



Battle : Cancer du Pancréas

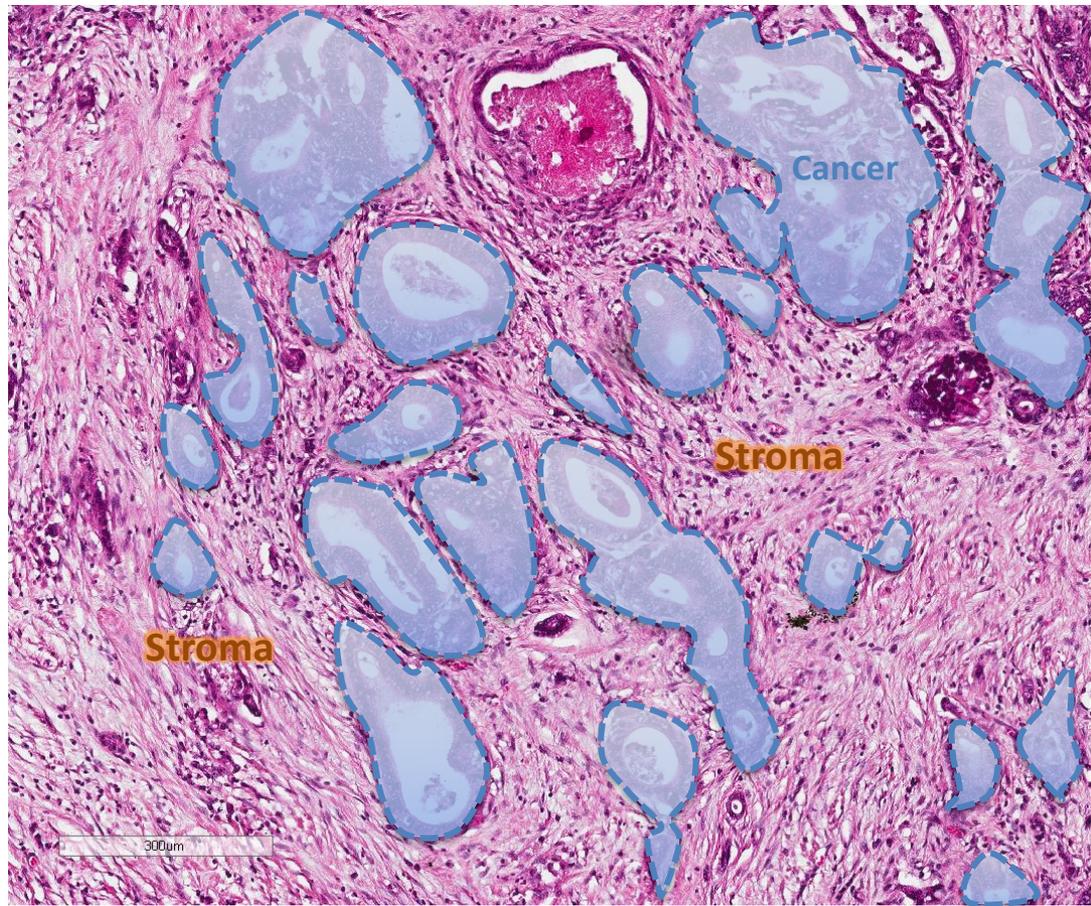
maladie du microenvironnement

XXXIV^e Réunion du CFP

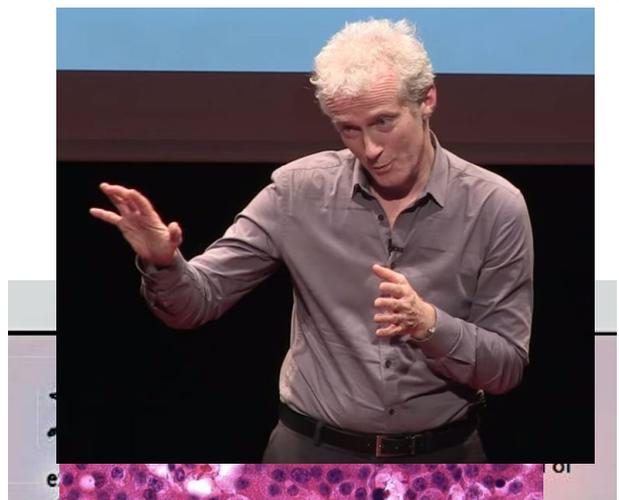
