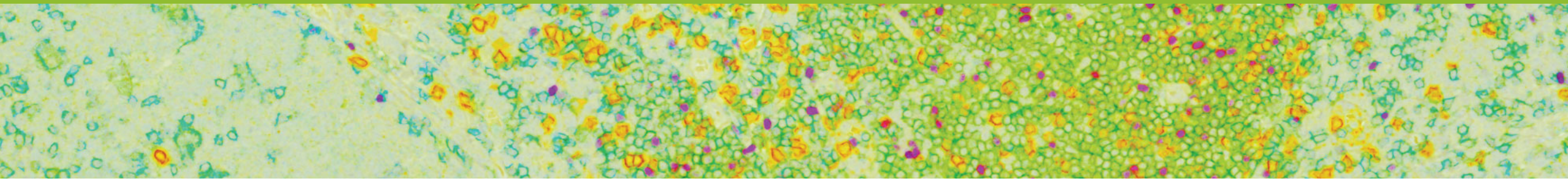


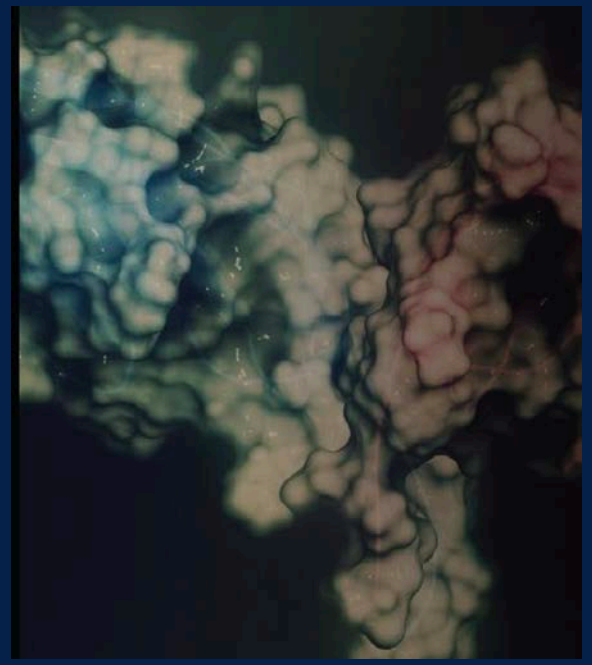
Understanding and Treating Cancer and Other Diseases through the Immune System

IMMUNOX

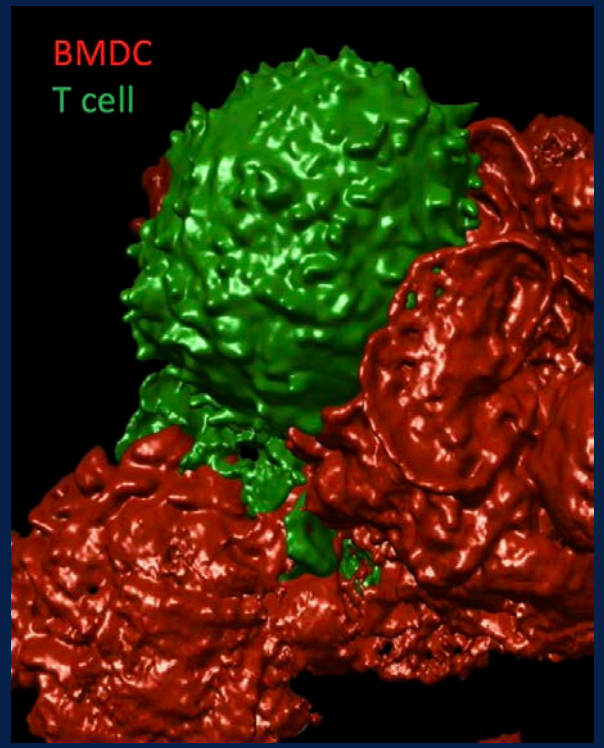
Matthew Krummel, PhD
Professor, Department of Pathology
Chair, ImmunoX

UCSF

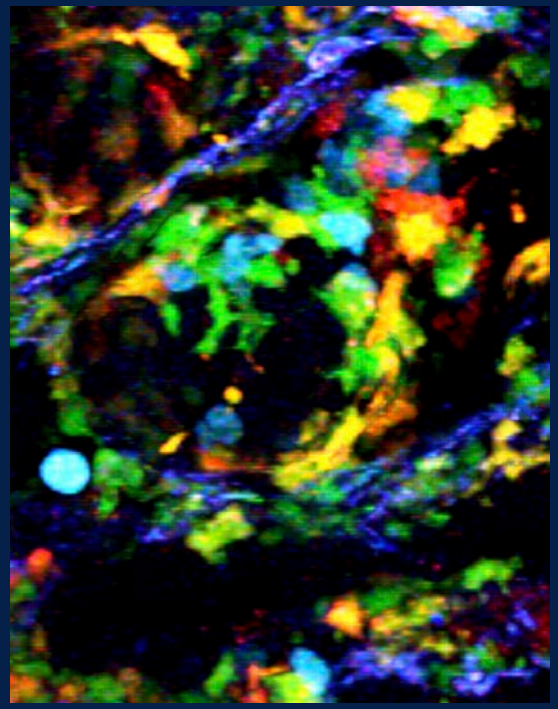
My Views of the Immune System.



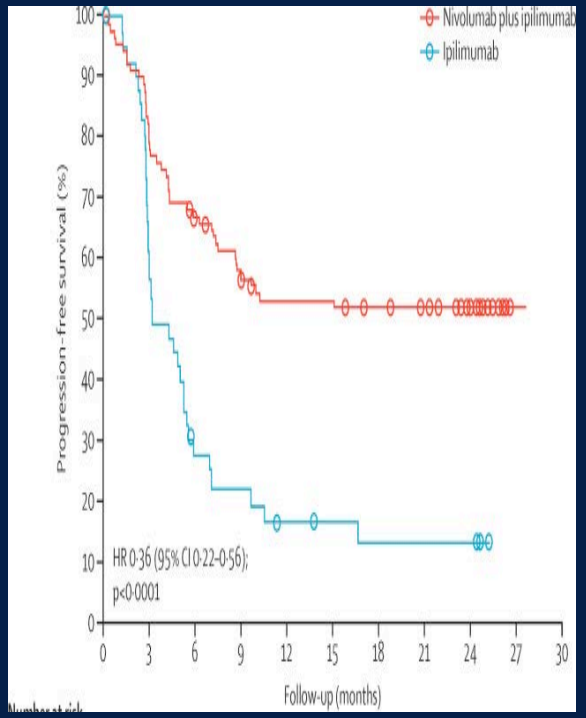
Molecular



Subcellular



Multicellular

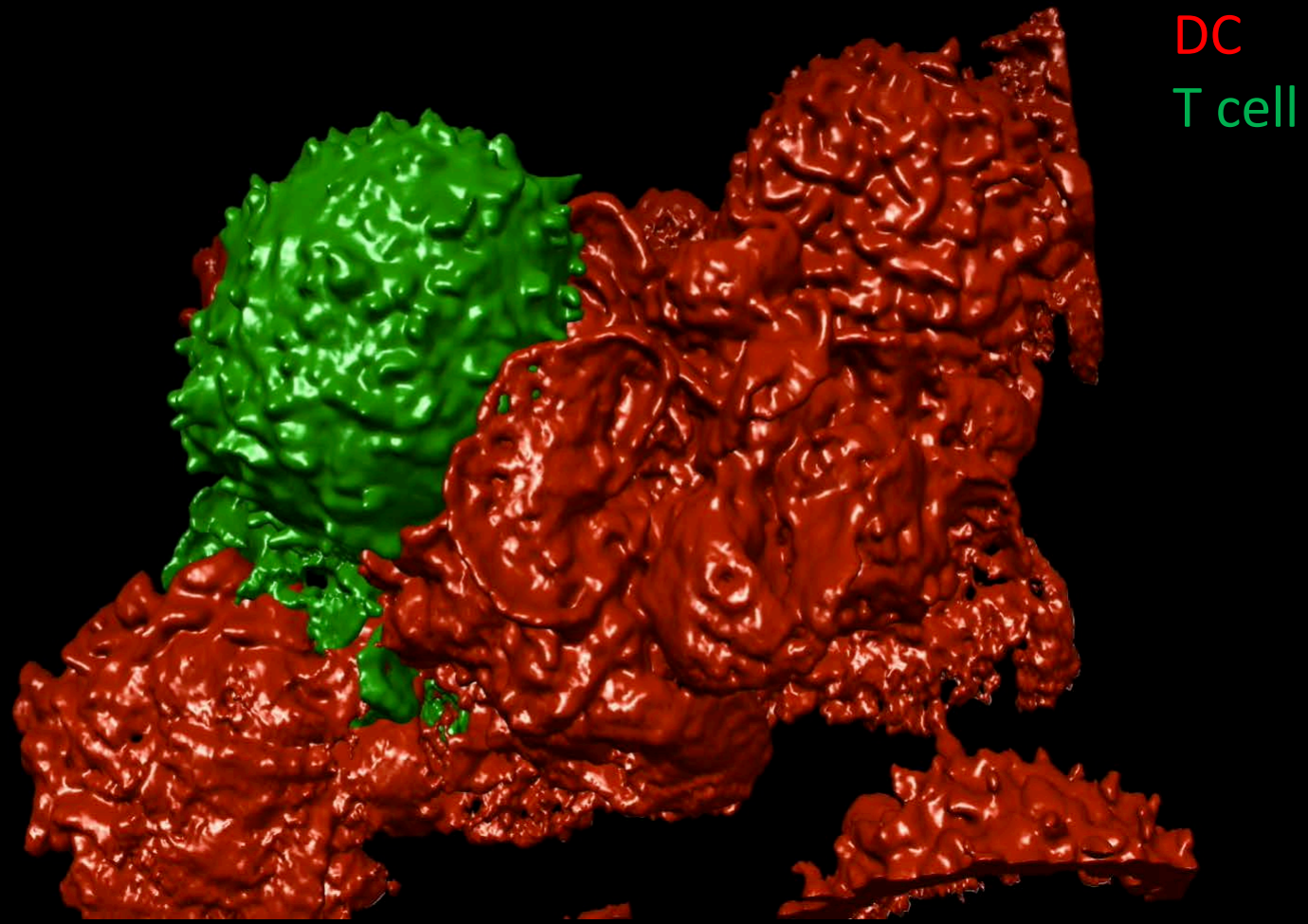


Clinical

BAKAR IMMUNO

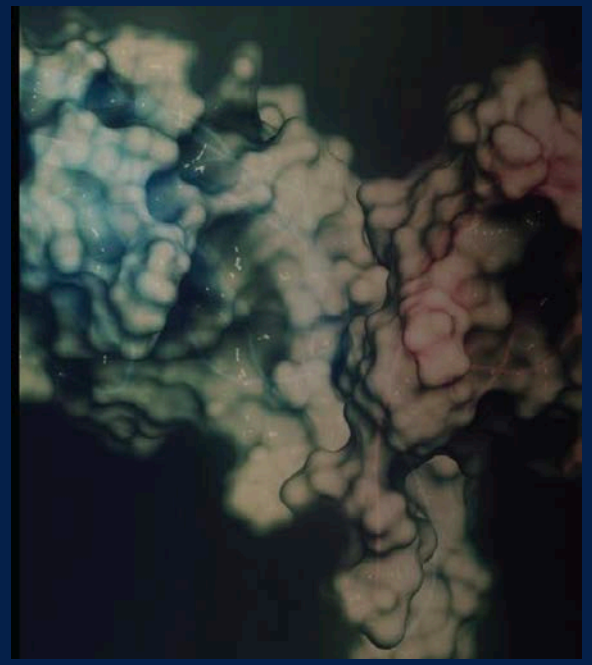
KRUMMELLab

T cell and APC interaction in 4 dimensions

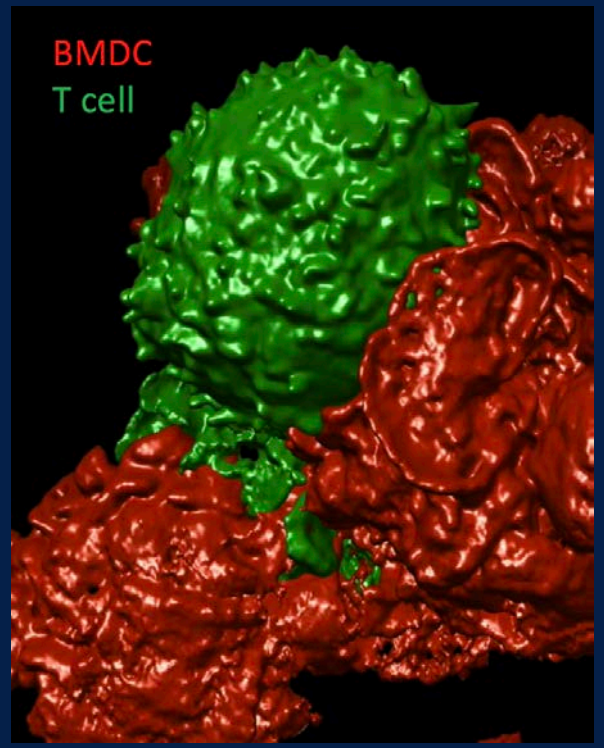


Cai et al. Unpublished

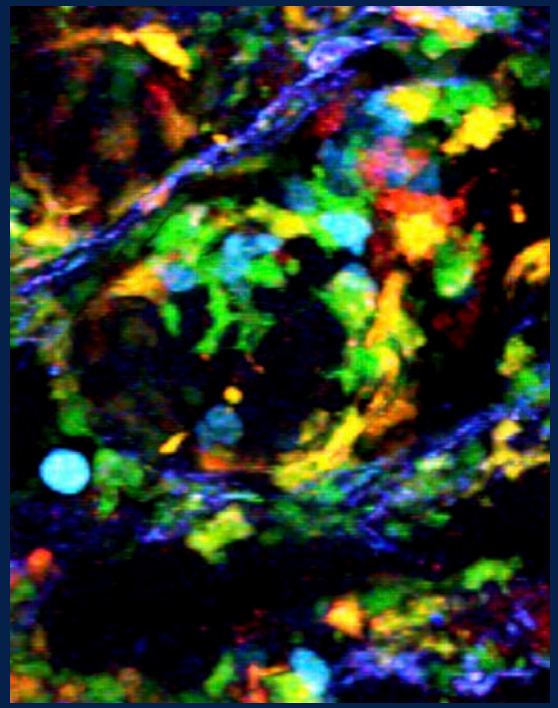
My Views of the Immune System



Molecular



Subcellular



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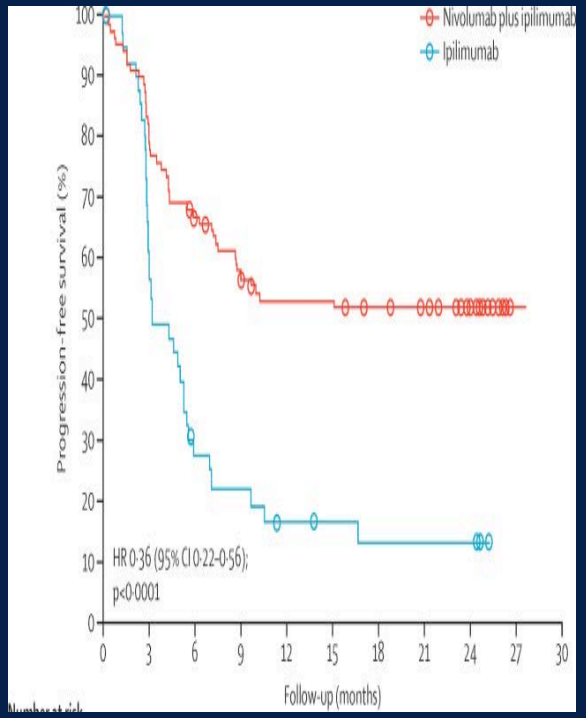

