FONDATION ARC POUR LA RECHERCHE SUR LE CANCER
Reconnue d'utilité publique

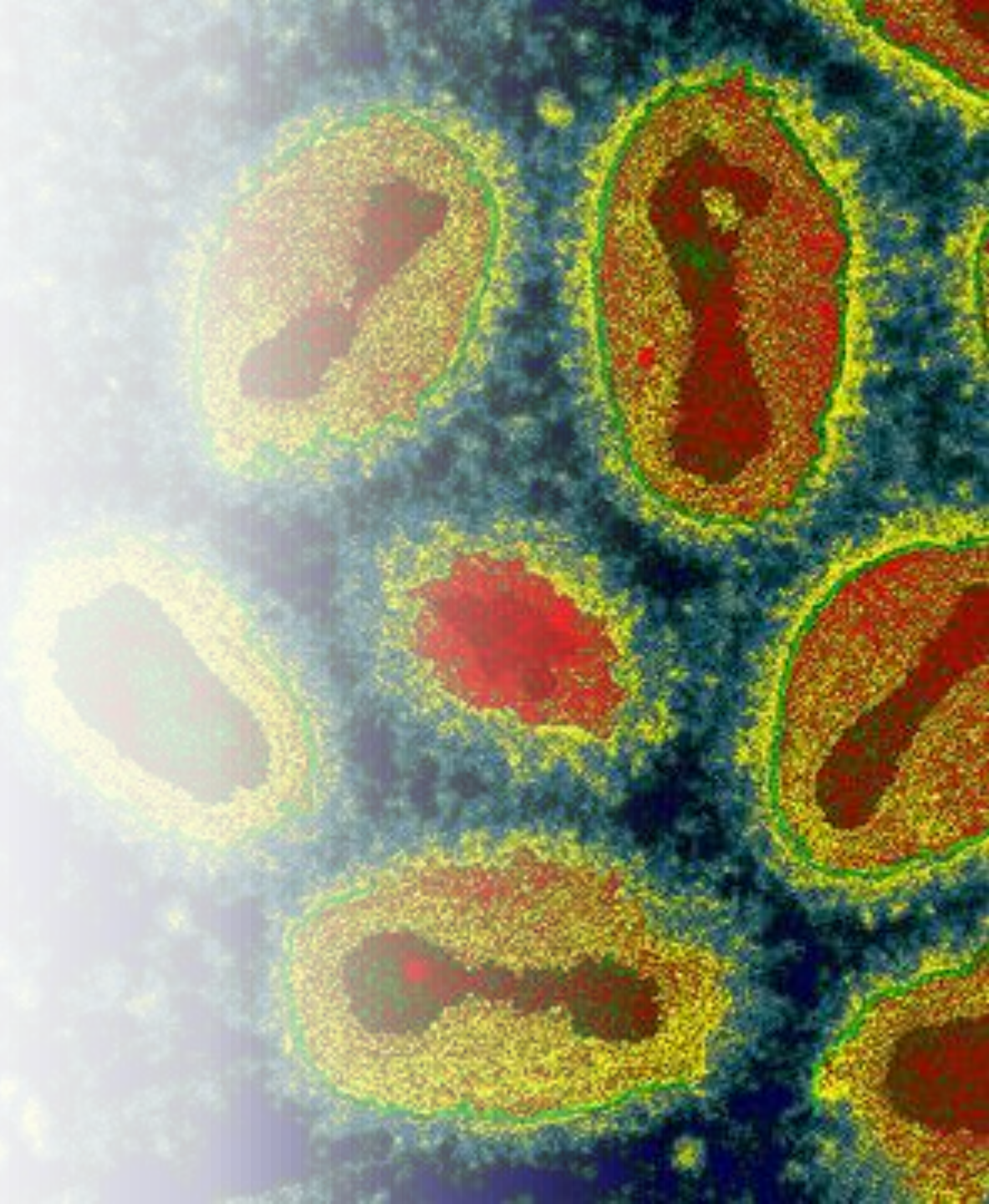
ONCOLYTIC VIRUS FOR THE TARGETED (IMMUNO)THERAPY OF PANCREATIC CANCER

Pierre Cordelier, PhD

Team « therapeutic innovation in pancreatic cancer »

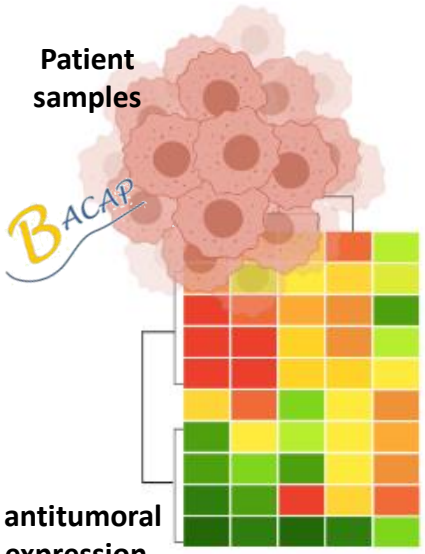
Cancer Research Center of Toulouse

CRCT
Centre de Recherches en Cancérologie de Toulouse
ONCOPOLE



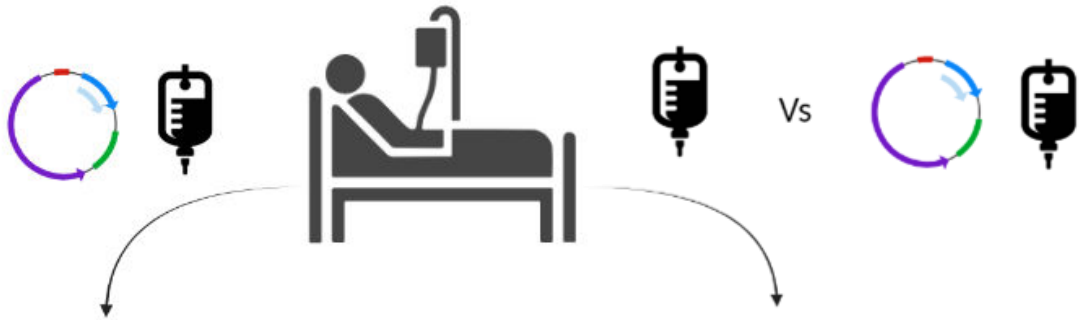
GENE THERAPY FOR PDAC

Patient samples



Loss of antitumoral genes expression

Non viral delivery

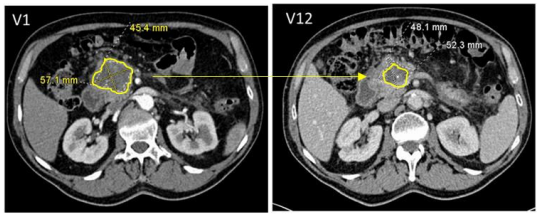


THERGAP-1
22 patients
Feasibility
Safety
Biomarkers

THERGAP-2
70 patients
Efficacy
Biomarkers

Closed Dec 2020

Clin Trial: NCT02806687



Baseline

Two months
Post gene therapy

But..
- Limited gene delivery efficacy
- Only few pathways targeted
- Antitumoral immune response

PNAS 1996, 2001, Hum Gene Ther 2006, Mol Ther 2007, 2015, 2019, Int J Mol Sci. 2017, BMC cancer 2018, Nat Rev Gastroenterol Hepatol. 2020

