Novedades en el tratamiento del Cáncer de Páncreas

CURSO DE AVANCES EN GASTROENTEROLOGÍA
"BUENAS PRÁCTICAS EN GASTROENTEROLOGÍA"

Erick Riquelme, PhD

Facultad de Medicina

Pontificia Universidad Católica De Chile

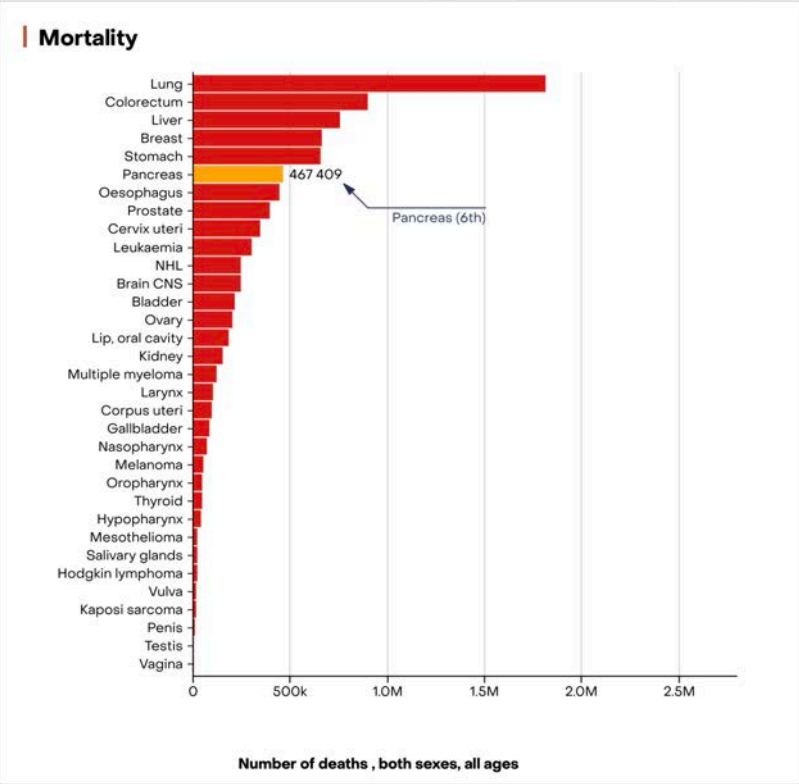
Pancreatic Cancer

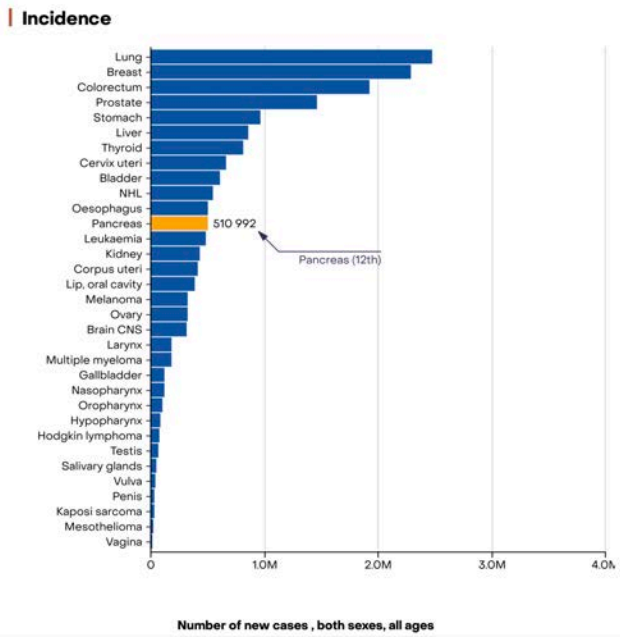
Mortality

Rank	Deaths	ASR (World)
6	467 409	4.2

510.992 / **467.409**

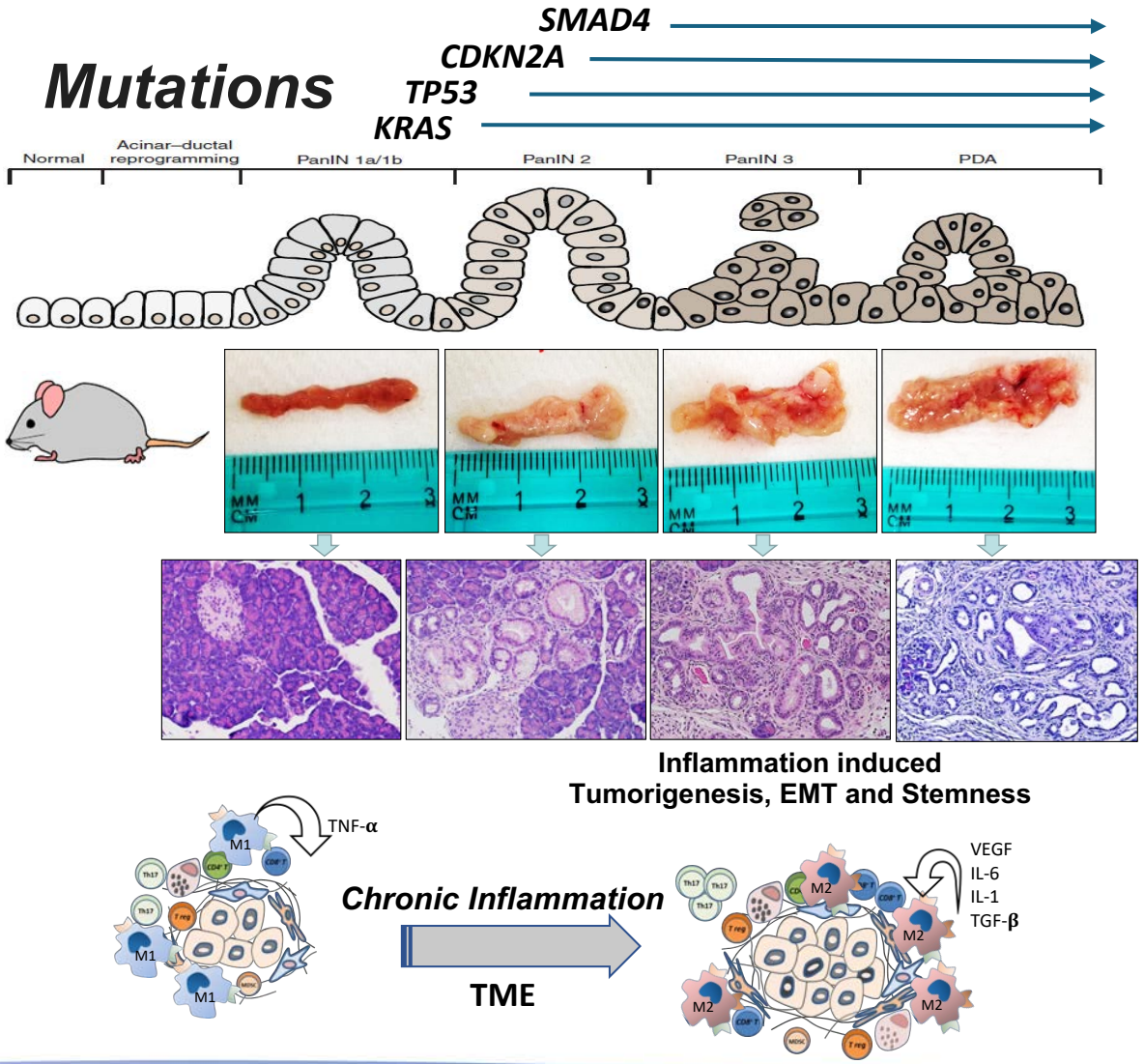
90% DEATHS

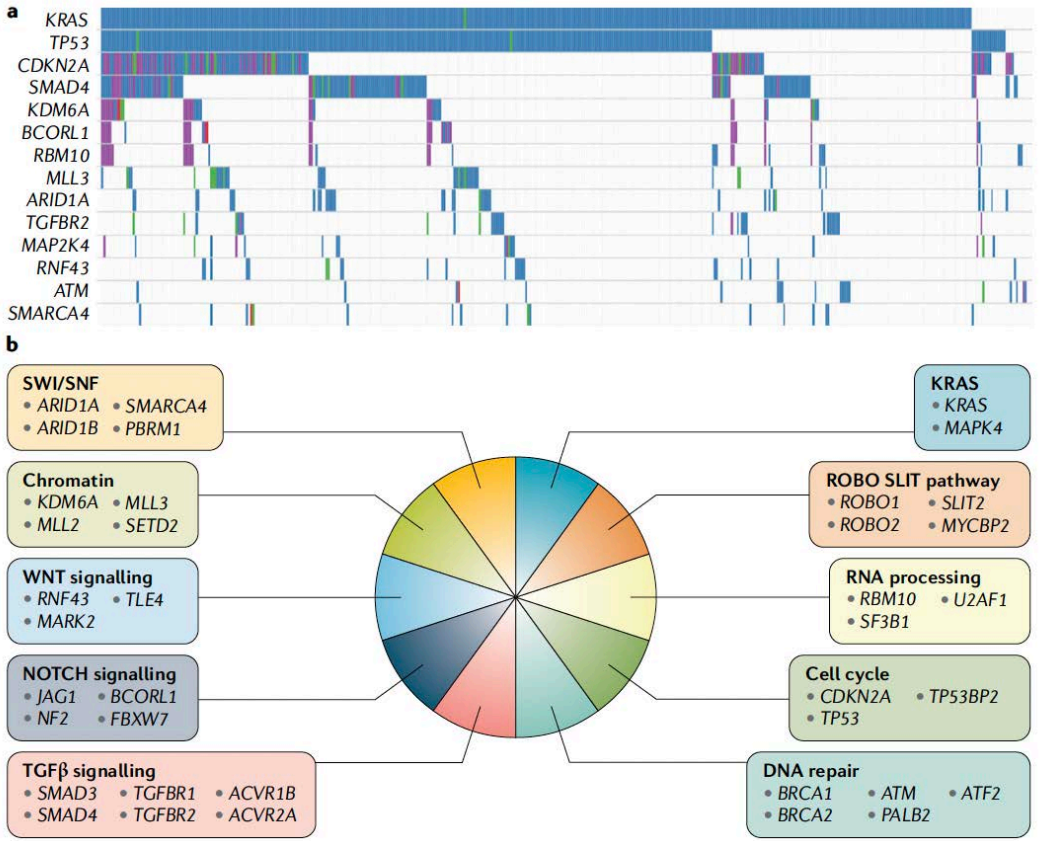




- Pancreatic cancer is the sixth leading cause of cancer death worldwide
- Pancreatic cancer present an enormous challenge, as they are naturally resistant to current therapy
- Most patients present with advanced stage disease and the prognosis is dismal
- **5-year overall survival of 9-11%**
- In resectable patients treated with neoadjuvant therapy and surgery, recurrence is common, **78% relapse within 5 years, typically around 1.2 years post-treatment.**

