AdoShell®, an encapsulation system for cell replacement therapy : application to Type 1 diabetes

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Abstract

Pancreatic islet transplantation is the only cure of Type 1 Diabetes (T1D). However, the need for lifelong immunosuppressive treatment limits its application. AdoShell® is a permselective, implantable and retrievable scaffold for islet transplantation without immunosuppression, allowing insulin diffusion while preventing immune cell invasion and antibody contact.
In vitro and in vivo studies with rodent and human islets were performed to meet requirements for a first in human study.
Allogeneic immunoprotection was demonstrated in vitro by preventing PBMC-mediated death. In vivo, allogenic transplant of rat islets in immunocompetent diabetic rats led to islets survival, steady insulin secretion, and glycemic regulation.

AdoShell® tolerance was evaluated in rodents, rabbits, and pigs. It was well tolerated and did not trigger inflammatory reaction or fibrosis.

In vitro, AdoShell® Human Islets showed gluco-responsive insulin secretion up to 4 months. In vivo, in immunodeficient NXG-mice, Human C-peptide (insulin precursor) secretion increased during the first two weeks and was maintained in 100% of mice for more than 2 months. Moreover, AdoShell® Human Islets regulated mouse glycemia to human levels. Ex vivo, explants maintained similar function compared to preimplantation values.

AdoShell® was scaled up and its manufacturing optimized for clinical application with donor islets. AdoShell® geometry and high resistance to mechanical constraints are compatible with implantation via laparoscopy, as demonstrated in domestic pig. Moreover, data suggests that it yields homogenous 3D-distribution of viable and functional islets.

AdoShell® has demonstrated tolerability, immunoprotection, and functionality with human donor islets. Ongoing work aims at preparing a first-in-human study in subjects with T1D

Methods

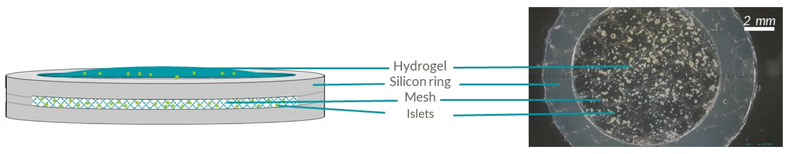
- AdoShell® Islets *in vitro* functionality
  - Hydrogel disks containing ~200 islet equivalents (IEQ) were assessed using static and dynamic glucose-stimulated insulin secretion (GSIS) assays and compared to naked islets. Adapted GSIS assays evaluated amylin and glucagon secretion.
- Islet architecture and viability
  - Histology (H&E) assessed morphology, while immunohistochemistry with insulin and glucagon antibodies and DAPI counterstaining evaluated cell distribution. Apoptosis was detected using TUNEL staining.
- AdoShell® immunoprotection
  - Activated human PBMCs were co-cultured with naked or encapsulated islets at increasing doses. Islet survival was assessed by counting and Live/Dead staining, and total insulin content was measured by ELISA.
- AdoShell® Human Islets in immunodeficient mice
  - NXG mice received intraperitoneal transplants of AdoShell® human islets (2.2–3.4 kIEQ/mouse). Function was monitored via human C-peptide levels and glycemia. Explants (D44–D90) were analyzed by GSIS and histology and compared to in vitro controls.
- Scaled-for-Human AdoShell® implantation in domestic pig
  - Human islets were encapsulated in scaled-for-human AdoShell® implants. Islet distribution, viability, and function were assessed by microscopy, Live/Dead staining, and GSIS. Implants were laparoscopically placed in the peritoneal cavity of domestic pigs and secured with sutures or clips.

