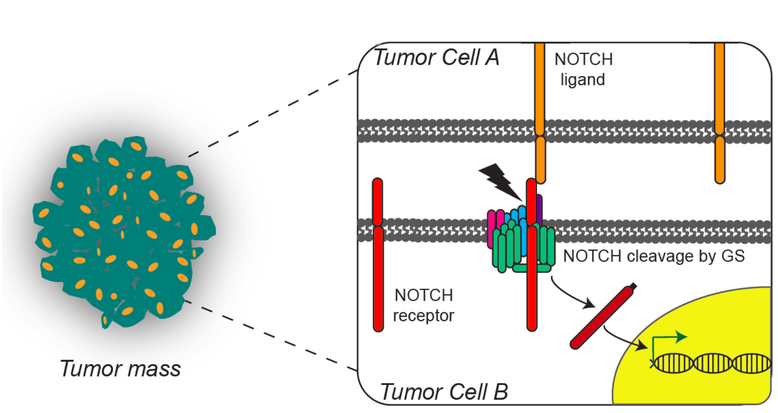
Predicting gamma-secretase inhibitor (GSi) responders pan-cancer

Medtech & Diagnostics

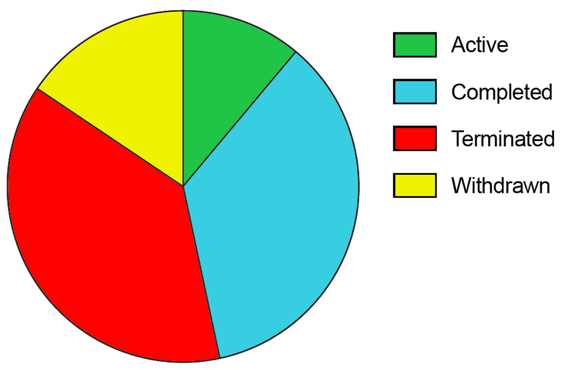
A pan-cancer gene expression panel which can predict cancer patient sensitivity to multiple types of GSi compounds

The Challenge

- Oncogenic NOTCH pathway activation occurs in many cancer types, driving aggressive tumor behavior and poor patient outcome

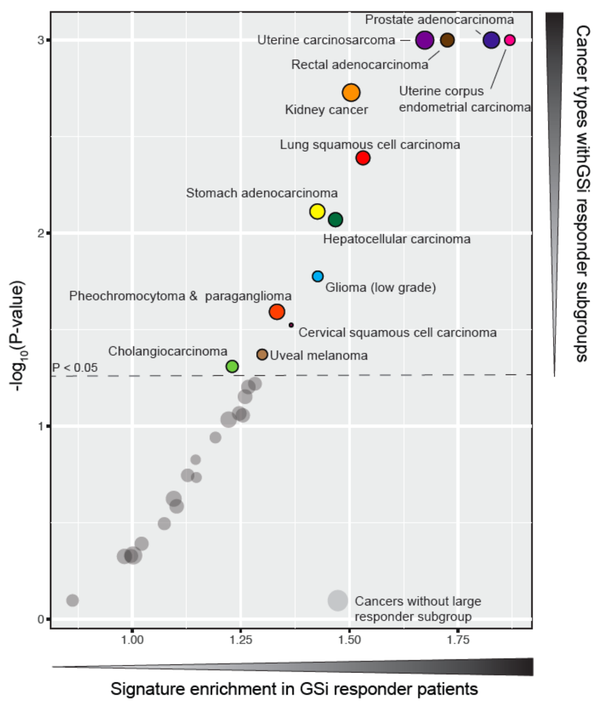


- NOTCH signaling can be inhibited by gamma-secretase inhibitors (GSi) but clinical trial termination rates are very high due to off-target toxicities in a subgroup of patients. Robust molecular tools to enable responder patient selection for inclusion in GSi trials are needed

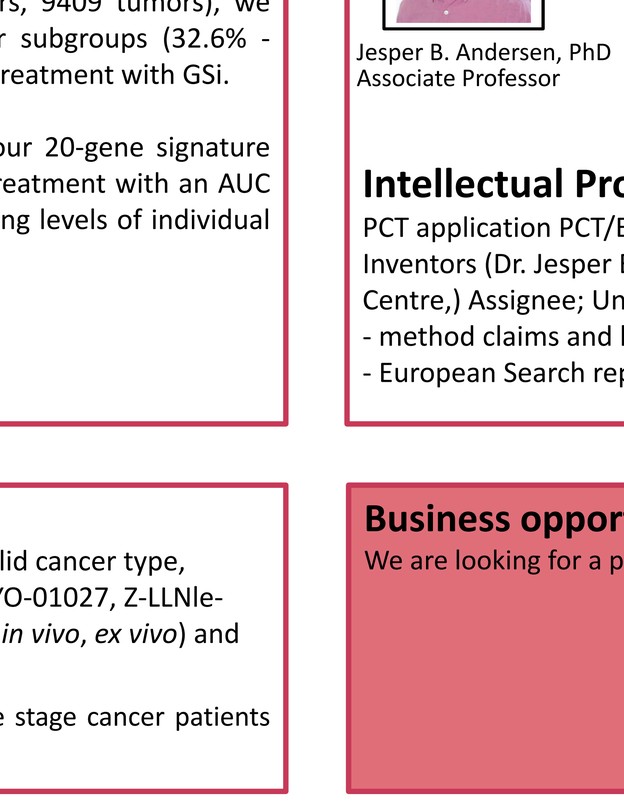


The Solution

- Our GSi sensitivity signature predicts large patient responder subgroups across multiple cancer types

