Cancer Immunity.

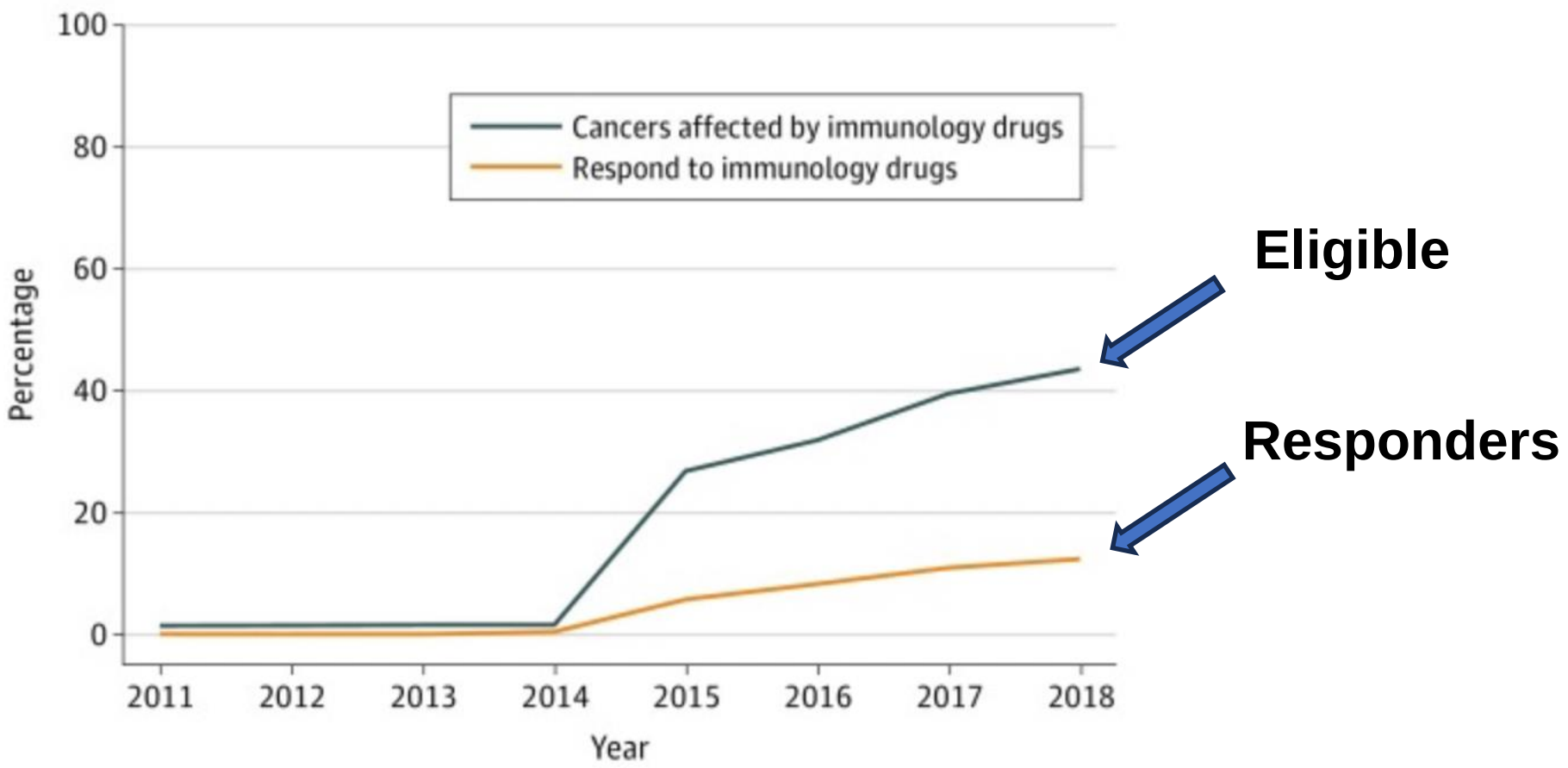
Maria Tsoumakidou, MD PhD

BSRC Fleming, Greece

Disclosures

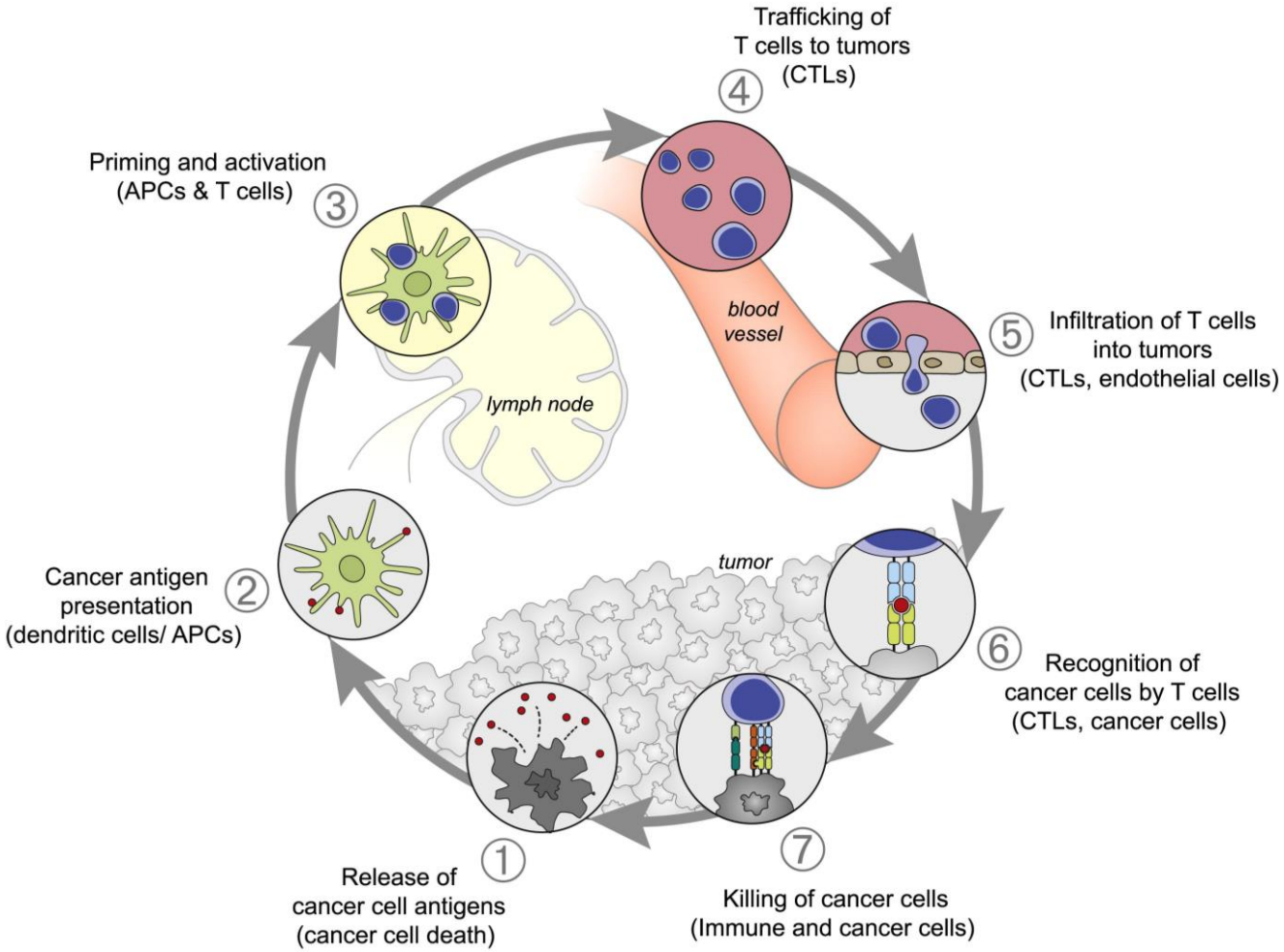
None

Low percentages of patients who are eligible for and who respond to checkpoint inhibitor drugs.



JAMA Netw Open. 2019 May; 2(5): e192535.

The Cancer Immunity Cycle



D.S. Chen and I. Mellman. Immunity 2013;39(1):1-10

Factors that can block the Cancer Immunity Cycle

1. Low amount cancer antigens (non-immunogenic tumors)
2. Few antigen-presenting cells in tumors
3. Low migration rates of cancer-antigen loaded cells to lymph nodes
4. Tolerogenic outcome of antigen presentation to T cells in lymph nodes
5. Inability of cancer-specific T cells to migrate from lymph nodes to tumors
6. Poor access of T cells to tumor nests
7. Immunosuppressive effect of the tumor microenvironment

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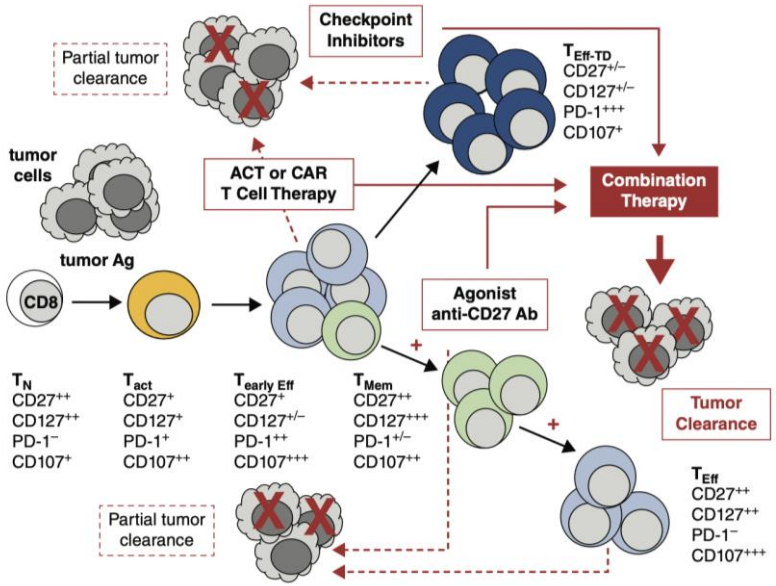
Topics to be discussed

Cancer antigen presentation by stromal cells in tumors.

Dendritic cell responses in tumor microenvironments.

