AdoShell®, a versatile encapsulation system for cell replacement therapy

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Abstract

AdoShell® is a permselective, implantable and retrievable scaffold for cell therapy without immunosuppression, allowing therapeutic peptide diffusion while preventing immune cell invasion and antibody contact.

This study aims at demonstrating AdoShell® stability, tolerance, immunoprotection, cell loading capacity, and versatility regarding cells and secretome.

Stability: AdoShell® is stable in PBS for over 35 months at 37°C and 60°C and withstands multiple bending cycles without damages.

Tolerance: No fibrosis nor inflammation were observed after implantation of AdoShell® in immunocompetent rats and pigs.

Immunoprotection: In vitro, AdoShell® prevented against allogeneic PBMC-mediated death. Moreover, allogenic transplantation of rat islets in immunocompetent diabetic rats led to islets survival, steady insulin secretion, and glycemic regulation.

Cell loading: The size of one AdoShell® implant is compatible with delivering ~1 billion cells. Studies in pig demonstrated that AdoShell® can be implanted by laparoscopy and that cell load can be extended by using several implants.

Versatility: Hydrogel properties can be tuned to modify the permeability for both mid-size proteins (70-150kDa) and large proteins (500kDa). AdoShell® maintains function of cell lines, as well as stem cell-derived and primary islets, both in vitro (>4 months) and in vivo (>2.5 months in NXG mice). Versatility to different therapeutic proteins was demonstrated for three different hormones: insulin, amylin, and glucagon.

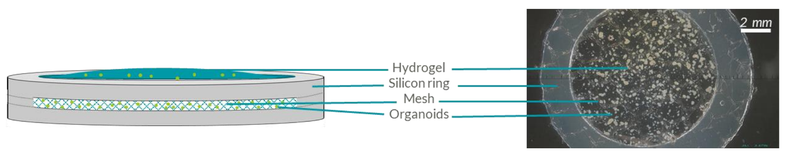
AdoShell® is an immunoprotective, non-biodegradable and retrievable encapsulation system capable of delivering a high cell load by minimally invasive surgery. Its compatibility with a wide range of cells and its tunable properties make it a promising piece of the cell therapy puzzle.

Introduction & Background

- Cell therapy is a promising treatment for many pathologies (diabetes, hemophilia, liver failure, …), however the requirement for immunosuppression makes the benefit/risk balance unfavorable for most patients. (Sandra Petrus-Reurer, et al., Communications biology. 2021).

- AdoShell® is an encapsulation system for cell therapy 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 cells. It is permselective for nutrients / hormones diffusion but prevents antibody and immune cell penetration.

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



Methods

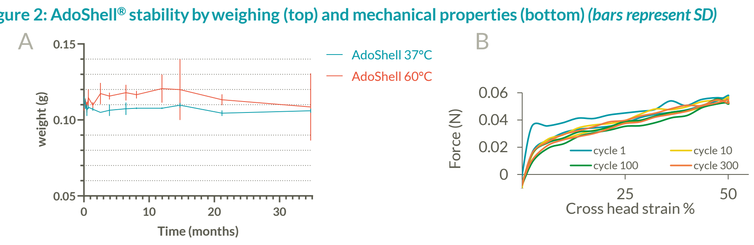
- AdoShell® stability and diffusion properties
  - AdoShell® stability was evaluated by weighing and cycling tests of repeated folding.
  - Diffusion properties were evaluated by measuring the diffusion of fluorescent Dextrans (3-500kDa) in the hydrogel and compared to a solution without hydrogel.
- AdoShell® Islets Tolerance studies
  - AdoShell® with or without pancreatic islets was implanted and sutured in the peritoneal cavity of immunocompetent rats.

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

- AdoShell® immunoprotection
  - Human peripheral blood mononuclear cells were obtained from the blood of donors (PBMCs) and activated by incubation with IL-2.
  - Naked and encapsulated primary human islets were exposed to increasing doses of PBMCs.
  - Islets were counted and their viability was measured by Live/Dead staining
- 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.
- *In vitro* functionality of encapsulated human Islets
  - Insulin secreting cell lines were cultured in 3D to form organoids.
  - Stem cell- derived islets were obtained from 3 different lines following the protocol described in *Balboa et al. Nat Biotechnol. 2022*.
  - Human islets were isolated from deceased donors pancreas and encapsulated by simple mixing with hydrogel precursors.
  - Hydrogel disks containing ~300,000 cells were evaluated in dynamic or static glucose stimulated secretion assay and compared to naked organoids
- AdoShell® Human Islets in immunodeficient mice
  - Immunodeficient mice were intraperitoneally transplanted with AdoShell® Human Islets (3 to 4.5 millions cells/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 D84 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.
- AdoShell® rat Islets in immunocompetent rats
  - Immunocompetent rats were intraperitoneally transplanted with AdoShell® Islets (12 millions cells/rat). AdoShell® Islets function was assessed by quantifying insulin concentration in rat plasma (ELISA method).