Lyon – 13 Septembre 2019

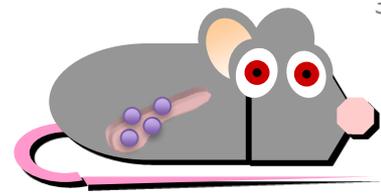
Cindy NEUZILLET

1. Question de volume...

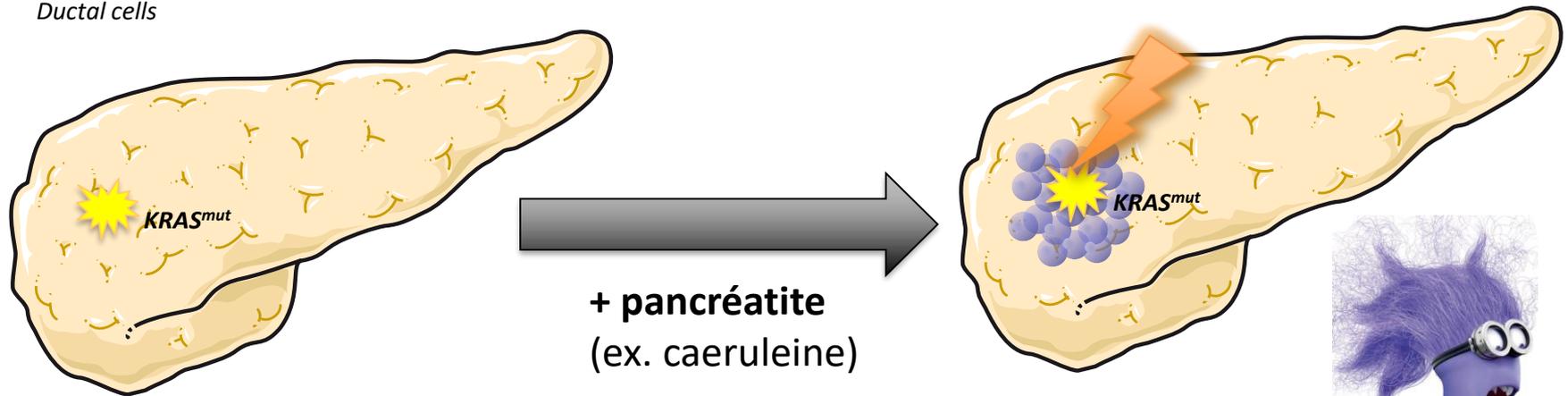
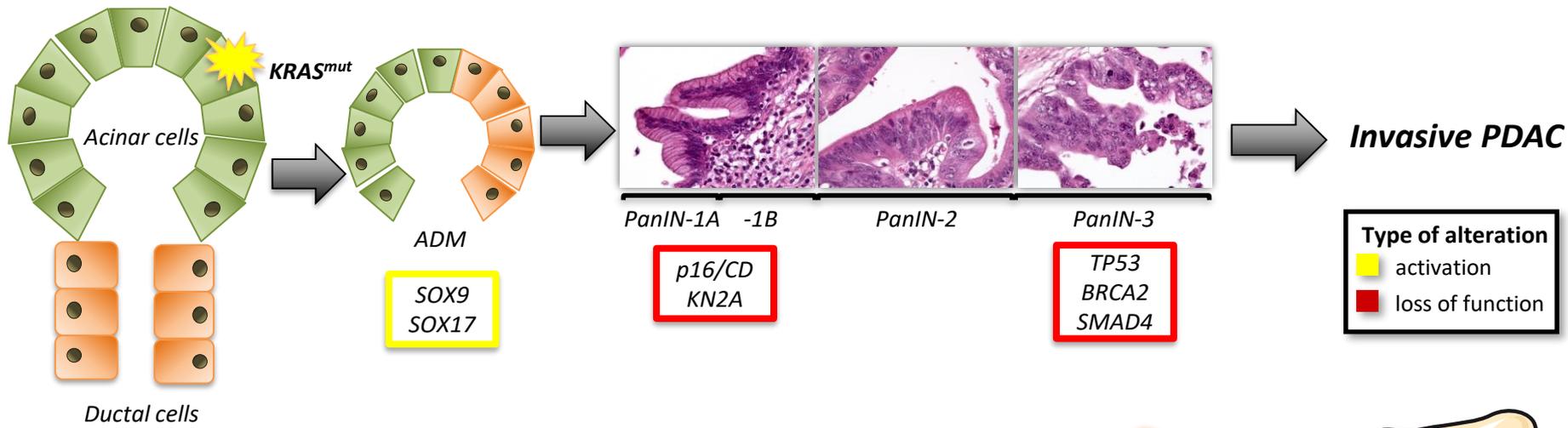


