IMODI initiative: a novel holistic and integrative approach with patient-derived tumor models against pancreatic cancer

#3846

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INTRODUCTION

What about IMODI

The national IMODI (**Innovative MODels Initiative**) consortium including **18 partners** (pharmas, SMEs, academic research labs and clinical centers) aims at developing more predictive tools for better 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 mutation, gene expression, pharmacological responses, gut microbiota,
- **Biobanks of tumors, blood, serum and stools**,
- Central data base,
- Data mining,

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

General process

Patient samples:
- Tumor
- Blood
- Stools
- Clinical history
- 800 patients

Tumor model development:
- 9 cancer pathologies
- 10-30 models / cancer
- 200 *in-vivo* models (SC & OT)
- 50 *in-vitro* cancer cell lines and CAF

PDX model samples:
- Tumor
- Blood
- Stools
- 200 models

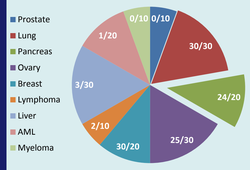
Tumor characterization
- **Histology**
- **Copy number & polymorphisms** (Cytoscan®, Affymetrix)
- **Gene Seq: Exome or panel of >100 genes** (Illumina, MySeq)
- **RNA expression:** Illumina **RNAseq** or U133-Affymetrix **transcriptome**
- ***In-vivo* & *ex-vivo* Pharmacology** (sensitivity to 4 standards of care)

Gut microbiota characterization
- **Microbiota gene metasequencing** (Microbiota identity card)

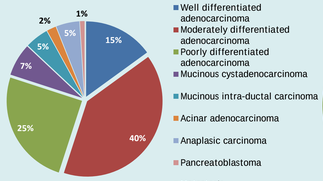
DATA MINING

Identification of biomarkers

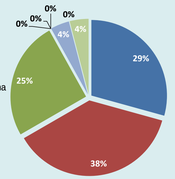
Nb PDX collection under development



Pancreas cancer patient population subtypes



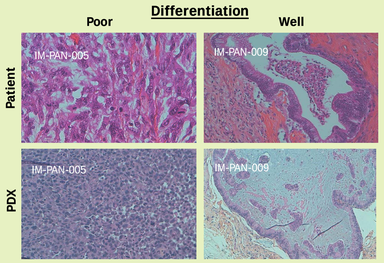
Pancreas PDX models (n=24)



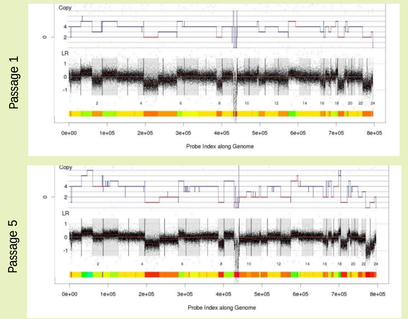
RESULTS

Histological and genomic characterization

Example of well or poorly differentiated pancreatic PDX models
- Histological PDX profiles are in concordance with those observed in the patient's tumor

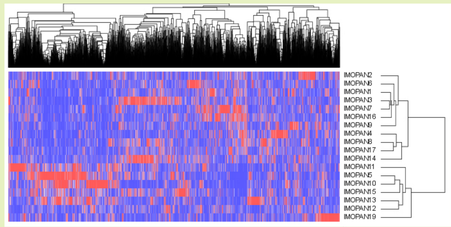


Cytoscan HD Affymetrix analysis
IM-PAN-001



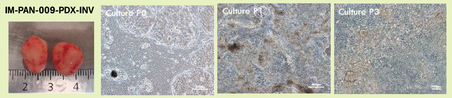
Highly conserved genotype between *in-vivo* passages

Unsupervised RNA expression analysis (Affymetrix U133)

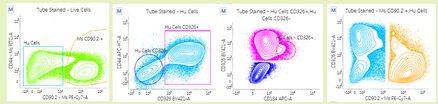


- Different phenotypes of the pancreatic PDX models are represented in the collection,
- NGS analyses (gene seq) did not permit clustering the tumors *(data not shown)*

PDX-Derived cell lines establishment & characterization



Culture at high confluency allowed isolation of epithelial cell organised in colonies. Different morphologies can be observed within the epithelial population. Mouse fibroblast can be depleted to produce a Human only epithelial population. Cell lines currently being characterized.