Hallmarks of PDAC; Genomic Aberrations

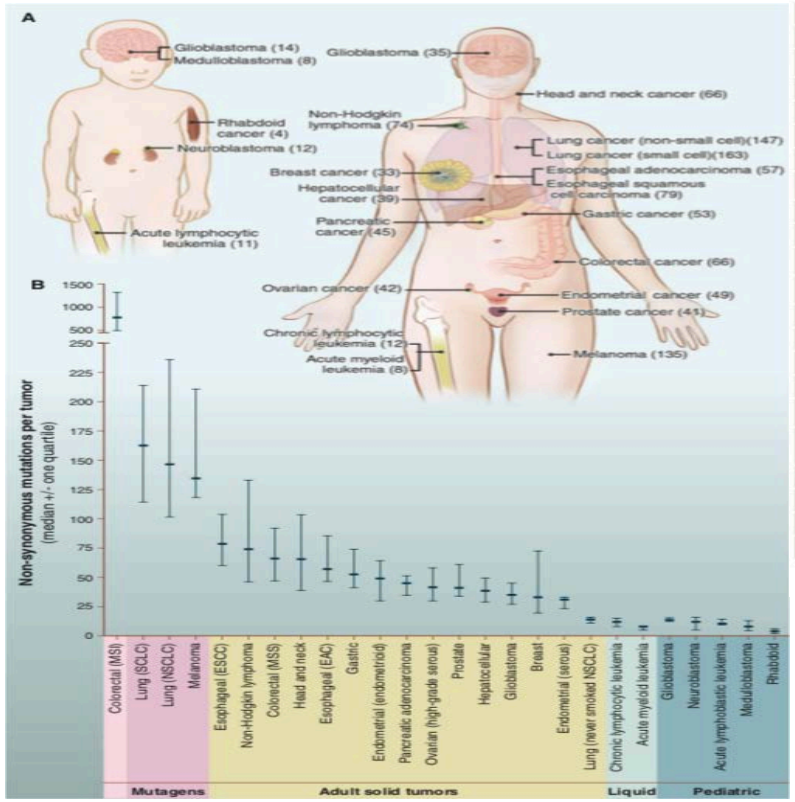


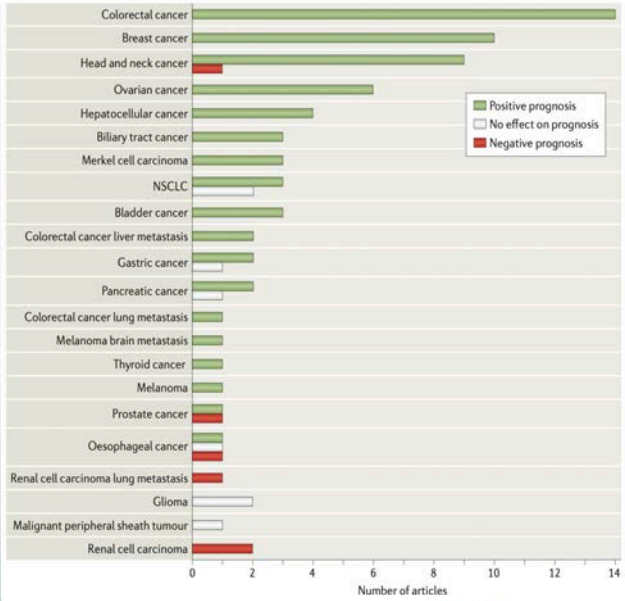


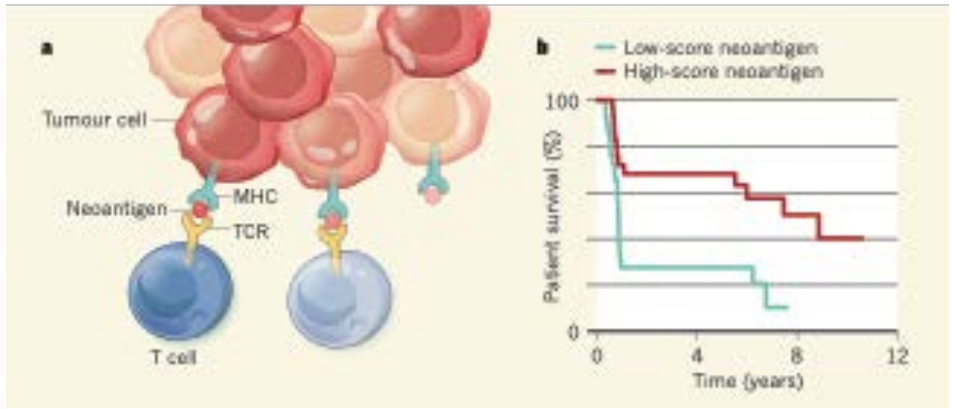
Gene	Frecuency
KRAS	>90%
TP53	75%
CDKN2A	>70%
SMAD4	>50%

Limited set of commonly mutated genes

Low Immunogenicity

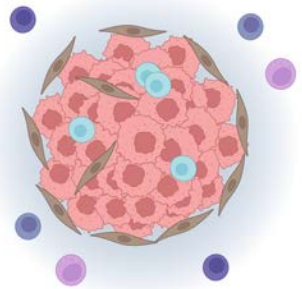






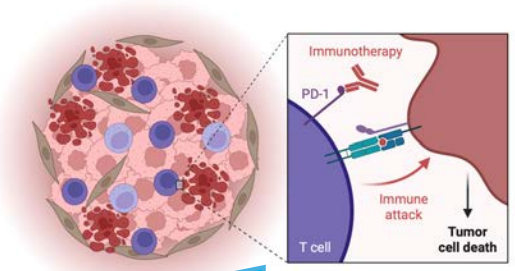
Cold Tumor

- Exclusion of CD8+ T cells and NK cells from the tumor
- Immunosuppressive immune cells in tumor (ie. Tregs)
- Poor prognosis and response to immunotherapy



Hot Tumor

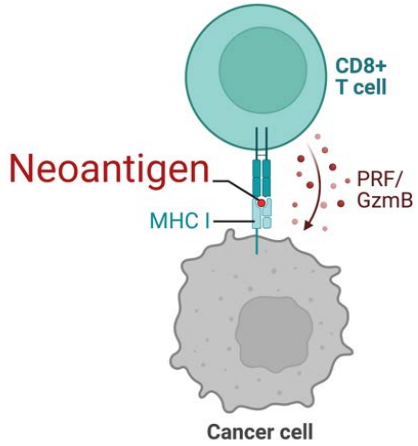
- CD8+ T cells and NK cells are present in tumor
- Suppression of immunosuppressive cell types
- Improved prognosis and killing of tumor cells with immunotherapy treatment



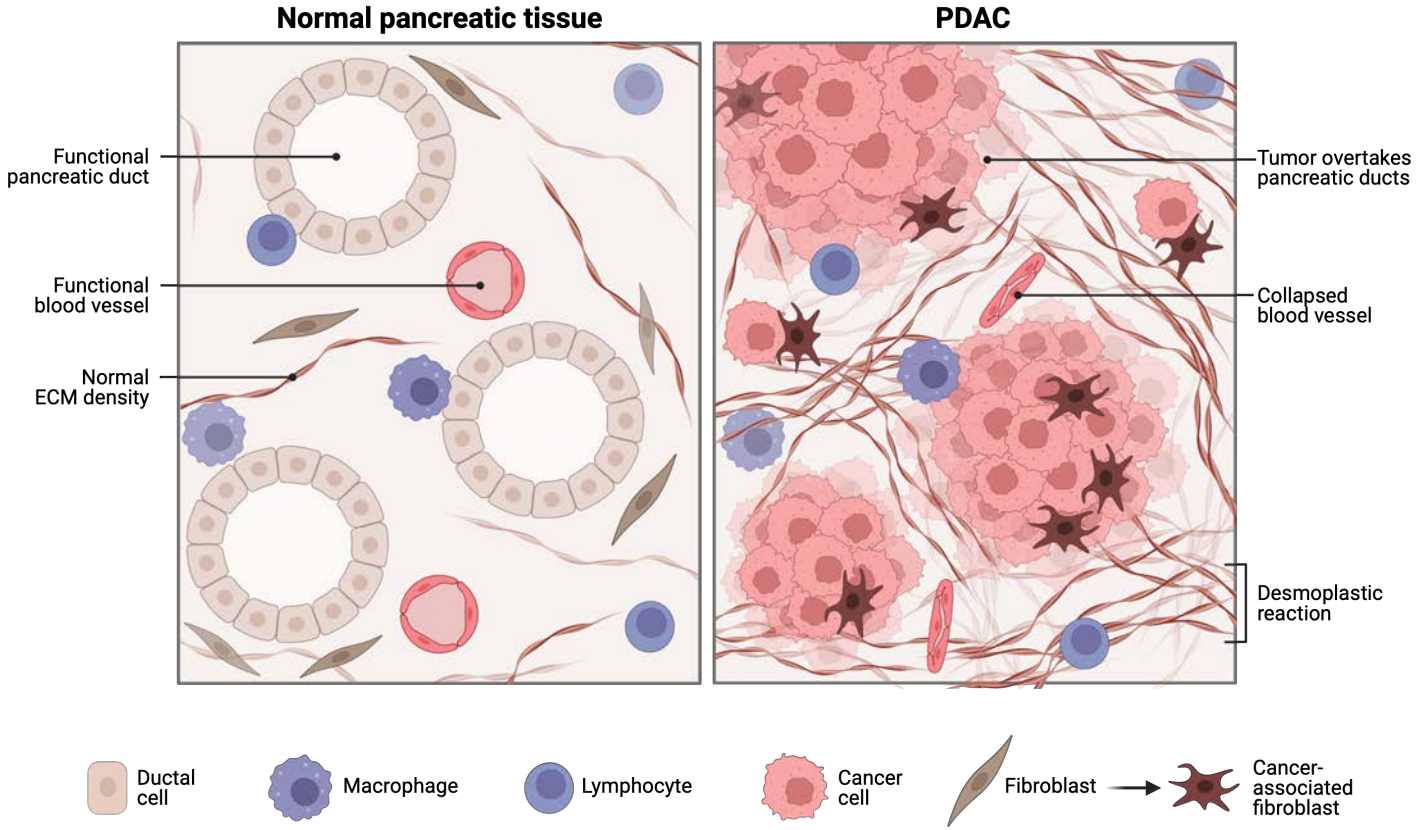
Mutations >Neoantigenos

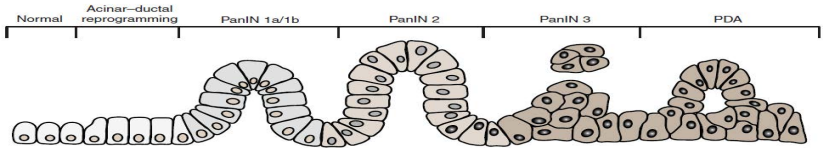
CD8+ T CELL

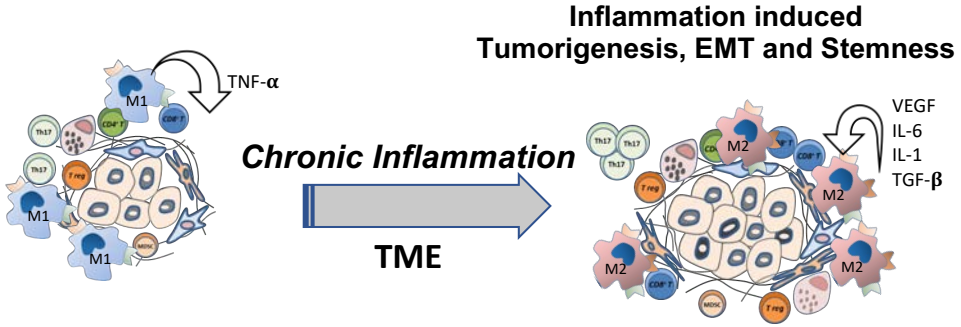
Adequate neoantigen presentation by MHC I



