

ADO12, a non-fibrotic immunoprotective hydrogel containing human islets shows efficient and sustained *in vivo* functionality for clinical use

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¹ ADOCIA, France

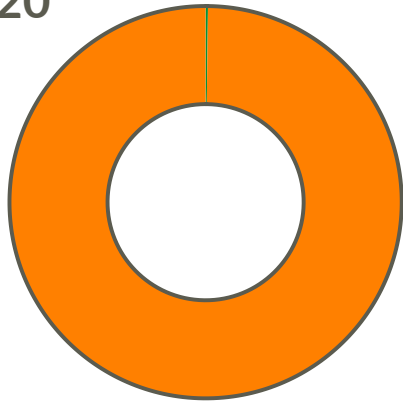
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³ CEED, France

⁴ Université de Lille, France

Transplantation: the only cure of T1D

2000-2020



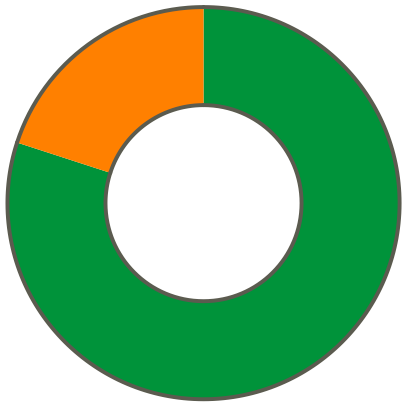
Islet transplant recipients
Ungrafted T1D

0.2% of
T1D have
received a
transplant

Berney *et al.*, Transpl Int.
2022



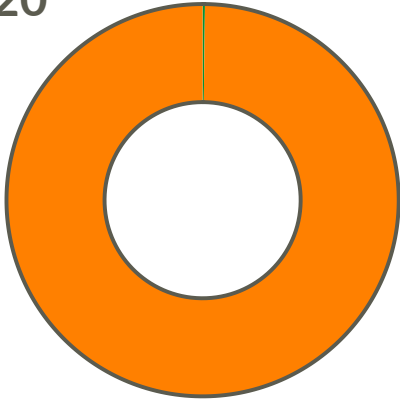
Future?



Transplantation: the only cure of T1D

Critical limitations

2000-2020



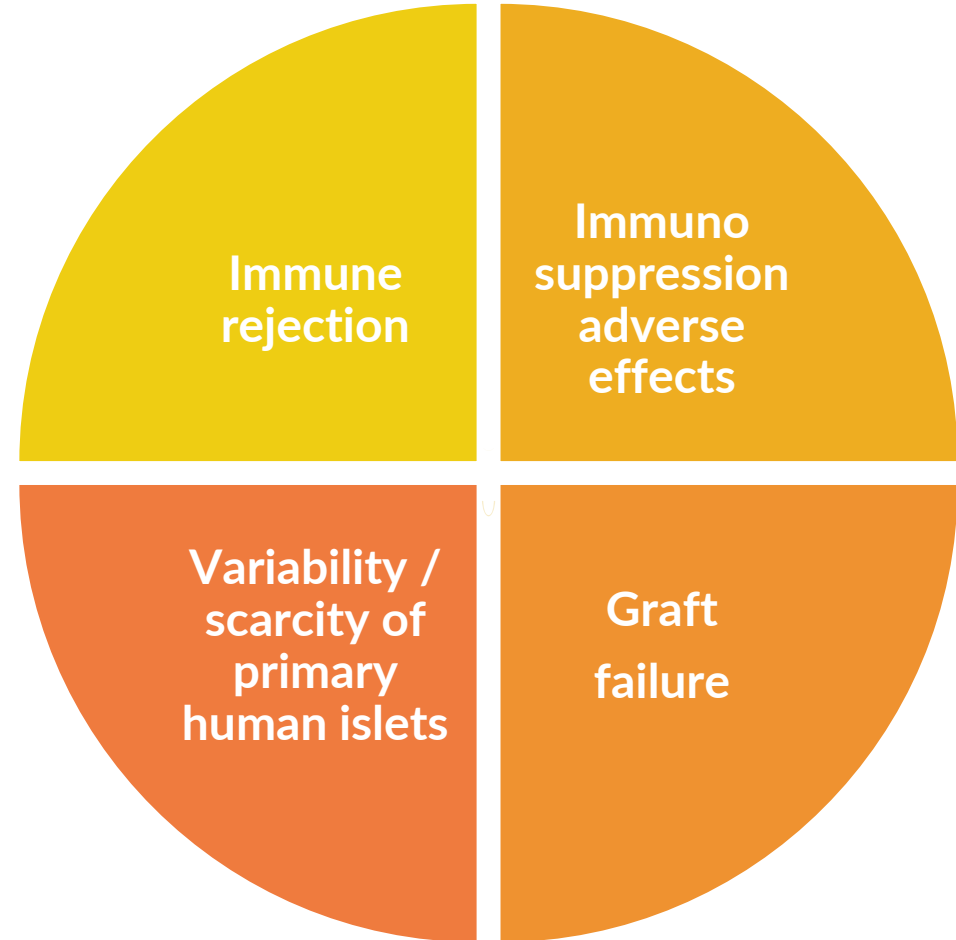
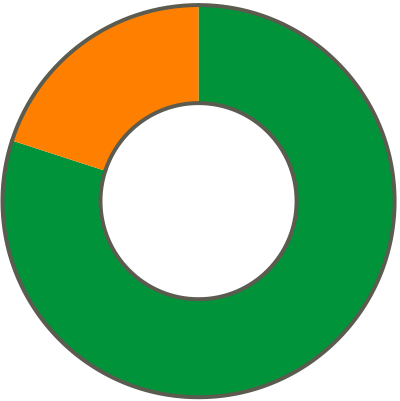
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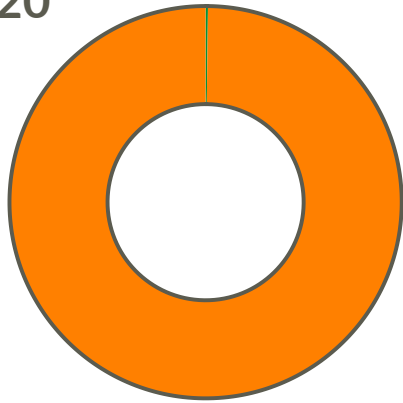
Future?



Transplantation: the only cure of T1D

Immunoprotective scaffold to solve critical limitations

2000-2020



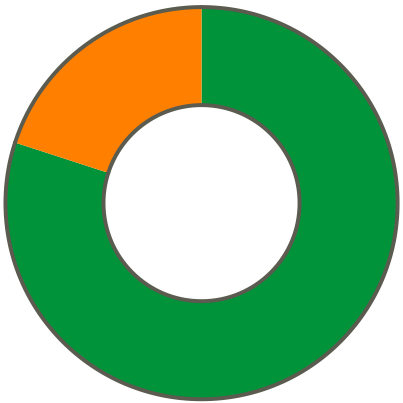
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Future?