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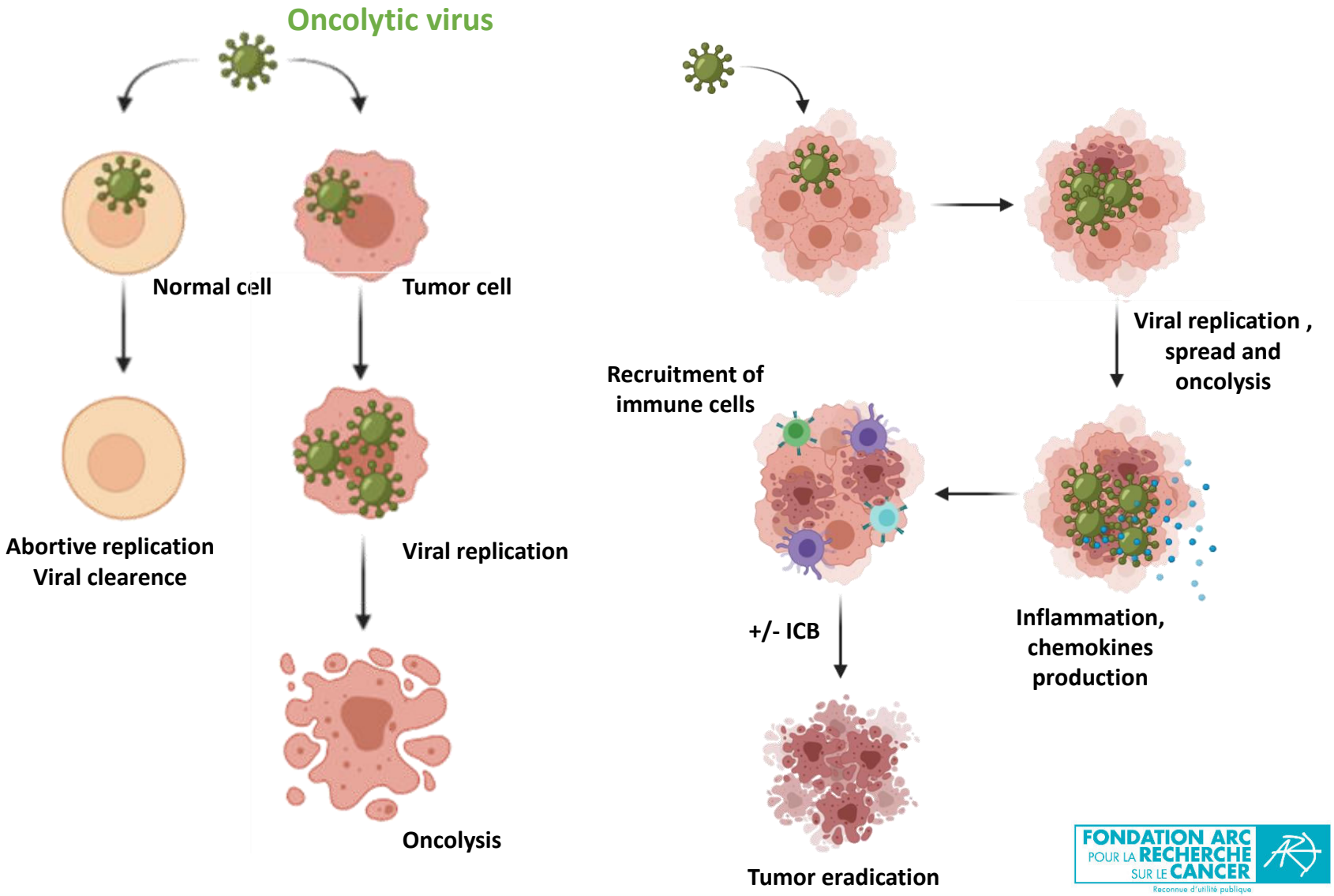
ONCOLYTIC VIRUS: MODE OF ACTION



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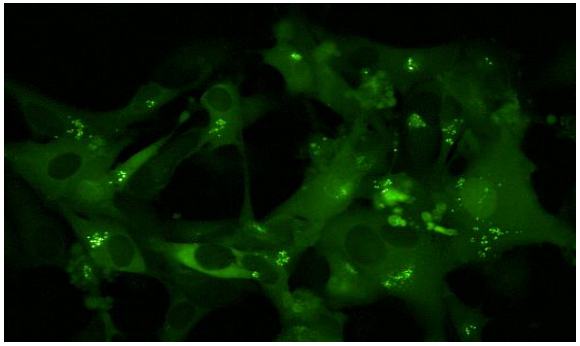
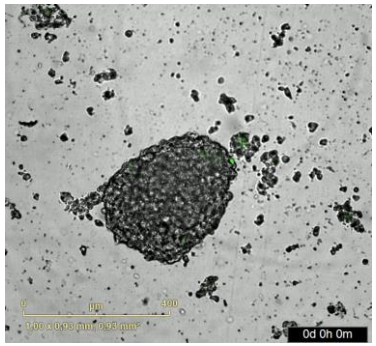
CAN WE SUCCESSFULLY TREAT PDAC PATIENTS WITH ONCOLYTIC VIRUSES?



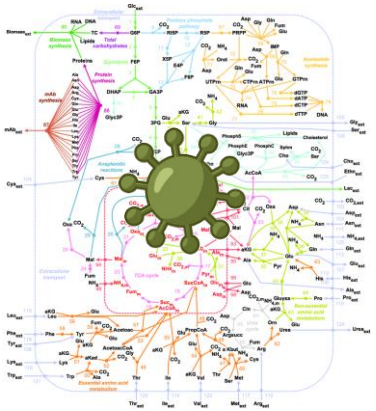


PDAC primary cells **Oncolytic virus**

Open questions :

a. Cellular determinants

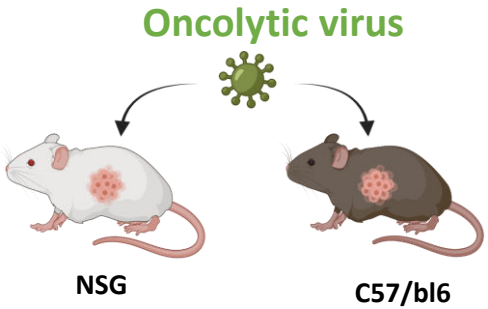
b. Mode of action

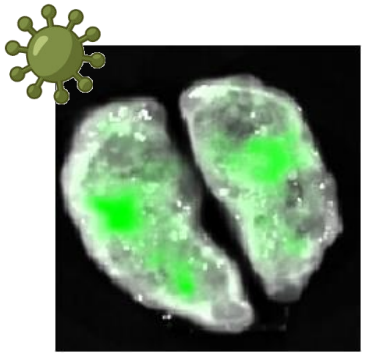


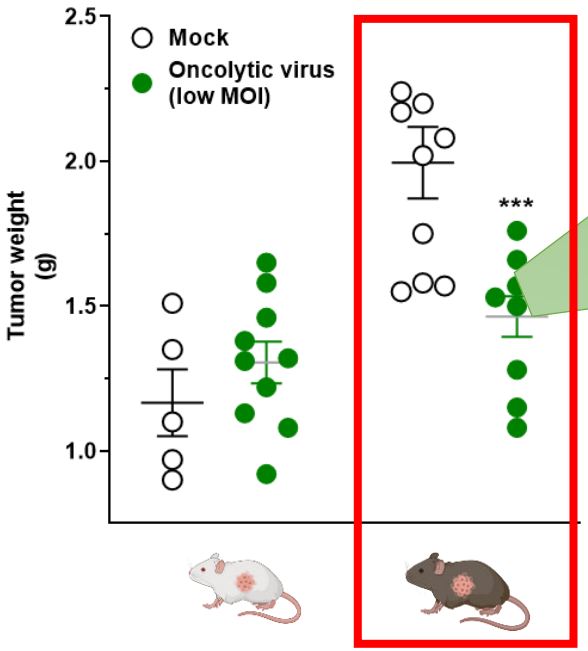
Institut de Recherche en Informatique de Toulouse

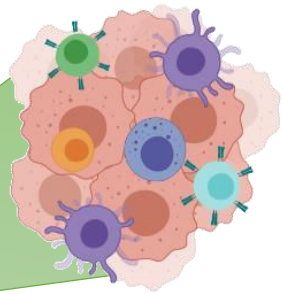
Nat Biotechnol. 2016, Hum Gene Ther. 2015, 2016a, 2016b, 2016c, 2021 + manuscript in preparation

CAN WE SUCCESSFULLY TREAT PDAC PATIENTS WITH ONCOLYTIC VIRUSES?









