Review

CellPress

Cell encapsulation: technical and clinical advances

Gorka Orive[1,2], Edorta Santos[1,2], Denis Poncelet[3], Rosa María Hernández[1,2], José Luis Pedraz[1,2], Lars U. Wahlberg[4], Paul De Vos[5], and Dwaine Emerich[4]

[1] Laboratory of Pharmacy and Pharmaceutical Technology, Faculty of Pharmacy, University of the Basque Country, Vitoria, Spain
[2] Networking Biomedical Research Center on Bioengineering, Biomaterials, and Nanomedicine, CIBER-BBN, SLFPB-EHU, 01006 Vitoria-Gasteiz, Spain
[3] ONIRIS, UMR CNRS GEPEA 6144 route de la Géraudière, BP 82225, 44322 Nantes Cedex 3, France
[4] NsGene, Inc., 225 Chapman Street, Providence, RI 02905, USA
[5] Department of Pathology and Medical Biology; Immunoendocrinology, University of Groningen, Hanzeplein 1, 9713 GZ Groningen, The Netherlands

Treating many chronic diseases will require a tight, minute-to-minute regulation of therapeutic molecules that is currently not achievable with most pharmaceutical therapies. For these diseases, implantable living cellular systems may be able to provide unlimited drug delivery, enabling seamless matching of treatment duration with disease longevity. Cell encapsulation is an advanced technology that achieves this goal and represents a viable therapeutic option. The advanced state of the field has allowed researchers to inch forward into therapeutic domains previously untouchable because of the myriad disparate fields that intersect biomaterials and cells. Here, we discuss the next generation of clinical trials and potential approaches, 'smart' and responsive encapsulation systems, sophisticated and multifunctional devices, and novel imaging tools, together with the future challenges in the field.

Controlled drug delivery

Improvements in controlled drug delivery have silently crept into our everyday lives. Nasal sprays, rapidly degradable oral strips, transdermal patches, various coatings on pills, and injectable drug-loaded microspheres are all in routine medical and over-the-counter use [1]. However, many diseases are chronic, progressive, and characterized by a life-long struggle and poor symptomatic control using conventional daily systemic drug administration. These treatments cannot provide the minute-to-minute regulation offered by endogenous physiological cellular systems. While advances in mechanical- and material-based drug delivery systems have elongated the duration of drug effectiveness by substituting hourly dosing with daily to weekly dosing, long-term drug delivery is more than a simple engineering problem [2]. Effective, controllable, and tunable long-term drug delivery will likely require the use of long-living cellular systems for essentially unlimited drug delivery and the ability to match treatment duration with disease longevity [3].

Cell encapsulation is one of the current leading methodologies aimed at the immobilization of allogeneic or xenogeneic cells in a semipermeable but immunoprotective membrane to deliver biological products to patients without the need of immunosuppression. The overarching principle of this technology is to provide a long-lasting, perhaps life-long, solution for treating secretory cell dysfunction [4–6]. This is accomplished with the added benefits of reducing the burden of cell sourcing, obviating the need for complex repeated surgical procedures, and providing targeted drug delivery with more beneficial safety profiles. While other approaches that are currently under investigation (including direct tissue infusions [7], various gene therapy approaches [8], cell therapies [9,10], and biomaterial-based drug-delivery systems [11,12]), cell encapsulation is the only approach that, in principle, meets all of the essential prerequisites for a truly transformative medicine. This technology overcomes many of the fundamental obstacles encountered by other approaches by providing a targeted, continuous, *de novo* synthesized source of molecules that can be distributed over significant portions of the body or within tightly regulated compartments, such as the brain [13]. *A priori*, encapsulated cell therapy combines the potency of *de novo in situ* synthesis of cell-derived molecules with the safety of an implantable and retrievable medical device. Cells are enclosed in a semipermeable capsule that is implanted into the desired region. The capsule is constructed with a pore structure that allows oxygen and other nutrients to nourish the encapsulated cells while providing diffusive control of proteins and other molecules as they exit the capsule into the surrounding vasculature or tissue. Rejection of the cells is prevented by the construction of the immuno-isolating membrane, eliminating the entry of the most damaging elements of the host immune system into the cell-containing lumen. This is accomplished by the control of nominal pore size, distribution, tortuosity, and surface chemistry. An additional advantage of the technology is that the capsule can be configured so that it is easily removed and/or replaced if necessary or desired. The continued refinement in imaging

Corresponding authors: Orive, G. (gorka.orive@ehu.es); De Vos, P. (p.de.vos@umcg.nl); Emerich, D. (dwaine.emerich@gmail.com).
Keywords: alginate; microcapsules; cell transplantation; drug delivery; allografts.

0165-6147/
 http://dx.doi.org/10.1016/j.tips.2015.05.003

and robotic surgical procedures inherently provides a means of selectively targeting those areas of the body where the secreted factor will be optimally therapeutic. Given that multiple implants can be used within the same target region, it is possible to achieve greater spread of the molecule throughout the targeted region than can be achieved with crude infusion of protein [14]. Fifty years after the initial bench-top studies, we describe here the state-of-the-art and the new directions in the basic research and translational medicine aspects of field of cell encapsulation (Figure 1). We highlight the next generation of clinical trials and potential approaches, 'smart' and responsive encapsulation systems, sophisticated and multifunctional devices, and imaging tools, together with future challenges in the field.