CAFs - OPPORTUNITIES FOR NOVEL IMMUNOTHERAPIES

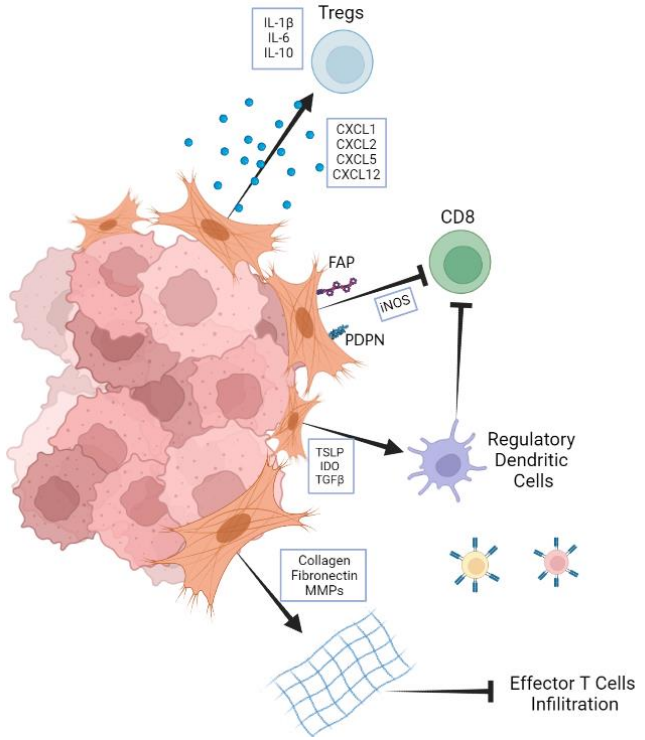
CURRENT IMMUNOTHERAPIES
Directly targeting immune cells.
Efficacy limited.



K. De Paris. J Leukocyte Bio (2019).

AN ALTERNATIVE STRATEGY
Indirectly target immune cells by targeting the non-immune stroma?

STATE-OF-THE ART
CAFs, the most abundant tumor stroma cells, are immunosuppressive.
Therapeutic Deletion/Blockade sought.

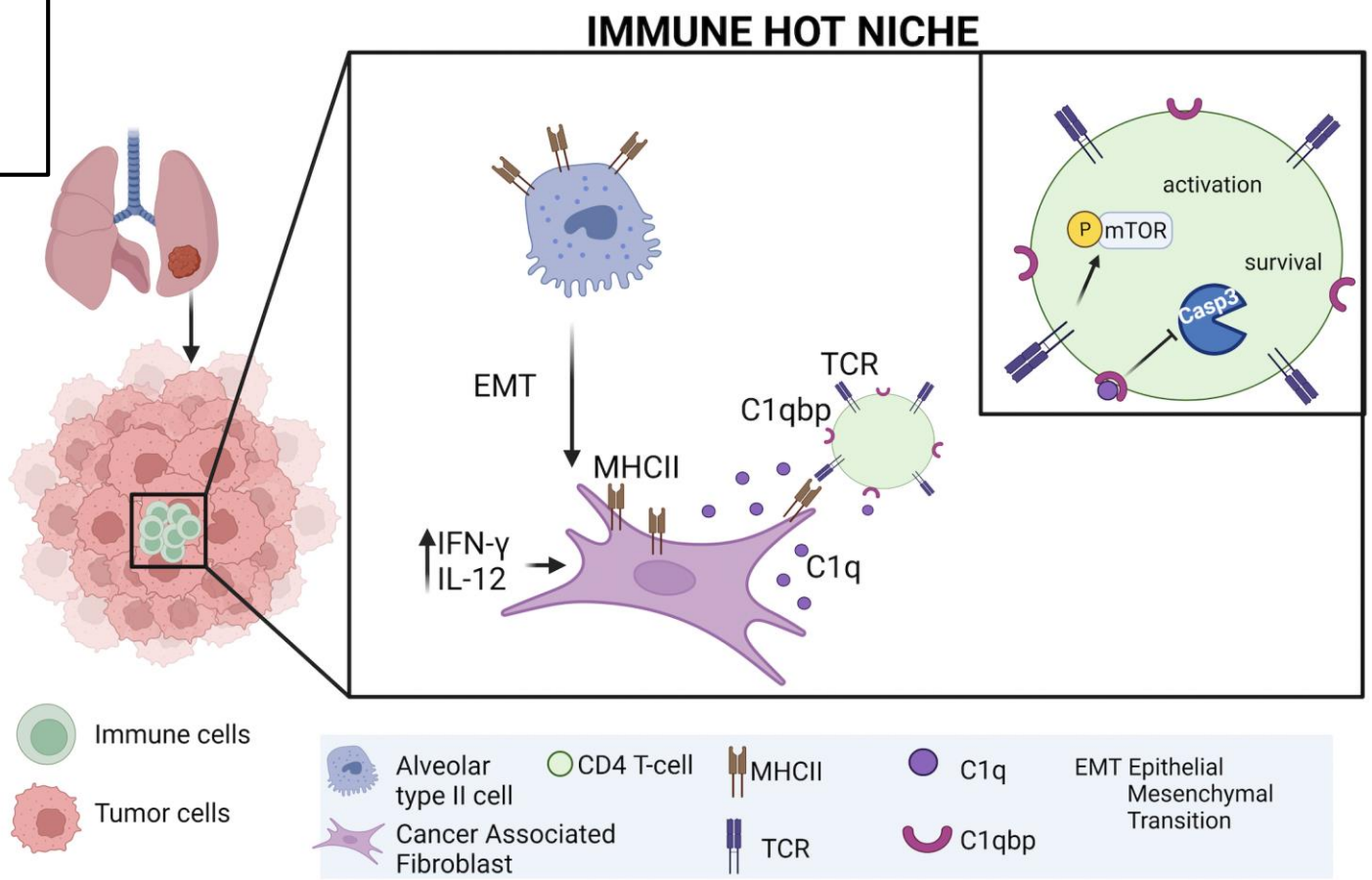


Mhaidly R & Mechta-Grigoriou F. *Immunological Reviews* (2021).

CAFs = CANCER ASSOCIATED FIBROBLASTS

CONCEPTUAL ADVANCE - LUNG MHII FIBROs ARE IMMUNOSTIMULATORY

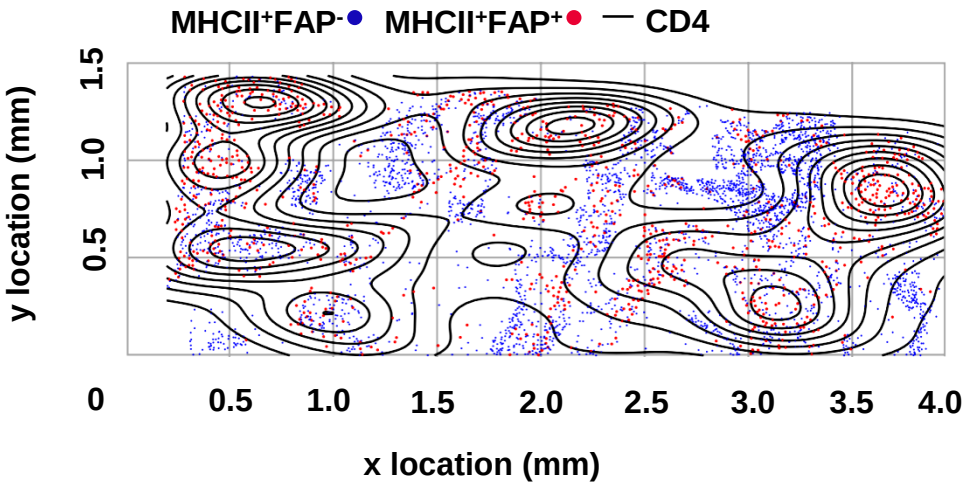
MHCII FIBROs
- **Lung Cancer**
- Pancreatic Cancer
- Breast Cancer
- Liver Cancer

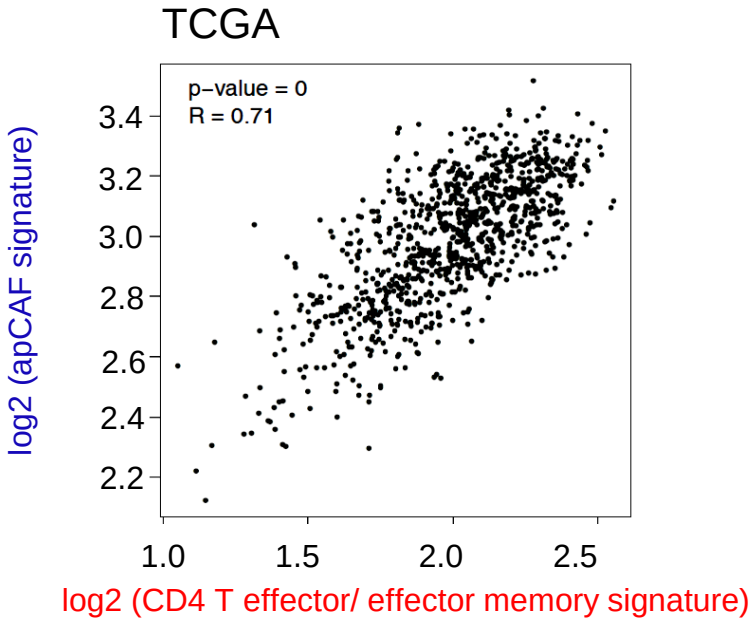


Lung MHCII FIBROs
- present Ags
- activate T effectors
- prevent T apoptosis
- create immune spots

Kerdidani D, et al.
J Exp Med (2022).

MHCII fibroblasts form T cell hubs within human lung tumors.