Introduction & Background

- Cell therapy is the most effective treatment of Type 1 Diabetes, 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 enable 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® description (left) and prototype for rodent studies (right)



• AdoShell® in vitro immunoprotection

- Naked and encapsulated human islets were incubated for 4 days in the presence of activated human peripheral blood mononuclear cells (PBMCs).
- Contrary to naked islets, no impact on the intracellular insulin content was observed in encapsulated islets (**Figure 2**).
- **AdoShell allows immunoprotection of primary human islets versus PBMC-mediated death**

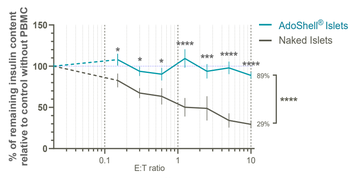
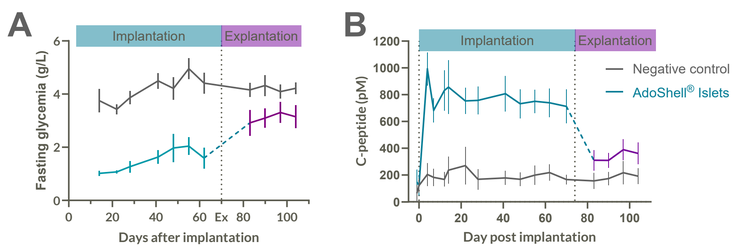


Figure 2 –AdoShell® Immunoprotection of human islets. Bar = SEM, 2-way ANOVA

• AdoShell® for allogeneic islet delivery in rat

- AdoShell® Rat Islets in immunocompetent diabetic rats
  - Immunocompetent diabetic rats were intraperitoneally transplanted with AdoShell® rat Islets (21kIEQ/rat). AdoShell® Islets function was assessed by measuring fasted glycemia and quantifying C-peptide concentration in rat plasma (ELISA method).

Figure 3 – AdoShell® Rat Islets survival and function in immunocompetent diabetic rats *(bars represent SEM)*

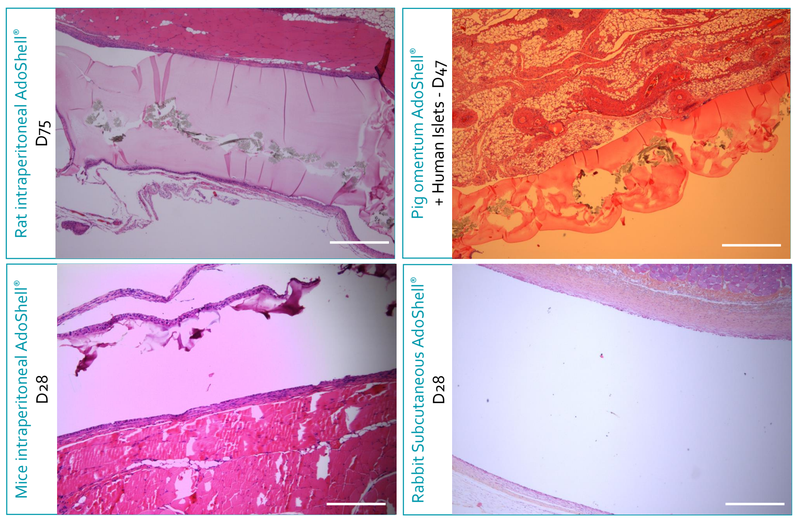


- Allogeneic rat islets encapsulated in AdoShell® and implanted in immunocompetent diabetic rats led to a reduction of hyperglycemia compared to untreated controls **(Figure 3 - A)**. This reduction is linked to an increase in rat C-peptide during the implantation period compared to both before implantation and after explantation **(Figure 3 – B)**.
- **AdoShell® ensures good engraftment, metabolic survival, and immunoprotection of encapsulated allogenic rat islets for at least two months *in vivo*.**

Results

• AdoShell® tolerance

Figure 4 – Histology analysis of AdoShell® tolerance in rodents, rabbit, and pig (scale bar is 250µm)