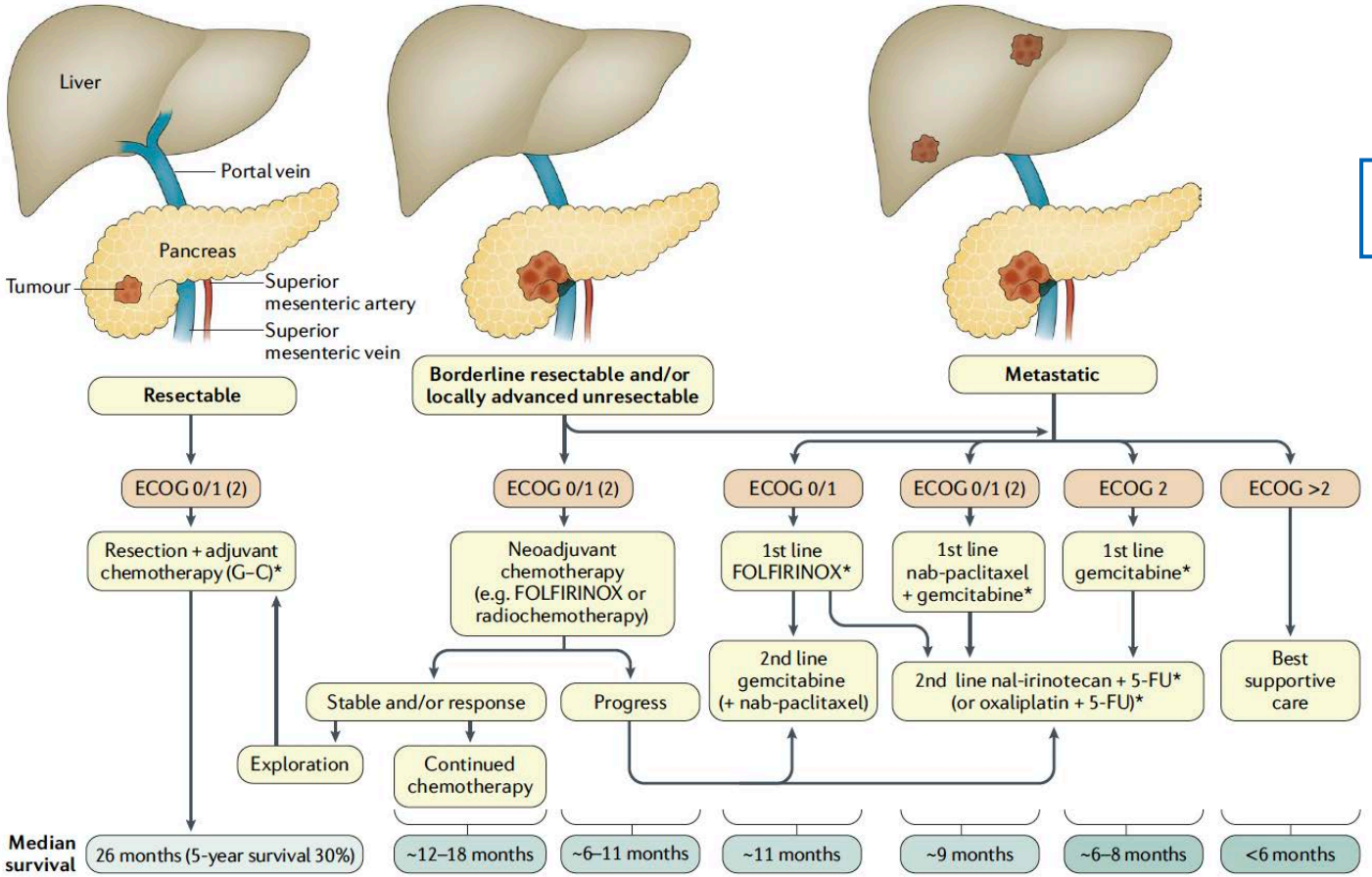
Pancretaic Ductal Adenocarcinoma (PDAC)

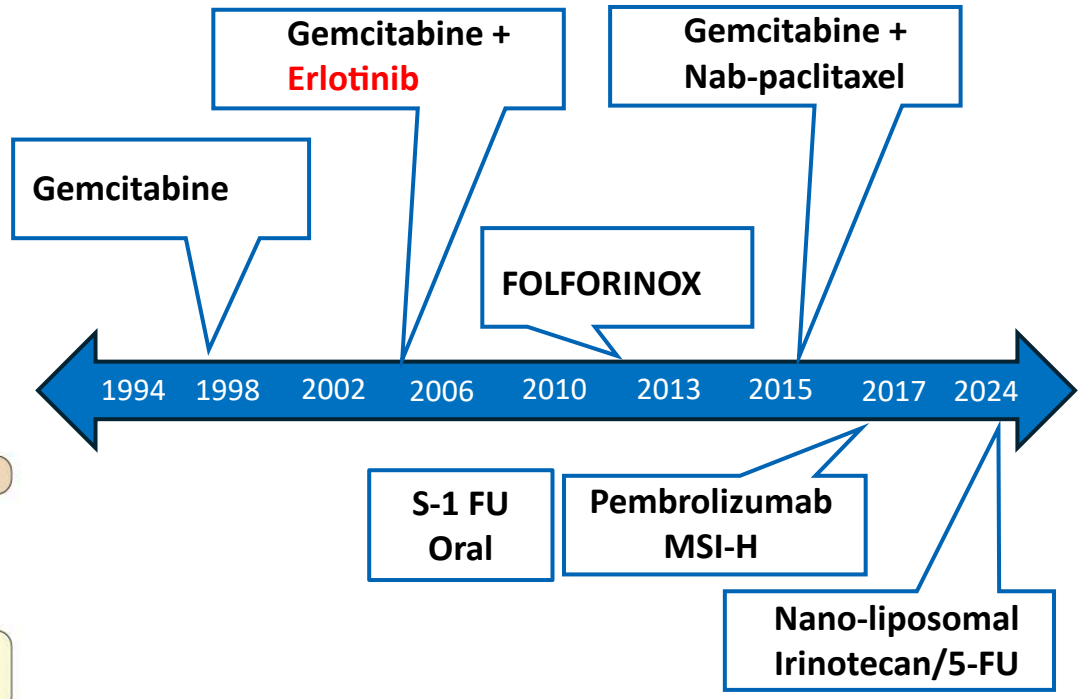






Therapeutic options are limited

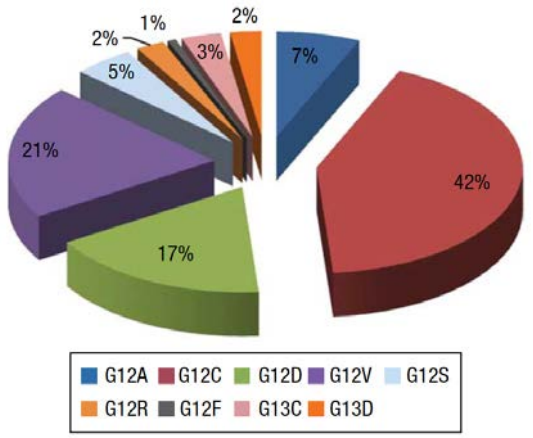


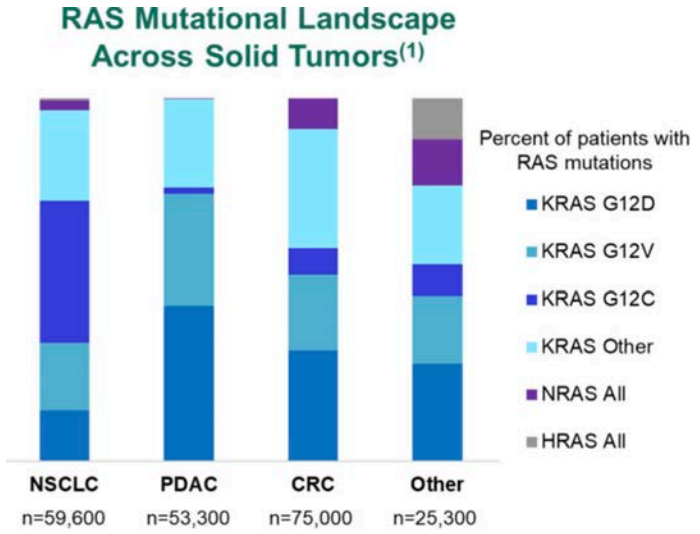


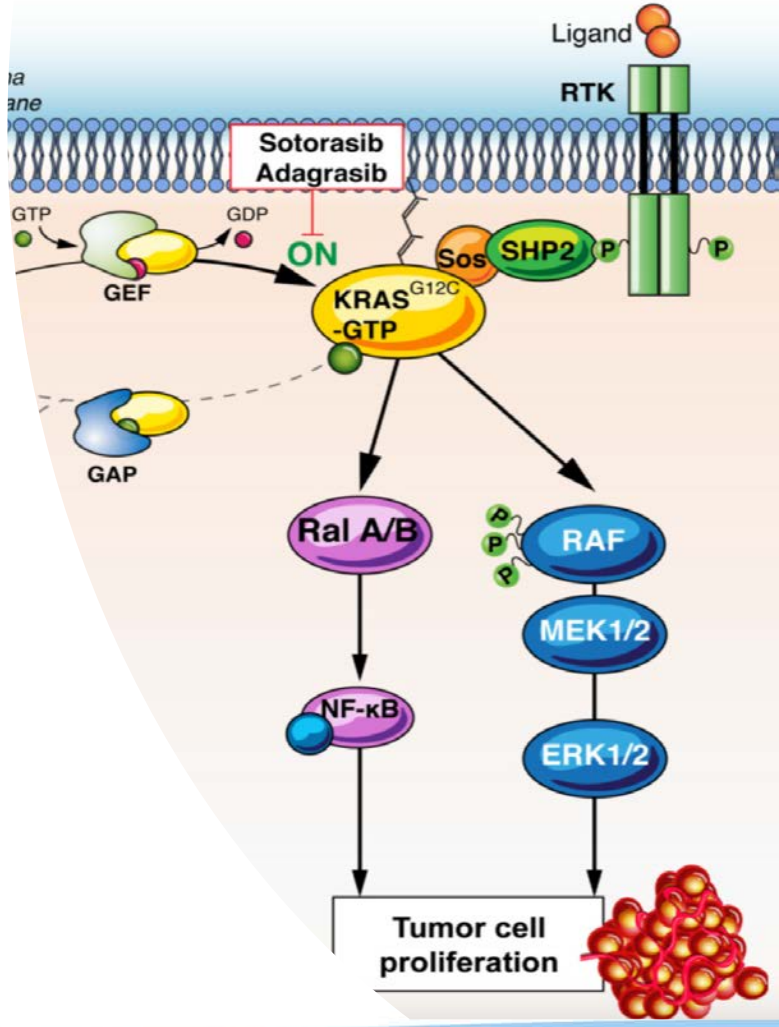
KRAS Treatments for PDAC

FDA Approval of KRAS Inhibitor Sotorasib for Lung Cancer (28 may, 2021)

