ALICE CARRIER, DR2 CNRS

GROUP « ENERGETIC METABOLISM & OXIDATIVE STRESS »

TEAM « PANCREATIC CANCER » (DIR. JUAN IOVANNA)

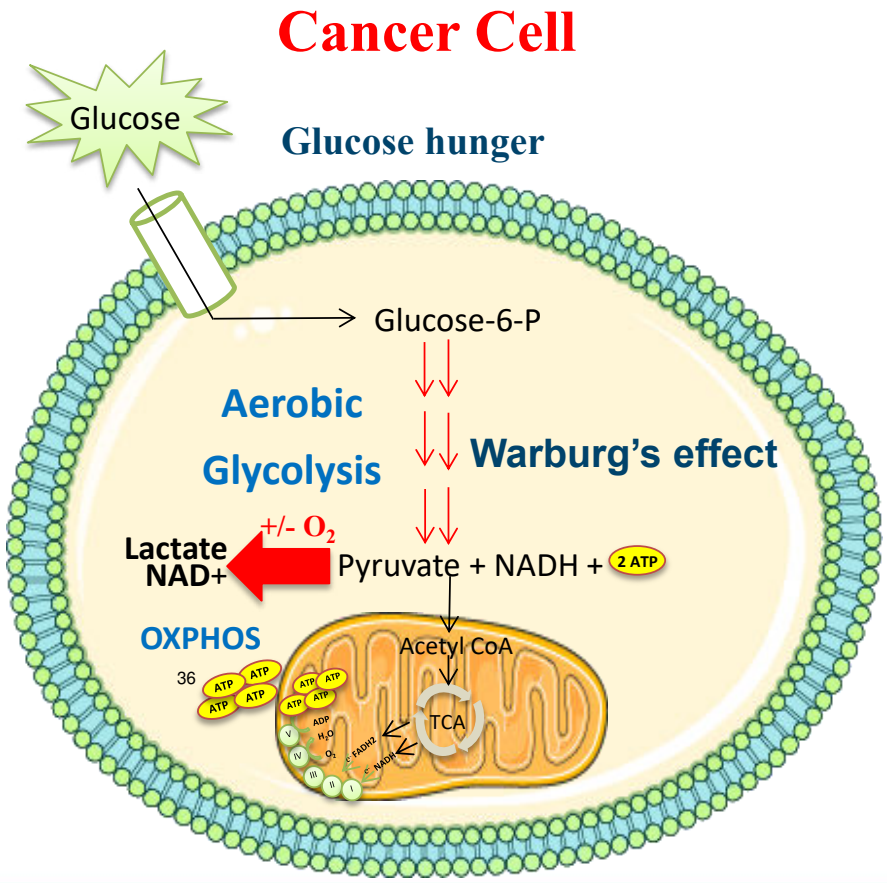
Targeting mitochondrial and redox metabolism in PDAC

1- Therapy ***Current projects***

2- Prevention ***Future projects (ongoing development)***

The role of mitochondria in cancer metabolism was ignored until recently

Warburg's effect: aerobic glycolysis (1924)

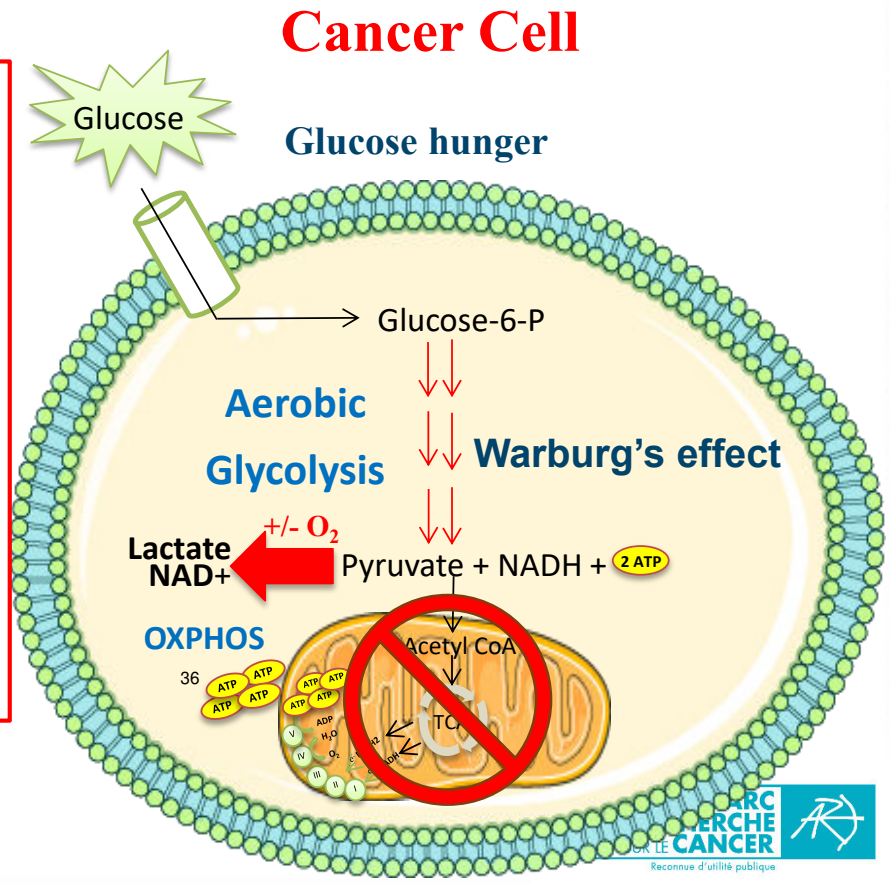


The role of mitochondria in cancer metabolism was ignored until recently

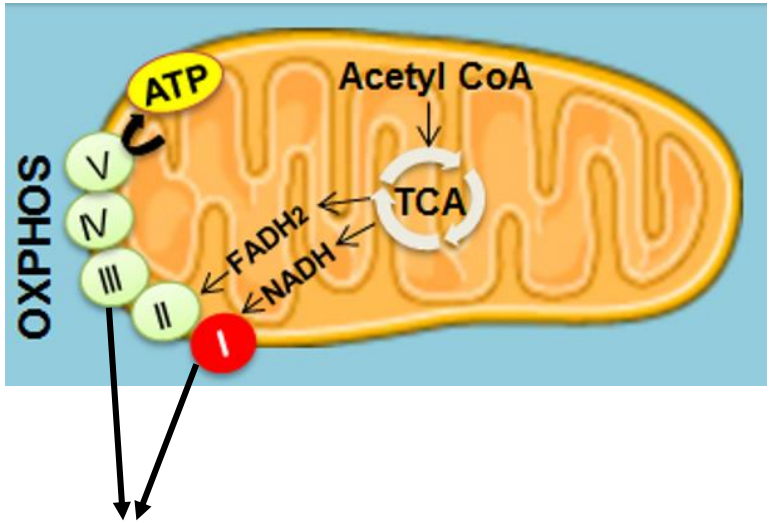
Warburg's hypothesis (1956):
mitochondria are dysfunctional in cancer cells

Current knowledge:

