

## **Survival of encapsulated islets: More than a membrane story**

Barkai et al.

### **Response to reviewers**

#### **Referee #1 (001609386):**

*On page number 11- The authors state that alginate based cell encapsulation is in urgent need. However they failed to mention that alginate microencapsulation which failed has been tried in humans.*

I agree with the referee that islet microencapsulation was tested in many animal models and in human trials. However, it is clearly stated (page 11) that many excellent reviews cover the field of islet microencapsulation and that the scope of this review is to focus on macro-encapsulation strategies. To our best understanding, clinical trials attempting to transplant macro-encapsulated islets began only recently (NCT02064309; NCT00790257; NCT01652911; NCT02239354), and there are no data (so far) on efficacy of this treatment.

*Page number 12- 2nd paragraph, last but one sentence; The authors need to make a correction to the sentence by adding monkeys also indicating that the device was tried in large animals (Elliot's work)*

I thank the referee for this valuable suggestion. One of the cited papers (#106) refers to xenotransplantation of porcine islets in pigs using the 'Theracyte' membrane and correction was made accordingly. Additional references are also included (#105, #107).

*To this effect they also need to correct the last sentence on page 12 and first sentence on page 13- which states that the Theracyte device success is currently limited to rodent recipients and no data on successful transplantation of donor islets into large animal models are available. Which is not correct.*

I thank the referee for this correction. The text was amended accordingly (p. 14).

*Please refer to the publication by Sasikala et al (2013) in TRANSPLANTATION; Which has used Theracyte device for encapsulation of islets in autologous and allogenic islet transplantation in non human primates.*

This reference was added (#107).

**Referee #2 (00503542):**

*A sentence, "Adding NEC-1, an inhibitor of necroptosis reduced DAMP release and activation of immune cells and rescued larger part of the islet cells." (page 28), seems to need reference(s).*

I thank the referee for this valuable note. An appropriate reference was added (#212).

*A sentence, "from a regulatory perspective, the use of pure pro-angiogenic factors may be problematic." (page 26), seems to need more explanation.*

The sentence was revised per the reviewers' comment (p. 27).

*As a scientific notation of partial oxygen pressure, "PO<sub>2</sub>(2 in subscript)" may be more common than "PO<sub>2</sub>".*

Per the reviewer's comment, PO<sub>2</sub> was changed to PO<sub>2</sub> throughout the manuscript.

*Edmonton protocol was reported in 2000 rather than 2001(page 4, line 8).*

Per the reviewers' comment, this was corrected (p. 5).