- More than 30 percent of all human cancers including **>90 % of pancreatic cancers**, 45 % of colorectal cancers, 32% of lung cancers are driven by mutations of the *RAS* family of genes
- KRAS mutations have long been considered impossible to treat with drugs
- *KRAS* mutations in lung cancer localize primarily to codons 12 and 13
- KRAS serves as an on-off switch that regulates cell growth



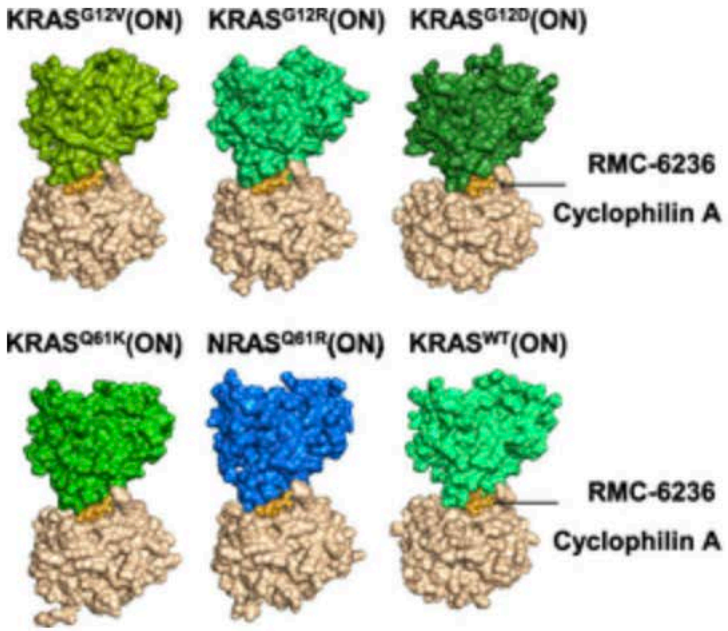


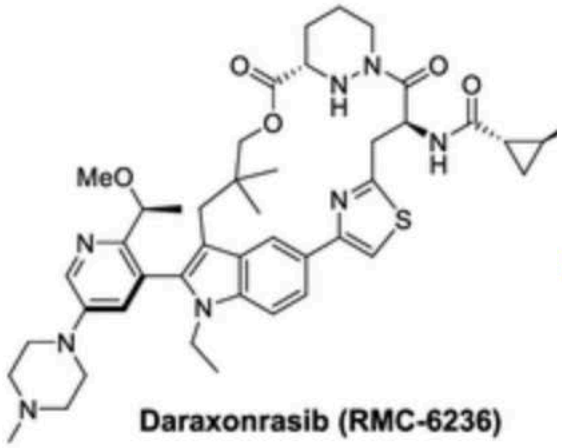


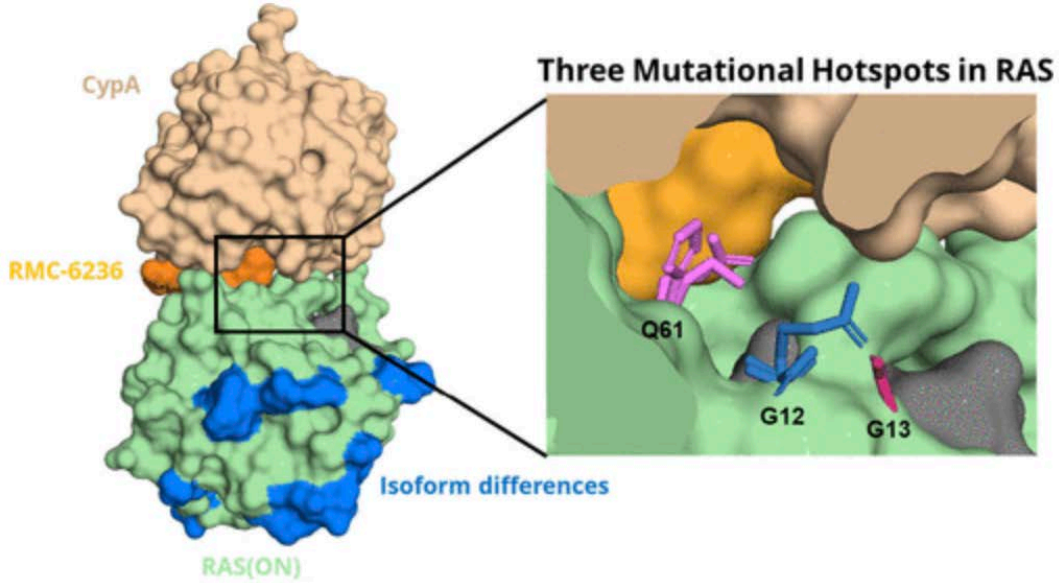
Hope placed on Daraxonrasib

Daraxonrasib (RMC-6236), a Potent and Orally Bioavailable RAS(ON) Multi-selective, Noncovalent Tri-complex Inhibitor for the Treatment of Patients with Multiple RAS-Addicted Cancers

Phase 3 Study of Daraxonrasib (RMC-6236) in Patients With Previously Treated Metastatic Pancreatic Ductal Adenocarcinoma (PDAC) (RASolute 302)

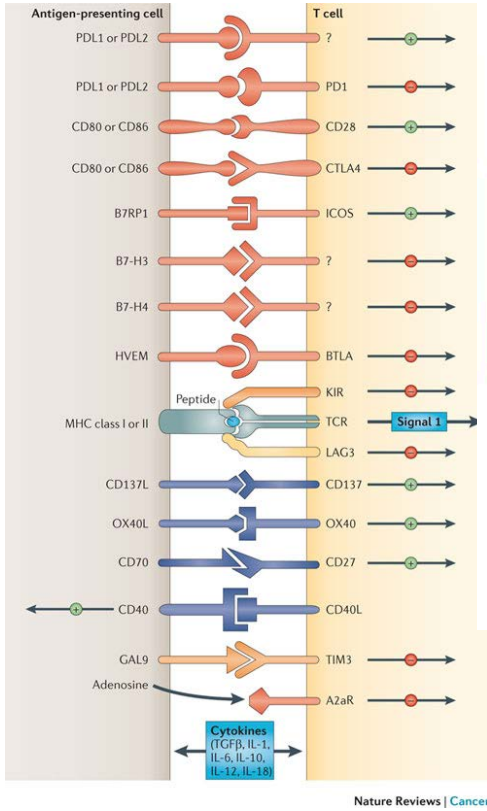


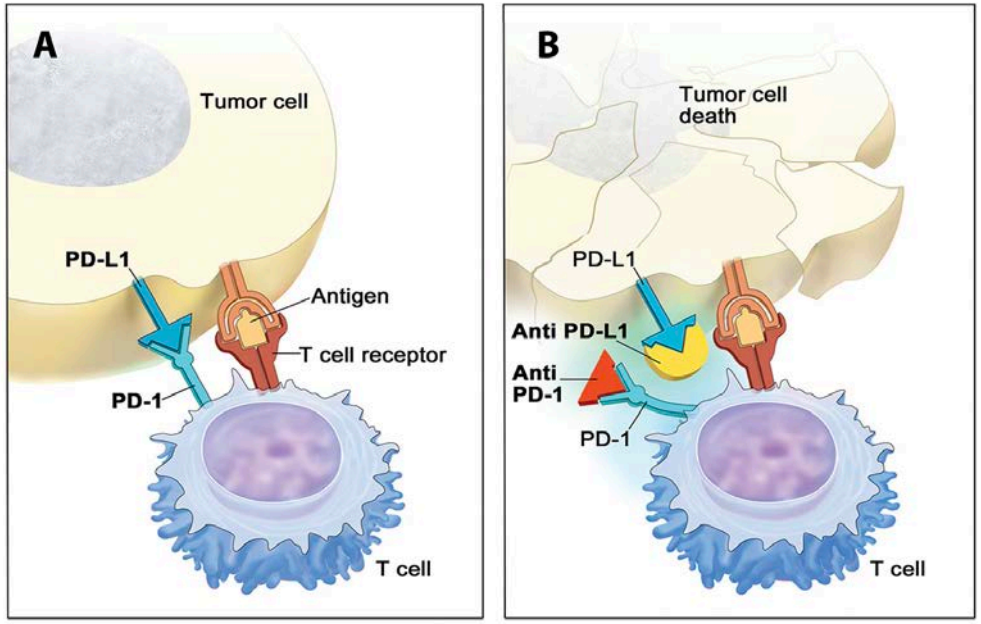




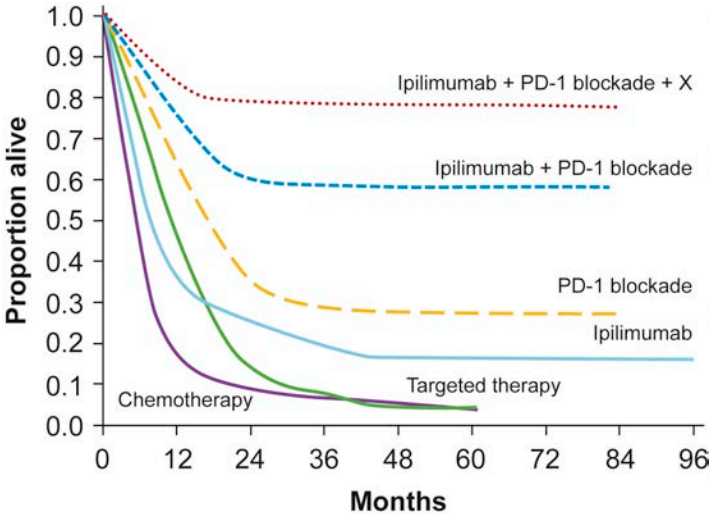
PDAC; Failure to Respond to Immunotherapy

Immune-based therapies aim to recruit and activate T cells that recognize tumor-specific antigens





