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Molecular subtyping in clinically relevant preclinical models of colorectal cancer.

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## Introduction

Colorectal cancer (CRC) is a highly heterogeneous disease in which four consensus molecular subtypes (CMS) have been recently described each one with a specific molecular and immune pattern. Despite this challenging approach will improve therapy decision and better predictive response, currently the response of CRC to standard and targeted therapies is still very limited. This obstacle is mainly due to the lack of preclinical models which more closely mimic the different CMS subtypes for this malignancy. A more practical and clinical closed immunohistochemistry (IHC)-based molecular subtype classification has been recently reported in human samples showing its predictive and prognostic potential. However, it remains still unsolved if those IHC-based molecular subtypes are maintained into their preclinical models in order to validate these models for the study of targeted therapy response.

## Objetives

Thus, the aim of this study was to examine and compare CRC primary tumours and their corresponding patient derived xenograft (PDX) models with regards to IHC-based molecular subtypes and other immune and stem cell properties.

## Methodology

A total of 40 human CRC samples were obtained just after surgical resection. For each sample, tumour pieces were immediately collected for histopathological and immunohistochemical studies, genomic and immune profiles and for the establishment of PDXs (flank and neck subcutaneous engraftments). In parallel, clinical and pathological data from enrolled patients was prospectively collected. Each sample (patient´s tumour and PDX model) was evaluated for IHC-based molecular subtypes, histological subtype, invasion, stromal and

inflammatory component, endothelial nitric oxide synthase (eNOS) expression and tumour budding. Additionally, RNA expression analysis of a panel of genes using nCounter® Elements™ TagSets and PanCancer immune-profiling panel from NanoString Technologies was also performed in a set of human and their corresponding PDX samples.

## Results

We successfully established 40 subcutaneous CRC PDXs with an overall take rate of 88% (35/40). The mean latency period was shorter in flank engraftment than in neck engraftment (32.7 days vs 62.5 days; 14 - 140 days). A lower latency period was also observed for right colon samples, higher tumour size, higher clinical stage tumours, and for those with lymphatic invasion. PDX models recapitulated the histopathological and molecular features of the patient tumors and regarding IHC-based molecular classification, CRC molecular subtypes highly correlated between patients and their corresponding PDX models. In addition, the poor-prognosis mesenchymal subtype (CMS4) was associated with a high eNOS expression and peritumoral budding growth compared to other subtypes.

## Conclusions

The capacity to define CRC molecular subtypes by IHC in clinically relevant preclinical models provides an opportunity to validate the feasibility of this practical approach for improving targeted therapies.

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