

IMODI Initiative: a Novel Holistic and Integrative Approach with Patient-Derived Tumor Models

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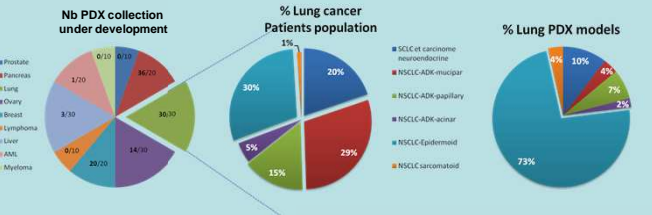
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What about IMODI

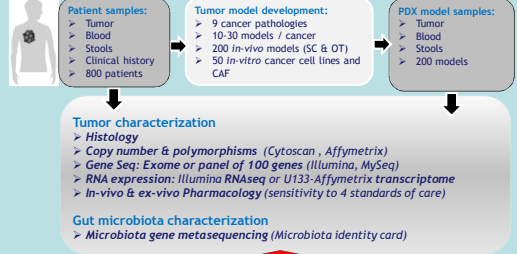
The national IMODI (Innovative MODels initiative) consortium includes 25 partners (pharma, SMEs, academic research labs and clinical centers) with the aim of developing more predictive tools to improve the selection of new effective treatments to combat 9 cancer pathologies. These developments include:

- Collection of *in-vivo* PDX models,
- Collection of *in-vitro* derived cell lines,
- 2D & 3D *ex-vivo* assays,
- In-vivo* humanized models (immune system, liver and tumor stroma),
- Characterization of tumor histology, gene mutations, gene expression, pharmacological responses and gut microbiota,
- Biobanks of tumors, blood, serum and stools,
- Central data base,
- Data mining,

Results on NSCLC lung cancer model developments, characterization and data analysis are presented as an example of the IMODI holistic and integrative approach.

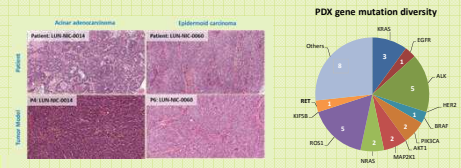


General process



Histology and Genomic Characterization

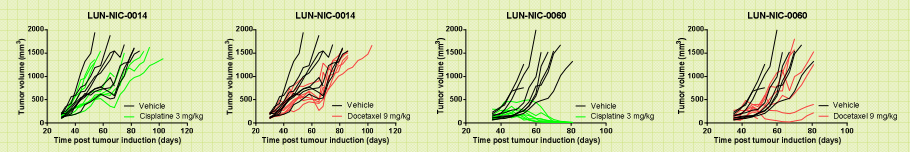
- Example of a well characterized NSCLC PDX collection
- Highly conserved phenotype and genotype
 - Histological PDX profile are in concordance with those observed in patient tumors
 - Major molecular subtypes are represented in the NSCLC collection
 - EGFR-mutated models are under development



In-vivo Pharmacological Response to Standards of Care

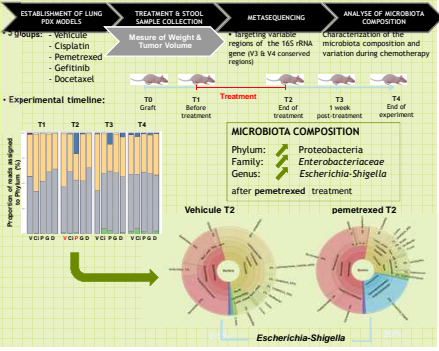
- Significant efficacy of cisplatin and gemcitabine on the LUN-NIC-0060 epidermoid model
- Marginal activity of gefitinib on the LUN-NIC-0014 acinar adenocarcinoma model (EGFR wt, KRAS wt, BRAF wt, ALK wt, ROS1 wt)
- LUN-NIC-0014 PDX response to cisplatin and docetaxel correlates with patient outcome (non responsive to cisplatin + docetaxel)

Drug	ΔT/ΔC (%) (LUN-NIC-0014)	ΔT/ΔC (%) (LUN-NIC-0060)	Activity
Cisplatin 3 mg/kg	64	-4	High antitumor activity (with regression)
Pemetrexed 75 mg/kg	51	Non-tested	Marginal antitumor activity
Gefitinib 100 mg/kg	37	Non-tested	No antitumor activity
Docetaxel 9 mg/kg	59	75	High antitumor activity (with regression)
Gemcitabine 120 mg/kg	Non-tested	-10	No antitumor activity



RESULTS

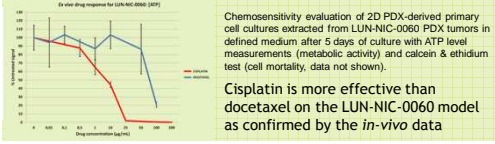
Gut Microbiota Analyses



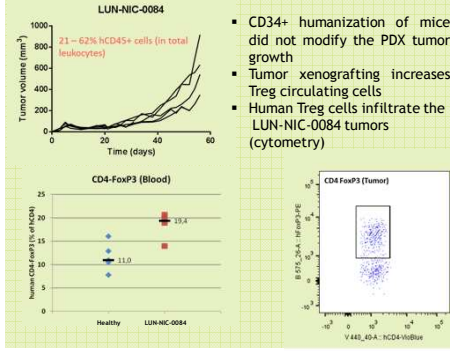
Establishment of In-vitro PDX-Derived Cell Line



Ex-vivo Pharmacology Assay



Tumor Microenvironment Humanization



- CD34+ humanization of mice did not modify the PDX tumor growth
- Tumor xenografting increases Treg circulating cells
- Human Treg cells infiltrate the LUN-NIC-0084 tumors (cytometry)

Conclusion and Perspectives

- IMODI is an operational consortium to continuously deliver new predictive models in regards to specific clinical needs and diversity,
- All results are available for new therapeutic and diagnostic candidate selection,
- IMODI has developed ex-vivo models/assays that can accurately predict in-vivo cisplatin and docetaxel sensitivity in lung PDX models (other drugs and models are under investigation)
- Currently evaluating the effect chemotherapeutic agents can have on microbiota composition, and the impact of the microbiome on drug efficacy and toxicity
- Developing a platform of 2nd generation PDX models with human immune systems; "humanized" mice to better evaluate the next generation of immuno-oncology therapies

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