Immunoprotection

Immune
rejection

Immuno
suppression
adverse
effects

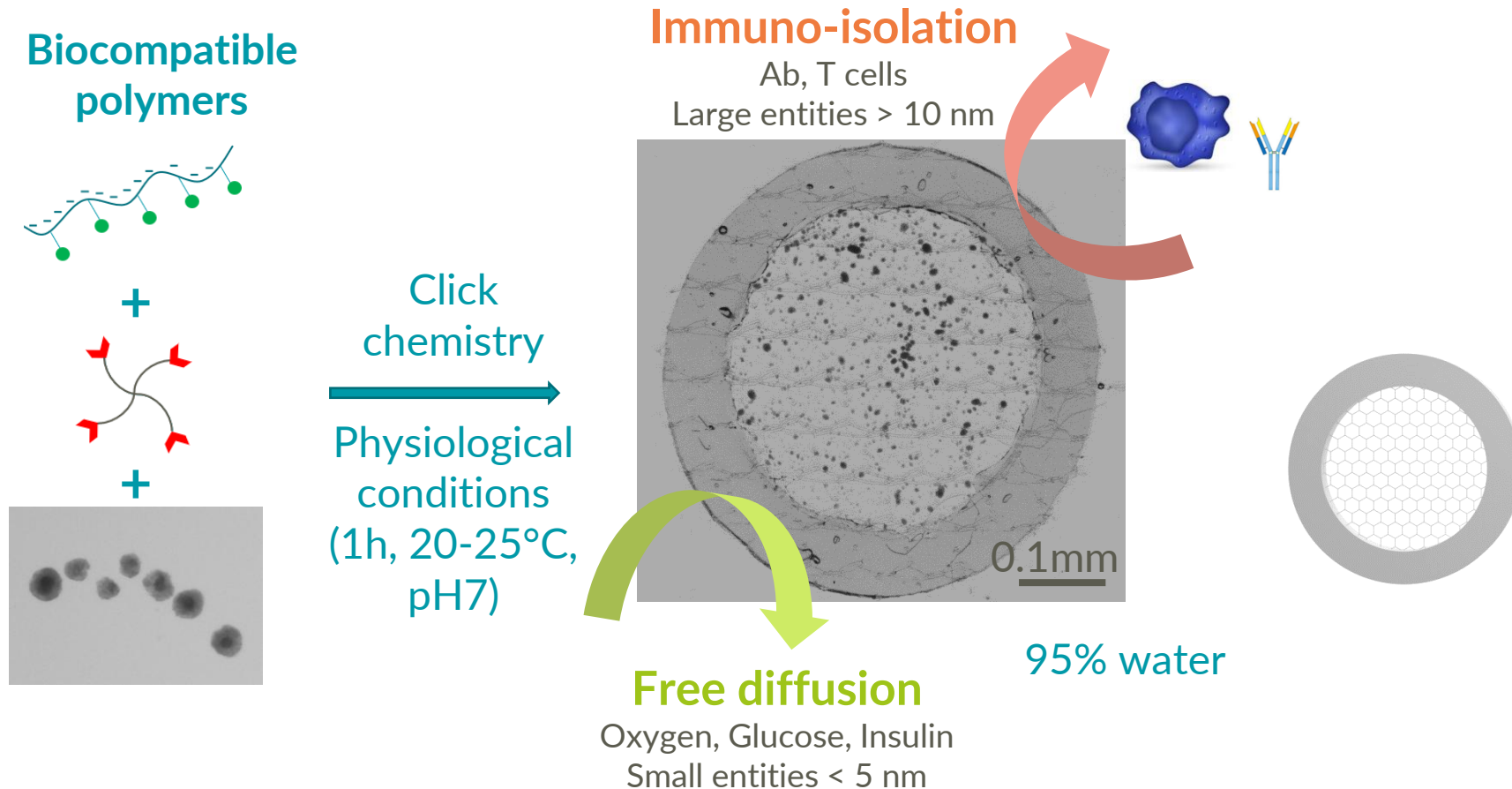
Variability /
scarcity of
primary
human islets

Graft
failure

SC derived islets

Retrievability

ADO12: Immunoprotective hydrogel for pancreatic islets transplantation without immunosuppression



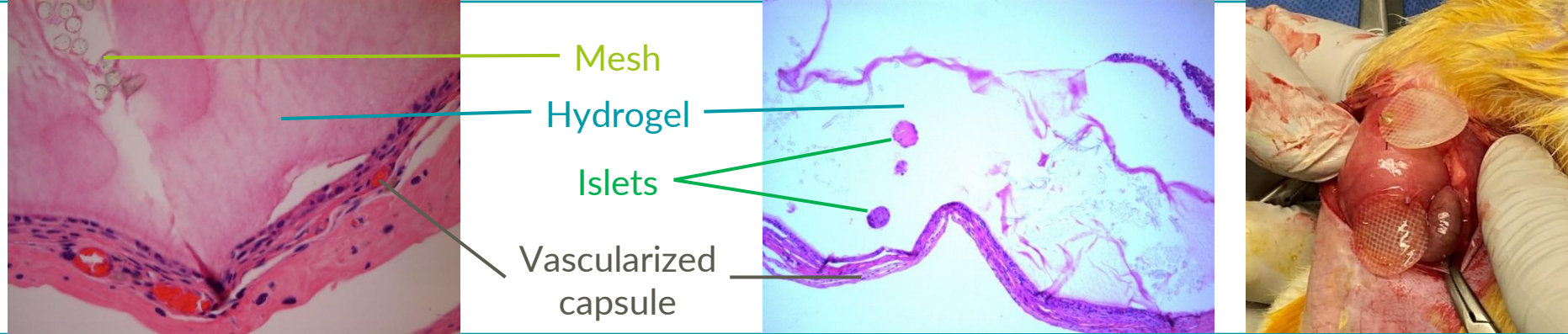
Simple, aqueous and biocompatible process including reinforcement frame for mechanical resistance, manipulability and suturing

Background: Allogeneic transplantation of ADO12 rat islets



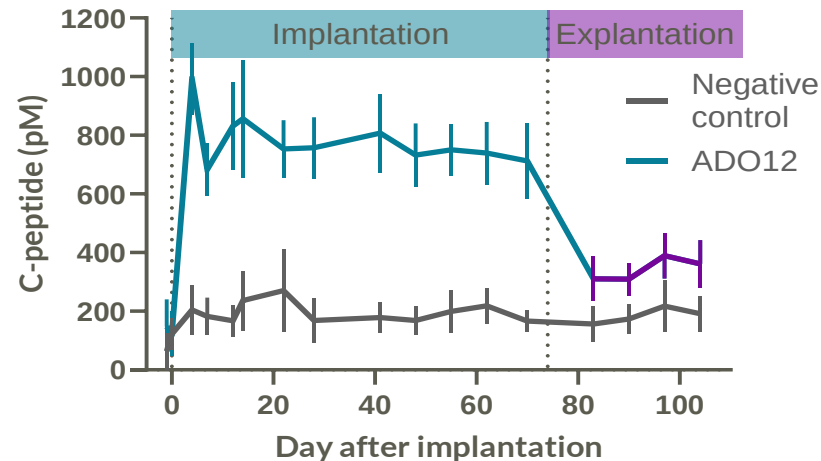
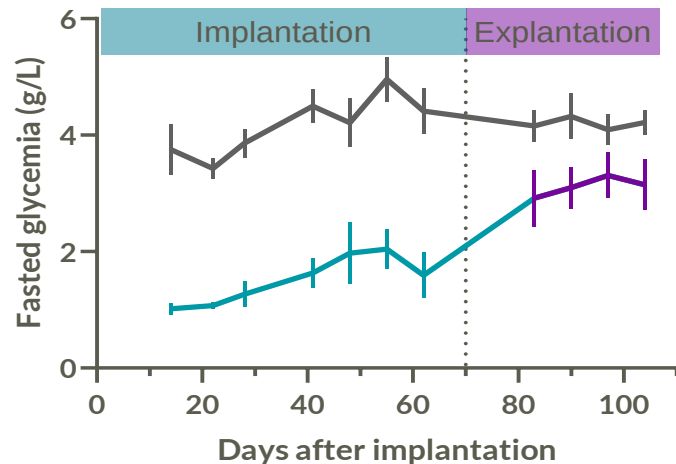
Allogeneic transplantation of ADO12 rat islets in immunocompetent diabetic outbred rats

