Single Mouse Preclinical Trial (SMPT): a tool for translational research

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INTRODUCTION

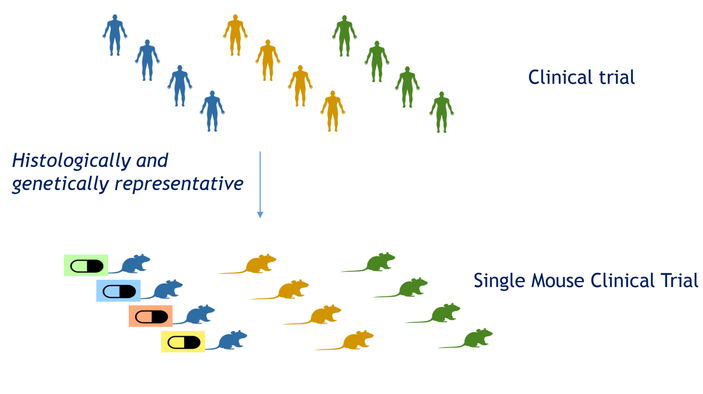
Roughly, 85% of preclinical drug candidates entering oncology clinical trials fail to demonstrate sufficient safety or efficacy to gain regulatory approval. Hence, there is a need for experimental systems which better mimic the inter-patient response heterogeneity observed in the clinic.

Patient-derived tumor xenograft (PDX) mouse models have emerged as a relevant oncology research tool to study tumor evolution, drug response, biomarkers, resistance phenomenon and personalized reatments to each patient.

Oncodesign PDX Surrogate Clinical Trial

We will here expose the effectiveness of the Single Mouse Preclinical Trial (SMPT) paradigm for evaluating drug response, as mono or combo therapy using our well-characterized PDX collection.

Based on the "1 PDX tumor/1 mouse/1 treatment" experimental design, a cohort of colorectal and breast PDX models was used to explore response to Standard Of Care (SOC) and combo therapy used in clinic.

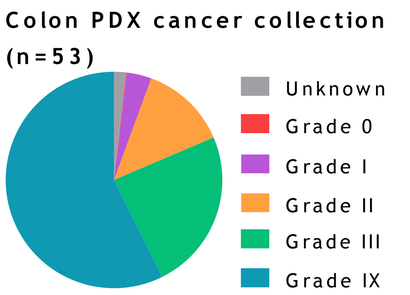


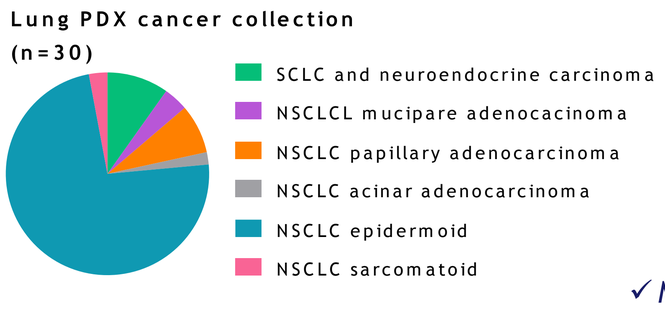
Increase the power of translational research using predictive PDX cohorts reflecting the human tumor heterogeneity and diversity (each model represents 1 patient) to:

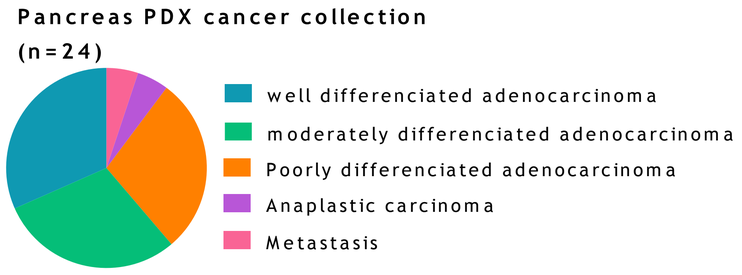
- ✓ Support Go-NoGo decision for early clinical proof of concept
- ✓ Patient stratification - Identify responsive sub-populations
- ✓ Identification of drug resistance mechanism
- ✓ Drug combination evaluation
- ✓ Drug positioning / re-positioning
- ✓ Expansion of clinical indications by exploring other tumor types
- ✓ Biomarker identification and companion diagnostic development
- ✓ With SMPT, increase the power of your translational research with limited cost:
  - -one study with one pathology with several drug candidates
  - -one study with several pathologies with one drug candidate

