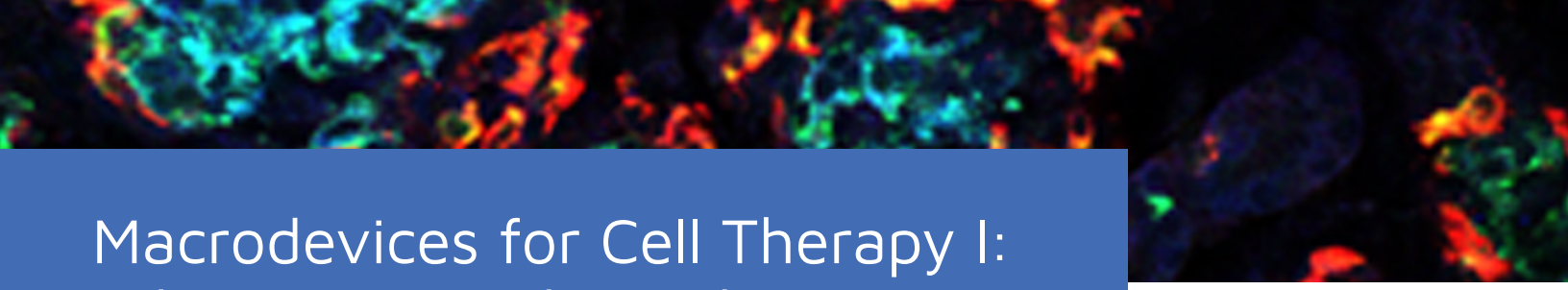

Macrodevices for Cell Therapy I: Advantages and Disadvantages

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On average, there are over 2600 clinical trials for cell and gene therapy products on any given day. Yet very few of these products have made it to market to have an impact on society.

For example, the largest number of newly approved cell or gene therapies were in the years 2017 and 2021 where only 3 new products were approved each year.

Why are so many promising cell therapies failing to make it to market?

One reason that is becoming clear is the inability to protect the cells from destruction by the recipient's immune system.

Research across the globe is focused on solving the challenge of cell protection resulting in multitudes of different approaches all aimed at maintaining cell function while protecting them from the surrounding environment. These approaches can be categorized as either macrodevices or hydrogel microdevices (typically as microspheres).

The distinction between the two is based on the size of the device. Procedures classified as microencapsulation or microdevices are typically under 1500µm in diameter, while macrodevices are larger, such as the size of a credit card or larger.

While macroencapsulation technologies come in a wide variety of shapes and sizes, the category is comprised of devices that trap the cells internally and typically are surgically placed within the body at a target location. Currently, the most common applications of macrodevices for cell therapies focus on diabetes, heart disease, central nervous system diseases, and cancer.

Generally, the materials used to construct macrodevices are durable lasting months to years after implantation, and all devices used to transplant cells must support the long term viability of the transplanted cells by providing an optimized environment including sufficient nutrients and oxygenation, while initiating a minimal negative response by the host body.

This article is the first in a two-part series on macrodevices, focusing on the advantages and disadvantages.

In part two, we review the different types of macrodevices and summarize the clinical trials using them.