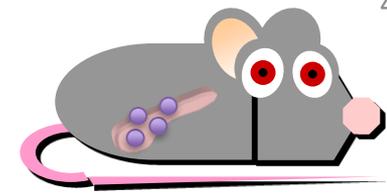
PDAC



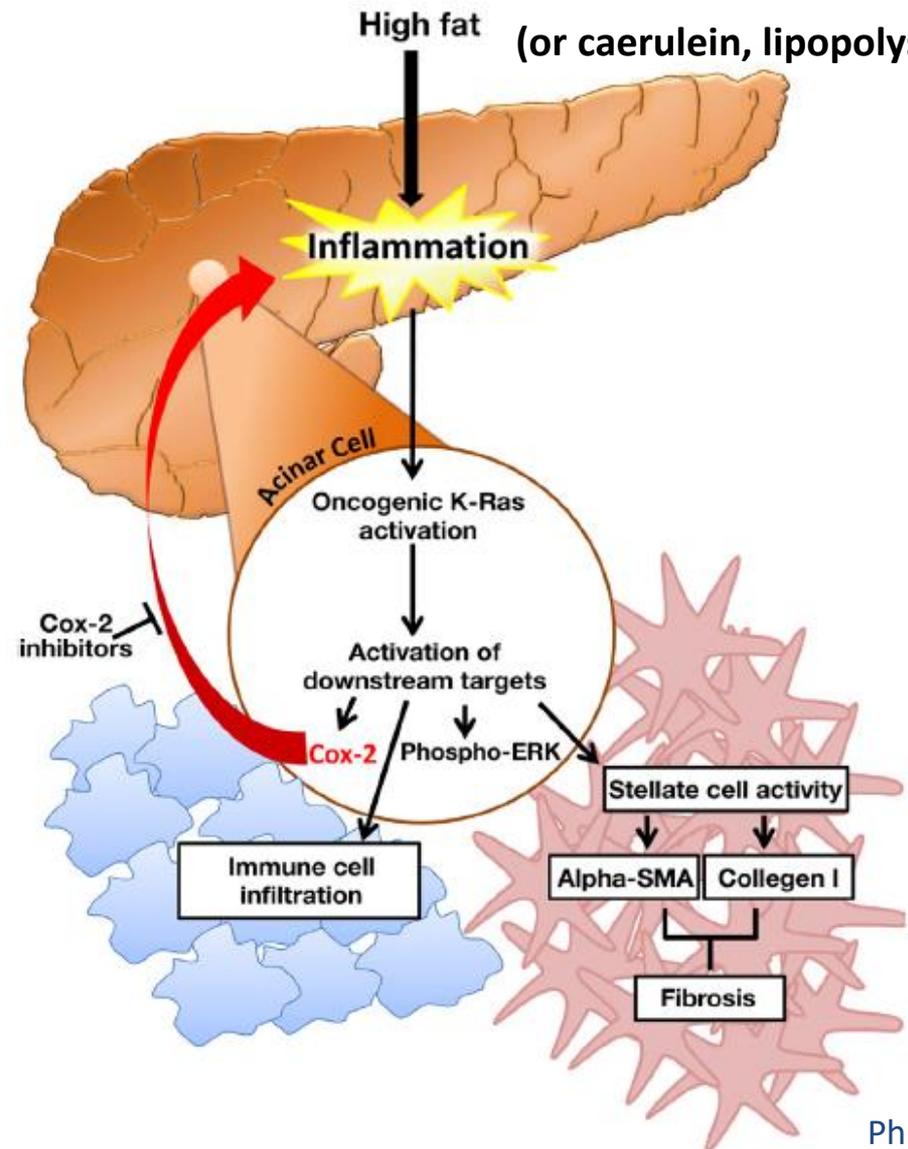


2. Au commencement...



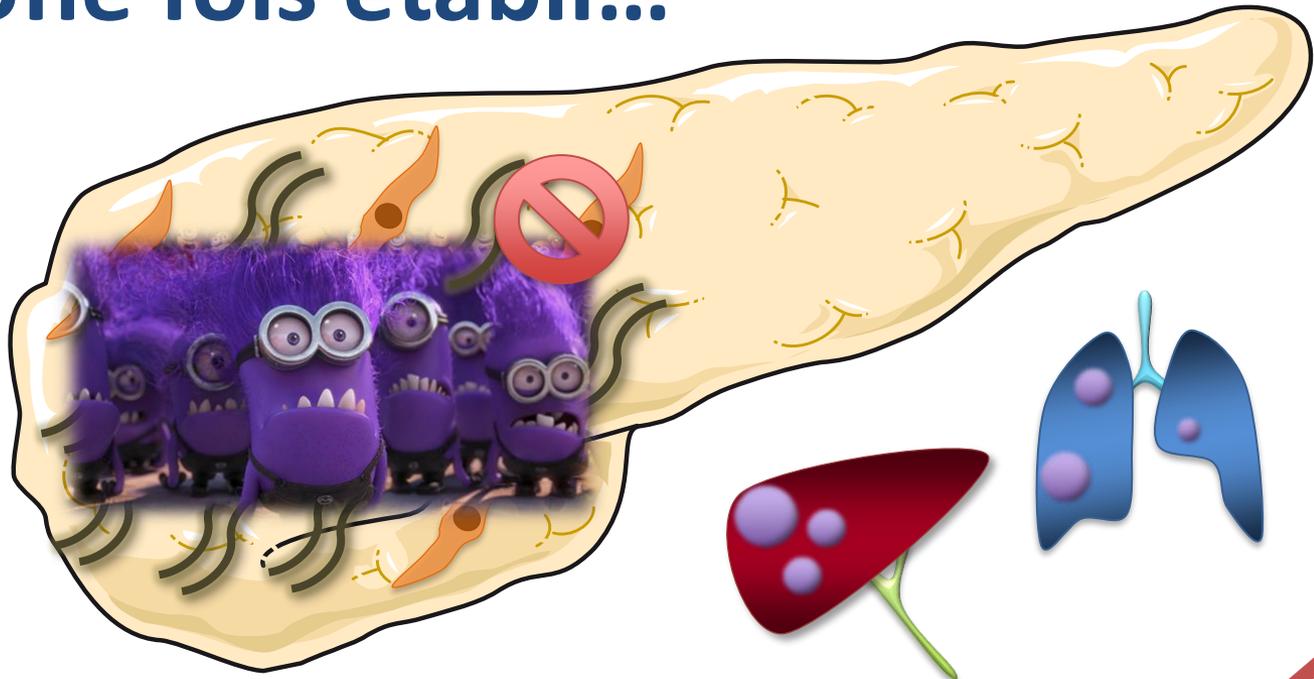


2. Au commencement...





3. Une fois établi...



Hh deletion
 ↓ differentiation,
 ↑ vascularization,
 ↑ prolifération

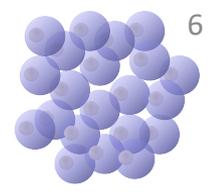
