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EDITORIAL

Advances in cell-laden hydrogels for delivering therapeutics

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1. Introduction

Almost six decades ago, a visionary scientist reported a new method for encapsulating aqueous solutions of protein within semipermeable polymer membranes [1]. This approach was successfully tested in the 1970s and 1980s by immobilizing xenograft islet cells to control glucose metabolism in small animal models [2,3]. Since then, the concept of cell-laden hydrogels has evolved and progressed but still those pioneering works are perfect examples of the theoretical advantages that this approach may offer in terms of long-term delivery and immune protection [4].

In its most basic form, cell-laden hydrogels or bioartificial organs consist of a polymeric or synthetic membrane structure that entraps a wide range of cells releasing bioactive drugs or proteins [5,6]. The three-dimensional (3D) constructs, typically either shaped as a microcapsule or a hollow-fiber, will regulate with different efficiency the permeability and mechanical stability of the cell-based medicine [7]. The semipermeable membrane is responsible for preventing high molecular weight molecules, antibodies and other immunologic components from entering within the construct but also controls the inward/outward diffusion of critical agents for cell survival and therapeutic efficacy including nutrients, oxygen, waste agents and therapeutic protein products (Figure 1). Even though the journey from theory to practice has been demanding and challenging, recent progress in the field is creating new avenues of hope to use this approach in several unmet clinical needs ranging from diabetes to ophthalmological disorders or rare diseases.

2. Advances in cell-laden hydrogels

Developing an optimized, cell-laden hydrogel with excellent biocompatibility, mechanical stability, permeability, lack of fibrotic overgrowth and the ability to create an appropriate 3D environment for the enclosed cells is one of the holy grails in the field. In the search for better biomaterials, many types of natural and synthetic materials have been explored, with alginates the most frequently employed biomaterial for cell-laden hydrogels-based spheres. Alginate is a polysaccharide that lines the cell walls of brown algae. When combined with water, alginate can also be made into a gel that safely encapsulates cells without limiting function [8–10]. Recently, the MIT-based Sigilon Therapeutics, developed a new type of cell-loaded capsule coated by a chemically modify alginate known as Afibromer [11]. To do so, they attached different molecules to the alginate's polymer chain, chemically modifying the structure multiple times until they found a material that rendered the enclosed cells invisible to the immune system [12]. This polymer could also be modified as a coating for implanted medical devices, such as coronary stents or insulin pumps.

The company has recently partnered with pharmaceutical Eli Lilly and Company to develop 'living drug factories' for patients with type 1 diabetes. However, though promising, there are still several important challenges including batch to batch reproducibility, type of crosslinking ions, smoothness and charge of the surface of the capsules, type of microencapsulation technology and the particularly large diameter of the reported capsules.

3. Cell candidates

The choice of cell type to interface with the encapsulating biomaterial is critical. To date, the most successful approaches to cell therapy have involved the use of mature or adult cell lines. For cell encapsulation purposes, recombinant clonal ARPE-19 cell lines have been developed and are currently in various stages of clinical evaluation for sustained and local delivery of proteins to both the eye (retinitis pigmentosa, wet AMD) and brain (Alzheimer's). A major challenge of this approach is the development of a system capable of sustained

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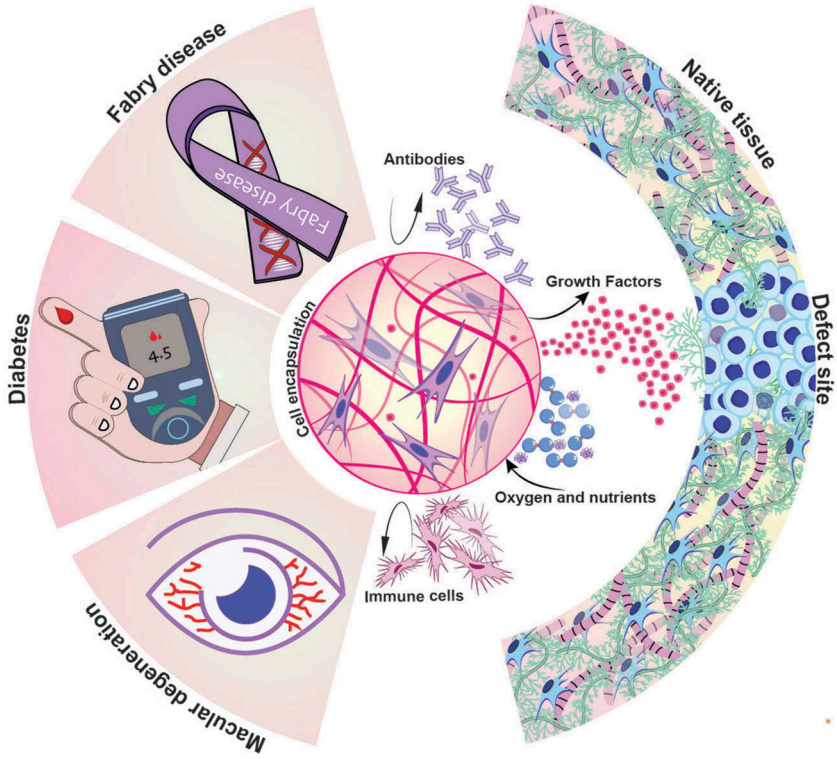

