Stratification of cell therapies in solid tumor organoids using deep learning-derived imaging metrics

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INTRODUCTION

High-throughput screening of immunotherapies is crucial for identifying promising candidates against various cancer indications and accelerating the pre-clinical development of cell therapies. Patient-derived organoid (PDO) models, co-cultured with cell therapies and combined with deep learning-based computer vision facilitate large-scale, automated image analysis to extract quantitative metrics of treatment efficacy and cell biology effects.

METHODS

- **Time-lapse confocal microscopy** was used to record images of a large cohort of **16 cell therapies co-cultured with 60 different PDO** lines across 9 cancer indications.
- A convolutional deep neural network (CNN) was trained to perform **label-free predictions of PDO viability** from brightfield images only, at each timepoint.
- Deep learning **segmentation models** (UNET) were further used to **co-localize tumoroids and immune cells** in brightfield images, and extract a set of interpretable **features** (**phenotypes) of response**.

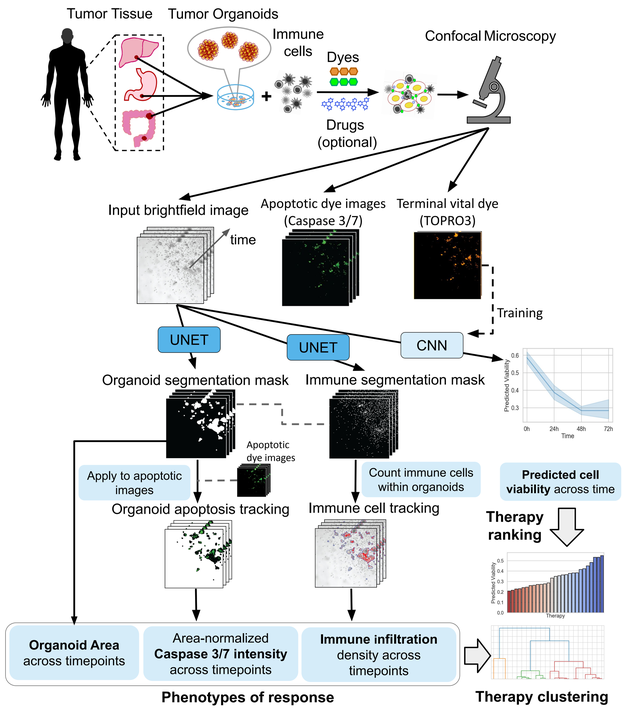

Figure 1. Imaging and modeling workflow

SUMMARY

- We present a highly scalable pipeline based on brightfield imaging to quantify treatment efficacy and provide insights into the pharmacokinetics and activation mechanisms for specific immune cell therapies.
- Stratification of therapies using CNN-based label-free viability prediction shows high concordance with ground truth, eliminating the need for fluorescent vital dye stains and enabling dynamic response readouts without impairing cell function.
- Interpretable features of response cluster therapies into functional groups, capturing differential mechanistic effects such as infiltration and apoptosis dynamics and offer a more comprehensive view of therapy efficacy compared to standard terminal viability readouts.

RESULTS

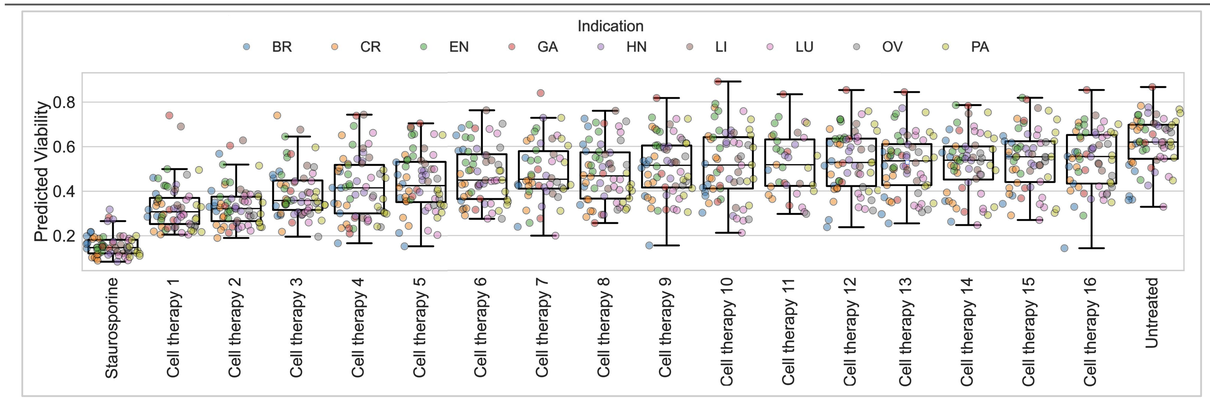

Figure 2. Stratification of therapies across all PDO lines and treatments by predicted terminal viability. Data are sorted by the median viability. Cell therapy viabilities span a wide range of values encompassed by the positive (Staurosporine) and negative (untreated) controls.