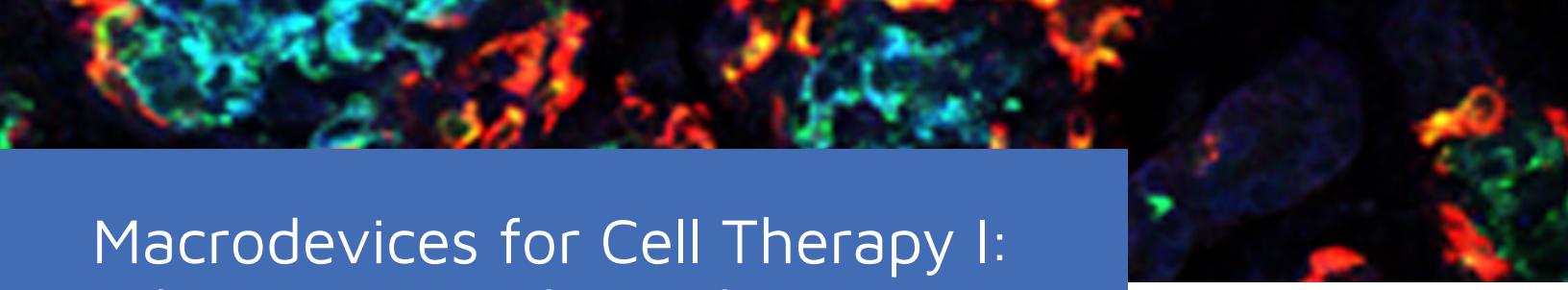
Advantages of Macrodevices

There are a number of advantages associated with macrodevices, including their:

- relative ease in retrieval from the body
- longer in vivo lifespan compared to other smaller encapsulation technologies
- immune protection
- refillable cell chambers

Retrievable

One of the most important advantages of macrodevices is their relative ease in retrieval from the body in case of therapeutic failure of rejection. This is particularly important when the starting cell material is a pluripotent cell line, which may have tumorigenic potential[1].



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While retrievability was an important characteristic early in the use of stem cells to treat chronic diseases[2], more recently, regulatory concerns about retrievability have begun to fade. This is likely due to the increased number of patients being administered stem cells in a form that is not retrievable. For example, Vertex's current clinical trial to treat diabetes is based on differentiated stem cells without use of any encapsulating device (macro or micro), but the patients are administered immunosuppressors long-term.

Durable

Macrodevices have a longer in vivo lifespan compared to other smaller encapsulation technologies (micro or nano). For example, when compared to microspheres made of hydrogels, the hydrogel microbeads may be broken down under physiological and pathological conditions, whereas the materials used for the outer shell of most large devices are not susceptible to enzymatic or hydrolytic breakdown.

This is important when treating chronic diseases such as diabetes or other endocrine disorders. Ideally, the transplanted cells would continue to function for 10 years or more. Placing the device in tissues that do not undergo physical stresses, such as avoiding muscle or joints can also assist in the total durability of the therapeutic.

Immune Protection

The pore size of the microdevice appears to be essential to blocking immune rejection of the transplanted cells. Most important is the ability of the device to block entrance of the host's cells, such as immune cells. To do so, the pores of the microdevice should be less than 500nm – 800nm[1,3]. The macrodevice manufacturing process is more amenable to consistent control over pore size compared to microencapsulation using hydrogels[4]. In addition, because devices can be made of multiple layers each made of different materials, each layer can have a different pore construct to block immune cells from reaching the therapeutic cells[5].

Refillable Cell Chambers

For chronic diseases where the therapeutic cells must continue to function long-term, a refillable cell chamber is a great advantage. It is assumed that no cells within a device will maintain viability and function for the life of a patient. In fact, 5-8 years is likely the maximum that any cell type could survive in a device that also inhibits immune rejection. Thus, devices that have a chamber that can be filled with fresh cells without retrieval of the device are very appealing. Multiple groups are working on such products including Ma's lab at Cornell[6] and scientists associated with Sernova[7]. Although the concept of secondary fillings of the chambers have been shown in animal models and the devices have been placed in humans, they have not been refilled to date in clinical trials. However, for some devices the chamber is never filled with cells initially until already implanted in the body[8].

