



Regione del Veneto
Istituto Oncologico Veneto
Istituto di Ricovero e Cura a Carattere Scientifico

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REGIONE DEL VENETO

SITC Immune Exclusion Virtual Summit

Mechanism of immune exlusion

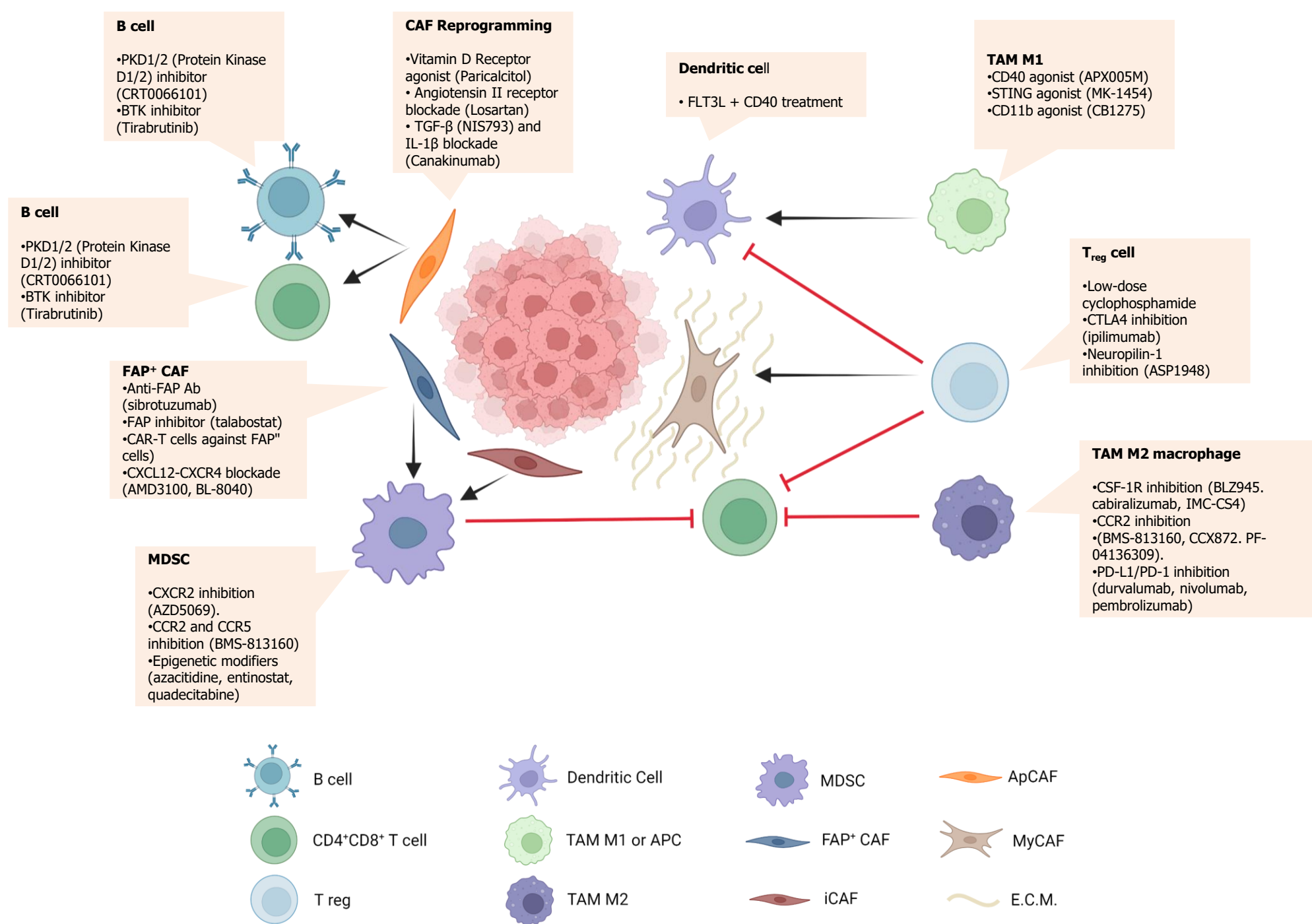
September 18, 2023

"Myeloid cells , NETs and arginase in pancreatic cancer"