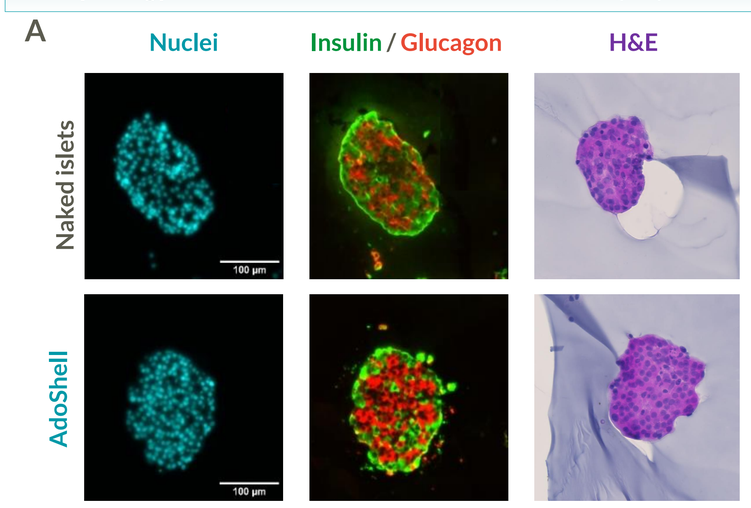


- AdoShell® does not lead to inflammation nor fibrosis in rodents, rabbit, and pigs. Only a thin vascularized capsule is formed at its surface (**Figure 4**).

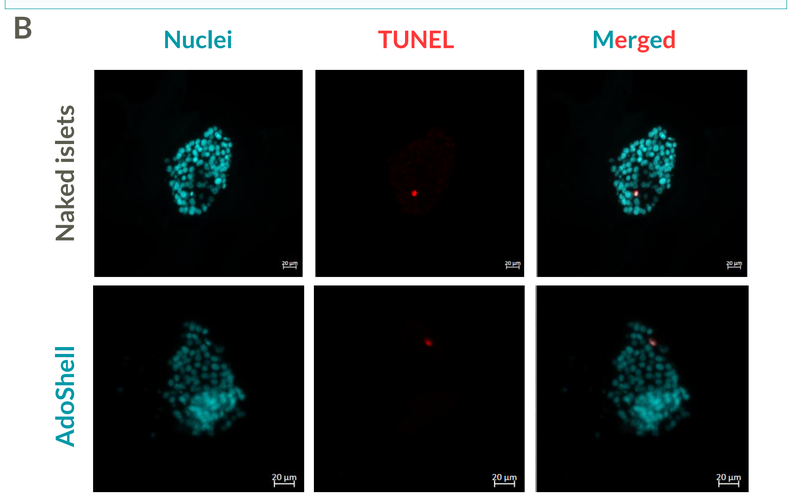
• Maintenance of islet viability, function and morphology after encapsulation in AdoShell®

Figure 5 – *In vitro* characterization of AdoShell® Human Islets *(bars represent SEM)*

Morphology assessment - Tested within 1 week, N=3 preparations

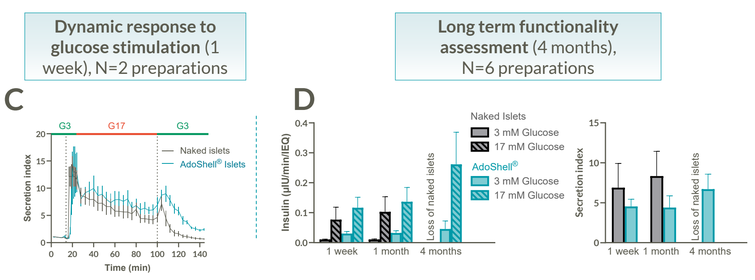


Viability assessment - Tested within 1 week, N=2 preparations



Dynamic response to glucose stimulation (1 week), N=2 preparations

Long term functionality assessment (4 months), N=6 preparations



Amylin functionality assessment (1 week), N=6 preparations

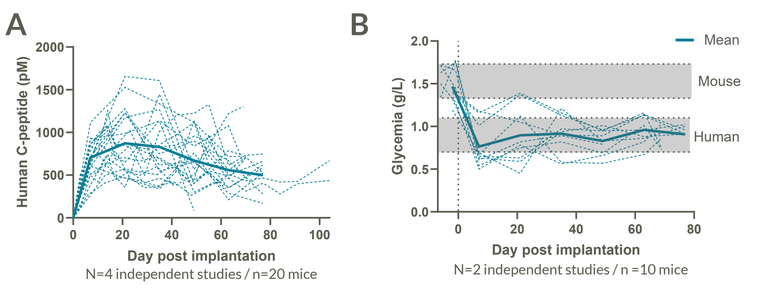
Glucagon functionality assessment (1 week), N=5 preparations