Tolerance (210 days)



- ✓ No cell infiltration
- ✓ No fibrosis
- ✓ No inflammation
- ✓ No degradation

In vivo functionality



- ✓ Sustained C-peptide secretion
- ✓ Regulation of glycemia

Objective & Plan



Demonstrate that ADO12 is a biocompatible, immunoisolating biomaterial **compatible with human islets** and **scalable** for Human application

1

In vitro and *in vivo*
functionality

Long-term *in vitro* and *in vivo* functionality of encapsulated islets

2

Allogenic
Immunoprotection

In vitro
immunoprotection of
ADO12 against allogenic
rejection

3

Scale up

Manufacture and
implantation of human
sized ADO12

4

Stem cell derived
islets

In vitro and *in vivo*
compatibility with stem
cell derived islets
(preliminary results)

1

In vitro long-term dynamic functionality of ADO12

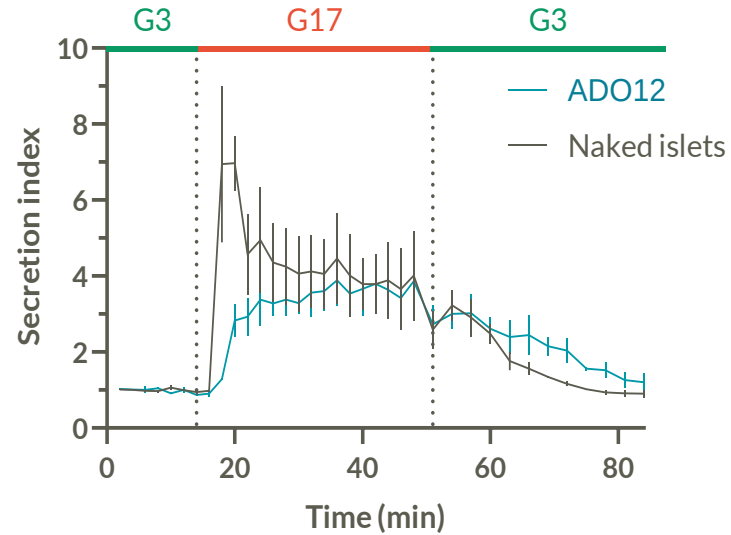


2

Dynamic response to glucose stimulation,
N=1 human preparation

3

4



Maintenance of rapid insulin release

- 2 min delay to the first peak
- 12 min delay to return to basal secretion

1

In vitro long-term dynamic functionality of ADO12

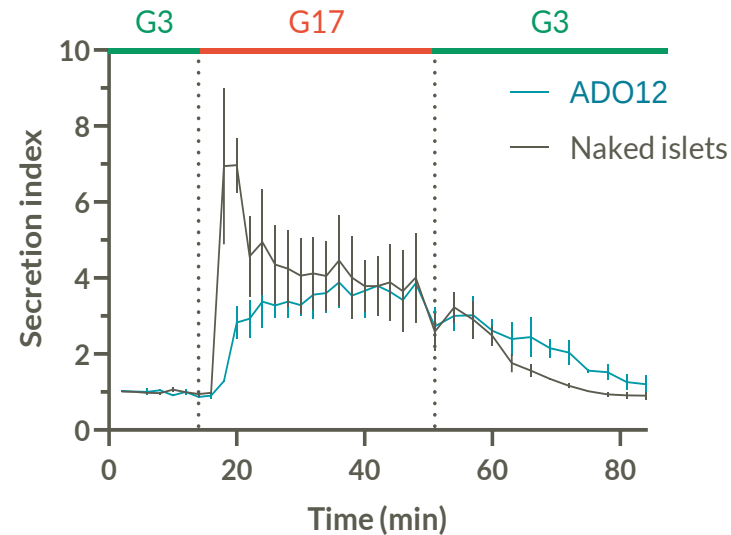


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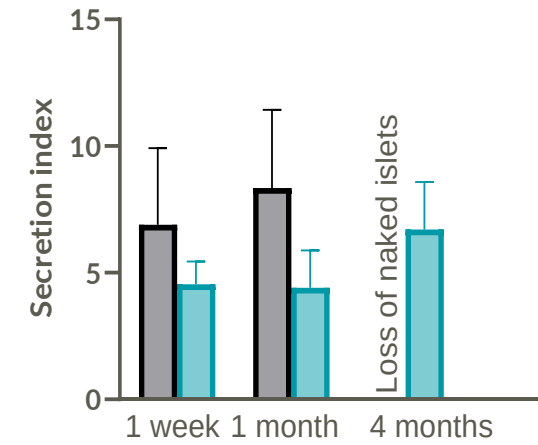
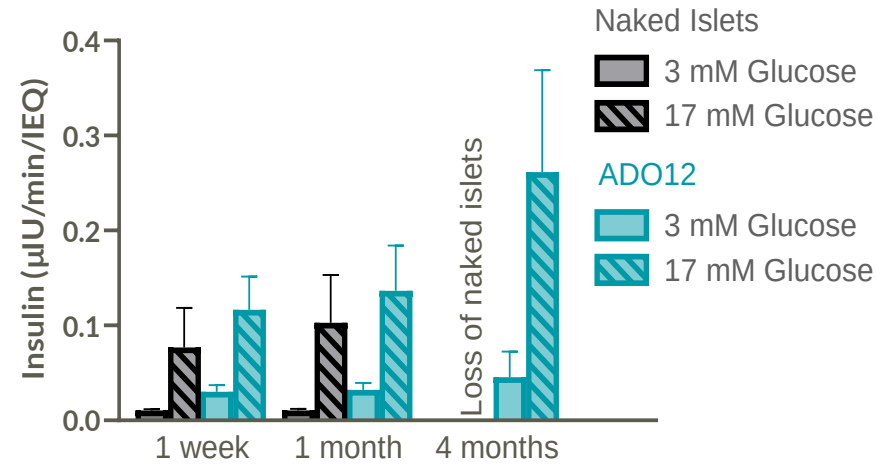
4



Maintenance of rapid insulin release

- 2 min delay to the first peak
- 12 min delay to return to basal secretion

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



Mean $\pm$ S.E.M.

