SITC Immune Exclusion Virtual Summit
Mechanism of immune exlusion
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"Myeloid cells, NETs and arginase in pancreatic cancer”

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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-CTL4 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.
CAF Reprogramming
- Vitamin D Receptor agonist (Paricalcitol)
- Angiotensin II receptor blockade (Losartan)
- TGF-β (NIS793) and IL-1β blockade (Canakinumab)

B cell
- PKD1/2 (Protein Kinase D1/2) inhibitor (CRT0066101)
- BTK inhibitor (Tirabrutinib)

MDSC
- CXCR2 inhibition (AZD5069)
- CCR2 and CCR5 inhibition (BMS-813160)
- Epigenetic modifiers (azacitidine, entinostat, quadecitabine)

FAP+ CAF
- Anti-FAP Ab (sibrotuzumab)
- FAP inhibitor (talabostat)
- CAR-T cells against FAP+ cells
- CXCL12-CXCR4 blockade (AMD3100, BL-8040)

Dendritic cell
- FLT3L + CD40 treatment

TAM M2 macrophage
- CSF-1R inhibition (BLZ945, cabiralizumab, IMC-CS4)
- CCR2 inhibition
- (BMS-813160, CCX872, PF-04136309).
- PD-L1/PD-1 inhibition (durvalumab, nivolumab, pembrolizumab)

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Treg cell
- Low-dose cyclophosphamide
- CTLA4 inhibition (ipilimumab)
- Neuropilin-1 inhibition (ASP1948)

Dendritic cell
- FLT3L + CD40 treatment

TAM M1
- CD40 agonist (APX005M)
- STING agonist (MK-1454)
- CD11b agonist (CB1275)

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Myeloid ARG1 is an obstacle to tumor rejection following ACT

Survival without ACT

Survival with ACT

Marigo I. et al., Cancer Cell, 2016
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
- ARG1 is stored in the tertiary granules as inactive protein
- L-arginine hydrolysis takes place extracellularly
- Secreted ARG1 is active as a full-length protein at alkaline pH but inactive at physiological pH unless cleaved by PMN-derived proteases.

macrophages monocytes MDSCs

neutrophils

G-CSF  TGFβ  ARG1
ROS  NO

CD4+ T cell  CD8+ T cell  γδ T cell
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

- 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

*Adapted from Papayannopoulos V., Nature, 2018*

*Adapted from Albrengues et al., Science, 2018*
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

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

F. De Sanctis et al. – JITC 2022
AT38 modifies the immune landscape of PDAC and reprograms myeloid cells

F. De Sanctis et al. – JITC 2022
Tumor microenvironment preconditioning improves the efficacy of adoptive cell therapy

F. De Sanctis et al. – JITC 2022
Metabolic circuits in myeloid cells can shape the TME immune landscape