18-19 novembre 2024

Retraite LITO

Séance 1

Past achievement 2019-2024

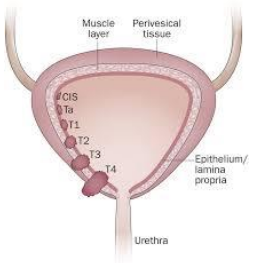
Molecular Oncology Team

> Integrated Molecular PAthology and pre-Clinical Testing (IMPACT)

ENSEMBLE, PRENONS LE
CANCER DE VITESSE

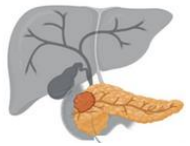
General strategy: Network analysis to inform personalized medicine

Anotated human tumour samples



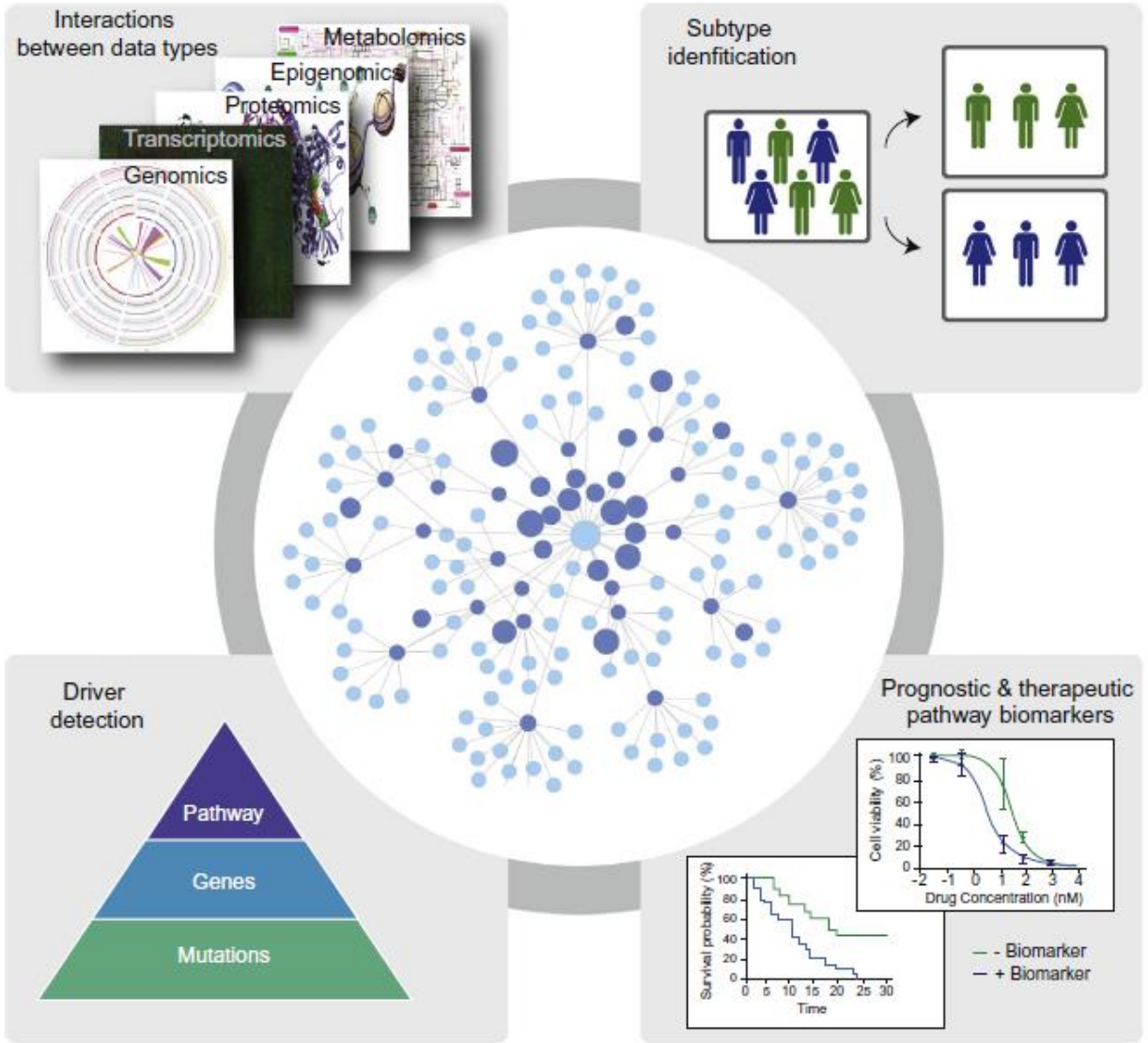
bladder cancer

Cohorts:
- CIT program
- COBLAnCE
- VESPER



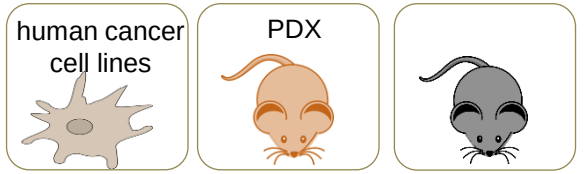
Pancreatic cancer (from 2022)

Cohorts:
- PRODIGE
- TEDOPAM
- APACAP…



Ozturk et al., J Mol Biol 2018

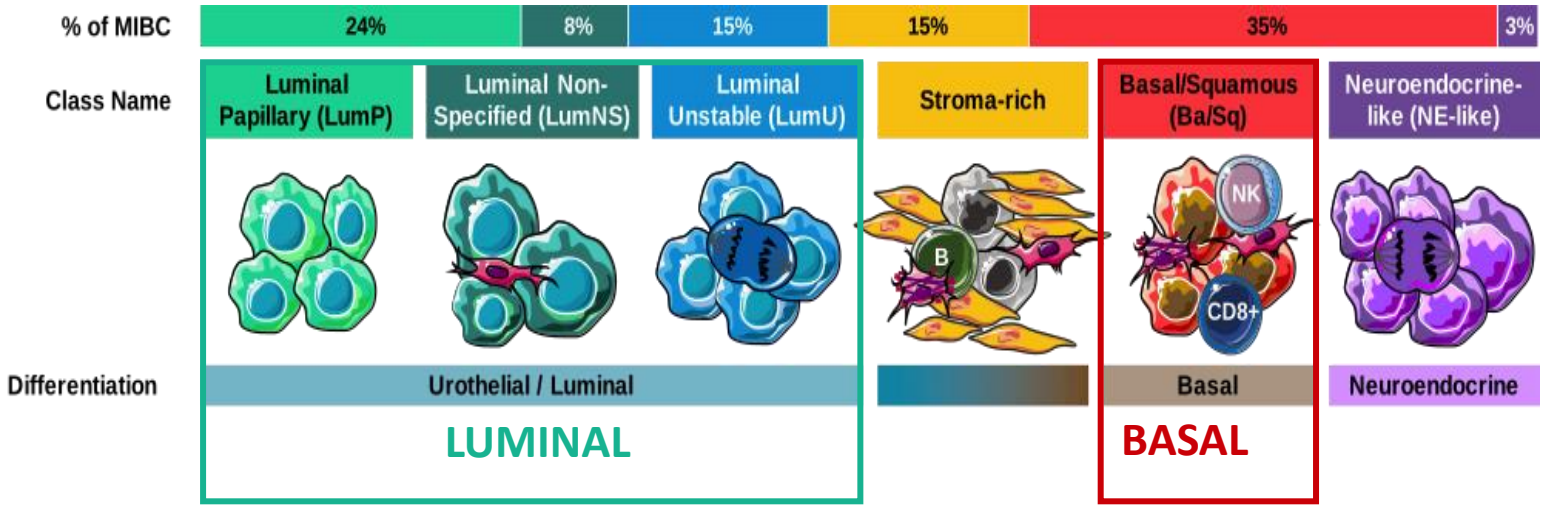
Preclinical models



Functional validation/ drug development /

institutCurie

Establishment of a Consensus Molecular classification for MIBC : 6 subtypes



Kamoun et al. *Eur. Urol.* (2020)

http://cit.ligue-cancer.net:3838/apps/consensusMIBC_web/

Can further be subdivided in Basq1/ Basq2 based on LncRNA
Estrada et al., in preparation

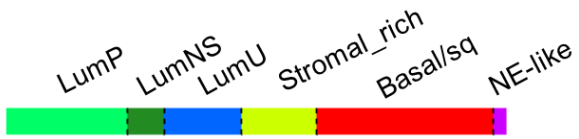
Lilia Estrada

Actionable driver for the different subgroups ?

-> Hypothesis based on mutational/ CNV/ pathway enrichment analysis : EGFR/FGFR3/PPARG
-> tests required *in vitro* and *in vivo* preclinical models

institutCurie

Establishment and characterization of pre-clinical models- Validation of new targets



Human cell lines

Xiangyu Meng

4

8

=> FGFR3, PPARG, AHR, as therapeutic targets

Shi, Meng et al., Genome med 2020
Rochel et al., Nat commun 2019

12

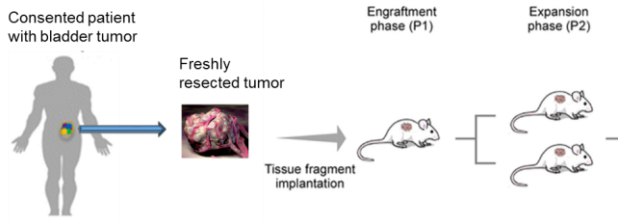
=>EGFR as therapeutic target

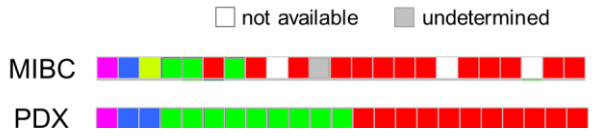
Rebouissou, Bernard-Pierrot et al., *Science Transl. Med*. 2014