Clinical

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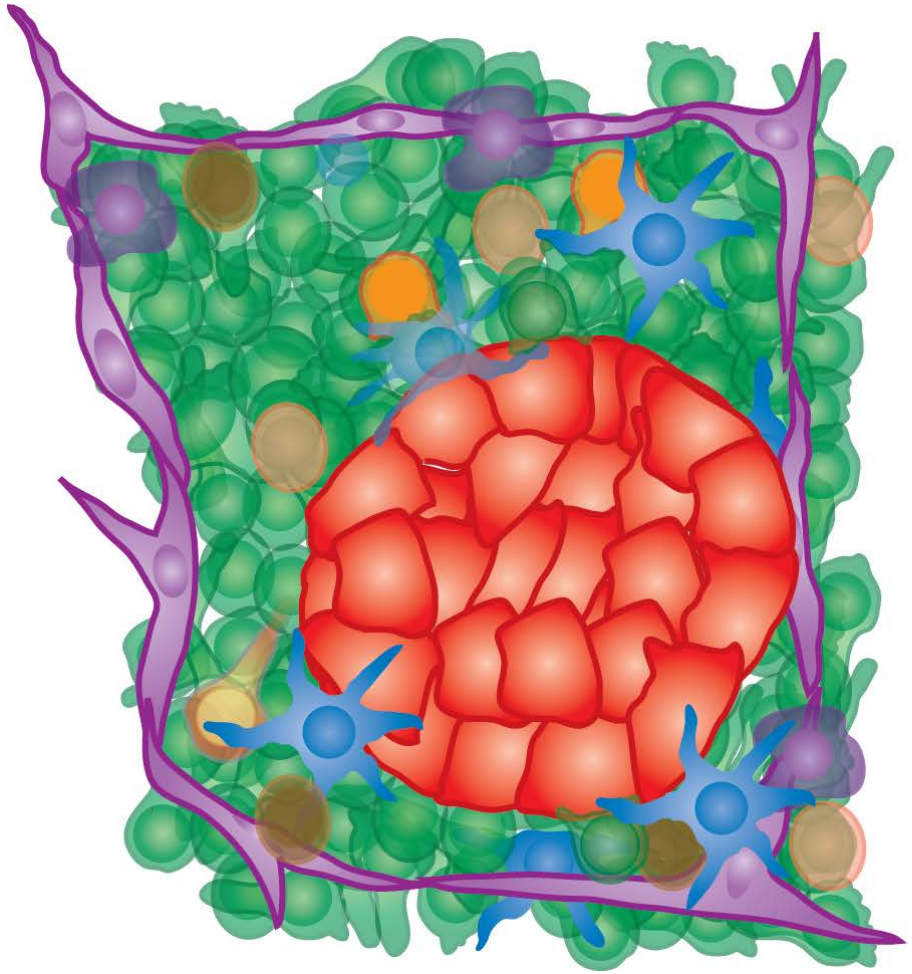
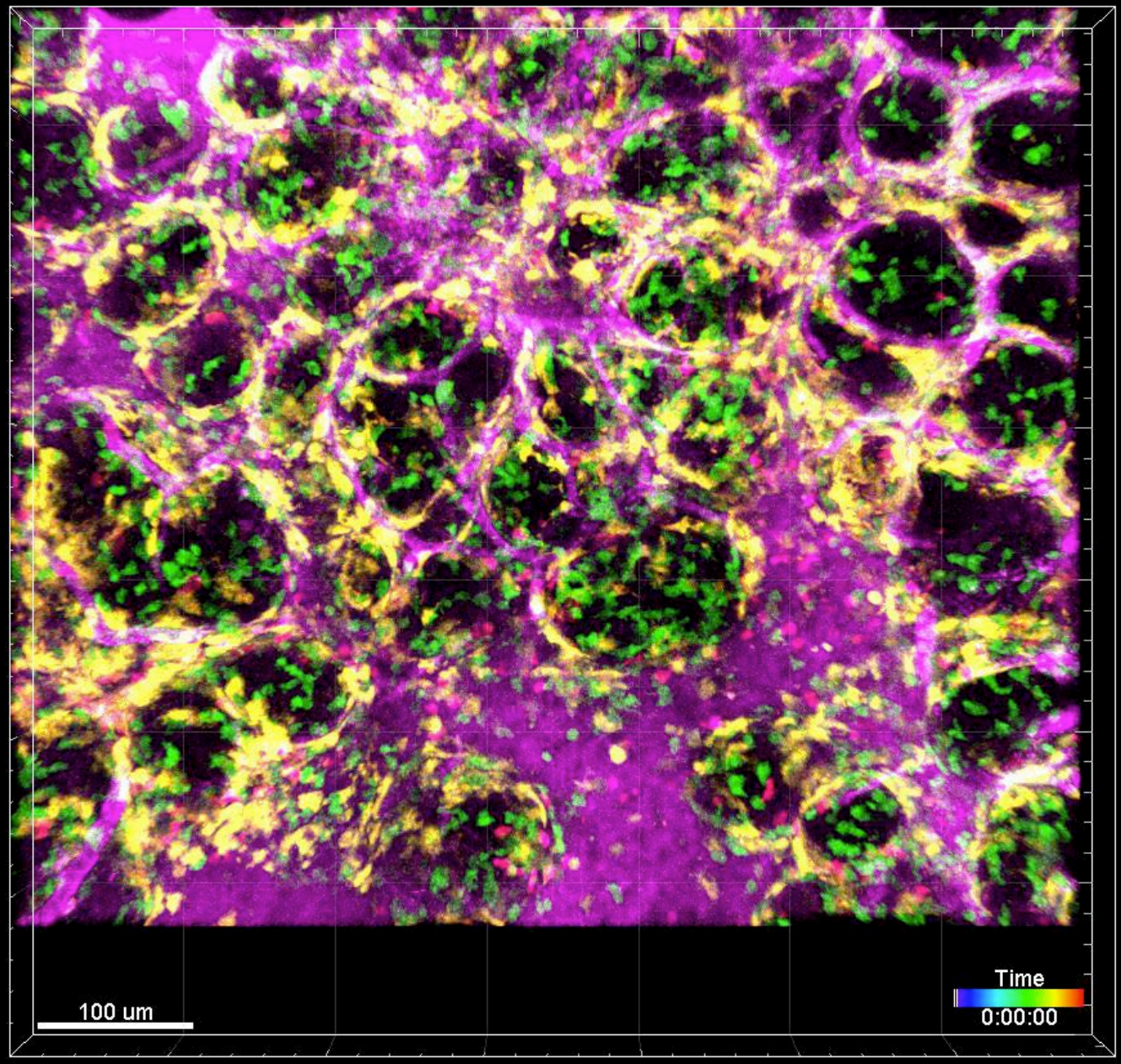
Interactive Immune Systems are at the Center of Cancer (And Other Diseases)

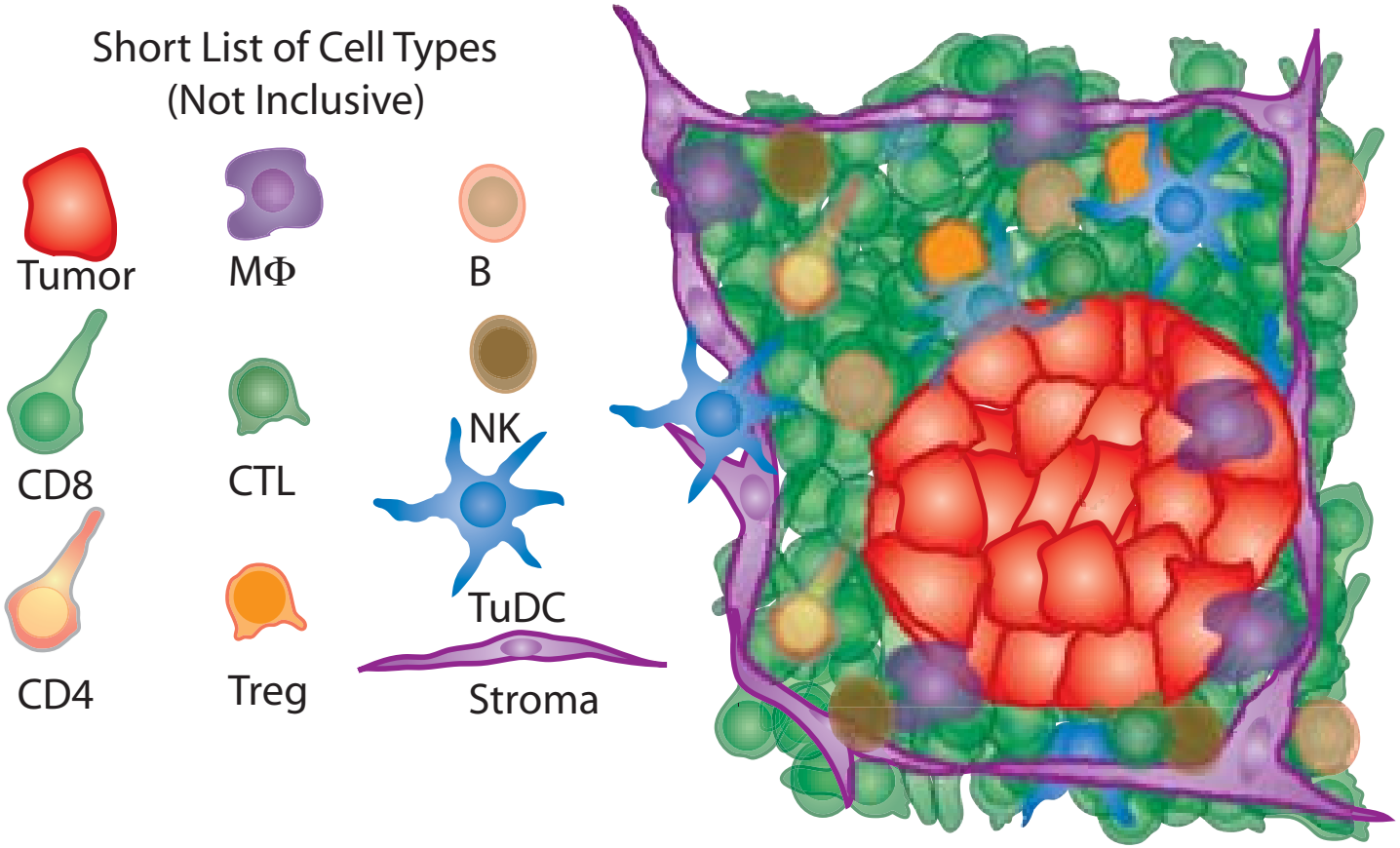


Immune Systems Within Actively Growing Tumors

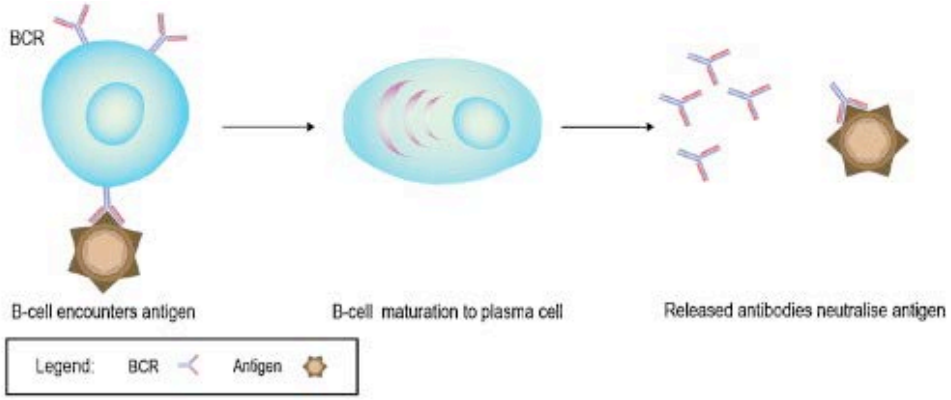


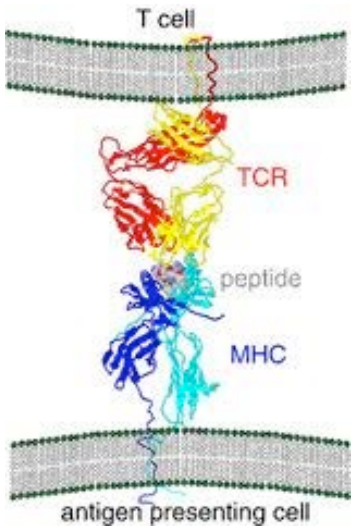
Can the Immune system regulate Cancer Progression?

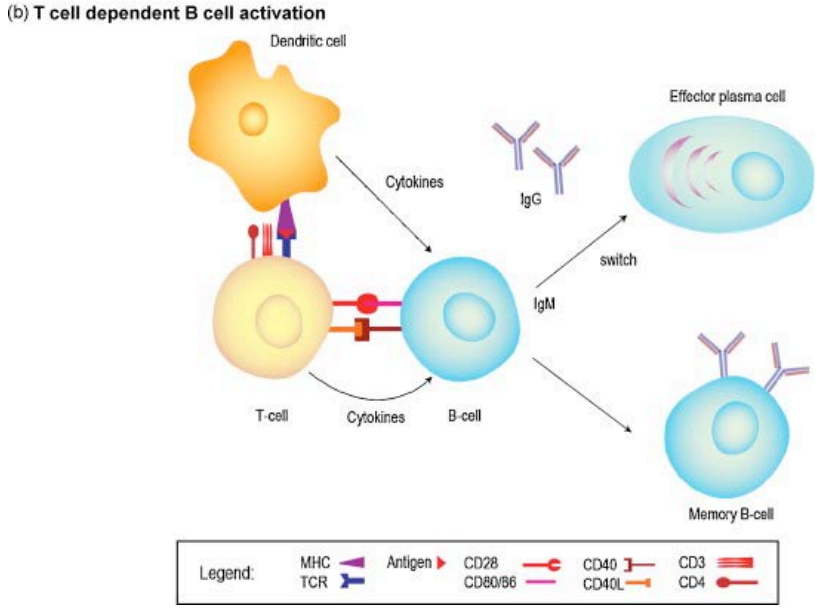
- A primer on adaptive and innate Immunity
- Cells of the Immune system in the context of the tumor microenvironment



A primer on adaptive Immunity: How do our bodies recognize non-self?