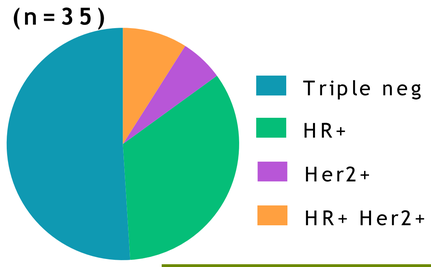
RESULTS

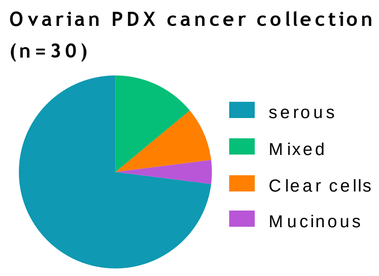
PDX cohots available to design SMPT











- ✓ More than 172 PDX well characterized tumor models are available
- ✓ Highly conserved phenotype and genotype
- ✓ Available annotation:
  - ❖ Patient information (diagnostic and outcome),
  - ❖ Histology
  - ❖ Genomic profile (polymorphism exome seq, RNA seq)
  - ❖ Pharmacological profile to 4 standard of care

IMODI

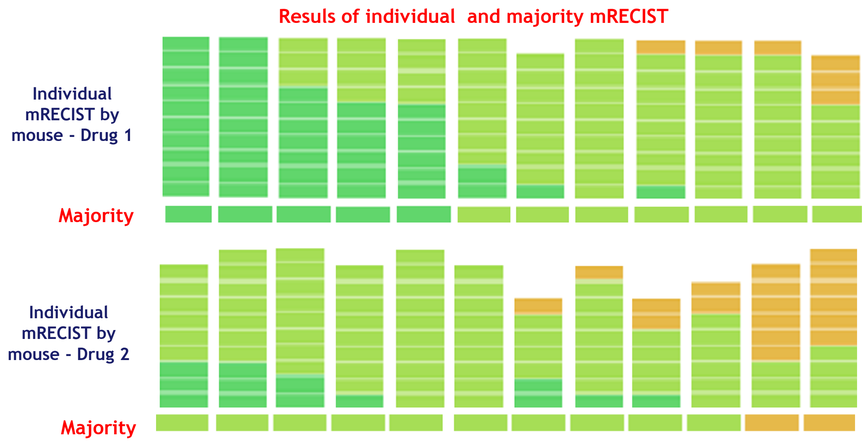
All models were developed in partnership with the members of the consortium IMODI

SMPT validation in breast PDX models

Evaluation of reproducibility of 225 single-animal response data among 24 treatments groups including 12 different breast PDX models, subcutaneously xenografted in 7 to 10 mice per breast PDX treated model.

Readouts were based on RECIST criterias adapted on readouts PDX SMPT
mRECIST : Mouse Response Evaluation Criteria in Solid Tumors.
$\Delta Vol_t = 100x((V_t - V_{initial})/V_{initial})$ was calculated for each animal at each time.
Best Response is the minimum value of ΔVol_t for t≥10 days.
Average of ΔVol_t was calculated for each t from t≥10 days.
Best Average Response is the minimum value of Average of ΔVol_t.

