

Modeling of standard vs. novel, oncogene-specific therapeutic protocols in digestive system cancers organoids.

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OVERVIEW

Digestive system cancers remain a significant clinical challenge. By using patient-derived cancer organoids and applying drug sensitivity and organoid assembly assays, we tested new therapeutic protocols developed in our laboratory, comparing them to standard chemotherapy. Organoid model allowed to monitor how different parameters of the 3D culture respond to the used protocols.

INTRODUCTION

Pancreatic and colon cancers are among the most common causes of death in Polish and EU neoplasia patients. Improvement of patient outcomes in these diseases requires personalized therapeutic approaches and a larger choice of treatment protocols. A broad aim of this project is to develop and test new experimental therapeutic protocols using patient-derived cancer organoids.

Experimental drug combination	Targets	Mutational and oncogene context	Original publication/project
APR-246 + Carfilzomib	Mutant p53 + proteasome	Gain-of-function mutant p53	Walerych et al. Proteasome machinery is instrumental in common gain-of-function program of the p53 missense mutants in cancer. Nat Cell Biol 2016
MKT-077/ CB6644 + Selinexor	HSPA9/ RUVBL1-2 helicases + XPO1	Mutant TP53 and/or mutant KRAS and/or MYC hyperactivation	Grześ et al. A common druggable signature of oncogenic CMYC, mutant KRAS and mutant p53 reveals functional redundancy and competition of the oncogenes in cancer. bioRxiv 2023.12.20.572548
Carfilzomib + VER-155008 + Nelfinavir	HSP70 + proteasome + NRF1	none	Oroń et al. The molecular network of the proteasome machinery inhibition response is orchestrated by HSP70, revealing vulnerabilities in cancer cells. Cell Rep 2022

METHODS

- ▷ Patient-derived colon and pancreatic cancer organoids
- ▷ Organoid Drug Sensitivity Assay
- ▷ Organoid Assembly Assay based on Spinning Disc Microscopy
- ▷ ImageJ with TrackMate and GraphPad Prism software used for analysis