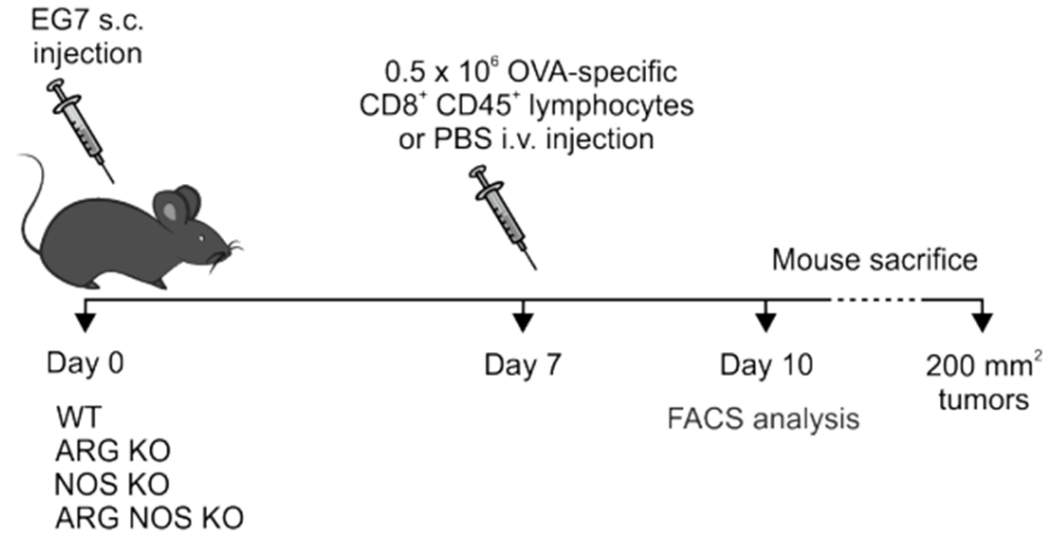
vincenzo.bronte@iov.veneto.it

PDAC is poorly responsive to immunotherapy

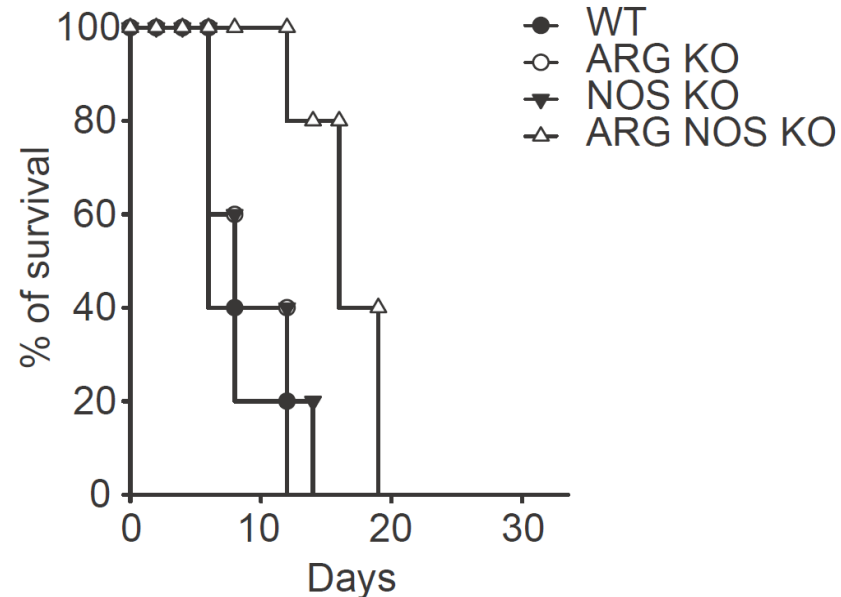
- Tumor mutational burden (TMB) and microsatellite status: only a small proportion of PDAC tumors are microsatellite instability-high (MSI-H), DNA mismatch repair deficient, or with high TMB.
- Homologous repair deficiency (HRD) can be associated with better response to platinum-based therapies, PARP inhibitor and anti-CTLA4 therapy: more frequent than MSI-H in PDAC patients but still a fraction of them.
- Liver metastases and poorer response to immunotherapy.
- Poor T cell infiltration and low PD-L1 expression.
- Immune excluded tumor microenvironment (TME) and systemic immune dysfunctions.



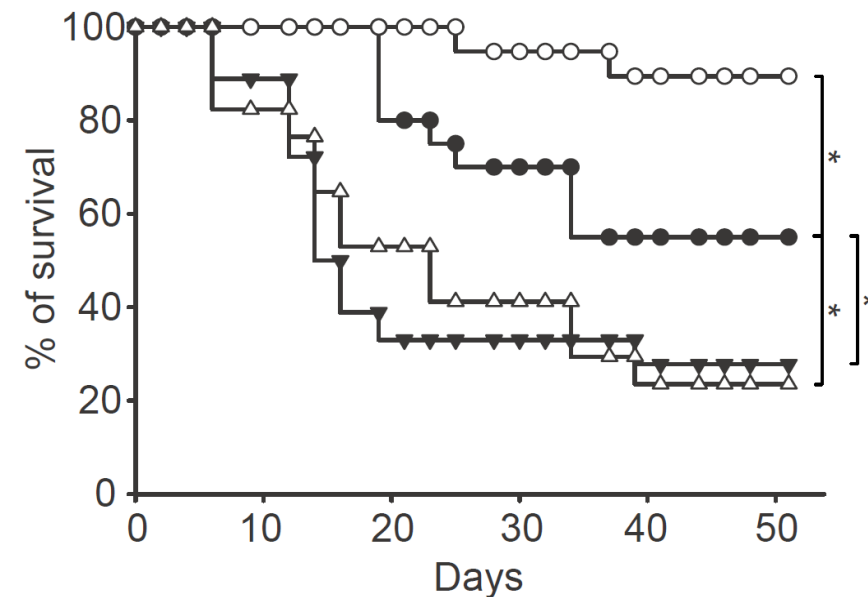
Myeloid ARG1 is an obstacle to tumor rejection following ACT