Collaboration with urosphere

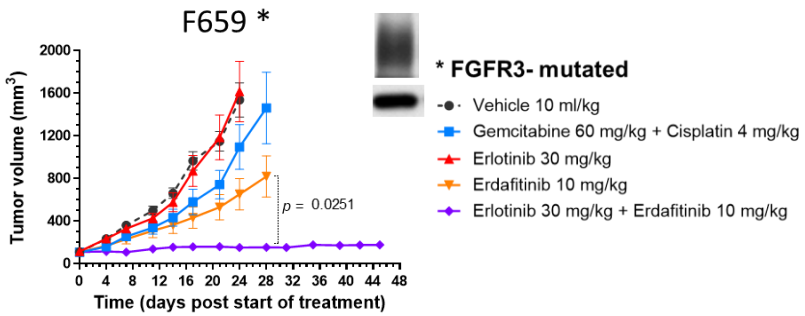
PDX models

Luc Cabel





LumP



⇒ Synergy of FGFR and EGFR inhibitors for FGFR3 mutated tumors

Sarcomatoid tumors are resistant to anti-EGFR <=

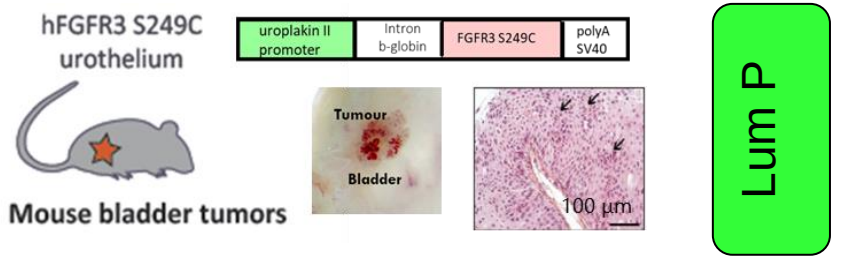
Lang, Cabel et al., Front Oncol. 2022

Mouse models

Mingjun Shi

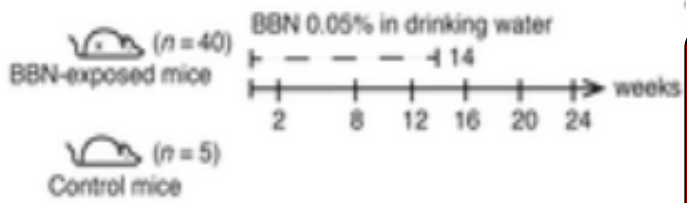
Aura Moreno-Vega

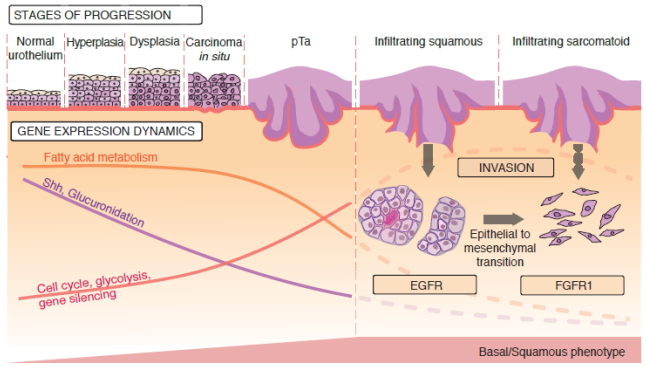
Jacqueline Fontugne



Lum P

Shi, Moreno-Vega, Fontugne et al., Eur Urol 2022





Basal /sq

Fontugne et al., J Pathol 2023

Identification of a dual subtype-dependent role of PPARG

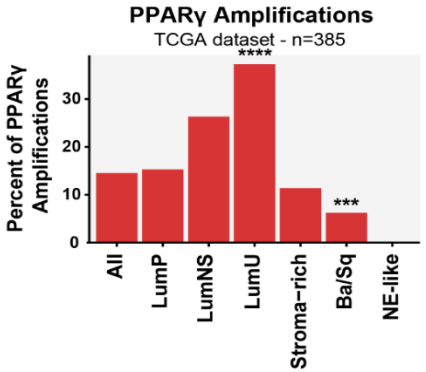

Natacha Rochel

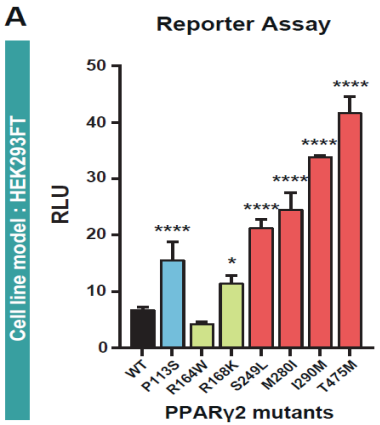

Laure Coutos-Thévenot

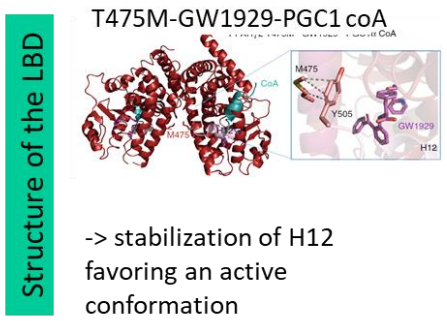

Clémentine Krucker

Oncogene in luminal tumors

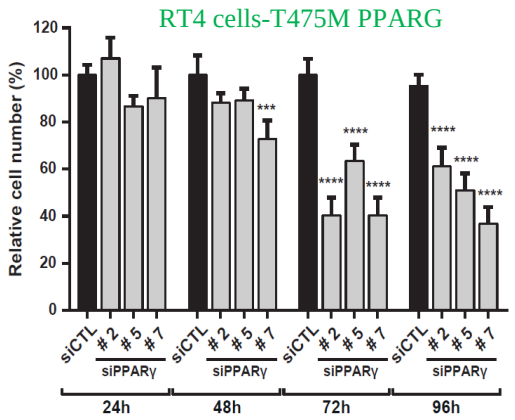
Amplification and activating mutations







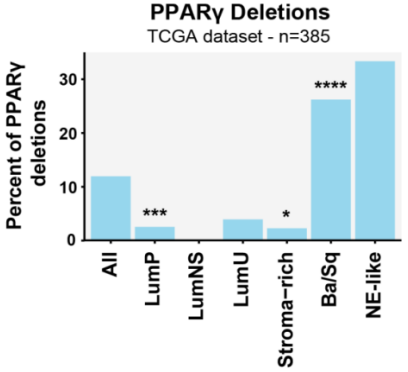
-> stabilization of H12 favoring an active conformation

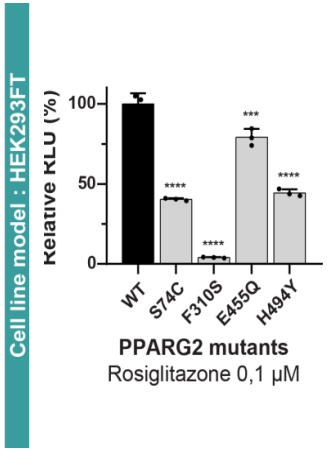


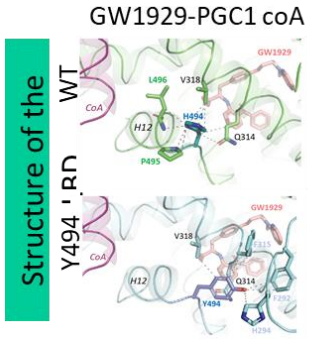
Biton, Bernard-Pierrot et al., cell report 2014
Rochel et al., Nat. Commun. 2019

Tumor suppressor in basal tumors

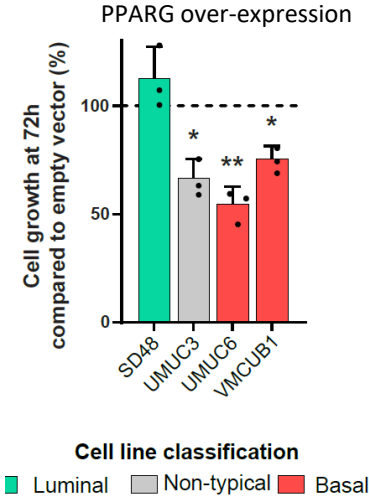
Deletion, methylation and inactivating mutations







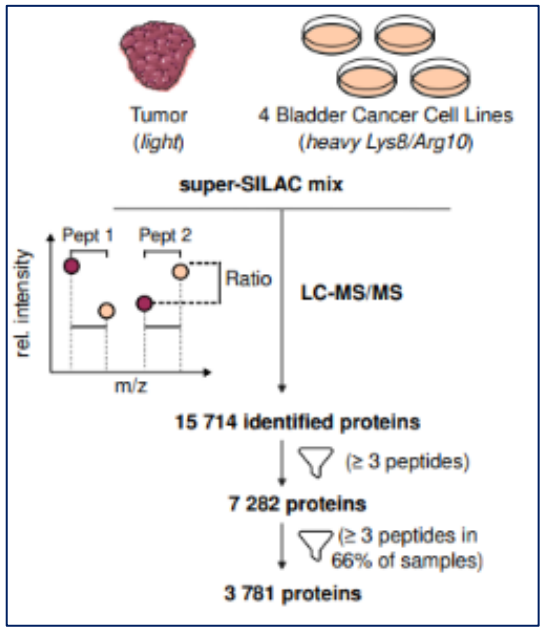
-> destabilization of H12 favoring an inactive conformation



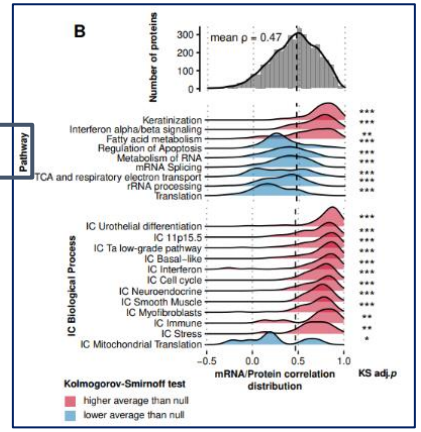
Coutos-Thevenot et al., BioRIXV 2024

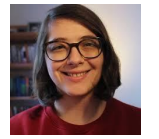
Proteogenomic characterization of bladder cancer reveals sensitivity to TRAIL-induced apoptosis in *FGFR3*- mutated tumors patient

Proteomic characterization of 40 MIBC and 23 NMIBC
with available transcriptomic and genomic data