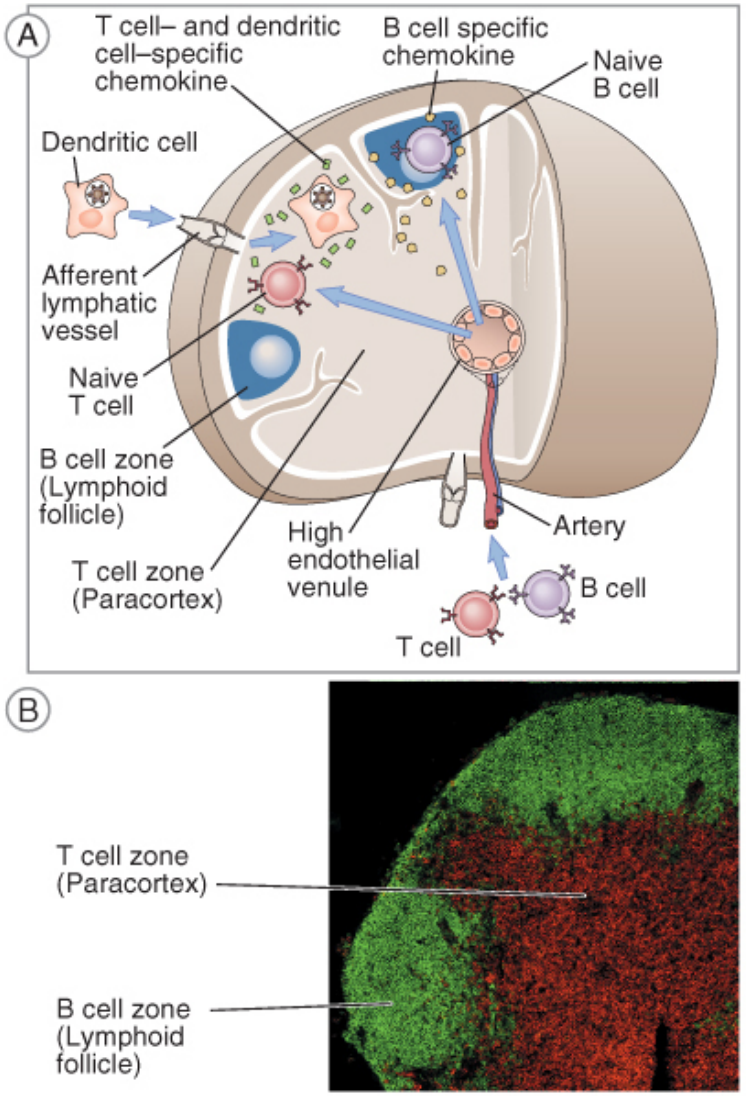




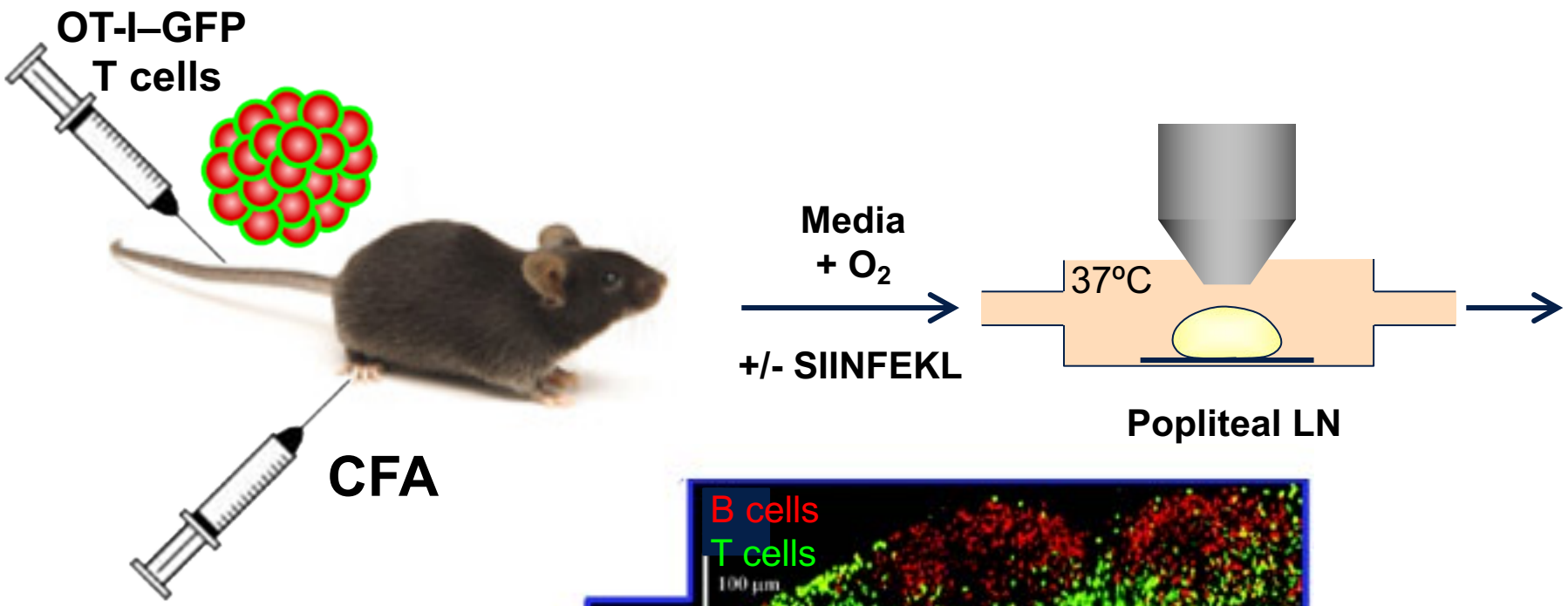


BCRs and TCRs are selected against self-reactivity

Organization of the Lymph Node

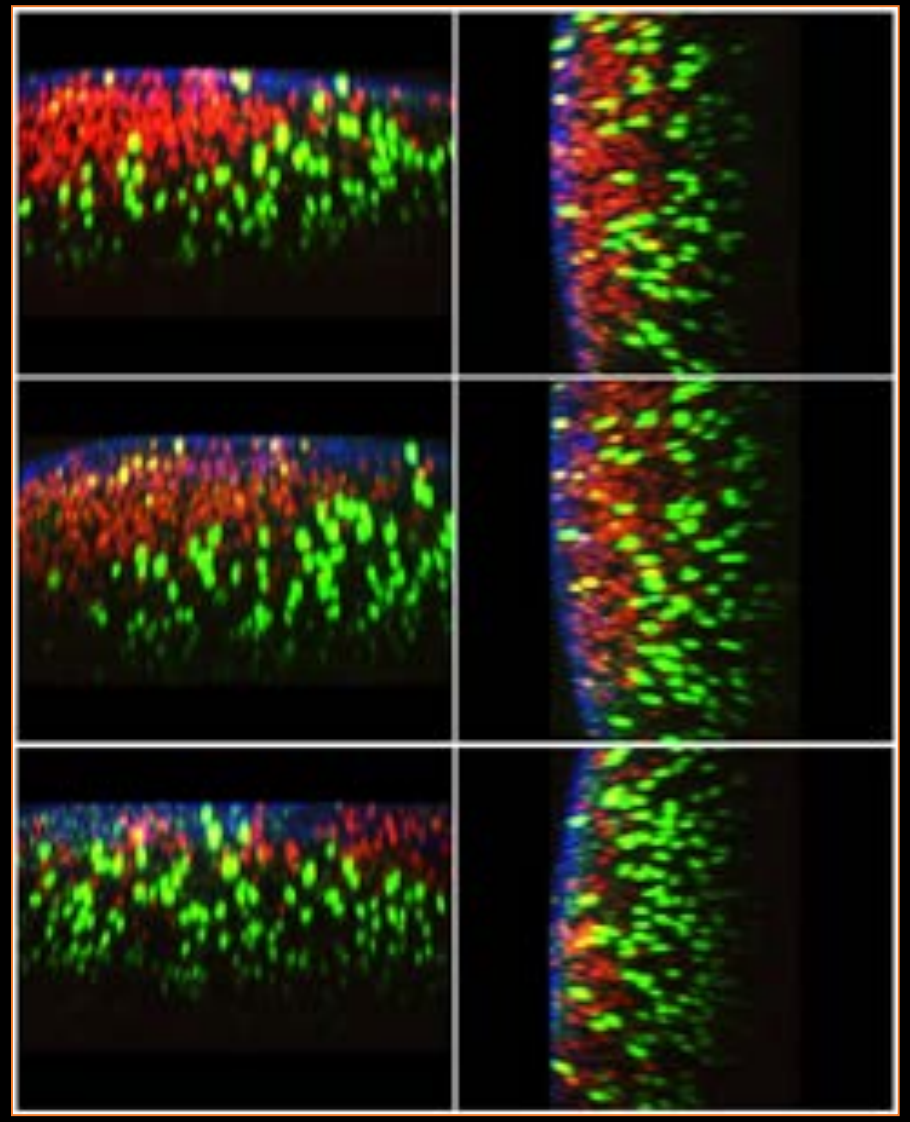


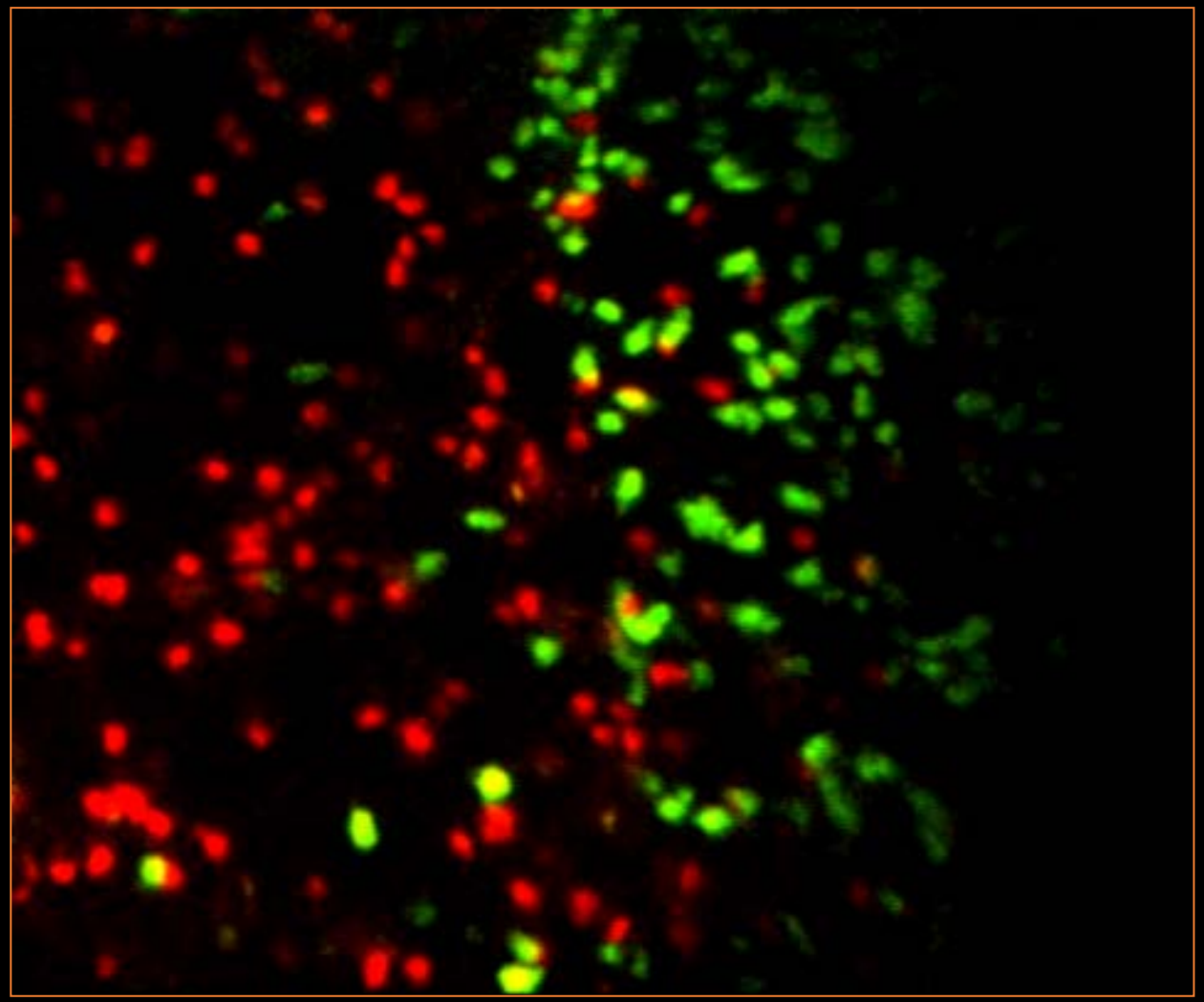
Experimental system for 2-photon imaging of OTI-GFP



Miller et al, Science, 2002.

