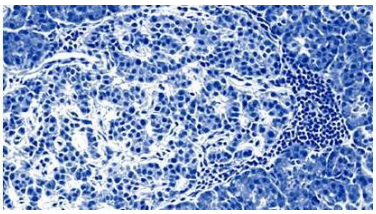
nPOD
Network for Pancreatic Organ Donors with Diabetes



Neratinib is a novel inhibitor of MST1 and protects pancreatic beta-cells in diabetes

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PURPOSE

The failure of pancreatic insulin producing β-cells is a central pathogenic hallmark of all forms of diabetes. The identification of relevant molecular pathways and pathophysiological events that are responsible for β-cell demise in diabetes is instrumental for the better understanding of disease mechanisms and to ultimately establish a novel diabetes therapy directed toward restoration of beta-cell mass and function. The serine/threonine kinase Mammalian Sterile 20-like kinase 1 (MST1), a core kinase of the Hippo developmental pathway, is a critical regulator of β-cell death and dysfunction in diabetes and its inhibition restores normoglycemia and β-cell function and prevents the development of diabetes. Here we aimed to find a pharmacological MST1 inhibitor with robust β-cell protective actions.

METHODS

With the strategy of repurposing FDA-approved drugs for the therapy of diabetes, we performed a high throughput MST1 inhibition screen across a highly-privileged collection of 641 drug-like kinase inhibitors together with a triaging strategy for selective, non-cytotoxic compounds, and identified neratinib, approved for cancer therapy, as potent MST1 inhibitor. Neratinib was then tested *in vitro* for its efficacy to inhibit MST1 activation and cell death in human islets and INS-1E cells and *in vivo* in a pre-clinical study in type 1 (multiple-low dose streptozotocin; MLD-STZ) and type 2 (obese $Lepr^{db/db}$) diabetic mouse models. Glycemia, glucose and insulin tolerance and β-cell function were tightly monitored during the study and β-cell mass, survival, proliferation and β-cell identity marker expression analyzed in the isolated pancreata.

SUMMARY OF RESULTS

Neratinib improved β-cell survival under multiple diabetogenic conditions in β-cells and primary human and mouse islets. Without any glucose lowering or β-cell effects in control mice, neratinib restored normoglycemia and β-cell function, survival, and mass, as well as β-cell identity in the MLD-STZ and obese diabetic $Lepr^{db/db}$ mice. MALDI imaging mass spectrometry (MALDI-IMS) showed neratinib distributed throughout the pancreas after i.p.

injection. Neratinib's effect was further confirmed in a therapeutic approach; it fully restored β-cell survival in isolated mouse islets from severely diabetic db/db mice, as well as in pro-inflammatory cytokine treated mouse islets.

CONCLUSIONS

Neratinib is a previously unrecognized inhibitor of MST1 and represents a potential β-cell-protective drug with proof-of-concept *in vitro* in human islets and *in vivo* in rodent models of both type 1 and type 2 diabetes.