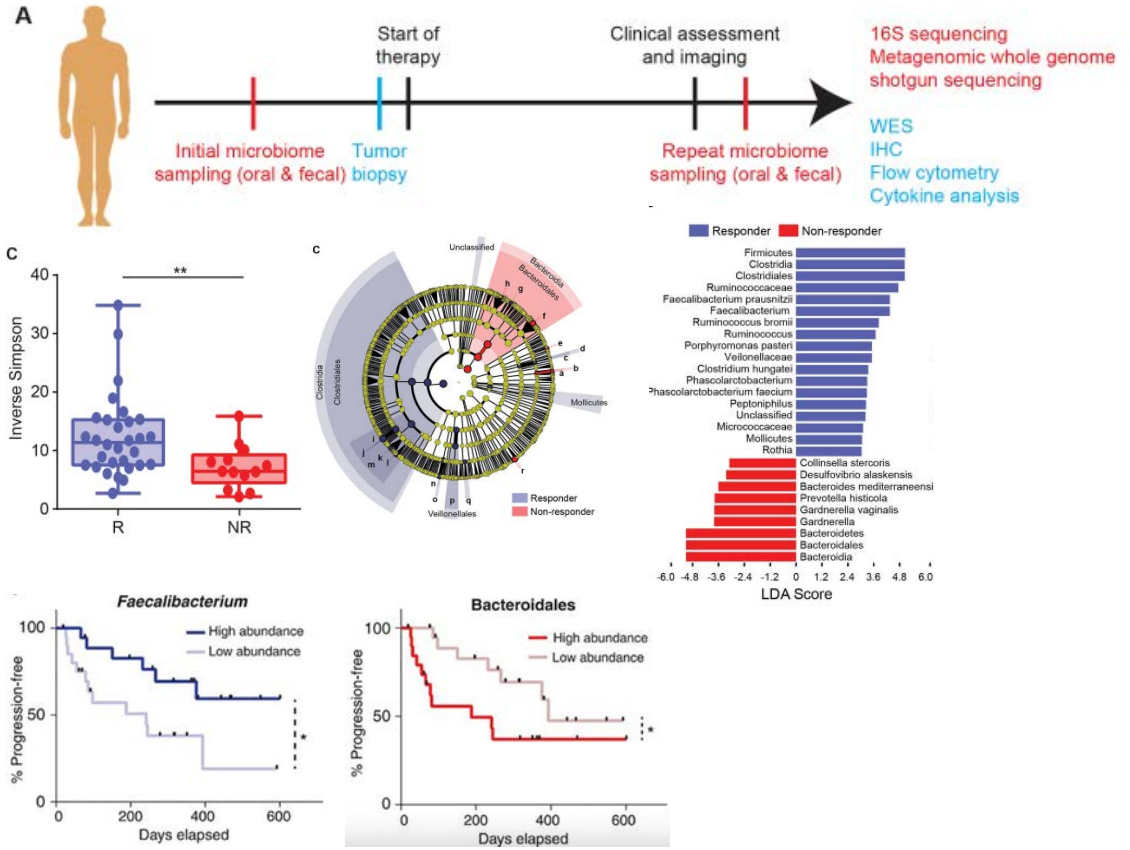
Clinically approved checkpoint inhibitors		
Agent	**Mechanism of action**	**Approved for**
Ipilimumab (Yervoy)	mAb targeting CTLA-4	Metastatic melanoma
Pembrolizumab (Keytruda)	mAb targeting PD-1	Metastatic melanoma, non-small-cell lung cancer, head and neck squamous cell cancer, classical Hodgkin's lymphoma
Nivolumab (Opdivo)	mAb targeting PD-1	Metastatic melanoma, non-small-cell lung cancer, renal cell carcinoma, Hodgkin's lymphoma, head and neck cancer, urothelial carcinoma
Atezolizumab (Tecentriq)	mAb targeting PD-L1	Non-small-cell lung cancer, bladder cancer
Avelumab (Bavencio)	mAb targeting PD-L1	Urothelial carcinoma, Merkel cell carcinoma
Durvalumab (Imfinzi)	mAb targeting PD-L1	Urothelial carcinoma

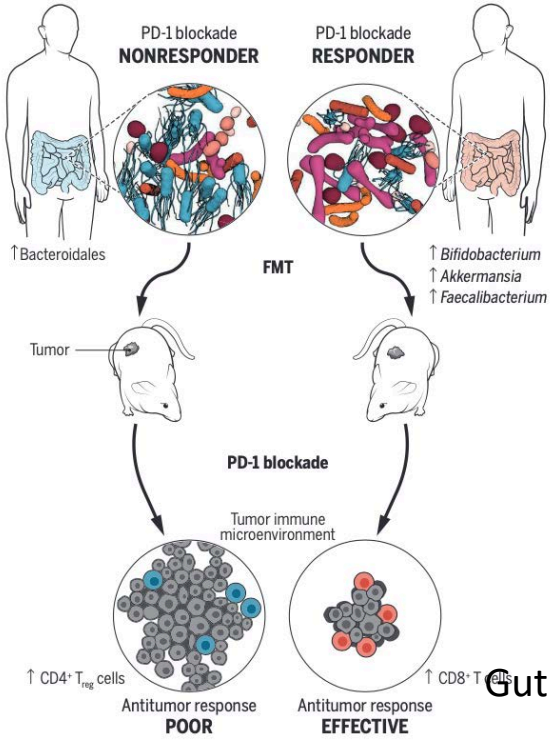


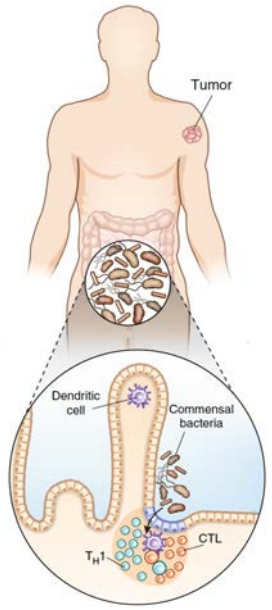
PDAC; Failure to Immunotherapy

- Cancer antigens have generated relatively weak immune responses
- Low among of Neoantigen
- Low inflammatory infiltrate

Microbiota and Cancer Immunotherapy



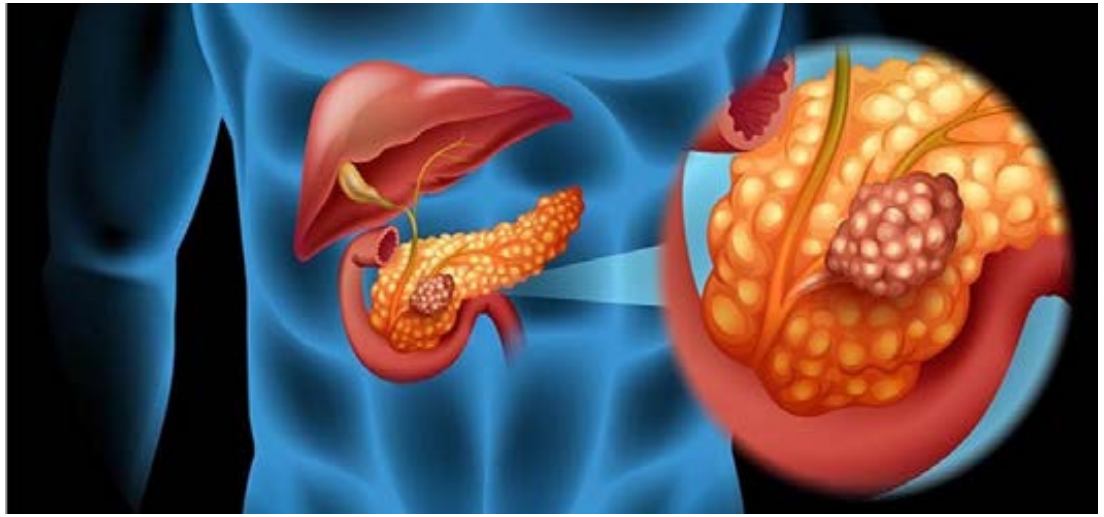


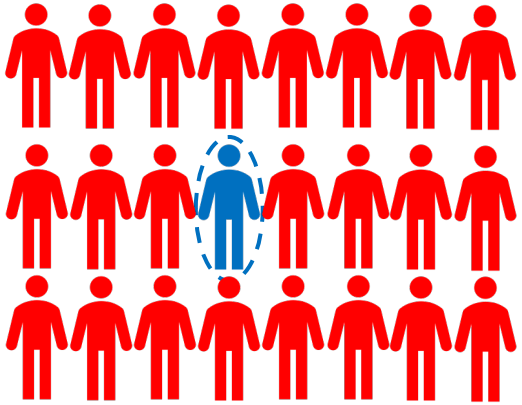


Gut microbiota influences the immune response of distant tumors

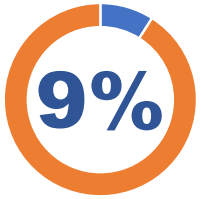
The Gut microbiome analysis suggest that gut microbiota is a clinically relevant predictive biomarker for the response to immunotherapy