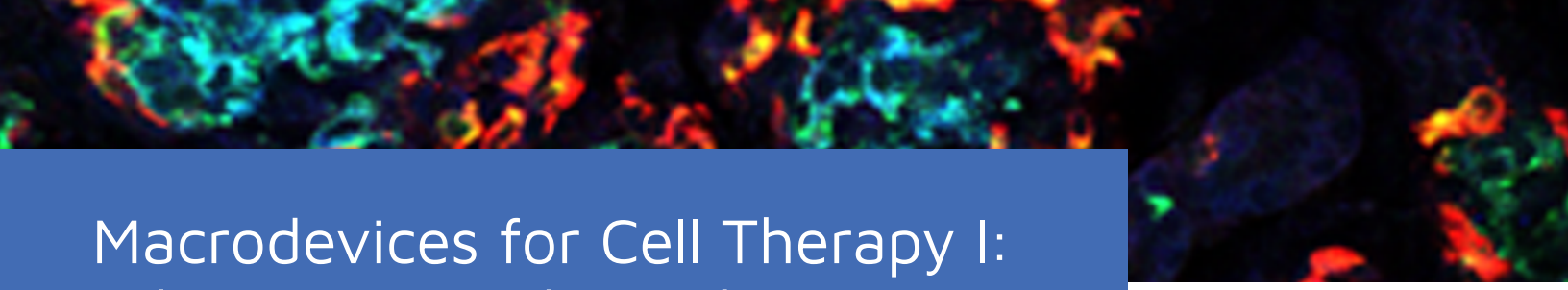
Disadvantages of Macrodevices

While there are advantages to macrodevices, there are also some disadvantages. These include:

- limited diffusion into and out of the device
- device volume limits
- poor vascularization
- immune rejection
- storage and shipping challenges

Diffusion

A common limitation of macrodevices is limited diffusion into and out of the device. Transplanted



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cells require significant oxygen and nutrients for their survival. When cells are packed into the core of a solid material, the surface area to mass transfer oxygen and nutrients into the device and waste and other molecules out of the device, is extremely limited[9,10]. The distance between the cells and the surface of the device is critical in the success of the transplant, with distances of less than 500µm as optimal[11]. Device diffusion has been a long-term issue with macrodevices and some companies have tried to solve it by pumping oxygen into the core of the device using either small storage units[12] or designing ports with direct access to ambient air[13].

Other groups have designed devices that encourage blood vessel growth into the core of the device where the cells are in close contact with the vessels. Often the transplant site is first prepared by encouraging angiogenesis with exposure to growth factors such as VEGF. The negative side of this approach is that by placing the transplanted cells in contact with the blood supply, immune protection is lost, and the recipient must be on systemic immunosuppressors for the lifetime of the transplant.

A completely different approach is to engineer oxygen generation biomaterials for use in the devices. A group out of the University of Florida designed a device that contained an oxygen generating form of polydimethylsiloxane and implanted the device in diabetic rodents showing improved function even at high cellular loading densities[14]. Yet the durability of such chemistry is still in question.

Limited Volume

Because all of the cells must be packed into a defined space, the device volume limits the number of cells that can be delivered. Often the volume is less than the therapeutic dose of cells. Such is the case for treating diabetes, where groups have transplanted multiple devices to get to the therapeutic dose. Some devices hold as few as 70 islet equivalents[15] equating to 65,000 cells[16], which is far short of the recommended 9 million cells/kg used in the Edmonton protocol for islet transplantation[17]. For example, the ViaCyte PEC-Encap, discussed in Part II of this paper, went into diabetic patients in a clinical trial. However, to reach the target dose of cells, 12 separate devices had to be implanted in each patient[18].