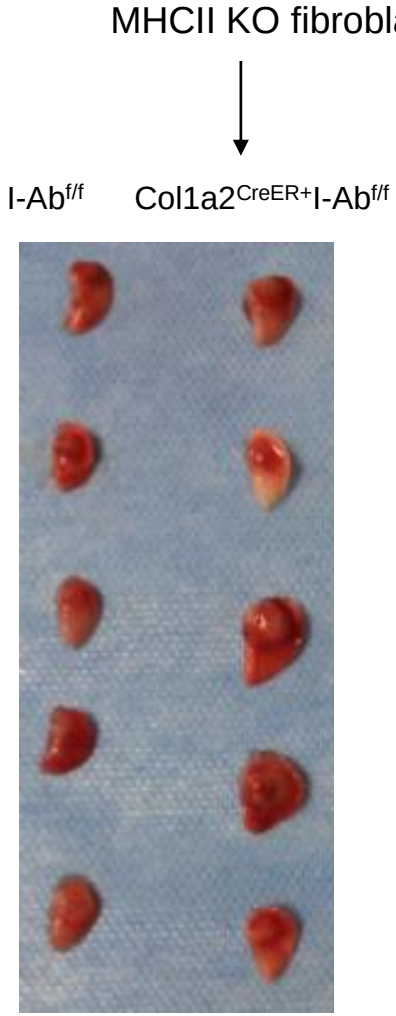




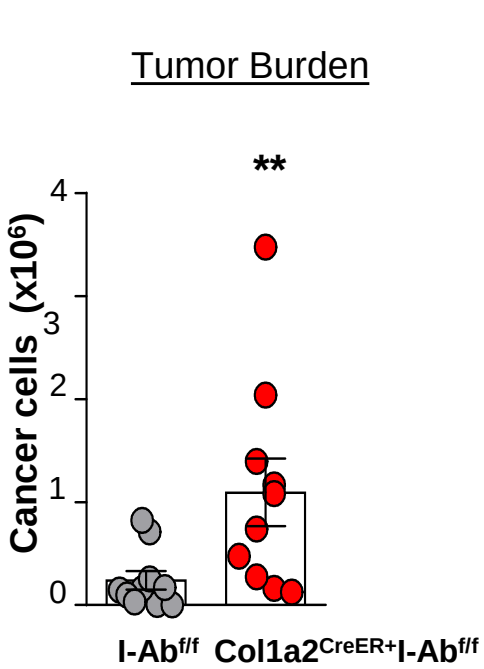
D. Kerdidani, et al. JExpMed. (2022)

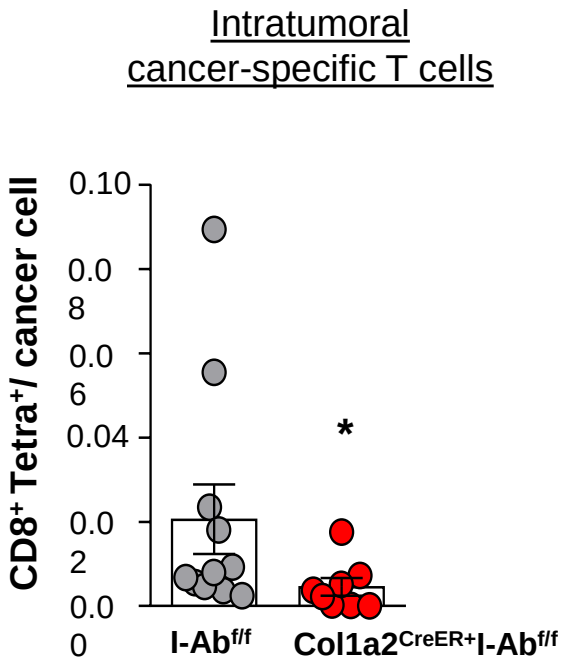
Conditional knock out of MHCII in fibroblasts increases tumor growth.

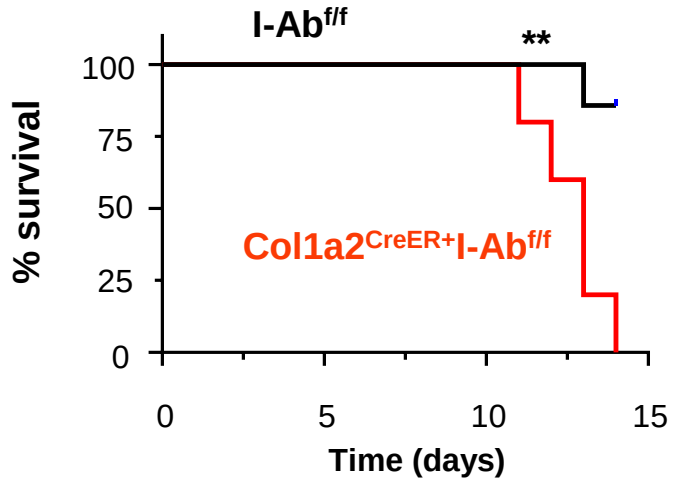
MHCII KO fibroblasts



I-Ab$^{f/f}$ Col1a2^{CreER+}I-Ab$^{f/f}$

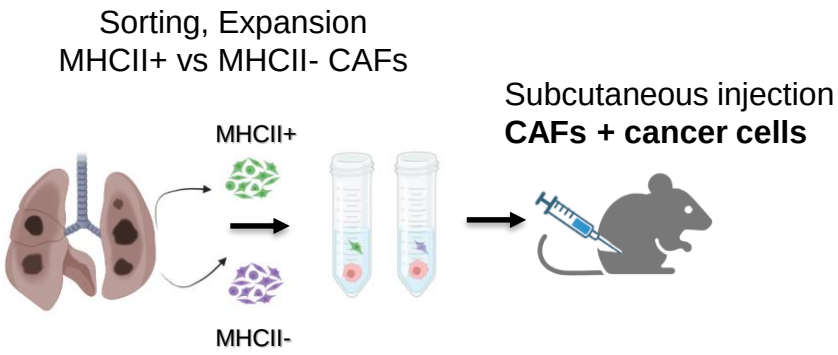






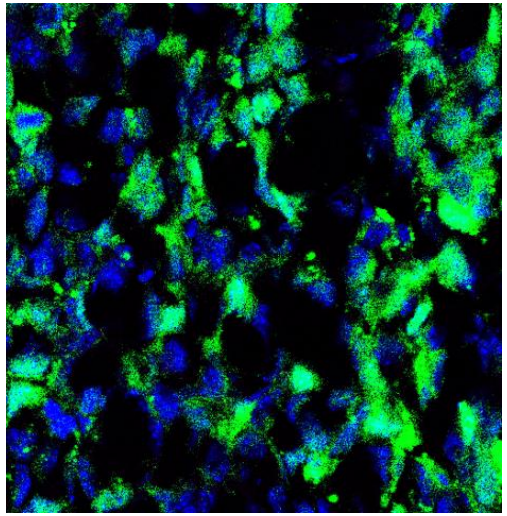
D. Kerdidani, et al. JExpMed. (2022)

MHCII+ fibroblasts impede tumor growth in transplantation studies.



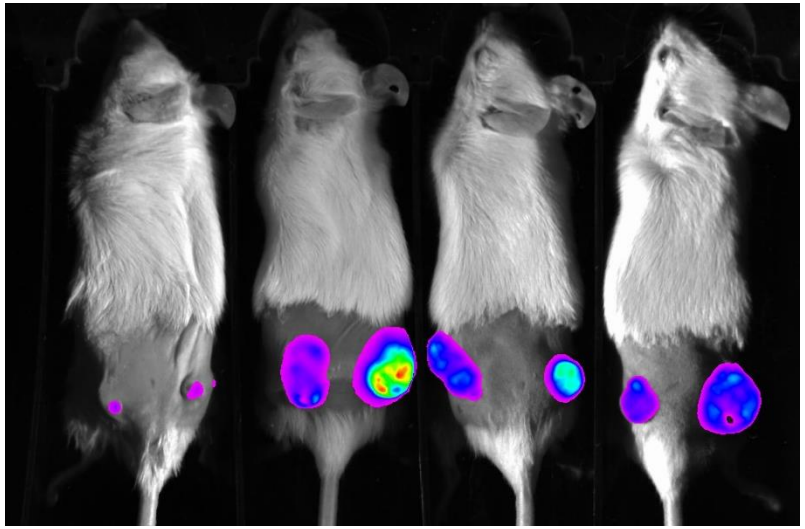
Flank tumors_DAY13

DAPI CAFs^{zsGreen}



L: MHCII^{+} CAFs+KPM-Luc

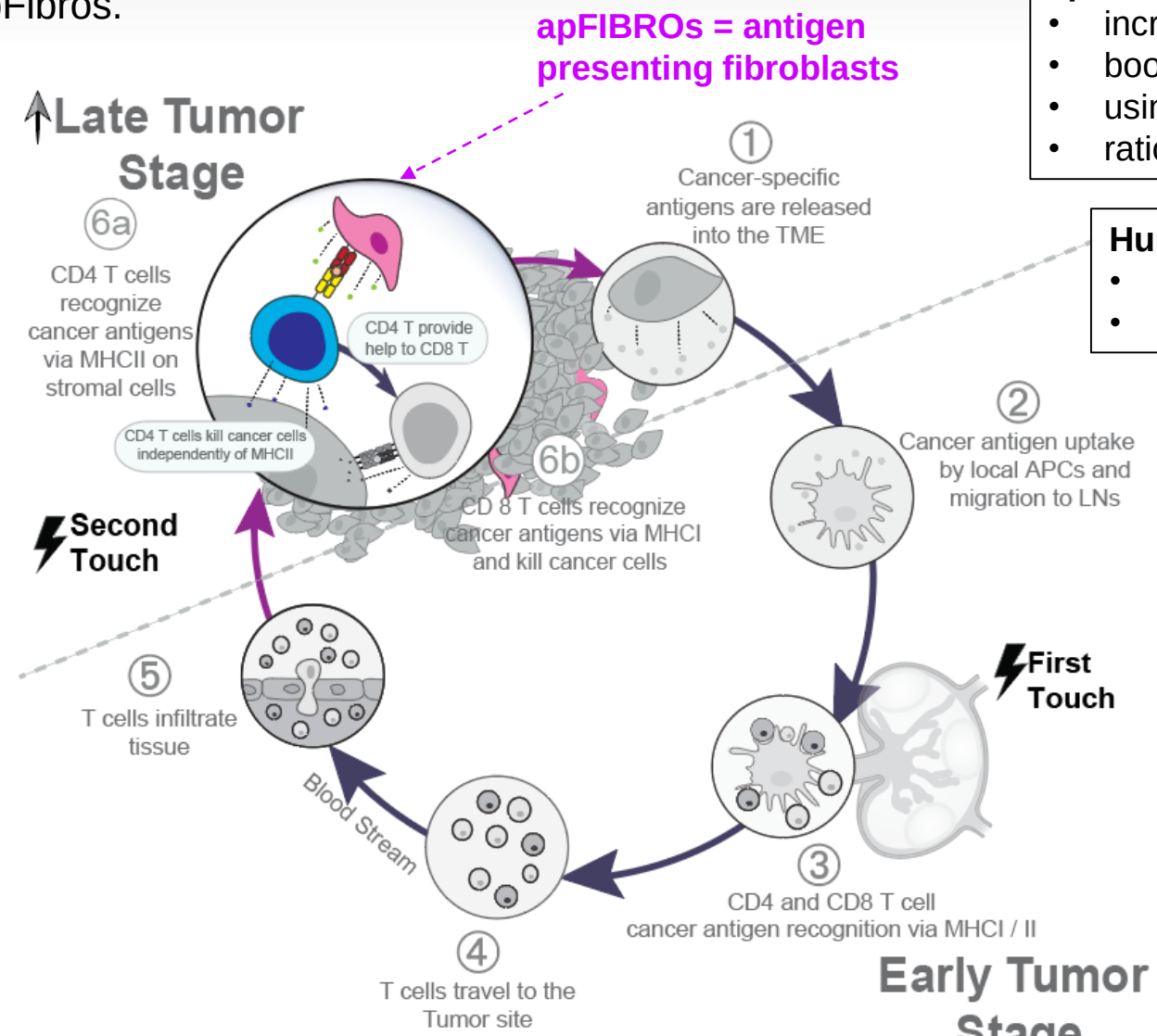
R: MHCII^{-} CAFs+KPM-Luc



D. Kerdidani, et al. JExpMed. (2022)

NEW CONCEPT FOR CANCER IMMUNITY -THE SECOND TOUCH HYPOTHESIS

After first touch in dLNs CD4 T depend on antigen re-encounter in tumors.
Second touch provided by apFibros.



apFIBRO therapeutic opportunities

- increasing their numbers
- boosting effector functions on T cells
- using them as in vivo vaccination platforms
- rational combination therapies

Hurdles

- Low numbers (<10% of total fibroblasts)
- Incomplete understanding

Modified from:
Chen, D.S. & Mellman, I. *Immunity* (2013).

