Cellular, Tissue and Gene Therapies Advisory Committee Meeting

AM Session Product Characterization

BLA 125734

donislecel

Applicant: CellTrans, Inc.

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Purpose of Morning Session

1. Discuss the critical quality attributes of donislecel (product purity and potency).
2. Discuss whether product quality attributes of purity and potency are sufficient to evaluate lot-to-lot consistency in manufacturing, product quality, and product strength.

Three Key Product Controls

1. Source Control

Organ procurement, shipping
Organ screening and testing
Organ acceptance
Certification
In-house testing
Microbiological safety

2. Process Control

Process design
Process controls
Validation
current Good Manufacturing Practices (cGMPs)

3. Product Testing

Critical quality attributes
Lot release testing

Critical Quality Attributes (CQAs)

- Quality attribute (QA): a molecular or product characteristic that is selected for its ability to help indicate the quality of the product.
- Critical quality attribute (CQA): a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality.
- Collectively, QAs define the adventitious agents, safety, purity, potency, identity, and stability of the product.

Donislecel Properties

Adapted from Applicant Briefing Document (Table 3)

- Islet shape-spherical
- Average mean diameter of 150 µm
- Islet volume of ~180,000 μm^3

Islet Composition	Percent of Islet	Endocrine Secretion
Beta cells	~55%	Insulin
Alpha cells	~35%	Glucagon
Delta and Pancreatic peptide cells	~10%	Somatostatin, Pancreatic Peptide
Epsilon cells	<1%	Ghrelin

Donislecel Lot Release Testing

Adapted from Applicant Briefing documents (Table 8, Quality Control Specification for donislecel)

Quality Parameter	Test Method
Safety: Sterility	Rapid Culture Method (aerobic and anaerobic)
Safety: Fungal	Mycology Culture
Safety : Bacterial	Gram Stain
Safety: Endotoxin	Endotoxin (Limulus Amebocyte Lysate), EndoSafe
Identity: Estimated Tissue volume	Visual quantification of pelleted Islets
Identity: Islet Morphology	Dithizone (DTZ) staining and microscopic examination
Potency: Glucose Stimulation Index (GSI)	ELISA (enzyme linked immunosorbent assay) Quantification of Insulin release in Glucose Stimulated Islets
Potency: Islet Yield	DTZ stain and microscopic quantification (Islet Yield)
Potency: Viability	SYTO® 13 Green/Ethidium Bromide staining and microscopic evaluation
Purity: Endotoxin	Endotoxin (Limulus Amebocyte Lysate), EndoSafe
Purity: Islet Purity	DTZ stain and microscopic quantification

Purity: Regulatory Definition

A BLA may be approved on the basis of a demonstration that the biological product that is the subject of the application is "safe, **pure**, and **potent**" (42 USC 262(a)(2)(C)(i)(I)).

- "Purity means relative freedom from extraneous matter in the finished product, whether or not harmful to the recipient or deleterious to the product" (21 CFR 600.3(r)).

- "Products shall be free of extraneous material except that which is unavoidable in the manufacturing process described in the approved biologics license application" (21 CFR 610.13).

Purity: Donislecel

- Allows for multiple cell types in the final product that may not contribute to the product's mechanism of action.
- Lot release criteria are established to reflect all cells present in the final formulated cellular product including those that are not anticipated to have a therapeutic effect.
- Donislecel – the minimum criteria for purity is set such that it allows for up to 70% of cells types.
- Other cells in the islets also regulate glucose and may aid in engraftment.

Potency: Regulatory Definition

Biological Products: “the specific ability or capacity of the product, as indicated by appropriate laboratory tests or by adequately controlled clinical data obtained through the administration of the product in the manner intended, to effect a given result” (21 CFR 600.3(s)).

Ideally, potency assay will represent the product's mechanism(s) of action (MOAs).

- MOAs may be very complex.

- Bioassays: *in vivo* animal studies, *in vitro* organ, tissue or cell culture systems.

- Non-Biological Assays
  - Analytical assays are methods that measure immunochemical, molecular or biochemical properties of the product outside of a living system.
  - Surrogate measurement(s) can be substantiated by correlation to a relevant product-specific biological activity(s).

Multiple assays (Matrix Approach)

If one assay is not sufficient to determine potency, multiple complementary assays that measure different product attributes associated with quality, consistency and stability may be used.

- Combination of biological assays.
- Biological and analytical assays.
- Analytical assays alone.
- Quantitative readout and/or qualitative readout.
- Qualitative assays should be accompanied by one or more quantitative assays.

Developing rapid analytical methods for cadaveric islets is challenging.