• AdoShell® stability

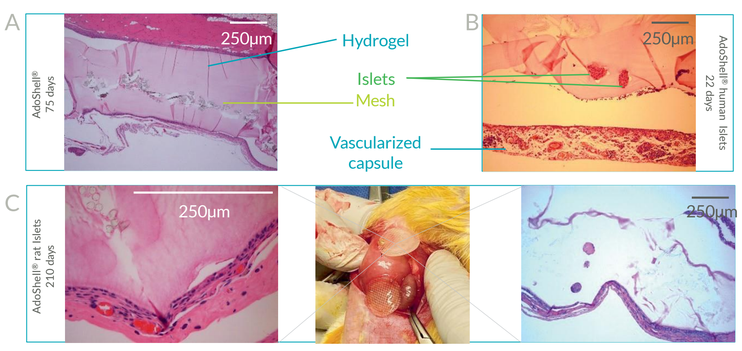
Figure 2: AdoShell® stability by weighing (top) and mechanical properties (bottom) *(bars represent SD)*



- AdoShell® showed stability over 35 months both at 37°C and 60°C. **(Figure 2 – A).**
- Folding cycles show no degratation of the machanical properties. **(Figure 2 – B)**.
- **These results demonstrate that the stability of AdoShell® is compatible with long term implantation *in vivo*.**

• AdoShell® Islets tolerance studies

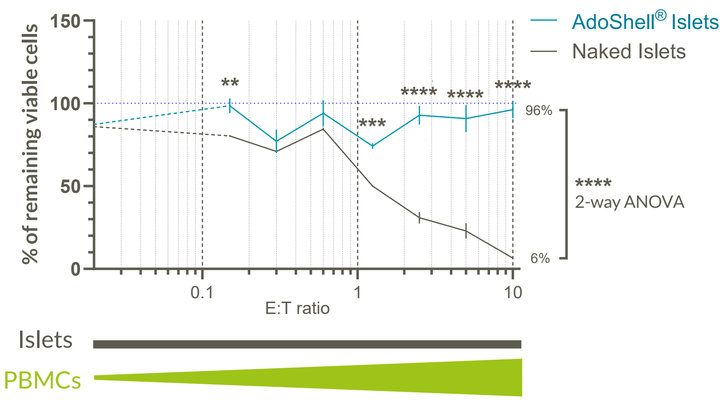
Figure 3 – Local tolerance of AdoShell® and AdoShell® Islets in immunocompetent rats



- AdoShell® showed good local tolerance after 75 days of implantation in the peritoneal cavity of immunocompetent rats. **(Figure 3 – A)**.
- Similar results were obtained for AdoShell® containing xenogeneic human islets after 22 days **(Figure 3 – B)** and with AdoShell® containing allogeneic rat islets after 210 days **(Figure 3 – C)** of implantation in the peritoneal cavity.
- **These results demonstrate that the tolerance of AdoShell® containing allogeneic or xenogeneic material is compatible with long term graft survival *in vivo*.**

• AdoShell® Immunoprotection

Figure 4 – Immunoprotection of AdoShell® from IL-2 activated PBMCs *(bars represent SEM)*



- Primary human islets were destroyed by exposure to increasing dose of primary human PBMCs. Encapsulation in AdoShell® showed strong resistance to cell-mediated death. **(Figure 4)**.
- **These results demonstrate the capacity of AdoShell® for allogeneic immune protection.**

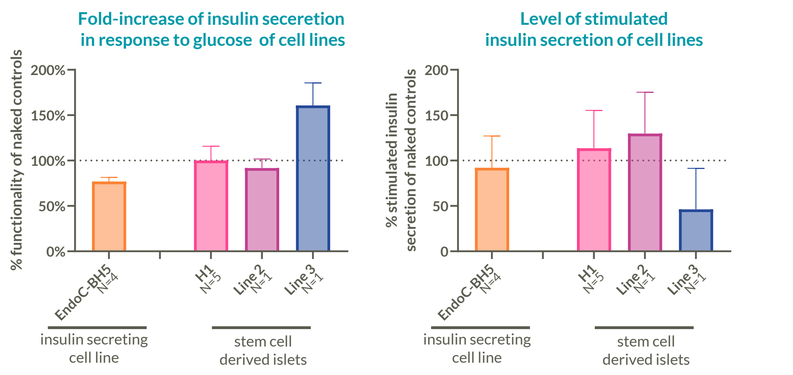
• AdoShell® delivery in domestic pig

Figure 5 – Scaled-for-Human AdoShell® implantation in domestic pig by laparoscopy

- AdoShell® with dimensions allowing the delivery of 150 million cells (at 4% v/v) was successfully implanted in the preperitoneal space of a domestic pig by laparoscopy and immobilized with sutures **(Figures 5)**.
- At least 3 implants can be delivered in humans.
- **A clinically relevant dose of cells for human application can be delivered by a mini-invasive procedure**

