situ. *Cell Transplant*, 18 (3):297-304.
- Martin, I., Baldomero, H., Tyndall, A., Niederwieser, D. and Gratwohl, A., (2010). A survey on cellular and engineered tissue therapies in europe in 2008. *Tissue Eng Part A*, 16 (8):2419-2427.
- Mavroudis, D., Read, E., Cottler-Fox, M., Couriel, D., Molldrem, J., Carter, C., Yu, M., Dunbar, C. and Barrett, J., (1996). CD34+ cell dose predicts survival, posttransplant morbidity, and rate of hematologic recovery after allogeneic marrow transplants for hematologic malignancies. *Blood*, 88 (8):3223-3229.
- Miles, E.J., Dunn, E., Howard, D. and Mangram, A., (2004). The role of laparoscopy in penetrating abdominal trauma. *JSLS*, 8 (4):304-309.

- Montes, J.M., Wong, J.H., Fayad, P.B. and Awad, I.A., (2000). Stereotactic computed tomographic-guided aspiration and thrombolysis of intracerebral hematoma : protocol and preliminary experience. *Stroke*, 31 (4):834-840.
- Moon, J.J., Hahn, M.S., Kim, I., Nsiah, B.A. and West, J.L., (2009). Micropatterning of poly(ethylene glycol) diacrylate hydrogels with biomolecules to regulate and guide endothelial morphogenesis. *Tissue Eng Part A*, 15 (3):579-585.
- Mooney, D.J. and Vandenburgh, H., (2008). Cell delivery mechanisms for tissue repair. *Cell Stem Cell*, 2 (3):205-213.
- Nagaoka, M., Si-Tayeb, K., Akaike, T. and Duncan, S.A., (2010). Culture of human pluripotent stem cells using completely defined conditions on a recombinant E-cadherin substratum. *BMC Dev Biol*, 10:60.
- Newman, J., (2009). Review of soft tissue augmentation in the face. *Clin Cosmet Investig Dermatol*, 2:141-150.
- Ochi, M., Adachi, N., Nobuto, H., Yanada, S., Ito, Y. and Agung, M., (2004). Articular cartilage repair using tissue engineering technique--novel approach with minimally invasive procedure. *Artif Organs*, 28 (1):28-32.
- Patel, P.N., Smith, C.K. and Patrick, C.W., Jr., (2005). Rheological and recovery properties of poly(ethylene glycol) diacrylate hydrogels and human adipose tissue. *J Biomed Mater Res A*, 73 (3):313-319.
- Penolazzi, L., Tavanti, E., Vecchiatini, R., Lambertini, E., Vesce, F., Gambari, R., Mazzitelli, S., Mancuso, F., Luca, G., Nastruzzi, C. and Piva, R., (2010). Encapsulation of mesenchymal stem cells from Wharton's jelly in alginate microbeads. *Tissue Eng Part C Methods*, 16 (1):141-155.
- Phelps, E.A., Landazuri, N., Thule, P.M., Taylor, W.R. and Garcia, A.J., (2010). Bioartificial matrices for therapeutic vascularization. *Proc Natl Acad Sci U S A*, 107 (8):3323-3328.
- Phillips, J.E., Burns, K.L., Le Doux, J.M., Guldberg, R.E. and Garcia, A.J., (2008). Engineering graded tissue interfaces. *Proc Natl Acad Sci U S A*, 105 (34):12170-12175.
- Poltorak, A. and Lemer, P., (2004). *Essentials of Licensing Intellectual Property*. Hoboken, NJ: John Wiley and Sons, Inc.
- Prestwich, G.D., (2008). Engineering a clinically-useful matrix for cell therapy. *Organogenesis*, 4 (1):42-47.
- Raeber, G.P., Lutolf, M.P. and Hubbell, J.A., (2005). Molecularly engineered PEG hydrogels: a novel model system for proteolytically mediated cell migration. *Biophys J*, 89 (2):1374-1388.
- Rajasingh, J., Lambers, E., Hamada, H., Bord, E., Thorne, T., Goukassian, I., Krishnamurthy, P., Rosen, K.M., Ahluwalia, D., Zhu, Y., Qin, G., Losordo, D.W. and Kishore, R., (2008). Cell-free embryonic stem cell extract-mediated derivation of multipotent stem cells from NIH3T3 fibroblasts for functional and anatomical ischemic tissue repair. *Circ Res*, 102 (11):e107-117.
- Read, E. and Khuu, H. (eds), (2009). *Use of a facility master file to facilitate regulatory submissions for cell therapy products*. New York, NY: Springer.
- Reilly, G.C. and Engler, A.J., (2009). Intrinsic extracellular matrix properties regulate stem cell differentiation. *J Biomech*, 43 (1):55-62.
- Reiner, B.I., (2009). The challenges, opportunities, and imperative of structured reporting in medical imaging. *J Digit Imaging*, 22 (6):562-568.