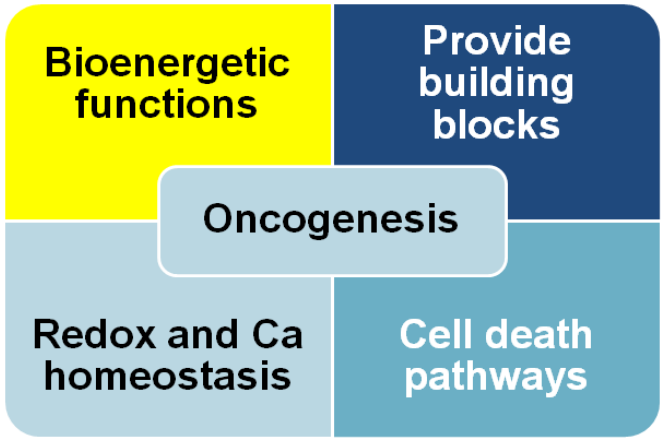
- ✓ **Mitochondria are functional in most of cancer cells**
- ✓ Mitochondrial metabolism is necessary for cancer cell proliferation and survival
- ✓ Mitochondria are involved in cancer therapeutic resistance

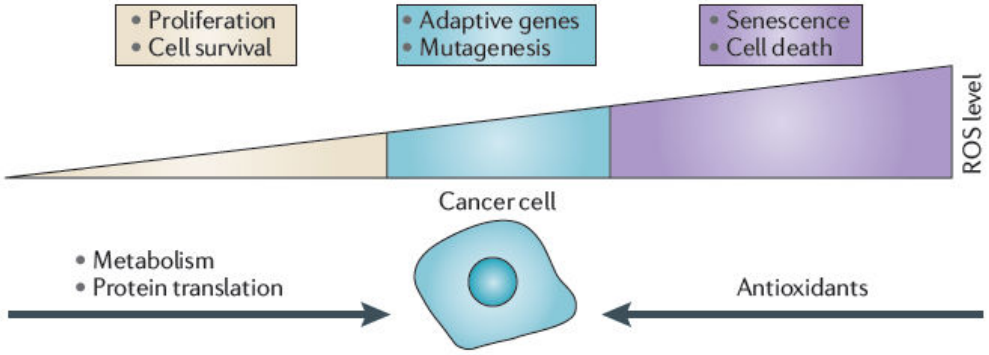


Mitochondria are functional in most of cancer cells



Reactive Oxygen Species (ROS)





Cairns RA et al. Nature Reviews Cancer 2011

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Reconnue d'utilité publique

Mitochondria are functional in most of cancer cells

In PDAC ?

2014 LETTER

doi:10.1038/nature13611

Oncogene ablation-resistant pancreatic cancer cells depend on mitochondrial function

Andrea Viale[1,2]*, Piergiorgio Pettazzoni[1,2]*, Costas A. Lyssiotis[3], Haoqiang Ying[1], Nora Sánchez[1,2], Matteo Marchesini[1,2], Alessandro Carugo[1,2,4], Tessa Green[1,2], Sahil Seth[5], Virginia Giuliani[5], Maria Kost-Alimova[5], Florian Muller[1], Simona Colla[1], Luigi Nezi[1,2], Giannicola Genovese[1], Angela K. Deem[1], Avnish Kapoor[1], Wantong Yao[1,2], Emanuela Brunetto[6], Ya'an Kang[7], Min Yuan[8], John M. Asara[8], Y. Alan Wang[1], Timothy P. Heffernan[5], Alec C. Kimmelman[9], Huamin Wang[10], Jason B. Fleming[7], Lewis C. Cantley[3], Ronald A. DePinho[11] & Giulio F. Draetta[1,2]

Role in resistance

2015

MYC/PGC-1α Balance Determines the Metabolic Phenotype and Plasticity of Pancreatic Cancer Stem Cells

Cell Metabolism
Article

Patricia Sancho,[1,2,*] Emma Burgos-Ramos,[2] Alejandra Tavera,[2] Tony Bou Kheir,[1] Petra Jagust,[1] Matthieu Schoenhals,[1] David Barneda,[1] Katherine Sellers,[5] Ramon Campos-Olivas,[3] Osvaldo Graña,[4] Catarina R. Viera,[2] Mariia Yuneva,[5] Bruno Sainz, Jr.,[2] and Christopher Heeschen[1,2,*]

Mitochondria are functional in most of cancer cells

In PDAC ?

2020 Cell Reports Medicine

CellPress
OPEN ACCESS

Article

Targeting Mitochondrial Complex I Overcomes Chemoresistance in High OXPHOS Pancreatic Cancer

Rawand Masoud,[1,3,*] Gabriela Reyes-Castellanos,[1,3] Sophie Lac,[1,4] Julie Garcia,[1] Samir Dou,[1] Laetitia Shintu,[2] Nadine Abdel Hadi,[1] Tristan Gicquel,[1] Abdessamad El Kaoutari,[1] Binta Diémé,[2,5] Fabrice Tranchida,[2] Laurie Cormareche,[1] Laurence Borge,[1] Odile Gayet,[1] Eddy Pasquier,[1] Nelson Dusetti,[1] Juan Iovanna,[1] and Alice Carrier[1,6,*]

→ Heterogeneity

→ Targeting

2020 biomedicines

MDPI

Review

Mitochondrial Metabolism in PDAC: From Better Knowledge to New Targeting Strategies

