



AdoShell®, a non fibrotic, immunoprotective encapsulation system for human islets transplantation shows promising results for clinical application as a cure for people with Type 1 Diabetes

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Abstract

AdoShell® is an easily implantable and fully retrievable scaffold for islet transplantation without immunosuppression. It is based on a permselective hydrogel film allowing insulin diffusion while preventing immune cell invasion. Allogenic transplantation of rat islets in immunocompetent diabetic rats has already demonstrated encapsulated islets survival, insulin secretion, and glycemic regulation.

Compatibility with human islets, good local tolerance, and scalability to deliver a therapeutic dose were studied.

In vitro, AdoShell® Human Islets has shown gluco-responsive insulin secretion for at least 7 months.

After implantation in immunodeficient mice, human C-peptide secretion increased during the first two weeks to reach a plateau until explantation. Explants showed 26 - 66% of preimplantation insulin secretion levels, while the mean secretion index was maintained. AdoShell® was also well tolerated.

An upscaling of AdoShell® to deliver a therapeutic islet dose was manufactured and implanted by laparoscopy in domestic pig.

AdoShell® Islets is suitable for human islets delivery showing good local tolerance without fibrosis and sustained islet functionality.

Introduction & Background

- Requirement for immunosuppression after pancreatic islet transplantation makes the benefit/risk balance unfavorable for most patients. (Holmes-Walked DJ, et al., Transplantation. 2017).
- AdoShell® is an encapsulation system for islets to achieve transplantation without immunosuppression, which consists of (Figure 1) :
 - A silicon ring sandwiching a surgical mesh
 - A hydrogel formed by click-chemistry cross-linking of biocompatible precursors encapsulating islets. It is permselective for nutrients / hormones diffusion but prevents antibody and immune cell penetration.

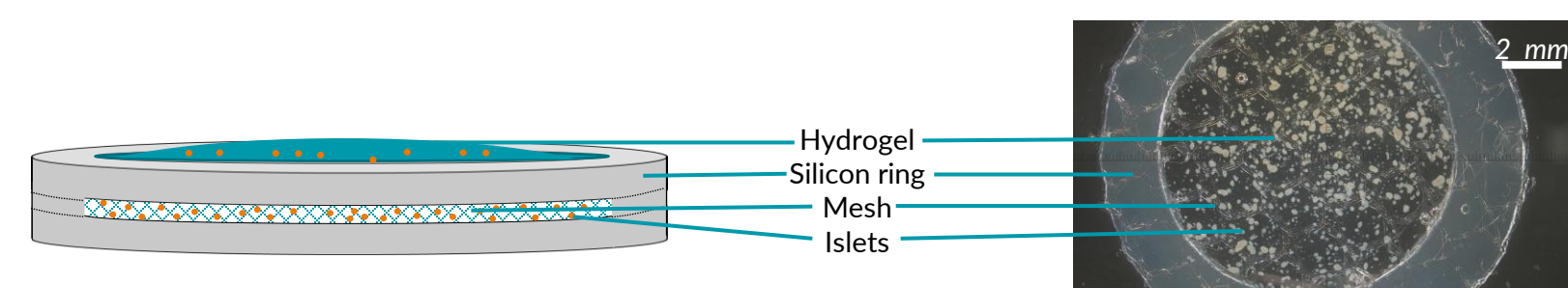


Figure 1: AdoShell® Islets description (left) and prototype for rodent studies (right)

- Encapsulation in the hydrogel maintains islet morphology, as well as insulin (INS) and glucagon (GLC) expression (Figure 2).

