# Immune Exclusion: Therapeutic approaches to ECM

*Mechanisms of immune exclusion are complex* and can be due to activated oncogenic pathways, hypoxia, degenerated blood vessels, cytokines and chemokines released by tumor, stromal cells, immune infiltration of immunosuppressive cells and ECM that limit lymphocyte access to the tumor nest.

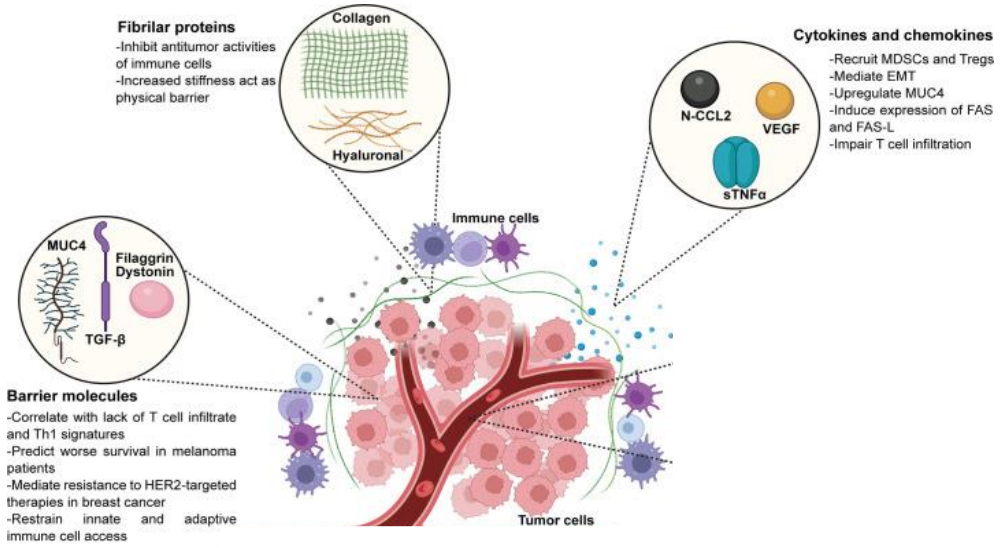
## Major ECM Constituents & Targets

### Matrix scaffold macromolecules

- Proteoglycans
- Fibrous matrix forming proteins
  - Collagens I, III, IV needed for cancer cell survival; fibronectin, etc.
    - **Collagen receptors**, e.g. discoidin domain receptor 1 (DDR1) and **lysyal oxidase** as targets
- **Hyaluronan** forms a hydrogel-like matrix surrounding the tumor cells acting as an exclusion barrier > pegylated **hyaluronidase**, PEGPH20.

### Cytokines & Chemokines

- **N-CCL2** > TAM and MDSC recruitment
- TGFb > collagen > fibrosis
  - **Collagen is a LAIR-1 ligand** – LAIR-1 ICB




*Bruni. et al. Frontiers in Oncol, 22 May 2023*

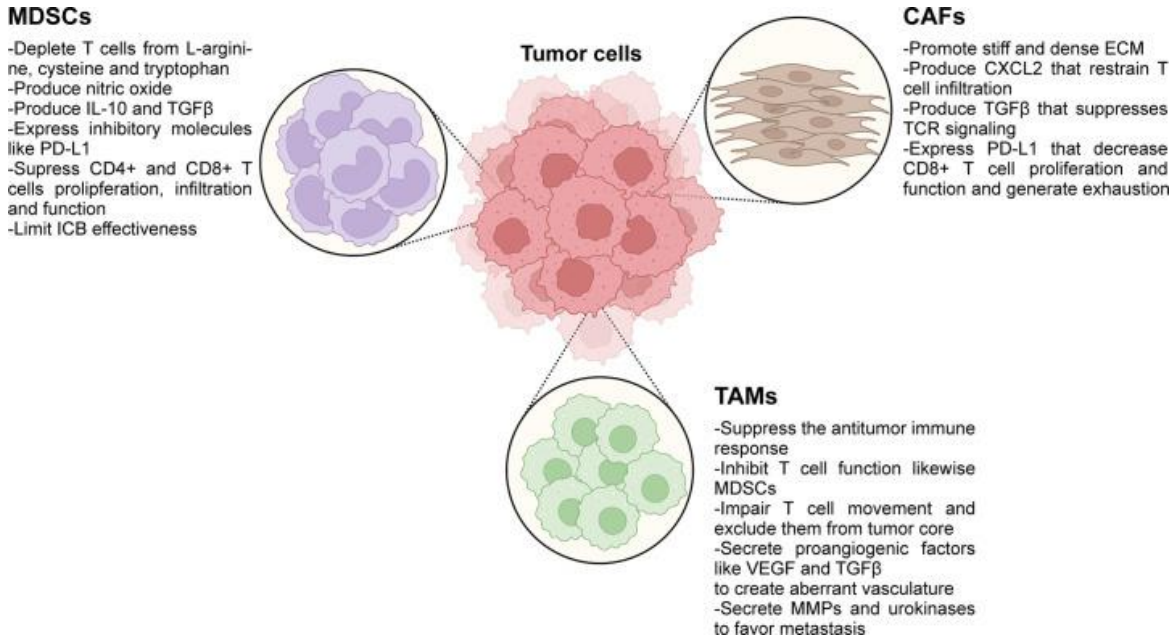
## Proteins with known barrier functions

e.g. filaggrin and desmosomal proteins like dystonin.