- Roth, J.C., Curiel, D.T. and Pereboeva, L., (2008). Cell vehicle targeting strategies. *Gene Ther*, 15 (10):716-729.
- Ruoslahti, E., (1996). Brain extracellular matrix. *Glycobiology*, 6 (5):489-492.
- Sands, R.W. and Mooney, D.J., (2007). Polymers to direct cell fate by controlling the microenvironment. *Curr Opin Biotechnol*, 18 (5):448-453.
- Sasportas, L.S., Kasmieh, R., Wakimoto, H., Hingtgen, S., van de Water, J.A., Mohapatra, G., Figueiredo, J.L., Martuza, R.L., Weissleder, R. and Shah, K., (2009). Assessment of therapeutic efficacy and fate of engineered human mesenchymal stem cells for cancer therapy. *Proc Natl Acad Sci U S A*, 106 (12):4822-4827.
- Scadden, D.T., (2006). The stem-cell niche as an entity of action. *Nature*, 441 (7097):1075-1079.
- Schmitz I., Ariyoshi W., Takahashi N., Knudson C.B., and Knudson W. (2010). Hyaluronan oligosaccharide treatment of chondrocytes stimulates expression of both HAS-2 and MMP-3, but by different signaling pathways. *Osteoarthritis Cartilage*, 18 (3):447-454.
- Semino, C.E., (2008). Self-assembling peptides: from bio-inspired materials to bone regeneration. *J Dent Res*, 87 (7):606-616.
- Serban, M.A. and Prestwich, G.D., (2008). Modular extracellular matrices: solutions for the puzzle. *Methods*, 45 (1):93-98.
- Sheyn, D., Pelled, G., Zilberman, Y., Talasazan, F., Frank, J.M., Gazit, D. and Gazit, Z., (2008). Nonvirally engineered porcine adipose tissue-derived stem cells: use in posterior spinal fusion. *Stem Cells*, 26 (4):1056-1064.
- Shikanov, A., Xu, M., Woodruff, T.K. and Shea, L.D., (2009). Interpenetrating fibrin-alginate matrices for in vitro ovarian follicle development. *Biomaterials*, 30 (29):5476-5485.
- Slayton, W.B., Li, X.M., Butler, J., Guthrie, S.M., Jorgensen, M.L., Wingard, J.R. and Scott, E.W., (2007). The role of the donor in the repair of the marrow vascular niche following hematopoietic stem cell transplant. *Stem Cells*, 25 (11):2945-2955.
- Snyder, B.R., Chiu, A.M., Prockop, D.J. and Chan, A.W., (2010). Human multipotent stromal cells (MSCs) increase neurogenesis and decrease atrophy of the striatum in a transgenic mouse model for Huntington's disease. *PLoS One*, 5 (2):e9347.
- Soen, Y., Mori, A., Palmer, T.D. and Brown, P.O., (2006). Exploring the regulation of human neural precursor cell differentiation using arrays of signaling microenvironments. *Mol Syst Biol*, 2:37.
- Stern, E., Jay, S.M., Demento, S.L., Murelli, R.P., Reed, M.A., Malinski, T., Spiegel, D.A., Mooney, D.J. and Fahmy, T.M., (2009). Spatiotemporal control over molecular delivery and cellular encapsulation from electropolymerized micro- and nanopatterned surfaces. *Adv Funct Mater*, 19 (18):2888-2895.
- Suzuki, K., Murtuza, B., Beauchamp, J.R., Smolenski, R.T., Varela-Carver, A., Fukushima, S., Coppen, S.R., Partridge, T.A. and Yacoub, M.H., (2004). Dynamics and mediators of acute graft attrition after myoblast transplantation to the heart. *FASEB J*, 18 (10):1153-1155.
- Taichman, R.S., (2005). Blood and bone: two tissues whose fates are intertwined to create the hematopoietic stem-cell niche. *Blood*, 105 (7):2631-2639.
- Takahashi, K., Tanabe, K., Ohnuki, M., Narita, M., Ichisaka, T., Tomoda, K. and Yamanaka, S., (2007). Induction of pluripotent stem cells from adult human fibroblasts by defined factors. *Cell*, 131 (5):861-872.