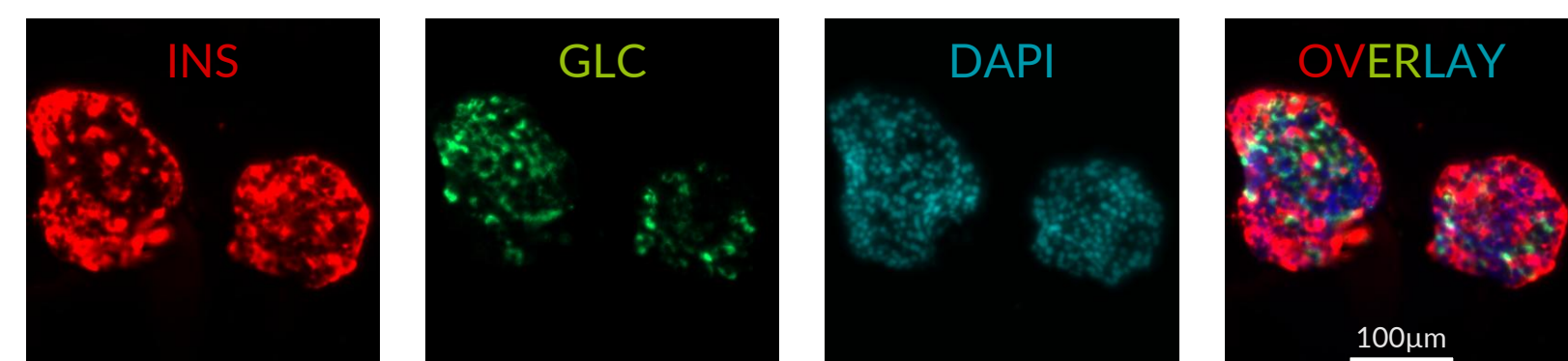


Figure 2 - Immunofluorescence of human islets encapsulated in AdoShell®

- Allogenic transplantation of AdoShell® rat islets in immunocompetent outbred rats led to sustained C-peptide secretion paired with a regulation of glycemia. These results showed the ability of AdoShell® Islets to maintain islet viability and functionality by allowing immunoisolation and access to essential nutrients. (Figure 3).

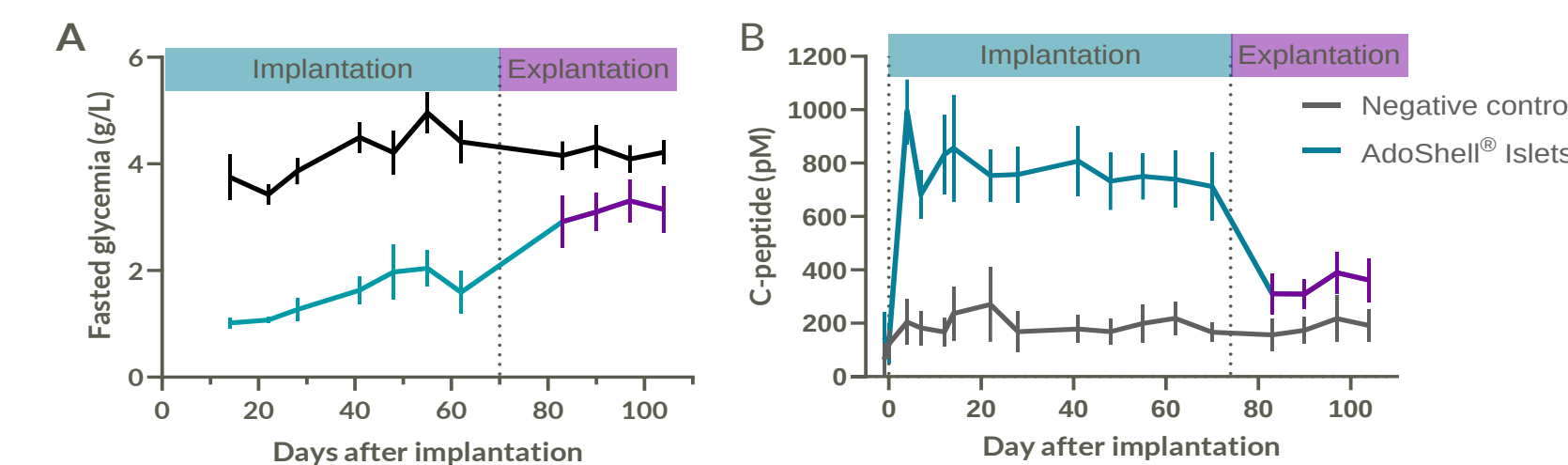


Figure 3 - Allograft of AdoShell® rat islets in immunocompetent rats (bars represent SEM)