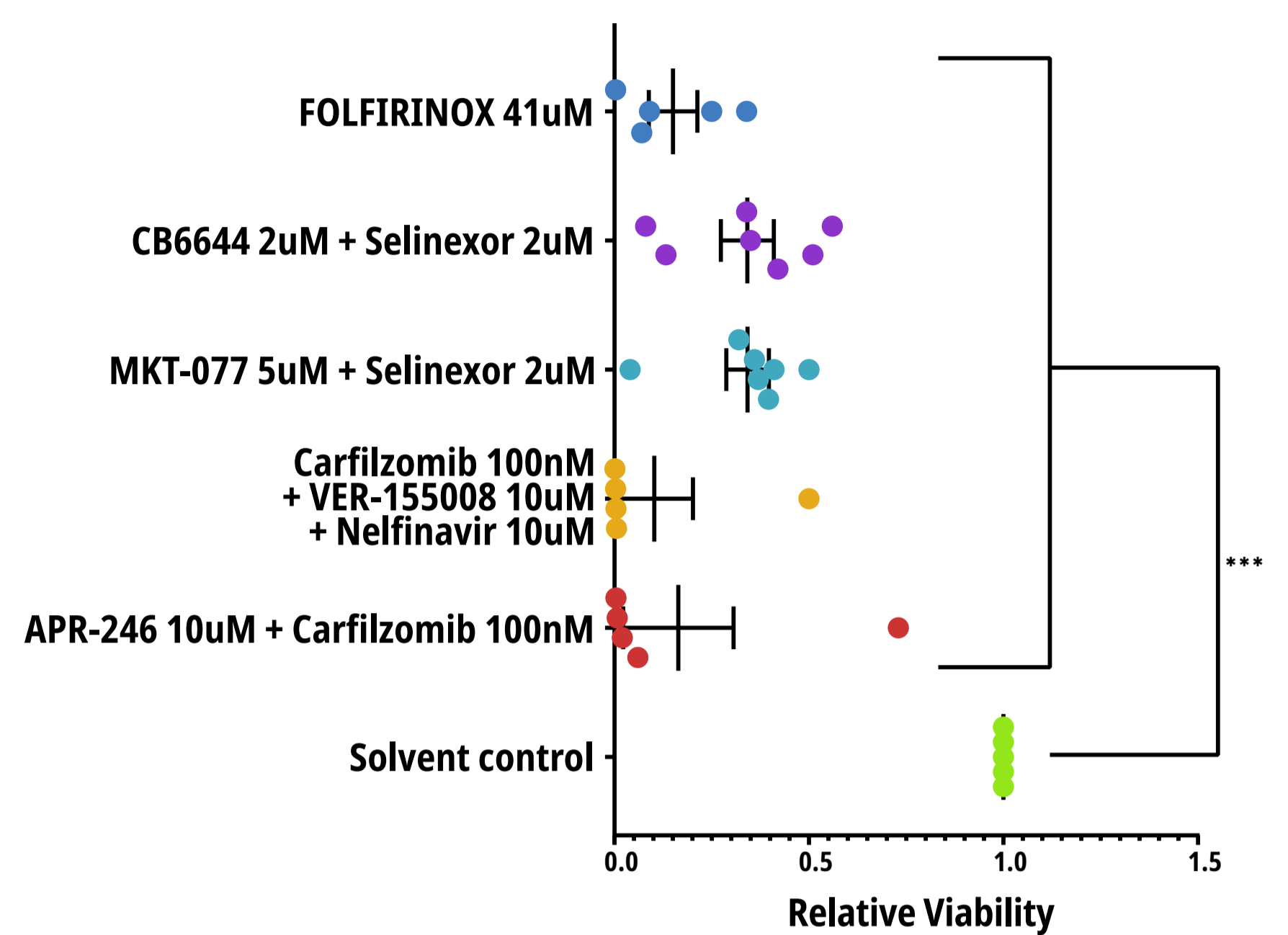
RESULTS

- The efficiency of experimental therapeutic protocols matched or surpassed standard chemotherapeutic protocols in killing cancer organoids characterized by either TP53 mutations, KRAS mutations or MYC activation.
- Organoid assembly assay allowed to distinguish effects on cell migration in 3D environment and formation of organoids in time. The used drug combinations decreased only the assembly, while sgRNA-mediated mutant p53 knockdown affected the migration.