- Tate, C.C., Shear, D.A., Tate, M.C., Archer, D.R., Stein, D.G. and LaPlaca, M.C., (2009). Laminin and fibronectin scaffolds enhance neural stem cell transplantation into the injured brain. *J Tissue Eng Regen Med*, 3 (3):208-217.
- Taylor, T.N., Davis, P.H., Torner, J.C., Holmes, J., Meyer, J.W. and Jacobson, M.F., (1996). Lifetime cost of stroke in the United States. *Stroke*, 27 (9):1459-1466.
- Terrovitis, J., Kwok, K.F., Lautamaki, R., Engles, J.M., Barth, A.S., Kizana, E., Miake, J., Leppo, M.K., Fox, J., Seidel, J., Pomper, M., Wahl, R.L., Tsui, B., Bengel, F., Marban, E. and Abraham, M.R., (2008). Ectopic expression of the sodium-iodide symporter enables imaging of transplanted cardiac stem cells in vivo by single-photon emission computed tomography or positron emission tomography. *J Am Coll Cardiol*, 52 (20):1652-1660.
- Thompson, D. (ed), (2006). *Cyclodextrins-enabling excipients: a case study of the development of a new excipient- sulfobutylether  $\beta$ -cyclodextrin (Captisol)*. New York, NY: Informa Healthcare USA, Inc.
- Thomson, J.A., Itskovitz-Eldor, J., Shapiro, S.S., Waknitz, M.A., Swiergiel, J.J., Marshall, V.S. and Jones, J.M., (1998). Embryonic stem cell lines derived from human blastocysts. *Science*, 282 (5391):1145-1147.
- Thornton, A.J., Alsberg, E., Albertelli, M. and Mooney, D.J., (2004). 'Shape-defining scaffolds for minimally invasive tissue engineering'. *Transplantation*, 77 (12):1798-1803.
- Tibbitt, M.W. and Anseth, K.S., (2009). Hydrogels as extracellular matrix mimics for 3D cell culture. *Biotechnol Bioeng*, 103 (4):655-663.
- Toh, W.S., Lee, E.H., Guo, X.M., Chan, J.K., Yeow, C.H., Choo, A.B. and Cao, T., (2010). Cartilage repair using hyaluronan hydrogel-encapsulated human embryonic stem cell-derived chondrogenic cells. *Biomaterials*, 31 (27):6968-6980.
- Vanderhooft, J.L., Alcoutlabi, M., Magda, J.J. and Prestwich, G.D., (2009). Rheological properties of cross-linked hyaluronan-gelatin hydrogels for tissue engineering. *Macromol Biosci*, 9 (1):20-28.
- Ventura, C., Maioli, M., Asara, Y., Santoni, D., Scarlata, I., Cantoni, S. and Perbellini, A., (2004). Butyric and retinoic mixed ester of hyaluronan. A novel differentiating glycoconjugate affording a high throughput of cardiogenesis in embryonic stem cells. *J Biol Chem*, 279 (22):23574-23579.
- Wei, Y.T., Tian, W.M., Yu, X., Cui, F.Z., Hou, S.P., Xu, Q.Y. and Lee, I.S., (2007). Hyaluronic acid hydrogels with IKVAV peptides for tissue repair and axonal regeneration in an injured rat brain. *Biomed Mater*, 2 (3):S142-146.
- Weisel, J.W., (2004). The mechanical properties of fibrin for basic scientists and clinicians. *Biophys Chem*, 112 (2-3):267-276.
- West, E.R., Xu, M., Woodruff, T.K. and Shea, L.D., (2007). Physical properties of alginate hydrogels and their effects on in vitro follicle development. *Biomaterials*, 28 (30):4439-4448.
- Wilson, J.T. and Chaikof, E.L., (2008). 'Challenges and emerging technologies in the immunisolation of cells and tissues'. *Adv Drug Deliv Rev*, 60 (2):124-145.
- Wosnick, J. and Shoichet, M., (2008). Three-dimensional Chemical Patterning of Transparent Hydrogels. *Chemistry of Materials*, 20:55-60.
- Wu, Y., Wu, J., Lee, D.Y., Yee, A., Cao, L., Zhang, Y., Kiani, C. and Yang, B.B., (2005). Versican protects cells from oxidative stress-induced apoptosis. *Matrix Biol*, 24 (1):3-13.