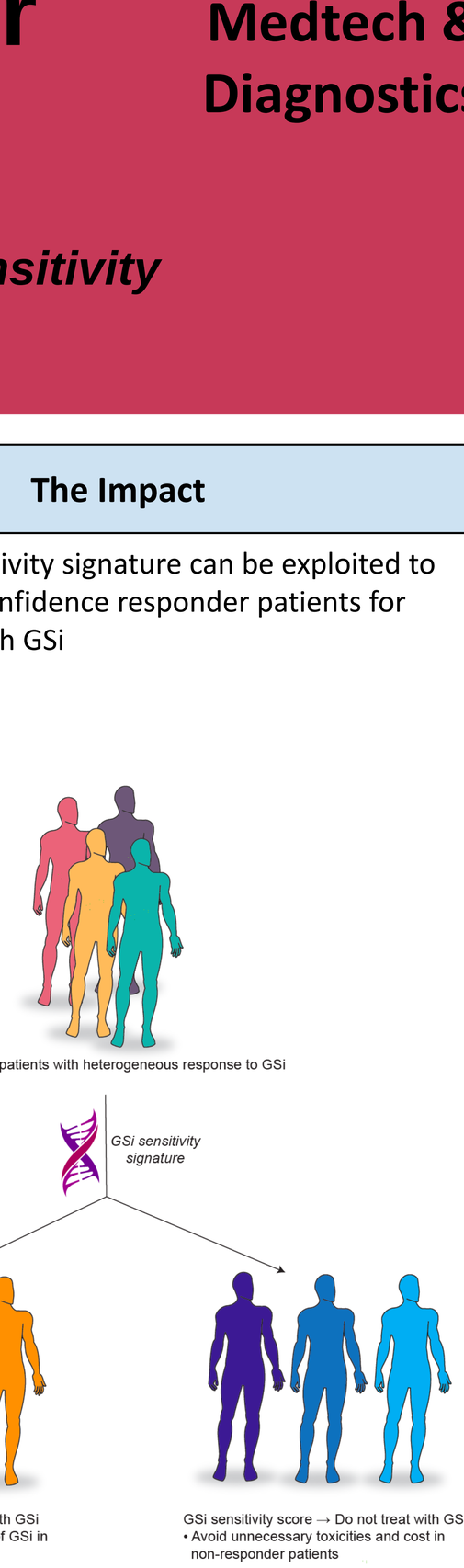


- Our GSi sensitivity signature significantly outperforms measurements of target pathway expression in classifying sensitivity of cell lines to these drugs



The Impact

- Our GSi sensitivity signature can be exploited to select high-confidence responder patients for treatment with GSi



- **clinical development tool for GSi**
- **specific theranostic tool for personalised treatment strategies**

Technology Description

Initially developed through analysis of bile duct cancers (O'Rourke et al. Hepatology 2020), we identified a transcriptomic signature capable of identifying GSi-sensitive versus GSi-resistant tumors.

By evaluating our GSi sensitivity signature pan-cancer (31 cancers, 9409 tumors), we predicted 41.9% of cancers to have large prospective responder subgroups (32.6% - 59.6% patients within a given cancer type) who many benefit from treatment with GSi.

In GSi-treatment screening of 60 diverse solid cancer cell lines, our 20-gene signature could discriminate nanomolar from micromolar sensitivity to GSi treatment with an AUC of 1, significantly outperforming the predictive capacity of measuring levels of individual NOTCH signalling genes.

Team

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Intellectual Property Rights

PCT application PCT/EP2020/059091 was filed 1st April 2020
Inventors (Dr. Jesper B. Andersen, Dr. Colm J. O'Rourke, Biotech Research and Innovation Centre,) Assignee; University of Copenhagen)
- method claims and kits/product
- European Search report positive for claims claiming use of three or more genes of panel

Current State

Theranostic assay has shown predictive potential independent of solid cancer type, NOTCH mutational status and specific GSi compound (RO4929097, YO-01027, Z-LLNle-CHO). Signature has been optimized across diverse models (*in vitro*, *in vivo*, *ex vivo*) and technologies (gene expression array, RNA sequencing).

Next steps Validation of panel in small group of GSI-treated late stage cancer patients currently; and Development of a signature-specific assay.

Business opportunity and Call to action

We are looking for a potential licensee.

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