Figure 1. The guidance of therapeutic products by cell-laden hydrogels. The cells are encapsulated in the practical three-dimensional environment with the selectively permeable frontier. This boundary protects the cell against the antibodies and immune cells while enabling the entrance and the exit of nutrient, oxygen and therapeutic products, respectively.

and predictable dosing with acceptable cell viability and high, controlled secretion. Neurotech USA appears to have made considerable progress along these lines and recently reported that intravitreal implants of CNTF secreting ARPE-19 cells slowed the progression of retinal degeneration in patients with macular telangiectasia type 2 [13].

More recent efforts have focused on the development of non-adult stem cells lines including embryonic (ESC) and induced pluripotent stem cell lines (iPS) given the holy grail promise of and infinite supply of an unlimited repertoire of cell types. Contemporary examples include ViaCyte, inc which is developing both encapsulated (PEC-Encap system) and non-encapsulated ES-based beta cell transplants for diabetes [14]. The cells are partially differentiated prior to subcutaneous implantation where further *in vivo* differentiation occurs to the point of insulin secretion. ViaCyte has also recently announced a strategic collaboration with CRISPR Therapeutics, inc [15] to work on the fascinating possibility of creating pancreatic cells that are immunologically 'invisible'. Interestingly, Semma Therapeutics is also developing pancreatic stem cells but these cells are more fully differentiated into cells capable of insulin secretion in response to glucose prior to encapsulation and implantation.

The development of iPS cells is further behind and both the ESC and iPS approaches will ultimately need to overcome obstacles associated with complex, multi-step differentiation protocols that control cell composition and biological function and must be integrated with optimal encapsulation, dosing, and surgical implantation. Despite these challenges, it is possible that in hindsight we will recognize these advancements as a turning point in cell encapsulation therapy.

4. Towards clinical translation

Traditionally, advancements in cell encapsulation have been made in academic research institutions with few industrial efforts. In the last decade, though, there has been a notable surge in corporate efforts toward developing and commercializing encapsulated cell products. These efforts have been largely focused on diabetes with companies such as ViaCyte, Sernova, Semma Therapeutics, and Sigilon developing various approaches to islet cell transplantation. Additionally, continued efforts are ongoing in other therapeutic areas including ophthalmic and CNS indications. Neurotech recently described the results of a randomized Phase 2 trial in which invitreal implantation of CNTF secreting encapsulated cells slowed retinal degeneration in patients with MacTel type 2 [13]. Neurotech has also reported that the FDA has granted fast track designation for this approach [16]. Using a similar approach, Gloriana Therapeutics recently reported that encapsulated cells secreting GDNF reduced both behavioral and electrophysiological seizures as well as epilepsy-related anatomical changes when implanted into the hippocampus of epileptic rats [17]. Similar devices were neuroprotective in an excitotoxic rat model of Huntington's disease [18]. These recent reports not only support the basic concepts of cell encapsulation but also bode well for the use of these technologies in a wide range of human conditions. Last but not least, the new emerging New-York-based CapCell Biologics is developing new living implants that will include a proprietary human cell line engineered to over produce and secrete an

a-galactosidase A analog in a collagen-based hydrogel with pro-vascular and cell sustaining properties.

5. Expert opinion

Cell therapy has always seemed like an inherently appealing means of treating a myriad of life-threatening diseases. However, the complexity of controlling and maintaining the function of transplanted cells has been difficult to overcome. High levels of variability have been challenging obstacles requiring decades long sequential studies to identify the sources and devise counter strategies. We believe that the convergence of material sciences, genetic engineering, and cell biology has pushed the prospects of cellular encapsulation to the forefront of clinically viable cell therapy approaches [19]. Current clinical trials, largely in diabetes, have provided an unprecedented optimism and the next several years could be breakthrough times. This optimism is based largely on the growing ability to control the inherent variability mentioned above. On a cellular basis, this is manifested in the ability to controllably differentiate cells and tissues on large scales. New technologies including CRISPR will further allow us to control cell viability and function by eliminating immunological targets within encapsulated cells or producing cells with greater tolerance to various transplantation sites. On a materials level, manipulating the basic chemistry of the encapsulation material will likely further perfect the ability to avoid cellular inflammatory responses. Finally, technologies including, but not limited to, 3D printing, droplet extrusion, microfluidics, and laser molding will be increasingly incorporated into clinical development plans [20,21]. Ultimately, these approaches will converge creating a gestalt with each individual technology becoming more powerful than when used alone. We hypothesize that over the next 10 years this new era will be characterized by significant improvements in manufacturing control, reductions in biological variability, and greater clinical control.

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Declaration of interest

G Orive is scientific advisor of CapCell Biologics. D Emerich is employed at Gloriana Therapeutics,inc. developing encapsulated cell products for CNS diseases. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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