Open questions:

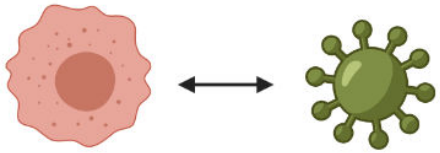
a. Immune cells involved

b. ICB combos

Hum Gene Ther. 2021 + manuscript submitted

CURRENT AND FUTURE DIRECTIONS

PDAC cell and oncolytic virus crosstalk

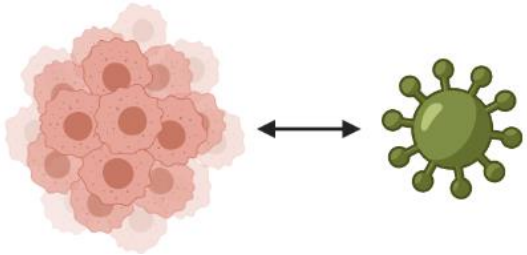


a. Oncolytic signature for patients' stratification

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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N. Kontopoulos, PhD trainee
G. Labrousse, PhD, research engineer
C. Lopez, research engineer
A. Névot, research engineer
L. Quillien, PharmD, PhD trainee
A. Redouté, PhD trainee
M. Vienne, PhD, postdoc fellow

N. Béry, PhD, senior postdoc
B. Bournet, MD, PhD PU-PH
M. Brunet, PhD trainee
A. Cornebois, PhD trainee
N. Hanoun, INSERM research engineer
A. Lumeau, PhD trainee
C. Maulat, Surgeon trainee, PhD trainee
F. Muscari, MD , PhD PU-PH
M. Sorbara, research engineer
J. Teillet, PhD, research engineer
J. Torrisani, CRCN INSERM
C. Vargas, PhD trainee

Pr. S. Bertagnoli

Dr F. Gallardo
Dr E. Marcheteau

Dr S. Cussat-Blanc

Dr N. Dusetti

Roche Genentech A Member of the Roche Group
Fondation de France
Inserm Institut national de la santé et de la recherche médicale
TOULOUSE TECH TRANSFER
La Région Occitanie Pyrénées · Méditerranée
FONDATION ARC POUR LA RECHERCHE SUR LE CANCER Reconnue d'utilité publique

PANCREATIC CANCER INTRINSIC PI3KA ACTIVITY ACCELERATES METASTASIS AND REWIRES MACROPHAGE COMPONENT

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

EMBO Mol Med, Volume: 13, Issue: 7, First published: 25 May 2021, DOI: (10.15252/emmm.202013502)

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Reconnue d'utilité publique

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

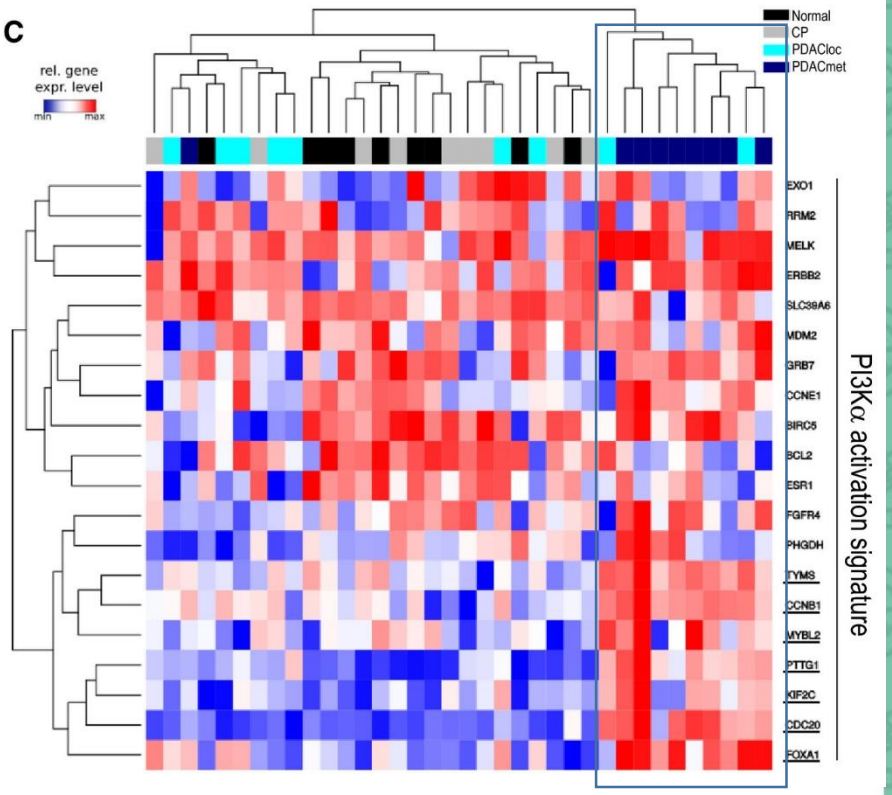
A Hallmarks

Pathways	Corr p value PDACmet vs normal	Corr p value PDACloc vs normal	Corr p value CP vs normal	Corr p value PDACmet vs PDACloc
Complement	0.0002	0.0000	0.0066	0.2773
Apical junction	0.0016	0.0000	0.0000	0.1524
Coagulation	0.0020	0.0000	0.0000	0.1487
Glycolysis	0.0021	0.0403	0.0482	0.8633
IL-2 STAT5 signaling	0.0022	0.0001	0.0014	0.0524
Reactive oxygen species pathway	0.0038	0.0075	0.0087	0.9235
Interferon alpha response	0.0042	0.0002	0.0008	0.3250
Heme metabolism	0.0043	0.0002	0.0006	0.1213
Interferon gamma response	0.0046	0.0001	0.0034	0.1668
IL-6 JAK STAT3 signaling	0.0049	0.0010	0.0230	0.1679
PI3K Akt mTOR Signaling	0.0077	0.0032	0.5960	0.3675
Hedgehog signaling	0.0081	0.9943	0.0002	0.0657
Early estrogen response	0.0098	0.0003	0.0000	0.0355
Myogenesis	0.0103	0.1399	0.0031	0.0048
TNFa signaling via NFKB	0.0121	0.0003	0.0038	0.0167
Inflammatory response	0.0155	0.0140	0.0082	0.0568
Oxidative phosphorylation	0.0205	0.0002	0.0002	0.0234
Mitotic spindle	0.0218	0.0030	0.0061	0.6924
Epithelial mesenchymal transition	0.0219	0.0000	0.0004	0.0031
Xenobiotic metabolism	0.0226	0.0829	0.2647	0.0163
Allograft rejection	0.0230	0.0335	0.0141	0.7627
Wnt beta catenin signaling	0.0301	0.0000	0.0157	0.3125
UV response up	0.0445	0.6722	0.0604	0.1190