Pancreatic Cancer Kill thousands of People Every Year

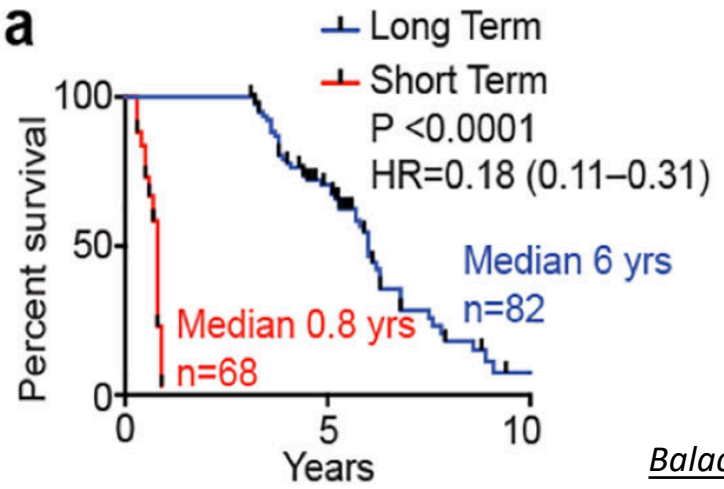




MINOR SUBSET
OF PATIENTS SURVIVE MORE THAN 5-YEARS POST-SURGERY

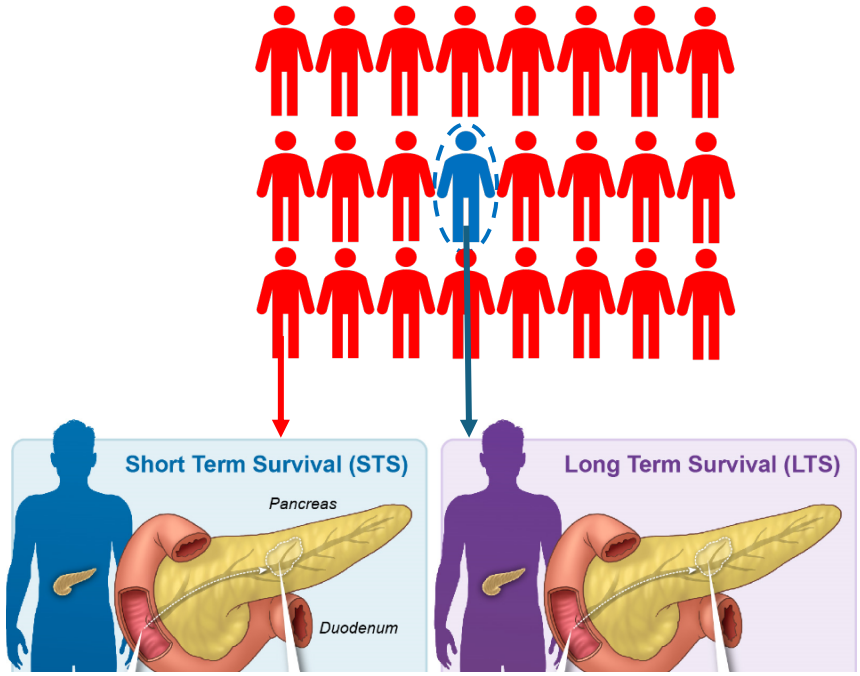


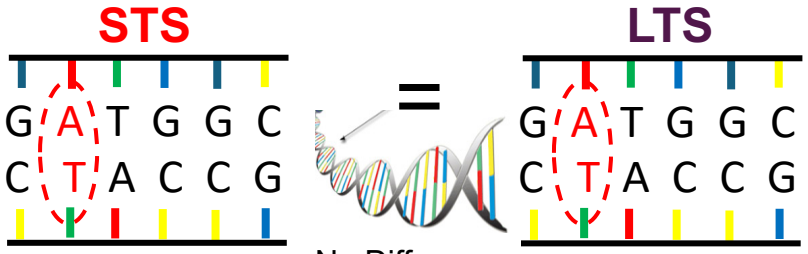
MEDIAN 5 YEAR SURVIVAL



Balachandran et al., 2017

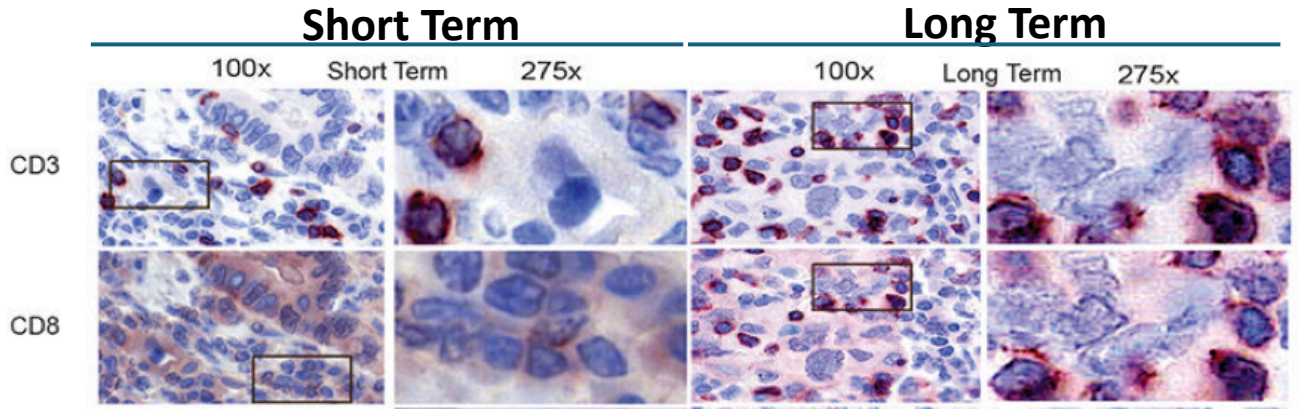
PDAC survivors, a subgroup with special characteristics

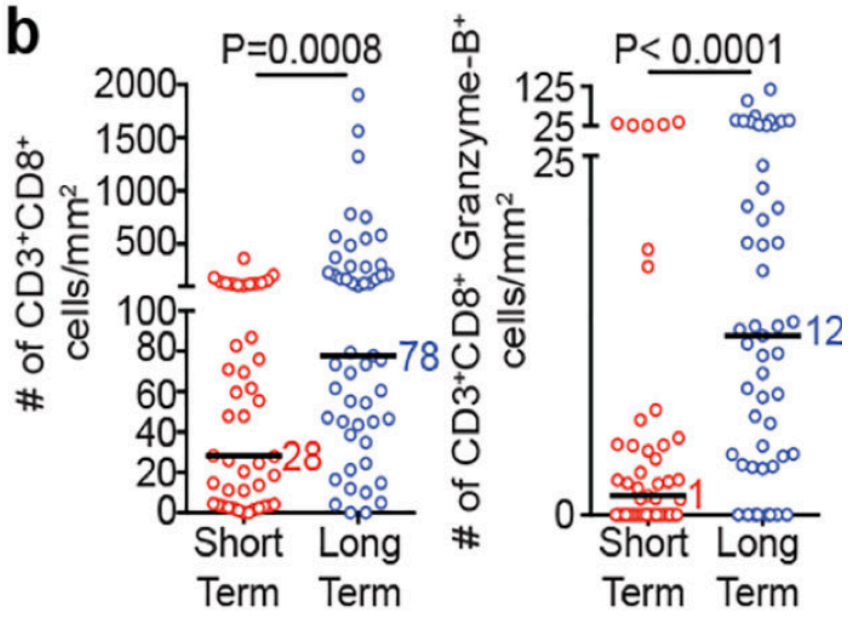


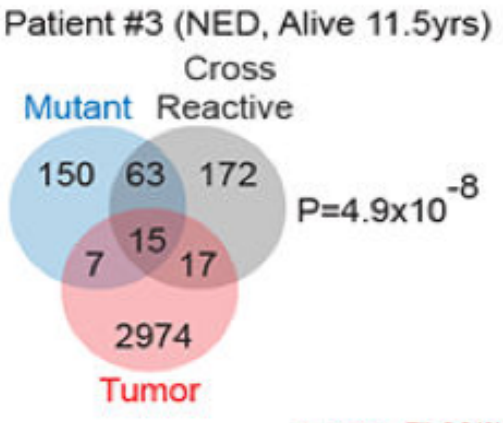


No Difference in Somatic Mutations

Dal Molin et al., 2015





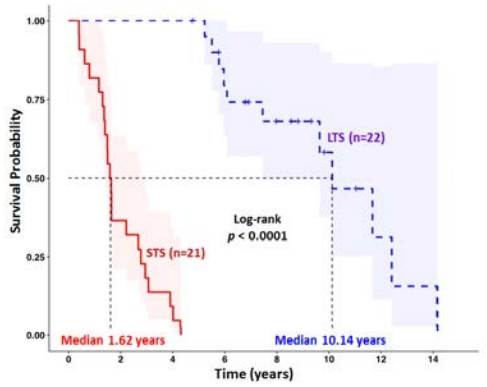


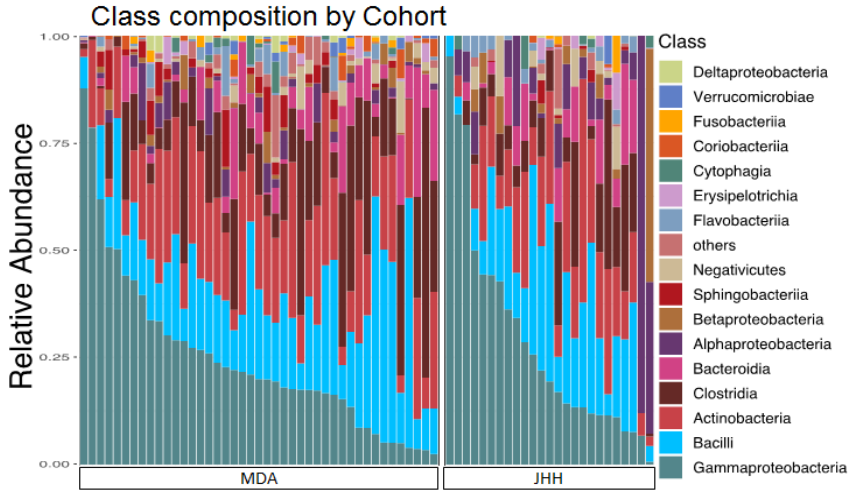
Balachandran et al., 2017

PDAC survivors, a subgroup with special characteristics

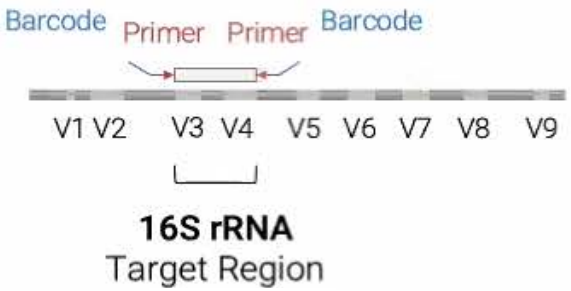
Short Term Survival STS
$< 5\ years$

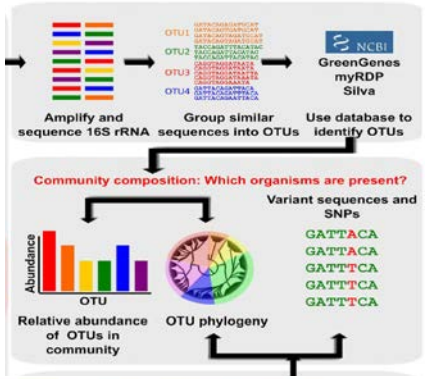
Long Term Survival LTS
$> 5\ years$

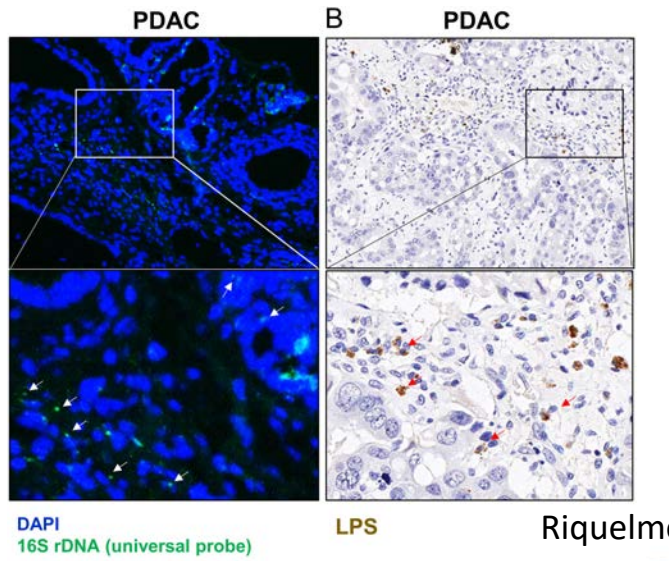




16S Sequencing



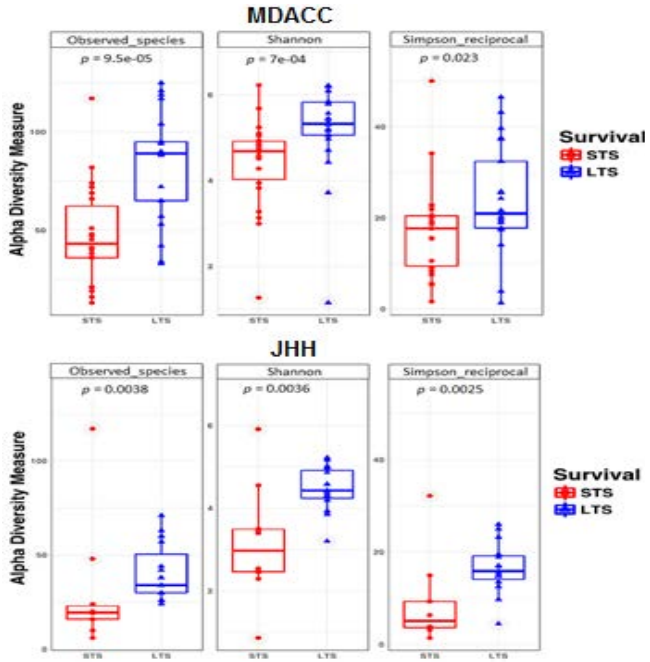


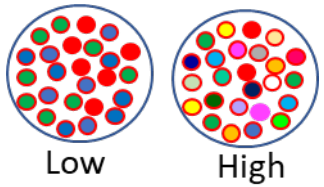


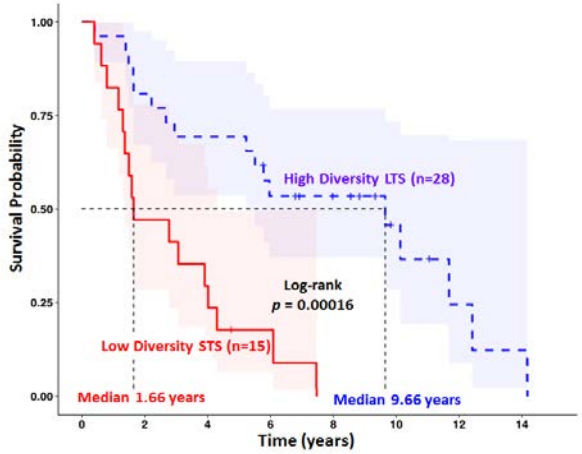
Riquelme E, *et al*, Cell. 2019

Tumor microbial diversity was higher in LTS patients, influencing in the Outcome of PDAC patients

