ONCOLYTIC VIRUS FOR THE TARGETED (IMMUNO)THERAPY OF PANCREATIC CANCER

Pierre Cordelier, PhD
Team « therapeutic innovation in pancreatic cancer »
Cancer Research Center of Toulouse
GENE THERAPY FOR PDAC

Patient samples

Loss of antitumoral genes expression

Non viral delivery


THERGAP-1
22 patients
Feasibility
Safety
Biomarkers

THERGAP-2
70 patients
Efficacy
Biomarkers

Closed Dec 2020

Clin Trial: NCT02806687

But...

Limited gene delivery efficacy
Only few pathways targeted
Antitumoral immune response
ONCOLOYTIC VIRUS: MODE OF ACTION

Oncolytic virus

Normal cell
- Abortive replication
- Viral clearance

Tumor cell
- Viral replication
- Oncolytic activity

Recruitment of immune cells
- +/- ICB

Inflammation, chemokines production

Viral replication, spread and oncolysis

Tumor eradication
CAN WE SUCCESSFULLY TREAT PDAC PATIENTS WITH ONCOLYTIC VIRUSES?

Open questions:

a. Cellular determinants
b. Mode of action

PDAC primary cells Oncolytic virus

CAN WE SUCCESSFULLY TREAT PDAC PATIENTS WITH ONCOLOYTIC VIRUSES?

Open questions:

a. Immune cells involved
b. ICB combos
CURRENT AND FUTURE DIRECTIONS

**PDAC cell and oncolytic virus crosstalk**

- a. Oncolytic signature for patients' stratification
- b. Increase permissiveness, expose novel vulnerabilities
- c. With AI support, define best therapeutic scenario

**PDAC tumors and oncolytic virus crosstalk**

- a. TME repolarization characterization
- b. Extra gene delivery (ICB, TME disrupting agents...)
- c. Metastasis targeting
THERAPEUTIC INNOVATION IN PANCREATIC CANCER “IMPACT”

P. Cordelier, DR INSERM

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Pr. S. Bertagnoli
Dr F. Gallardo
Dr E. Marcheteau

Roche
Genentech
Fondation de France
Inserm
Toulouse Tech Transfer
PANCREATIC CANCER INTRINSIC PI3Kα ACTIVITY ACCELERATES METASTASIS AND REWIRES MACROPHAGE COMPONENT

Thibault B., Ramos-Delgado F., Pons-Tostivint E., et al

QUESTIONS ASKED

• Oncogenic drivers of metastatic dissemination

• Importance of tumour-intrinsic oncogenic signals to shape a tumour-promoting microenvironment
PI3Kα activation gene signature is increased in metastatic pancreatic cancer patients

**A** Hallmarks

<table>
<thead>
<tr>
<th>Pathways</th>
<th>Corr p value PDACmet vs normal</th>
<th>Corr p value PDACloc vs normal</th>
<th>Corr p value CP vs normal</th>
<th>Corr p value PDACmet vs PDACloc</th>
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<tr>
<td>Complement</td>
<td>0.0002</td>
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<td>Apical junction</td>
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<td>Coagulation</td>
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<td>Glycolysis</td>
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<td>IL-2 STAT5 signaling</td>
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<td>Reactive oxygen species pathway</td>
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<td>Interferon alpha response</td>
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<td>Interferon gamma response</td>
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<td><strong>PI3K Akt mTOR Signaling</strong></td>
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<td>Hedgehog signaling</td>
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<td>Myogenesis</td>
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<td>TNFα signaling via NFKB</td>
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<td>UV response up</td>
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<td>0.0604</td>
<td>0.1190</td>
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**B** PI3K-related Reactome

<table>
<thead>
<tr>
<th>Pathways</th>
<th>Corr p value PDACmet vs PDACloc</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI3K Akt activation</td>
<td>0.0603</td>
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<tr>
<td>PI3K Akt signaling in cancer</td>
<td>0.0741</td>
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<tr>
<td>PI3K cascade FGFR2</td>
<td>0.0162</td>
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</tbody>
</table>
PI3Kα inhibition prevents development of macrometastasis

Pharmacological

BYL719=Alpelisib

Genetic

In situ KPC Mice

Tail vein injection

Tail vein injection
PI3Kα inhibition prevents development of macrometastasis

Pharmacological
BYL719=Alpelisib

Genetic

In situ KPC Mice

Tail vein injection

Tail vein injection
Pharmacological PI3Kα inhibition prevents the acquisition of tumour-associated inflammatory (CD206+) macrophages
Macrophage TNFα secretion is promoted by PI3Kα activity-induced IL-3 in tumour cells.
IN SUMMARY
ANTIBODY THERAPY IN PANCREATIC CANCER: HUGE EFFORTS, MUCH DISAPPOINTMENT AND FUTURE CHALLENGE

Christel Larbouret

Institut de Recherche en Cancérologie
“Drug resistance and new cancer treatment”
Robust target selection

- Well understood role in tumor biology (initiation and progression of PC)
- Near exclusive expression in the tumor vs normal tissues
- Avoid secretion into circulation

Targets of antibodies that have undergone pre-clinical evaluation in pancreatic cancer

![Diagram of potential therapeutic targets in pancreatic cancer](image)
Targets of antibodies that have undergone clinical evaluation (phase I/II) in pancreatic cancer

Arias-Pinilla GA, Cancers 2021; Boland AJ, BBA 2021
Implicated in metastasis and resistance to therapies (chemo or targeted)

Antibody combination (simultaneous targeting of signaling pathways- heterodimers) – inhibition of escape response
Anti-EGFR + anti-HER2 antibody combination

Pancreatic tumor xenograft (K-ras M)

Effect independently of Kras and in first and second line of treatment Pan-HER in GR PDx pancreatic models (Rabia E, Mabs 2021)
33 patients evaluable for efficacy: **27% of stabilization**
- Correlation between the **OS and the cutaneaous toxicity**
- **Doses of cetuximab and trastuzumab**
- Second or more lines of treatment
- No biomarker
Targeting the NRG1/HER3 pathway in tumor cells and CAF
With an anti-neuregulin 1 antibody

Orthotopic Pancreatic tumor xenograft (mix CAF/TC))

Ogier C, Larbouret C. Cancer letters, 2019
Challenge and future perspectives with antibody therapeutics in PC

- Promising pre clinical studies but disappointing clinical benefit. Why?
  - heterogeneous nature of PC
  - identify biomarkers of therapeutic response
  - innovation is required to develop models reflected molecular aspects of PC

- Physical barrier and effective dose of antibody

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Hoogstins CES et al. *Ann Surg Oncol* 25:3350-3357, 2018 and Vahrmeijjer AL, personnal communication
Challenge and future perspectives with antibody therapeutics in PC

• Promising pre clinical studies but disappointing clinical benefit. Why?
  - heterogeneous nature of PC
  - identify biomarkers of therapeutic response
  - innovation is required to develop models reflected molecular aspects of PC

• Physical barrier and effective dose of antibody

• Effective dose and injection sequence of each antibodies need to be optimized

• Improved Ab efficacy: antibody drug conjugated (Bourillon L, Int journal of Cancer 2019)

• Simultaneous targeting of signaling pathways, tumor stroma and immune check point inhibitors (Labex Mabimprove- PhD)