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Preface

Cell encapsulation: ready for the next step ☆

Microencapsulation of therapeutic cells is proposed to be a technology to treat diseases that require a minute-to-minute regulation of therapeutics. The advantage of microencapsulated cells is that the cells sense the demand of the host for therapeutics in real time and release therapeutics precisely according to the demands in the absence of side effects that are often associated with pharmaceutical interventions. An additional benefit is that the capsules can be made immunoprotective by regulating the permeability of the membranes which avoids the application of immunosuppression to prevent rejection of the cells.

Important advances have been made during recent years in understanding the requirements the microcapsules have to meet in order to accommodate the survival of the enveloped cells and to be tolerated by the host. The current issue contains nine reviews of leading scientists from different areas of application of microencapsulation of therapeutic cells and with different views on how to proceed towards the next generation of devices. The authors were invited not only to summarize the progress in their field, but also to provide recommendations for future research. This is timely as cell encapsulation is gaining much attention by some major grant giving agencies. The advantage of availability of large grants is that financial support for progress is available. However at the same time it holds the threat that the numerous new players in the field 'invent the wheel again' and are stopped by issues such as biocompatibility issues that leaders have already solved more than a decade ago. Many examples of this are already available. Wrong choices for types of polymers resulting in inflammatory responses or the use of encapsulation systems that lack immunoprotective properties are just a few of them.

In general the complexity of cell encapsulation is underestimated and every leader in the field will agree that application of microencapsulation for treatment of disease is far from easy. There are many encapsulation systems available with all their own pros and cons. The right choice for the type of system depends on the therapeutic application. Gorka Orive and colleagues (doi: http://dx.doi.org/10.1016/j.addr.2013.07.009) give in their overview entitled 'Application of cell encapsulation for controlled delivery of biological therapeutics' the current view on where and how encapsulation can be therapeutically applied. They review the benefits that encapsulation systems can have in the application of stem-cell technologies for treatment of disease. The second review (doi: http://dx.doi.org/10.1016/j.addr.2013.11.005) is about the current view on polymers that qualify for application in encapsulation systems. For many years there have been two categories of researchers in this area. The first concentrated completely on natural polymers because of the 'cell-friendly' encapsulation methods that can be applied with natural polymers. The second group almost exclusively concentrated on synthetic polymers as these researchers believe that reproducible production of polymers is a 'key' for success. When taking into account all the arguments the honest conclusion should be that the same issues challenge both natural and synthetic polymers. They both sometimes contain contaminants such as pathogen associated molecular patterns that may lead to host responses. Also, both groups of researchers should focus more on how the polymers accommodate the cells in the capsules. Almost all overlook this critical issue. When working with cadaveric donors, loss of cells should be reduced to an absolute minimum. Losses of up to 60% of cells have been reported with some polymers.

The majority of studies on encapsulated cells involve microencapsulation of pancreatic islets for immunoprotection and treatment of Diabetes. David Scharp and Piero Marchetti (doi: http://dx.doi.org/10.1016/j.addr.2013.07.018) give an overview of the challenges they have met as academical and industrial researcher. David and Piero share results of not previously published industrial trials in primates that are important for adequate design of future trials. Ron Neufeld and co-workers (doi: http://dx.doi.org/10.1016/j.addr.2013.09.015) review in the follow-up paper the technologies that have been developed or are currently designed to encapsulate cells in an efficient manner while preserving functionality and survival. Riccardo Calafiore and Giuseppe Basta (doi: http://dx.doi.org/10.1016/j.addr.2013.09.020) are giving insight into the clinical trial results with their alginate-poly-L-ornithine system. Riccardo is one of the few experts that are knowledgeable on the area of islet-biology and the physical-chemistry of microcapsules. With medical ethical permission for transplanting suboptimal amounts of islets in immunoprotective capsules he was able to show that the procedure is safe and reduces insulin demand.

A crucial factor in functional survival and longevity of tissue in capsules is sufficient nutrition. An important factor in survival of islet-tissue and other metabolic active cells is a sufficient supply of oxygen. Clark Colton (doi: http://dx.doi.org/10.1016/j.addr.2014.02.007) reviews in a timely fashion all the achievements and solutions, including external oxygen supply, for prolongation of longevity of grafts. However, oxygen is not the only factor. Also other essential nutrients should be supplied to the encapsulated tissue. With taking into account all the lessons from the past Annemarie Rokstad and colleagues (doi: http://dx.doi.org/10.1016/j.addr.2013.07.010) review all the assays and tools that are available for predicting efficacy of capsules in vivo in animals and humans. Emphasis is on the definition of biocompatibility that is very different for encapsulated cells than for classical devices such as artificial hips and knees. To avoid cell-loss the responses should be minimal and not associated with impairment of function of the cells in the capsules. For that reason, in the field the term biotolerability is preferred over biocompatibility.

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The above principles and tools apply not only to encapsulation of pancreatic islets but also to other emerging areas where immunoprotection by encapsulation is considered to be a promising option. Dwaine Emerich and co-workers (doi: http://dx.doi.org/10.1016/j.addr.2013.07.008) give their view on how encapsulated cell systems can lead to solutions for neurodegenerative diseases. A huge advantage over other therapeutic approaches is that capsules with cells can be placed beyond the blood–brain barrier in exactly the side where therapeutic intervention is required. The same goes for treatment of brain tumors. Simone Niclou and colleagues (doi: http://dx.doi.org/10.1016/j.addr.2014.01.010) review the advances in that area and gives their view on which therapeutics produced by cells holds the highest chance on success in the near future.

Finally, as theme editor I'm extremely thankful for all the contributions by the experts and for the reviewers sharing their expertise and insights that have enabled this theme issue. The contributors have expressed their gratitude to the editorial board for the opportunity to make this theme issue at this moment. It is timely because of the rapid expansion of the field. Researchers that are not familiar with physical chemical demands or knowledgeable about the concepts of immunoprotection will meet many disappointments. We hope the current series of reviews will prevent this or at least gives some guidance to find the right directions. In the reviews leaders have given their view on how to proceed to make cell-encapsulation a broadly clinical applicable technology. A critical, repeated item is overcoming the enormous lab-to-lab variations by documentation of the critical capsule properties and quality of the cellular grafts. Guidelines to do so have been published by a European consortium in 2009 and are updated in this issue. Unfortunately many groups, especially from the USA, still do not follow the guidelines. This leads to many misinterpretations of results and interferes with adequate comparisons between labs. We hope the collection of papers in this issue will change this attitude since it is our belief that in a multidisciplinary field only collaboration and stepwise approaches will ultimately lead to sufficient knowledge to reproducibly make successful encapsulated cellular grafts.

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