αSMA deletion
 ↓ differentiation,
 ↑ EMT/stem cells,
 ↑ hypoxia, ↑ Treg

Stromal Elements Act to Restrain, Rather Than Support, Pancreatic Ductal Adenocarcinoma

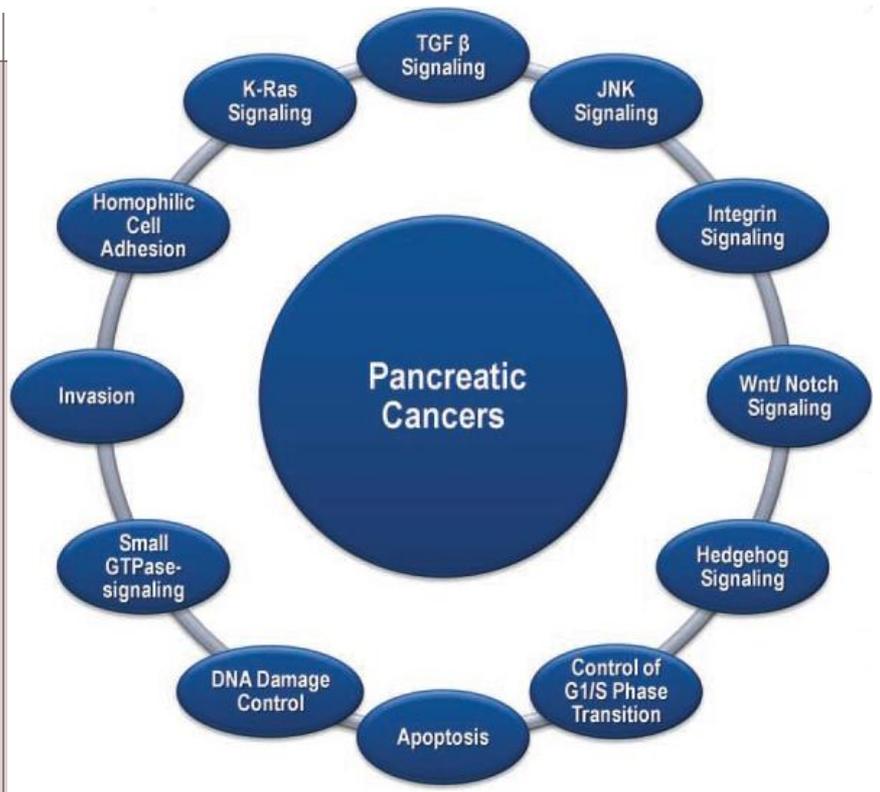
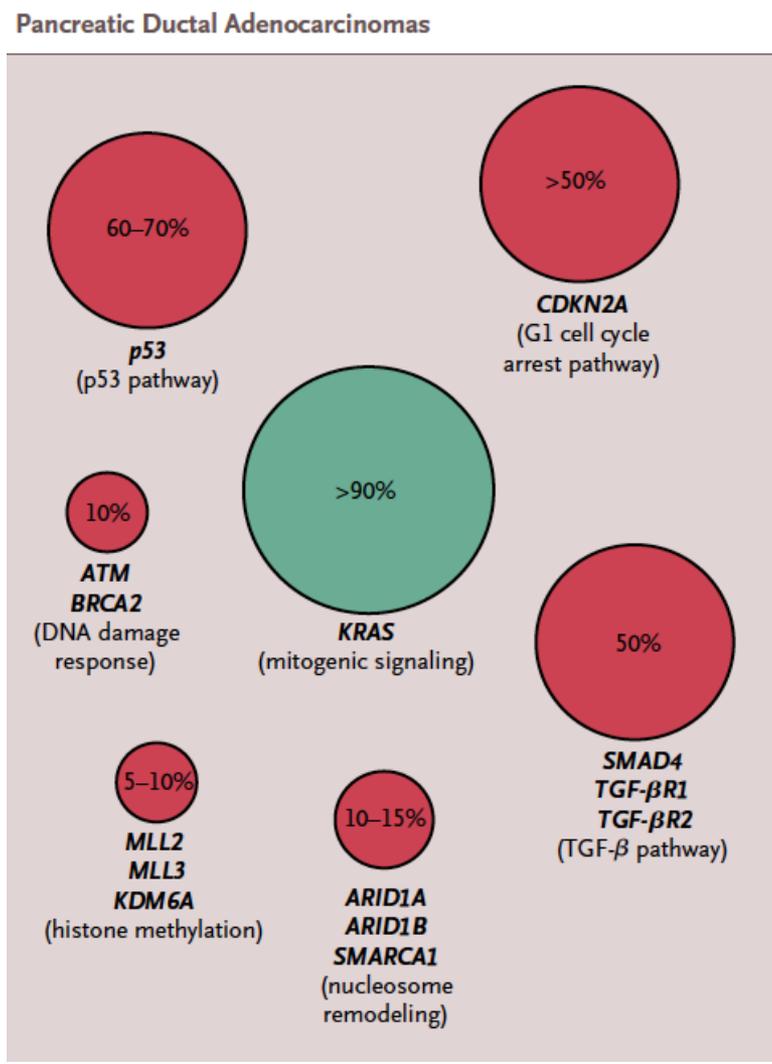
Andrew D. Rhim,^{1,2,8} Paul E. Oberstein,^{3,8} Dafydd H. Thomas,^{4,5,8} Emily T. Mirek,² Carmine F. Palermo,^{4,5} Stephen A. Sastra,^{4,5} Erin N. Dekleva,² Tyler Saunders,⁶ Claudia P. Becerra,⁵ Ian W. Tattersall,⁵ C. Benedikt Westphalen,⁴ Jan Kitajewski,⁵ Maite G. Fernandez-Barrena,⁷ Martin E. Fernandez-Zapico,⁷ Christine Iacobuzio-Donahue,⁶ Kenneth P. Olive,^{4,5,*} and Ben Z. Stanger^{2,*}