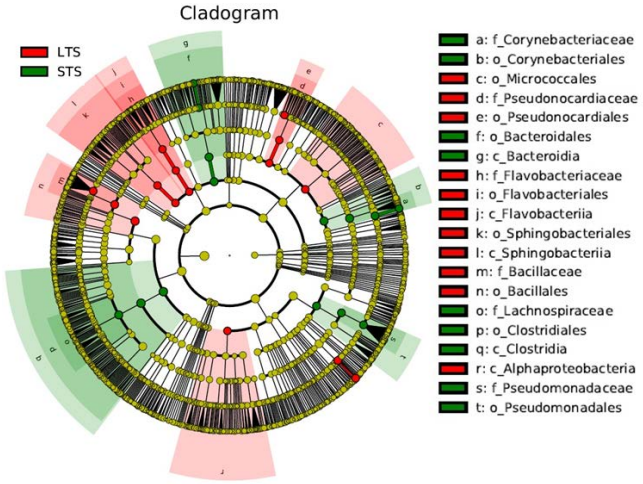
Alpha diversity

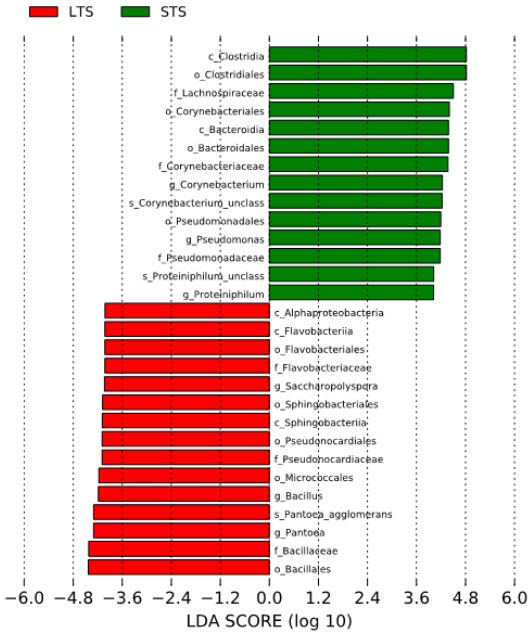


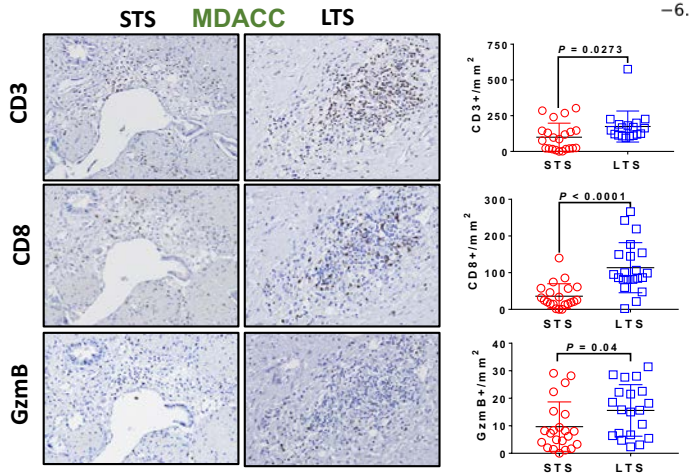


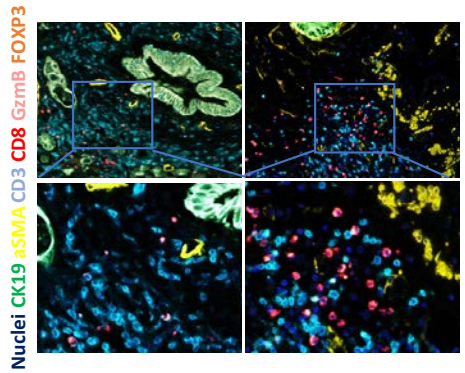


Kaplan-Meier plot patients defined by alpha diversity



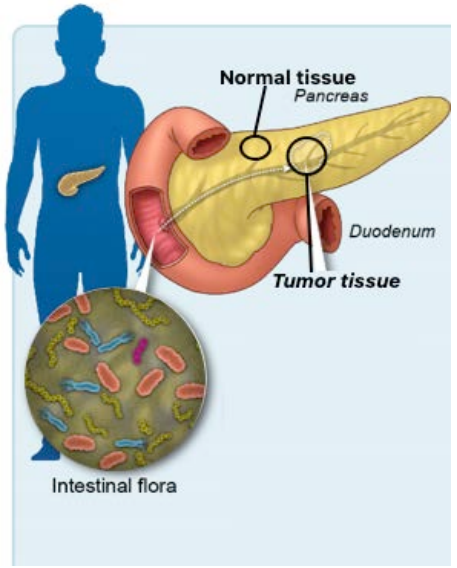


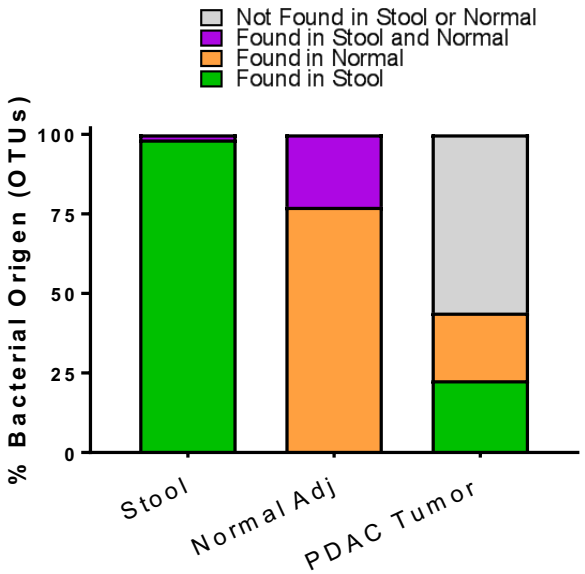




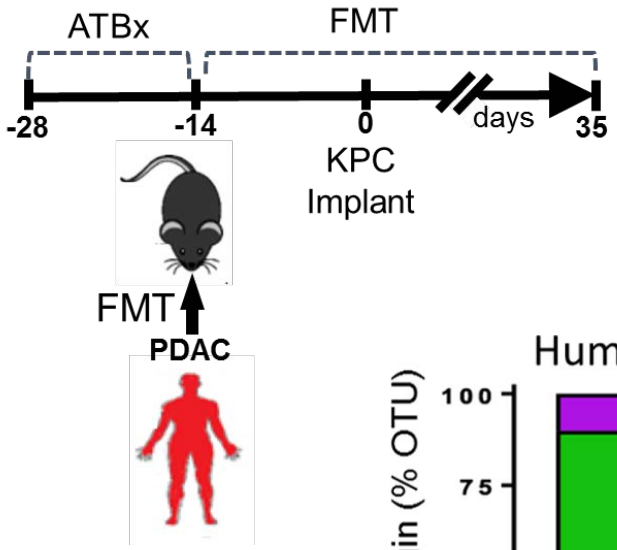
Tumor Microbiome shapes Immune Tumor Microenvironment and T cells Activation

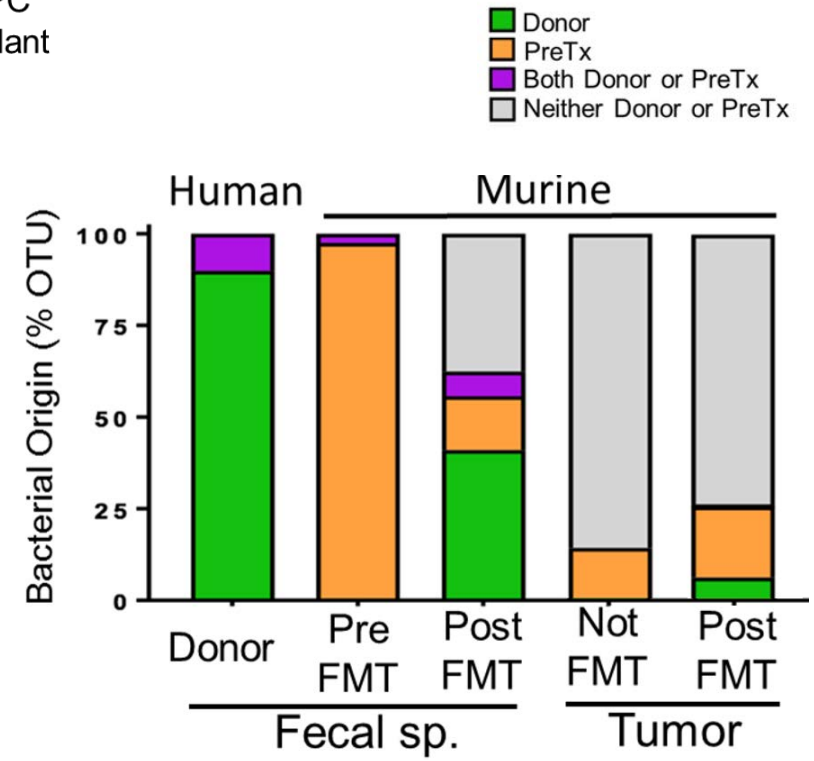
We can Modify the Mice Gut and Tumor Microbiota by Changing the Gut Microbiota?



