HUMAN CELL DESIGN
ACCELERATING DISCOVERY

ENDOC-βH5® IS A ROBUST AND RELIABLE HUMAN PANCREATIC BETA CELL FOR TYPE 1 AND 2 DIABETES MODELING

T lymphocyte beta cell killing, cytokine inflammation and glucolipotoxicity for drug screening and target validation

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BACKGROUND AND OBJECTIVES

Diabetes research and drug discovery would strongly benefit from reproducible and easily accessible human cellular disease models. In this study, we developed models for beta cell glucolipotoxicity, cytokine mediated inflammation, T lymphocyte activation and T cell mediated killing that combine the unique properties of EndoC-βH5® cells and their capacity to be modified into derivative models.

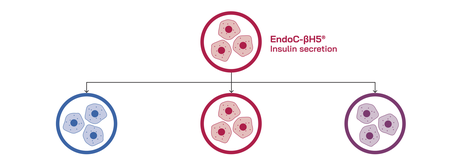
We developed a cell line that models glucolipotoxicity, GLTx EndoC-βH5®. GLTx EndoC-βH5® undergo cytotoxicity when cultured in presence of palmitate and elevated glucose, recapitulating a hallmark of type 2 diabetes.

We then developed a model of cytokine mediated inflammation in EndoC-βH5® cells. Cytokine treated EndoC-βH5® cells undergo cell death which is accompanied by impaired insulin secretion, confirming the mechanistic relevance of the model. In addition, these effects are prevented by JAK1/2 inhibitor, Baricitinib, a clinically approved molecule for rheumatoid arthritis.

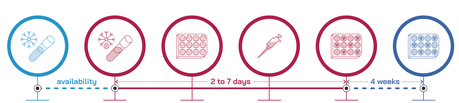
Finally, we further addressed modeling of type 1 diabetes with beta cell/T lymphocyte interaction assays. We generated HLA-A2 expressing EndoC-βH5® cells which elicit HLA-A2 allo-reactive CD8 T cell activation. This effect is potentiated by IFNγ and blocked by Baricitinib. We also demonstrated HLA-A2 EndoC-βH5® specific killing by diabetogenic HLA-A2 restricted prepro-insulin PPI15-24 epitope recognizing CD8 T lymphocytes, thus also showing that they efficiently present a T1D-related peptide at their surface.

Overall, EndoC-βH5® cells and their derivatives allowed us to model several beta cell defects that are associated to type 1 and type 2 diabetes and thus represent models for screening new therapeutic approaches, validating candidate molecules and characterizing molecular targets at small, medium and large scale taking advantages of readily available and highly reproducible EndoC-βH5® cells.

EndoC-βH5®: from 100% functional healthy human beta cells to a unique panel of physiological type 1 and type 2 diabetes models

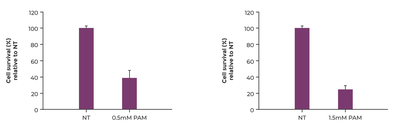


Ready to use human beta cells for rapid disease modeling and results



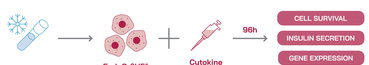
GLUCOLIPOTOXICITY

Palmitate/glucose treatment induces cytotoxicity in GLTx EndoC-βH5® cells

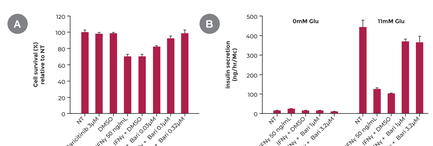


Palmitate/glucose treatment induces glucolipotoxicity and beta cell death in GLTx EndoC-βH5® cells relative to non treated GLTx EndoC-βH5®. GLTx EndoC-βH5® cells were treated with 30mM glucose and 0.5mM (left) or 1.5mM (right) palmitate for 96 hrs. n=4.