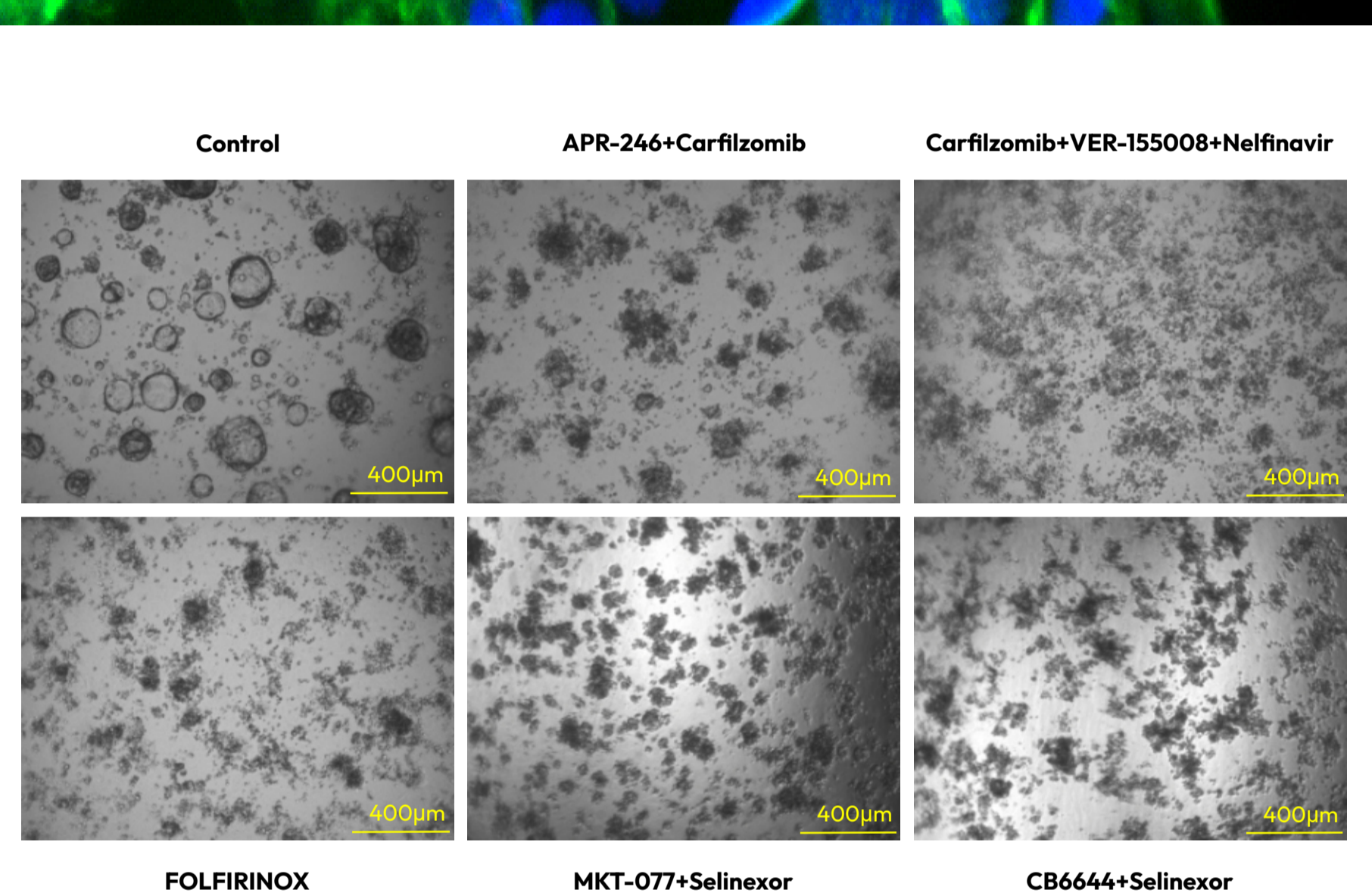
CONCLUSIONS

- Heterogeneous colon and pancreatic cancer organoid model confirms high efficacy of novel pre-clinical targeted drug combinations earlier developed using 2D cancer cell line cultures.
- Organoid assembly assay allows to analyze and distinguish how cell migration and cell group formation towards organoids may be differentially affected by anti-cancer drug treatment and direct oncogene targeting.