B PI3K-related Reactome

Pathways	Corr p value PDACmet vs PDACloc
PI3K Akt activation	0.0603
PI3K Akt signaling in cancer	0.0741
PI3K cascade FGFR2	0.0162

C



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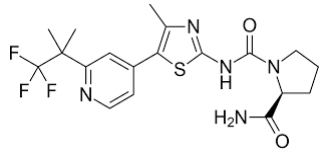
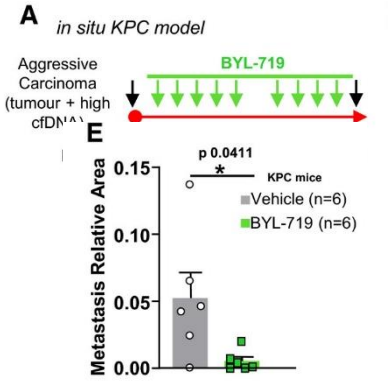
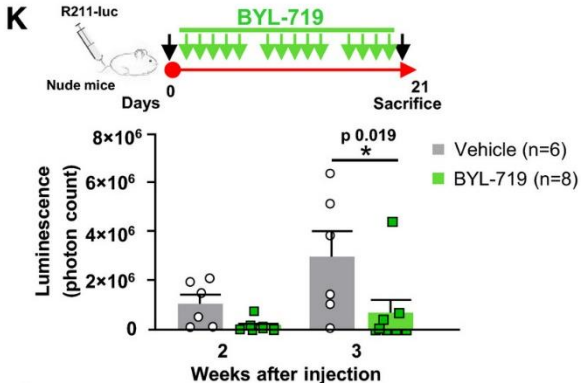
PI3Kα inhibition prevents development of macrometastasis

Pharmacological

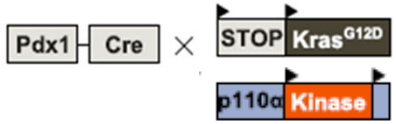
BYL719=Alpelisib

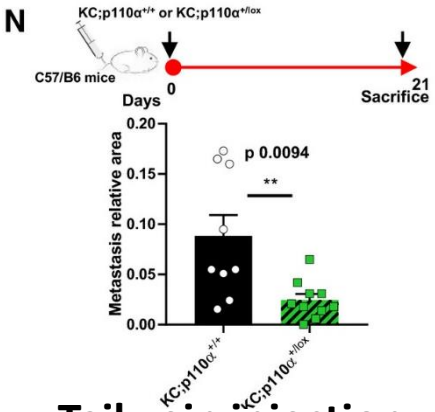






Genetic





In situ KPC Mice

Tail vein injection

Tail vein injection

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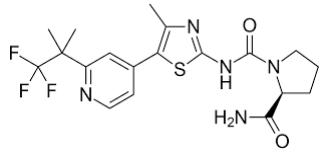
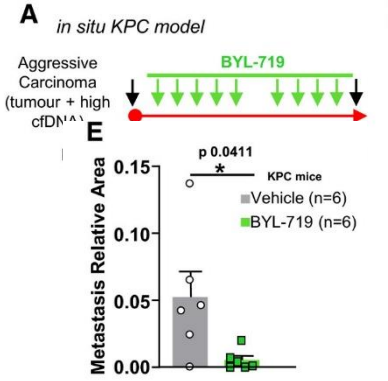
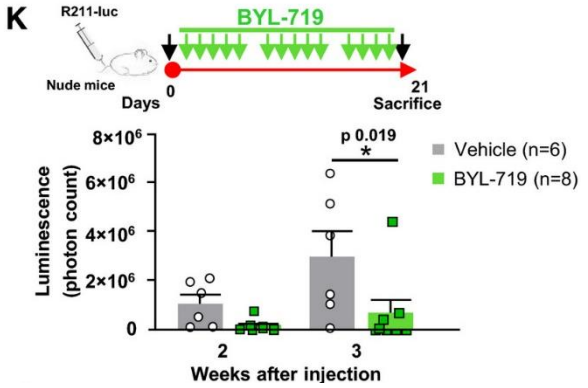
PI3Kα inhibition prevents development of macrometastasis

Pharmacological

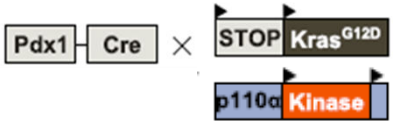
BYL719=Alpelisib

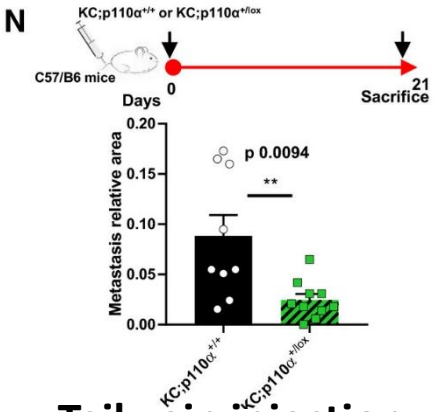






Genetic

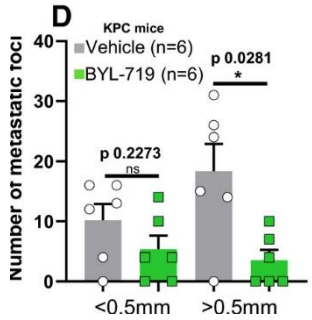




In situ KPC Mice

Tail vein injection

Tail vein injection



Micro-metastasis

Macro-metastasis

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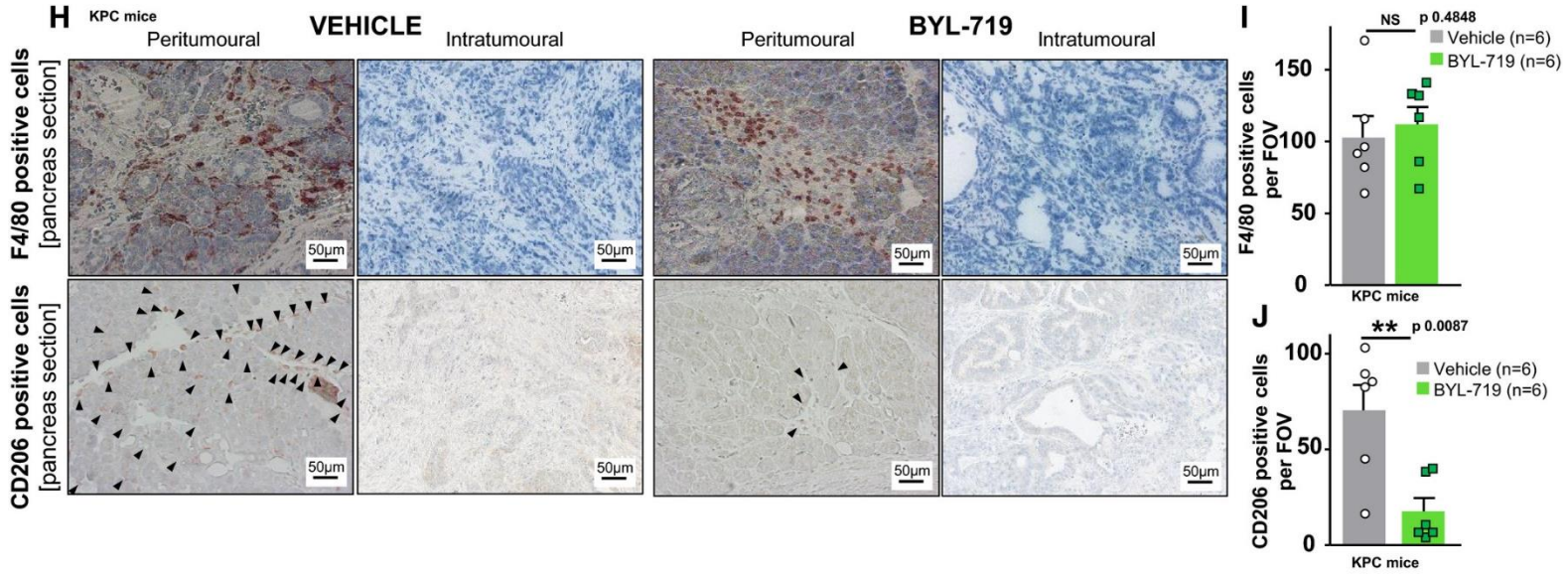
Pharmacological PI3Kα inhibition prevents the acquisition of tumour-associated inflammatory (CD206+) macrophages