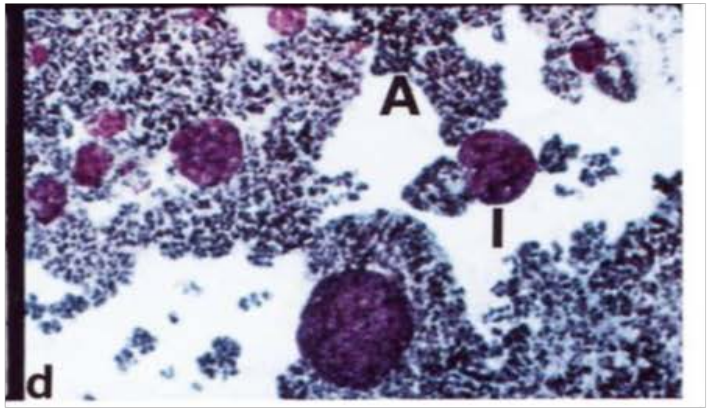
Donislecel Critical Quality Attributes

Adapted from Applicant Briefing Document Table 8

	Attribute	Method	Specification
	Sterility	BacT/Gram Stain/Endotoxin	None detected
	Identity	Presence of islets (β cells) by DTZ staining	Presence of Islets
	Purity	Percentage of Beta Cells by DTZ staining	≥ 30%
Matrix Approach	Yield/Islet Count (Equivalent Islet number or EIN)	DTZ staining	>5000 EIN/kg
Matrix Approach	Viability	Staining with SYTO 13	>70%
Matrix Approach	Potency	Glucose Stimulation index (GSI)	≥ 1

Mode of Action – Purity and Potency

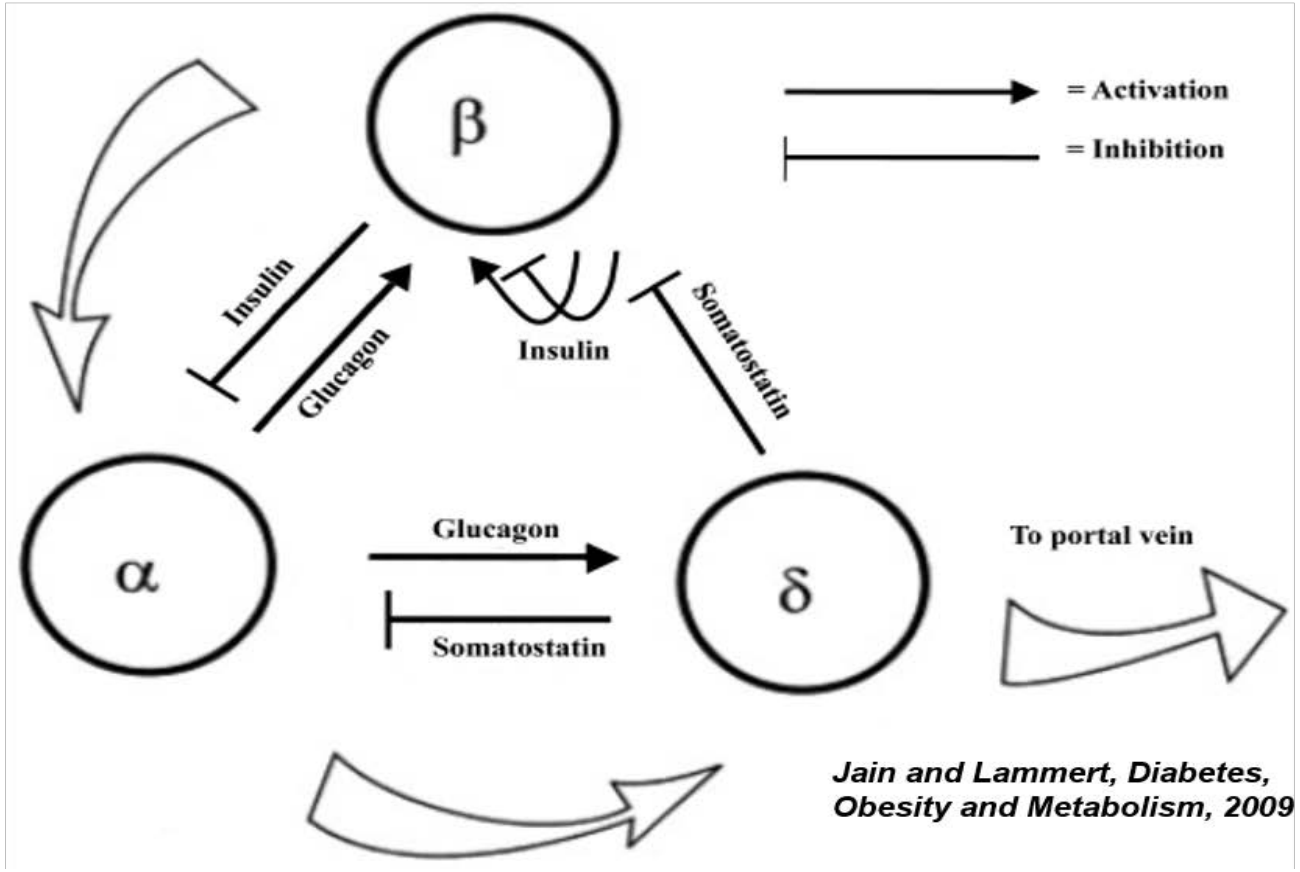
A. Human Islets (40X)