M. Tsoumakidou. Nat Rev Cancer. 2023 23(4):258-269.

PERTURBATION MODELLING IN THE LUNG TUMOR PHASE SPACE TO REWIRE FIBROBLASTS FOR IMMUNOTHERAPY.

European Research Council

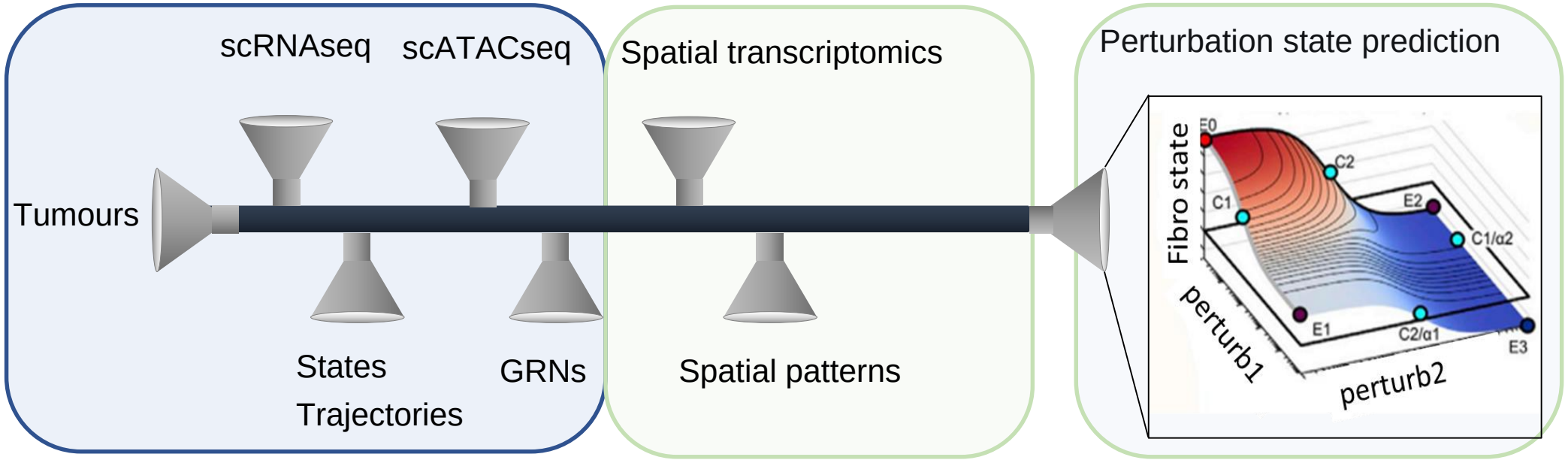
apFIBRO DECOMPOSITION

GRN MINING

AIM 1
ORIGINS-DIVERSITY-REGULATION

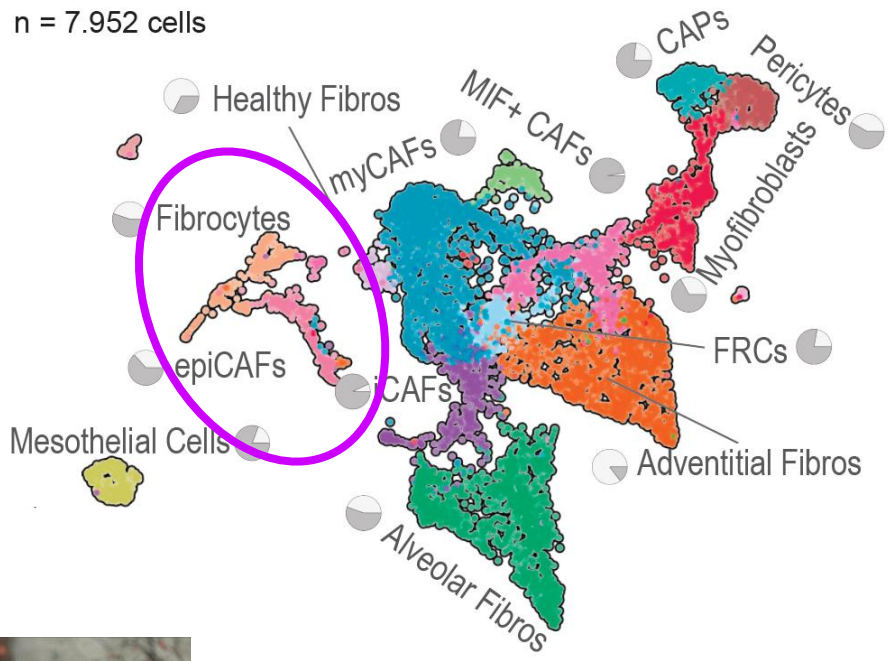
AIM 2
HETEROTYPIC INTERACTIONS

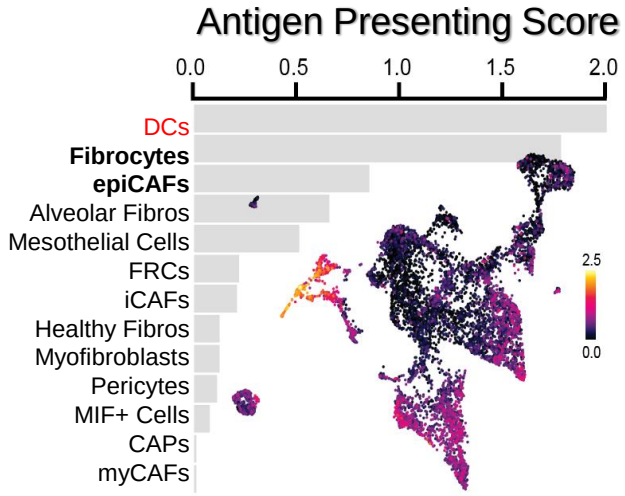
AIM 3
REPROGRAMMING CAFs to apFIBROs

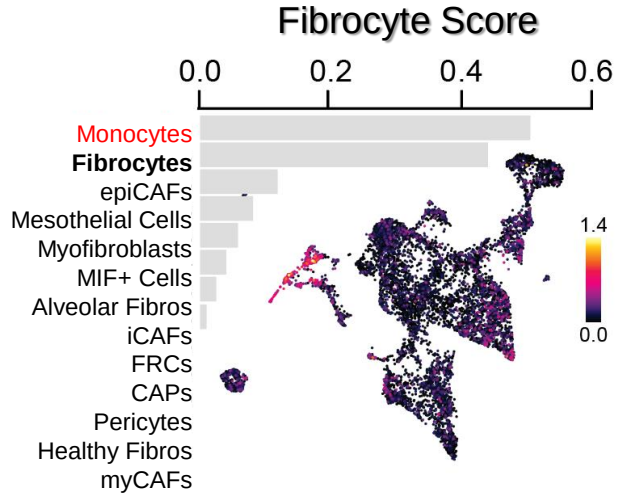


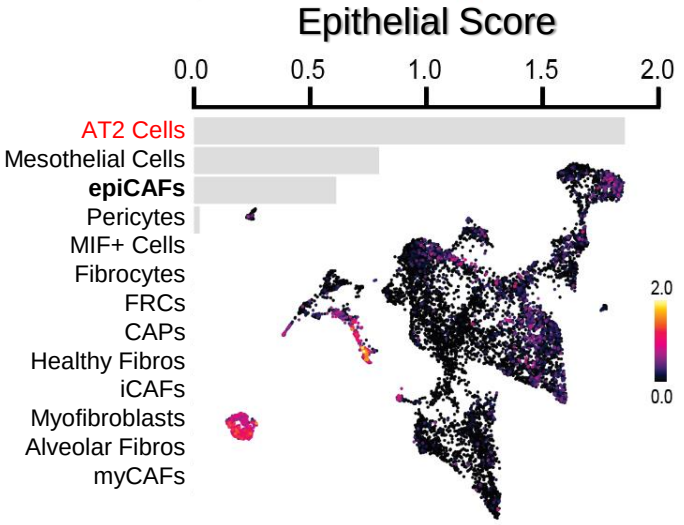
RECOVERY OF DRIVERS AND EFFECTORS (novel targets)

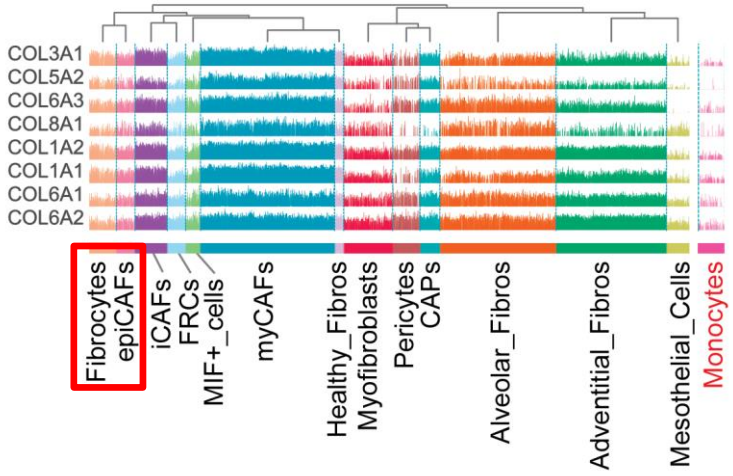
Unbiased clustering of lung fibroblasts in an epithelial cell-like and a fibrocytes MHCII expressing cluster.





