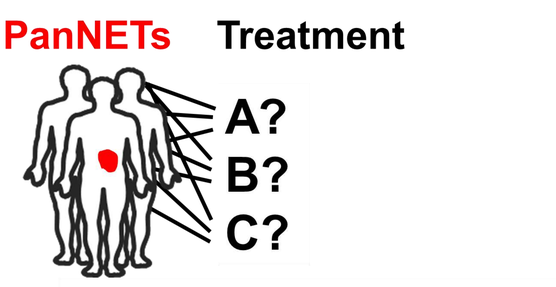
Patient-derived Islet-like tumoroids - Towards more personalized medicine in PanNETs

S. L. April-Monn[1,2], M. Schiavo Lena[3], M. Trippel[1], R. Maire[1], F. Muffatti[4], V. Andreasi[4], C. Doglioni[3,5], C. Kim-Fuchs[6], B. Gloor[6], S. Partelli[4,5], M. Falconi[4,5], A. Perren[1] and I. Marinoni[1]

[1] Institute of Pathology, University of Bern, Bern, Switzerland.
[2] Graduate School for Cellular and Biomedical Sciences University of Bern, Bern, Switzerland.
[3] Unit of Pathology, San Raffaele Scientific Institute, Milan, Italy.
[4] Pancreatic Surgery Unit, Pancreas Translational & Clinical Research Center, San Raffaele Scientific Institute, Milan, Italy.
[5] Università "Vita e Salute", Milan, Italy
[6] Inselspital, University of Bern, Switzerland

Aims & Scope

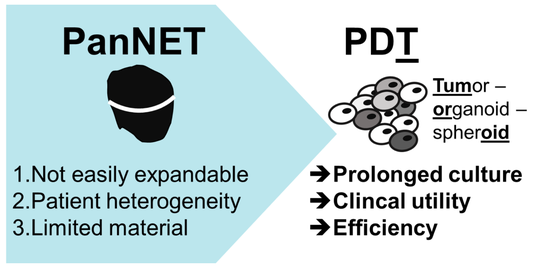
PanNETs are rare and heterogenous tumors that are difficult to treat



A challenge in the clinical management of PanNETs is to predict the aggressiveness of individual tumors and identifying patients who will benefit from early aggressive therapy while minimizing harm of patients with indolent disease. **One of the major issue to improve this situation is the lack of relevant models to explore treatment options and investigate predictive biomarkers.** With the presented PanNET screening platform we aspire to correlate in vitro drug sensitivity profiles with molecular and clinical profiles from patients and to promote more personalized therapies in PanNETs.

Modelling PanNETs

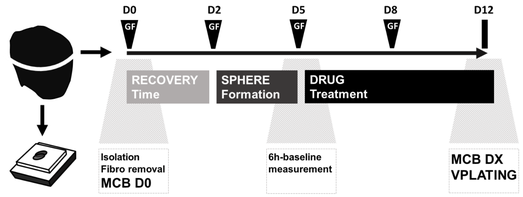
Patient-derived Islet-like tumoroids (PDT)



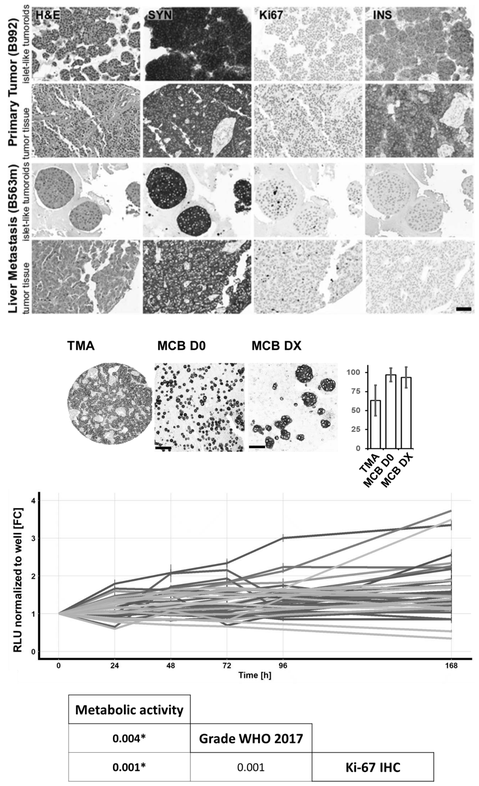
Modelling PanNET disease in vitro is challenging: Neuroendocrine tumors represent an extremely heterogenous group of neoplasm. While highly proliferative cases are invariably lethal, slower-proliferating PanNETs - representing predominant cases - have unpredictable clinical course that varies from indolent to malignant. Primary PanNETs are not easily expandable in culture. Current preclinical mouse- and cell line models do not accurately reflect tumor heterogeneity and patient situation in PanNETs. The rarity of the disease and limited starting material require highly optimized and efficient isolation-, culture-, and screening conditions.
These challenges lead us to establish a hybrid model of so-called **Patient-derived islet-like tumoroids (PDT)** which factors in the challenging nature of PanNET disease. PDTs facilitate culture of PanNETs within clinical useful time frames and efficient usage of limited starting material. Due to its straightforward applicability PDTs currently hold a high potential for clinical utility in PanNET disease.