Before depletion : Ms Fib = 25% Hu Cells = 75%
Hu Cells = 75% CD326+ / 72% CD44+ / 6% CD184+

Mecanic and enzymatic dissociation → Isolation of epithelial colonies with fibroblasts → Expansion caracterisation and banking → Immunomagnetic depletion of mouse fibroblasts → Expansion caracterisation and banking of Human cells

Ex-vivo & *In-vivo* Pharmacological Response to Standards of Care

IC_{50} (µM) of 4 drugs tested in 2D primoculture of cells extracted from PDX models

Model ID	CPT11	GEM	5FU	L-OHP
IM-PAN-001	0	11	>1000	90
IM-PAN-002	0	1	95	8
IM-PAN-003	0	0	160	15.7
IM-PAN-004	16	0	>1000	48
IM-PAN-005	0	0	2	23.5
IM-PAN-006	0	7	62	33
IM-PAN-012	0	0	>1000	400
IM-PAN-013	0	0	205	7.8
IM-PAN-014	0	0	191	158
IM-PAN-015	0	0	>1000	530
IM-PAN-016	0	3	>1000	62

High responder
Moderate responder
No responder

ΔT/ΔC (%) of 4 drugs tested in PDX *in-vivo* models

PDX model	CPT-11	GEM	5FU	L-OHP
IM-PAN-001	69	69	63	59
IM-PAN-002	9	-34	22	105
IM-PAN-003	41	15	62	79
IM-PAN-004	43	18	19	65
IM-PAN-009	60	55	32	44
IM-PAN-013	-59	-52	93	
IM-PAN-014	57	-20	142	120
IM-PAN-015	33	-22	56	115
SA-PAN-0035	31	34	22	
SA-PAN-0077	36	4	53	95
SA-PAN-0092	62	-28	50	73

Nb of sensitives/resistant PDX models *ex-vivo*

DRUGS	LOW	MODERATE	HIGH
Irinotecan	2	4	5
Gemcitabine	4	5	2
5-FU	5	5	1
Oxaliplatin	4	5	2

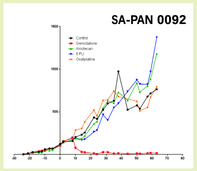
CPT-11 is the most effective drug in a short panel of 11 PDX models tested ex-vivo

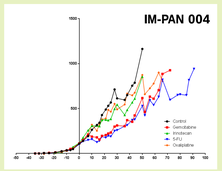
Nb of sensitives/resistant PDX models *in-vivo*

DRUGS	LOW	MODERATE	HIGH
Irinotecan	5	4	2
Gemcitabine	2	3	6
5-FU	7	4	0
Oxaliplatin	9	0	0

GEM is the most effective drug in a short panel of 11 PDX in-vivo models

- The SA-PAN-0092 PDX model is very sensitive to Gemcitatabin while 5-FU, CPT-11 and Oxaliplatine are inactive
- The IM-PAN-004 is marginaly sensitive to Gemcitabin and 5-FU and not sensitive to CPT-11 and Oxaliplatin





CPT-11 – IV – 22mg/kg – Q2Dx3
GEM – IV – 120mg/kg – Q3Dx4
5-FU – IV – 56mg/kg – Q4Dx2
L-OHP – IV – 5mg/kg – Q4Dx2

CONCLUSION AND PERSPECTIVES

- **IMODI is an operational consortium to continuously deliver new representative models in regards to specific clinical needs and diversity,**
- **All results are available for new therapeutic and diagnostic candidate selection,**
- ***Ex-vivo* drug efficacy does not completely correlate with *in-vivo* PDX responses to gemcitabine, 5-FU, cisplatin and Irinotecan,**
- ***In-vitro* PDX-derived cell lines in co-culture with CAF are under characterization for further screening of new compounds,**
- **No correlation between drug sensitivity and genetic characteristics (mutations or CNV) or histological properties was found *(correlation with transcriptomic data under investigation)***

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