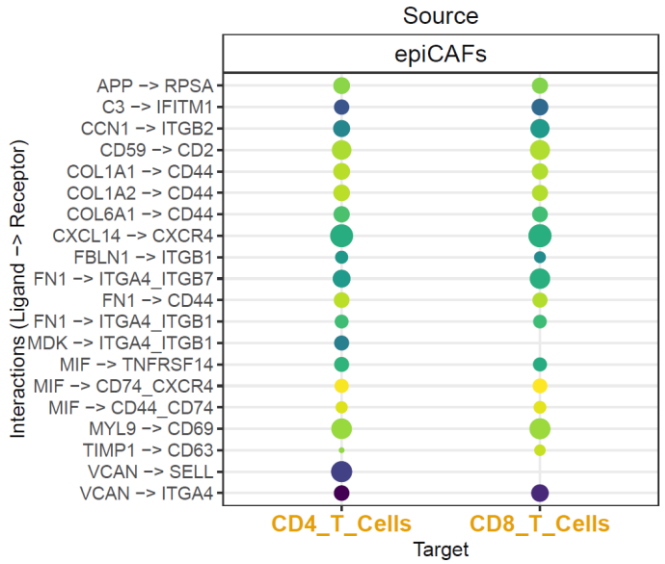


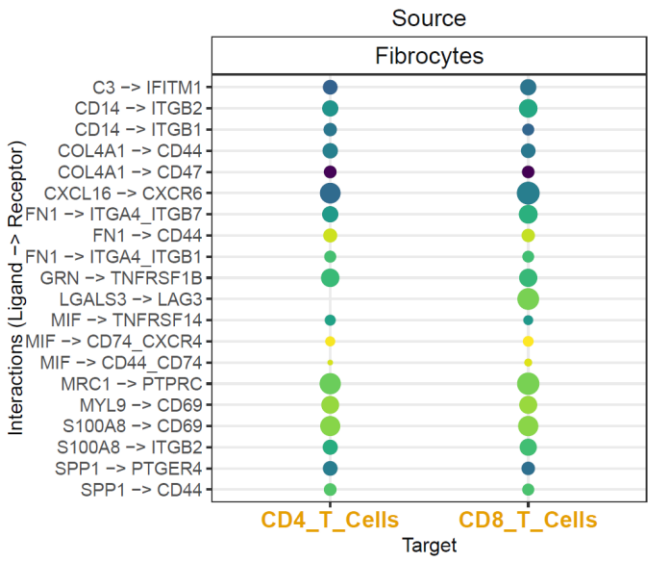


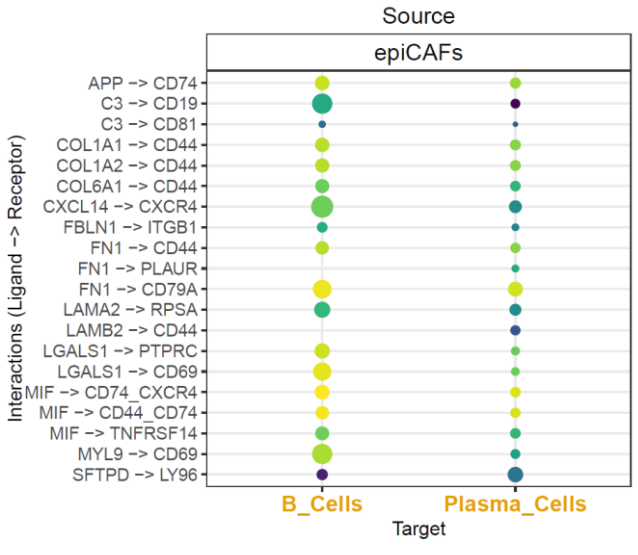


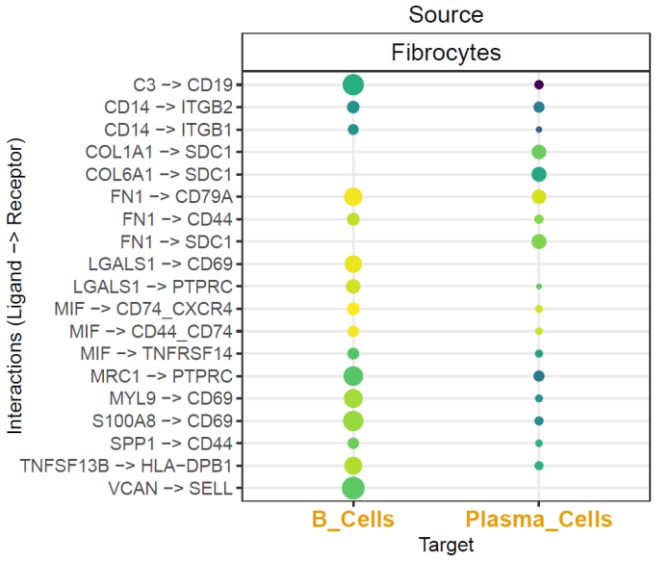
I. Angelidis. Unpublished data.

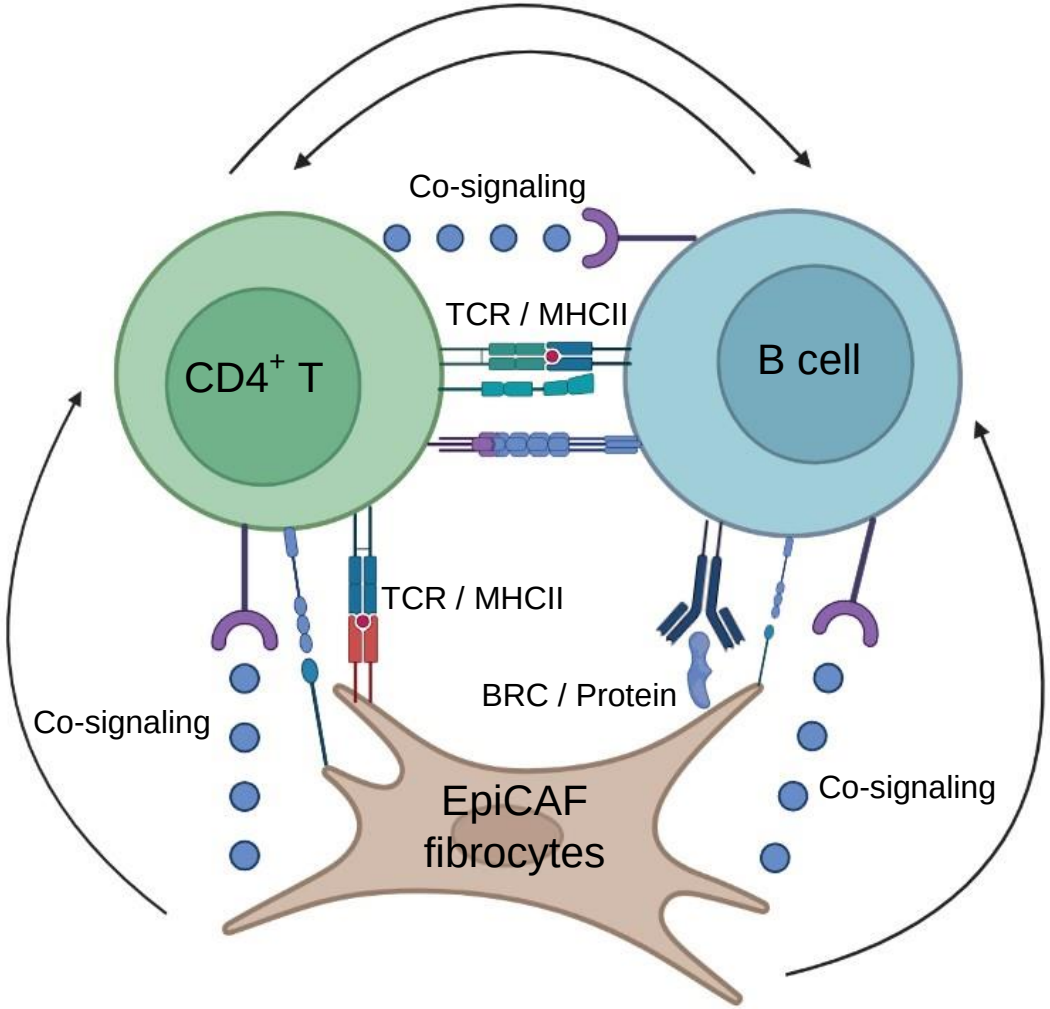
CCC Sender cells: epiCAFs, fibrocytes Receiver cells: CD4 T, CD8 T, B cells, plasma cells





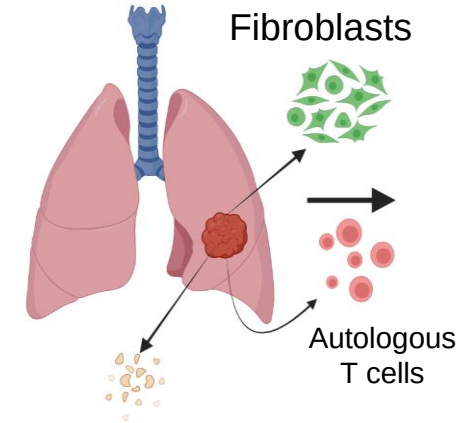


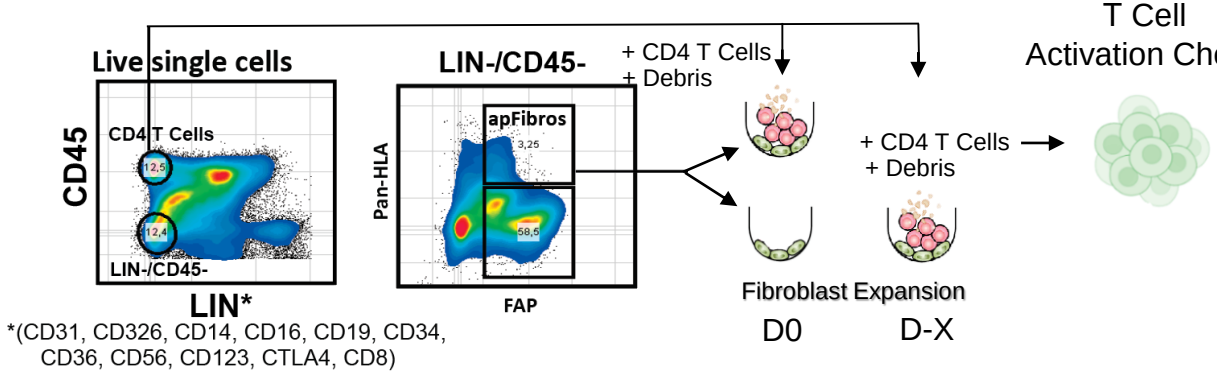


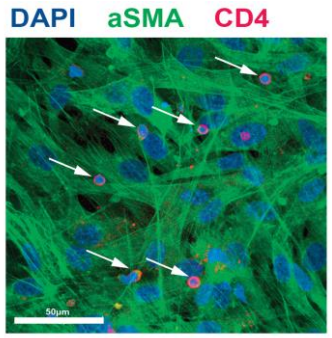


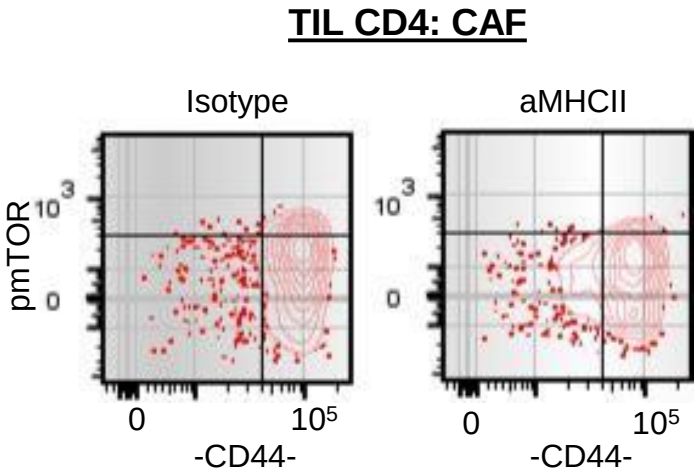
Unpublished data

Ex-vivo modelling of fibroblast-T cell interactions: Human lung fibroblasts present antigens and prime autologous tumor-infiltrating CD4 T cells.