- Robust *in vitro* functionality of encapsulated human islets
- No loss of functionality over at least 4 months, while naked islets are lost after 1 month

1

Functionality of ADO12 Human Islets in immunodeficient mice



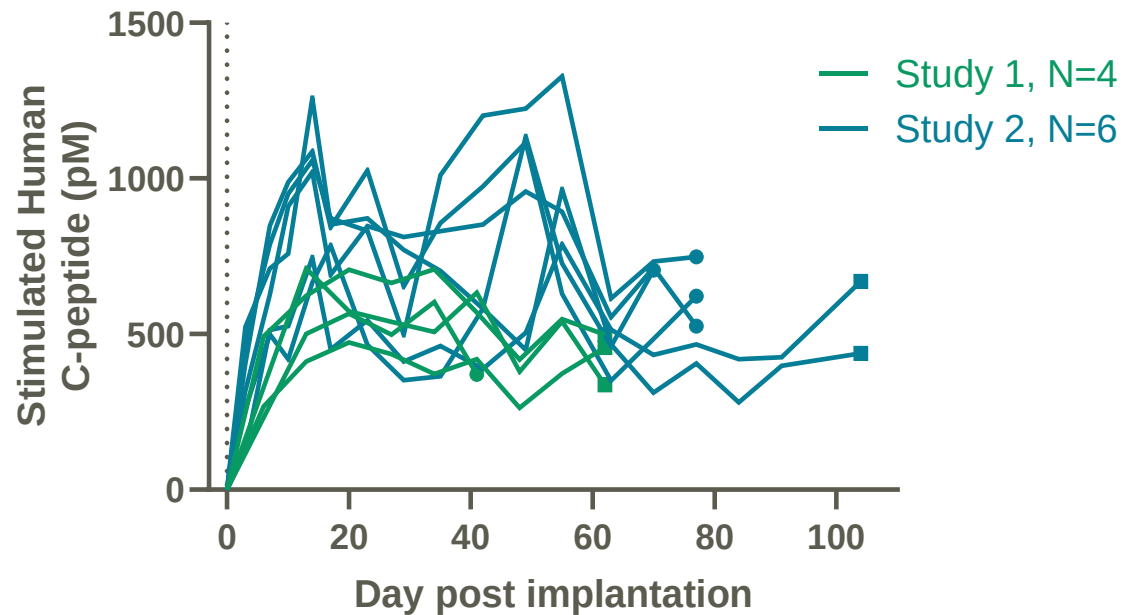
2

- Xenogeneic transplantation of Human islets in NXG mice (2.2 to 3.1 kIEQ/mouse).

3

Long term *in vivo* C-peptide secretion (2 months),
N=2 independent studies, n=10 mice

4



- Functionality of ADO12 Human Islets demonstrated in 100% of immunodeficient mice for at least 2 months
- Two mice were maintained until 104 days with no decrease in C-peptide secretion

1

Functionality of ADO12 Human Islets in immunodeficient mice



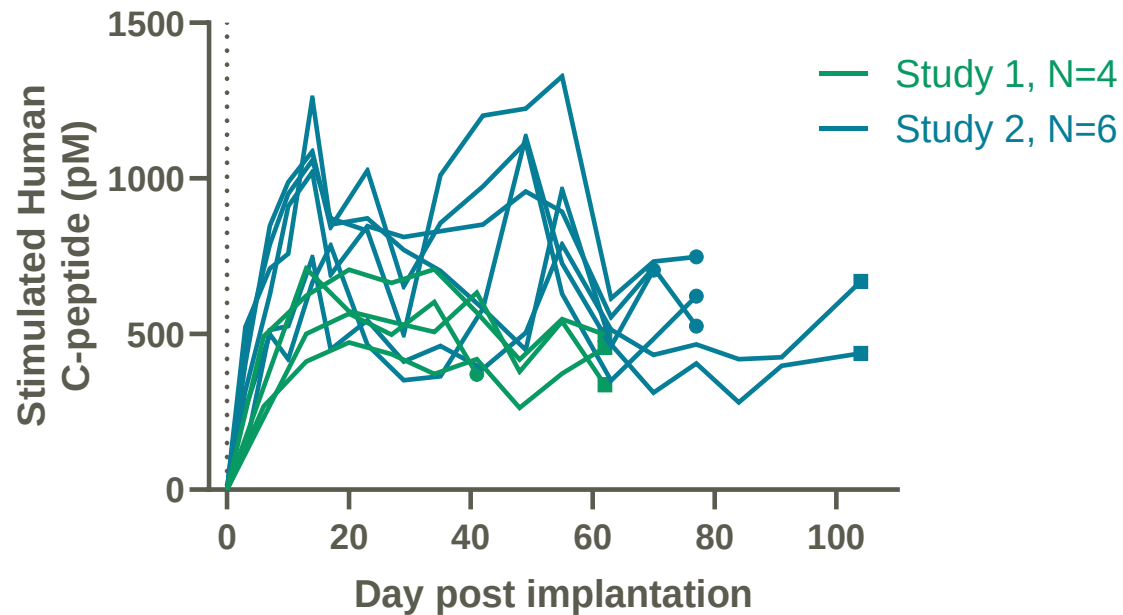
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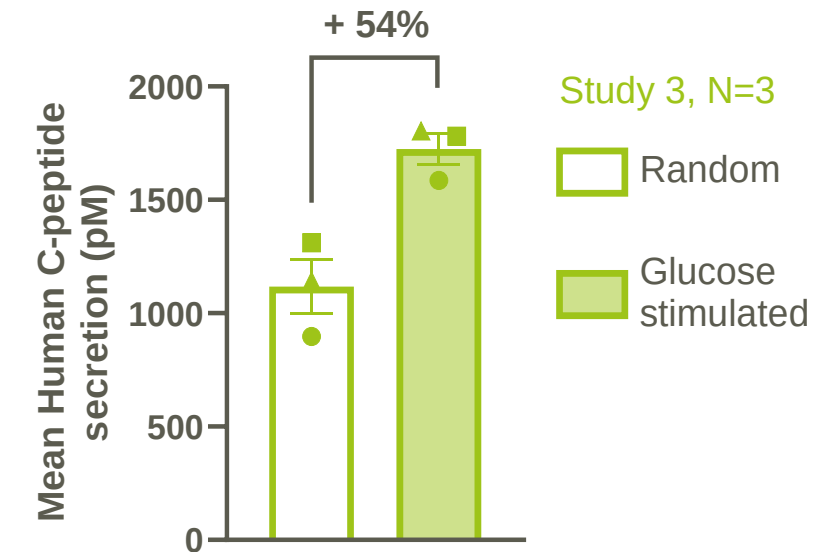
3

Long term *in vivo* C-peptide secretion (2 months),
N=2 independent studies, n=10 mice

4



Response to glucose stimulation,
N=1 study, n=3 mice



- Functionality of ADO12 Human Islets demonstrated in 100% of immunodeficient mice for at least 2 months
- Two mice were maintained until 104 days with no decrease in C-peptide secretion

