

# Application of Imaging Cytometry to the Molecular Therapeutics of Human Solid Tumours

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*David Hedley is a medical oncologist at the Princess Margaret Hospital, and Senior Scientist at the Ontario Cancer Institute, University of Toronto. His laboratory studies solid tumour biology, with particular emphasis on the tumour microenvironment, and investigates novel approaches to cancer treatment that can be tested in the clinic. The laboratory has a particular interest in pancreatic cancer, and makes extensive use of primary xenografts derived from pancreatic cancers, maintained orthotopically. Dr Hedley is experienced in the use of flow and image cytometry techniques to study complex biological processes in heterogeneous cell populations.*

## Abstract

Pancreatic cancers are almost 100% lethal because the large majority are unresectable at the time of diagnosis due to local invasion or metastasis, and because these cancers show high levels of resistance to standard chemotherapy drugs. New approaches to treatment based on a better understanding of the underlying biology are therefore needed. Our laboratory makes extensive use of primary xenografts, derived from surgical samples and maintained in the pancreas of immune-deprived mice, in order to study the molecular features of pancreatic cancer in relation to growth characteristics and the tumour microenvironment. Orthotopically-grown primary pancreas cancer xenografts strikingly resemble pathological features of the original surgical samples, and are typically moderately-differentiated, mucin-secreting adenocarcinomas embedded in a dense fibro-vascular stroma. These models also allow tests of novel, molecular-targeted drugs in a clinically-relevant setting, as well as tests of hypothesis-driven approaches to individualized treatment.

Recently we identified the presence of tumour hypoxia, which occurs when the consumption of oxygen exceeds its supply by the vascular system, as a major determinant of biological aggression in primary pancreatic cancer xenografts. Using nitroimidazole probes to map the extent of hypoxia in histological sections, tumours segregate into hypoxic or non-hypoxic with almost no overlap. Consistently, the hypoxic tumours show higher proliferation, determined by BrdU uptake and *in vivo* growth rate relative to the non-hypoxic models, and they also metastasize from the orthotopic site to clinically-relevant sites (liver and peritoneum) to a much greater extent.

Tumour hypoxia has long been known to be an adverse prognostic feature of human cancers, and there is a considerable effort being made to develop novel agents that selectively target hypoxic tumours for clinical application. There is also current interest in the underlying mechanisms that link hypoxia to enhanced metastatic potential, including the potential for hypoxia to reprogram epithelial cells towards a more mesenchymal phenotype, and for the hypoxic microenvironment to provide a niche that favours the survival of cancer stem cells. Imaging cytometry lends itself to the study of these interactions, and examples of our ongoing work will be discussed.