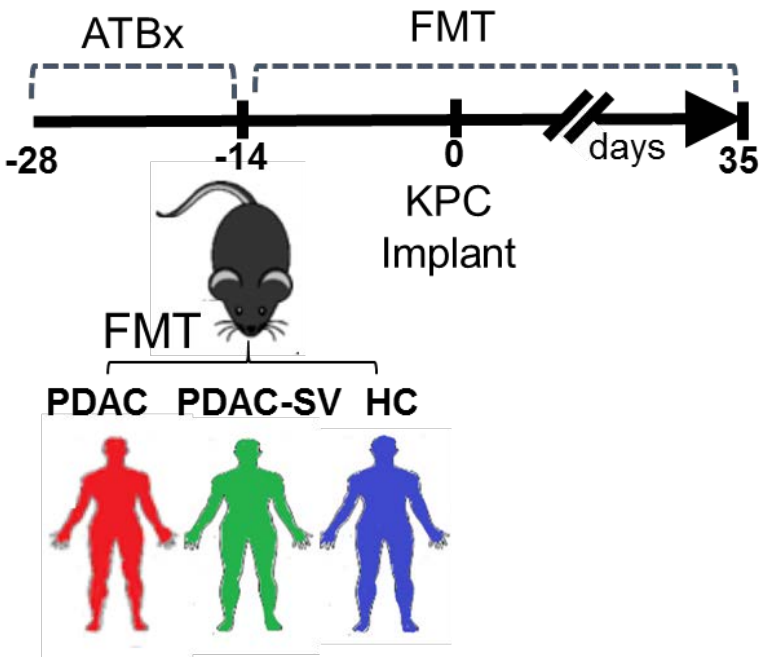


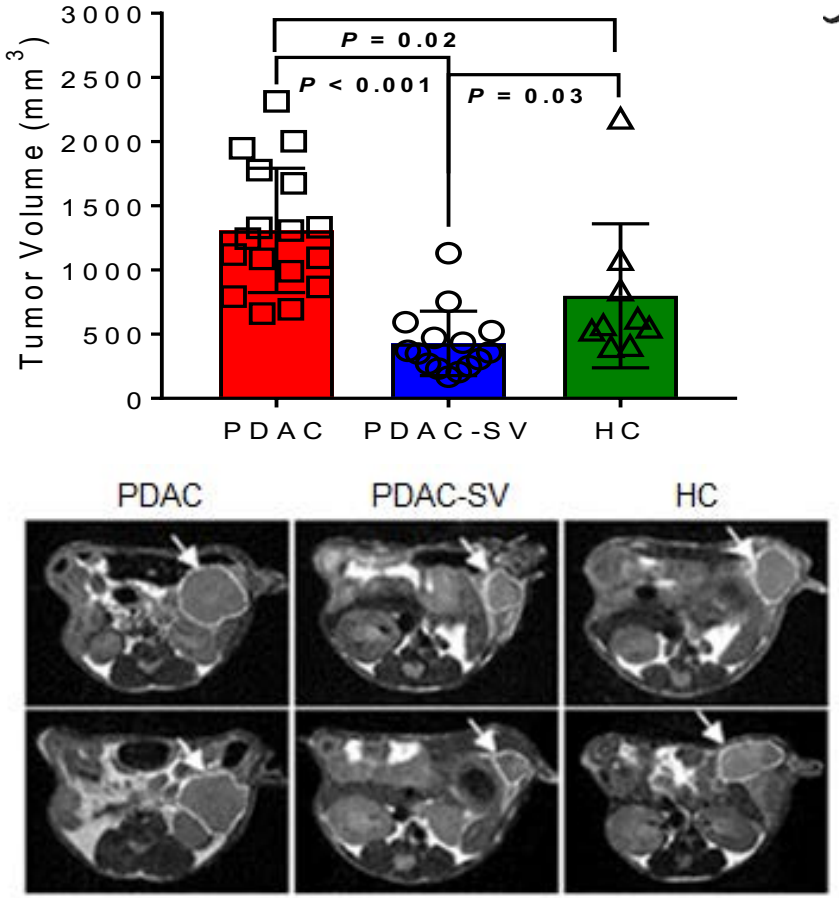
Gut microbiota has the capacity to colonize pancreatic tumors

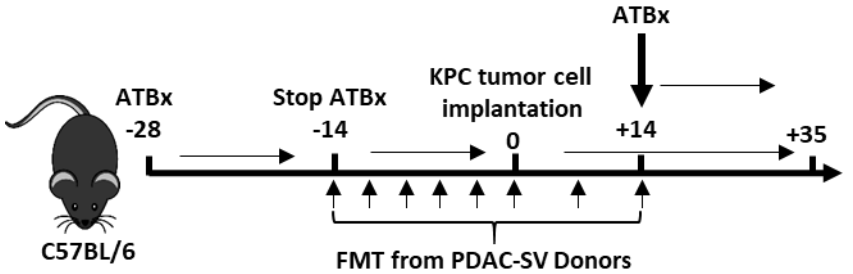


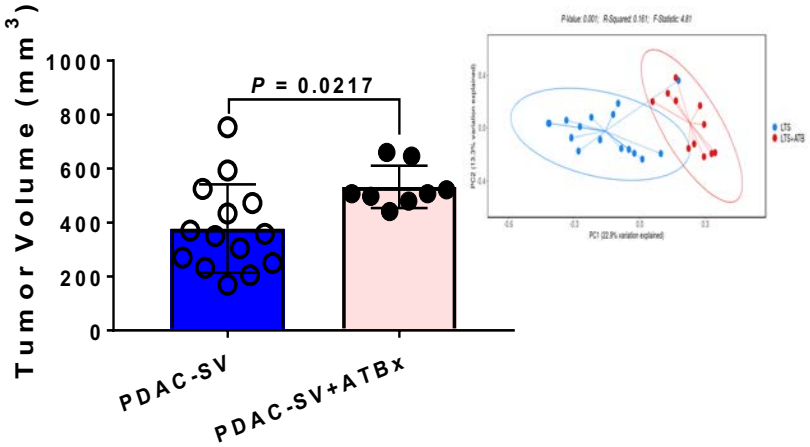


LTS Microbiome have an Antitumor Effects





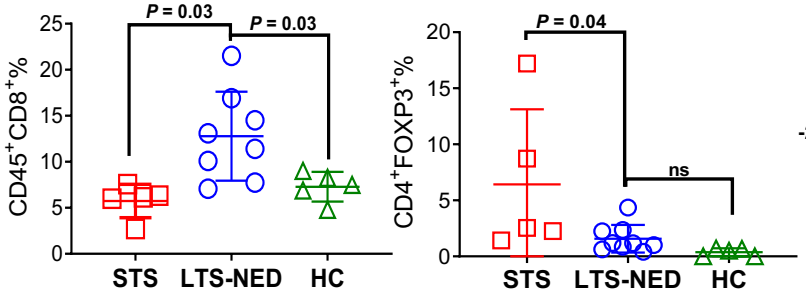


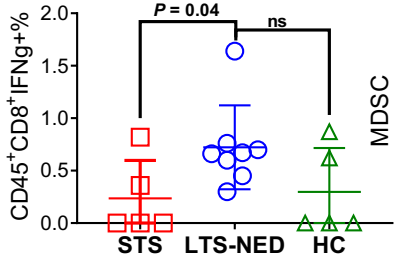


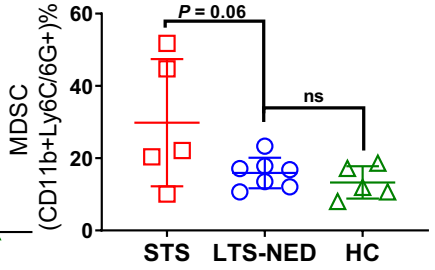
Bacteria Ablation can Decrease the Anti-tumoral Efficacy Induced by LTS FMT

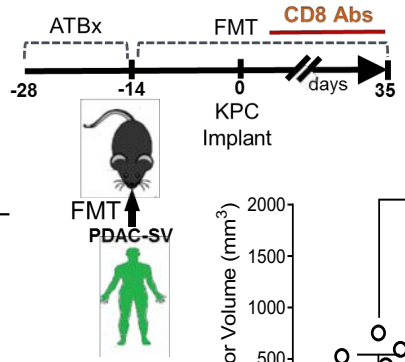
Riquelme E, *et al*, Cell. 2019

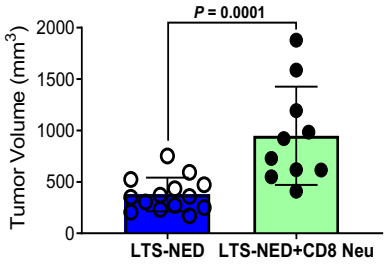
The Shift on the Gut and Tumor Microbiome Influences the Tumor infiltrates

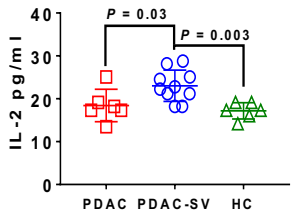


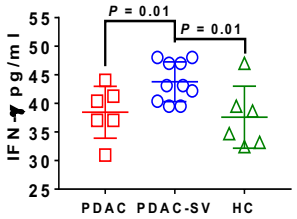


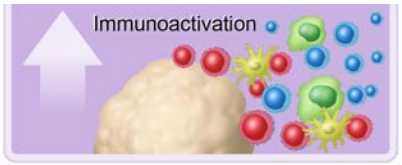


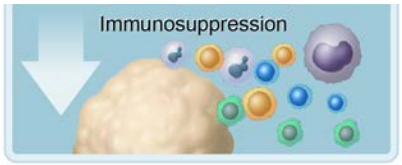


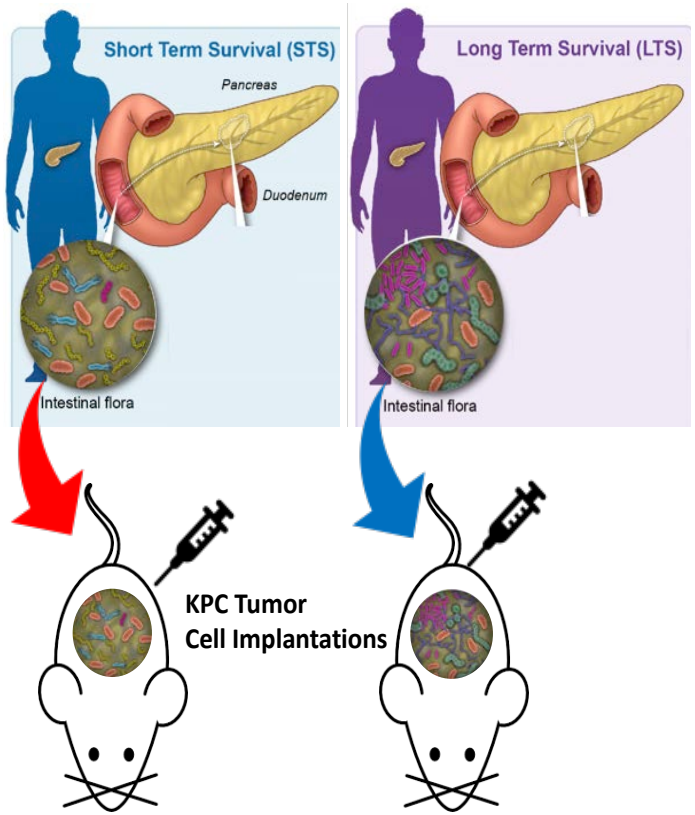












Mice that received FMT from LTS had higher numbers of CD8⁺T cells versus those with stools transferred from STS or HC donors

Riquelme E, *et al*, Cell. 2019

Conclusion

- PDAC are naturally resistant to current therapy; Chemotherapy, Immunotherapy
- Low mutations burden; cold tumor, Low among of Neoantigen, weak immune responses, Low inflammatory infiltrate, failure to Immunotherapy
- KRAS frequently mutated, G12D
- Gut and Tumor Microbiome Influences the Tumor infiltrates
- Intratumoral PDAC microbiota is influenced by the Gut microbiota, which impacts the host's antitumor immune response, which impacts the natural history of the PDAC patients.
- *FMT represent an immense therapeutic opportunity to manipulate the microbiome to improve the life expectancy of PDAC patients*

Aknowledgements

FONDECYT 1191526,
FONDECYT 1231629
Dr. Erick Riquelme

Erick Riquelme's Lab:
Ivania Valdés, PhDc
Fabian Oña, PhD Student

Collaborators:
McAllister Lab, MD Anderson Cancer Center
Akbay Lab, UT Southwestern Medical Center
Felipe Court (U. Mayor, CIB)
Estefania Nova-Lamperti (U.Concepción)

emriquel@uc.cl
emriquel@gmail.com