- ADO12 Human Islets is responsive to glucose stimulation *in vivo*

1

ADO12 Human Islets in immunodeficient mice: explant analysis



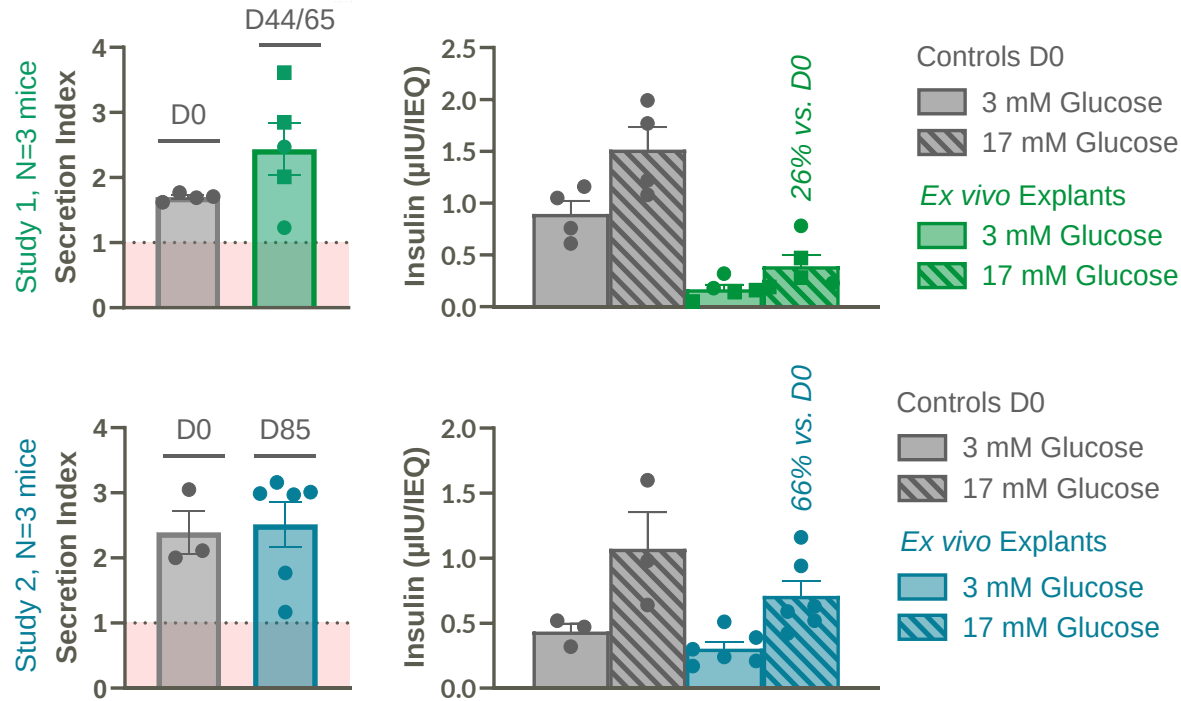
2

Studies 1 and 2: up to 85 days after implantation, mice were explanted, and explants were analyzed *in vitro* by static GSIS and histology

3

4

Static GSIS



- Explants responsive to glucose stimulation *in vitro*, with similar secretion indexes compared to pre-implantation despite a slight decrease in basal and secreted insulin levels.

1

ADO12 Human Islets in immunodeficient mice: explant analysis



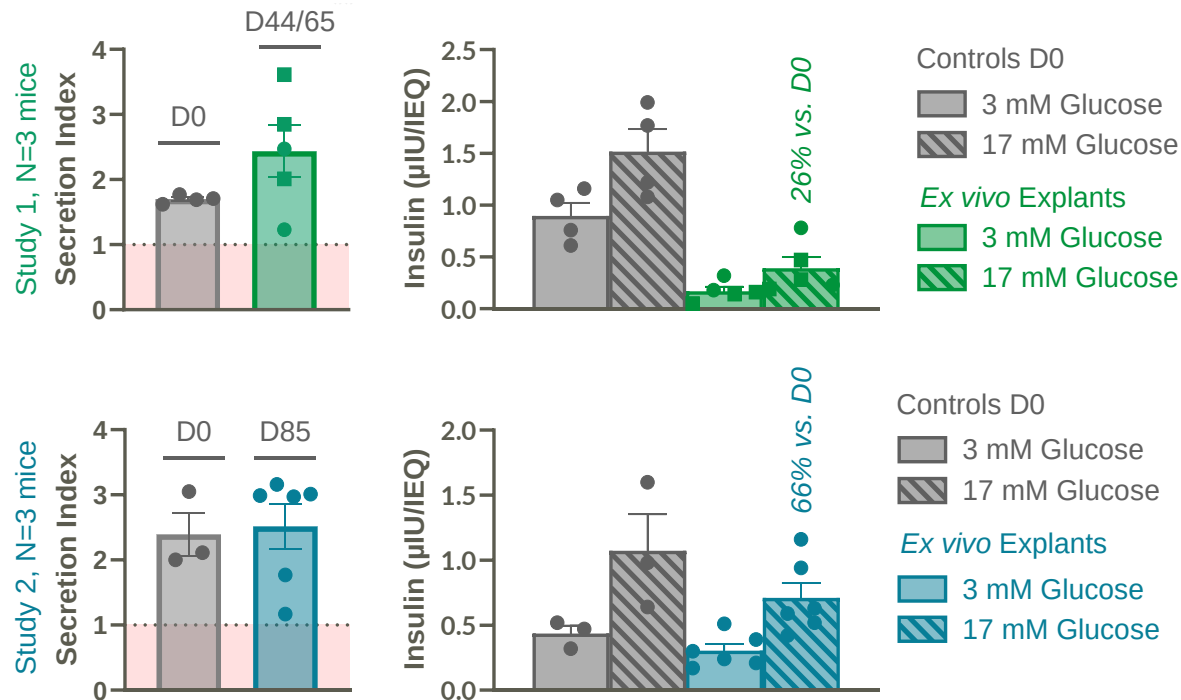
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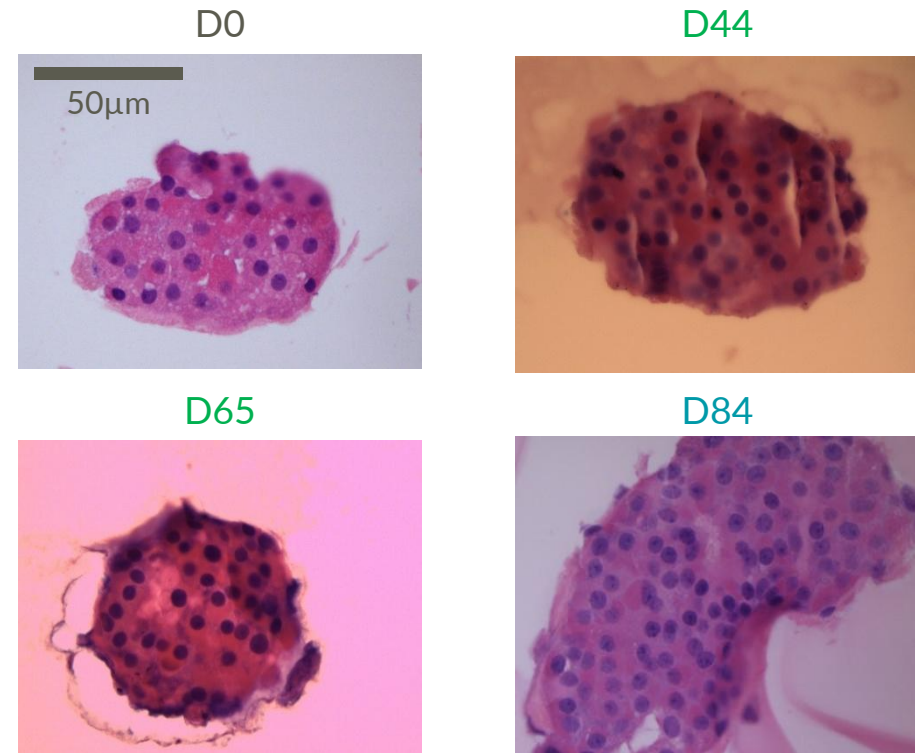
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4

Static GSIS



Histology



- Explants responsive to glucose stimulation *in vitro*, with similar secretion indexes compared to pre-implantation despite a slight decrease in basal and secreted insulin levels.
- Islets maintained their structure, confirming islet survival.