CYTOKINE MEDIATED INFLAMMATION

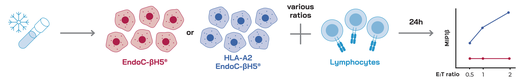


Cytokine treatment induces cytotoxicity and impaired insulin secretion in EndoC-βH5® cells

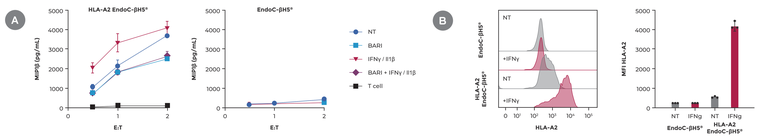


IFNγ treatment in EndoC-βH5® cells induces beta cell death and impaired insulin secretion :
A Histogram showing cell survival relative to non treated cells in EndoC-βH5® cells treated with IFNγ (50 ng/mL, 96 hrs) or IFNγ + Baricitinib (Bari). IFNγ induces beta cell death which is dose dependently prevented by Baricitinib, n=3.
B Representative histogram showing basal (0mM glucose) and stimulated (11mM glucose) insulin secretion, normalized to cell number, in EndoC-βH5® cells treated with IFNγ or IFNγ + Baricitinib. IFNγ impairs insulin secretion which is partially normalized by Baricitinib.

CD8 T CELL ACTIVATION

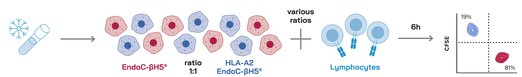


HLA-A2 EndoC-βH5® cells activate HLA-A2 reactive CD8 T cells

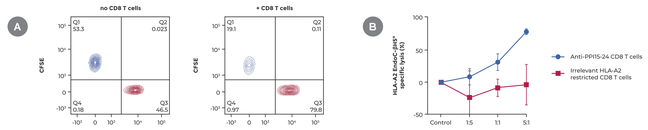


HLA-A2 EndoC-βH5® cells activate allo-HLA-A2 reactive CD8 T lymphocytes:
A MIP1β secretion by allo-HLA-A2 reactive CD8 T cells that were co-cultured for 24h with HLA-A2 EndoC-βH5® cells (left) but not control EndoC-βH5® cells (right), as a marker of CD8 T cell activation. T cell activation is further potentiated by treating HLA-A2 EndoC-βH5® cells with IFNγ (1000 U/ml) and Il1β (2 ng/ml) and partially prevented by JAK1/2 inhibitor Baricitinib (BARI) (4µM), n=3.
B Flow cytometry results of HLA-A2 expression by control EndoC-βH5® and HLA-A2 EndoC-βH5® cells in untreated and IFNγ/IL1β treated condition (left). Data are also presented as mean fluorescent intensity (MFI) (right).

T CELL MEDIATED BETA CELL KILLING



HLA-A2 EndoC-βH5® cells present endogenous diabetogenic peptide and undergo PPI15-24 reactive CD8 T lymphocyte mediated killing



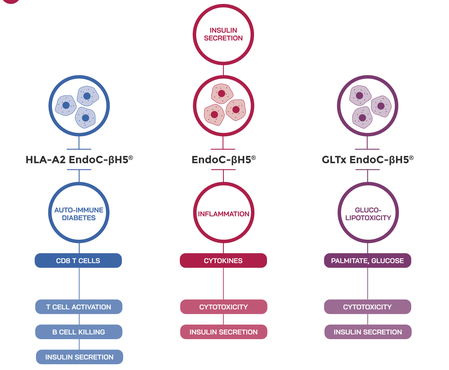
HLA-A2 EndoC-βH5® cells are specifically killed by HLA-A2 restricted anti-PPI15-24 CD8 T lymphocytes:
A Representative flow cytometry results showing relative number of live control (Cell trace violet, red) and HLA-A2 (CFSE, blue) EndoC-βH5® cells after their co-culture in absence (left panel) or presence (right panel) of HLA-A2 restricted anti-PPI15-24 CD8 T lymphocytes (E:T ratio 5:1).
B Specific killing of HLA-A2 EndoC-βH5® cells (blue line) by HLA-A2 restricted anti-PPI15-24 CD8 T lymphocytes but not irrelevant HLA-A2 restricted T cells (red line), n=3.

CONCLUSION

Take advantage of EndoC-βH5® unique properties to study type 1 and type 2 diabetes using newly developed disease relevant models and functional assays:

- ✓ 100% pure population of functional human beta cells
- ✓ Reproducible data generation between batches
- ✓ Readily available as frozen systems
- ✓ GLP-1/GIP signaling

1 MODELS



2 PHYSIOLOGICAL READOUTS

GENERATE HUMAN RELEVANT DATA AND ACCELERATE SCIENCE AND DRUG DISCOVERY FOR TYPE 1 AND 2 DIABETES.

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