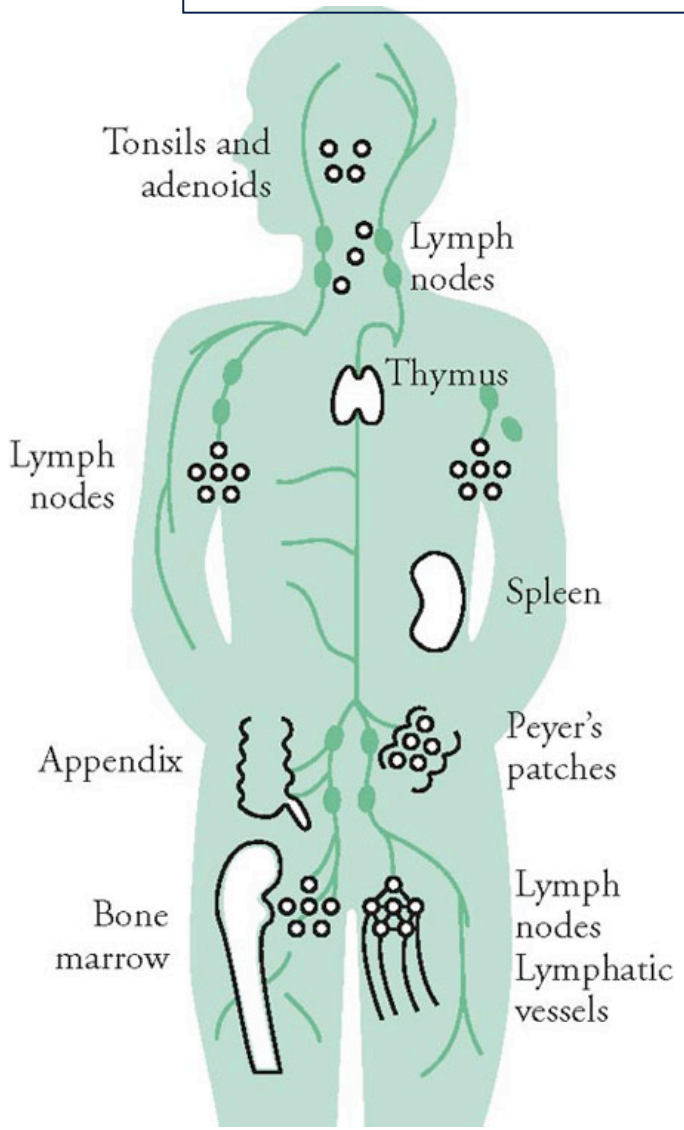
T cell and B cell Scanning in Lymph Nodes





B T

The Motile Nature of the Immune System



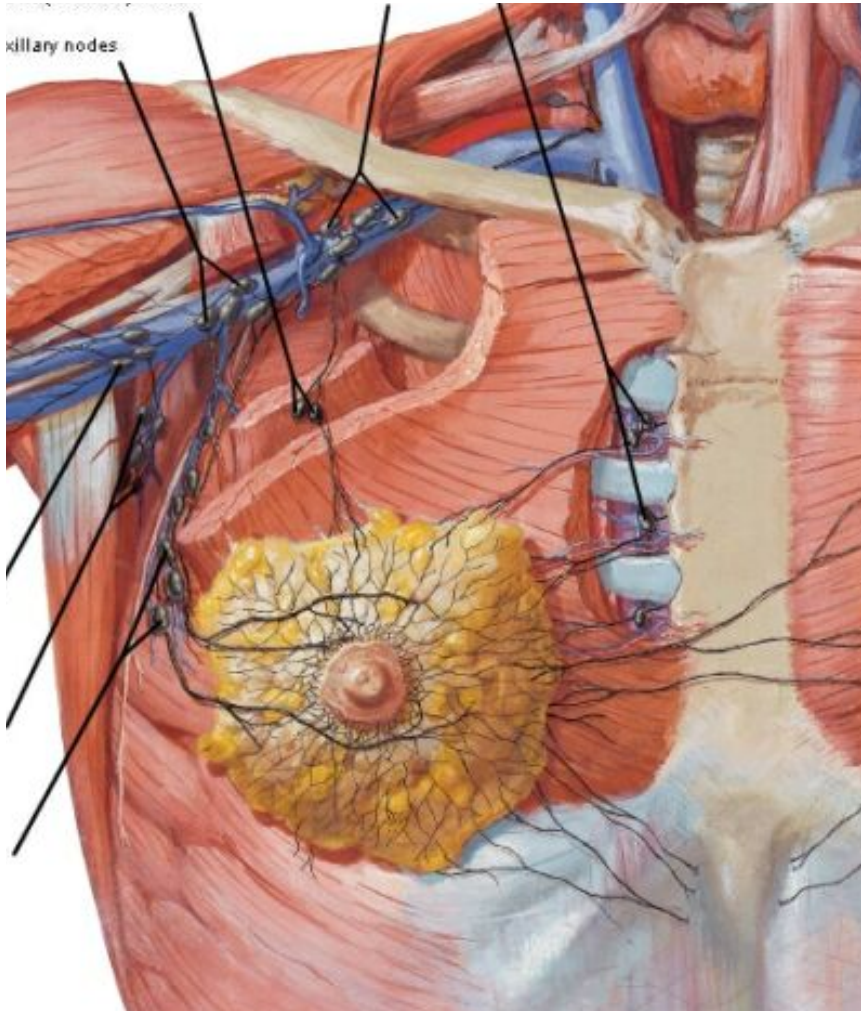
Estimates vary but suggest it takes a given lymphocyte 24 hours-1 week to survey all secondary lymphoid organs.

An insult to the host (e.g. infection) requires response ASAP.

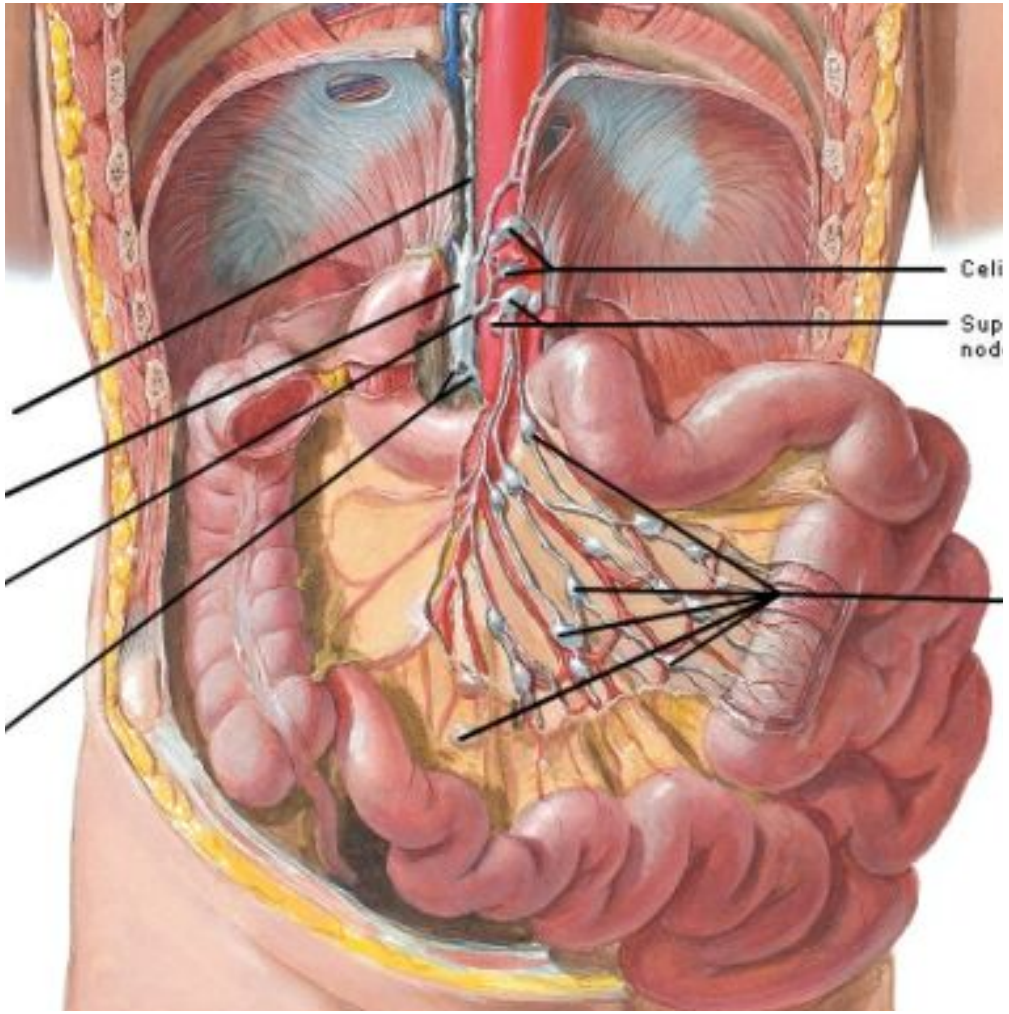
An insult does not necessarily occur within the secondary lymphoid organ but much of the action happens in secondary lymphoid organs (spleen, lymph nodes, peyers patches) as well as some specialized sites (such as in the gut).