Methods

In vitro functionality of encapsulated human Islets

- Human islets were isolated from deceased donors pancreata and encapsulated by simple mixing with hydrogel precursors.
- Hydrogel disks containing ~200 Islet Equivalents (IEQs) were evaluated in dynamic glucose stimulated insulin secretion assay (perfusion) and compared to naked islets

AdoShell® Islets Tolerance studies

- AdoShell® with or without islets was implanted and sutured in the peritoneal cavity of immunocompetent rats.

Study	Islets	Receiver	Duration
A	None	Wistar rats	75 days
B	Human	Wistar rats	22 days
C	Rat	Wistar rats	210 days

AdoShell® Human Islets in immunodeficient mice

- Immunodeficient mice were intraperitoneally transplanted with AdoShell® Human Islets (2 to 3 kIEQ/mouse) in 3 independent studies. AdoShell® Human Islets function was assessed by quantifying human C-peptide concentration in mouse plasma (specific ELISA method).
- Mice were explanted between D44 and D65 and analyzed by static GSIS and histology.
- Explant functionality was compared with one of *in vitro* control implants similarly analyzed on the day of implantation.

Scaled-for-Human AdoShell® implantation in domestic pig

- Large scale AdoShell® was rolled in a thin protective pocket and implanted by laparoscopy in the peritoneal cavity.
- It was immobilized with sutures or clips.

Results

In vitro functionality of encapsulated human Islets

- Encapsulation in AdoShell® maintains glucose stimulated insulin secretion, with a slight change in the kinetic response of insulin secretion: absence of the first phase, and a short ~2 min delay in reaching the peak, most likely due to the diffusion barrier of the hydrogel. Return to basal secretion shows a ~12 min delay. (Figure 4 - A).
- Insulin secretion levels are comparable between naked and encapsulated islets, with a slight increase of basal insulin secretion. (Figure 4 - B).
- The functionality of encapsulated islets is maintained for 7 months, albeit with a decrease of secreted insulin between 4 and 7 months, while naked islets are lost after 1 month in culture. (Figure 4 - B).
- These results demonstrate that AdoShell® Islet is compatible with human islets and maintains long term survival and functionality.