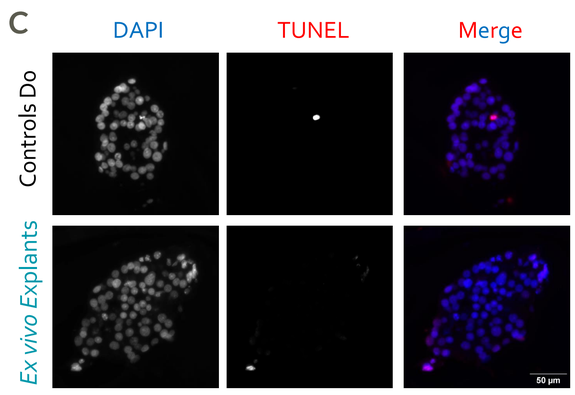


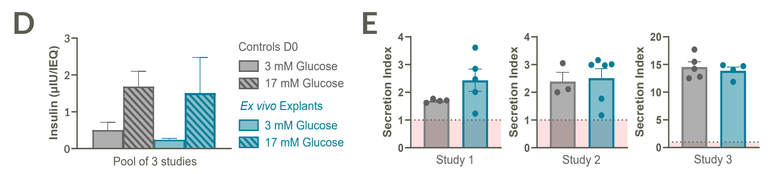
- Encapsulation in AdoShell® preserved the structural integrity of human islets and consistently demonstrates high compatibility with islets (**Figure 5 – A**).
- AdoShell® maintains the viability of encapsulated human primary islets (**Figure 5 – B**).
- Rapid insulin secretion was maintained, with a 2-minute delay to the first peak and a return to basal levels within 12 minutes (**Figure 5 - C**).
- Encapsulated human islets demonstrated stable and robust *in vitro* insulin functionality, preserved for at least 4 months post-encapsulation, whereas naked islets died after 1 month (**Figure 5 – D**).
- The functionality of amylin and glucagon was also maintained (**Figures 5 – E&F**)
- ***In vitro*, AdoShell® ensures good maintenance of morphology and viability of encapsulated islets and a stable metabolic survival for at least 4 months *in vitro*.**

• AdoShell® for human islet delivery in mice

Figure 6 – AdoShell® survival and function in immunodeficient 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 6 - A)**.
- This increase led to a decrease of glycemia from mouse to human levels (2 independent studies) **(Figure 6 - B)**.
- Apoptosis of explants was limited and comparable to controls **(Figure 6 - B)**.
- *Ex vivo*, explants were functional, with similar secretion indexes and insulin secretion levels before (D0) and after explantation (D44 to D90) **(Figure 6 – D & E)**.
- **These results demonstrate the maintenance of viability and function of transplanted AdoShell® for more than 3 months.**

• AdoShell® delivery in domestic pig

Figure 7 – Scaled-for-Human AdoShell® implantation in domestic pig by laparoscopy *(bars represent SEM)*

- AdoShell® was scaled up to ensure encapsulation of total islets from one human pancreas (**Figure 7 - A**).
- Preliminary experiments strongly suggest that human islets are well distributed in each compartment of the device (**Figure 7 - A**). Encapsulated primary human islets show a high viability and remain functional (**Figure 7 - B**).
- This prototype was successfully implanted in the preperitoneal space of a domestic pig by laparoscopy and immobilized with staples (**Figures 7 - C**).
- Dimension of AdoShell® allows to deliver at least 3 implants in humans.
- **A clinically relevant dose of viable and functional islets for human application can be delivered by a mini- invasive procedure.**

Conclusion

- **AdoShell® is well tolerated *in vivo* without any fibrosis.**
- **AdoShell® maintains islet viability, morphology and function after encapsulation.**
- **AdoShell® provides immunoprotection to encapsulated human islets.**
- **AdoShell® maintains long term *in vivo* function of xenogeneic human primary islets and allogeneic rat primary islets.**
- **AdoShell® allows for implantation of a therapeutic dose in human by mini-invasive surgery.**
- **AdoShell® is ready for GMP manufacturing and clinical testing.**