Patient-derived organoids as a reliable screening platform for assessing ADC efficacy and specificity

HUB ORGANOIDS

Poster 241

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Abstract

Antibody-drug conjugates (ADCs) are a new class of pharmaceutical drugs designed to deliver cytotoxic agents to cells expressing specific antigens selectively. Based on Paul Ehrlich's "magic bullet" concept, ADCs are designed to target cancer cells, minimizing systemic toxicity typical of conventional chemotherapy. ADCs structurally consist of a particular monoclonal antibody linked to a cytotoxic agent. Patient-derived Organoids (PDOs) provide a new tool for studying cancer biology and patient stratification. PDOs are adult stem cell-based culture systems maintaining the patient-specific genetic and phenotypic characteristics, including surface marker expression. The work presented here shows the suitability of the organoid platform for performing ADC screening. Organoids were selected based on their target-antigen (TA) expression, assessed by flow cytometry and RPKM. Organoid killing was assessed with a viability assay (luciferase-based readout) after five days of treatment. Results of viability screening show a correlation between TA-targeting ADC-induced organoid killing and TA expression in the organoids. These results reveal that PDOs hold value for the preclinical development of ADCs and for evaluating their tumor specificity.

Method

- Target-antigen expression was confirmed by RT-qPCR and flow cytometry analysis performed on three different tumor-derived PDOs (**Figure 1**).
- ADC-induced organoid killing was evaluated in a viability assay using a luciferase-based readout (ATP measurement) after 5 days of treatment (**Figure 2**).

Results

Figure 1 | Target antigen expression in three different colon PDOs

Expression levels of target-antigen (TA) were assessed by (**A**) RT-qPCR and (**B**) flow cytometry. PDO1 had a higher expression of TA than PDO2 and PDO3. For RT-qPCR, data represents the mean ± standard deviation (SD) of three technical replicates.

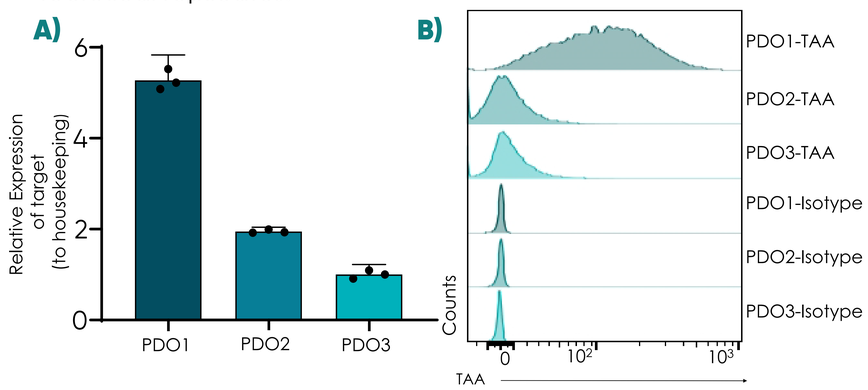
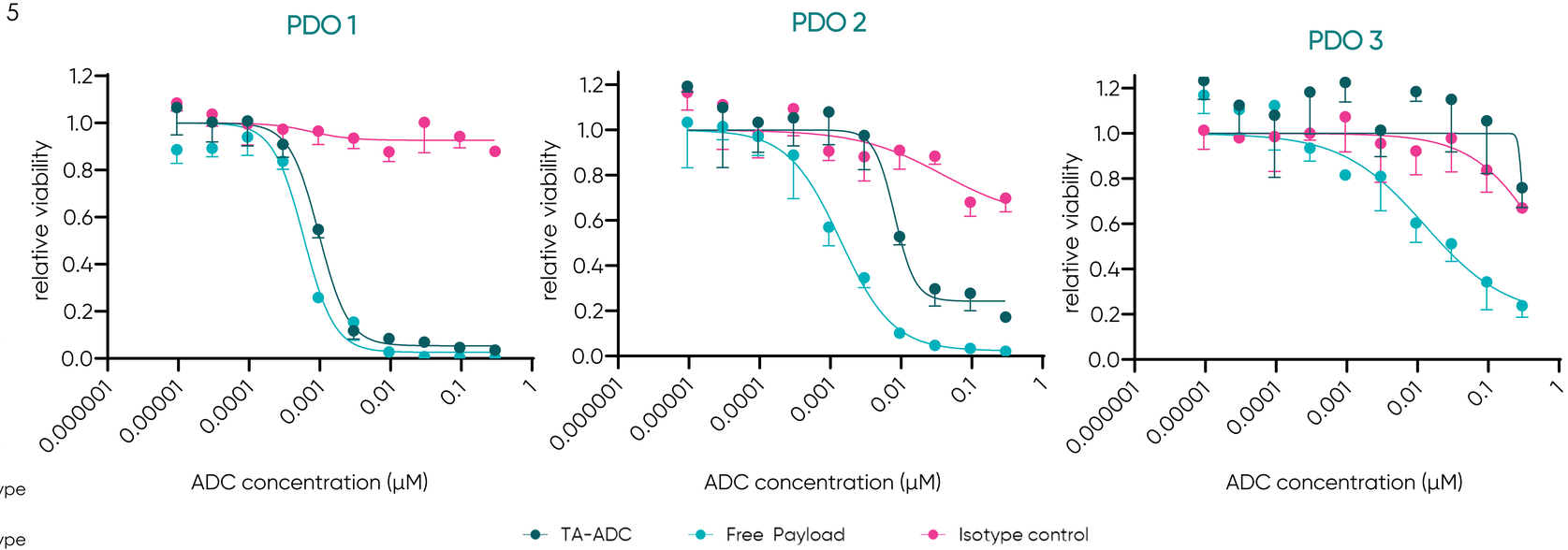


Figure 2 | CRC PDO models show differential responses to ADC treatment

Dose-response of a TA-ADC directed against target antigen expressed in three different PDOs (Figure 1). In the viability assay with a luciferase-based readout, the free payload (positive control) and the isotype control antibody (negative control) were included as controls. Data represents mean ± SD from technical triplicates.



Conclusion

HUB Organoid Technology allows adult stem cells to proliferate and organize into three-dimensional organotypic structures, representing original tissue genetics and phenotype, including tumor-specific antigens. Patient-derived organoids are generated from normal and malignant tissues, allowing the assessment of the tumor-specificity of drugs. Using our extended collection of tumor-derived organoids from solid cancers, we assess the efficacy of ADCs targeting tumor antigens.

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