Survival without ACT



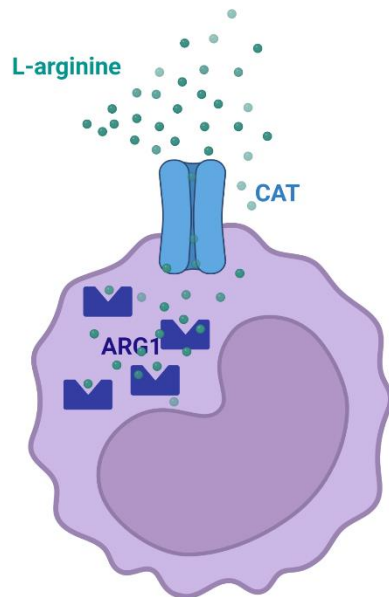
Survival with ACT



Divergent ARG1 biology in mice and humans



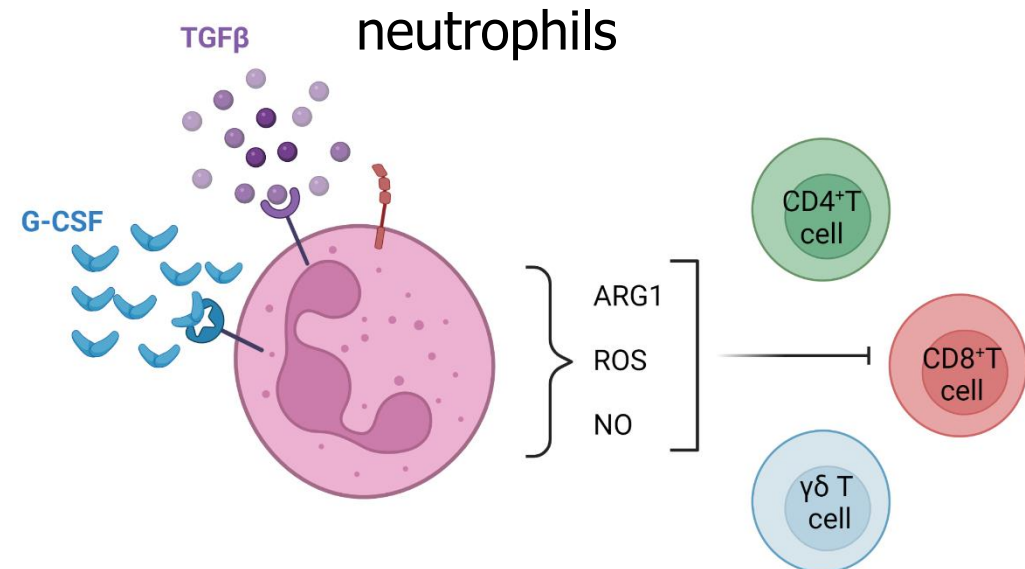
- ARG1 is a cytosolic enzyme
- L-arginine is imported in the cytosol
- L-arginine hydrolysis takes place intracellularly



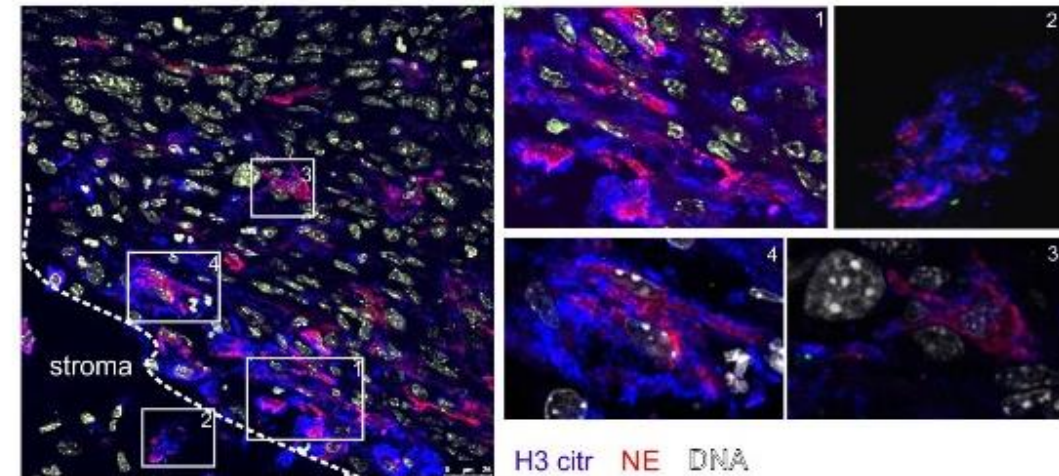
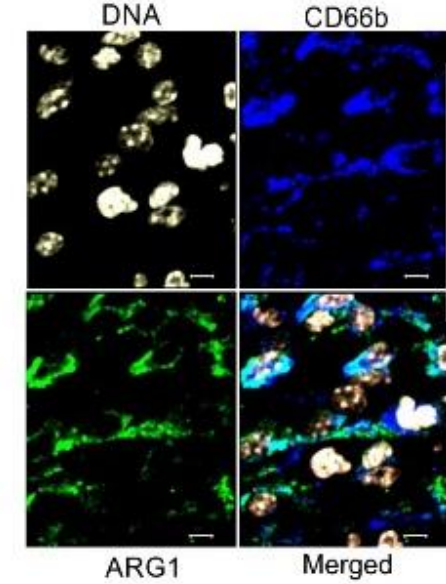
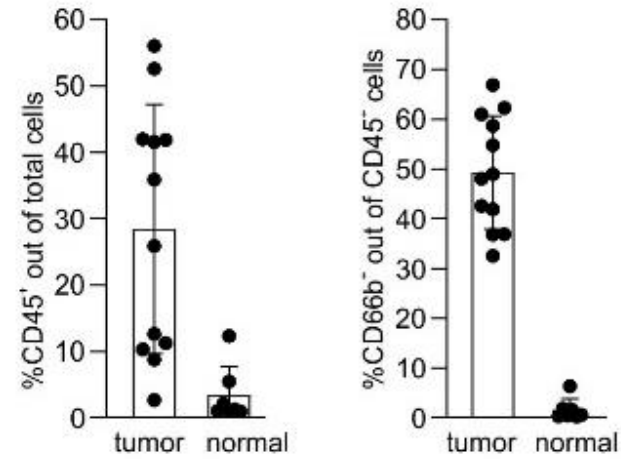
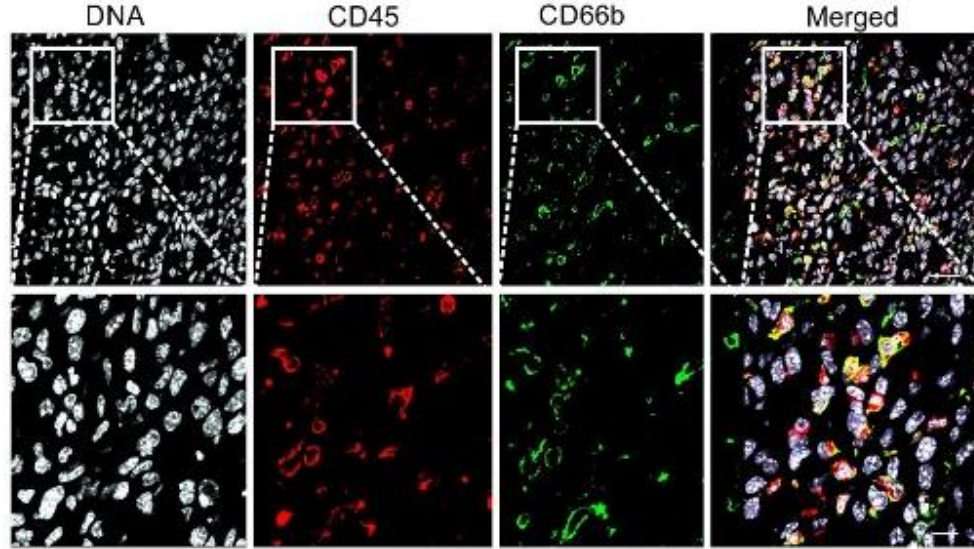
macrophages
monocytes
MDSCs