Unpublished Data

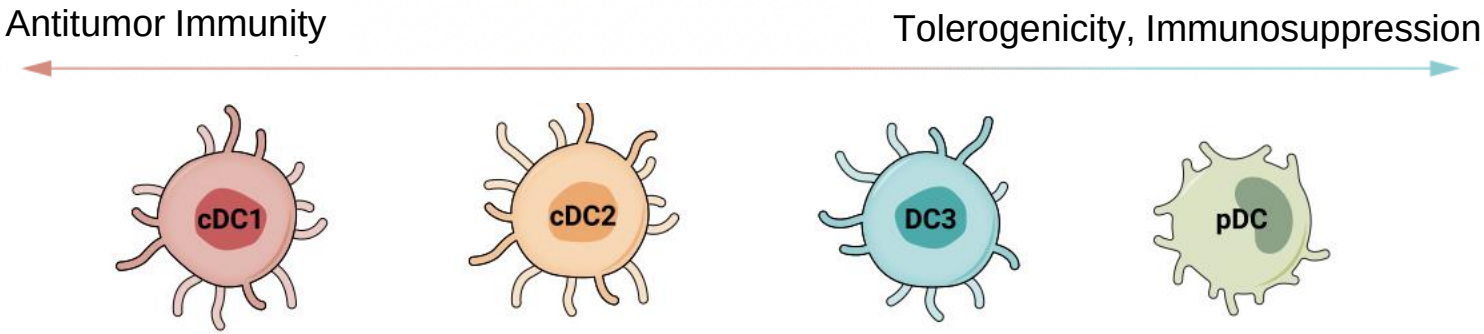
Topics to be discussed

Cancer antigen presentation by stromal cells in tumors.

Dendritic cell responses in tumor microenvironments.

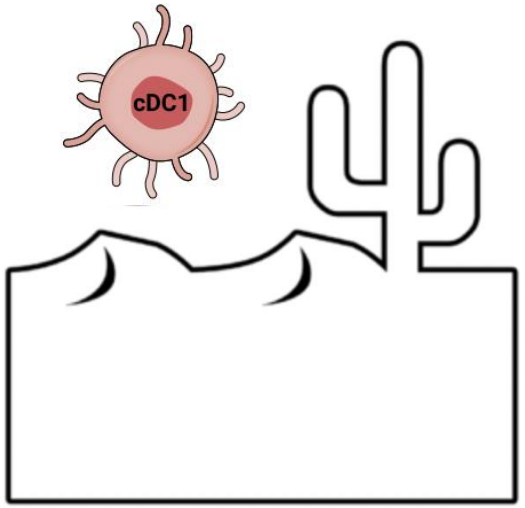
DC1 excel at cross-priming antitumor T cytotoxic cells in lymph nodes.

The abundance of intratumor DC1 correlates with survival prognosis and response to immunotherapy.

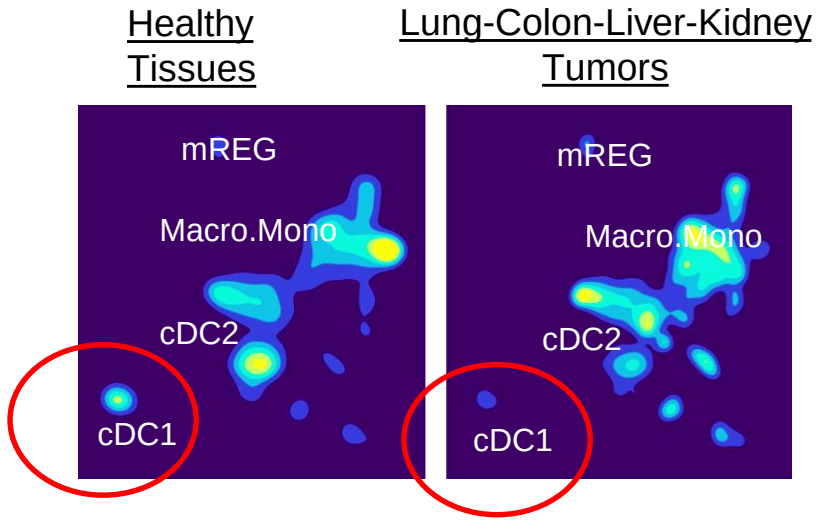


S. Ferris, et al. Nature 2020
B. Maier, et al. Nature 2020
J. Canton, et al. Nature Immunology 2021

DC1 become extinct from solid tumors: DC1 deserts.



- 39 paired human samples
- 178.651 human mononuclear phagocytes

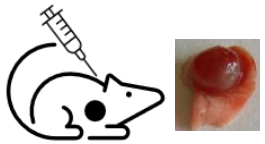


E. Aerakis

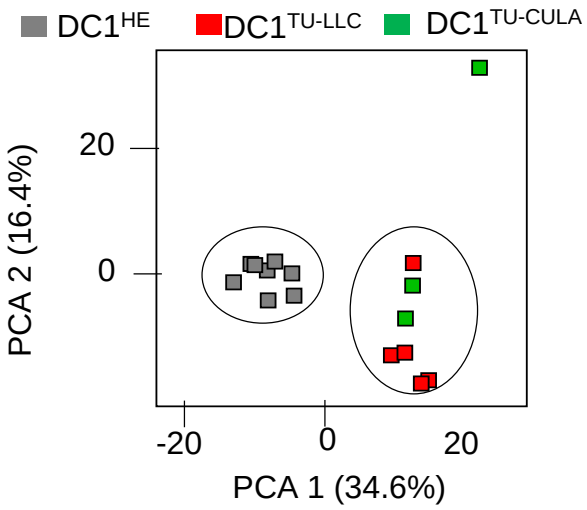
In revision.
bioRxiv doi.org/10.1101/2022.03.14.484263

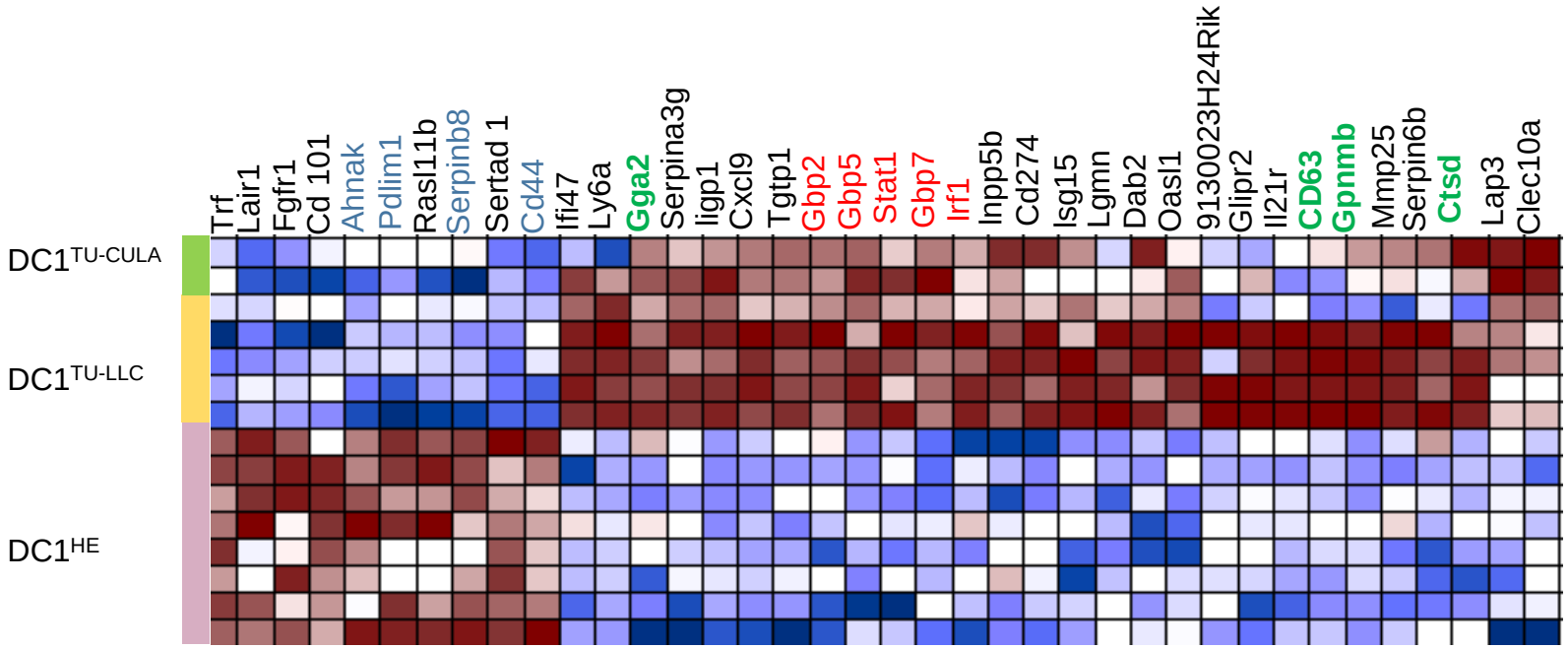
Up-regulated interferon-stimulated and lysosome-related genes in tumor DC1.