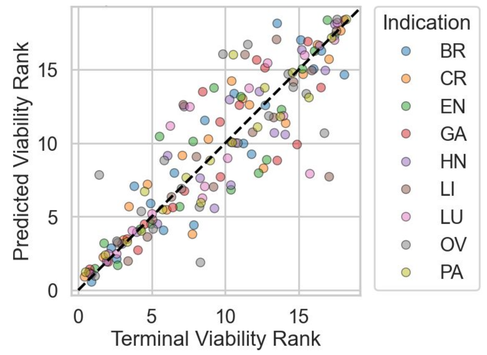

Figure 3. Ranking of cell therapies using the terminal predicted viability is highly correlated with the ground truth ranking obtained by terminal vital dye stain (Spearman correlation=0.88).

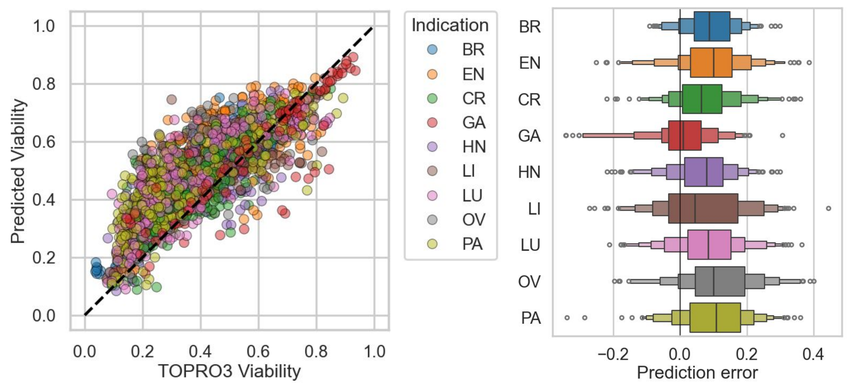

Figure 4. (left) Viability predictions from the convolutional deep network were highly concordant with those obtained from the TOPRO3 terminal vital dye stain (Pearson r=0.80, RMSE=0.14), with a distribution of errors largely uniform across the 9 indications **(right)**.

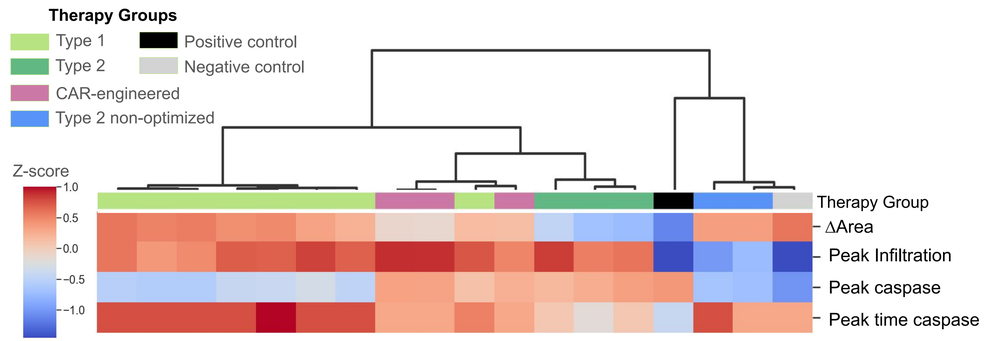

Figure 5. Phenotypes of response cluster therapies into consistent functional groups of immune cell types (1, 2, CAR-engineered). Phenotypes are derived from segmentation models and quantify changes in tumoroid area, cell apoptosis intensity and its temporal dynamics, as well as immune infiltration across all PDO lines. **Type 2** and **CAR-engineered** therapies inhibit growth, show higher infiltration and peak caspase, as well as lower peak apoptosis time than **Type 1**, suggesting a faster and more targeted tumor killing action. Negative controls and **non-optimized Type 2** therapies show lower caspase and infiltration, as well as increased PDO area, suggestive of both decreased killing and cytostatic action.

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