A High-Throughput In Vivo Platform (Perturb-map) Accurately Models Patient Immunophenotypes and Identifies Therapeutic Targets

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Introduction

Targeting the right patient population with any given therapeutic agent largely remains an unsolved problem, and successes in pre-clinical models often do not translate into positive outcomes for patients. Leveraging advances in multi-omics spatial profiling, we have trained foundational multimodal machine learning models that have deepened our understanding of human disease and further demonstrated that the handful of mouse models used for a large proportion of pre-clinical studies seldom recapitulate human biology and are unreliable predictors of clinical success.

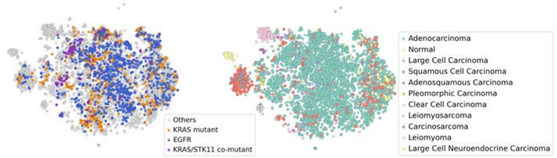

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Fig 1. Patient stratification with Octopia: sample-level embeddings reveal disease heterogeneity across cancer histology and genetic background.

Methods

Our high-throughput in vivo platform, based on Perturb-map, allows for multimodal phenotyping of 100s of tumor clones (and genetic perturbations) in the same animal. Perturb-map relies on a Protein Barcode (Pro-Code): hundreds of protein reporters created by combinatorial tagging of a scaffold protein. Each Pro-Code is linked to a specific genetic perturbation (CRISPR gRNA, point mutation, gene deletion,…). Pro-Codes can be introduced into any orthotopic model and their identification is compatible with multimodal tissue profiling. The Perturb-map pipeline thereby enables scaling up in vivo experimentation by orders of magnitude, without compromising high content tumor phenotyping.

Results

Perturb-map Spatially Resolves Genotype and Phenotype from the Same Sample and Reveals Distinct Tumor Immunotypes

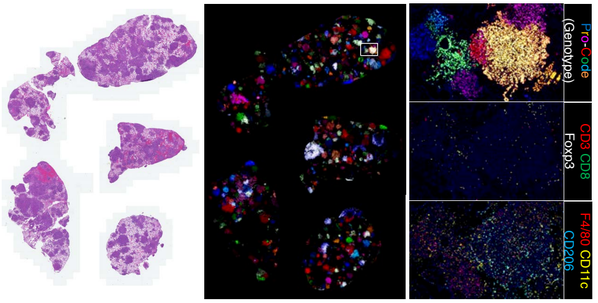

Fig 2. Representative example of 1 animal inoculated with a library of individual clones from a NSCLC pre-clinical model (KP, with mutations in KRAS and p53). Each clone is barcoded by a specific Pro-Code associated with a unique genetic perturbation. Multiplex immunofluorescence identifies the genetic perturbations and the TME composition associated with each individual tumor.

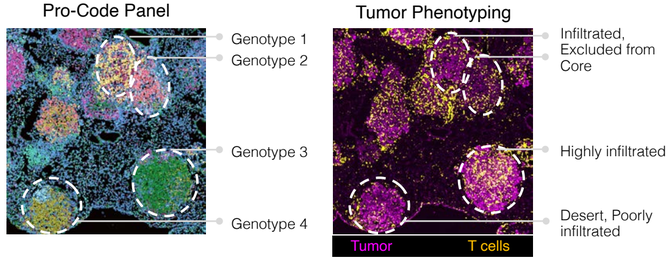

Fig 3. Four tumors, each associated with a different genetic perturbation, show different archetypes of immune infiltration (Desert, Excluded, Infiltrated) in the same animal.

Perturb-map Identifies Conserved Immunotypes Between Mouse and Human Tumors

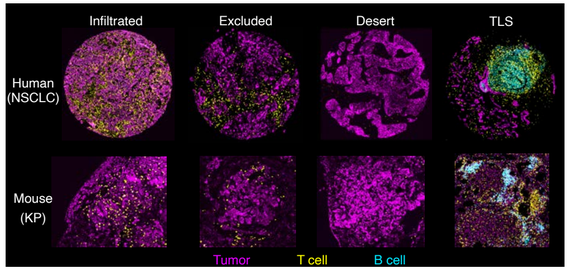

Fig 4. Selected examples of tumor immunotypes conserved between mouse and human tumors. By phenotyping tumors from hundreds of genetic perturbations, we identified specific genotypes in mice that reproduce tumor immunotypes found in patients, and a variant of the KP mouse model that develops tertiary lymphoid structures (TLS), which are found in patients but not in the baseline KP model.

Mapping tumor genotypes to phenotypes at scale

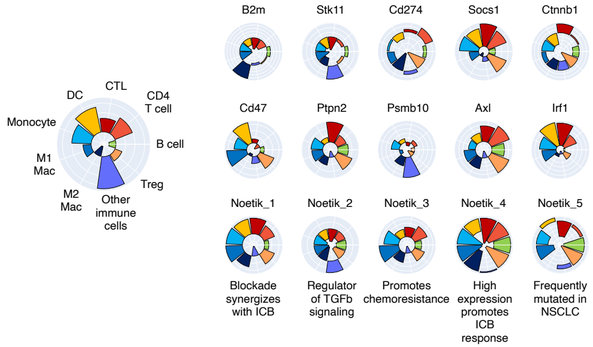

Fig 5. Representative sample from our Perturb-map dataset. Each radial plot represents the enrichment (outward) or depletion (inward) of a specific immune population in tumors carrying a gene KO.

Conclusion and Future Direction

Our high-throughput in vivo platform addresses 2 important unmet needs in drug development. First, we can generate at scale mouse models that better reflect human tumor biology. Second, we can map interactions between drugs and genotypes with multimodal phenotyping in a single experiment. We are currently building a dataset mapping interactions between 600+ genetic perturbations and 4 therapeutic interventions. ML models trained on both patients and mouse datasets will contribute to improving translatability from mouse to human.

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