ENDOC-βH5® HUMAN BETA CELLS: A UNIQUE "THAW AND GO" MODEL

for accelerating Diabetes research with highly functional and ready-to-use human beta cells

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BACKGROUND AND OBJECTIVES

More than 500 million adults are currently living with diabetes worldwide (90% Type 2), a number that is predicted to continue rising. Need for physiologically relevant human cellular models to study human beta cell function, diabetes development and treatment strategies is thus greater than ever.

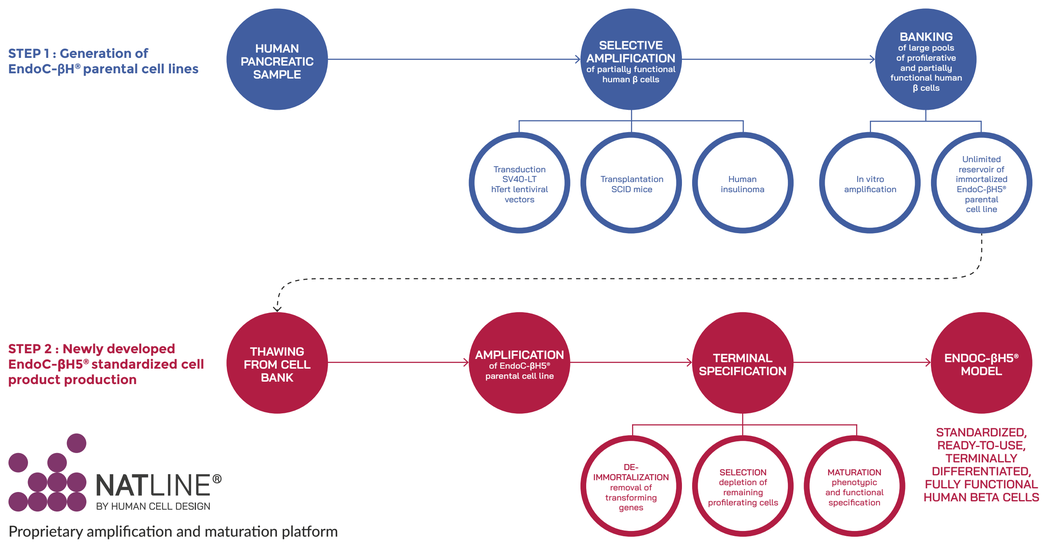
EndoC-βH1® cells, initially developed by ENDOCELLS SAS and the laboratories of Drs Scharfmann, Ravassard and Czernichow (INSERM/CNRS France) [1], have been adopted by more than 200 laboratories worldwide and used in more than 110 peer-reviewed articles to date. They became a reference model as an amplifiable human beta cell that retain ability to secrete insulin upon glucose stimulation and normalize glycemia in rodent models of diabetes [2]. Yet, they require intensive cell culture work and constant monitoring of the maintenance of their insulin secretion response and lack major beta cell functions such as robust response to incretins.

Newly and independently developed EndoC-βH5® cells represent a greatly optimized human beta cell model with, among other characteristics,

1) high sensitivity to physiological concentrations of glucose,
2) robust and dose dependent response to incretins,
3) high absolute values of insulin secretion and resolution of the assays,
4) direct availability as frozen stocks,
5) ready-to-use format that doesn't require extensive cell culture,
6) validated batch-to-batch reproducibility of functional responses.

Overall, EndoC-βH5® represent a novel human pancreatic beta cell solution with very high potential for developing human diabetes models, unraveling diabetes mechanisms in human cells and developing drug screening and hit validation platforms for anti-diabetic drugs.