Validation of transcriptomic data



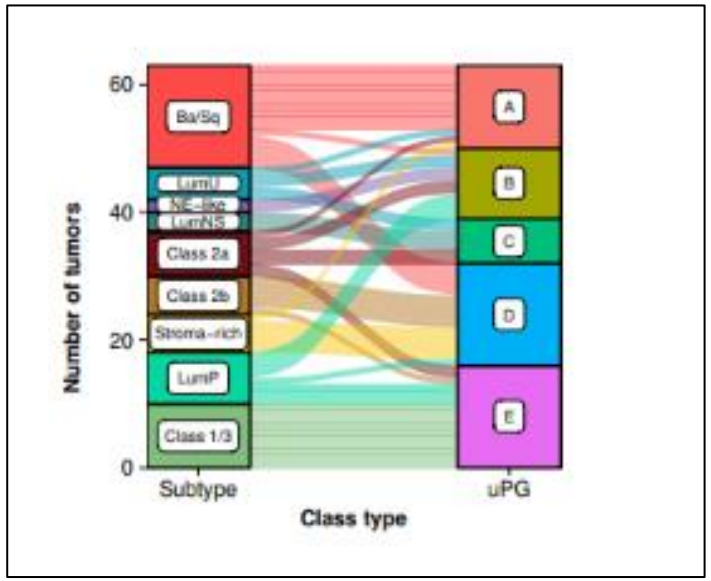

Clarice Groeneveld


Virginia Sanchez-Quiles

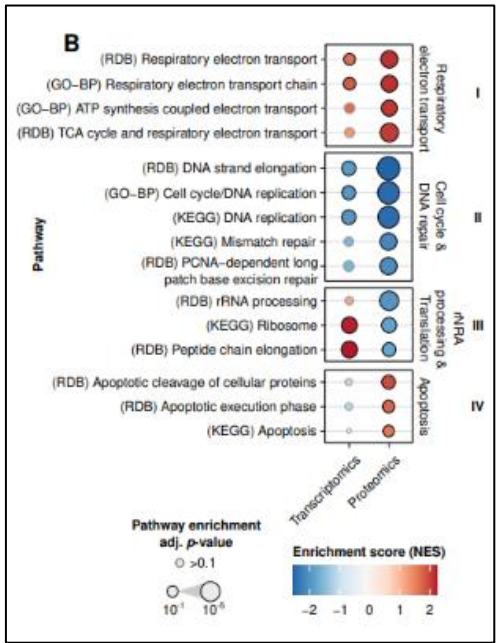

Florent Dufour

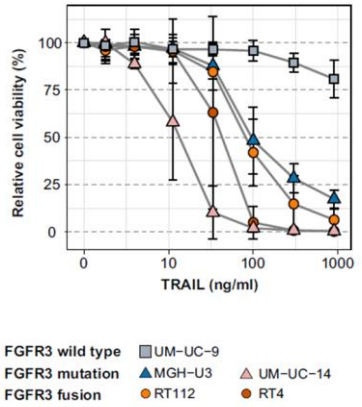
Highlights from analysis of proteomic data

Bolsters and refines existing classifications of bladder tumors



new insights underlying *FGFR3*-mutated tumors





Groeneveld, Sanchez-Quiles, Dufour et al., European Urology 2023 and patent 2022

Inference of Gene regulatory networks identifies candidate key driver TFs

Hélène Neyret-Kahn

Jacqueline Fontugne

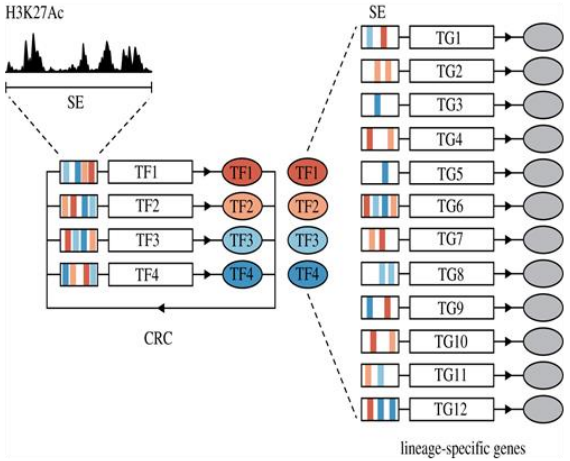
Aura Morena-Vega

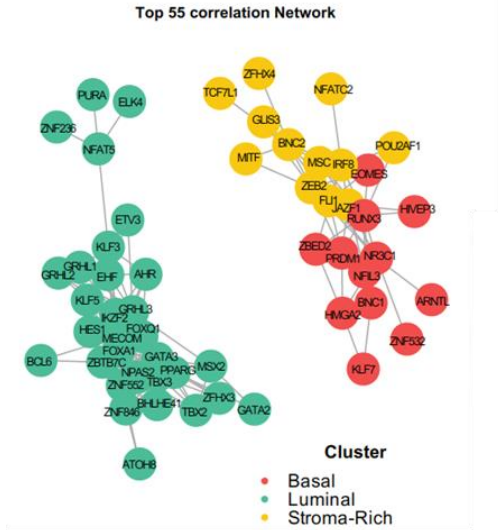
Macarena Zambrano

Lilia Estrada

Based on epigenetic data

Identification of core transcription regulatory circuitry (CRC) using H3K27Ac chip seq data from 12 lumP tumors

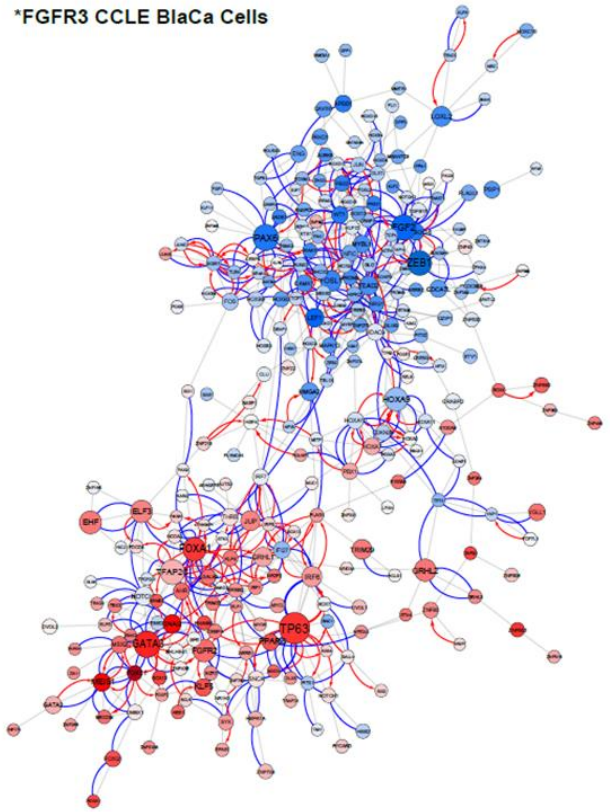




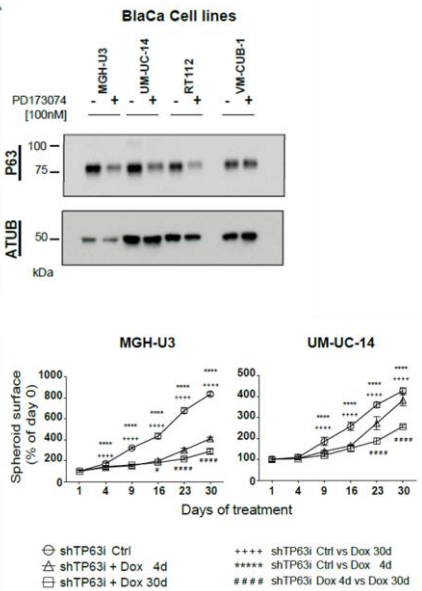
Adapted from Saint-André V. *et al.*, *Genome Res.* 2016

Based on transcriptomic data

Co-Reg Net algorithm (Nicolle et al., bioinformatics 2015)



Validation of key role of TP63 in FGFR3-mutated tumors

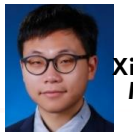


Moreno-Vega, Zambrano, Estrada et al, BioRXIV 2024

Neyret-Kahn H., Fontugne J et al., Oncogene 2023

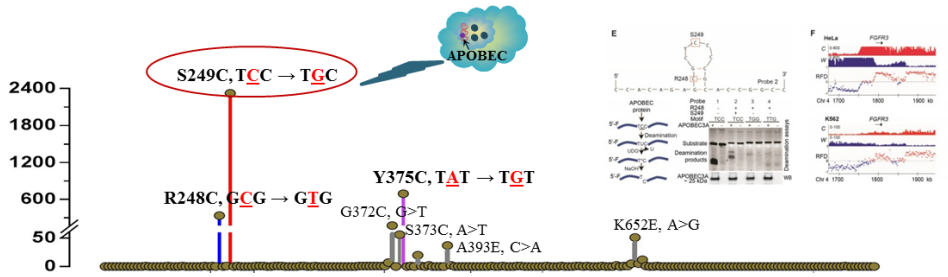
institutCurie

Highlights on 2 key mutagenesis processes in Bca


Xiangyu Meng

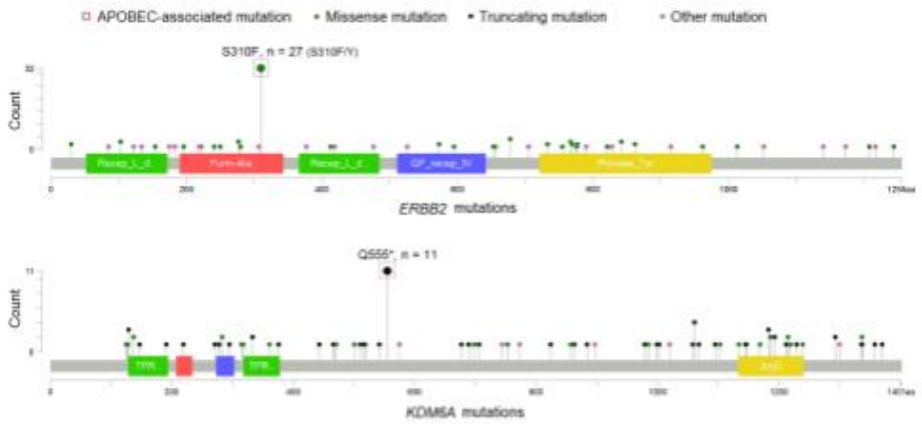

Mingjun Shi

APOBEC induces over-representation of mutations, including passenger mutations and mutations in TSG