From choosing biomaterials to developing 'smart' delivery systems

Criteria for selecting biomaterials

Over the past 20 years, numerous polymers have been proposed and evaluated for encapsulation purposes, including alginate, agarose, chitosan, poly(ethylene glycol) (PEG), polyvinyl alcohol, among others. Many never made it to the application phase because they did not meet one or more basic requirements for their use. Polymers for immuno-isolating capsules should never reduce the functionality or the viability of encapsulated cells. Also, the polymers should form scaffolds that are flexible, soft yet mechanically stable, and allow diffusion of the therapeutic molecules into the surrounding host. Of particular importance is that the polymers need to be compatible with host immune responses and should not provoke responses that interfere with viability of the enveloped cells.

The most commonly used polymers have been recently reviewed in view of their potential clinical application [15]. These are PEG, polyvinyl alcohol, polyurethane, polyethersulfone (PES), polypropylene, sodium polystyrene sulfate, polyacrylate, agarose, chitosan, cellulose, collagen, xanthan, and alginate [15]. Although many of these polymers have promising properties for cell encapsulation, a greater understanding is needed of the optimal structural conformation and how they can best be used to avoid inflammatory responses in humans. Currently, only one source, the naturally occurring polymer alginate, has passed most of the scientific and regulatory issues to qualify as safe for human application. Alginate is a heterogenic family of natural polymers obtained from algae that vary greatly in mannuronic (M) and glucuronic (G) acid content. It basically comprises homopolymers of M–M, G–G, and G–M. Variations in the ratios of these polymers determine the flexibility, pliability, and even the biological responses of final particles *in vivo*. Understanding how the basic chemical and physical properties of alginate improves the ability to manufacture implantable capsules could lead to the identification of synthetic molecules that can be reproducibly manufactured to have characteristics comparable or superior to those of alginate.

Smart delivery systems

Over the past few years, several important studies have examined the possibility of developing advanced 3D microcapsules capable of responding to external stimuli to provide

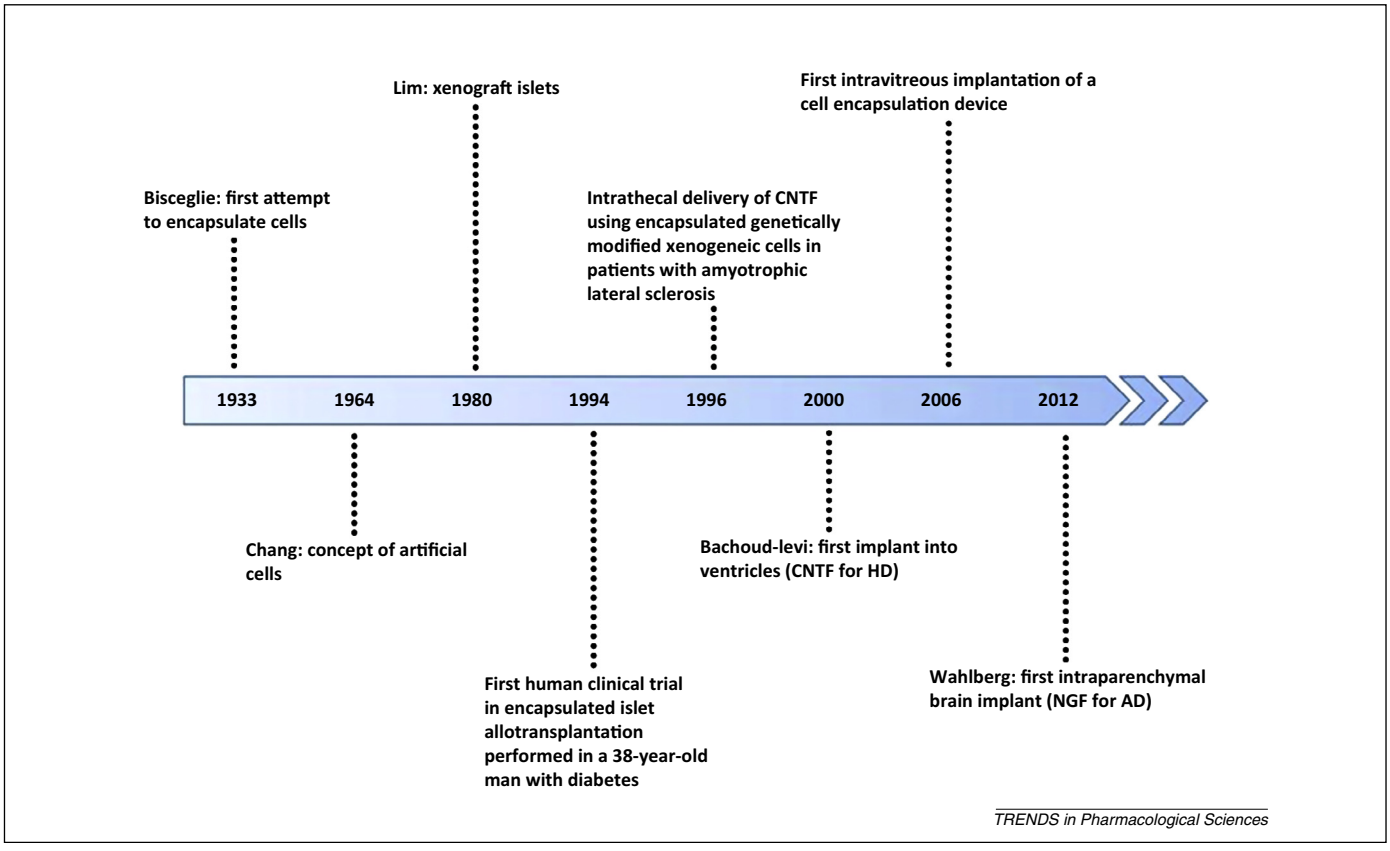

Figure 1. Timeline describing the milestones of cell microencapsulation since its first conception.