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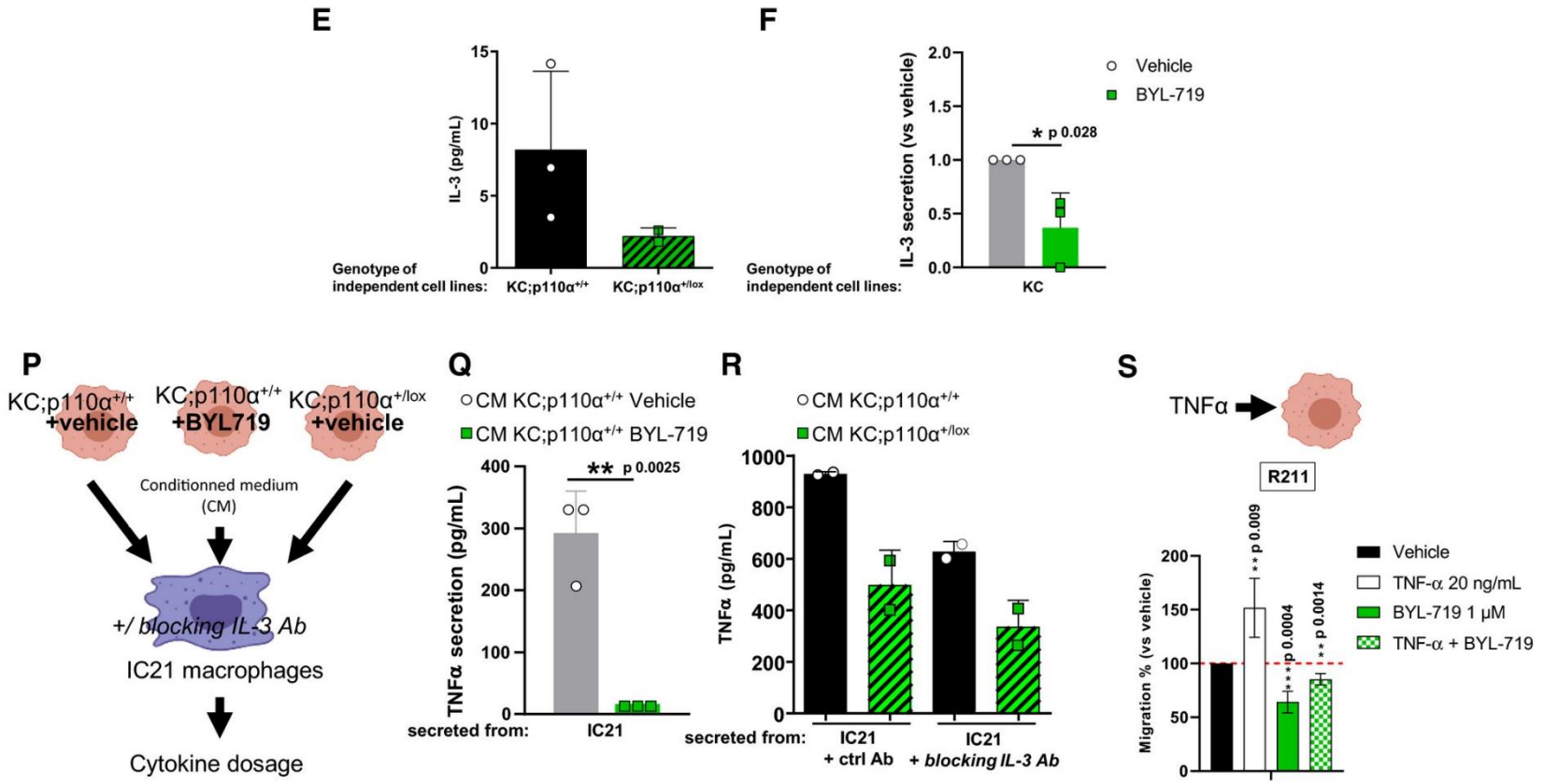
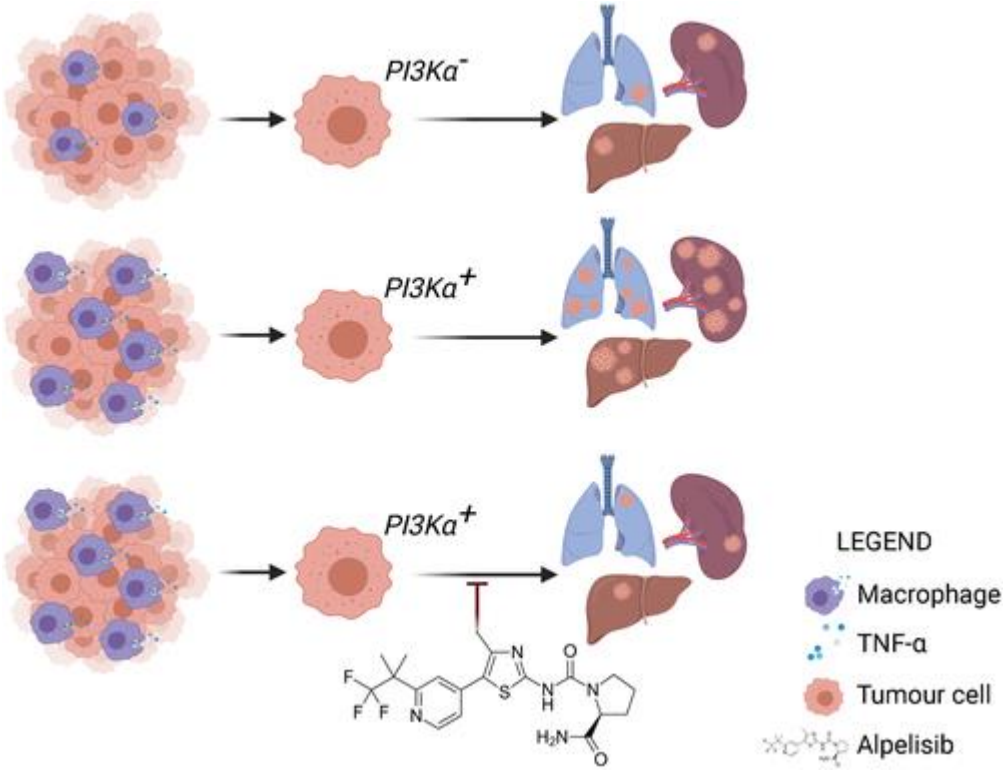
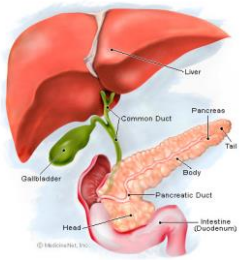
Macrophage TNFα secretion is promoted by PI3Kα activity-induced IL-3 in tumour cells.