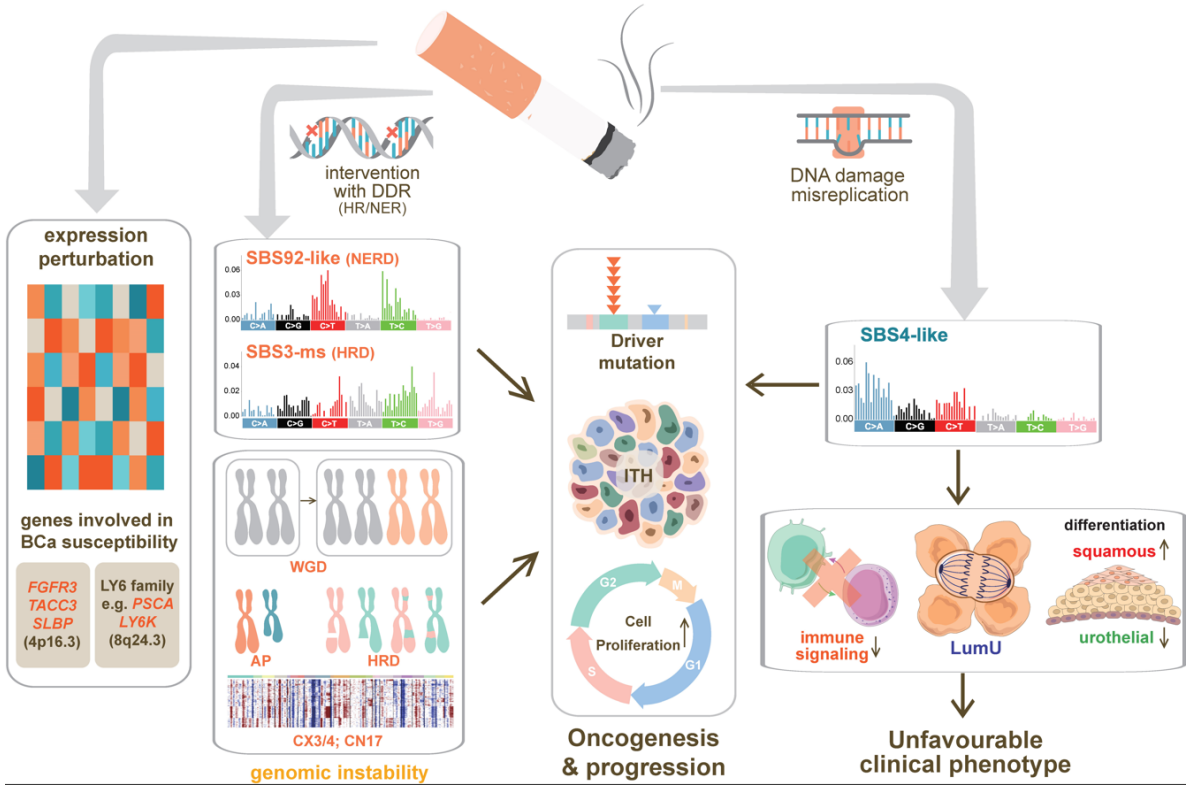
⇒ S249C is the only mutation corresponding to an APOBEC motif / in DNA loop / in lagging strand

⇒ Over-representation of APOBEC-induced mutation is systematically observed



Shi, Meng et al., Euro Urol 2019
Shi, Meng et al., Genome med 2020

Tobacco exposure is associated with multiple genomic and transcriptomic alterations favoring Bca development



Meng, Shi et al., under review in genomics, proteomics and bioinformatics

Transcriptomic molecular subtying and therapeutic consequences

sensitivity to chemotherapies ? But conflicting results...

Basal/Squamous are more sensitive to NAC and/or with better outcome after NAC than without NAC

Choi et al (2014)
PMID: 24525232

Seiler et al (2017)
PMID: 28390739

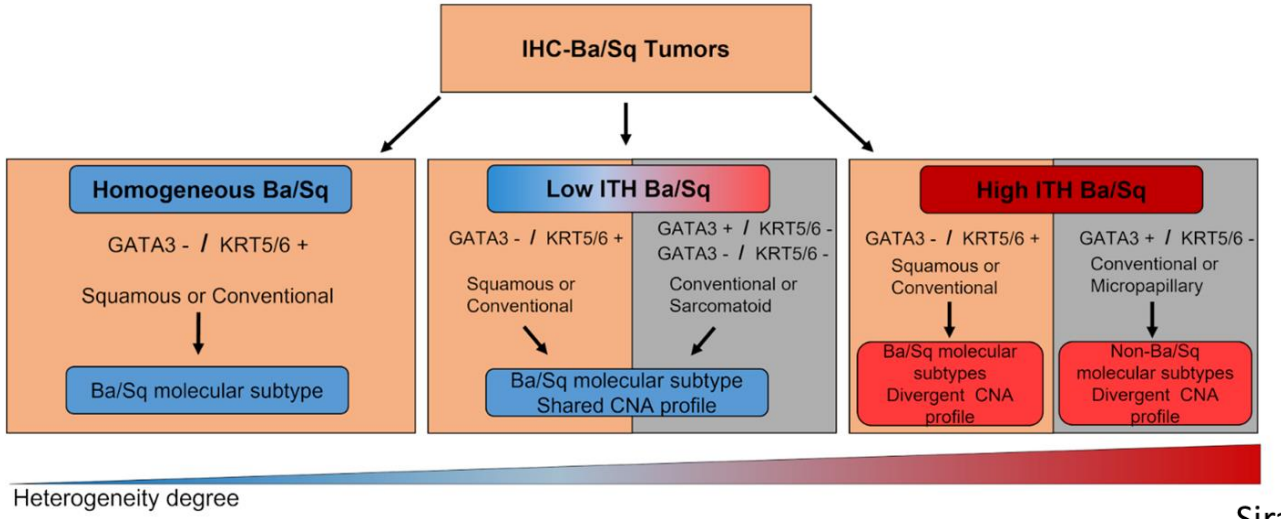
Lotan et al (2021)
PMID: 34643090

Taber et al (2020)
PMID: 32978382

Sjödahl et al (2021)
PMID: 32978382

Basal/Squamous have worse outcomes than other subtypes after NAC

Our hypothesis :
Intra-tumoral heterogeneity might be a confounder

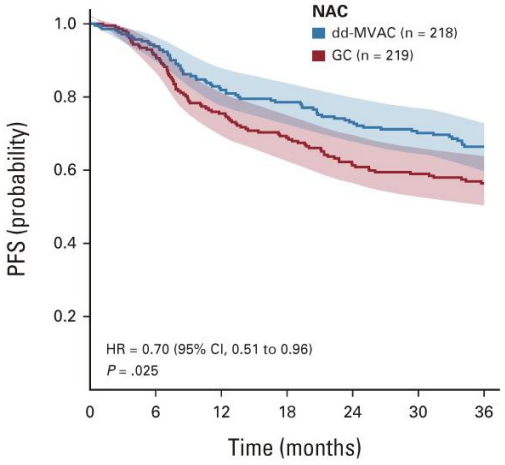


Sirab N, J Pathol 2022

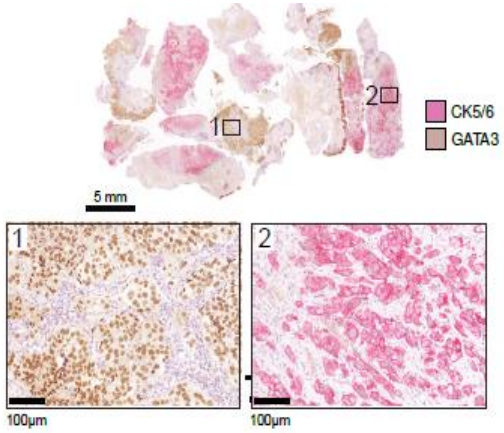
VESPER trial (GETUG – AFU)