Depletion of Carcinoma-Associated Fibroblasts and Fibrosis Induces Immunosuppression and Accelerates Pancreas Cancer with Reduced Survival

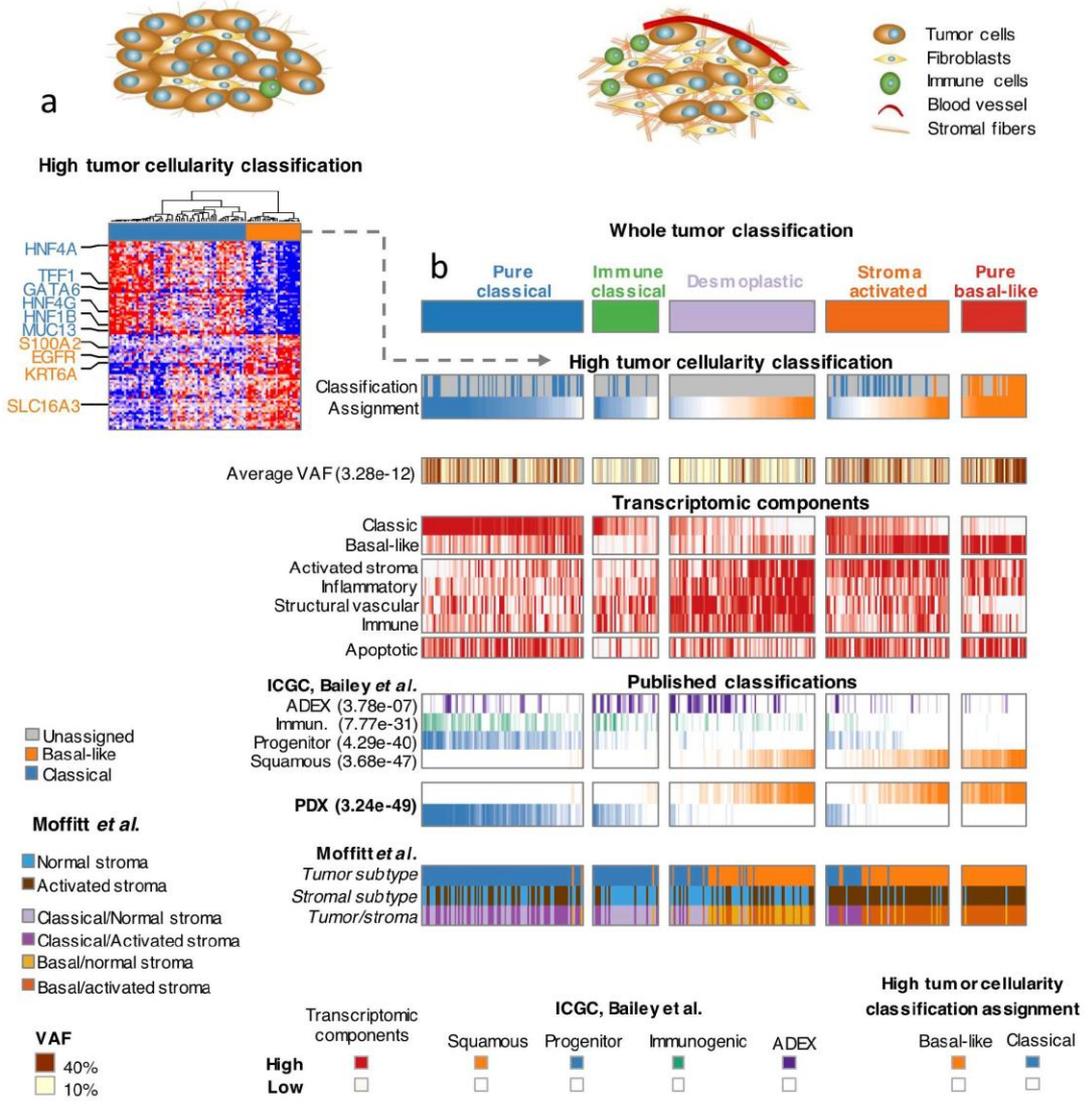
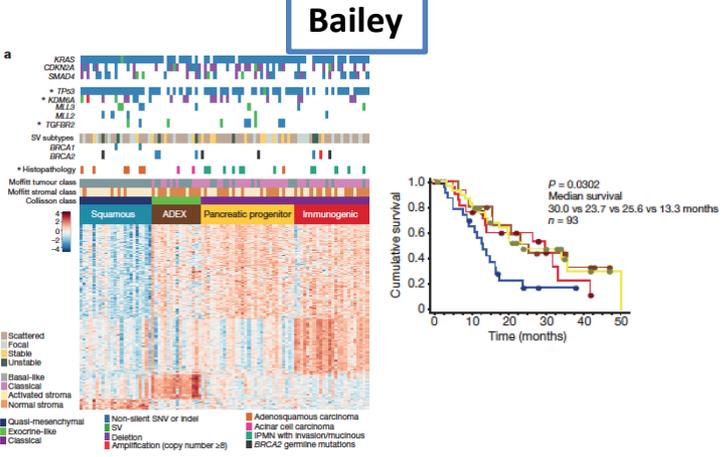
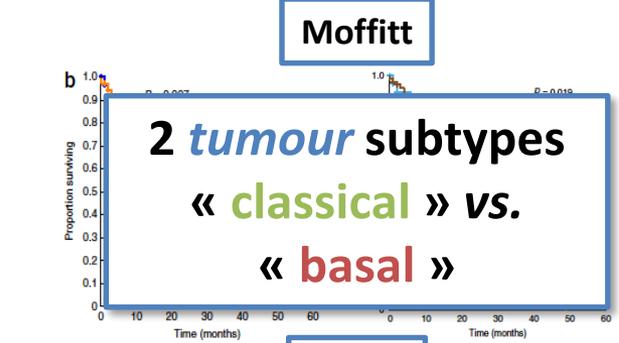
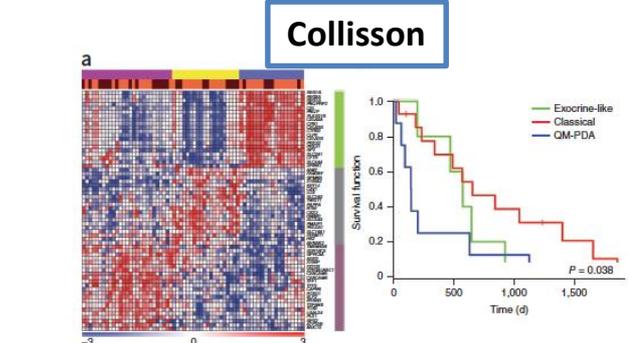
Berna C. Özdemir,^{1,2} Tsvetelina Pentcheva-Hoang,³ Julienne L. Carstens,¹ Xiaofeng Zheng,¹ Chia-Chin Wu,⁴ Tyler R. Simpson,³ Hanane Laklai,⁵ Hikaru Sugimoto,^{1,2} Christoph Kahlert,^{1,2} Sergey V. Novitskiy,⁶ Ana De Jesus-Acosta,⁷ Padmanee Sharma,³ Pedram Heidari,⁸ Umar Mahmood,⁸ Lynda Chin,⁴ Harold L. Moses,⁶ Valerie M. Weaver,⁵ Anirban Maitra,⁹ James P. Allison,³ Valerie S. LeBleu,^{1,2} and Raghuram Kalluri^{1,2,*}