- T cell infiltration to the tumor bed is modulated by filaggrin mutational state.
- Dystonin > loss of Th1-like immune signature
- Can disrupting agents be developed and safe??

# Immune Exclusion: Therapeutic approaches to CAFs and Vessels

## Cellular Gatekeepers




*Bruni. et al. Frontiers in Oncol, 22 May 2023*

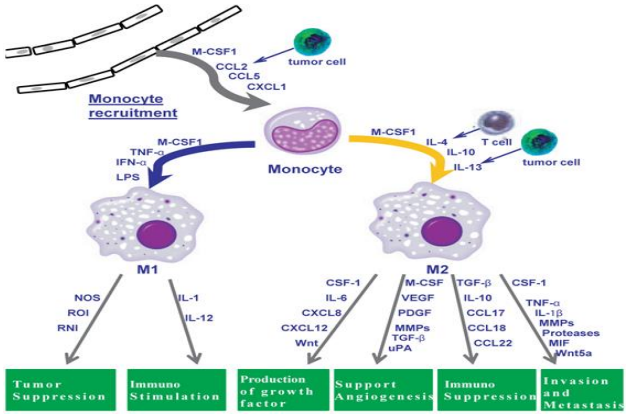
## Major Stromal Constituents & Targets

- **Cancer Associated Fibroblasts**
  - Fibroblast activation protein (FAP)
  - FAP targeting CART – but *anemia*, bone marrow hypoplasia

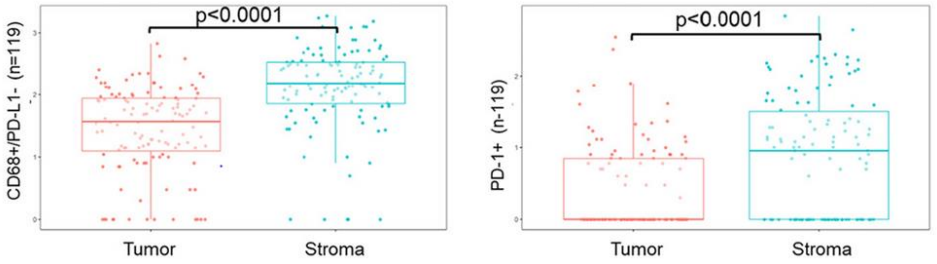
- **Endothelial cells**
  - PSMA
    - ICANS Neurotoxicity from PSMA-specific, TGFβ-resistant CART
  - VEGFR2
    - Tolerable but no response –combo?
  - FSHR
    - Untested in patients

# Immune Exclusion: TAMs/MDSCs as gatekeepers & targets

- Accumulation is **a poor prognostic factor in most solid cancer types.**
- **Associated with resistance to ICB and CART therapies.**
- **Recruited and corrupted** by tumor cells.
- Commonly have an **alternative or wound-healing phenotype and <u>often reside in stroma</u>.**
  - Immunosuppressive cytokines (e.g. IL-10; TGFβ) and ligands (PD-L1)
  - Pro-angiogenic factors (e.g. VEGF-A)
  - Poor antigen presentation
  - Growth factors and matrix remodeling
  - Promote tumor growth, angiogenesis, metastasis, and immune evasion

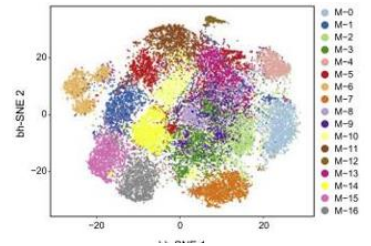



[Frontiers in Bioscience S4, 787-798, January 1, 2012



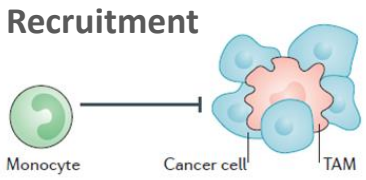

Meagher NS, Gyn Onc. 2023 Jan; 168: 23–31.