Lymph Nodes

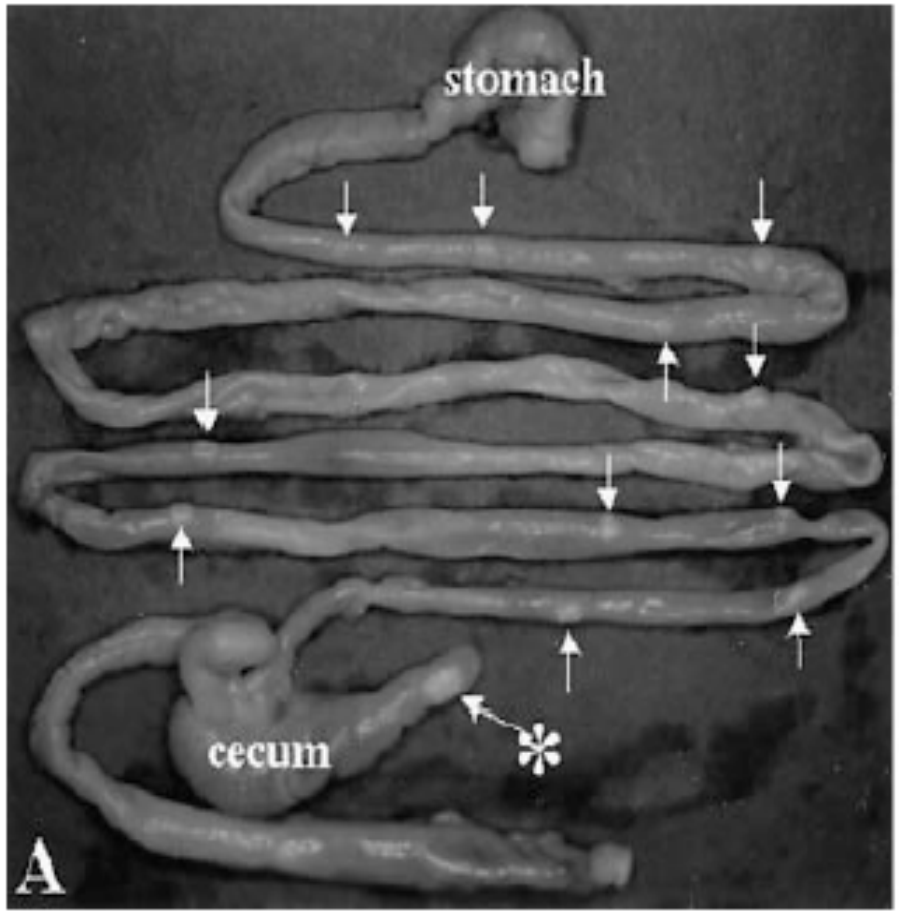
Axillary

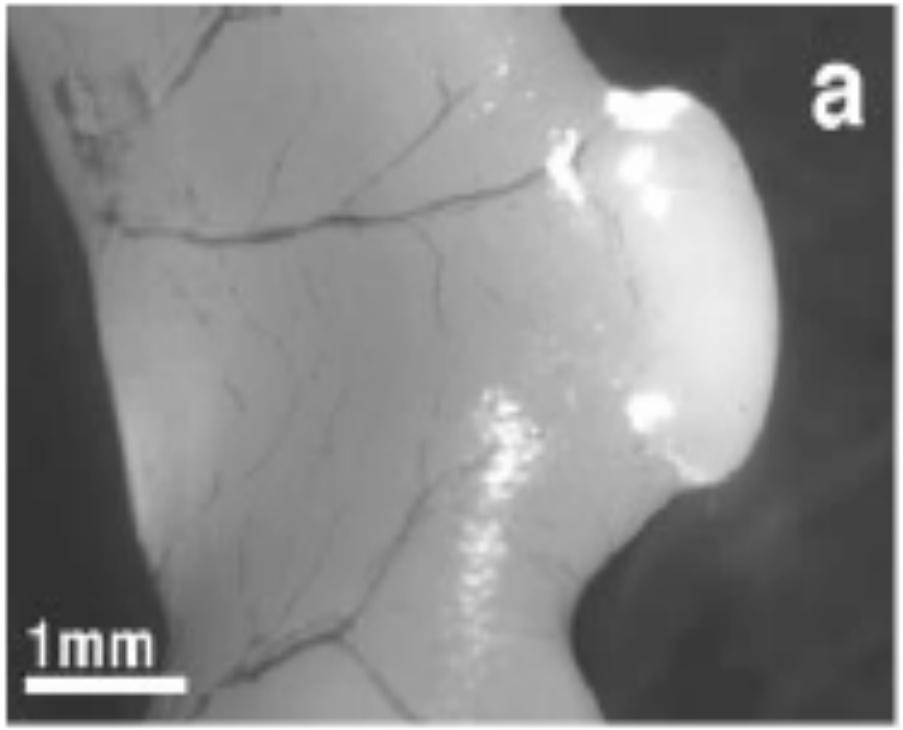


Mesenteric

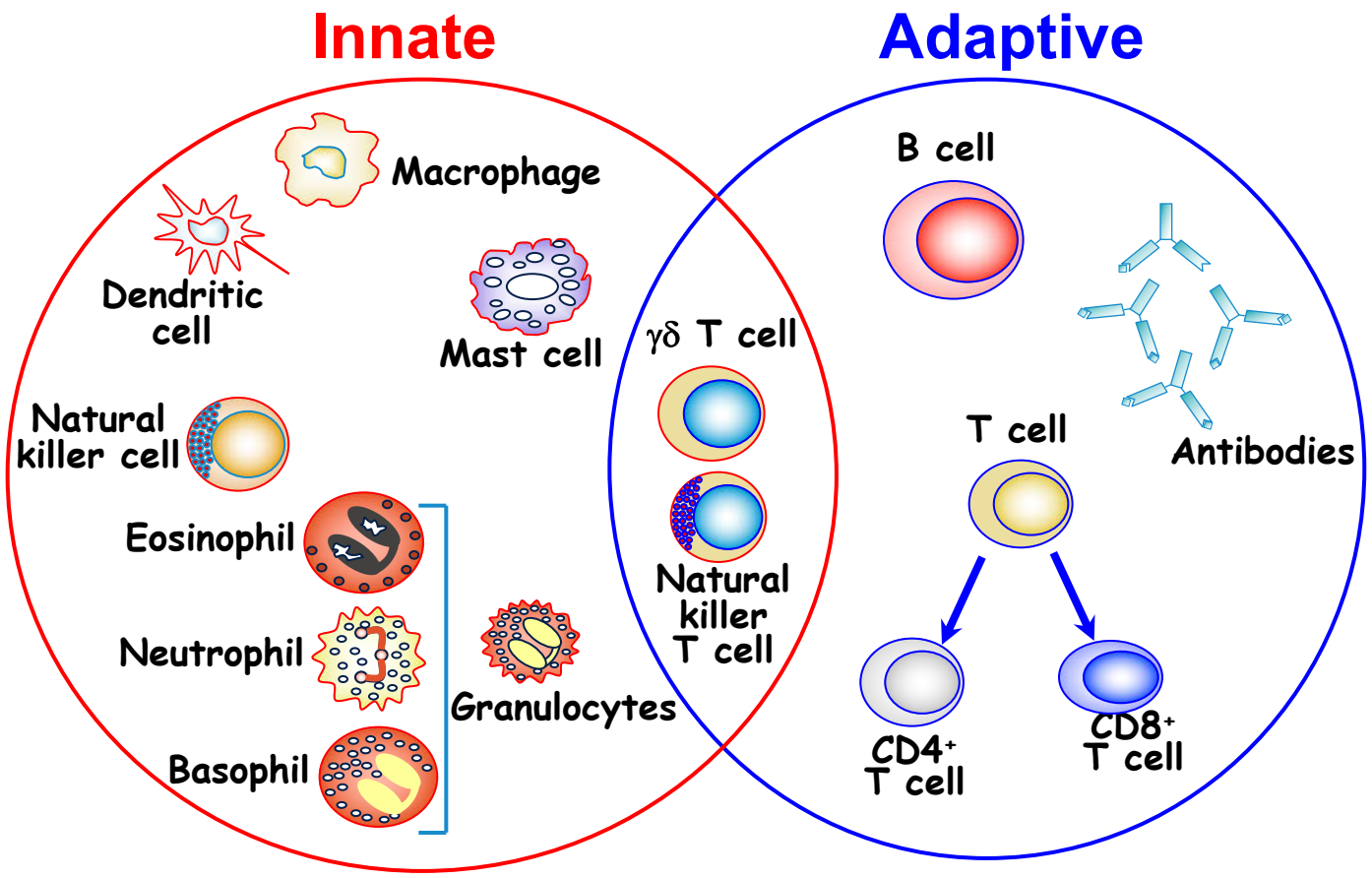


Peyers Patches





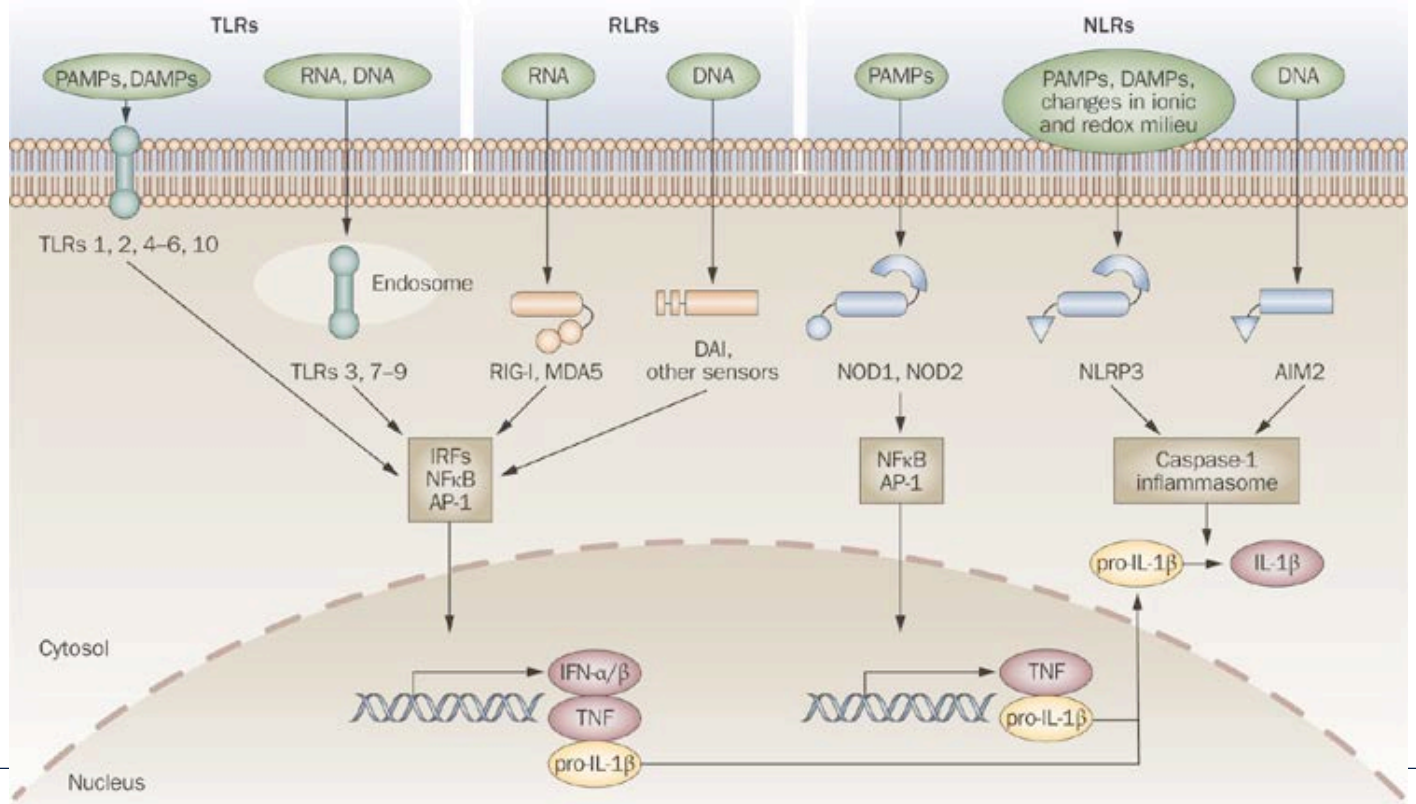
Immune Components of Host Response



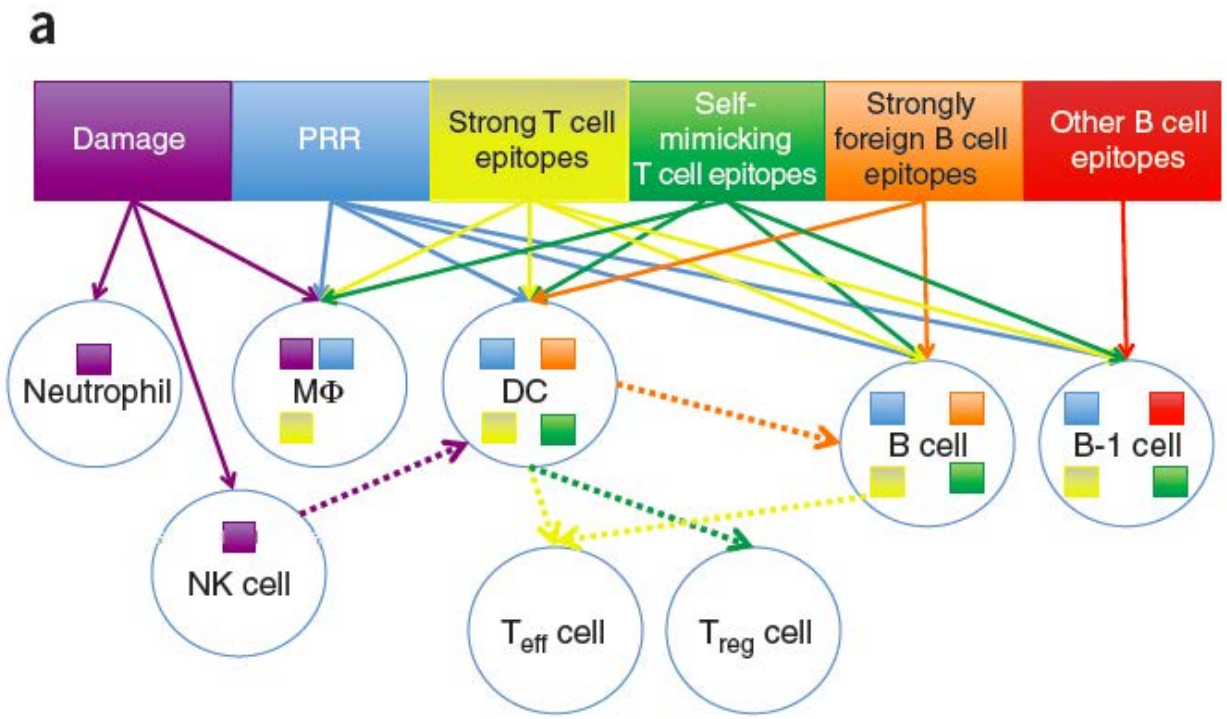
A primer on Innate Immunity

Blood Neutrophils + Myeloid Cells (Macrophages, Dendritic Cells) + Epithelium/Endothelium

Can all recognize patterns that initiate ‘innate’ programs within these cells.
PAMPs (Pathogen-Associated Molecular Pattern)

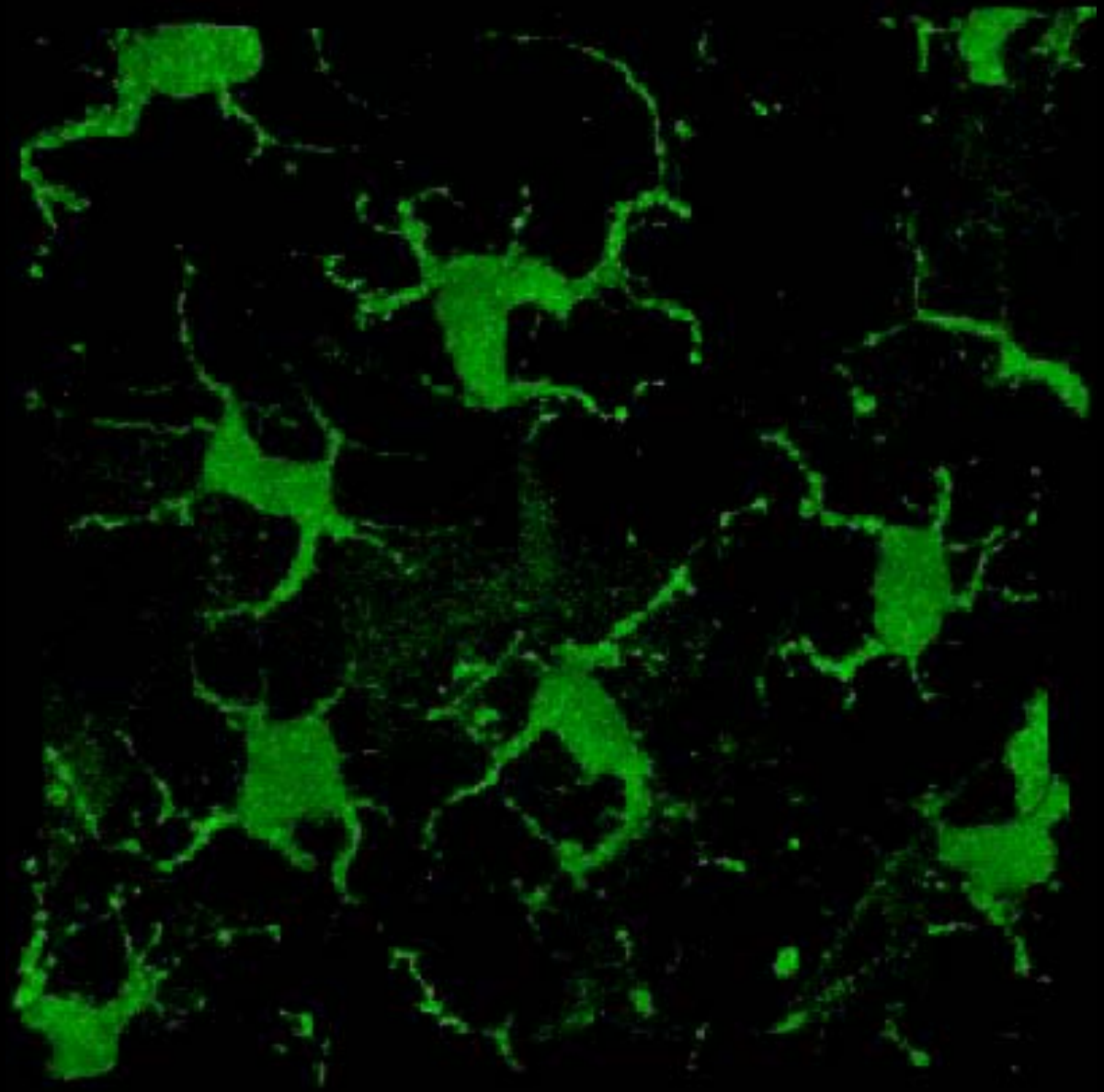


The Immune System as a Spatiotemporal Information System and a Spatial Coincidence Detector?



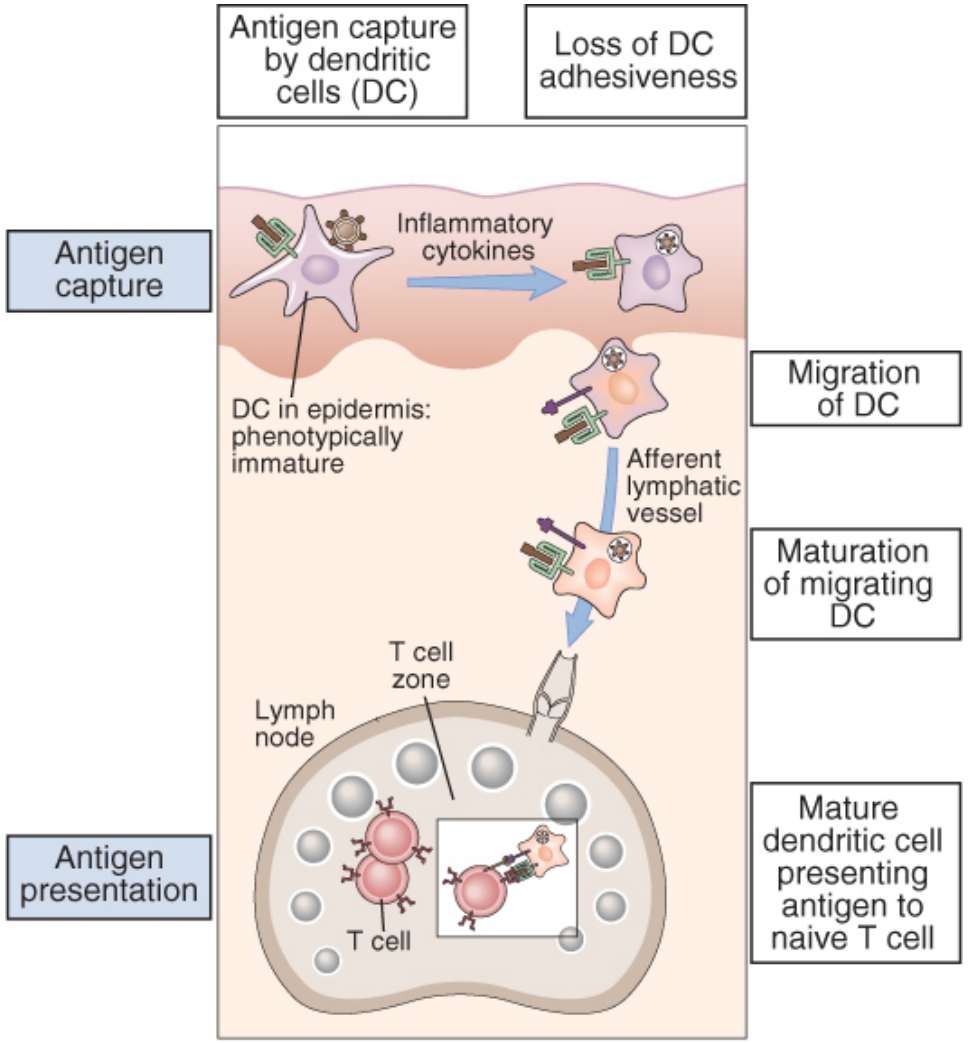
"The Insult"