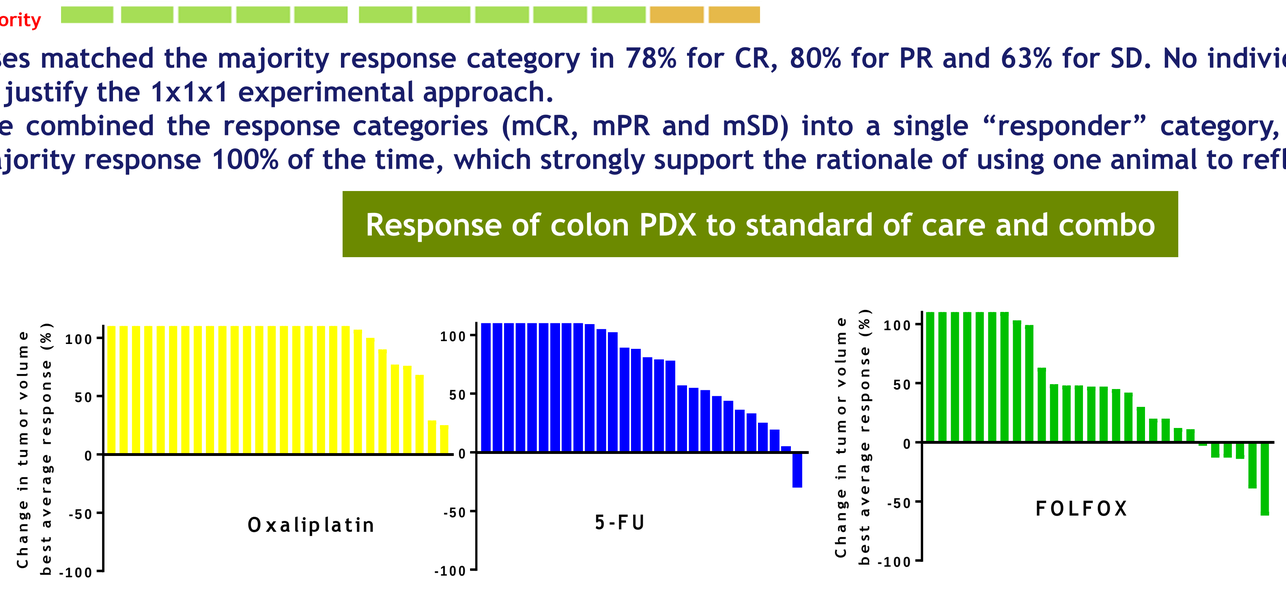
mRECIST	Best response	Best Avg Response
CR (Complete Response)	< -95%	<-40%
PR (Partial Response)	<-50%	<-20%
SD (Stable Disease)	<35%	<30%
PD (Progressive Disease)	not other categorized	



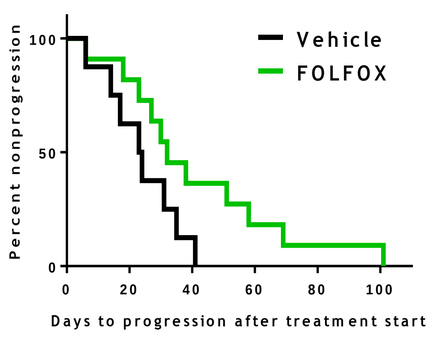
The individual responses matched the majority response category in 78% for CR, 80% for PR and 63% for SD. No individual response were off by more than one mRECIST category. This analysis justify the 1x1x1 experimental approach.
Furthermore, when we combined the response categories (mCR, mPR and mSD) into a single "responder" category, the response calls made on a single mouse were consistent with the majority response 100% of the time, which strongly support the rationale of using one animal to reflect the true response.

Response of colon PDX to standard of care and combo

SMPT study including 27 colon PDXs. Tumor models were treated with SOC alone (5-FU or Oxaliplatin) and FOLFOX (5-FU, Oxaliplatin, folinic acid).



- ✓ FOLFOX increased the tumor response when compared with both mono therapies.



- ✓ Analysis of time-to-tumor-progression (TTP). Kaplan-Meier curves shows TTP, with RTV4 considered as progression.
- ✓ As survival of patient in clinical trials, delay of tumor progression for each treated mouse is used as readout.

CONCLUSIONS AND PERSPECTIVES

- ✓ We demonstrate that individual response matched the treatment group data, supporting the concept to use SMPT.
- ✓ Our SMPT study demonstrates a synergy of combination compared with 2 standards of care alone in a cohort of 27 colon PDX.
- ✓ SMPT aims to predict the clinical outcome of new drug candidates.

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