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"

Inserm
Institut national de la santé et de la recherche médicale

ICM
Institut régional du Cancer Montpellier | Val d'Aurelle

Institut de Recherche en Cancérologie
I R C Montpellier

SIRIC MONTPELLIER CANCER
Site de Recherche Intégrée sur le Cancer

MAbimprove
LabEx Tours Montpellier

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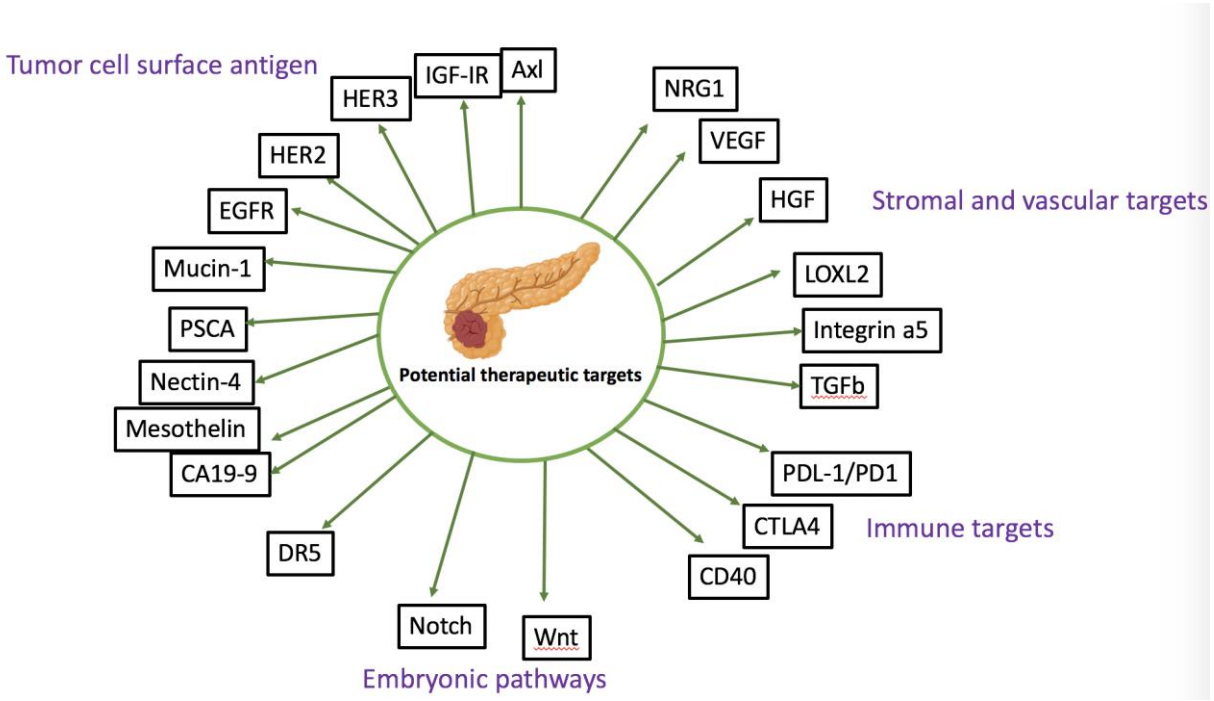
Robust target selection

- 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



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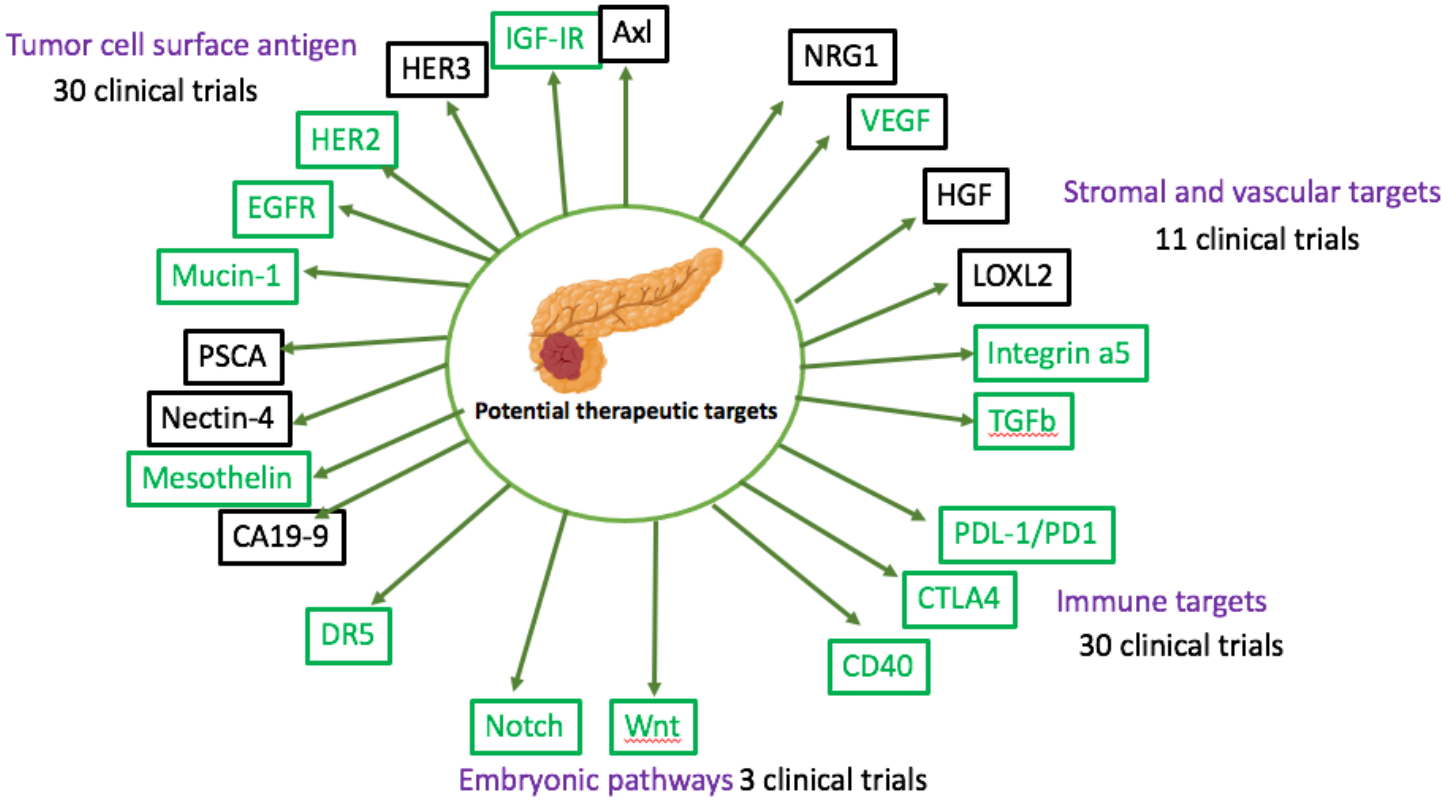
Targets of antibodies that have undergone **clinical evaluation (phase I/II)** in pancreatic cancer



