



Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

journal homepage: www.elsevier.com/locate/addr

1 Preface

2 Cell encapsulation: ready for the next step[☆]

3
4 Microencapsulation of therapeutic cells is proposed to be a technol-
5 ogy to treat diseases that require a minute-to-minute regulation of ther-
6 apeutics. The advantage of microencapsulated cells is that the cells
7 sense the demand of the host for therapeutics in real time and release
8 therapeutics precisely according to the demands in the absence of side
9 effects that are often associated with pharmaceutical interventions. An
10 additional benefit is that the capsules can be made immunoprotective
11 by regulating the permeability of the membranes which avoids the
12 application of immunosuppression to prevent rejection of the cells.

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

31 In general the complexity of cell encapsulation is underestimated
32 and every leader in the field will agree that application of microencap-
33 sulation for treatment of disease is far from easy. There are many encap-
34 sulation systems available with all their own pros and cons. The right
35 choice for the type of system depends on the therapeutic application.
36 Gorka Orive and colleagues (doi: <http://dx.doi.org/10.1016/j.addr.2013.07.009>)
37 give in their overview entitled 'Application of cell encapsulation for controlled delivery of biological therapeutics' the current
38 view on where and how encapsulation can be therapeutically applied.
39 They review the benefits that encapsulation systems can have in the ap-
40 plication of stem-cell technologies for treatment of disease. The second
41 review (doi: <http://dx.doi.org/10.1016/j.addr.2013.11.005>) is about the
42 current view on polymers that qualify for application in encapsulation
43 systems. For many years there have been two categories of researchers
44 in this area. The first concentrated completely on natural polymers
45 because of the 'cell-friendly' encapsulation methods that can be applied

47 with natural polymers. The second group almost exclusively concen-
48 trated on synthetic polymers as these researchers believe that repro-
49 ducible production of polymers is a 'key' for success. When taking into
50 account all the arguments the honest conclusion should be that
51 the same issues challenge both natural and synthetic polymers. They
52 both sometimes contain contaminants such as pathogen associated
53 molecular patterns that may lead to host responses. Also, both groups
54 of researchers should focus more on how the polymers accommodate
55 the cells in the capsules. Almost all overlook this critical issue. When
56 working with cadaveric donors, loss of cells should be reduced to an
57 absolute minimum. Losses of up to 60% of cells have been reported
58 with some polymers.

59 The majority of studies on encapsulated cells involve microencapsu-
60 lation of pancreatic islets for immunoprotection and treatment of Dia-
61 betes. David Scharp and Piero Marchetti (doi: <http://dx.doi.org/10.1016/j.addr.2013.07.018>)
62 give an overview of the challenges they have met as academical and industrial researcher. David and Piero
63 share results of not previously published industrial trials in primates
64 that are important for adequate design of future trials. Ron Neufeld
65 and co-workers (doi: <http://dx.doi.org/10.1016/j.addr.2013.09.015>) re-
66 view in the follow-up paper the technologies that have been developed
67 or are currently designed to encapsulate cells in an efficient manner
68 while preserving functionality and survival. Riccardo Calafiore and
69 Giuseppe Basta (doi: <http://dx.doi.org/10.1016/j.addr.2013.09.020>) are
70 giving insight into the clinical trial results with their alginate-poly-L-
71 ornithine system. Riccardo is one of the few experts that are knowlege-
72 able on the area of islet-biology and the physical-chemistry of microcap-
73 sules. With medical ethical permission for transplanting suboptimal
74 amounts of islets in immunoprotective capsules he was able to show
75 that the procedure is safe and reduces insulin demand.

76 A crucial factor in functional survival and longevity of tissue in
77 capsules is sufficient nutrition. An important factor in survival of islet-
78 tissue and other metabolic active cells is a sufficient supply of oxygen.
79 Clark Colton (doi: <http://dx.doi.org/10.1016/j.addr.2014.02.007>) re-
80 views in a timely fashion all the achievements and solutions, including
81 external oxygen supply, for prolongation of longevity of grafts. Howev-
82 er, oxygen is not the only factor. Also other essential nutrients should be
83 supplied to the encapsulated tissue. With taking into account all the les-
84 sons from the past Annemarie Rokstad and colleagues (doi: [http://dx.2013.07.010](http://dx.doi.org/10.1016/j.addr.2013.07.010)) review all the assays and tools
85 that are available for predicting efficacy of capsules in vivo in animals
86 and humans. Emphasis is on the definition of biocompatibility that is
87 very different for encapsulated cells than for classical devices such as ar-
88 tificial hips and knees. To avoid cell-loss the responses should be mini-
89 mal and not associated with impairment of function of the cells in the
90 capsules. For that reason, in the field the term biotolerability is preferred
91 over biocompatibility.
92
93

[☆] This preface is part of the *Advanced Drug Delivery Reviews* theme issue on "Cell encapsulation and drug delivery".

94 The above principles and tools apply not only to encapsulation of pan- 116
 95 creatic islets but also to other emerging areas where immunoprotection 117
 96 by encapsulation is considered to be a promising option. Dwaine Emerich 118
 97 and co-workers (doi: <http://dx.doi.org/10.1016/j.addr.2013.07.008>) give 119
 98 their view on how encapsulated cell systems can lead to solutions for 120
 Q1 neurodegenerative diseases. A huge advantage over other therapeutic ap- 121
 100 proaches is that capsules with cells can be placed beyond the blood–brain 122
 101 barrier in exactly the side where therapeutic intervention is required. The 123
 102 same goes for treatment of brain tumors. Simone Niclou and colleagues 124
 103 (doi: <http://dx.doi.org/10.1016/j.addr.2014.01.010>) review the advances 125
 104 in that area and gives their view on which therapeutics produced by 126
 105 cells holds the highest chance on success in the near future. 127

106 Finally, as theme editor I'm extremely thankful for all the contribu- 128
 107 tions by the experts and for the reviewers sharing their expertise and in- 129
 108 sights that have enabled this theme issue. The contributors have 130
 109 expressed their gratitude to the editorial board for the opportunity to 131
 110 make this theme issue at this moment. It is timely because of the rapid ex- 132
 111 pansion of the field. Researchers that are not familiar with physical chem- 133
 112 ical demands or knowledgeable about the concepts of immunoprotection 134
 113 will meet many disappointments. We hope the current series of reviews 135
 114 will prevent this or at least gives some guidance to find the right direc-
 115 tions. In the reviews leaders have given their view on how to proceed

to make cell-encapsulation a broadly clinical applicable technology. A 116
 critical, repeated item is overcoming the enormous lab-to-lab variations 117
 by documentation of the critical capsule properties and quality of the 118
 cellular grafts. Guidelines to do so have been published by a European 119
 consortium in 2009 and are updated in this issue. Unfortunately many 120
 groups, especially from the USA, still do not follow the guidelines. This 121
 leads to many misinterpretations of results and interferes with adequate 122
 comparisons between labs. We hope the collection of papers in this issue 123
 will change this attitude since it is our belief that in a multidisciplinary 124
 field only collaboration and stepwise approaches will ultimately lead 125
 to sufficient knowledge to reproducibly make successful encapsulated 126
 cellular grafts. 127

Paul de Vos 130
 (Theme Editor) 131

132
 University of Groningen, Pathology and Medical Biology, 133
 Section of Immunoendocrinology, Hanzplein 1, EA 11, 134
 9713 GZ Groningen, The Netherlands 135

Available online xxxx