Gabriela Reyes-Castellanos, Rawand Masoud and Alice Carrier *

2021 International Journal of *Molecular Sciences*

Review

Targeting Redox Metabolism in Pancreatic Cancer

Nadine Abdel Hadi, Gabriela Reyes-Castellanos and Alice Carrier *

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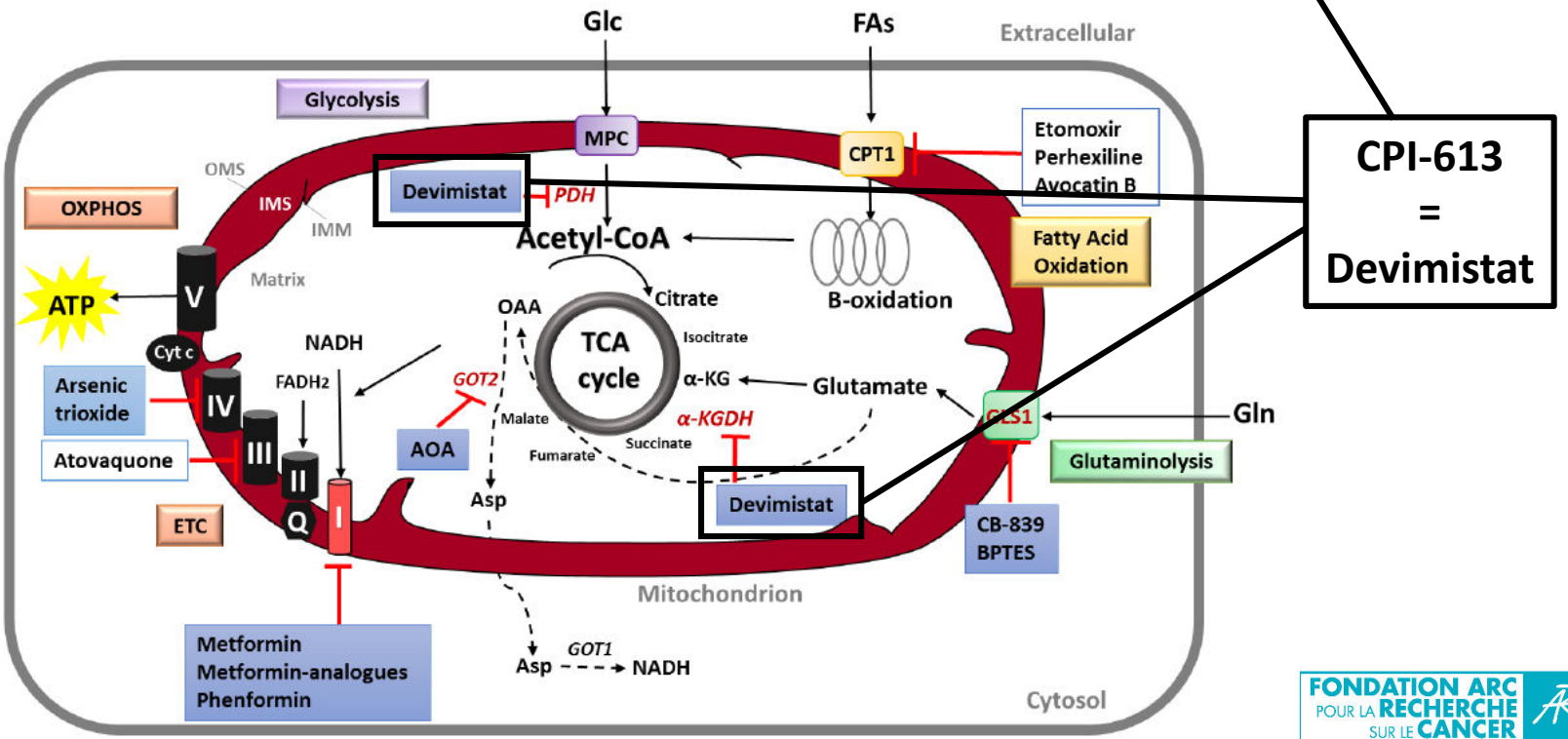
Mitochondria are functional in most of cancer cells

2017

Safety and tolerability of the first-in-class agent CPI-613 in combination with modified FOLFIRINOX in patients with metastatic pancreatic cancer: a single-centre, open-label, dose-escalation, phase 1 trial

Lancet Oncol 2017; 18: 770–78

Angela Alistar, Bonny B Morris, Rodwige Desnoyer, Heidi D Klepin, Keyanoosh Hosseinzadeh, Clancy Clark, Amy Cameron, John Leyendecker, Ralph D'Agostino Jr, Umit Topaloglu, Lakmal W Boteju, Asela R Boteju, Rob Shorr, Zuzana Zachar, Paul M Bingham, Tamjeed Ahmed, Sandrine Crane, Riddhishkumar Shah, John J Migliano, Timothy S Pardee, Lance Miller, Gregory Hawkins, Guangxu Jin, Wei Zhang, Boris Pasche



CPI-613 = Devimistat

Adapted from Reyes-Castellanos et al. Biomedicines 2020

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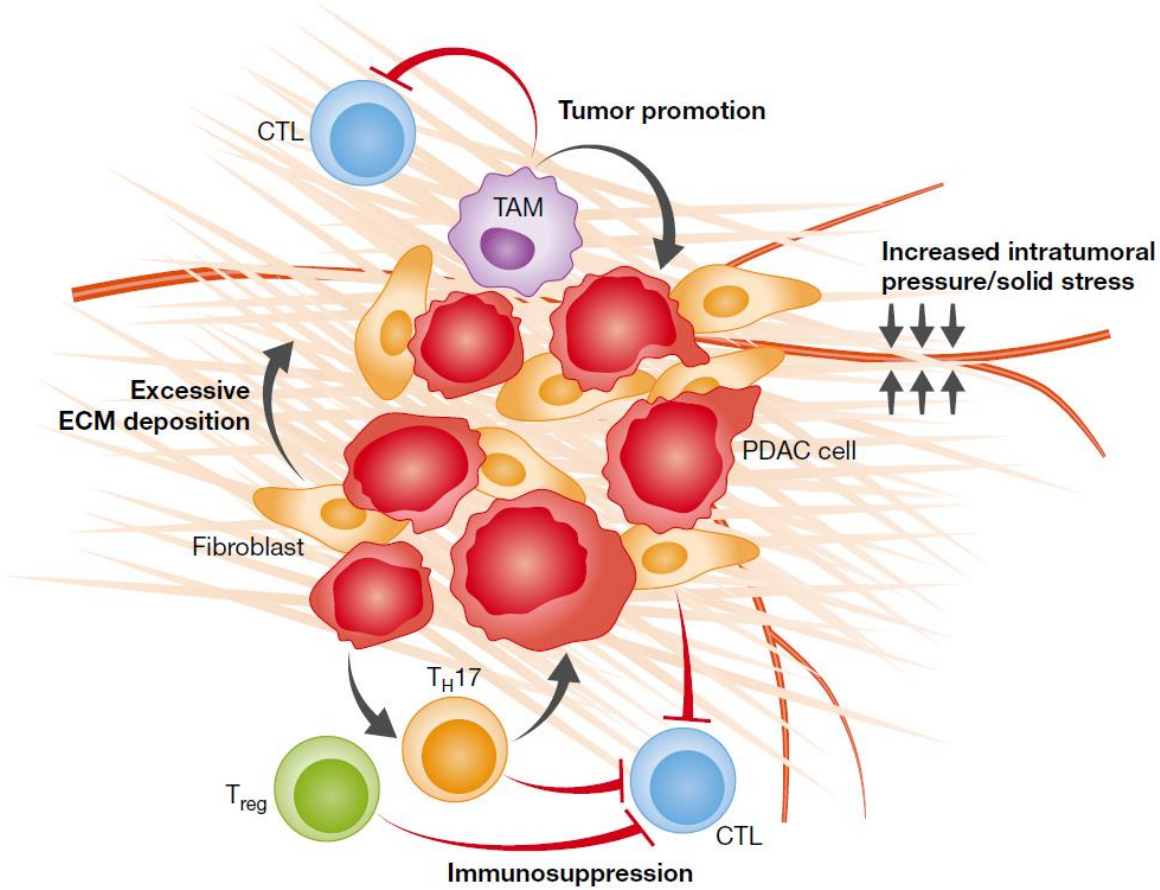
Mitochondria are important for the function of TME cells surrounding cancer cells