Cancer Cells Lung Injection



Tumor Digestion
FACs Sort
Bulk Seq





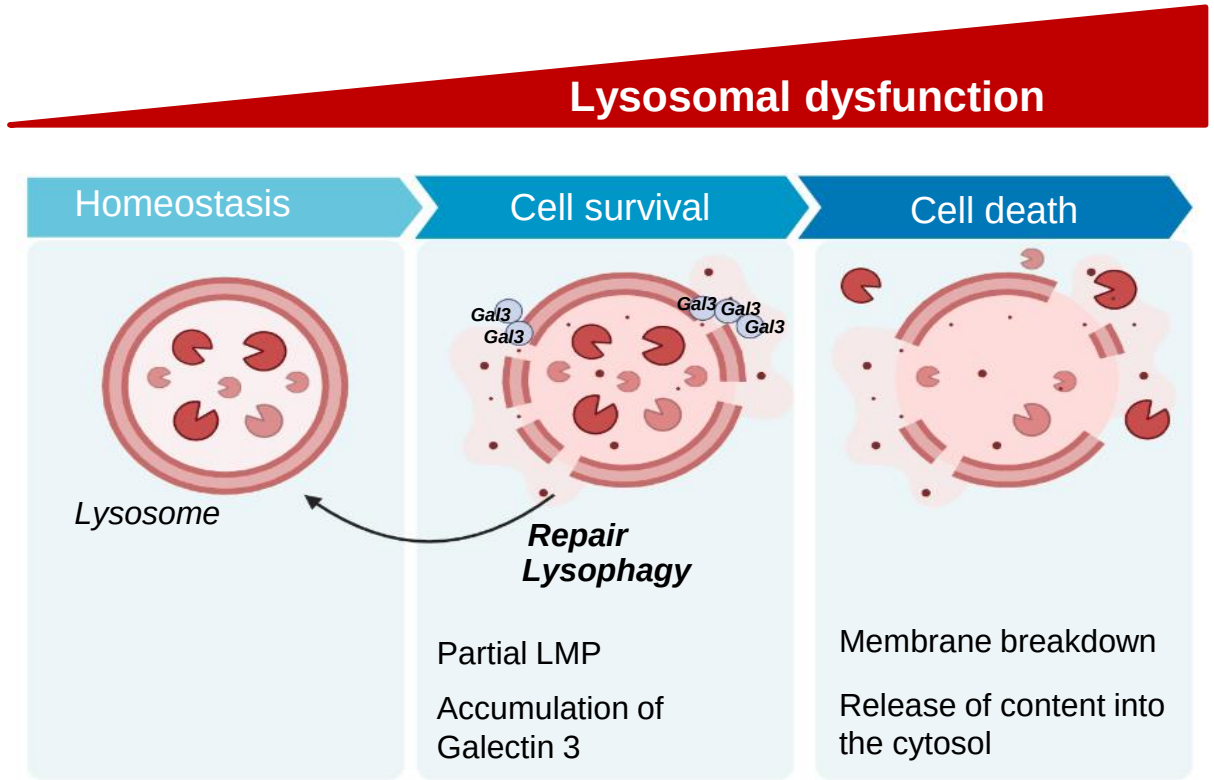
ISGs: Interferon Stimulated Genes

LRGs: Lysosome- Related Genes

Cytoskeleton and Adhesion Genes

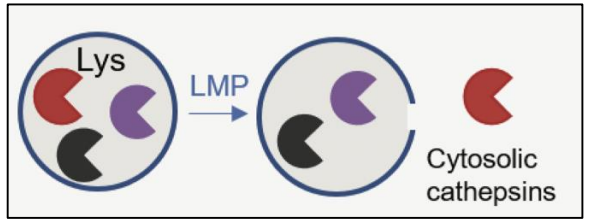
E. Aerakis, et al. In revision.
bioRxiv doi.org/10.1101/2022.03.14.484263

Lysosomal stress : from dysfunction to death.

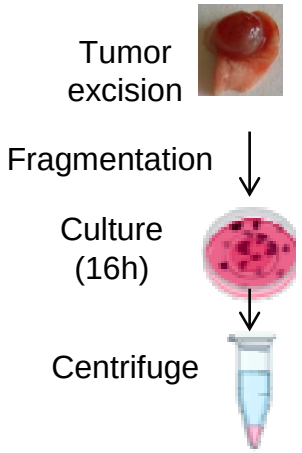


The tumor microenvironment induces lysosomal membrane permeabilization in DC1.

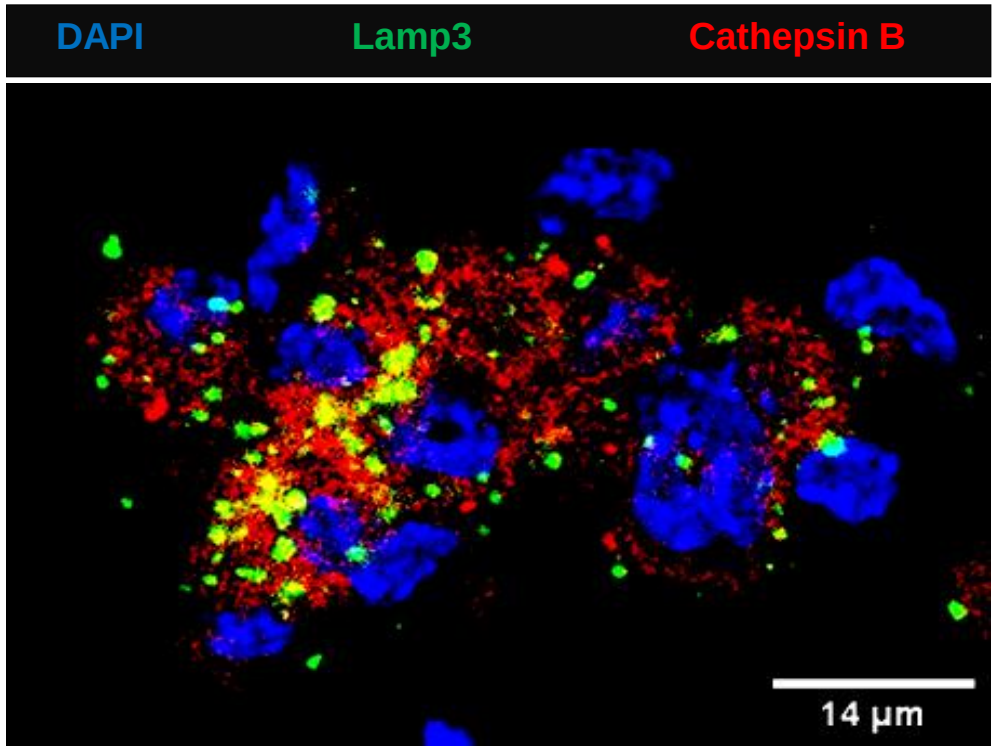
Cathepsin release due to LMP



Tumor Culture Medium (TCM)



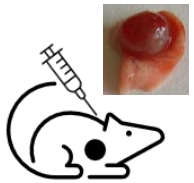
TCM-exposed MutuDC1



E. Aerakis, et al. In revision.
bioRxiv doi.org/10.1101/2022.03.14.484263

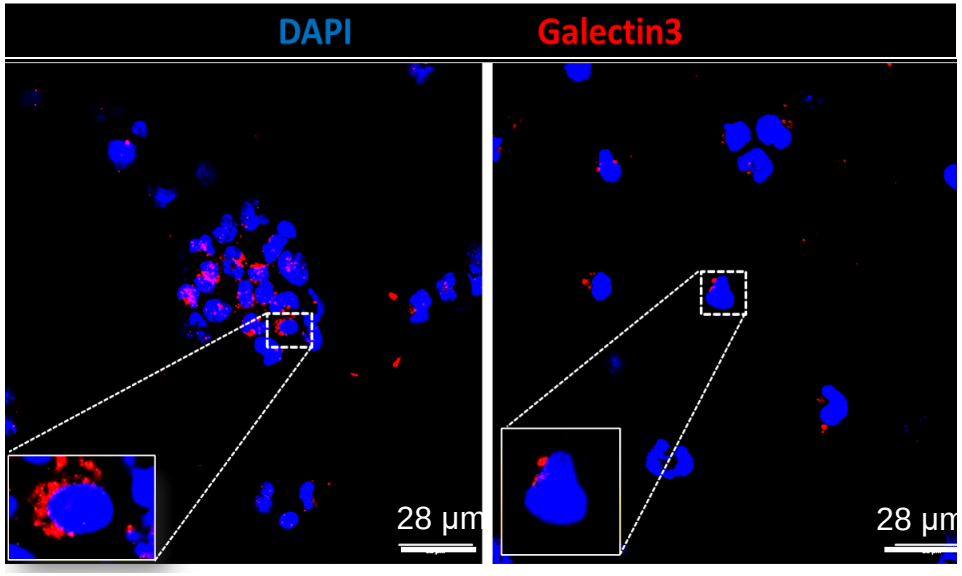
Knocking out IFNAR1 protects DC1 from lysosomal membrane permeabilization.