I= Islets, A =Acinar Cells, D= ductal cells

Alejandro et. al, Transplantation, 1987

B. Interactions between the secretory products of the major islet cell types



Jain and Lammert, Diabetes, Obesity and Metabolism, 2009

- 95% of pancreases is exocrine cells: acinar and ductal cells
- 2-5% are endocrine cells: islets
- Controlling the composition of the product is crucial to maintaining consistent product quality

Donislecel Lots Produced for Clinical Trials

Phase 1-2 proof-of-concept study (UIH-001)

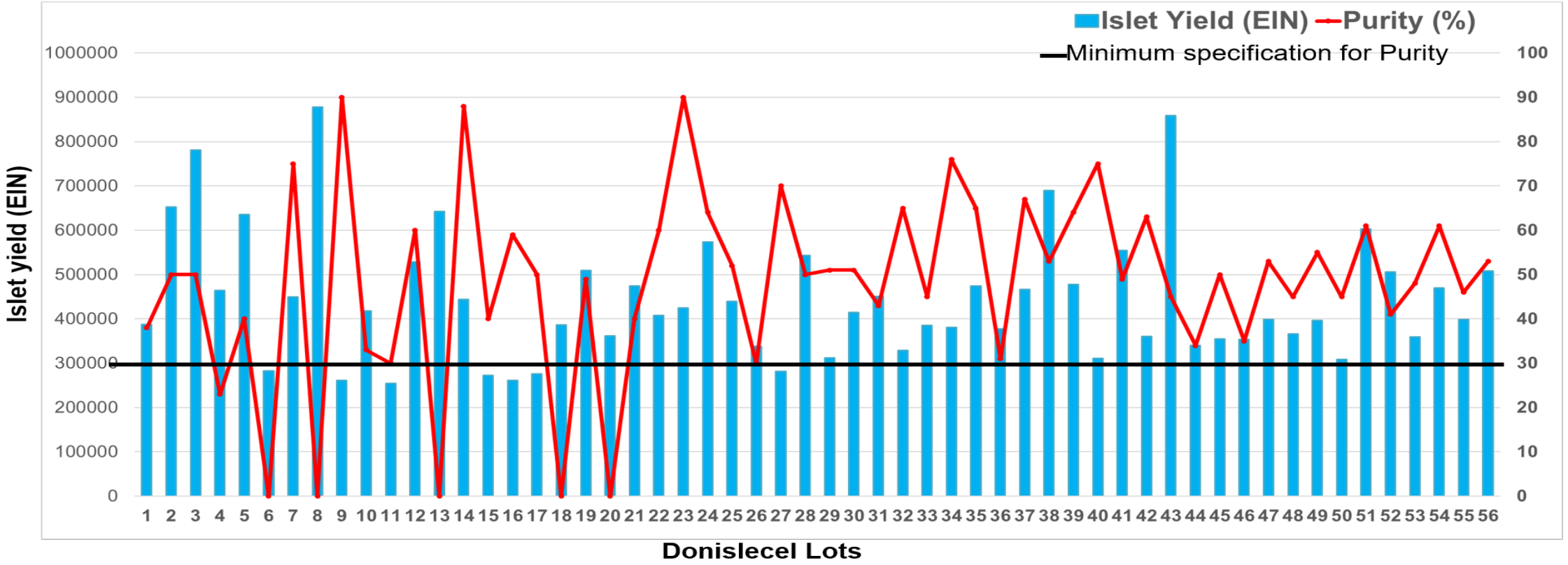
UIH-001 Subjects	Number of Transplants	Total Lots /Doses Manufactured
3	1	3
2	2	4
5	3	15
10	**22**	**22**

Phase 3 pivotal study (UIH-002)

UIH-002 Subjects	Number of Transplants	Total Lots /Doses Manufactured
8	1	8
10	2	20
2	3	6
20	**34**	**34**