Carr RM & Fernandez-Zapico ME, EMBO Mol Med 2016

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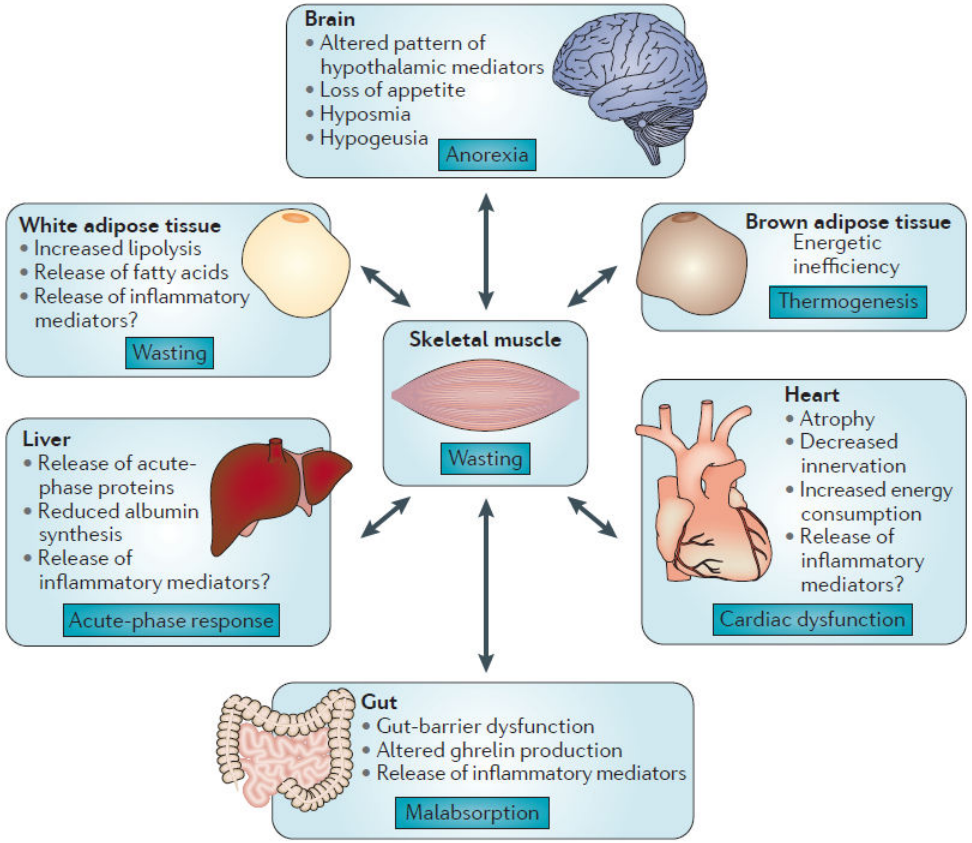
Mitochondria are dysfunctional in distant organs during cancer



CACHEXIA AS A MULTI-ORGAN SYNDROME
Argilés JM et al. Nature Reviews Cancer 2014

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Reconnue d'utilité publique

Our goal: Exploration of mitochondrial metabolism in PDAC

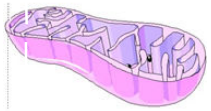
→ Considering tumor cells, TME cells, and distant organs

Nutrition

STRESS

INFLAMMATION

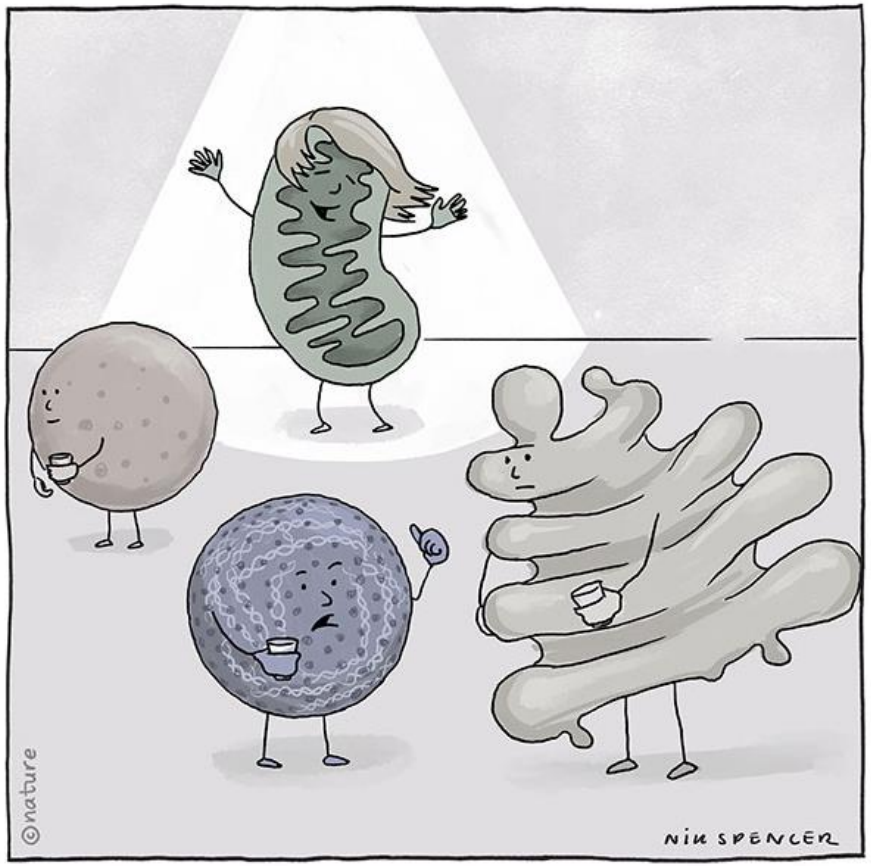
METABOLIC ALTERATIONS



CANCER
Initiation
Progression
Resistance

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

Thank you for your attention



"I don't know where she gets all that energy."

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Journée scientifique
« Cancer du pancréas »

10H00 – SESSION 2 : QUELLES CIBLES POTENTIELLES POUR LE CANCER DU PANCRÉAS ?