- ARG1 is stored in the tertiary granules as inactive protein
- L-arginine hydrolysis takes place extracellular
- Secreted ARG1 is active as a full-length protein at alkaline pH but inactive at physiological pH unless cleaved by PMN-derived proteases.

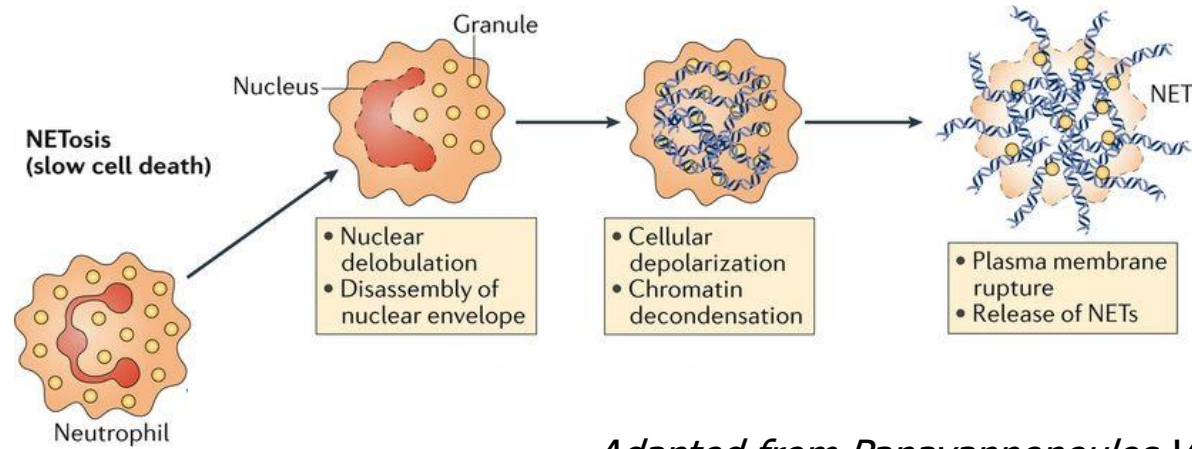


The TME is enriched in neutrophils producing NETs in PDAC

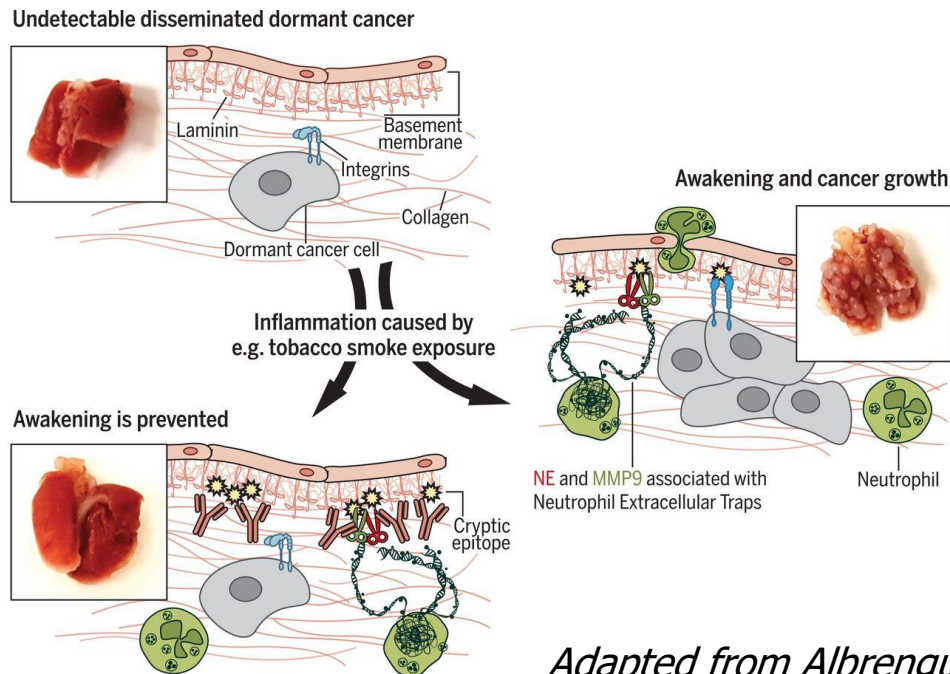


Neutrophil extracellular traps (NETs)

NETs: extracellular DNA web-like structures, generated by the decodensation of chromatin, which carry nuclear, cytoplasmic and granule proteins