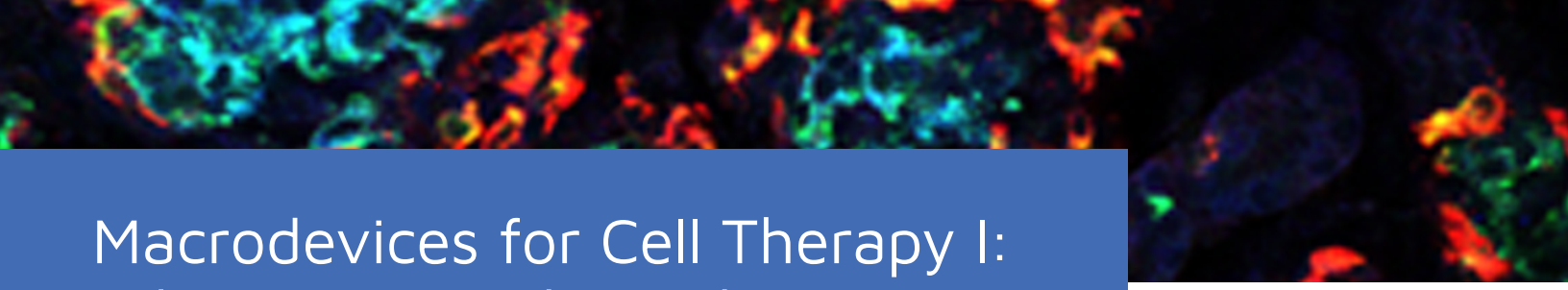
Poor Vascularization

Most cells transplanted were highly vascularized in their native state in the body. The blood vessels that traverse native tissues are required to maintain the health of all of the surrounding cells and to distribute factors, such as hormones, secreted by the cells. But when cells are transplanted, vascularization to the new transplant is a challenge. Most macrodevices are classified as extravascular, meaning that they do not have blood vessels or blood flow traversing through the device itself[4]. If an extravascular microdevice is simply placed in a convenient location, such as under the skin, the significant distance between the cells in the core of the device and the surrounding blood vessels is too great to overcome and cells die due to a lack of nutrients and oxygen[14].

Immune Rejection

In the review of advantages discussed above, the plethora of materials that can be used for macrodevice manufacturing helps in the ability to find substances that do not elicit a foreign body response. However, whenever any foreign object is placed in the body, it will respond, as was described in our earlier article on Biocompatibility. This is particularly true for macrodevices as their large size disrupts the normal microanatomy of the tissues instigating a stronger foreign body response than a micro or nano technology.

When a foreign body reaction is initiated multiple types of



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cells are attracted to the area such as macrophages. Finding that they cannot destroy or engulf the device, the invading fibroblasts will wall it off from the rest of the body by creating a fibrotic capsule around the device[1]. The separation of the device from the rest of the tissue exacerbates the already limited oxygenation of the cells and typically results in their death and failure of the transplant.

The choice of materials for the surface of the device can greatly affect the presence or even the extent of fibrosis surrounding the device. For example, it has been well documented that the hydrogel, alginate elicits a strong foreign body response. Some groups have worked with synthetic zwitterionic coatings that are reported to prevent fibrosis in rodents and block the response to alginate[1]. Other groups have simply impregnated the alginate slabs with exogenous oxygen in an attempt to maintain healthy cells[12].

Storage and Shipping

The regenerative medicine field is just coming to terms with how to ship and store live cells as a medicine. The normal shipping conditions used for traditional drugs do not transfer to living cells as drugs. Even complex shipping distribution channels worked out for the COVID vaccines have limitations when applied to cells. Most cells will survive above freezing temperatures for only a few hours to days making shipping across a continent challenging[19]. For long term storage (months to years), cells need to be cryopreserved at -80C or colder. Cryopreservation can be accomplished when cells are free-floating in a cryopreservation media.

Attempting to cryopreserve cells while in a macrodevice would result in failure as the device would create a significant barrier to controlled-rate freezing and also to consistent thawing. Thus, ice crystals would form in and around the cells that would destroy the cell's outer membrane and result in cell death.

Conclusions

Macrodevices offer many advantages compared to injecting cell therapies intravenously and hoping that they arrive at the target destination. Depending on the reactive chemistry and pore size of the surface substance, macrodevices can block an immune attack of the protected cells without eliciting a foreign body response that would eventually kill the therapeutic cells. They are also quite durable, and some designs include chambers that can be refilled with fresh cells. However, their large size itself tends to disrupt the surrounding tissue and elicit a foreign body response.

Traditionally, macrodevices have had poor diffusion characteristics, leading to necrosis of the entrapped cells. Further, because of the size limitation, there is a limit to the number of cells that can be packed into each device. Thus, multiple devices are likely required to treat systemic diseases.

Finally, storage and shipping of the cells in a device is problematic. One way around the issue is to ship the cryopreserved cells separate from the device. In this scenario, the end-user (the clinician) must place the cells into the device, which introduces errors and contamination.

With the widespread understanding that the delivery of cell therapies is an issue, a number of groups are working on unique approaches to solve the problem. Part II of this work dives into the different categories of macrodevices.

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