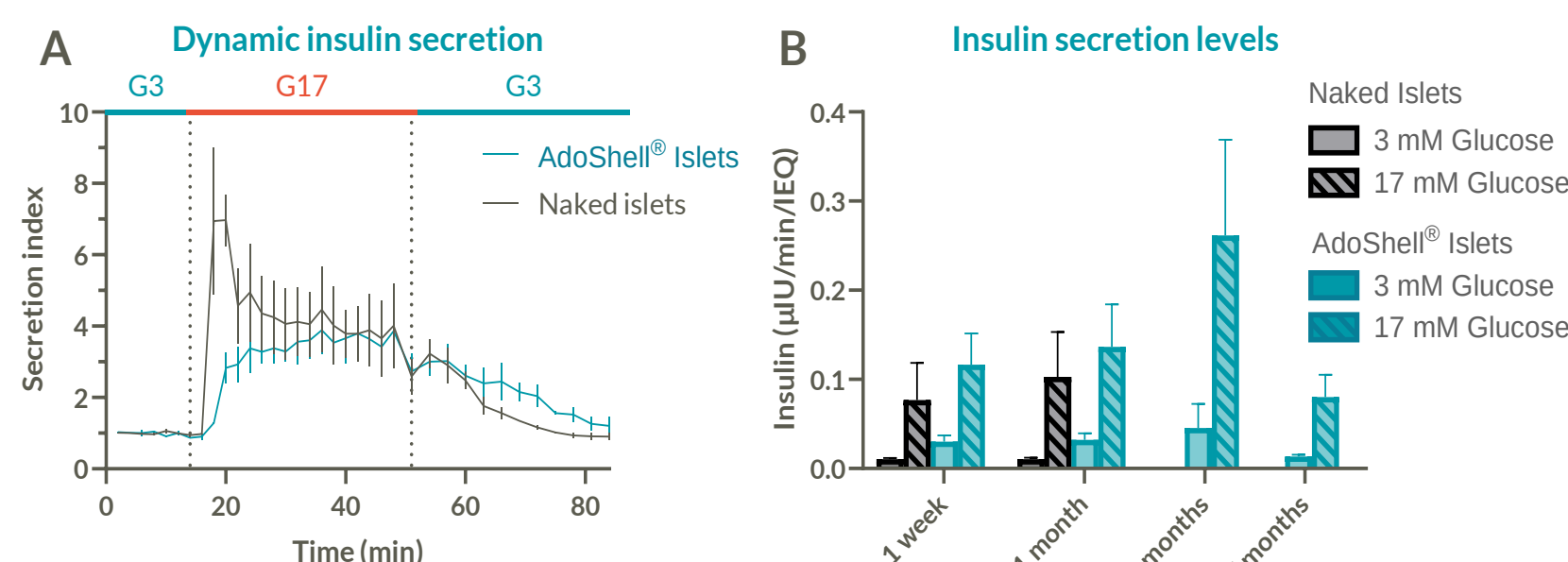


Figure 4 - In vitro insulin secretion (bars represent SEM)