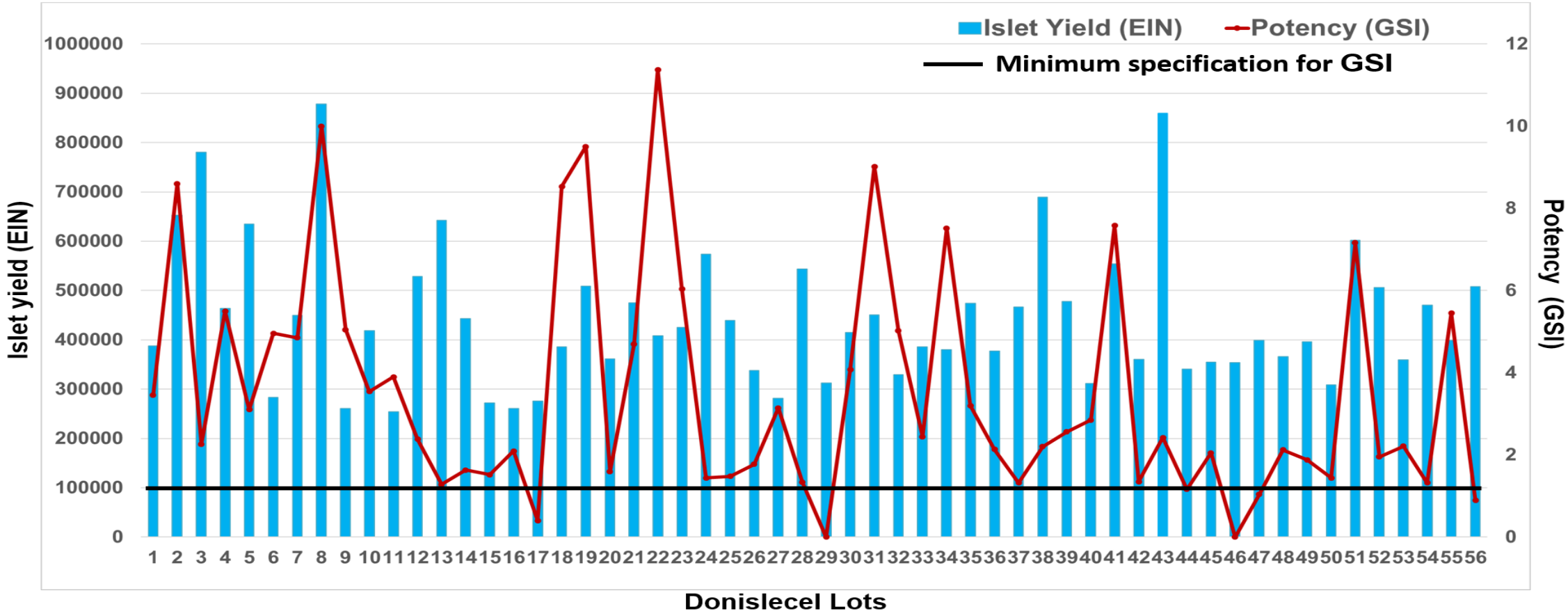
- Subjects received from 1 to 3 doses.
- Each dose or transplant is made from a different cadaveric donor pancreas.
- Lot-to-lot variability.
- Variability in quality attributes makes it difficult to correlate product attributes to clinical outcomes.

Donislecel Yield and Purity for UIH-001 and UIH-002 Lots



- Minimum dose >5000 EIN/kg body weight of recipient.
- DTZ over-estimates by 20-30%.
- Other cells in donislecel are not evaluated and the ratios of beta cells to non-beta cells present in donislecel are the same as in a healthy human islet.

Donislecel Yield and Potency for UIH-001 and UIH-002 Lots



- Minimum Dose >5000 EIN/kg body weight of receipt.
- In-vitro potency assay glucose-stimulated insulin secretion (i.e., GSI assay) has not been shown to correlate with clinical outcomes.

Conclusions

- CQAs as measured for purity (staining is specific to only beta cells) and potency of donislecel (drug product) do not correlate with the clinical effectiveness.
- CQAs may not adequately evaluate lot-to-lot manufacturing consistency.

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Back-up

Donislecel Lots Manufactured for the UIH-001 & UIH-002 Clinical Trials

UIH-001	Islet Yield (EIN)	Viability (%)	Purity (%)	Potency GSI
Mean	455629	90	51	4.55
SD	173587	5	19	3.16
Min	253924	80	23	0.40
Max	877677	98	90	11.37
Median	430697	90	50	3.72

UIH-002	Islet Yield (EIN)	Viability (%)	Purity (%)	Potency (GSI)
Mean	435377	95	54	3.05
SD	120093	2	13	2.23
Min	281299	89	30	0.89
Max	858856	99	90	9.02
Median	399068	95	52	2.17

Glucose Stimulation Index (GSI)

Method:

- GSI release measured by ELISA
- Islets are incubated first in the presence of a low glucose solution (2.8 mM) and in a high glucose solution (28 mM).

Purpose:

- $\text{GSI} = \frac{\text{insulin produced under high glucose stimulation}}{\text{insulin produced under low glucose stimulation}}$
- GSI ≥ 1 is considered indicative of islet potency.

Ricordi et.al., *Diabetes,* 2016