Modérateur : Juan IOVANNA

TUMOR MICROENVIRONMENT FOCUS ON THE NON-IMMUNE STROMA

Dr. Corinne BOUSQUET

Research Director, INSERM

Cancer Research Center of Toulouse

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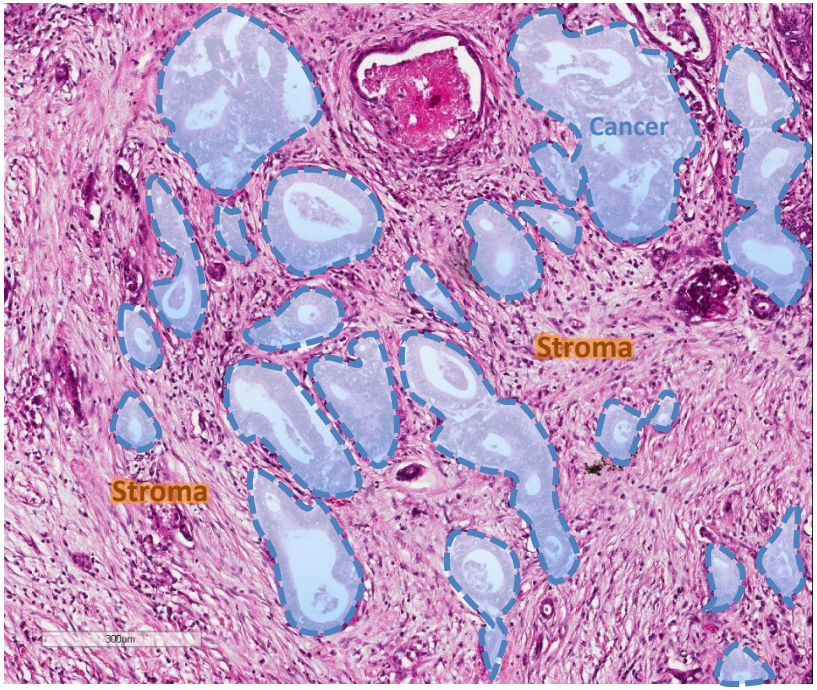
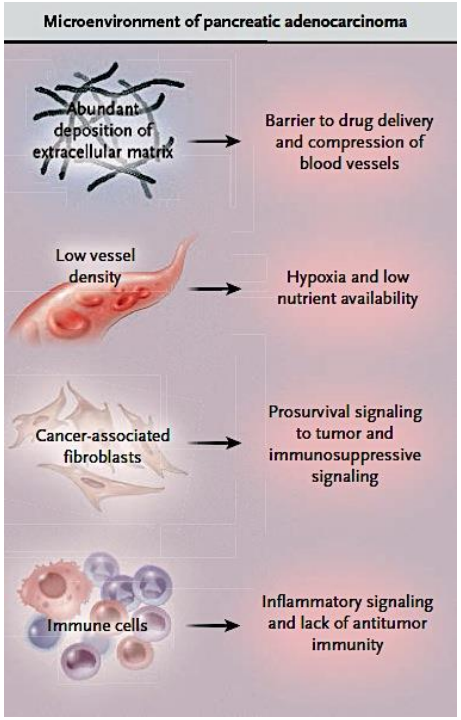
PANCREATIC DUCTAL ADENOCARCINOMA & MICROENVIRONMENT

Typical feature: Fibrotic stroma - **80% of the tumor mass**



Courtesy Dr J. Cros (Hôp. Beaujon)

PDAC



Ryan, *N Engl J Med* 2014

TME RNAseq SIGNATURES ARE CONSERVED ACROSS CANCERS & PROGNOSTIC

Unsupervised clustering of TME reconstructed from RNAseq (>10.000) across melanomas and carcinomas

- Adrenocortical Carcinoma
- Bladder urothelial Carcinoma
- Breast invasive Carcinoma
- Endocervical Adenocarcinoma
- Cervical SCC
- Cholangiocarcinoma
- Colorectal Adenocarcinoma
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- Head and Neck SCC
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- Renal Papillary Cell Carcinoma
- Renal Papillary Cell Carcinoma
- Liver Hepatocellular Carcinoma
- Lung Adenocarcinoma
- Lung Squamous Cell Carcinoma
- Ovarian Serous Cystadenocarcinoma
- Pancreatic Adenocarcinoma
- Pheochromocytoma and Paraganglioma
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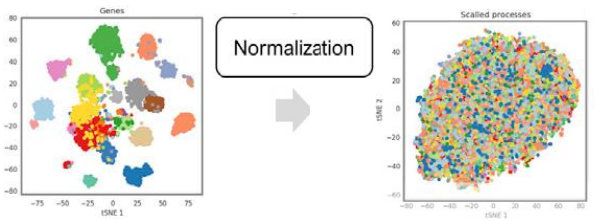
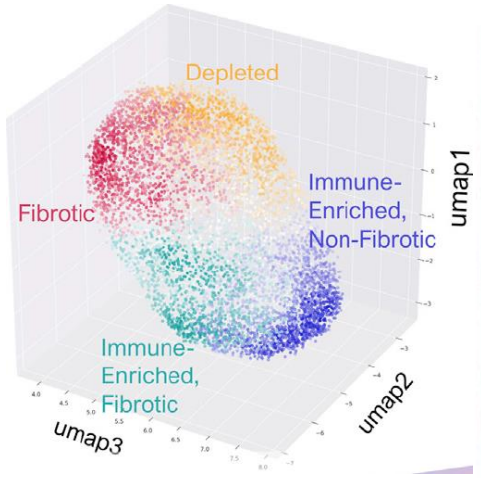
- Skin Cutaneous Melanoma
- Thyroid Carcinoma
- Uterine Corpus Endometrial
- Uterine Carcinosarcoma
- Uveal Melanoma



Bagaev A, *Cancer Cell 2021*



STATE OF THE ART

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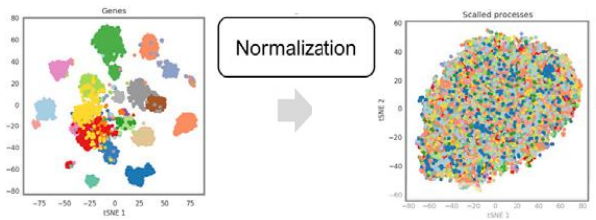

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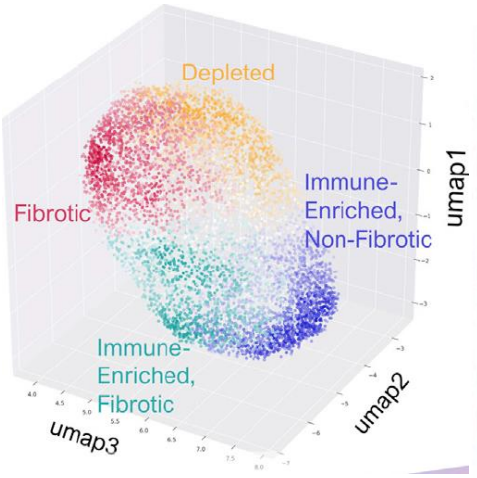

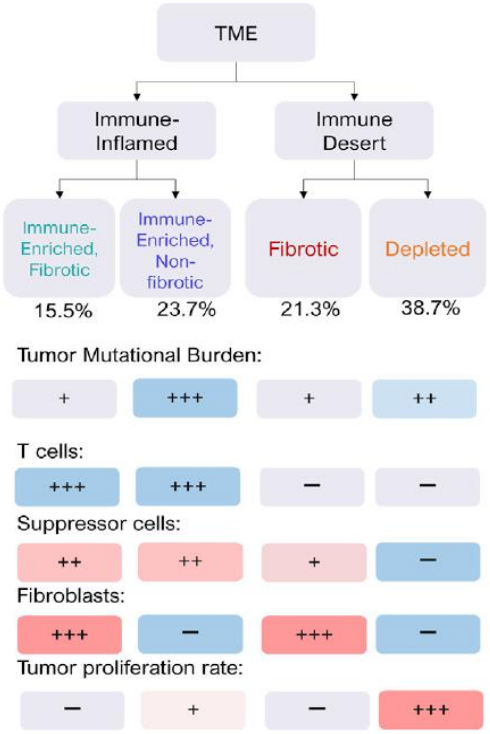

PDAC

Moffit et al, *Nature Genetics* 2015
Puleo et al, *Gastroenterology* 2018
Maurer et al, *Gut* 2019