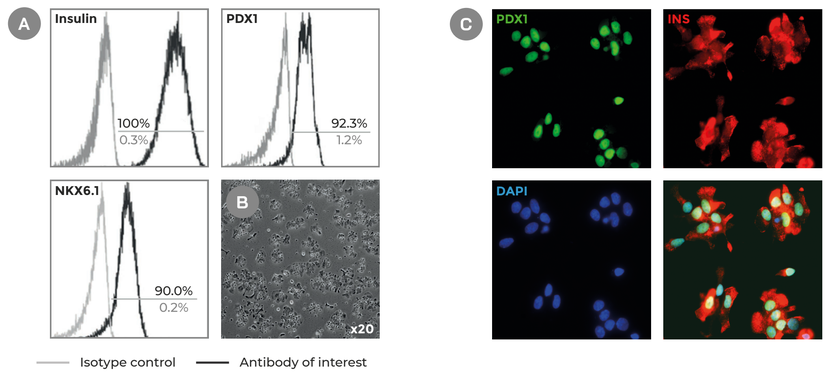
Process of generation of highly functional, reproducible and ready-to-use EndoC-βH5® human beta cells through maturation of proliferation induced human beta cells initially derived from primary tissue



NATLINE® BY HUMAN CELL DESIGN
Proprietary amplification and maturation platform

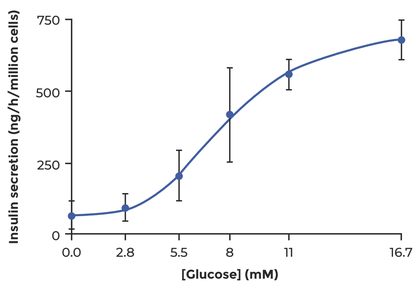
RESULTS

1 Homogeneous expression of functional human beta cell markers



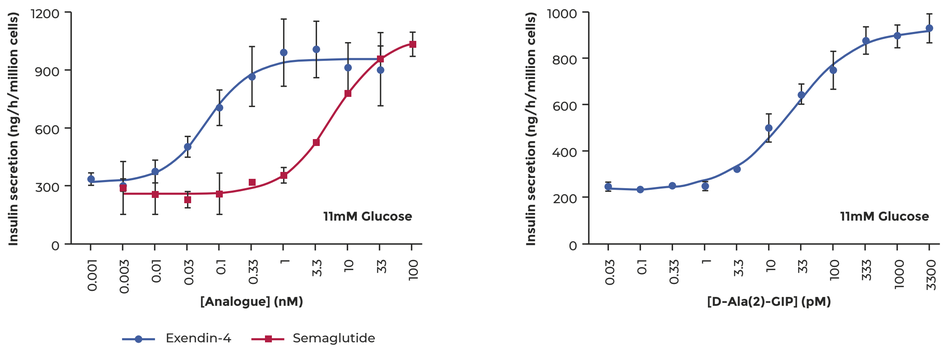
EndoC-βH5® is a pure population of human beta cells that homogeneously express high levels of insulin as well as PDX1 and NKX6.1 human beta cell transcription factors. A) flow cytometry analysis for Insulin, PDX1 and NKX6.1 expression, B) Morphology of EndoC-βH5® forming small adherent clusters of functional pancreatic beta cells and C) immunofluorescence images showing homogeneous co-expression of Insulin and PDX1 in EndoC-βH5® cells.

2 Dose dependent response to physiological concentrations of glucose



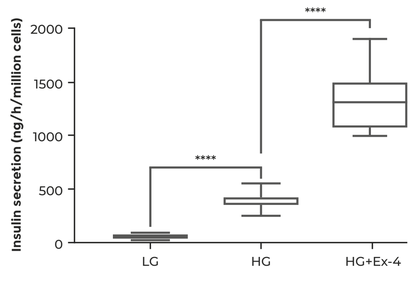
EndoC-βH5® dose dependently respond to glucose with highest potentiation of insulin secretion between 2.8mM and 11mM Glucose. GSIS assay performed on EndoC-βH5® cells 7 days post-thawing and seeding in a 96-well plate setting (100.000 cells per well).Fold increase of insulin secretion is up to 10 fold.

3 Dose dependant responses to GLP-1 and GIP analogues



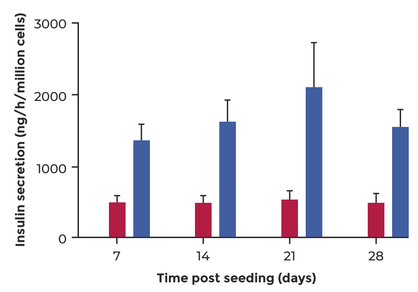
EndoC-βH5® dose dependently respond to GLP-1 and GIP receptor analogues Exendin-4, Semaglutide and D-Ala(2)-GIP. GSIS assay results showing Exendin-4 and Semaglutide (left panel) as well as D-Ala(2)-GIP (right panel) responses in presence of 11mM Glucose. Assays were performed 7 days post-thawing in a 96-well plate setting (100.000 cells per well). For all three agonists, potentiation of insulin secretion is up to 3.5-fold compared to 11mM glucose stimulation.