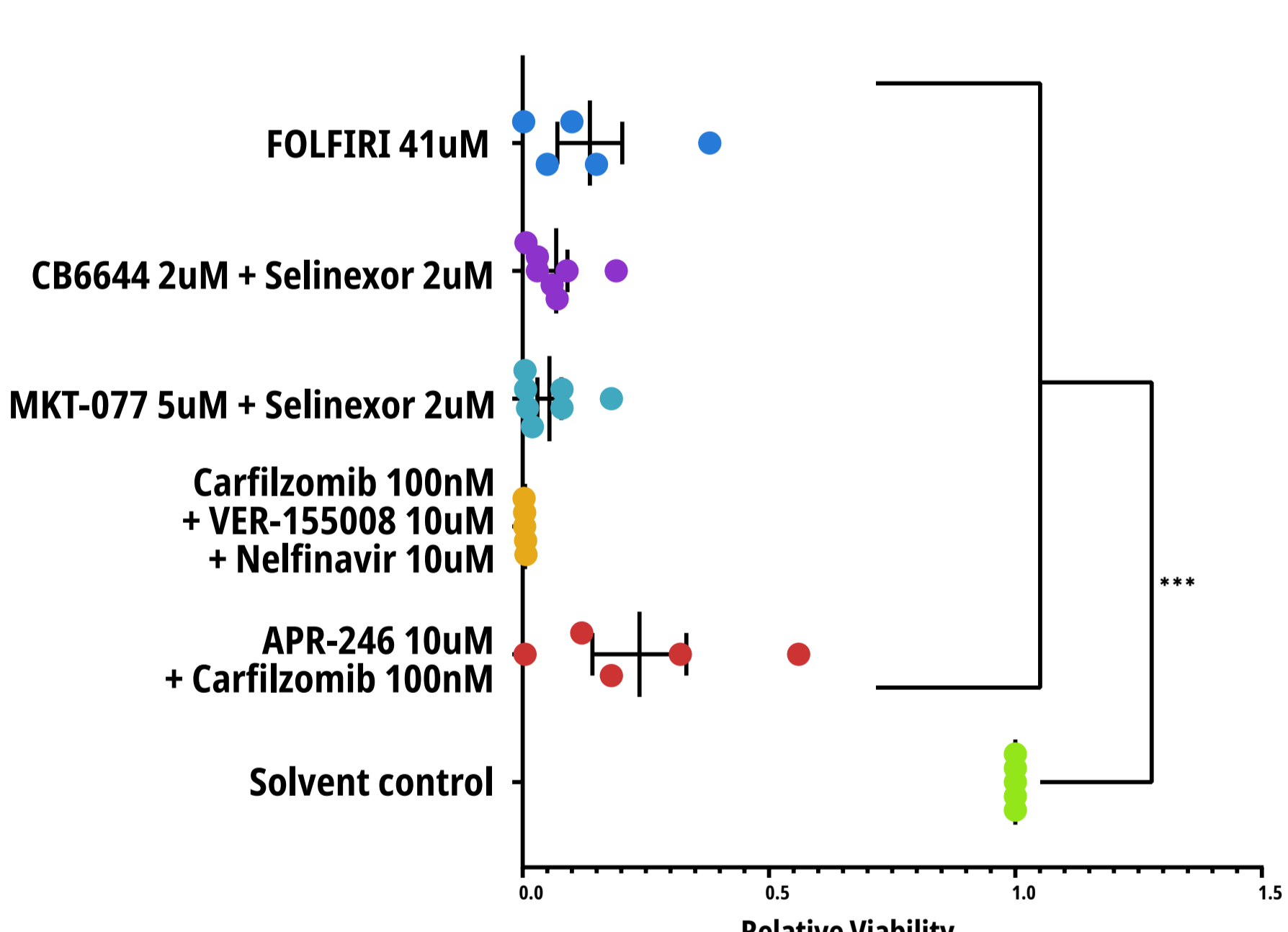
Pancreatic cancer organoids drug test



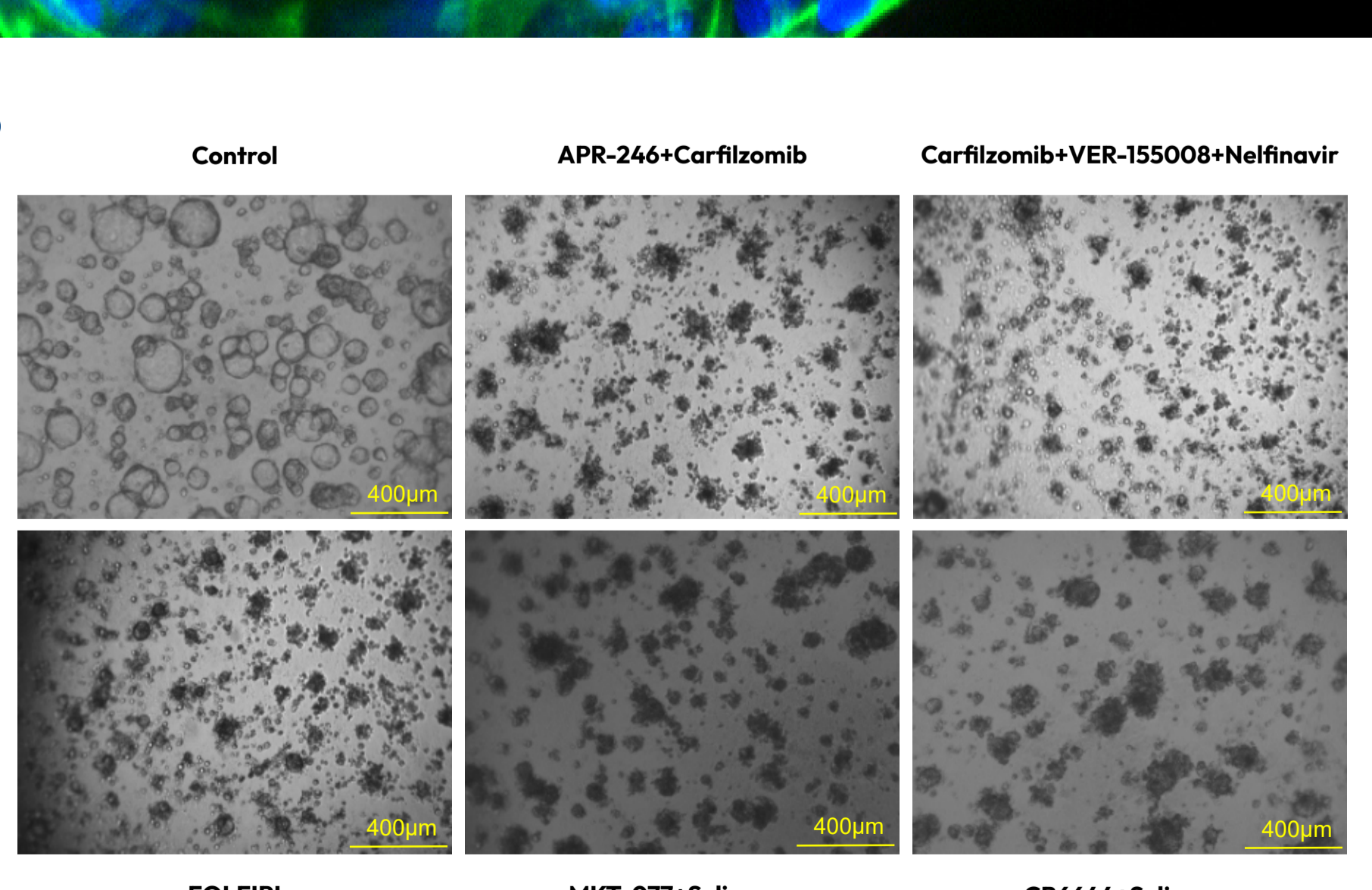
Pancreatic Cancer Organoids



Colon cancer organoids drug test



Colon Cancer Organoids



Organoid Assembly Assay