- Xu, M., West, E., Shea, L.D. and Woodruff, T.K., (2006). Identification of a stage-specific permissive in vitro culture environment for follicle growth and oocyte development. *Biol Reprod*, 75 (6):916-923.
- Yamaguchi, Y., (2000). Lecticans: organizers of the brain extracellular matrix. *Cell Mol Life Sci*, 57 (2):276-289.
- Young, J.L. and Engler, A.J., (2010). Hydrogels with time-dependent material properties enhance cardiomyocyte differentiation in vitro. *Biomaterials*, 32 (4):1002-1009.
- Yu, J., Vodyanik, M.A., Smuga-Otto, K., Antosiewicz-Bourget, J., Frane, J.L., Tian, S., Nie, J., Jonsdottir, G.A., Ruotti, V., Stewart, R., Slukvin, II and Thomson, J.A., (2007). Induced pluripotent stem cell lines derived from human somatic cells. *Science*, 318 (5858):1917-1920.
- Zheng Shu, X., Liu, Y., Palumbo, F.S., Luo, Y. and Prestwich, G.D., (2004). In situ crosslinkable hyaluronan hydrogels for tissue engineering. *Biomaterials*, 25 (7-8):1339-1348.
- Zhong, J., Chan, A., Morad, L., Kornblum, H.I., Fan, G. and Carmichael, S.T., (2010). Hydrogel matrix to support stem cell survival after brain transplantation in stroke. *Neurorehabil Neural Repair*, 24 (7):636-644.
- Zuk, P.A., Zhu, M., Mizuno, H., Huang, J., Futrell, J.W., Katz, A.J., Benhaim, P., Lorenz, H.P. and Hedrick, M.H., (2001). Multilineage cells from human adipose tissue: implications for cell-based therapies. *Tissue Eng*, 7 (2):211-228.

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## **Regenerative Medicine and Tissue Engineering - Cells and Biomaterials**

Edited by Prof. Daniel Eberli

ISBN 978-953-307-663-8

Hard cover, 588 pages

**Publisher** InTech

**Published online** 29, August, 2011

**Published in print edition** August, 2011

Tissue Engineering may offer new treatment alternatives for organ replacement or repair deteriorated organs. Among the clinical applications of Tissue Engineering are the production of artificial skin for burn patients, tissue engineered trachea, cartilage for knee-replacement procedures, urinary bladder replacement, urethra substitutes and cellular therapies for the treatment of urinary incontinence. The Tissue Engineering approach has major advantages over traditional organ transplantation and circumvents the problem of organ shortage. Tissues reconstructed from readily available biopsy material induce only minimal or no immunogenicity when reimplanted in the patient. This book is aimed at anyone interested in the application of Tissue Engineering in different organ systems. It offers insights into a wide variety of strategies applying the principles of Tissue Engineering to tissue and organ regeneration.

### **How to reference**

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Thomas I. Zarembinski, William P. Tew and Sarah K. Atzet (2011). The Use of a Hydrogel Matrix as a Cellular Delivery Vehicle in Future Cell-Based Therapies: Biological and Non-Biological Considerations, Regenerative Medicine and Tissue Engineering - Cells and Biomaterials, Prof. Daniel Eberli (Ed.), ISBN: 978-953-307-663-8, InTech, Available from: <http://www.intechopen.com/books/regenerative-medicine-and-tissue-engineering-cells-and-biomaterials/the-use-of-a-hydrogel-matrix-as-a-cellular-delivery-vehicle-in-future-cell-based-therapies-biologica>

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