4 High reproducibility



High batch to batch reproducibility as shown by box-plot diagram summarizing distribution of insulin secretion from a large number of representative EndoC-βH5® batches. 96-well plate GSIS assays using 20mM Glucose (HG) +/- 1nM Exendin-4 (Ex-4).

5 Chronic treatment



EndoC-βH5® cells maintain stable response to glucose and GLP-1 receptor agonist for at least 4 weeks. 96-well plate GSIS assays using 11mM Glucose (HG) +/- 1nM Exendin-4 (Ex-4).

CONCLUSIONS

- ✓ **Functionally validated** batches of **frozen cells**
- ✓ **Robustness** - batch to batch **high reproducibility**
- ✓ **Flexibility** - plan your experiments then thaw cells as needed
- ✓ **Availability** - large batches available
- ✓ **HTS** compatible - proven 96 and 384-well plate compatibility [3]
- ✓ **Chronic treatment** - at least 4 weeks
- ✓ **Time saving** "thaw and go" - results in few days

EndoC-βH5® is a unique "thaw and go" human beta cell model that can accelerate Diabetes research

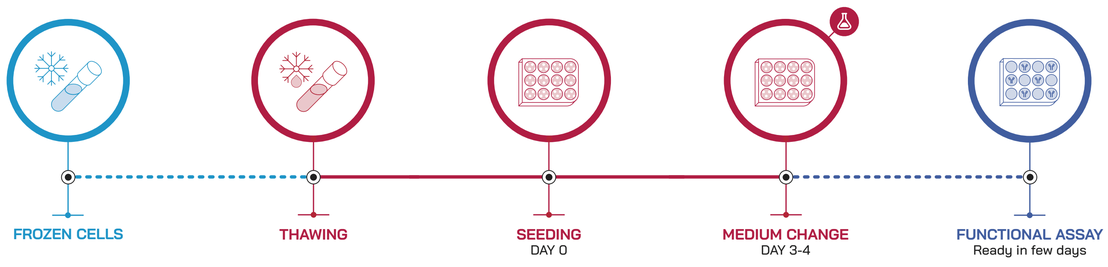


Diagram showing possible experiment time frame when using EndoC-βH5® cells

		ENDOC-βH1	ENDOC-βH5	NATIVE β CELLS
Functionality	Glucose response	+	+++	+++
	GLP-1/GIP response	No	Yes	Yes
	Insulin content (µg/MC)	0.5 – 1	Up to 10	Up to 10
Phenotype	Proliferation	Yes	No	No
	Functional maturity	No	Yes	Yes
	Amplification	> 100 passage	Single use	Single use
	Purity	100% β cells	100% β cells	α / β / δ cells
Logistics	Time before running functional assay	8 weeks	7 days	Islet preparation
	Chronic Treatment	Yes	> 4 weeks	Few days
	Handling	Culture and Preparation	Thaw-and-go / Ready to use	Preparation
	Reproducibility and Robustness	+	+++	+
	Flexibility	+	+++	-
	Availability	Unlimited	Unlimited	Limited
Screening	96/384 well miniaturization	Yes	Yes	Yes
	HTS	Conditional	Yes	Difficult due to availability

EndoC-βH5® is an optimized human beta cell model

HUMAN CELL DESIGN
ACCELERATING DISCOVERY

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(1) A genetically engineered human pancreatic β cell line exhibiting glucose-inducible insulin secretion. Ravassard P. J Clin Invest. 2011 Sep; 121(9):3589-97.
(2) The EndoC-βH1 cell line is a valid model of human beta cells and applicable for screenings to identify novel drug target candidates. Tsonkova VG *et al.* Mol Metab. 2018 Feb; 8:144-157.
(3) Large-Scale Functional Genomics Screen to Identify Modulators of Human β-Cell Insulin Secretion. Szczerbinska I *et al.* Biomedicines. 2022 Jan 4; 10(1):103.

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