Arias-Pinilla GA, Cancers 2021; Boland AJ, BBA 2021

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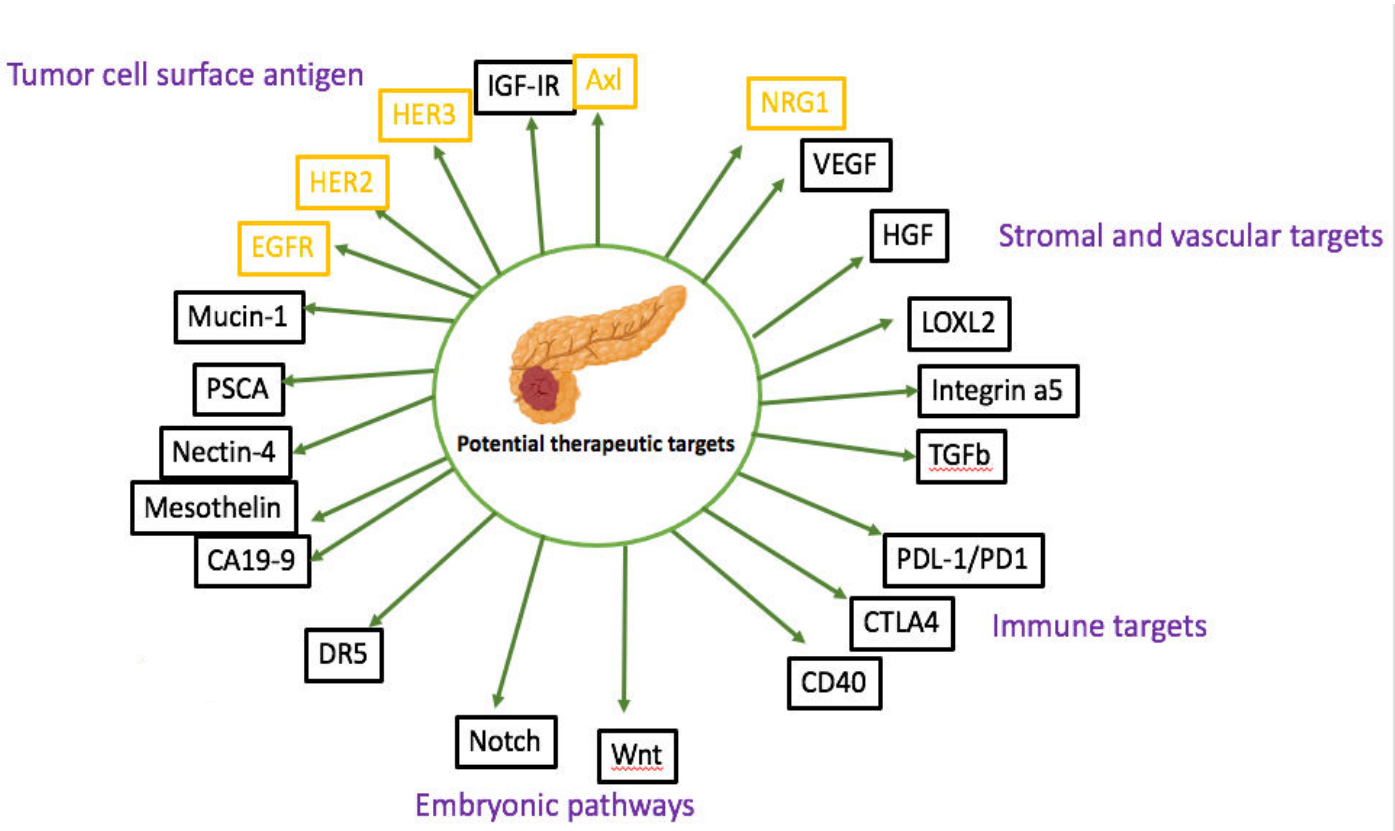
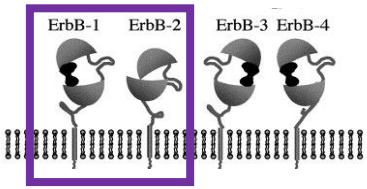
In the lab …



Implicated in metastasis and resistance to therapies (chemo or targeted)

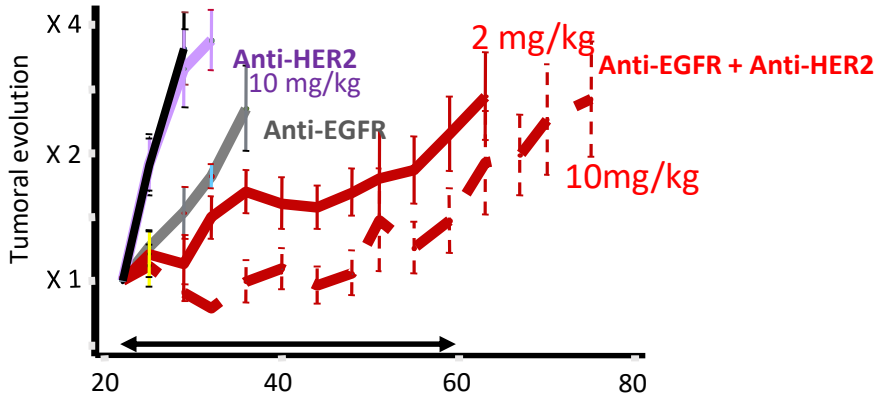
Antibody combination (simultaneous targeting of signaling pathways- heterodimers) – inhibition of escape response

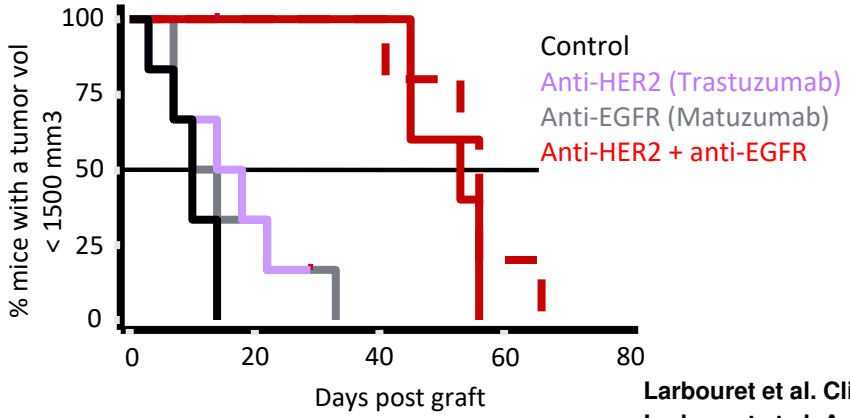


Coll. Merck/Roche

Anti-EGFR + anti-HER2 antibody combination

Pancreatic tumor xenograft (**K-ras M**)





Larbouret et al. Clin Cancer Res 2007 13:3356-3362
Larbouret et al. Annals Oncol 2010 21:98-103

➡ Effect independly of Kras and in first and second line of treatment
Pan-HER in GR PDx pancreatic models (Rabia E, Mabs 2021)