1

In vitro immunoprotection of ADO12 against allogenic rejection



2

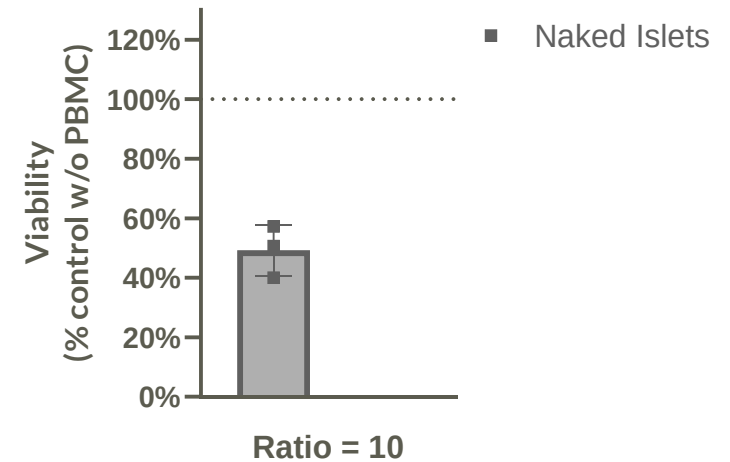
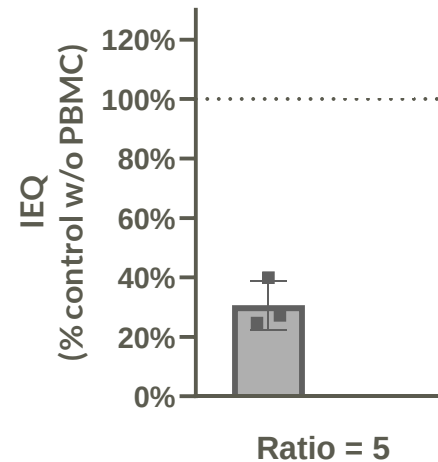
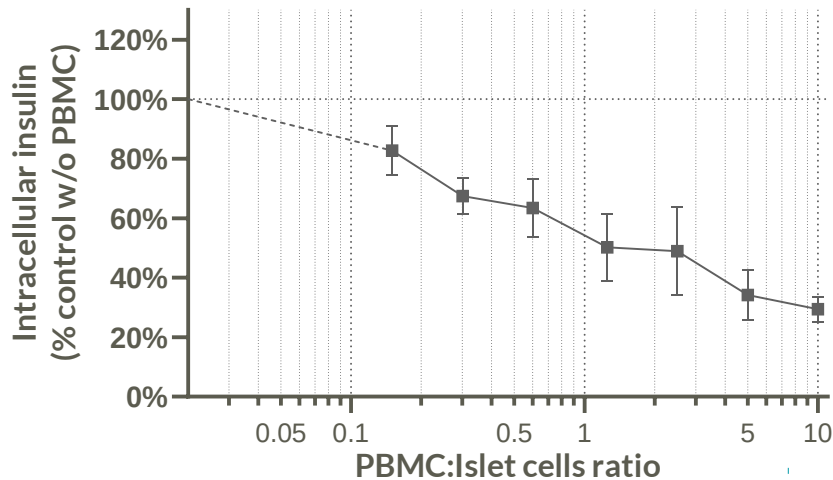
- Incubation of naked and ADO12 human islets with activated human primary PBMC for 4 days

3

Intracellular insulin
N=4 human preparations

4

Number and viability of human islets
Up to N=3 human preparations



AD012 protects human islets against PBMC mediated cell death, demonstrating its immunoisolation properties against allogenic rejection

1

In vitro immunoprotection of ADO12 against allogenic rejection



2

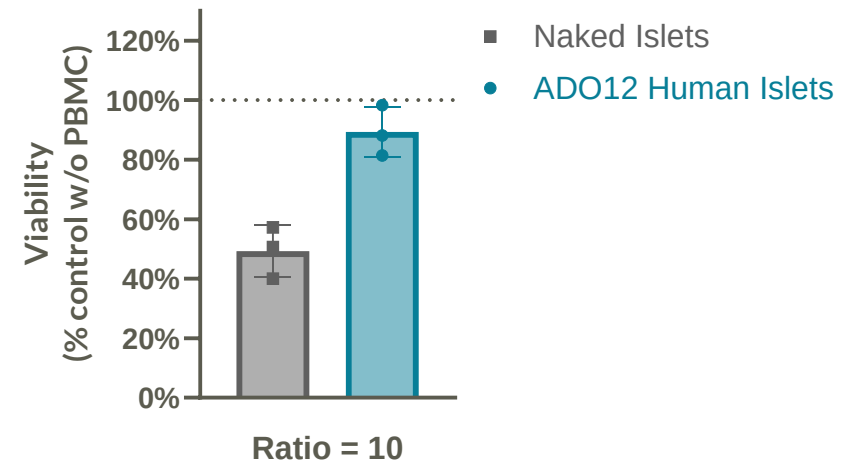
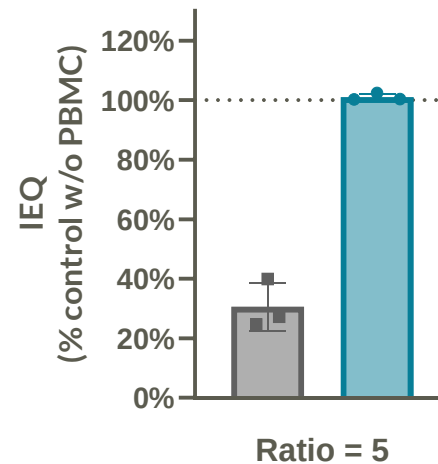
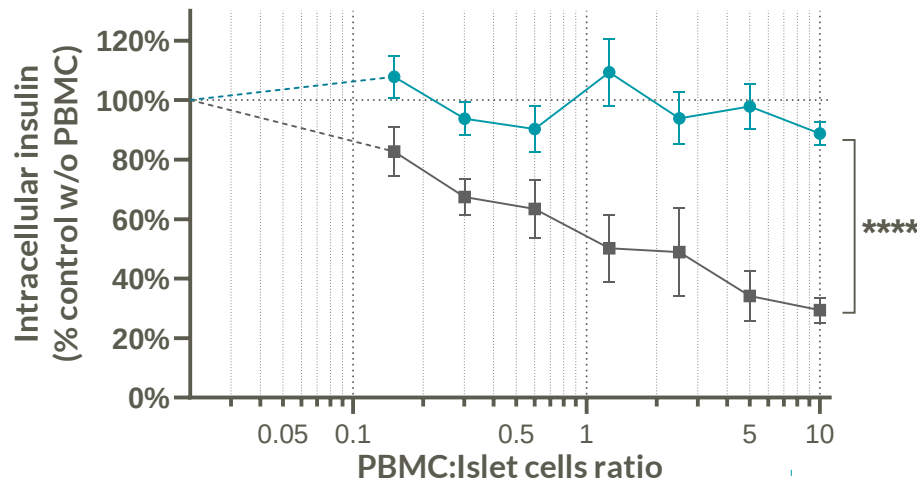
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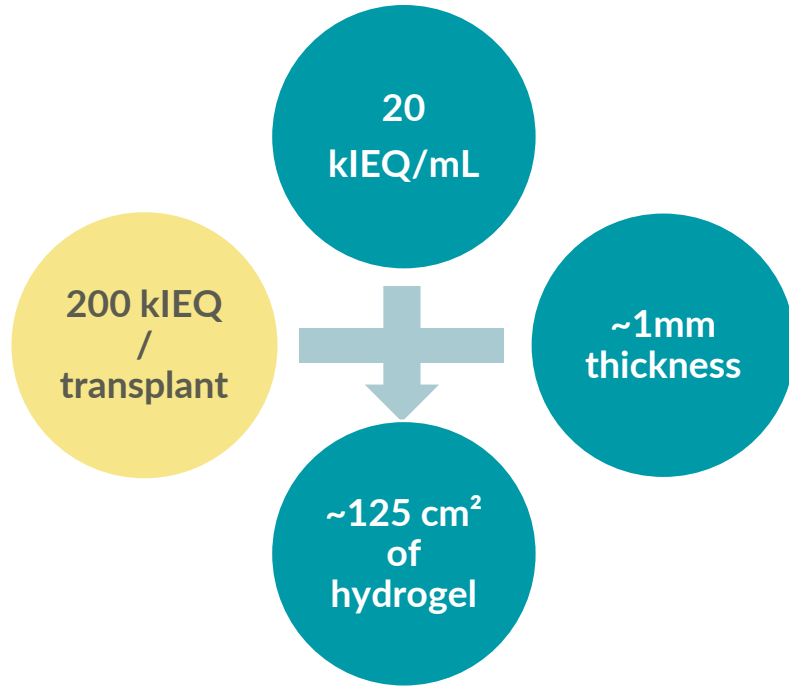
1