4. Qu'est ce que ça a d'original ??



4. Qu'est ce que ça a d'original ??

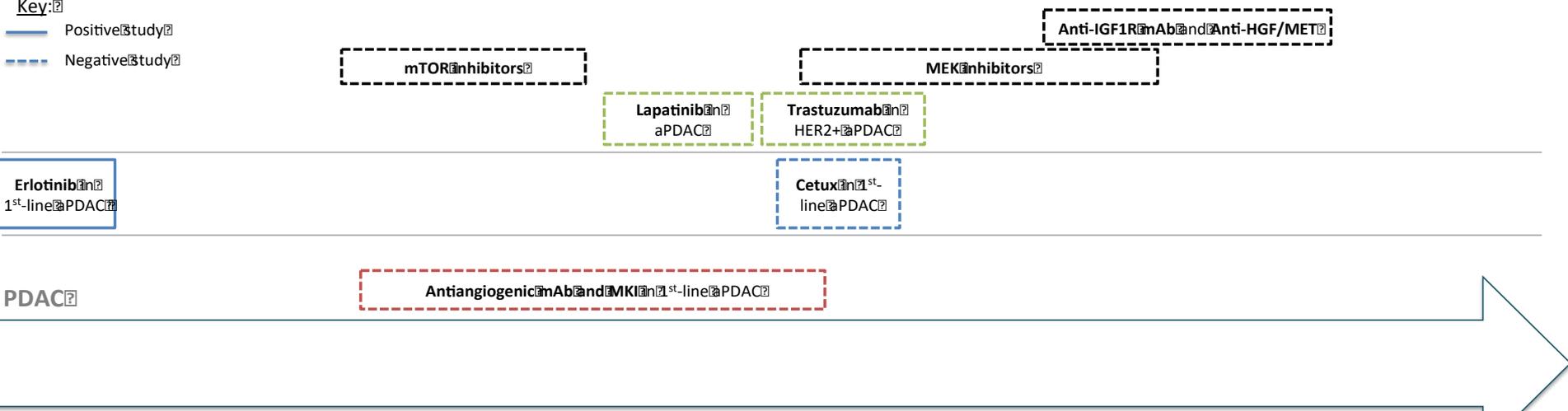


5. Les thérapies ciblées : bof...

Real-Time Genomic Profiling of Pancreatic Ductal Adenocarcinoma: Potential Actionability and Correlation with Clinical Phenotype

Lowery et al., *Clin Cancer Res* 2017

Key:
 — Positive study
 - - - Negative study



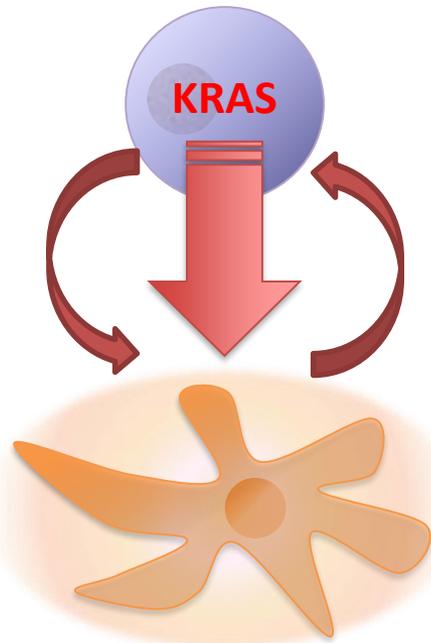
Echec de toutes les « thérapies ciblées » à ce jour
 Sauf

- erlotinib *mais* bénéfique de SG = 10 jours
- olaparib *mais* seulement dans les gBRCA (4-7%)
 - immunothérapie dans les MSI (<2%)
- altérations *ALK, NTRK, NRG-1* *mais* rare (<5%) et non spécifique

Neuzillet et al., *Pharmacol Ther* 2017

Singh et al., *Cancer Treat Rev* 2019 ; Herbst & Zheng, *Lancet Gastroenterol Hepatol* 2019

6. Le microenvironnement explique la résistance/agressivité



Chimiothérapie/
Thérapies ciblées

Composition, organisation et rigidité de la matrice

Laklai et al., *Nat Med* 2016
Erdogan et al., *J Cell Biol* 2017
Vasseur et al., *Nat Comm* 2017

Hypoxie

Erkan et al., *Neoplasia*, 2009 (review)

Facteurs de croissance, cytokines inflammatoires

Duluc et al., *EMBO* 2015
Apte et al., *Cancer Lett* 2016 (review)

Métabolites et a.a.

Sousa et al., *Nature* 2016
Kamphorst et al., *Cancer Res* 2015

Epigénétique

Ying et al., *Cell* 2012
Dangi-Garimella et al., *Plos* 2013
Hah et al., *CSHSQB* 2015 (review)