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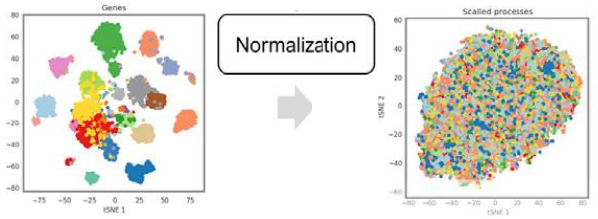
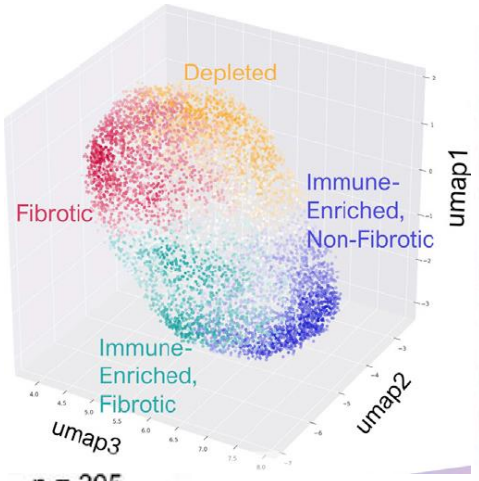
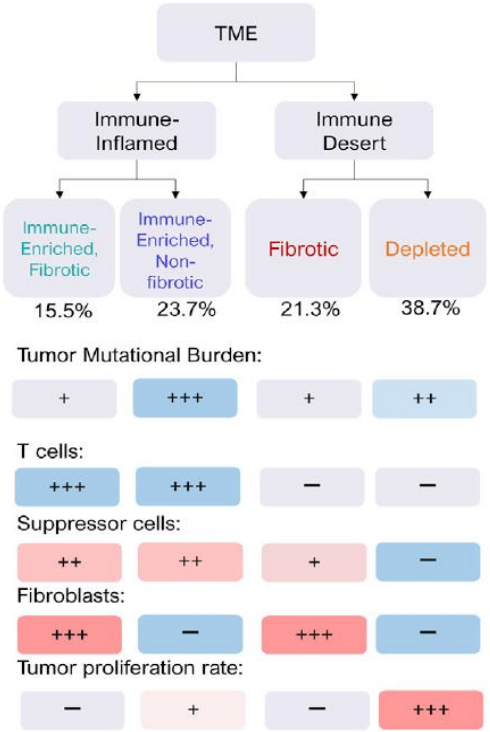
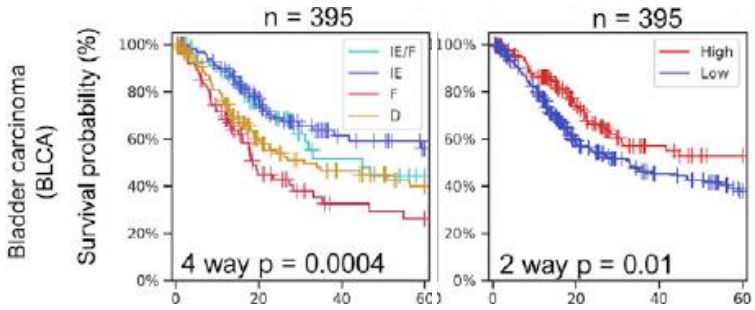


Bagaev A, *Cancer Cell 2021*







TME signatures **Immunophenoscore**

PDAC

Moffit et al, *Nature Genetics* 2015
Puleo et al, *Gastroenterology* 2018
Maurer et al, *Gut* 2019

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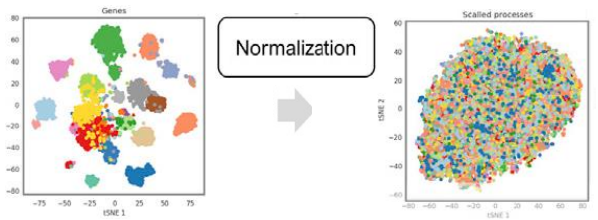

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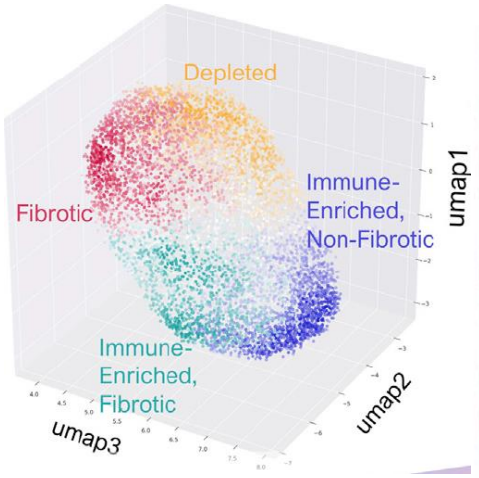

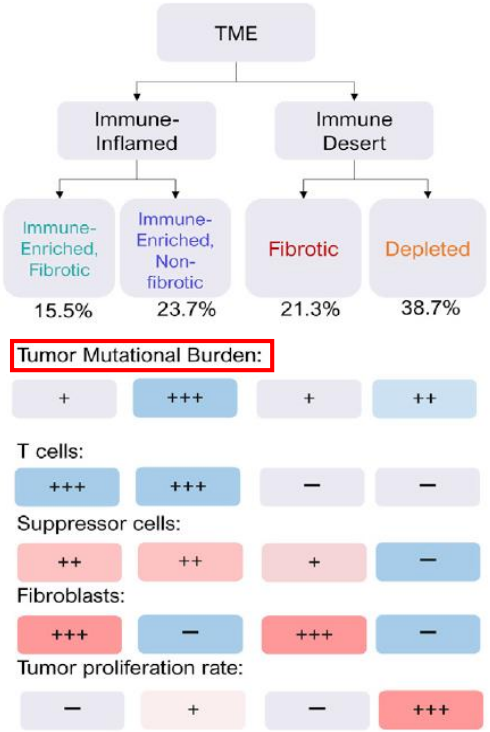

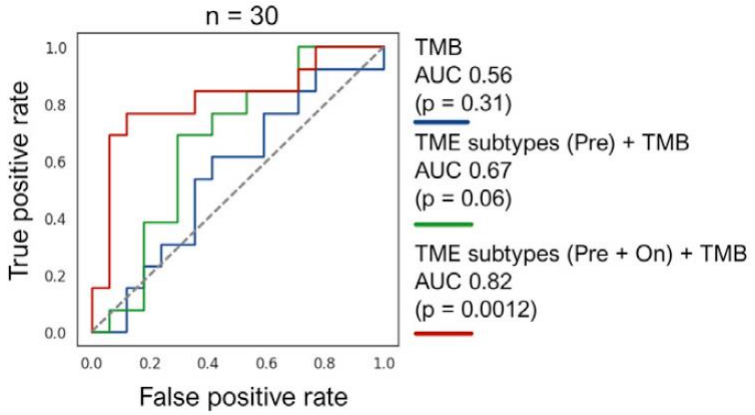

Response to immunotherapies (anti-PD1)