Scale up of ADO12 for human implantation

2

3

4



1

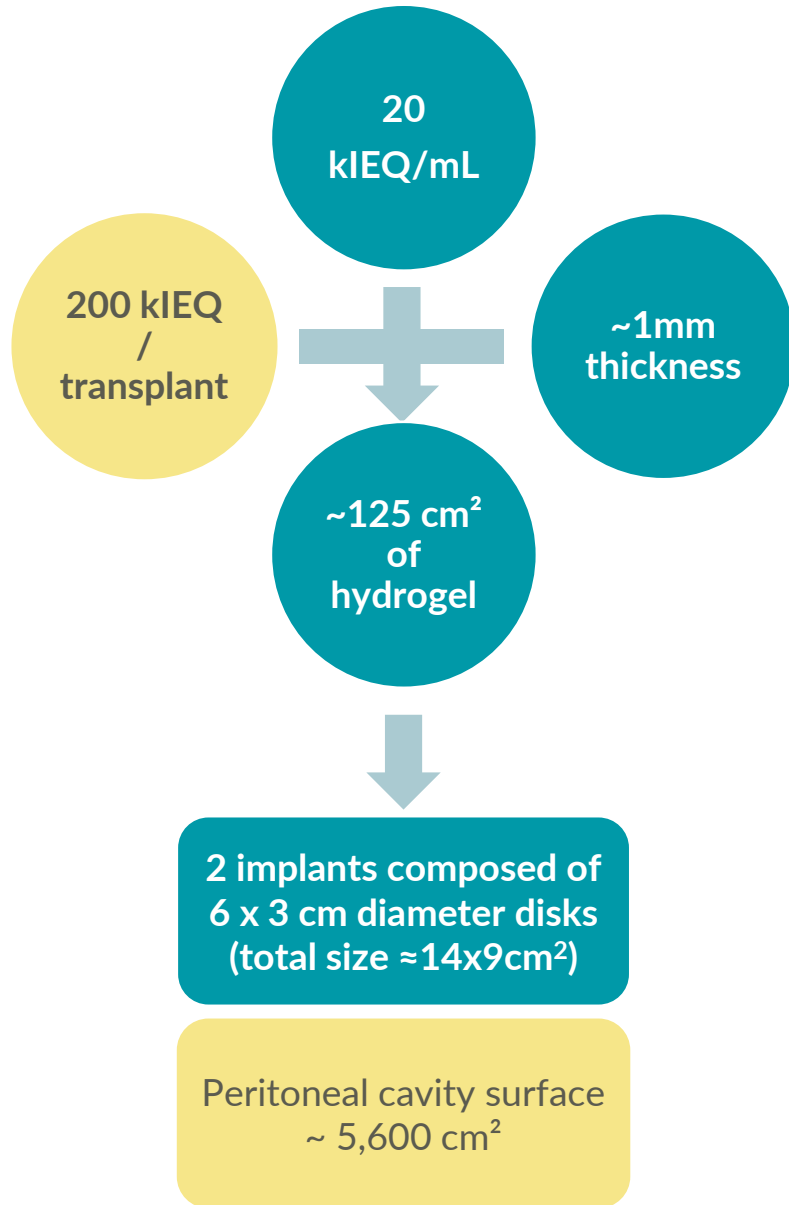
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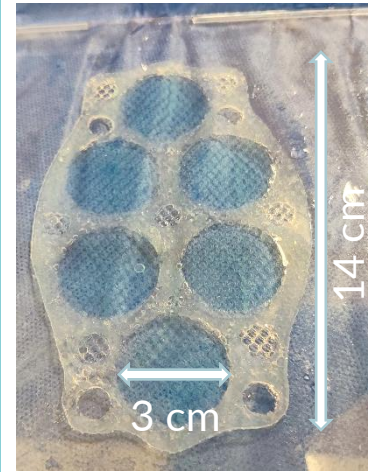
3

4



Human size ADO12 prototype

Trocar insertion (Ø12 mm)