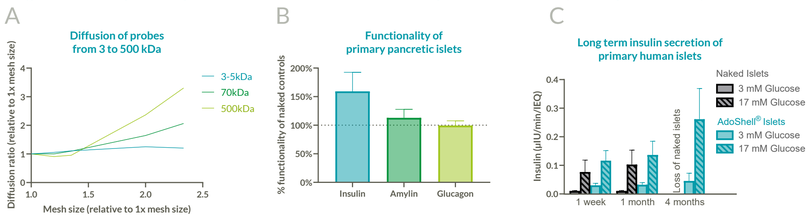
• AdoShell® compatibility with different cell clusters and hormone secretion

Figure 6 – Compatibility of AdoShell® with different cell lines *(bars represent SEM, N means number of independent experiments)*



- Encapsulated insulin-secreting organoids from cell line or stem cells maintained their functionality and insulin secretion levels compared to naked organoids. **(Figure 6)**

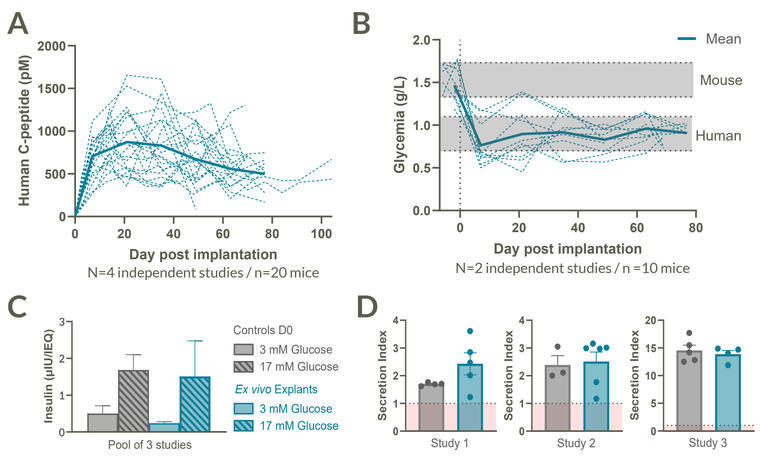
Figure 7 – Compatibility of AdoShell® with different therapeutic hormones (*bars represent SEM)*



- Mesh size of AdoShell® can be tuned by modifying the composition. The increase of a 2.3-fold of the mesh size led to an increase of the diffusion properties of Dextrans from 1.2 to 3-fold depending on the size. This allows to modulate permselectivity of the hydrogel. **(Figure 7 – A)**
- The ability of encapsulated primary human islets to secrete 3 different hormones (insulin, amylin and glucagon) was maintained compared to naked islets. **(Figure 7 – B)**
- The insulin functionality was maintained for over 4 months *in vitro*. **(Figure 7 – C)**
- **AdoShell® is compatible with multiple therapeutic hormone secretion and long-term functionality.**

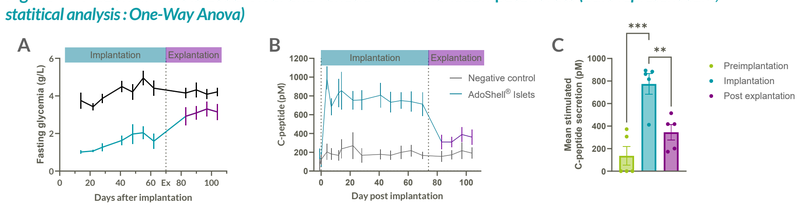
• AdoShell® for islet delivery in rodents

Figure 8 - AdoShell® Human Islet survival and function in immunodeprived mice *(bars represent SEM)*



- Human islets encapsulated in AdoShell® and implanted into immunodeficient mice led to mean Human C-peptide concentration of 872 pM at D20/21 followed by a plateau, up to 104 days post-implantation in four different studies **(Figure 8 - A)**.
- This increase led to a decrease of glycemia from mouse to human levels (2 independent studies) **(Figure 8 - B)**.
- *Ex vivo*, explants were functional, with similar secretion indexes and insulin secretion levels before (D0) and after explantation (D44 to D90) **(Figure 6 – C & D)**.
- **These results demonstrate the maintenance of viability and function of transplanted AdoShell® for more than 3 months.**

Figure 9 – AdoShell® Rat Islet survival and function in immunocompetent rats *(bars represent SEM, statitical analysis : One-Way Anova)*



- Allogenic rat islets encapsulated in AdoShell® implanted in immunocompetent diabetic rats led to a reduction of hyperglycemia compared to untreated controls **(Figure 9 - A)**. This reduction is associated with a significant increase in rat C-peptide during the implantation period compared to both before implantation and after explantation **(Figure 9 – B and C)**.
- **AdoShell® ensured good engraftment, metabolic survival, and immunoprotection of encapsulated islets for at least 104 days *in vivo*.**

Conclusion

- AdoShell® is a non-biodegradable cell encapsulation system capable of delivering a high cell load (~150 million cells / implant) by minimally invasive surgery with the possibility of full retrieval.
- AdoShell® is well tolerated without any fibrosis
- AdoShell® provides immunoprotection to encapsulated cells.
- AdoShell® is compatible with a wide range of cell sources.
- AdoShell® tunable properties allow to adapt to different therapeutical targets.
- AdoShell® maintains long term *in vivo* function of cells