C. Krucker

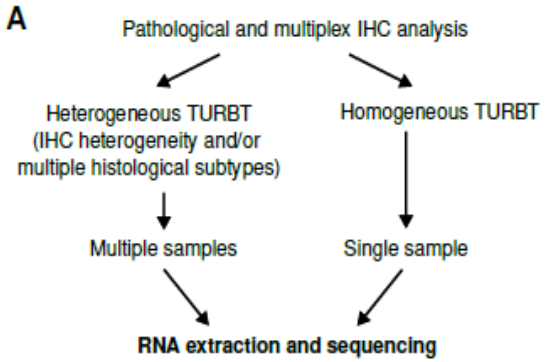
C. Groeneveld

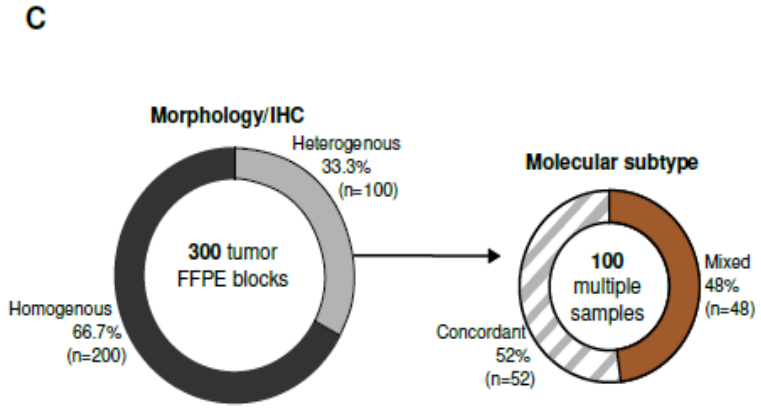


Pfister, J clin Oncol 2022

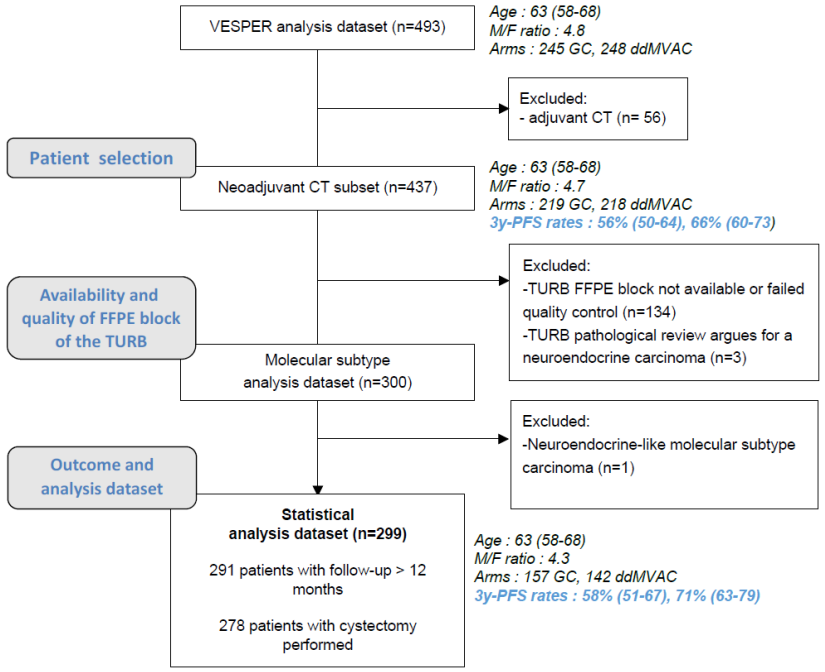


Sirab N, J Pathol 2022

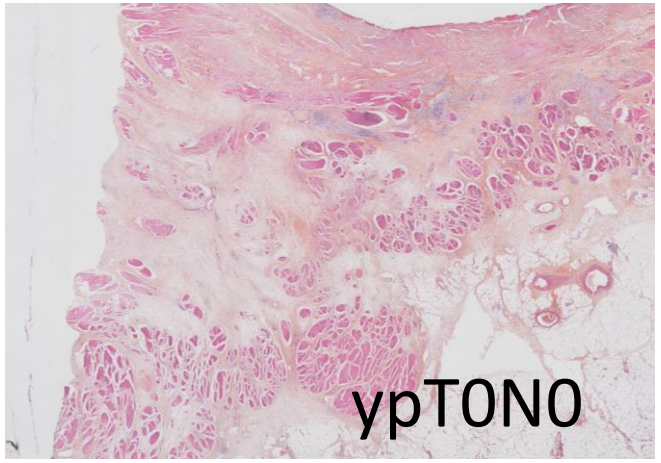


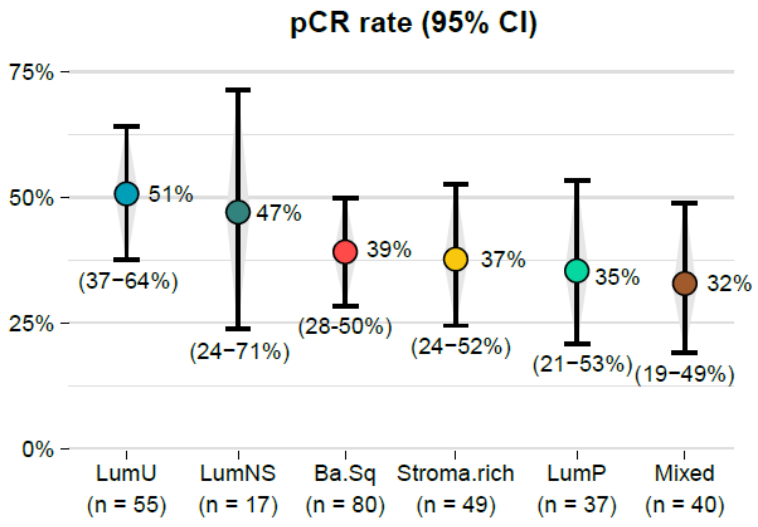


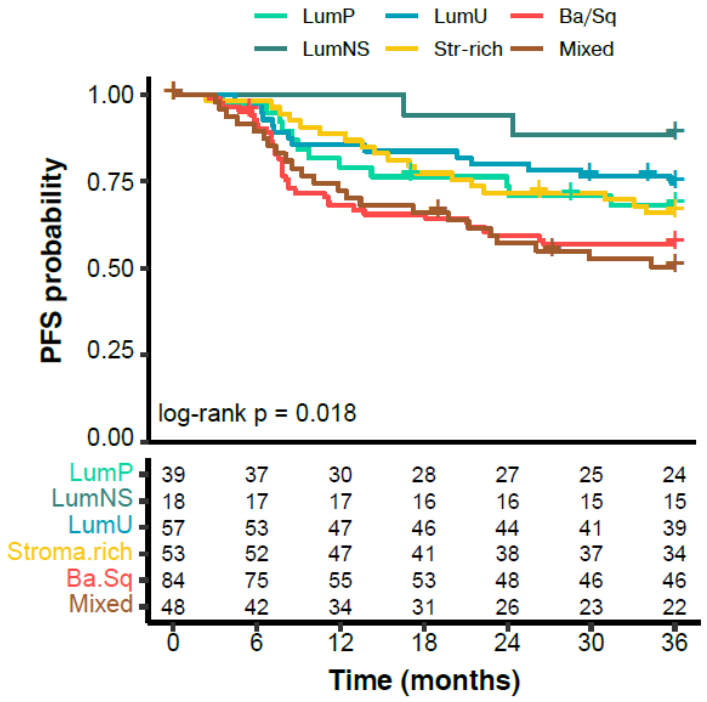
Groeneveld, Ann Oncol 2024

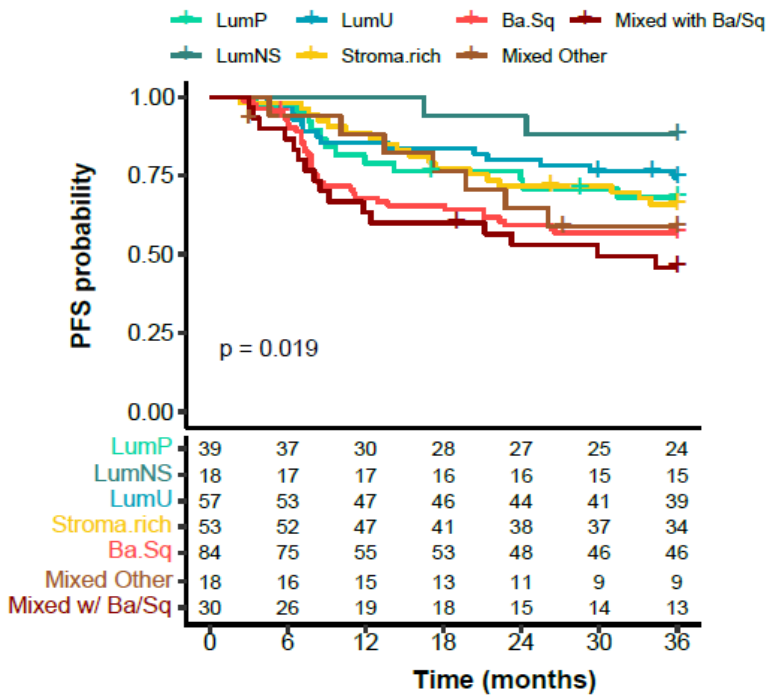


BaSq (pure or mixed) are associated with decreased Progression-Free Survival and Overall Survival compared to other subtypes in the VESPER trial, regardless of chemotherapy arm, despite of similar pathological complete response rate

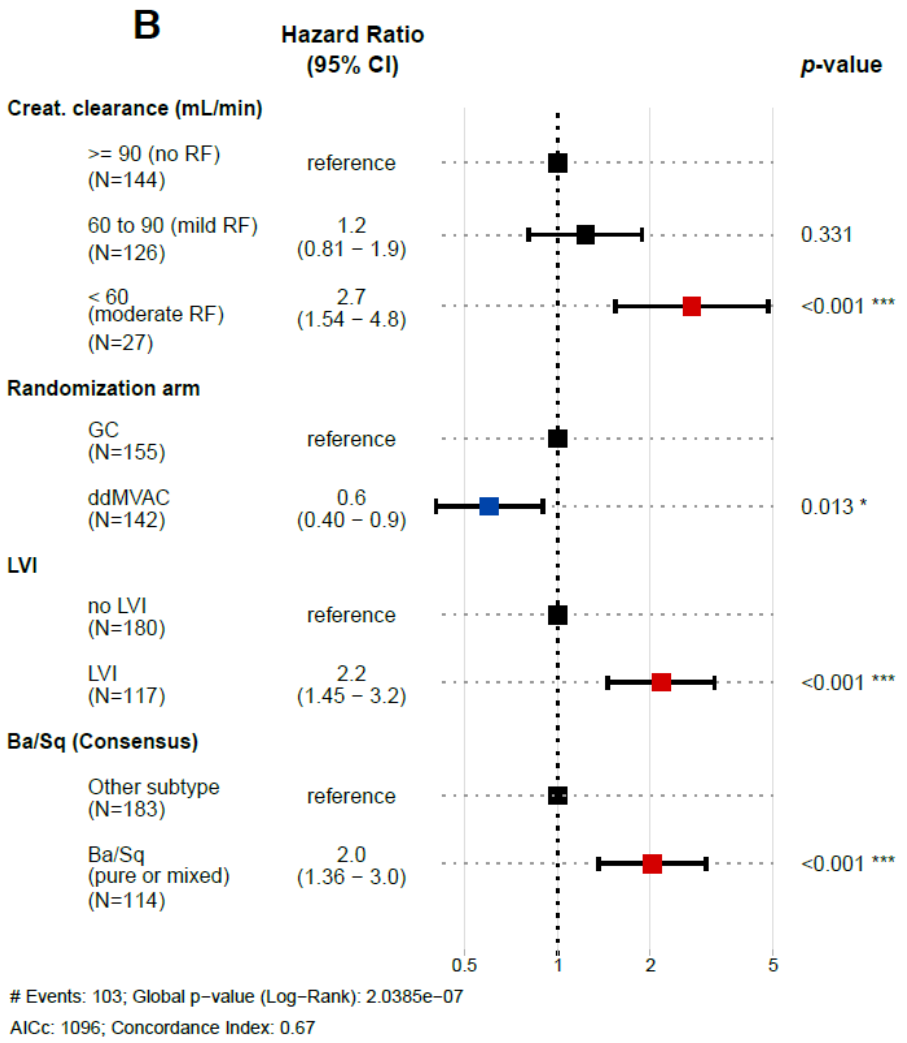


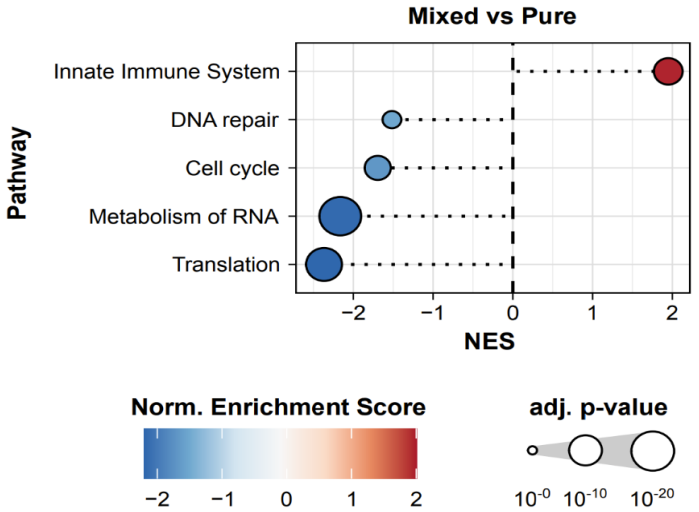






In multivariate Cox Model, BaSq (pure or mixed) is associated with PFS





Among questions

1) What are the biological bases for the mixed tumors ?
2) How to transfer in clinic heterogeneity detection ?
3) How to improve BaSq (pure or mixed) tumor prognosis ?