Roll-up

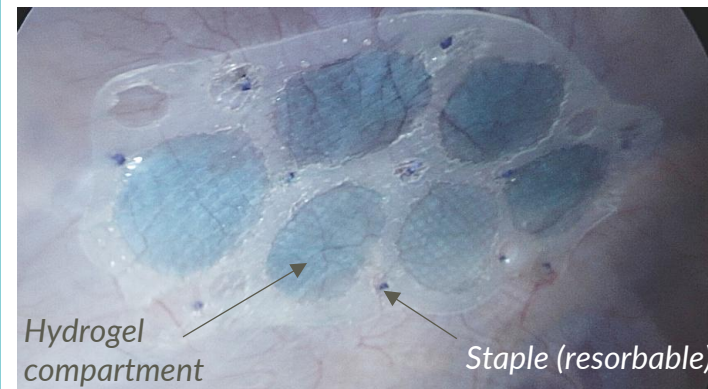


Insertion

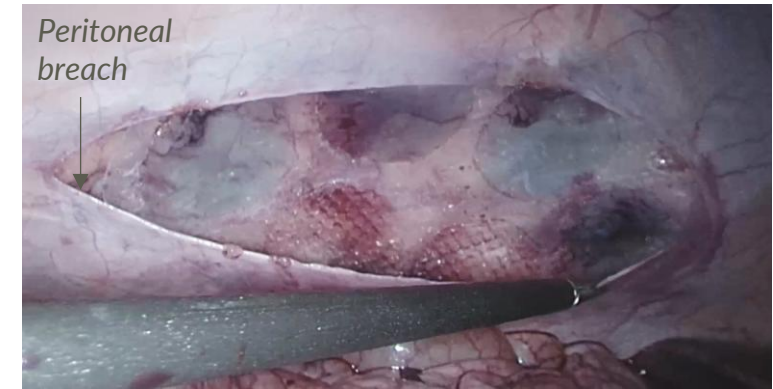


Implantation by laparoscopy in the minipig

Intraperitoneal



Pre-peritoneal



1

Compatibility of AD012 with stem cell derived clusters

hSCI



2

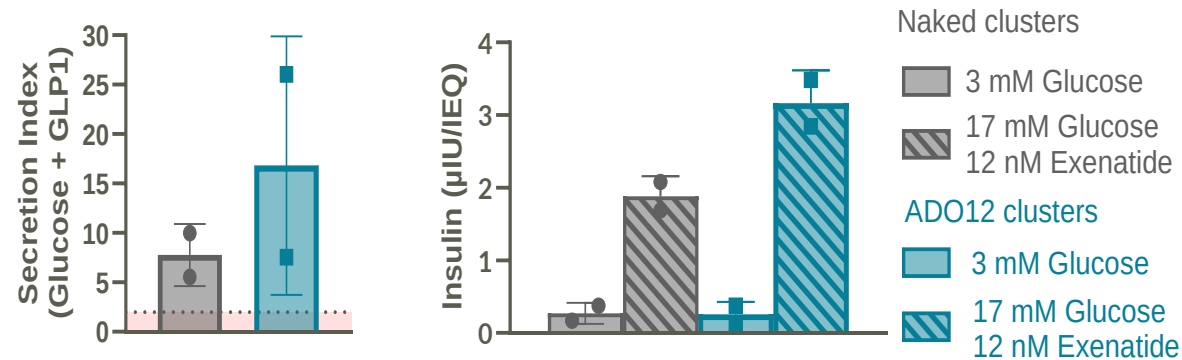
Preliminary results

3

- Stem cell derived clusters, obtained through a collaboration with University of Helsinki.
- *In vitro* characterization followed by xenogeneic transplantation of stem cell derived clusters in NXG mice (260 to 480 clusters/mouse)

4

Static response to glucose stimulation
N=1 preparation



- Maintenance of stem cell derived clusters *in vitro* functionality upon encapsulation in ADO12
- ADO12 is compatible with cluster *in vivo* maturation

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Compatibility of AD012 with stem cell derived clusters

hSCI



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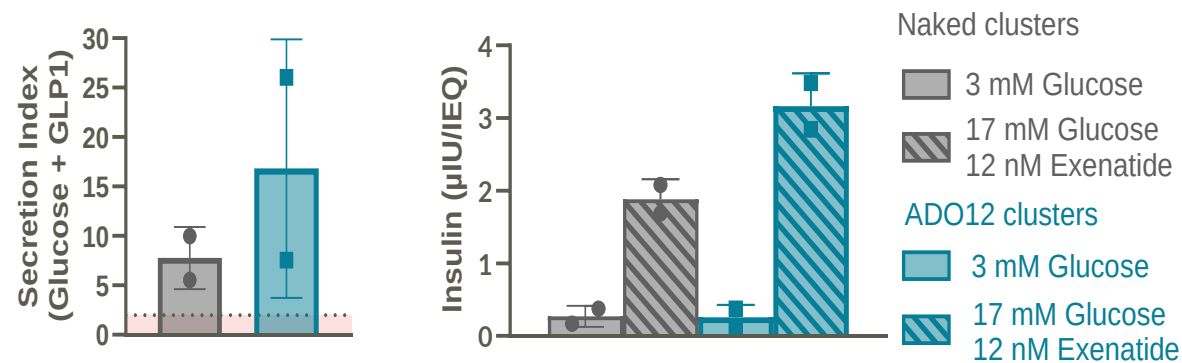
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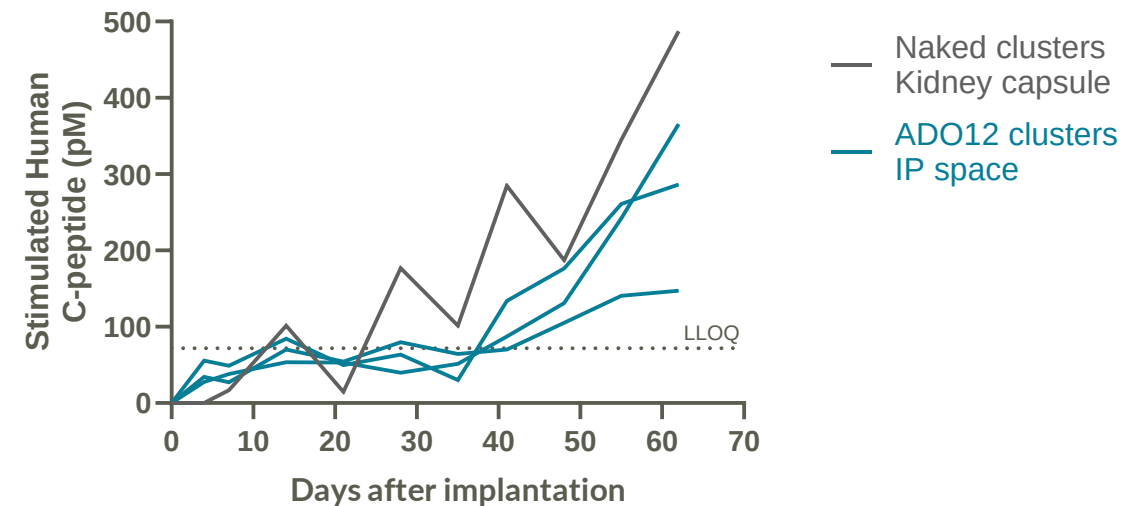
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Static response to glucose stimulation N=1 preparation



Long term *in vivo* C-peptide secretion (2 months), N=1 study, n=4 mice

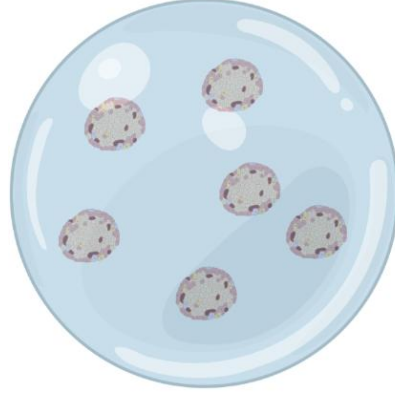


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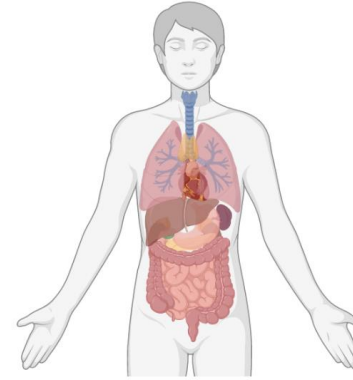
ADO12



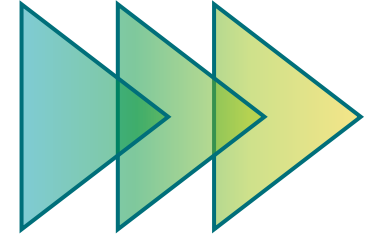
ADO12 Human Islets



Ongoing



Perspectives



Non biodegradable
biocompatible
hydrogel

Simple
encapsulation

First in Human
preparation

Partnership

Suturable
composite thin film

Long term *in vitro*
and *in vivo*
functionality

Regulatory
interactions

Clinical studies

Easily implantable
and retrievable

Immunoprotection

Scale up and
surgical procedure

Stem cells derived
islets

Other cell therapy
applications

Acknowledgements

- ADOCIA - *Lyon, France*
 - Ouardane Jouannot
 - Nicolas Laurent
 - Rosy Eloy
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 - Allan Langlois
- CHU Lille - *Lille, France*
 - François Pattou
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 - Timo Otonkoski
 - Diego Balboa
 - Jonna Saarimäki-Vire
- CHU Lyon - *Lyon, France*
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- IRCAD - *Strasbourg, France*
 - Jacques Marescaux



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Thank you
for your kind interest

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