BM Chimera:IFNAR1^{KO} / WT 1:1

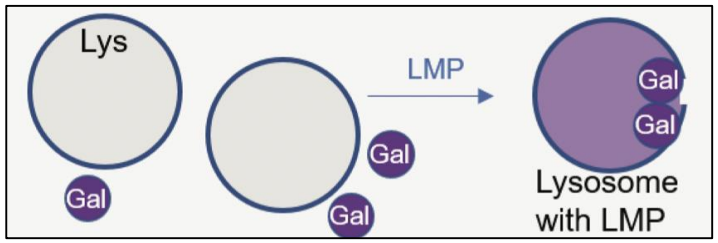


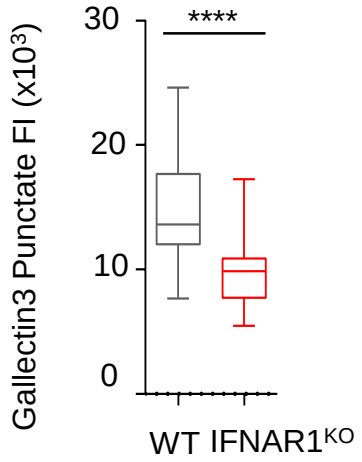
FACS-sorted intratumoral DC1

WT IFNAR1^{KO}



Galectin 3 translocation due to LMP

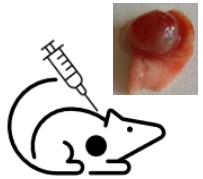


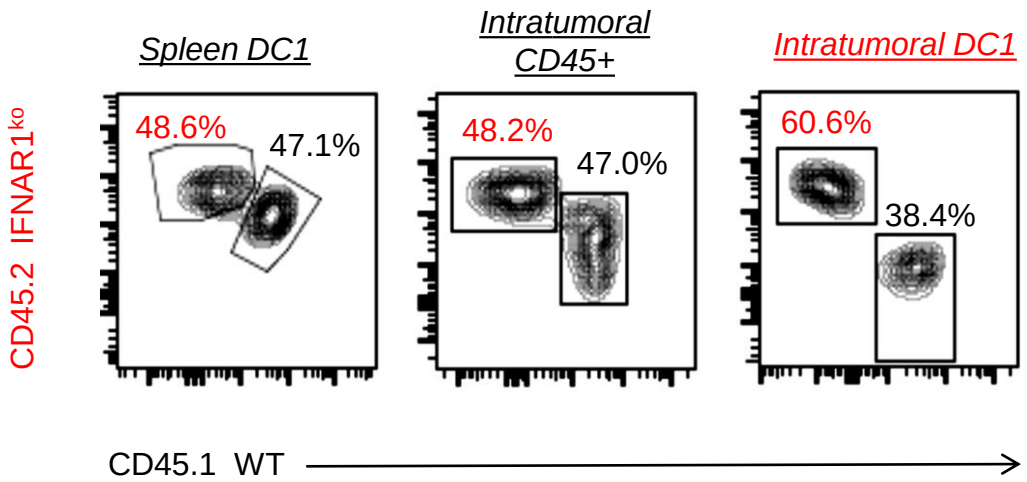


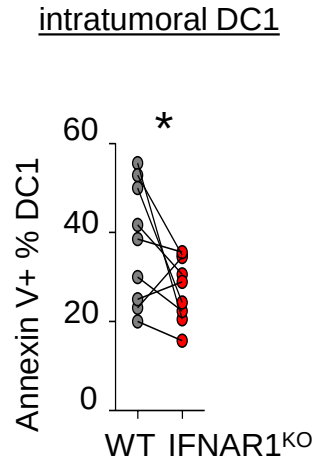
E. Aerakis, et al. In revision.
bioRxiv doi.org/10.1101/2022.03.14.484263

Knocking out IFNAR1 protects DC1 from intratumoral death.

BM Chimera:IFNAR1^{KO} / WT 1:1







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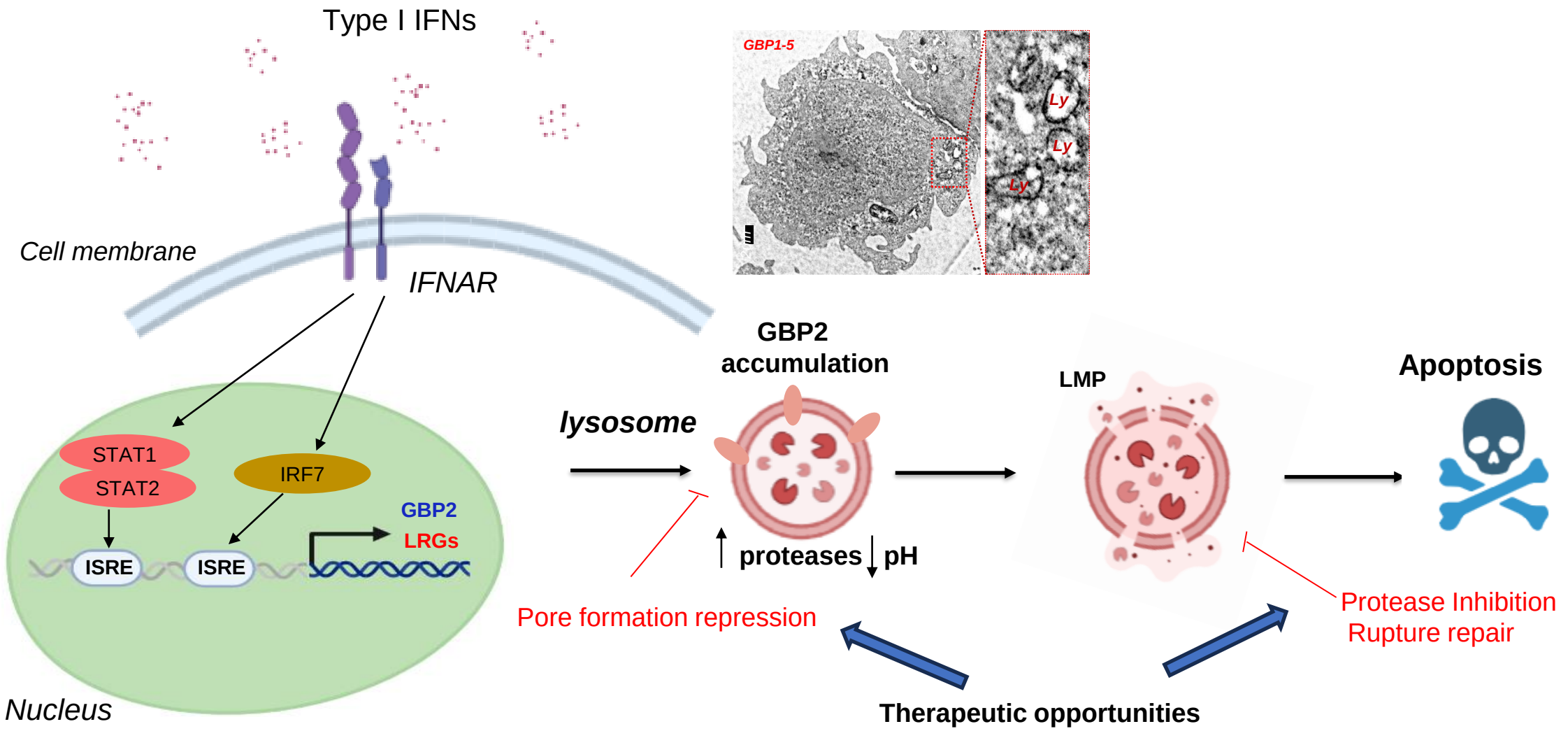
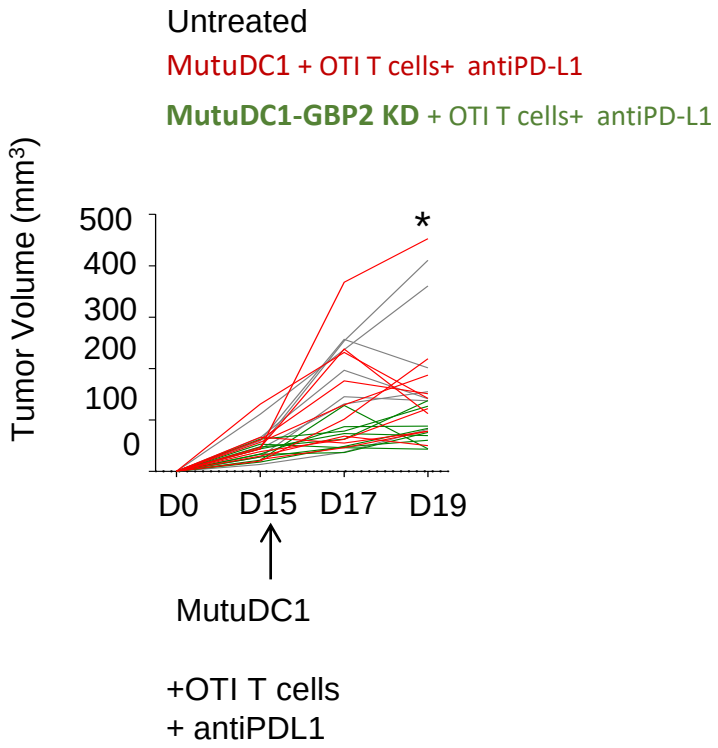
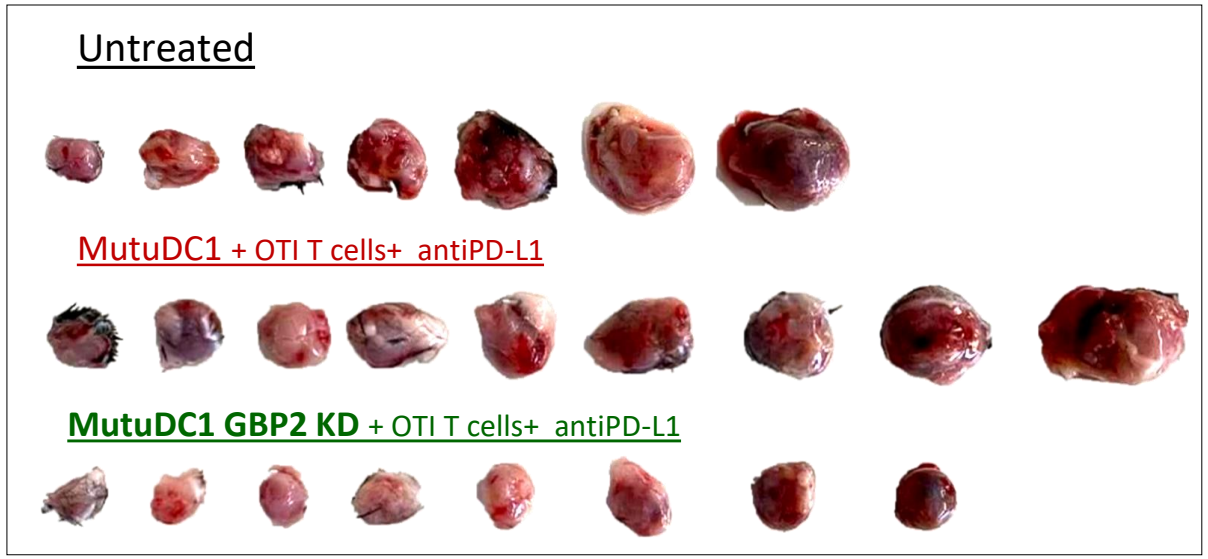
Type I interferons trigger a lysosomal death pathway that eliminates DC1 cells in solid tumors.



Repression of pore-forming GBP-2 increases the efficacy of DC1 immunotherapy.





Aerakis, E., et al. In revision.
bioRxiv doi.org/10.1101/2022.03.14.484263

Summary of Topics Discussed

Cancer antigen presentation by stromal cells in tumors.

- Fibroblasts present cancer antigens within lung tumors to CD4 T effector cells.
- Anti-tumor CD4 T cell immunity depends on de novo peripheral antigen presentation (The second touch hypothesis).
- There are two subsets of antigen presenting lung fibroblasts: an epithelial cell-like and fibrocytes.
- Numerous paracrine interactions between fibroblasts CD4 T and B cells in an intratumoral functional triad.

Dendritic cell responses in tumor microenvironments.

- Dendritic cells type 1 (DC1) are the most potent cross-presenting antigen-presenting cells.
- Type I interferons induce lysosomal stress in DC1 within tumors.
- Interferon-induced GBP2 forms pores and permeabilizes the membrane of stressed DC1 lysosomes.
- Release of proteolytic enzymes to the cytosol of DC1 induces DC1 death.

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We are looking for PhD students and postdocs!