3D culture and drug screening

3D human primary PanNET *in vitro* drug screening pipeline



PanNETs retain a neuroendocrine phenotype *in vitro* and form Islet-like structures that phenocopy growth characteristics of original tumor

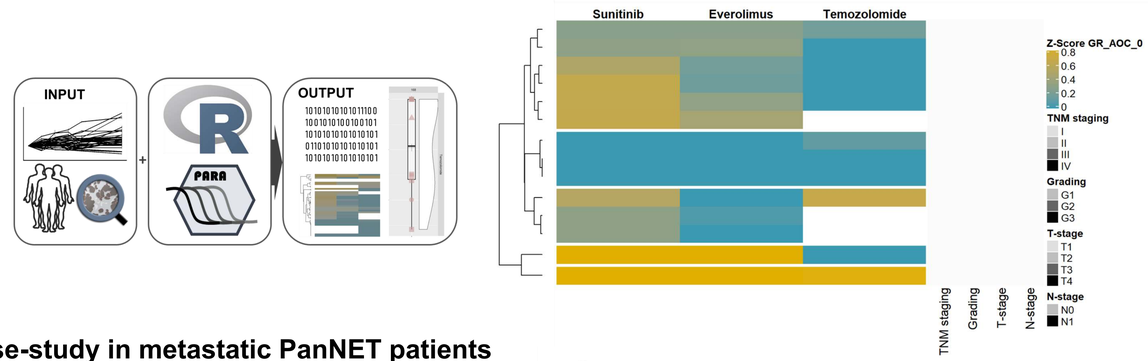


Metabolic activity		
0.004*	Grade WHO 2017	
0.001*	0.001	Ki-67 IHC

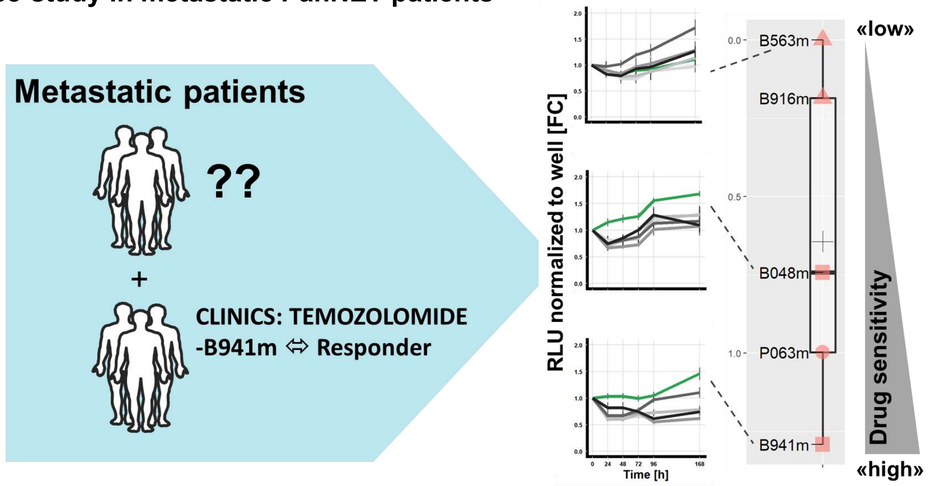
PanNETs form structures similar to non-neoplastic human pancreatic islets in vitro. These patient-derived Islet-like tumoroids retained expression of neuroendocrine tumor biomarker (SYN=Synaptophysin), tumor-type specific hormone expression (INS=Insulin), and proliferation status (Ki-67) (top). Tumor purity of cultured cells was high as seen in micro-cell-blocks from isolations (MCB D0). Partial fibroblast removal led to accumulation of tumor cells in 3D culture compared to tumor content to original tumor tissue (TMA). MCBs at the end of the screening (MCB DX) reconfirmed successful culture of tumor cells (middle). Time course growth monitoring indicates that untreated patient-derived Islet-like tumoroids remained viable over a prolonged period in culture and showed a strong association with patient proliferation indices (bottom). Data represent mean±SD. Bar = 50µm; mean±SEM (n≥3 technical replicates), X^2-test of independence.

Application

Patient-derived Islet-like tumoroids display distinctive drug sensitivity profiles *in vitro*



Case-study in metastatic PanNET patients



Patient-derived Islet-like tumoroids displayed noticeable inter-patient susceptibilities to clinically approved therapies. Clinical data and digital image analysis parameters from all PanNET patients were combined and integrated together with time course in vitro drug sensitivity measurements from clinically approved treatments. Parametrized DSM were extracted and used for downstream drug sensitivity profiling (top, left). Hierarchical clustering analysis revealed distinctive drug sensitivity profiles potentially reflecting patient pharmacotypes (top, right). On a case-study-level patient that clinically responded to a particular treatment also display higher in vitro drug sensitivity and vice versa

Conclusion & Outlook

We present a 3D human primary PanNET screening platform optimized for fast and efficient in vitro pharmacotyping holding potential clinical utility and promoting more personalized treatment in PanNETs.

Further comprehensive phenotypic characterisation of patient-derived Islet-like tumoroids and matching original tumors are currently under way and will provide novel insights into molecular mechanism of PanNETs.

For further information on the project...

➔Let's have a **vCoffee-break** or contact me **@SimonAprilMonn**

➔Check out our 3D Method Paper or visit NeuroEndoNow – Podcast

April-Monn et al. (2020), *Neuroendocrinology*