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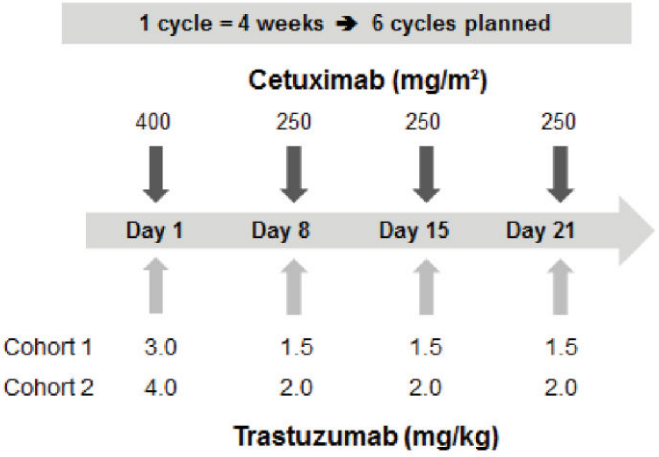
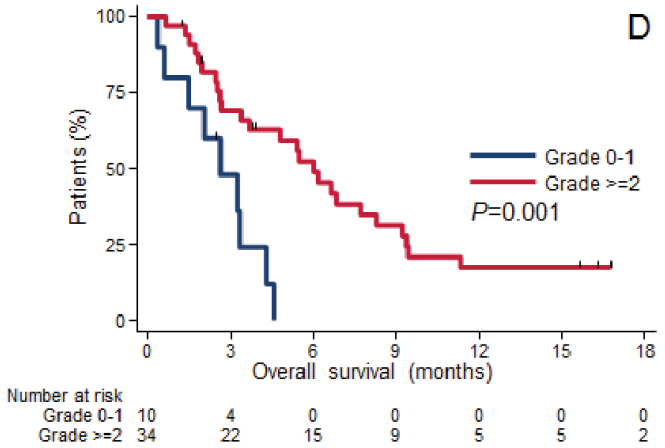
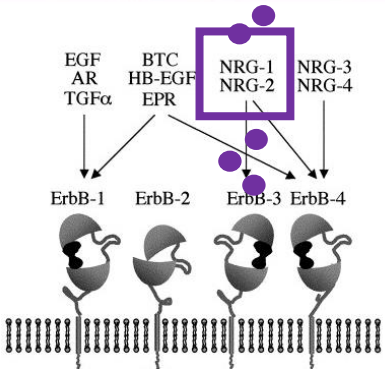
THERAPY: Phase I/II clinical trial (NCT00923299)



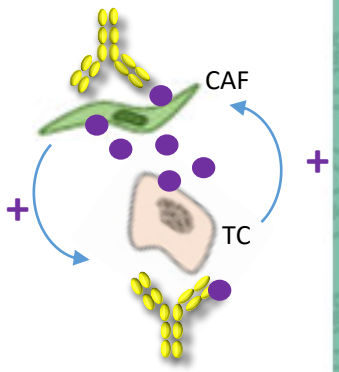


- 33 patients evaluable for efficacy: **27% of stabilization**
- Correlation between the **OS and the cutaneaous toxicity**
- **Doses of cetuximab and trastuzumab**
- Second or more lines of treatment
- No biomarker

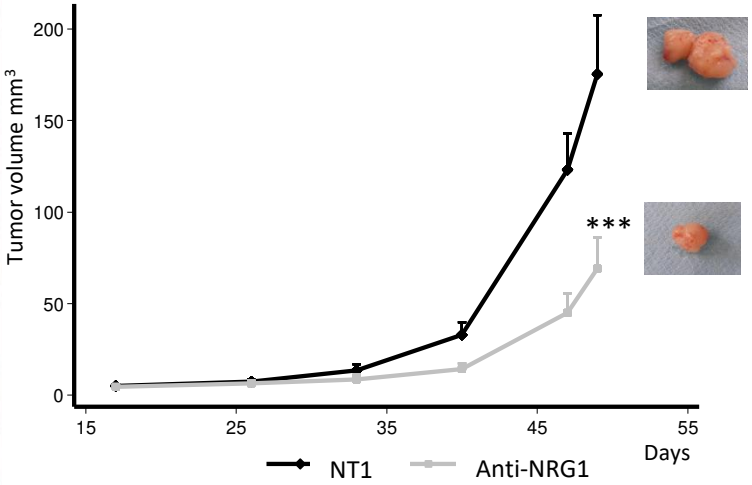
Assenat E et al. Oncotarget 2015 6:12796-808

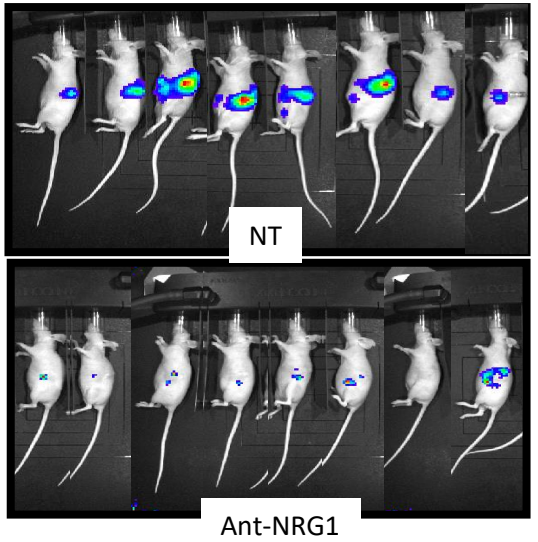


Targeting the NRG1/HER3 pathway in tumor cells and CAF With an anti-neuregulin 1 antibody



Orthotopic Pancreatic tumor xenograft (mix CAF/TC))





Ogier C, Larbouret C. Cancer letters, 2019

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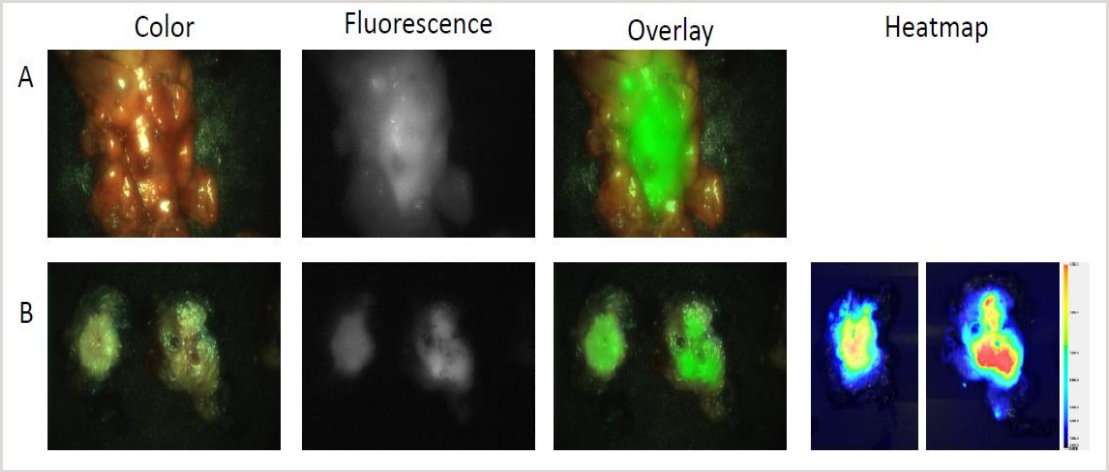
Challenge and future perspectives with antibody therapeutics in PC

- 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



Tumor pancreatic tail

ex vivo

CEA: carcino embryonic antigen

A: tumor in primary resection specimen

B: tumor in sliced speciment

Hoogstins CES et al. **Ann Surg Oncol** 25:3350-3357, 2018 and Vahrmeijjer AL, personnal communication

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- 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)

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