Langerhan Cells Interspersed in the skin (Langerin-GFP). Sentinels

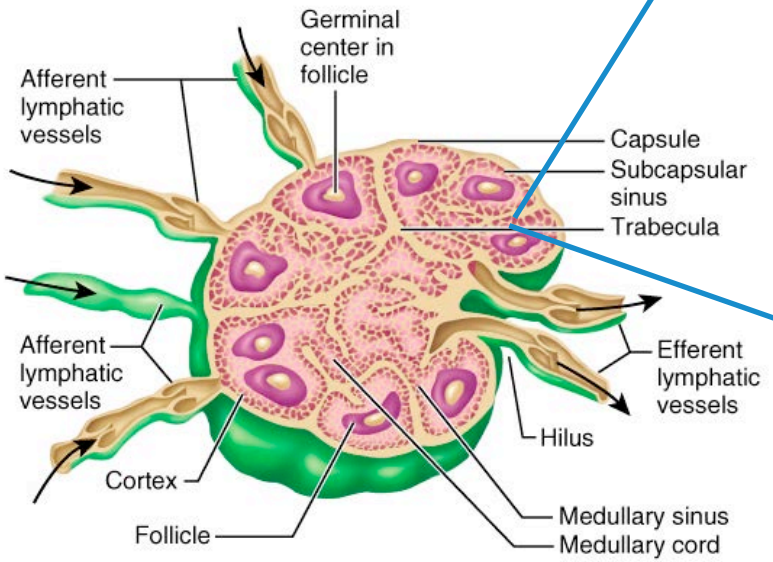


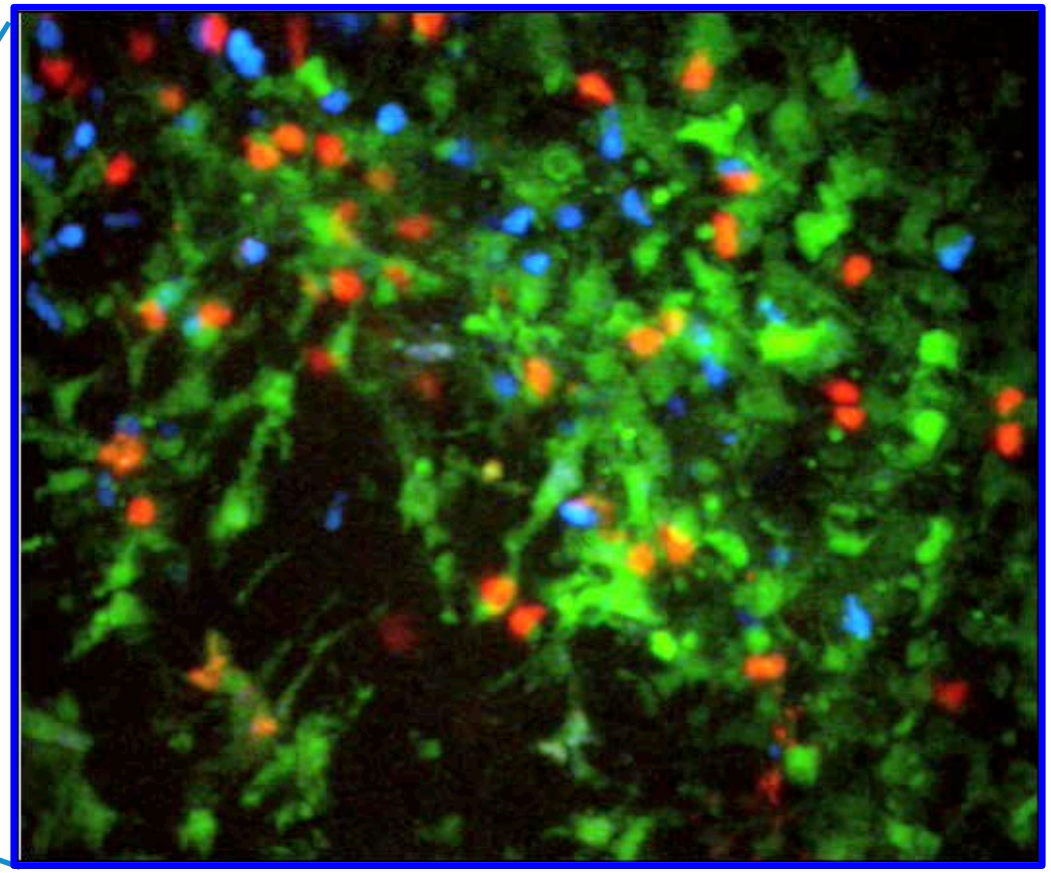
Kissenpfennig et al., Immunity *22*, pp.643-654

Innate Cells Carry Material from Tissue to Lymph Node



The principle of random motility→ recognition: synapse formation





CD11c+ Dendritic Cells OTI polyclonal T cells

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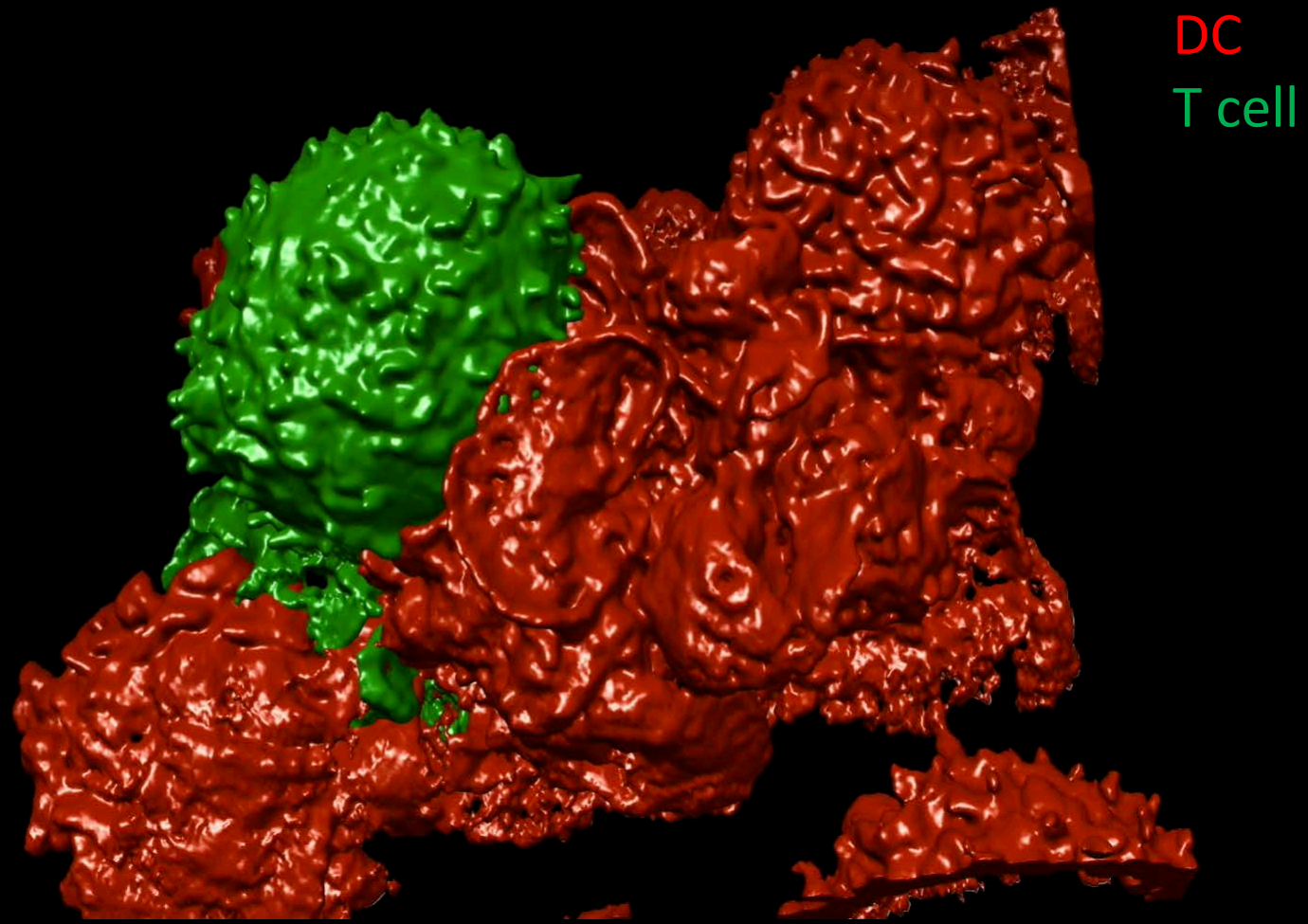
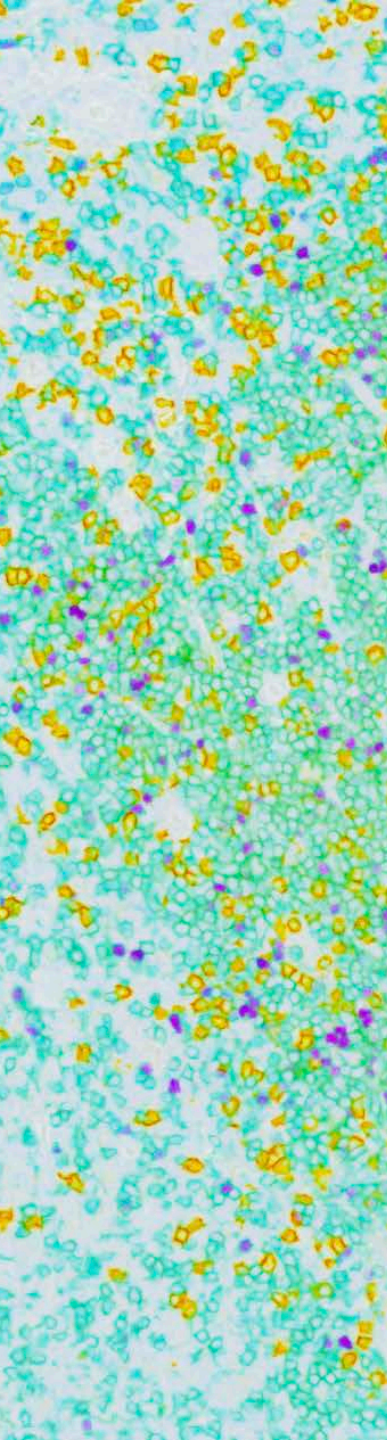
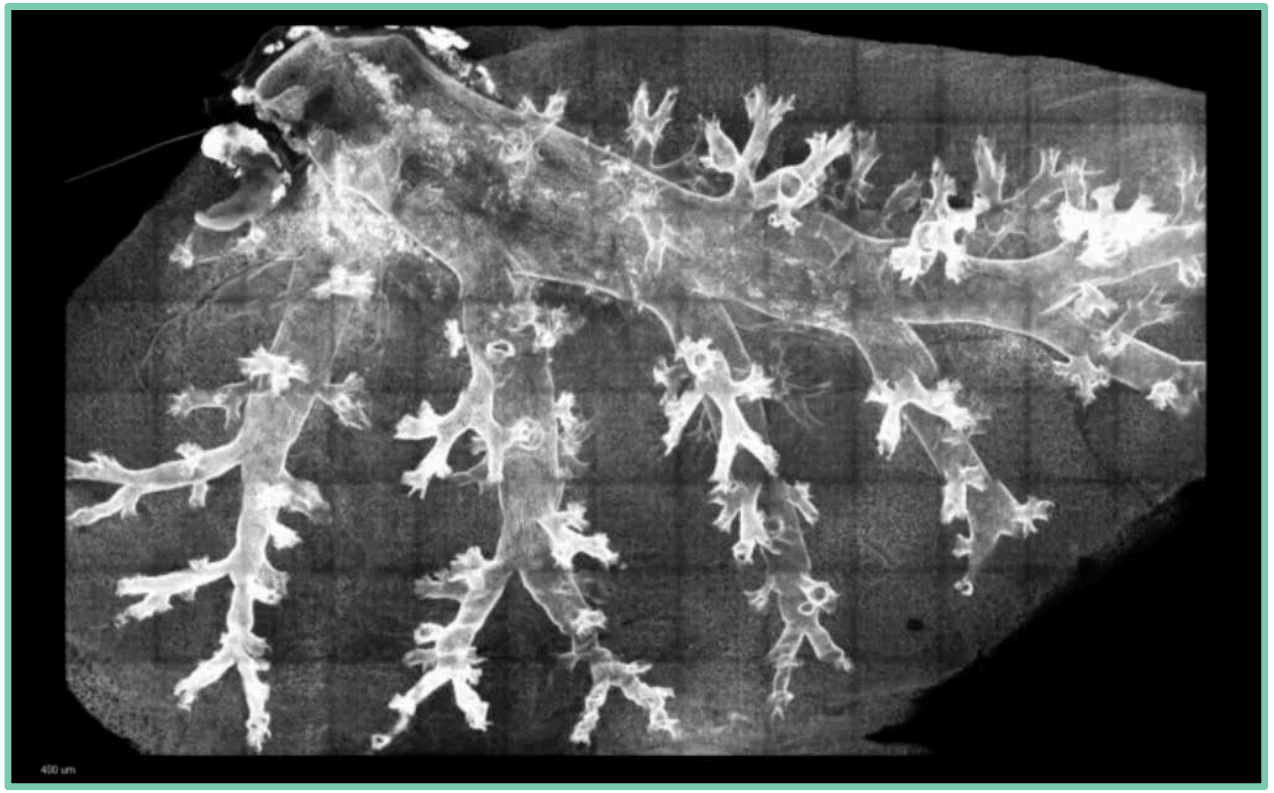
T cell and APC interaction in 4 dimensions