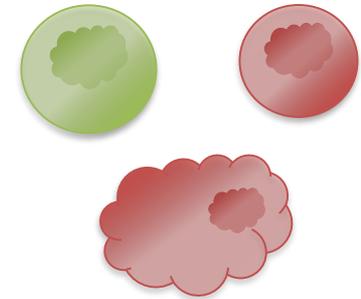
Vésicules

Leca et al., *J Clin Invest* 2016
Richards et al., *Oncogene* 2017

Drug scavenging

Hessman et al., *Gut* 2016

Immunothérapie



Hypoxie/ pression interstitielle élevée

Von Hoff et al., *Cancer Cell* 2009

Barrière physique/ cytokinique

Turley et al., *Nat Rev Immunol* 2015
Carstens et al., *Nat Comm* 2016

Infiltration par cellules immunosuppressives

Tsujikawa et al., *Cell Rep* 2017

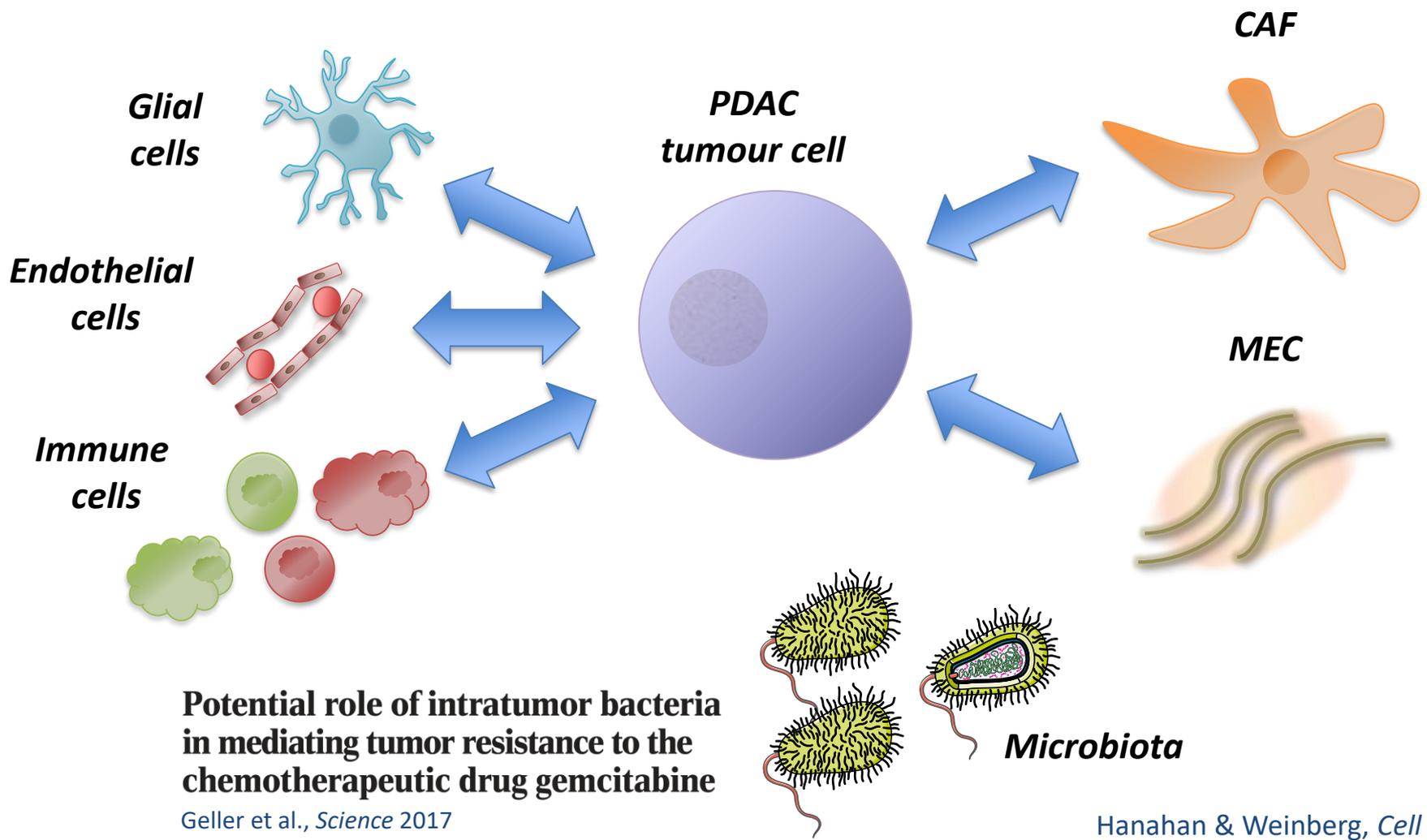
Cytokines (TGFβ)

Principe et al., *Cancer Res* 2016
Mariathasan et al., *Nature* 2018

...

Nesse et al., *Gut* 2019
Balachandran et al., *Gastroenterology* 2018

7. Cellules tumorales sous influence...



Potential role of intratumor bacteria in mediating tumor resistance to the chemotherapeutic drug gemcitabine

Geller et al., *Science* 2017

Hanahan & Weinberg, *Cell* 2011
 Neesse et al., *Gut* 2015

Conclusions

- Rôle central du microenvironnement :
 - Dans l'**initiation** de la carcinogenèse
 - Dans la **modulation de l'agressivité** des cellules tumorales
 - Dans la **résistance** aux traitements
- Echec du ciblage des cellules tumorales
- Dérégulation du microenvironnement, et au delà, de l'hôte (**cachexie**)