Groeneveld, Ann Oncol 2024

Intégration groupe "pancréas" dans l'équipe d'oncologie moléculaire (2022)

Decipher CAFs heterogeneity in PDAC

Journal of Pathology
J Pathol January 2021; **253:** 129
Published online 12 December 2020 in Wiley Online Library (wileyonlinelibrary.com) DOI: 10.1002/path.5593

ANNOUNCEMENT

Jeremy Jass Prize for Research Excellence in Pathology 2019

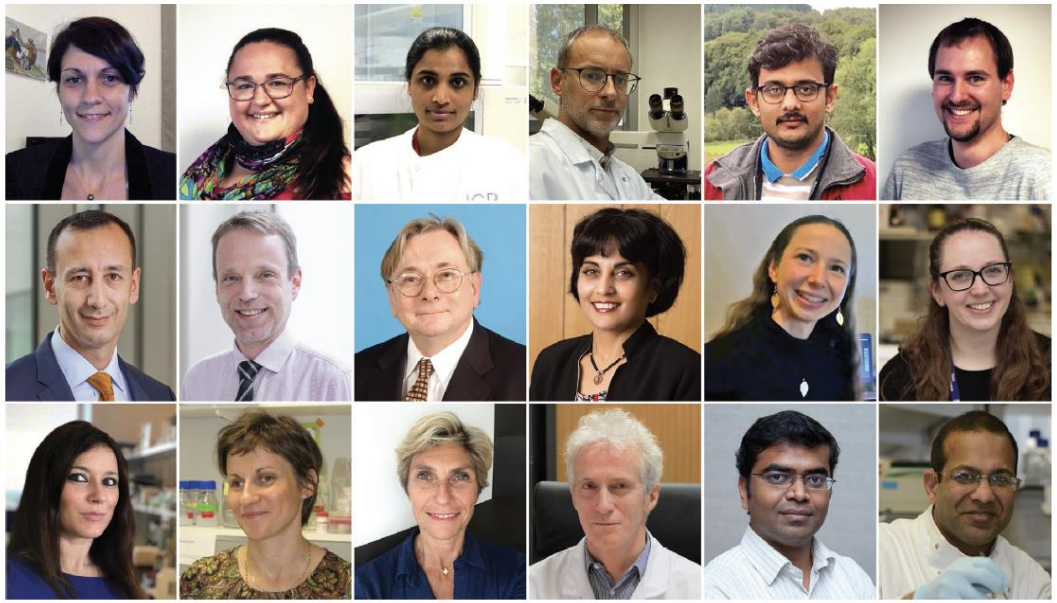
Every year the Editorial team of *The Journal of Pathology* awards the Jeremy Jass Prize for Research Excellence to the paper published in the prior calendar year that they perceive to be of the highest scientific calibre. Selection is always difficult because the standard of papers published in the Journal is so high.

The paper selected for the Jass Prize for the calendar year 2019 is:

Cindy Neuzillet*, Annemilaï Tijeras-Raballand, Chanthirika Ragulan, Jérôme Cros, Yatish Patil, Matthieu Martinet, Mert Erkan, Jörg Kleeff, Jeremy Wilson, Minoti Apte, Marie Tosolini, Abigail S Wilson, Francesca R Delvecchio, Corinne Bousquet, Valérie Paradis, Pascal Hammel, Anguraj Sadanandam* and Hemant M Kocher*. Inter- and intra-tumoural heterogeneity in cancer-associated fibroblasts of human pancreatic ductal adenocarcinoma. *J Pathol* **2019**; 248: 51–56. DOI: 10.1002/path.5224

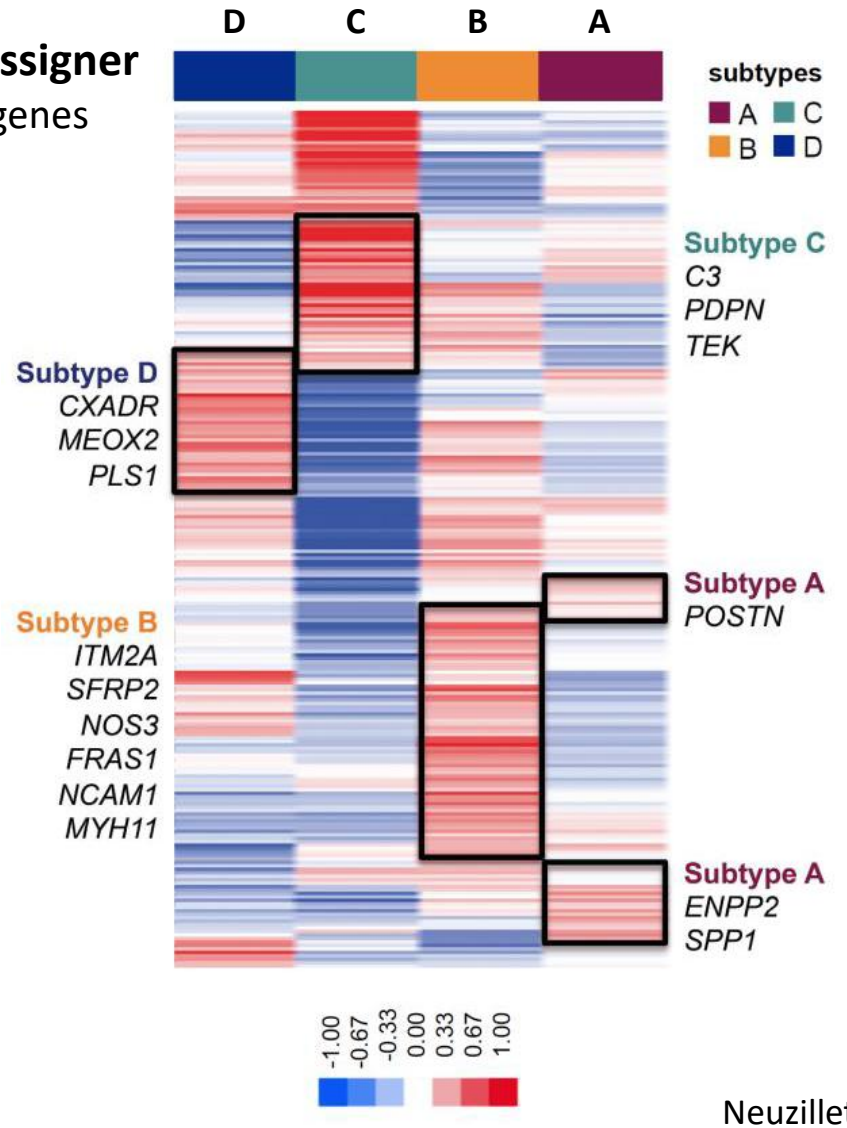
* *Co-corresponding authors*

We offer our congratulations to the authors, who are shown in Figure 1. The paper is available with Open Access at https://onlinelibrary.wiley.com/doi/full/10.1002/path.5224



