Image-Guided Drug Delivery | Seminar #4

Speaker #2 | TECHNIQUE

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ABSTRACT

Exploring the organizational principles of the tumor microenvironment to reveal functional heterogeneity

As a tumor progresses, the surrounding microenvironment co-evolves into an activated state through continuous paracrine communication with cancer-associated fibroblasts (CAFs), vascular cells, and immune cells, thus creating a dynamic signaling circuitry that promotes cancer initiation and growth, and ultimately leads to a fatal disease. Recent efforts analyzing tumor composition at single-cell resolution suggest a more intricate cellular complexity than previously recognized, indicating the need to study the context of the malignant microenvironment with improved detail. Conceivably, cellular microniches form functional units influenced by the origin and context of each constituent cell type. Our overarching aim is to functionally define the cellular elements of a tumor through an innovative set of integrated basic, pre-clinical and translational studies. Ultimately, we believe that decisive treatment benefit can only be achieved by targeting multiple, but distinct, cell types that collectively sustain malignant growth.

In previous efforts, we detailed the heterogeneity of CAFs in experimental breast tumors, and thus established the fundamental framework for efforts to explore the development of precision medicine tools based on CAF subtypes (Bartoschek et al, Nature Communications, 2018). Next, we set out to develop a pan-cancer appreciation of CAF subtypes. Through integration of scRNA-seq datasets from diverse malignancies, the generality of our proposed CAF taxonomy was confirmed, serving as a basis for a unifying nomenclature of CAF subtypes based on their origin from distinct progenitor pools. In related studies, we are detailing CAF substates and their definition by molecular or physiological stimuli. Through the use of spatially resolved high-content technologies, we are mapping cellular interplays in microniches in order to define organizational principles of the tumor microenvironment. Ultimately, we are aiming to couple functional properties to tissue architecture. We have detailed signaling pathways involving specific CAF subtypes with implications for tumor progression and response to therapy, for which we are now developing precision targeting strategies using both small molecule inhibitors, antibodies and antibody-drug conjugates. Notably, we have previously documented a reciprocal signaling network within a microniche composed of basal-like breast cancer cells and matrix CAFs that maintains the triple-negative phenotype through signaling mediated by paracrine PDGF-CC signaling (Roswall et al, Nature Medicine, 2018). Targeting of PDGF-CC induces a luminal phenotype with reinstated estrogen signaling, rendering previously impervious basal-like cancers sensitive to endocrine therapy. This concept is currently being explored by us in a clinical phase 2 trial with a window-of-opportunity trial design.

The stromal compartment in general, and CAFs in particular, comprise a hitherto underexploited source for factors harboring prognostic, predictive or therapeutic potential. Taken together, our current work defines a sustainable framework for exploring and implementing cellular microniches as drug targets and tools for precision cancer medicines.

BIO

Kristian Pietras received his PhD in 2002 at the Ludwig Institute for Cancer Research, Uppsala University, Sweden. He then performed postdoctoral work at the University of California in the laboratory of Douglas Hanahan.
Kristian returned to Sweden and in 2012, he was recruited to Lund University, where he became the founding Director of the Lund University Cancer Centre. As a well-positioned link between basic science, oncology and pharmaceutical industry, Kristian has made important contributions in defining tumours as communicating organs comprising multiple cell types that collectively sustain cancer progression. He has received numerous awards for his research, most notably the Anders Jahre's Medical Prize for young scientists by Oslo University, The Fernström Award for Young Scientist by Lund University, and the Göran Gustafsson Award by the Royal Swedish Academy of Sciences, Kristian is a member and chairman of the Young Academy of Sweden.