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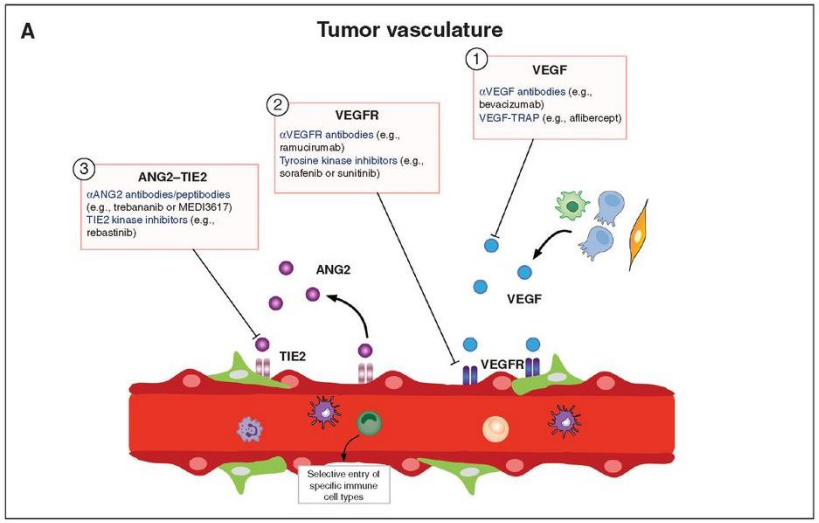
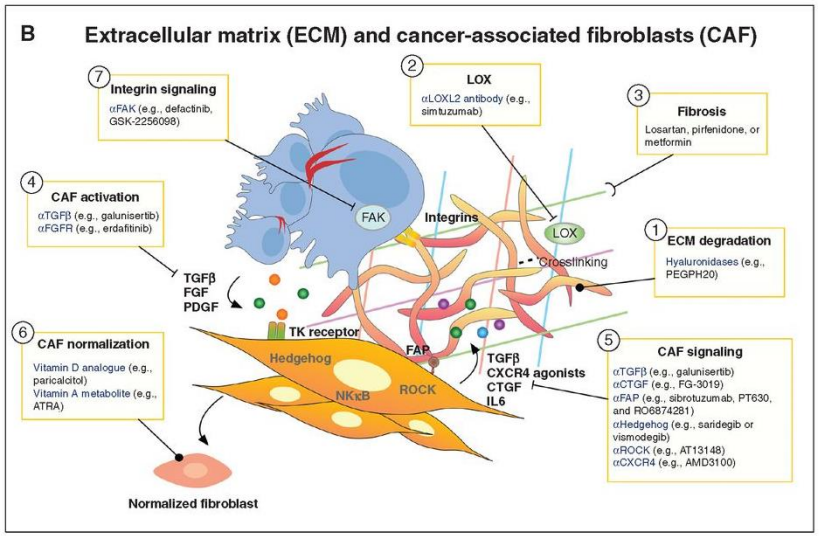
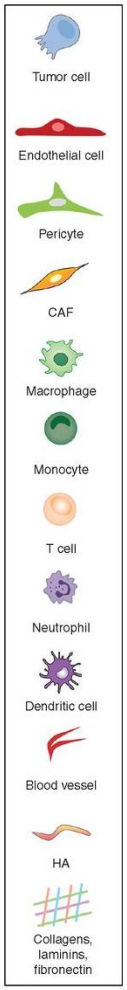
THERAPIES TARGETING THE NON-IMMUNE STROMA OF PDAC







Bejarano et al, *Cancer Discov 2021*

To enhance drug delivery
or block pro-tumor features
by **"normalizing"**
the non-immune stroma

But although **promising**
in pre-clinical models,
It resulted in **insufficient**
clinical successes

Why?
1) Lack of patient stratification?

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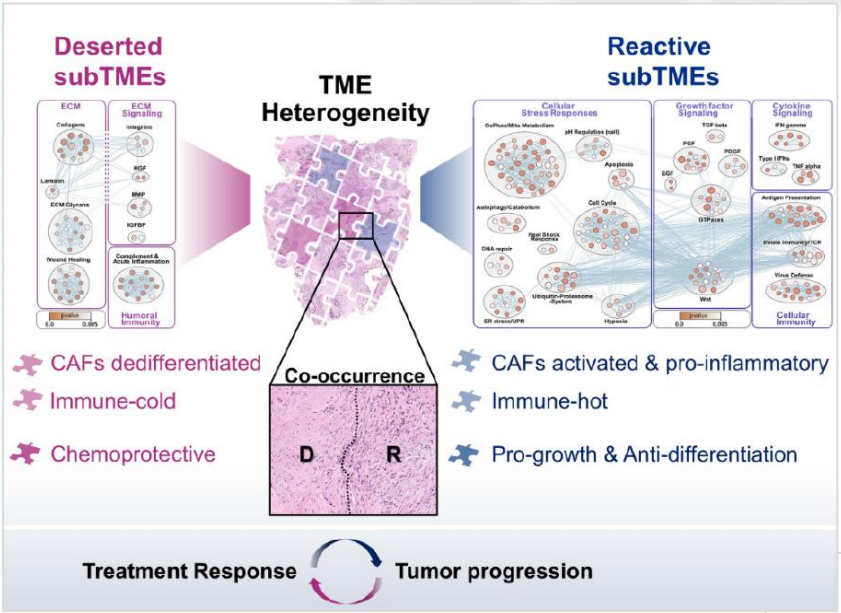
2) INTRA-TUMOR SPATIAL & CELL HETEROGENEITY



Different « subTME » spatially co-exist within a same tumor

« subTME » may evolve upon treatment

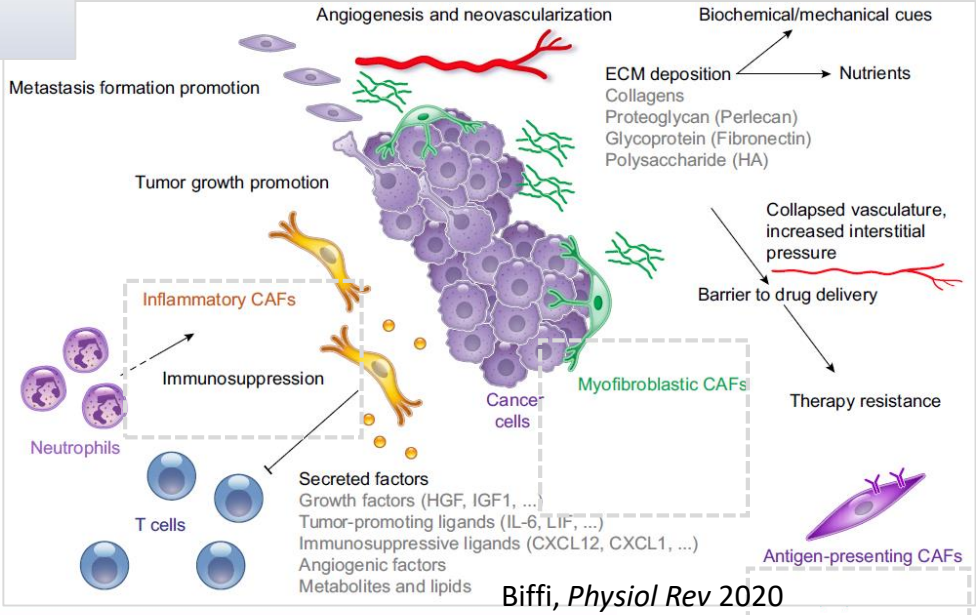
Grunwald, *BioRxiv* 2021

EXAMPLE OF CAFs

Different CAF subsets with different functions

Cell plasticity upon treatment
(*e.g.* SHH inhibition): ↓myCAF but ↑iCAF

Elyada, *Cancer Discov* 2019
Dominguez, *Cancer Discov* 2019
Steele, *Clin Cancer Res*, 2021



