



## PDAC Organoids Mimic Patient Disease

Romero-Calvo *et al.* \_\_\_\_\_ Page 70

Three-dimensional organoid systems have emerged as potentially powerful tools to understand cancer biology, and they show promise as personalized models that can be used to guide therapeutic decisions. However, their clinical use is limited by the lack of in-depth characterization of their morphological and genetic features. In this study, Romero-Calvo and colleagues describe comprehensive histopathological, genomic and transcriptomic comparisons between patient-derived pancreatic ductal adenocarcinoma (PDAC) organoids and their corresponding primary tumors. The organoid models recapitulate patient-specific structural and molecular features, making them potentially valuable in understanding the etiology and pathogenesis of the patient's tumor. Further, patient-specific drug sensitivities are also reproduced by the organoids, suggesting their utility as personalized models for drug testing. These findings potentiate patient-derived organoids as a promising system for precision oncology.

## Classification of BRCA1 BRCT Missense VUS

Petalot *et al.* \_\_\_\_\_ Page 54

Although the two major breast and ovarian cancer predisposing genes, *BRCA1* and *BRCA2*, were identified over 20 years ago, new variants are still identified daily. Half of them do not show a premature stop signal, but remain classified as variants of unknown significance (VUS), which does not guide the management of the index case and her relatives. Their classification is a major challenge for the diagnosis of breast and ovarian cancer predisposition. More than 1,000 different VUS of each gene are to be classified, each constituting an independent classification effort. The functional complexity of the *BRCA1* and *BRCA2* macroproteins is such that the silico VUS classification tools are insufficient. This project aims to strengthen the knowledge of the impact of large sets of *BRCA1* VUS on cancer risk. The current study identifies structural and functional defects in *BRCA1* VUS, to improve their classification and support clinical interpretation and therapeutic selection. *BRCA1/2* VUS are emblematic of the interpretation difficulties faced by geneticists with the explosion of next generation sequencing.

## CXCR7 Promotes Prostate Cancer Progression

Rafiei *et al.* \_\_\_\_\_ Page 263

C-X-C chemokine receptor type 7 (CXCR7), a seven-transmembrane G-protein-coupled chemokine receptor, is an androgen receptor (AR)-repressed gene in prostate cancer cells. Derepression of CXCR7 expression, after androgen deprivation therapy, is one of the survival mechanisms for castration-resistant prostate cancer (CRPC). This study suggests that CXCR7 plays more important roles than well-studied CXCR4 in CRPC development and progression. Both CXCR4 and CXCR7 are druggable targets. However, targeting CXCR7, in combination with anti-androgen, inhibits CRPC growth and potentially prevents incurable bone metastasis.

## TGFβ1 Inhibits MCM Assembly

Nepon-Sixt and Alexandrow \_\_\_\_\_ Page 277

Transforming growth factor β1 (TGFβ1) causes cell cycle arrest by suppressing transcriptional events and inhibiting activation of Cdc45-MCM-GINS (CMG) helicases. Notably, the retinoblastoma (Rb) tumor suppressor plays a pivotal role in both these mechanisms. However, in Rb-deficient cells, TGFβ1 remains potent at eliciting growth arrest due to a previously unknown ability of TGFβ1 to inhibit assembly of MCM hexamers. Overexpression of the Cdt1 oncoprotein promotes MCM assembly and abrogates this process, inducing G<sub>1</sub>-S transit in the presence of TGFβ1. These results demonstrate additional redundancy in the mechanisms underlying TGFβ1 growth arrest and highlight how cancer cells can overcome normal growth-regulatory signals.

# Molecular Cancer Research

## Highlights of This Issue

*Mol Cancer Res* 2019;17:1.

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