Cai et al. Unpublished



The Immune System is Embedded in your tissues



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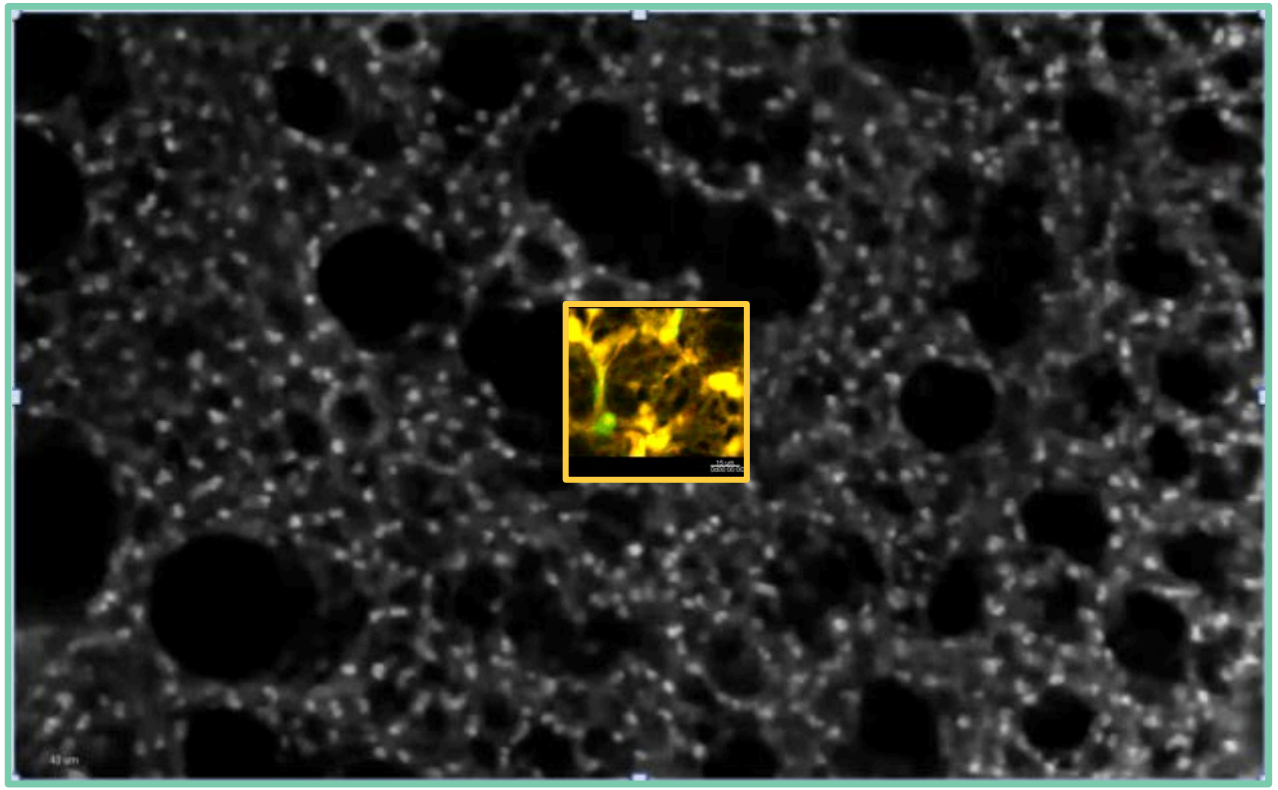
The Immune System is Embedded in your tissues



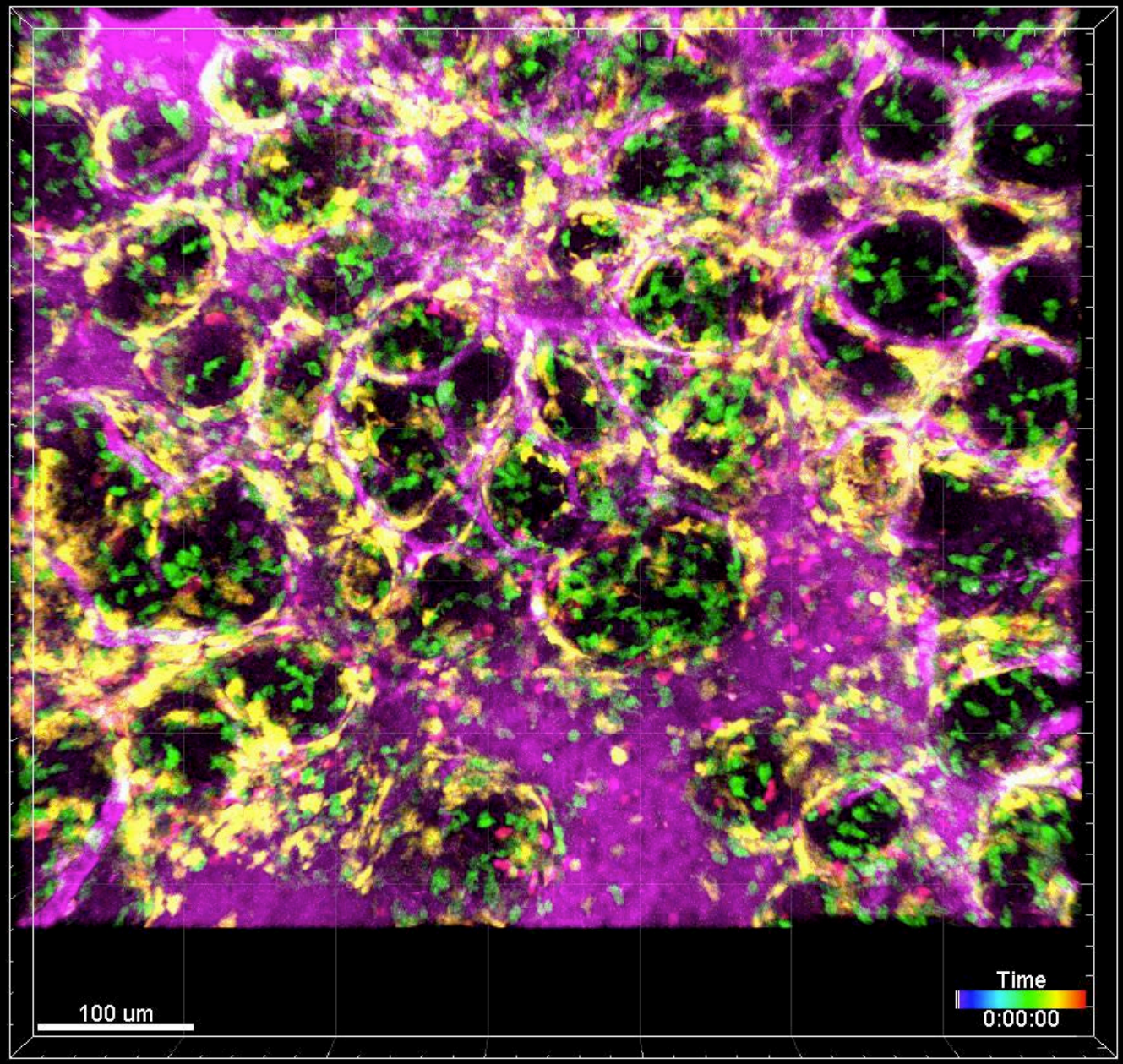
Lung epithelium
Immune cells

Reveal

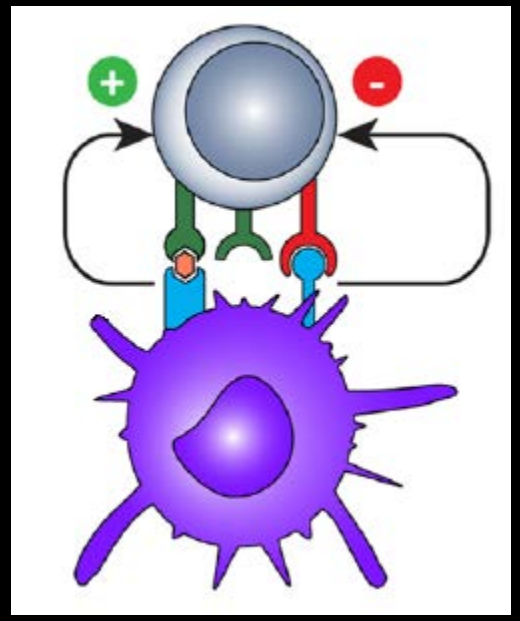
Innate And Adaptive
Immune Cells Can
Also live ‘Permanently’
within tissues

—within Tumors.

Immune systems are part
Of all your tissues.



Immune Cells Communicate Primarily through making Contact

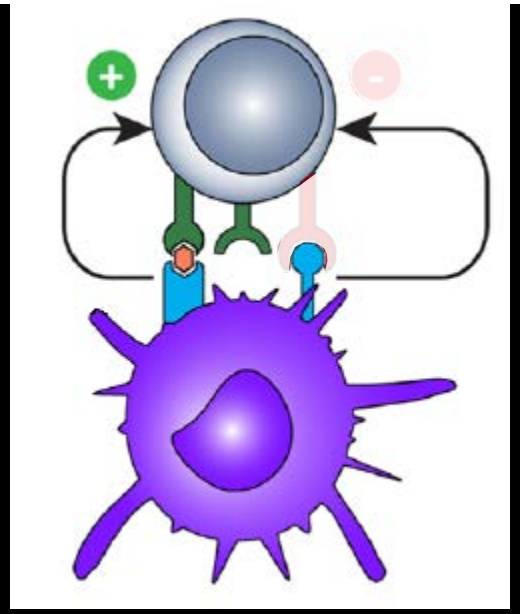


T cells—
Executioners

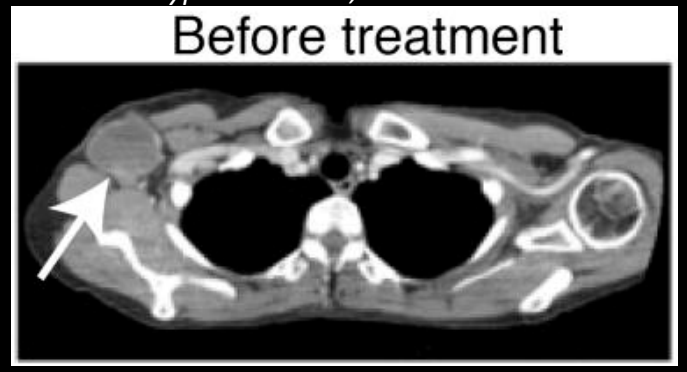
Instructive Cell
(Interprets the Tissue)

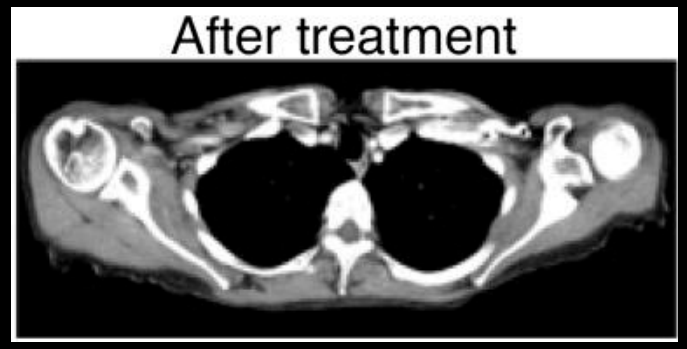
IMMUNOTHERAPY REMOVES THE BRAKES AND CURES CANCERS.

"CHECKPOINT BLOCKADE"



2016 Stage 4:
3 months typical survival, historical





Anti-CTLA-4 plus Anti-PD1: 6 weeks

THE IMPORTANT ROLE OF BASIC QUESTIONS & LOOK-SEE EXPERIMENTS.

Frasier,Straus,V

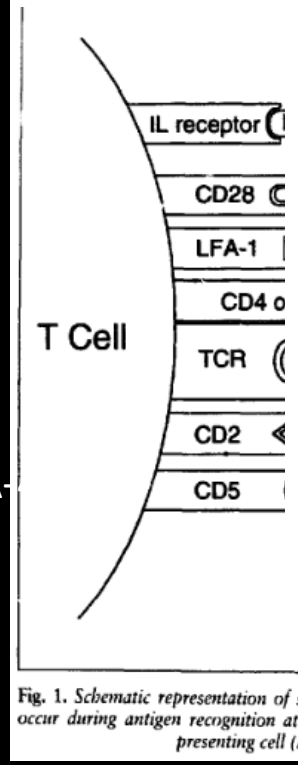
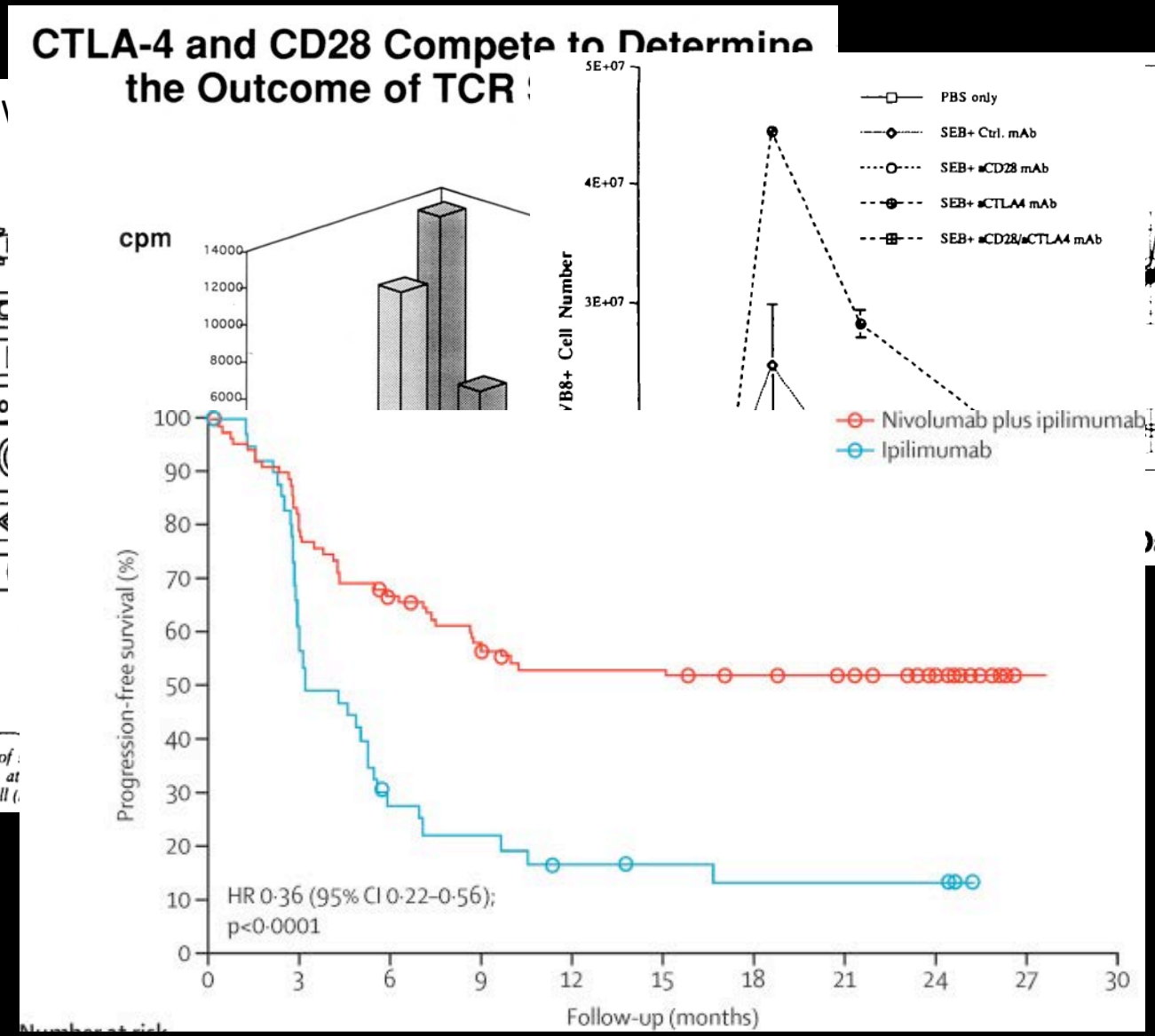
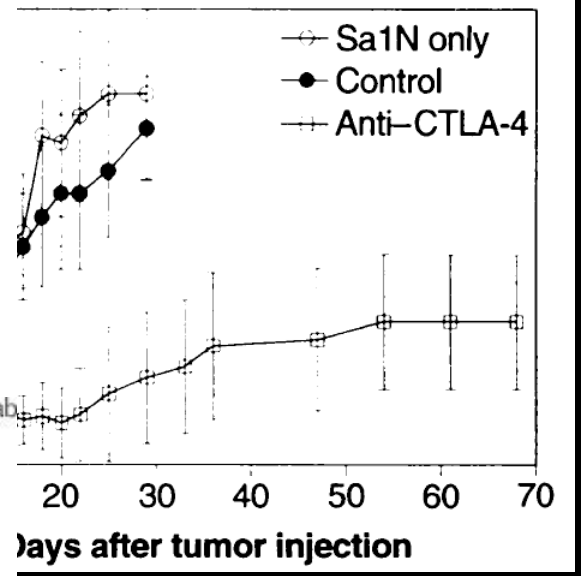