RNA signatures

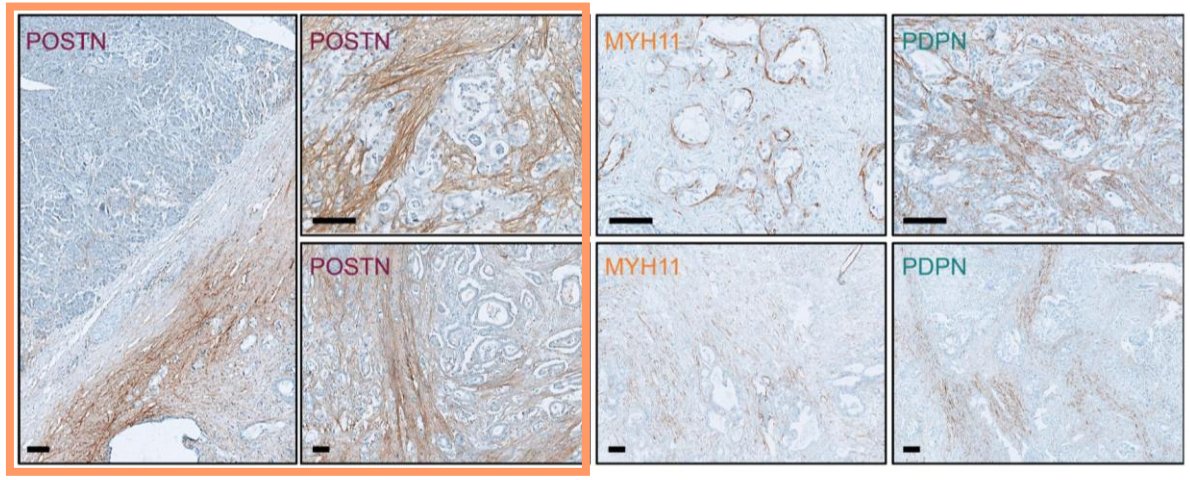
pCAF assigner
248 genes



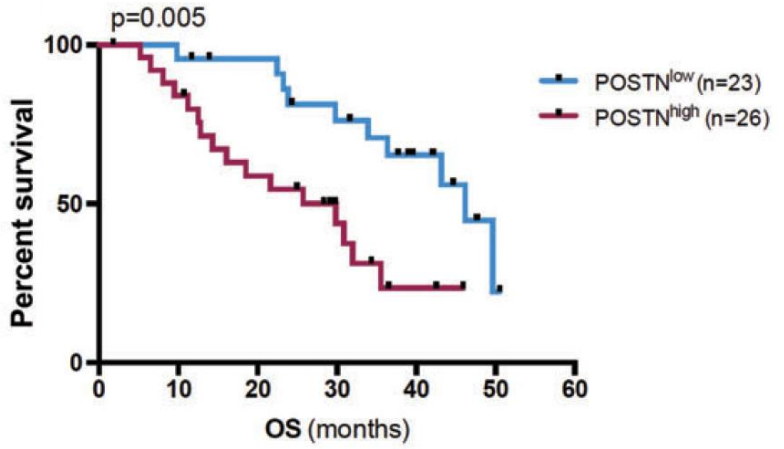
Neuzillet et al., *J Pathol* 2019

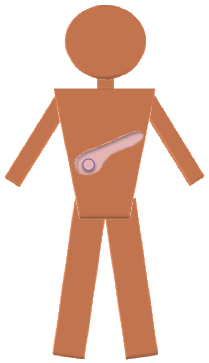
Decipher CAFs heterogeneity in PDAC

IHC markers

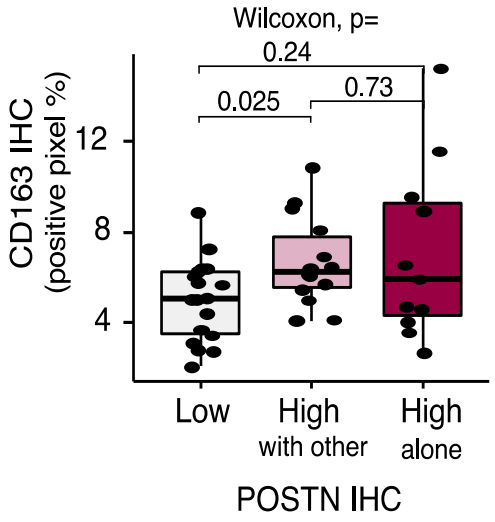


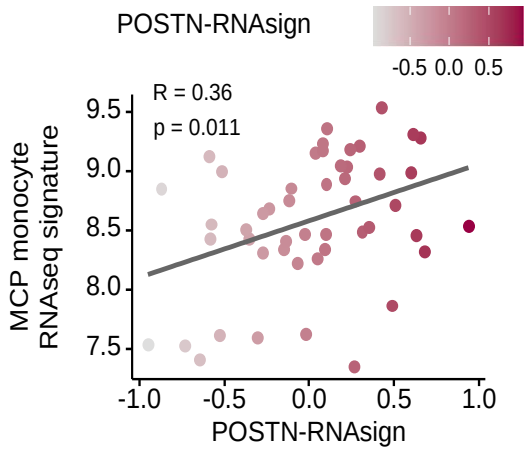
Subtype **A** **B** **C**

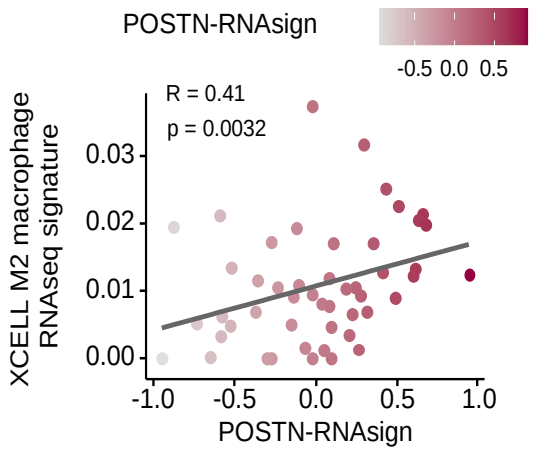




Resected PDAC samples
N=50







POSTN-positive CAF

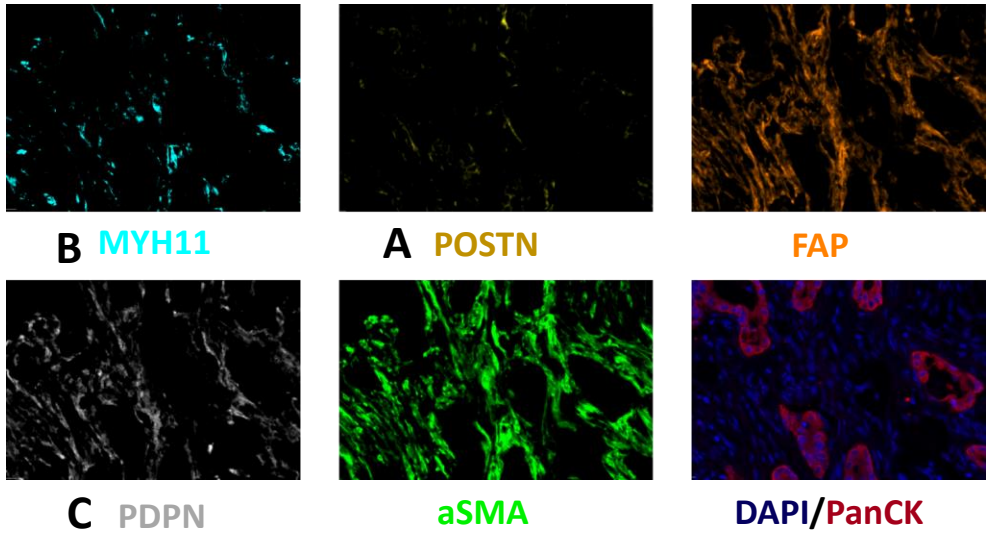
- ✓ Negative prognostic impact
- ✓ Association with immune TME (M2 macrophage infiltration)

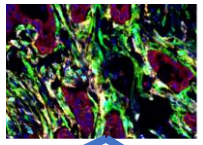
Neuzillet et al., *J Pathol* 2019

Neuzillet et al., *J Pathol* 2022

Decipher CAFs heterogeneity in PDAC

Multiplex IF





- Access to FFPE samples from operated PDAC
- No pre-operative treatment

Hôpital Beaujon AP-HP

Cohort 1 (n=44)

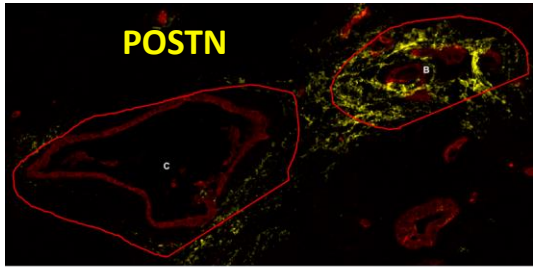
The New England Journal of Medicine

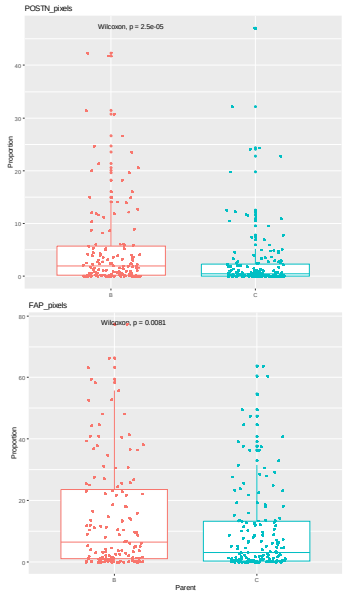
PRODIGE

FOLFIRINOX or Gemcitabine as Adjuvant Therapy for Pancreatic Cancer

PRODIGE 24 - Cohort 2 (n=209)

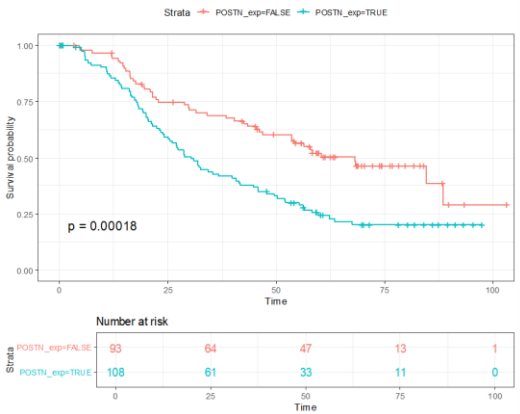
✓ FAP and POSTN are enriched in basal areas

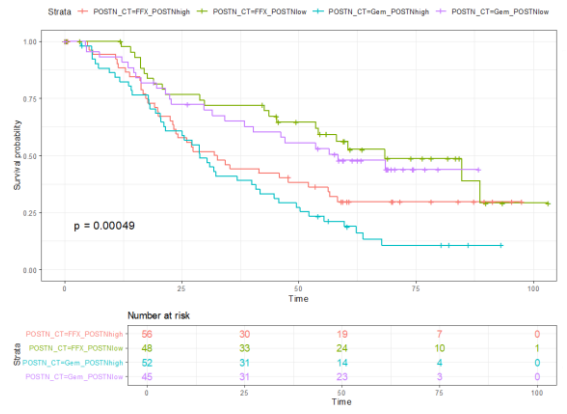




M. Hilmi

✓ High POSTN expression is an independent prognostic and predictive value (adjuvant chemo.)

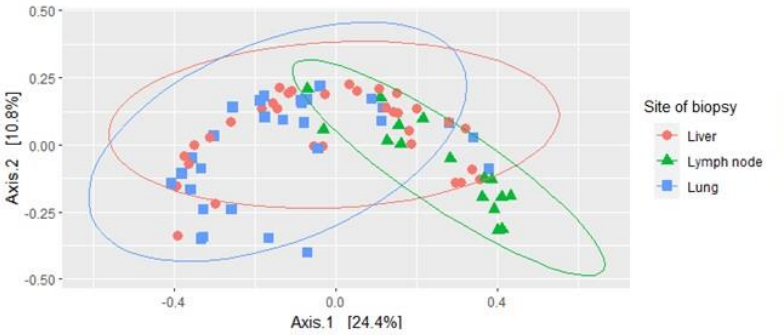


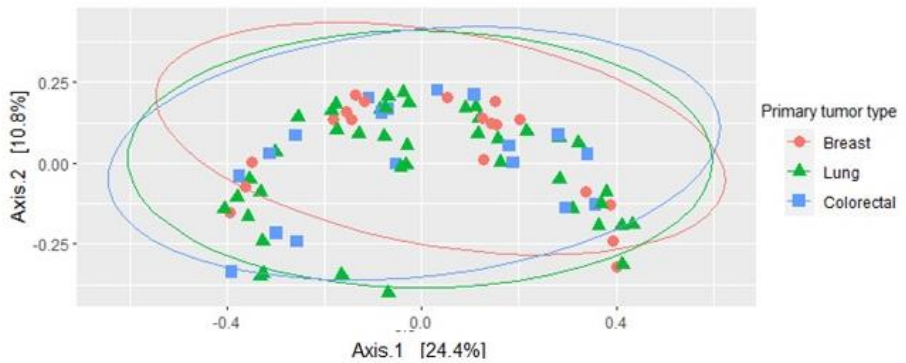


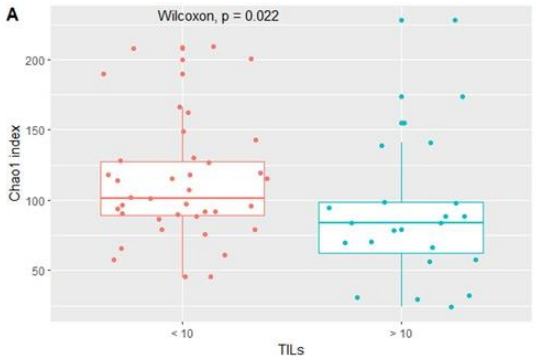
Hilmi et al., manuscript in preparation

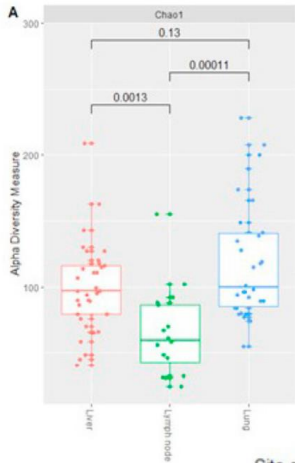
Study of intra tumoral microbiota

16S rRNA gene sequencing

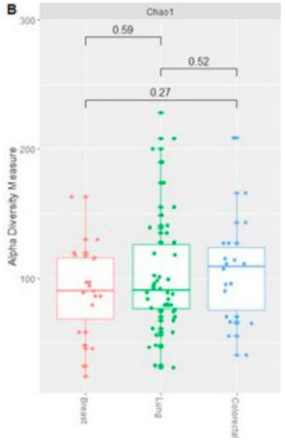




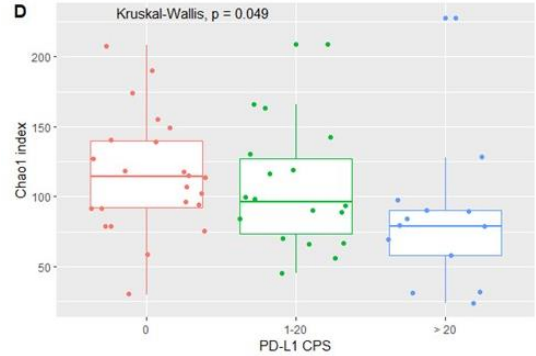




✓ Different intratumor microbiota in metastases depending on the biopsy site… (liver/lymph node/lung)



…and not the primary tumor type (breast/lung/colorectal)