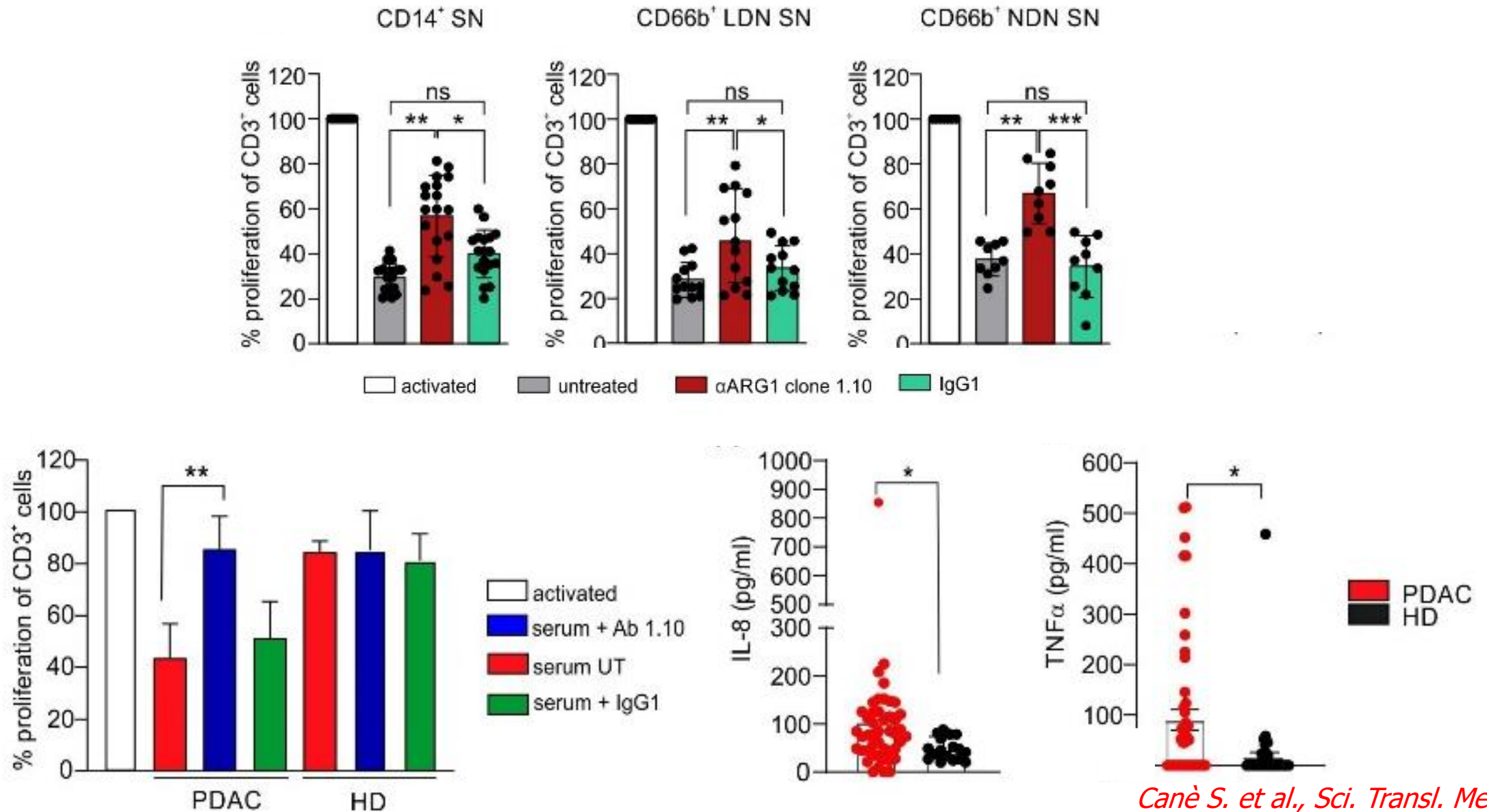
Adapted from Papayannopoulos V., Nature, 2018



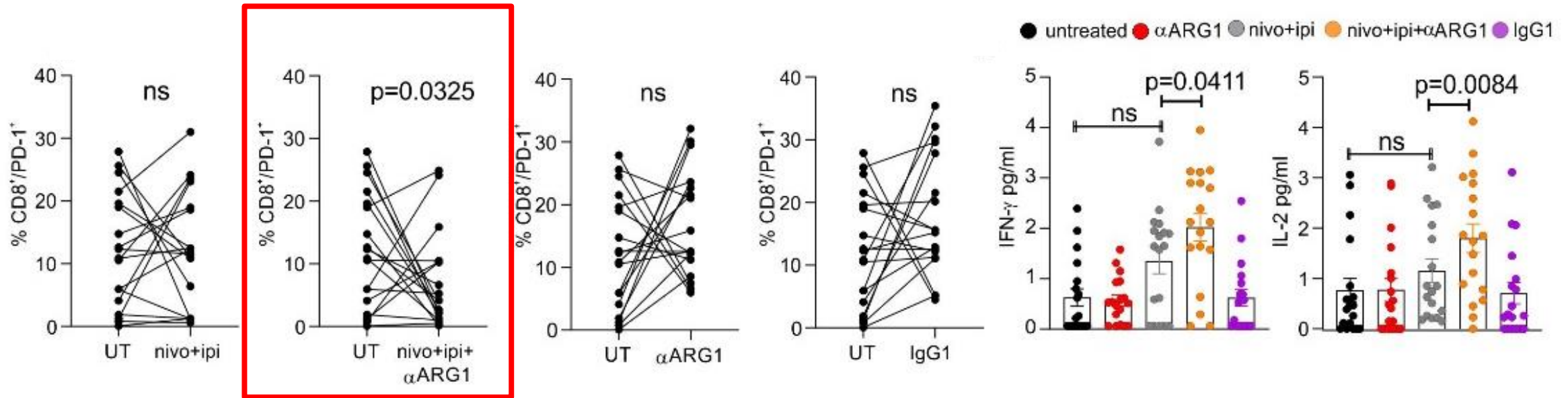
Adapted from Albregues et al., Science, 2018

- NET release is associated with increased metastasis formation
- NETs contribution to immunosuppression remains largely unknown
- Nothing is known about the presence and the mechanism of action of ARG1 in NETs