Biffi, *Physiol Rev* 2020

CHALLENGES & OPPORTUNITIES

TARGET THE NON-IMMUNE STROMA

IN ADDITION TO TUMOR & IMMUNE CELLS

- **Understand the biology of the non-immune stroma to discover novel therapeutic targets** (go beyond traditional tumor-centric studies and immuno-oncology efforts)

= **heterogeneity / plasticity along tumor progression & treatment**

* CAFs
* Other stromal cells: Neural / Endothelial / adipose tissue

= different cell interactions (& microbiome???)

= learn from **"omics" analyses (bulk/deconvolution, single cell/spatial**
Transcriptomics, translatomics, proteomics
Multiplexed imaging
Computational biology & AI)
on patient samples & clinical trials (ancillary studies)

Moncada, Nat Biotech 2020
de Vries, *Front Oncol* 2021
Lewis et al, *Nature Methods* 2021

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Moncada, Nat Biotech 2020
de Vries, *Front Oncol* 2021
Lewis et al, *Nature Methods* 2021

- **Test combinatorial / serial drug protocols** considering the triangular targets (tumor cells + immune + non-immune stroma)

- **Develop integrated "Tumor-TME" preclinical platforms** (e.g. microfluidic cancer-on-chips)

Colombo, *IJMS* 2021

CHALLENGES & OPPORTUNITIES

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* Other stromal cells: Neural / Endothelial / adipose tissue

= different cell interactions (& microbiome???)

= learn from **"omics" analyses (bulk/deconvolution, single cell/spatial**
Transcriptomics, translatomics, proteomics
Multiplexed imaging
Computational biology & AI)
on patient samples & clinical trials (ancillary studies)

Moncada, Nat Biotech 2020
de Vries, *Front Oncol* 2021
Lewis et al, *Nature Methods* 2021

- **Test combinatorial / serial drug protocols** considering the triangular targets (tumor cells + immune + non-immune stroma)

- **Develop integrated "Tumor-TME" preclinical platforms** (e.g. microfluidic cancer-on-chips)

Colombo, *IJMS* 2021

- **Find (bio)markers of drug response to stratify patients** (depending on their TME types)

- **Learn from other tumors** = **TME is conserved across cancers**!

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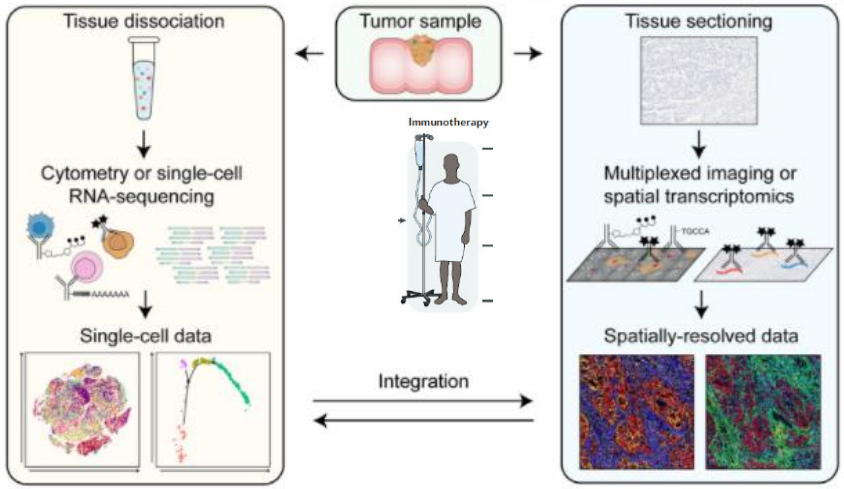
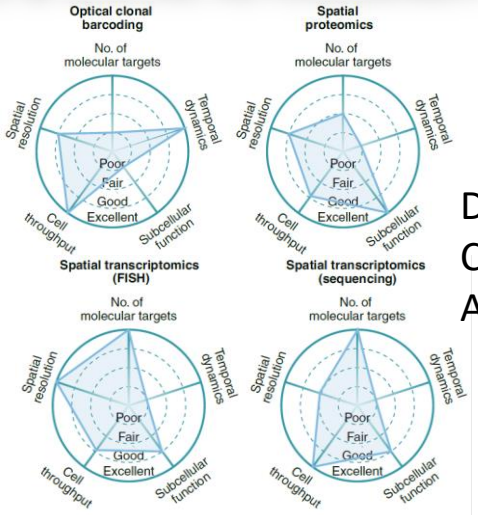
OPORTUNITIES

DECIPHER INTRA-TUMOR CELL & SPATIAL HETEROGENEITY



Moncada, Nat Biotech 2020
de Vries, *Front Oncol* 2021

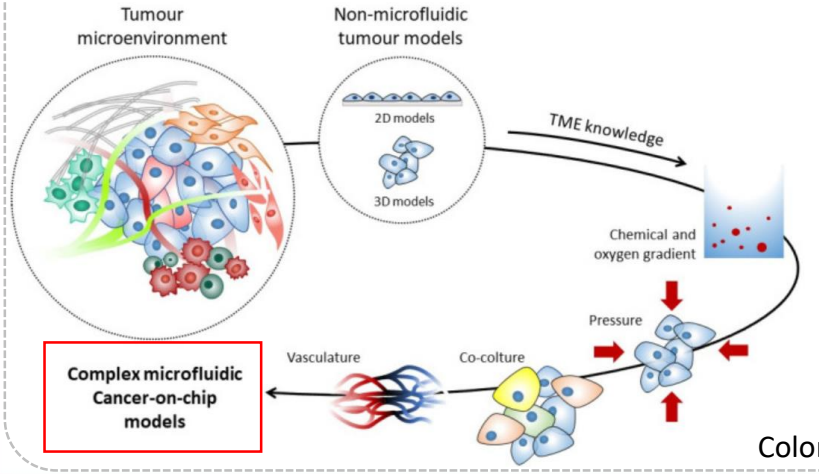


Lewis et al, *Nature Methods* 2021

Data integration
Computational biology
Artificial intelligence

IMPROVE PRECLINICAL MODELS

= TARGET VALIDATION & DRUG TESTING



GEMM
PDX
Humanized immunocompetent

Colombo, *IJMS* 2021

LEARN FROM CLINICAL TRIALS

ANCILLARY STUDIES

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