AdoShell® Islets tolerance studies

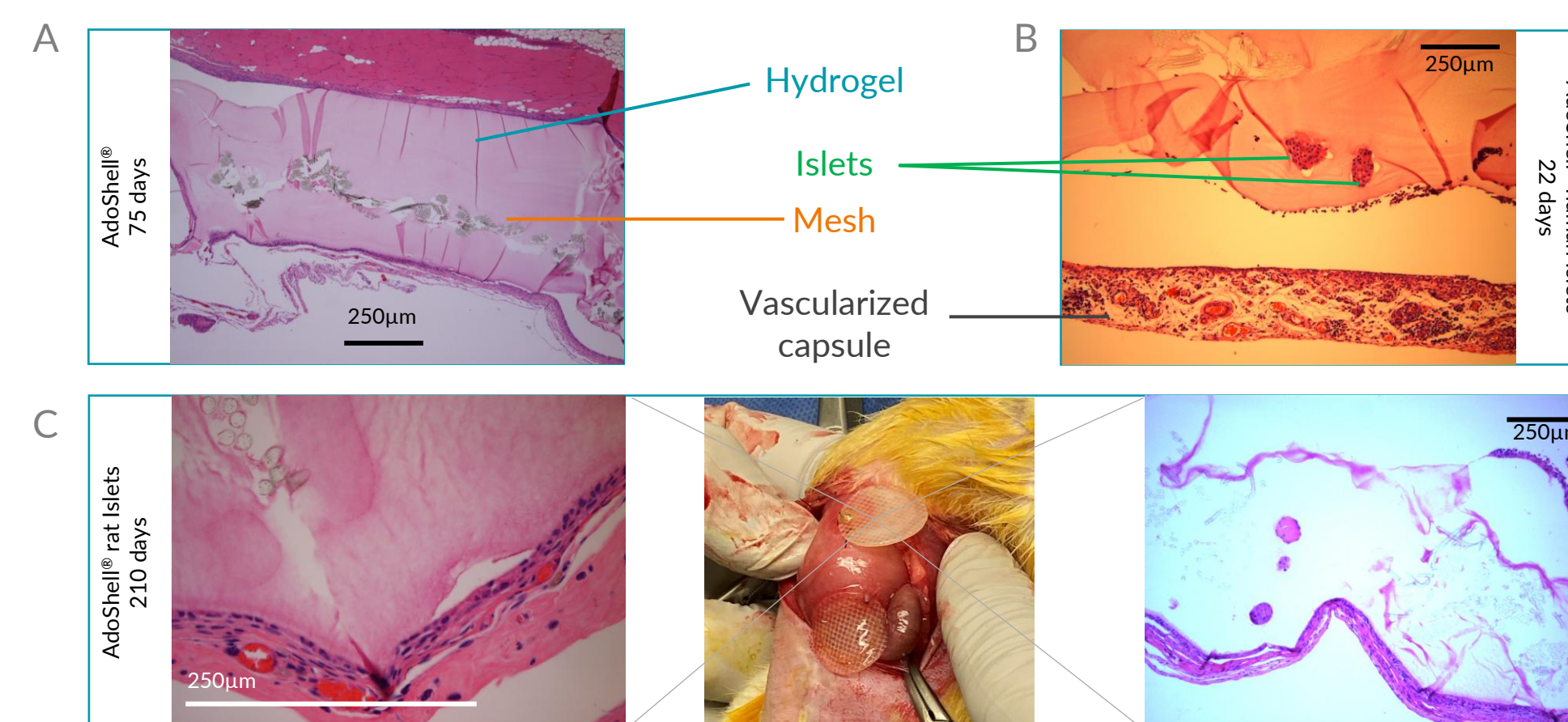


Figure 5 - Local tolerance of AdoShell® and AdoShell® Islets in immunocompetent rats

- AdoShell® showed good local tolerance after 75 days of implantation in the peritoneal cavity of immunocompetent rats. (Figure 5 - A).
- Similar results were obtained for AdoShell® Islets containing xenogeneic human islets after 22 days (Figure 5 - B) and with AdoShell® Islets containing allogenic rat islets after 210 days (Figure 5 - C) of implantation in the peritoneal cavity.
- These results demonstrate that the tolerance of AdoShell® Islets is compatible with long term graft survival *in vivo*.
- AdoShell® Human Islets in immunodeficient mice