✓ High microbial diversity associated with ($p<0.05$):
- Better survival
- Fewer TILs
- Less PDL1 expression

M. Hilmi

THE LANCET Oncology

SHIVA-01 ancillary study

ARTICLES | VOLUME 16, ISSUE 13, P1324-1334, OCTOBER 2015

Molecularly targeted therapy based on tumour molecular profiling versus conventional therapy for advanced cancer (SHIVA): a multicentre, open-label, proof-of-concept, randomised, controlled phase 2 trial

I. Bièche

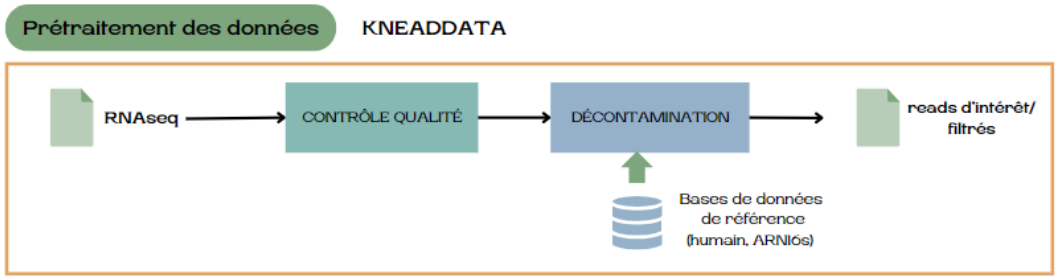
Hilmi et al., *Eur J Cancer* 2023

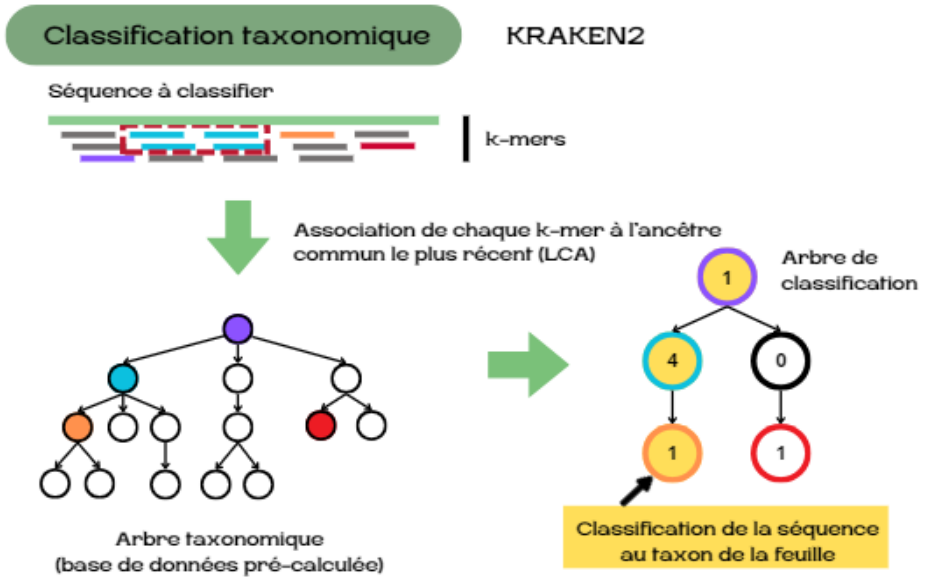
Study of intra tumoral microbiota

Metatranscriptomic (RNAseq Smarter)

Development of a pipeline to study intra tumoral microbiota on mRNA from FFPE samples (with R. Nicolle)

M. Hilmi





Dataset

Type d'échantillon	Nombre d'échantillons	Organe concerné	Source	Nature
Contrôle négatif	2	rétine	Curie	FFPE
	12	foie	Beaujon	Frozen
Contrôle positif	24	colon	Beaujon	FFPE
	9	duodenum	Beaujon	FFPE
	11	jejunum	Beaujon	FFPE
Tissu tumoral	14	voies biliaires	Beaujon	FFPE
	12	pancréas	Beaujon	FFPE
	21	vessie	Foch	FFPE
Tissu normal	5	vessie	Henri Mondor	FFPE

Tableau récapitulatif des échantillons à utiliser

- 110 échantillons RNAseq

CONTRÔLES POSITIFS:
- COLON
- JÉJUNUM
- DUODENUM

riches en bactéries ++

CONTRÔLES NÉGATIFS:
- FOIE
- RÉTINE

traités à l'antibiotique et antifongique
stériles

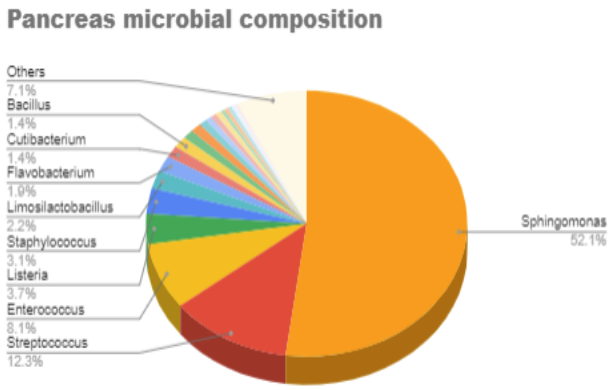
TISSUS AUTRES:
- PANCRÉAS
- VOIES BILIAIRES
- VESSIE

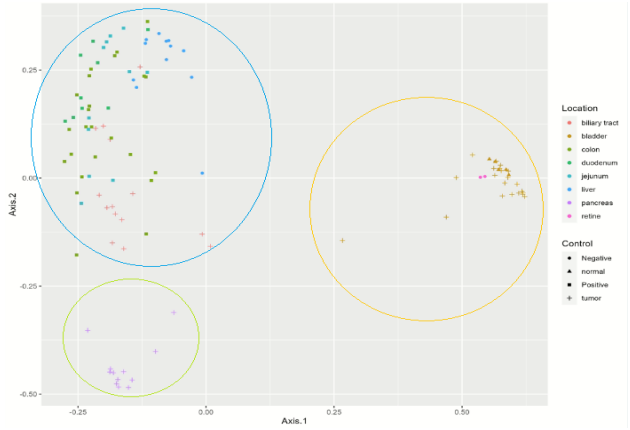
tumoraux
normaux

? ? ?

peu de littérature

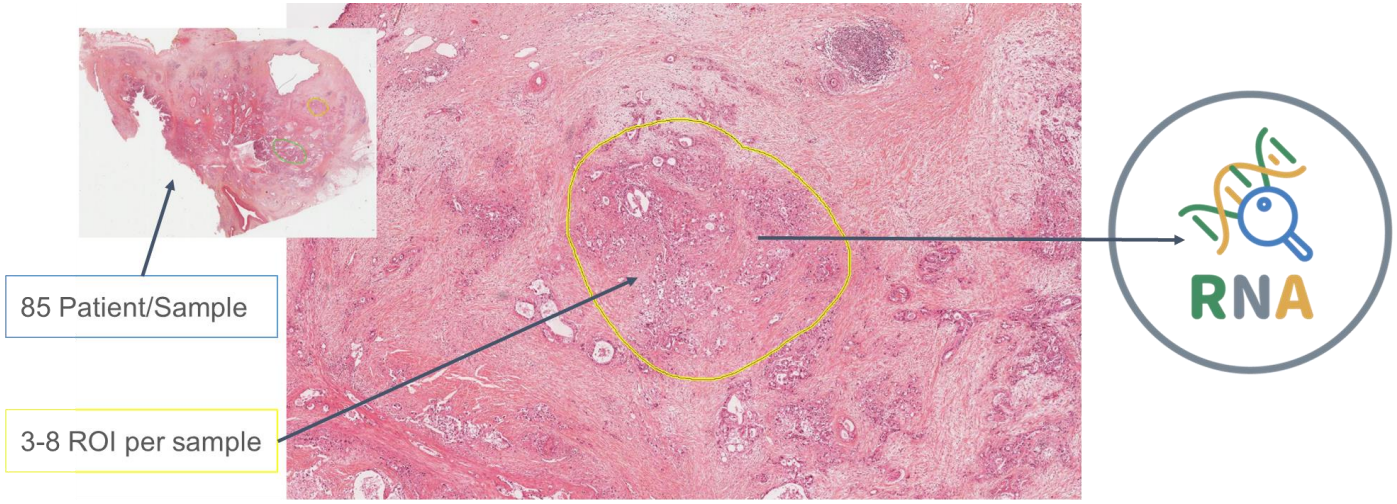
13/30





Hilmi et al., manuscript in preparation

Study of intra tumoral microbiota



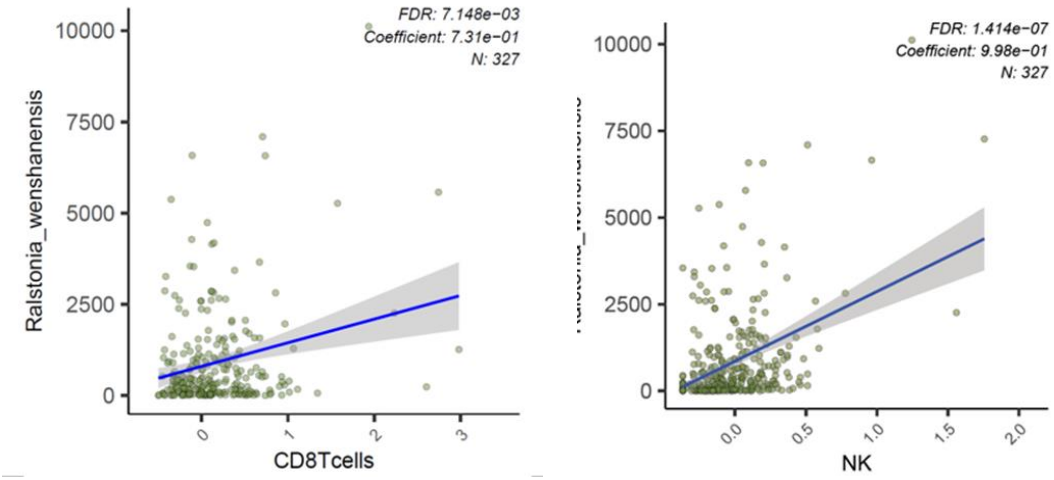
M. Hilmi

J. Cros

327 Small ROIs ⟹ Microdissection ⟹ 327 **RNAseq**

Matched Morpho-Molecular Dataset

- ✓ Bacterial species significantly associated with:
- Basal component (n=281)
- Classic component (n=63)
- POSTN expression (n=26)
- aSMA expression (n=245)
- NK (n=1,561)
- PNN (n=1,160)
- CD8 (n=375)



Hilmi et al., manuscript in preparation


précliniques
multiéchelle
interactions
résistance
intégration
intratumorale
cohortes
pronostic
modèles
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Réseau
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tumeur
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hétérogénéité