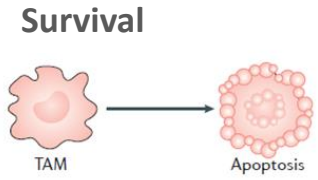
- **Challenges to targeting:**
  - Comprised of diverse phenotypic subsets
  - Hard to discriminate b/w suppressor and inflammatory subsets
  - Subsets dynamically change & continued TAM recruitment

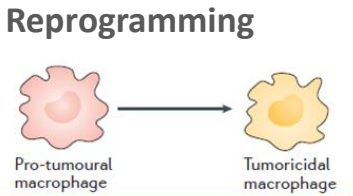



Chevrier, *et al.* Cell. 2017 May 4; 169(4): 736–749.e18.

# Targeting TAMs: Clinical Strategies to allow T cell infiltration and activity




| Drug name | Target | Inhibitor type |
|---|---|---|
| Carlumab | CCL2 | mAb |
| PF04136309 | CCR2 | Small molecule |
| PLX3397 | CSF1R | Small molecule |
| PLX7486 | CSF1R | Small molecule |
| JNJ-40346527 | CSF1R | Small molecule |
| ARRY-382 | CSF1R | Small molecule |
| BLZ945 | CSF1R | Small molecule |
| IMC-CS4 | CSF1R | mAb |
| R05509554 | CSF1R | mAb |
| RG7155 | CSF1R | mAb |
| FPA008 | CSF1R | mAb |

| Drug name | Target | Inhibitor type |
|---|---|---|
| Clodronate | NA | Small molecule |
| Zoledronic acid | NA | Small molecule |
| Trabectedin | Caspase 8 | Small molecule |
| PLX7486 | CSF1R | Small molecule |
| JNJ-40346527 | CSF1R | Small molecule |
| ARRY-382 | CSF1R | Small molecule |
| BLZ945 | CSF1R | Small molecule |
| IMC-CS4 | CSF1R | mAb |
| R05509554 | CSF1R | mAb |
| RG7155 | CSF1R | mAb |
| FPA008 | CSF1R | mAb |

| Drug name | Target | Inhibitor type |
|---|---|---|
| Hu5F9-G4 | CD47 | mAb |
| CC-90002 | CD47 | mAb |
| TTI-621 | SIRPα | Fusion protein |
| CP-870,893 | CD40 | Agonistic antibody |
| RO7009789 | CD40 | Agonistic antibody |
| Imiquimod | TLR7 | Small molecule |
| 852A | TLR7 | Small molecule |
| IMO-2055 | TLR9 | Small molecule |
| BLZ945 | CSF1R | Small molecule |

(Casseta and Pollard, *Nat Rev Drug Discovery*, 2018)

- ***CSF-1R inhibitors***
  - CSF-1 is implicated in tumor macrophage recruitment, survival, proliferation, and differentiation.
  - Expression identified in primitive multipotent hematopoietic cells and mononuclear phagocytic lineage cells.
  - Some evidence of clinical activity with some toxicity at current dose concentrations.

- ***CD47 blocking antibodies and SIRPαFc fusions***
  - provides a "do not eat" signal to macrophages by binding to signal regulatory protein alpha (SIRPα) on immune cells and suppresses phagocytosis.
  - Ubiquitously expressed in human cells.
  - Several trials; Some antitumor activity observed.

**Challenges:**

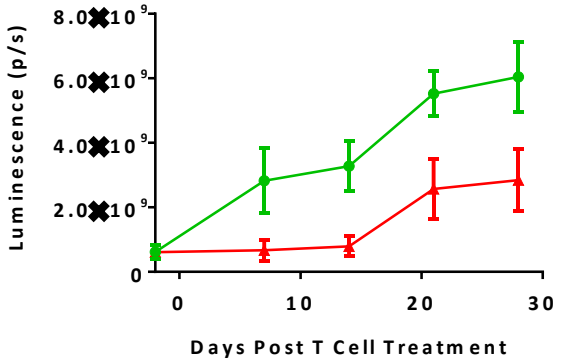
- **Indiscriminate of TAM subset (e.g. inflammatory vs. suppressive)**
- **Activity in the TME *and systemically;* toxicity**
- **Short term activity/half-lives**

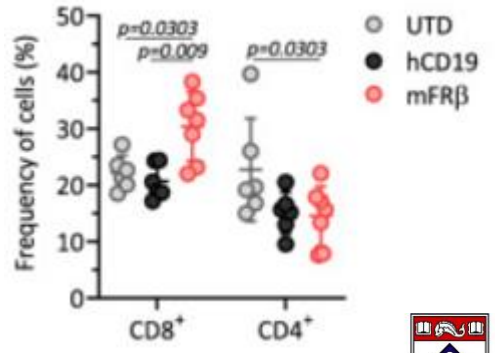
**New approaches:**

**CART: advantage - durability of depletion – "logic" gating.**

- **Promotes endogenous T cell infiltration and activity**

**Newer targets: CD200, CD163, CD206, FRb**




*Rodriguez-Garcia, A. et al. Nature Communications, 2021*