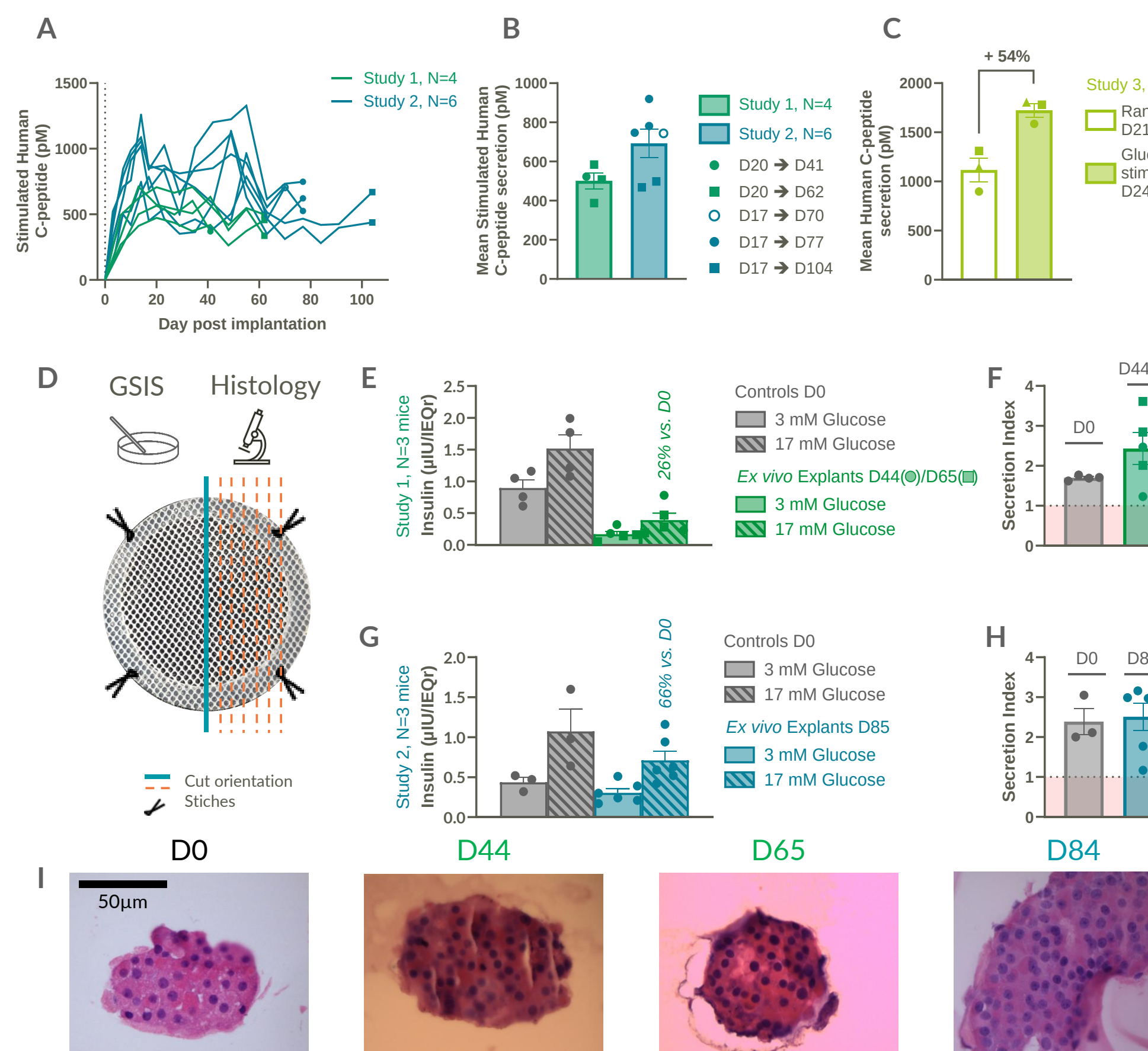


Figure 6 - AdoShell® Human Islets survival and function in immunodeficient mice (bars represent SEM)

- Human C-peptide concentration reached a mean concentration of 808.2 ± 280.5 pM at D13/14 followed by a plateau, up to 104 days post-implantation (Figure 6 - A). Mean stimulated human C-peptide plasmatic concentrations were 501.3 ± 82.3 pM in Study 1 and 692.9 ± 175.2 pM in Study 2 (Figure 6 - B).
- In a third study, an increase of 54% of human C-peptide plasmatic concentration 45 min following intraperitoneal glucose administration was observed (Figure 6 - C).
- Ex vivo*, explants were functional, with secretion index of 2.4 ± 0.9 for Study 1 (Figure 6 - F) and 2.5 ± 0.8 for Study 2 (Figure 6 - H). Stimulated insulin secretion levels were 0.39 ± 0.24 µUI/mL and 0.71 ± 0.28 µUI/mL for Study 1 and Study 2 respectively, corresponding to 26% and 66% respectively, compared to preimplantation values (Figure 6 - E and G).
- Histological evaluation of the explants showed the maintenance of islet structure, confirming islet survival (Figure 6 - I).
- AdoShell® ensured good engraftment and metabolic survival of human islets for at least 104 days *in vivo*.