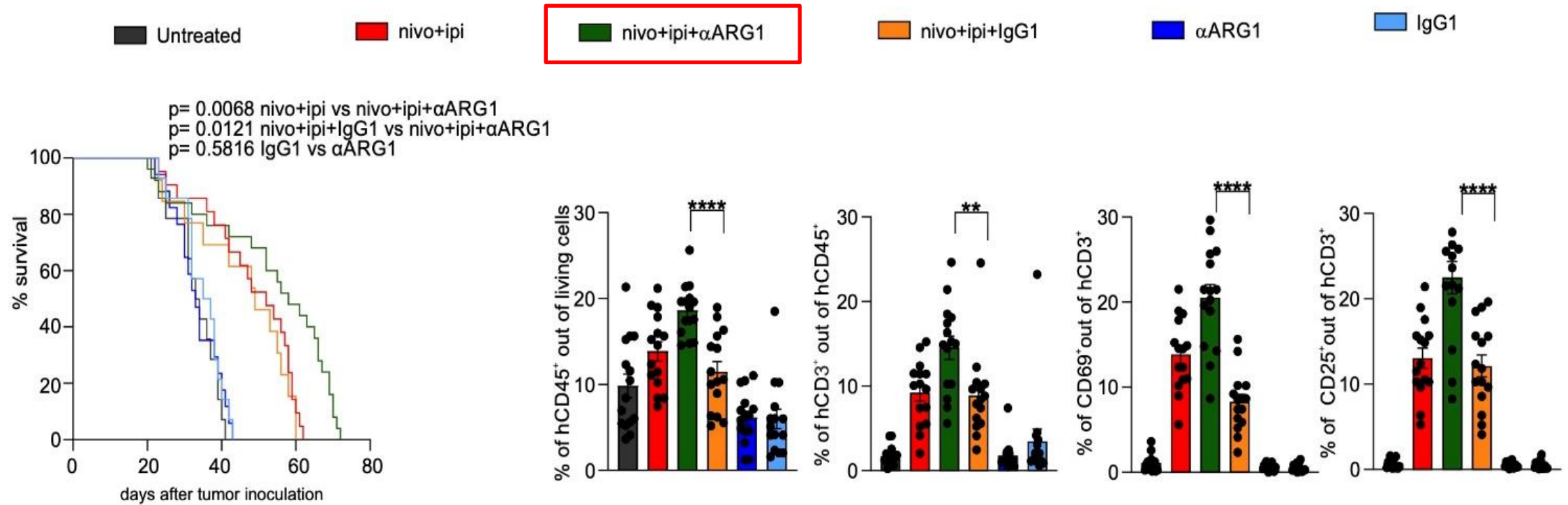
The blood of PDAC patients contains immune suppressive myeloid cells and ARG1



Neutralization of ARG1 increases the proportion and functional status of PDAC-infiltrating lymphocytes



ARG1 blockade increases the efficacy of ICI in humanized mice

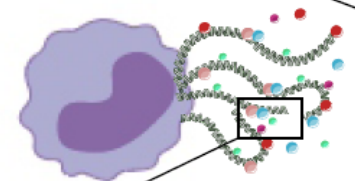
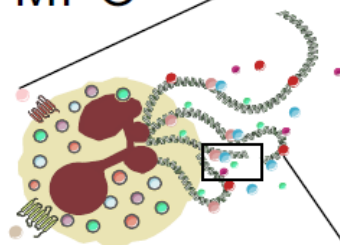


- ARG1 full length
- ARG1 31 kDa
- ARG1 25 kDa
- CTSS
- MPO



PDAC patient

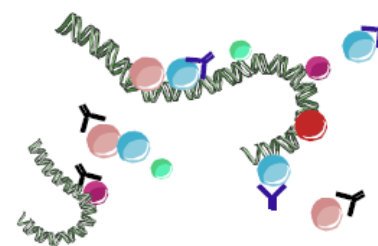
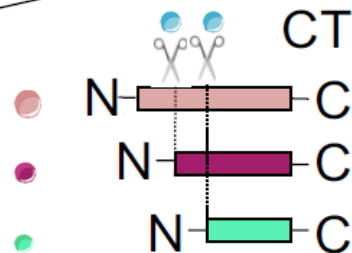
NDN/LDN
PMNs



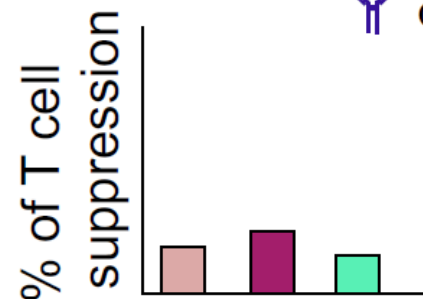
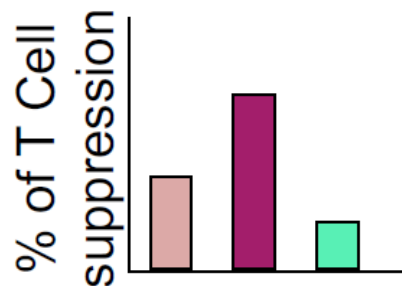
Function

Targeting

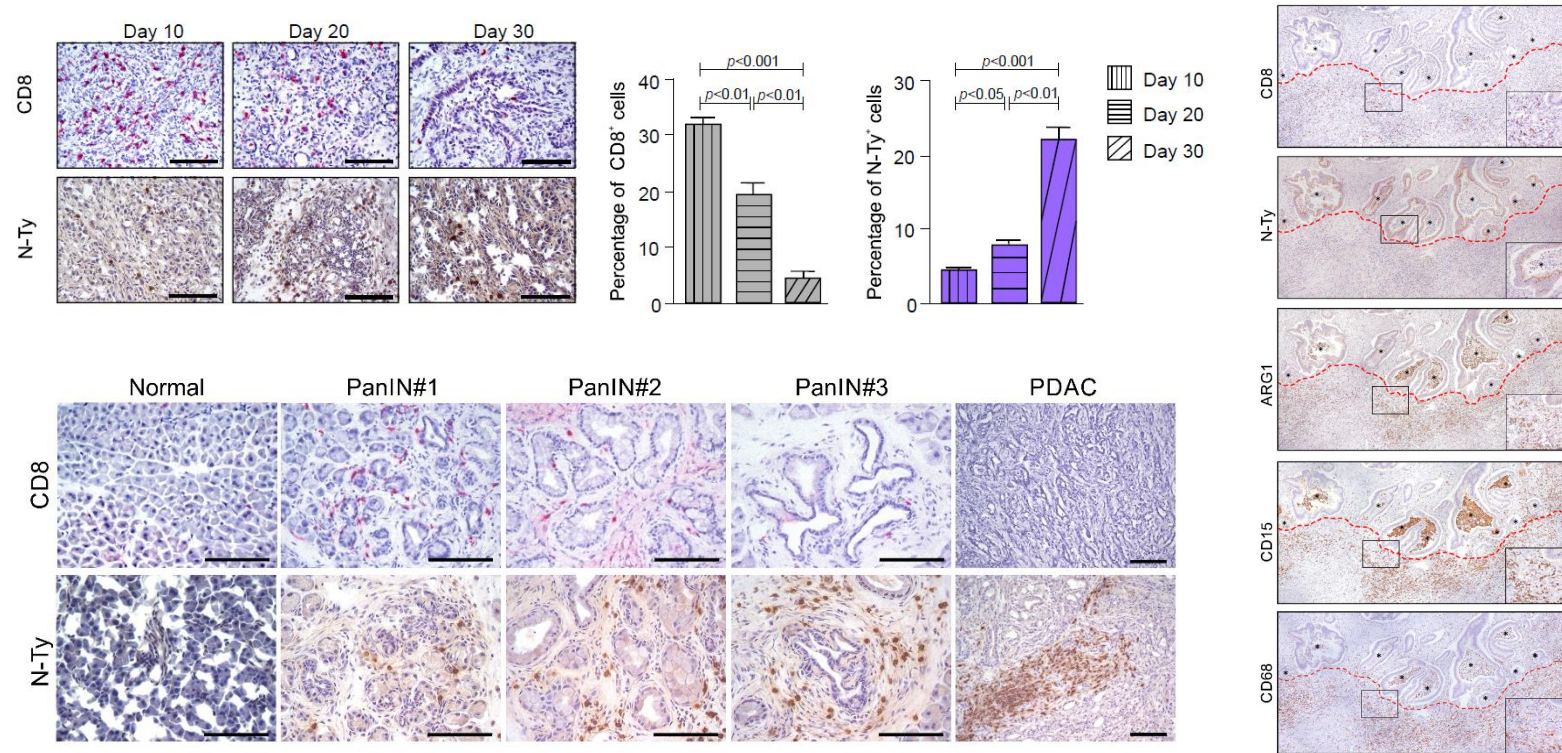
CTSS



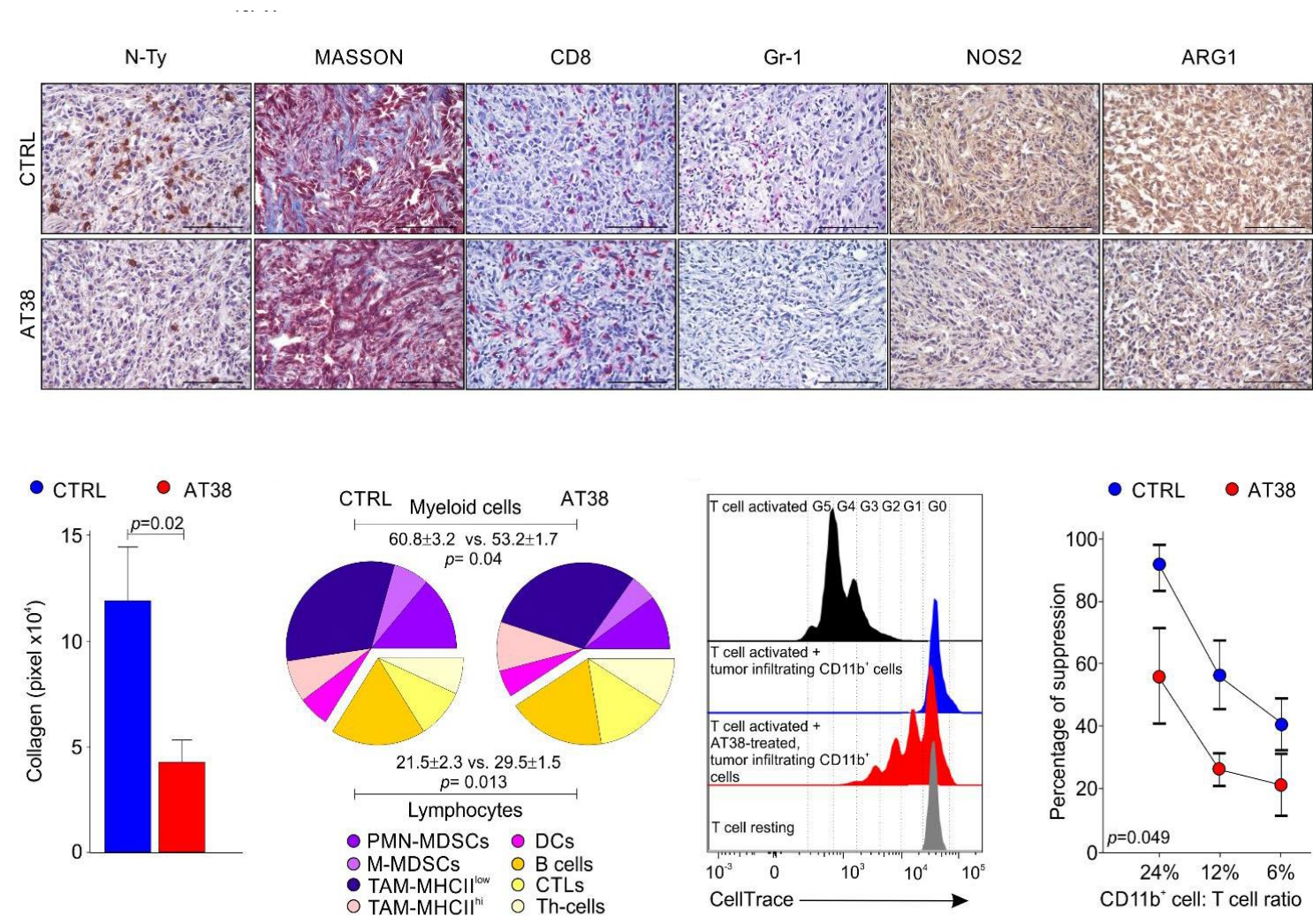
αARG1
clone
1.10
αCTSS



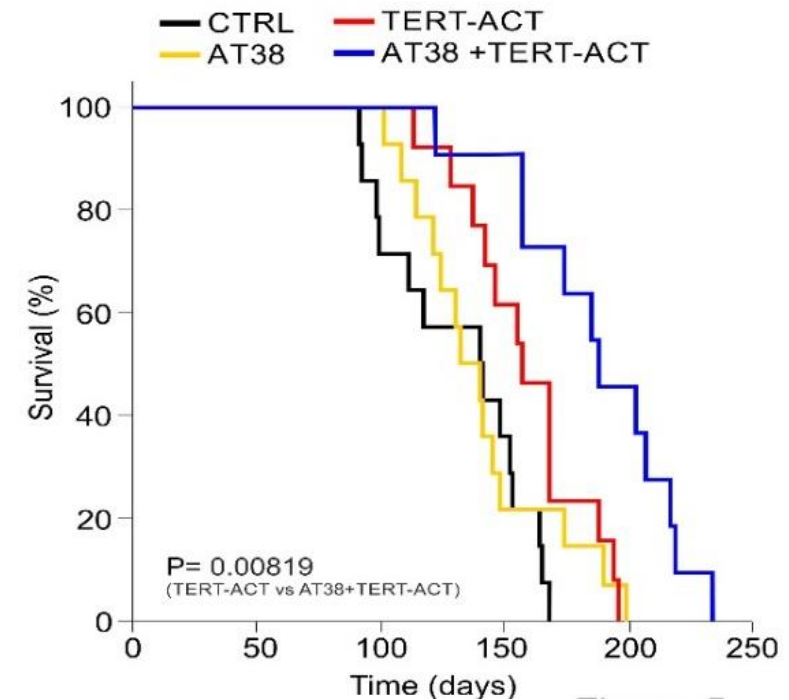
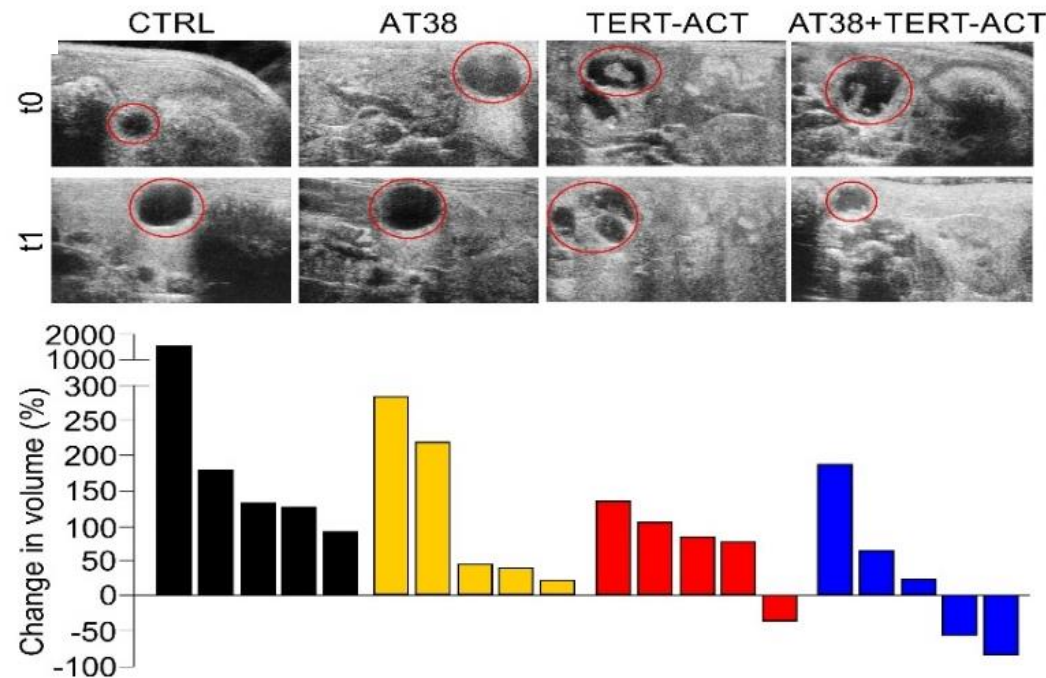
Pancreatic cancer progression is associated with progressive nitrotyrosine (N-Ty) accumulation and T cell exclusion in TME



AT38 modifies the immune landscape of PDAC and reprograms myeloid cells



Tumor microenvironment preconditioning improves the efficacy of adoptive cell therapy



Metabolic circuits in myeloid cells can shape the TME immune landscape