Scaled-for-Human AdoShell® delivery in domestic pig

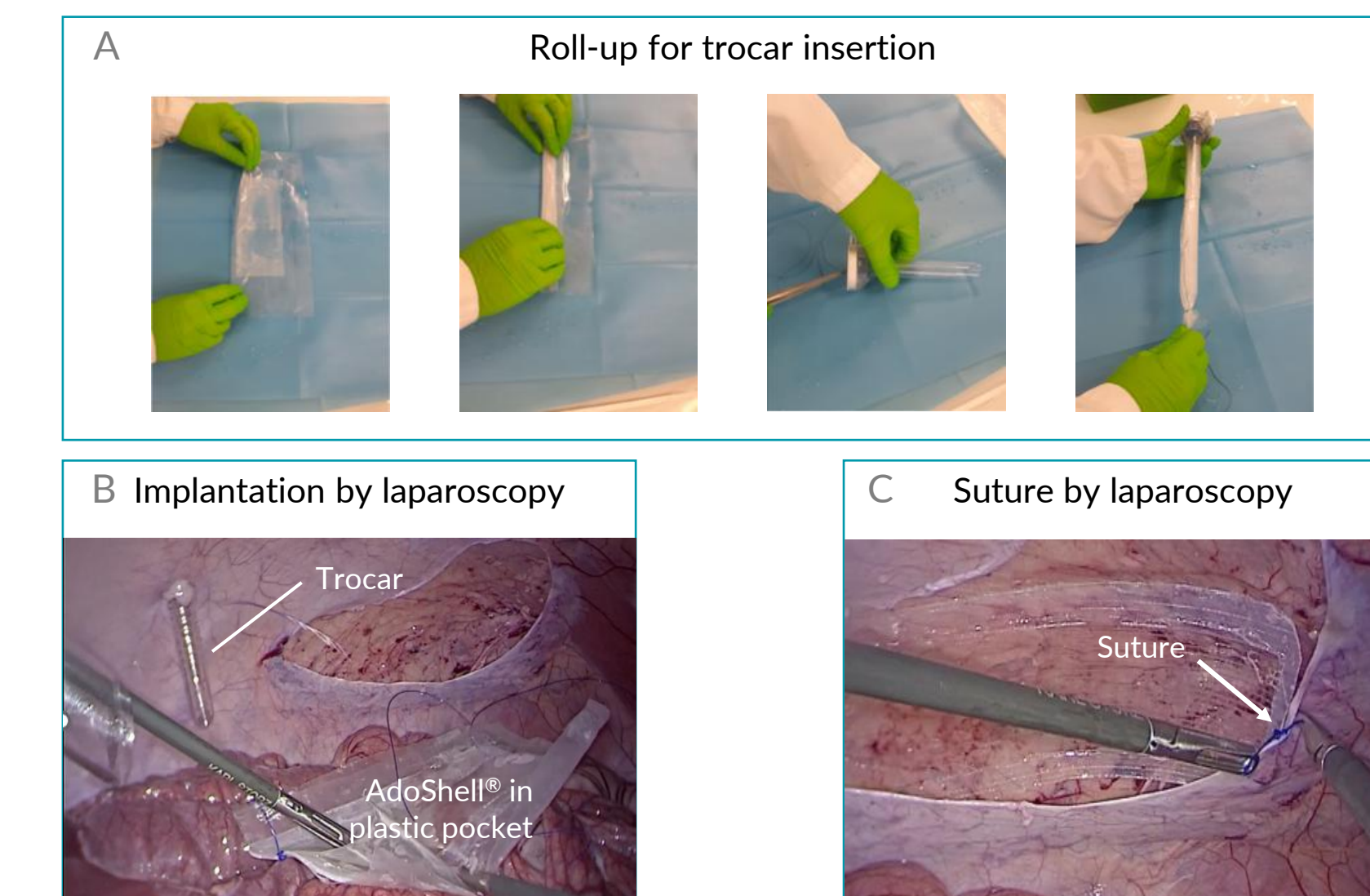


Figure 7 - Scaled-for-Human AdoShell® implantation in domestic pig by laparoscopy

- AdoShell® with dimensions allowing the delivery of 200 kIEQ was successfully implanted in the preperitoneal space of a domestic pig by laparoscopy and immobilized with sutures (Figures 7A-C).
- A clinically relevant number of islets for human application can be delivered by a mini-invasive procedure.

Conclusions

- ✓ AdoShell® provides immunoprotection in an allogenic context
- ✓ AdoShell® is compatible with human islets as it ensures *in vitro* and *in vivo* long-term survival and functionality
- ✓ AdoShell® Islets is well tolerated without any fibrosis
- ✓ Delivery of a therapeutic dose can be achieved with a scaled-for-human AdoShell® that can be implanted by mini-invasive surgery
- ✓ AdoShell® Islets is a promising candidate for a first-in-human study