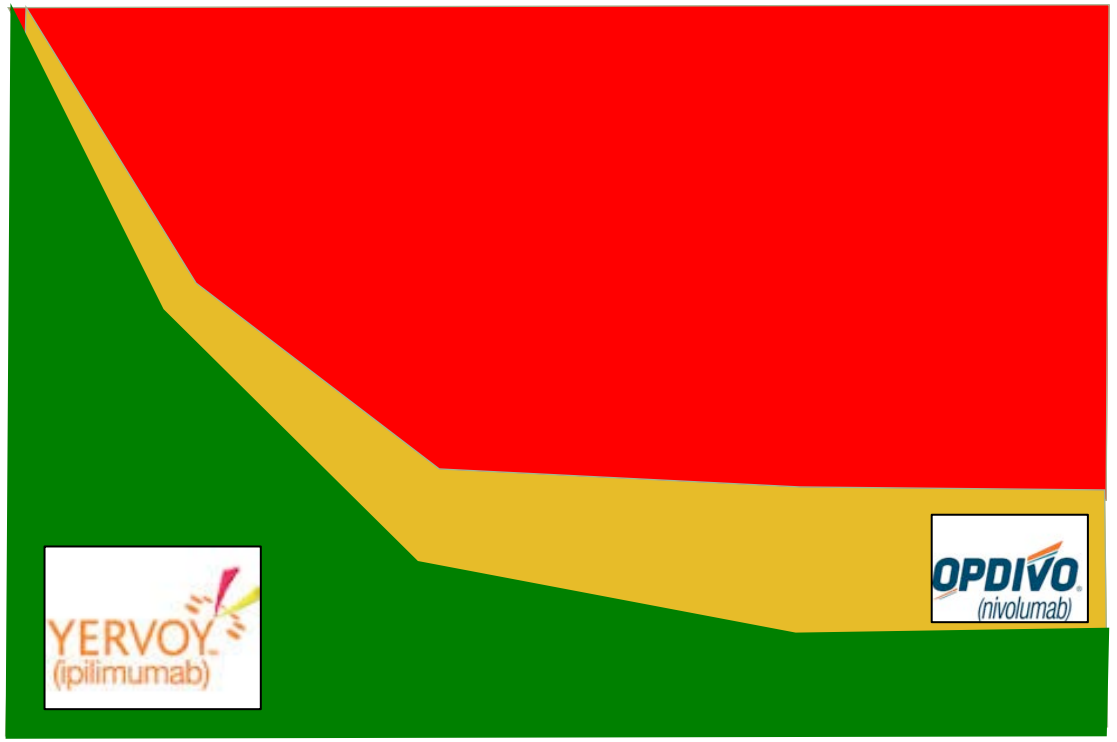
Fig. 1. *Schematic representation of occur during antigen recognition at presenting cell*

CTLA-



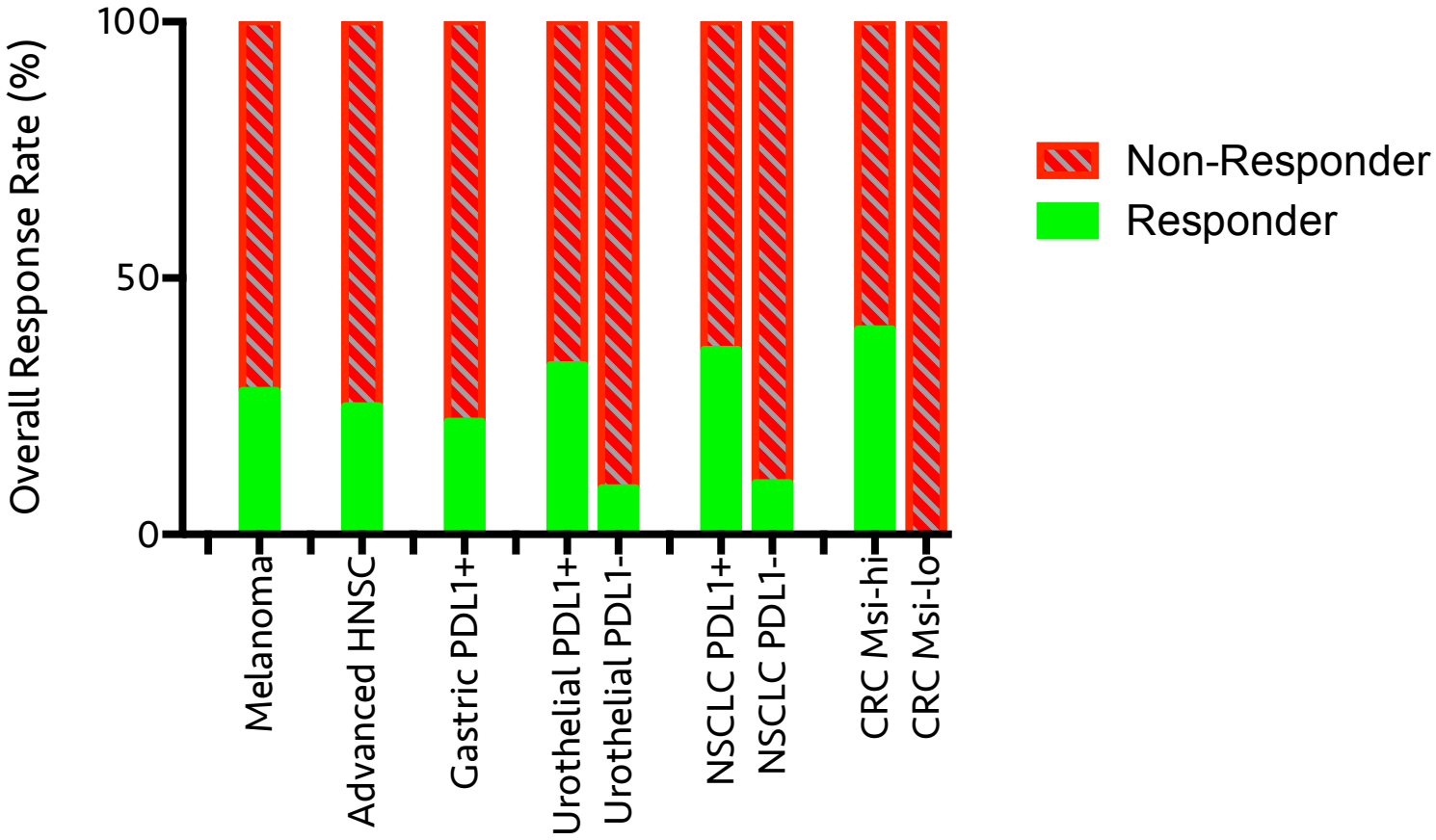


Checkpoint Inhibitors:
Breakthrough, Not a Panacea

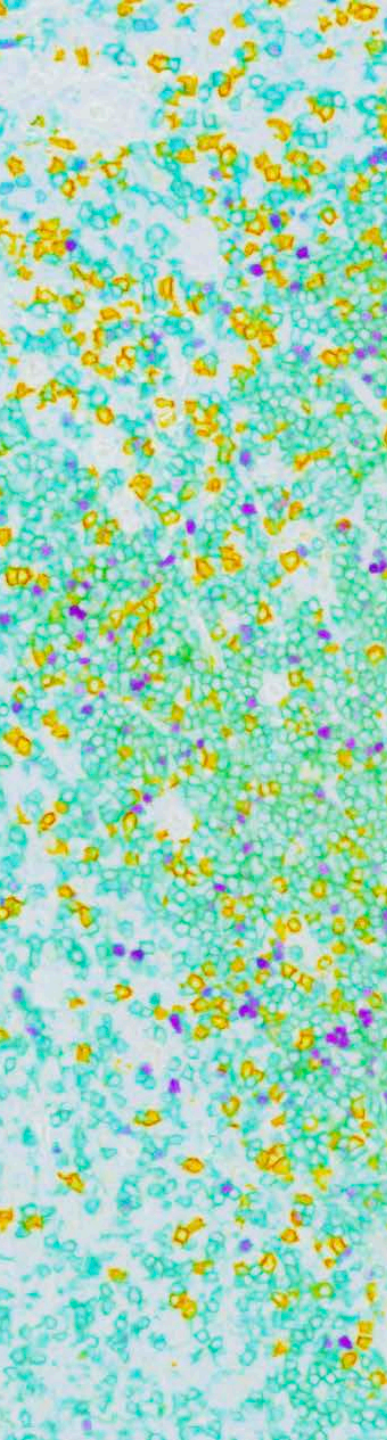


Graphic based on: Hodi. PMID: 20525992, Postow, PMID: 25891304

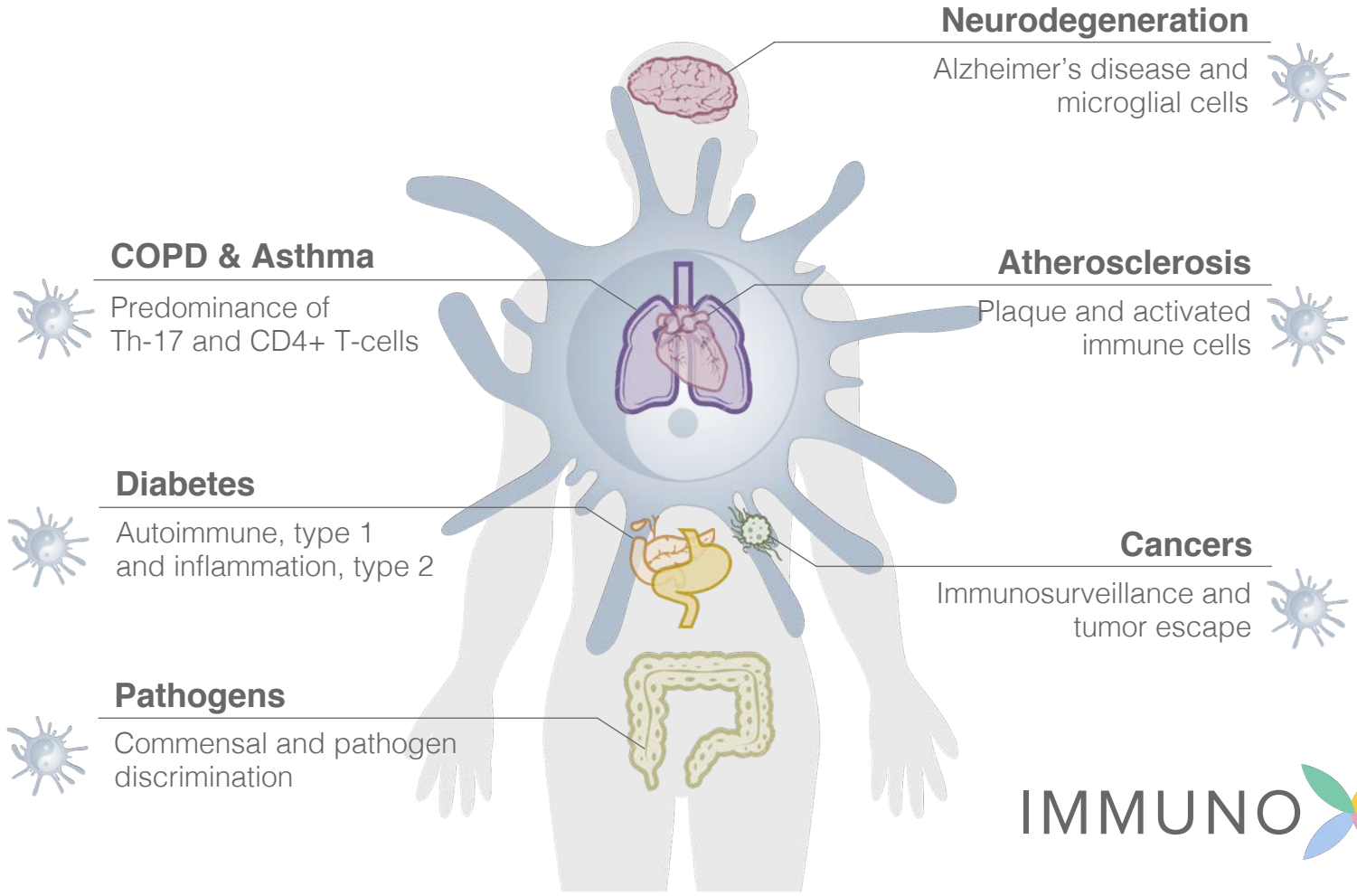
Different Tumor Types Respond Differently to Immunotherapy



Immunotherapies must be specific for the cancer biology



The Immune System and Disease—Not Just Cancers



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How Do We Proceed to Study these?

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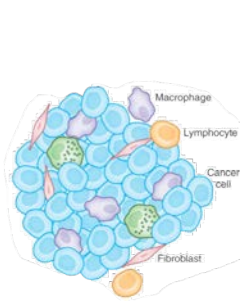
Linking Studies through Shared Data and CoLabs



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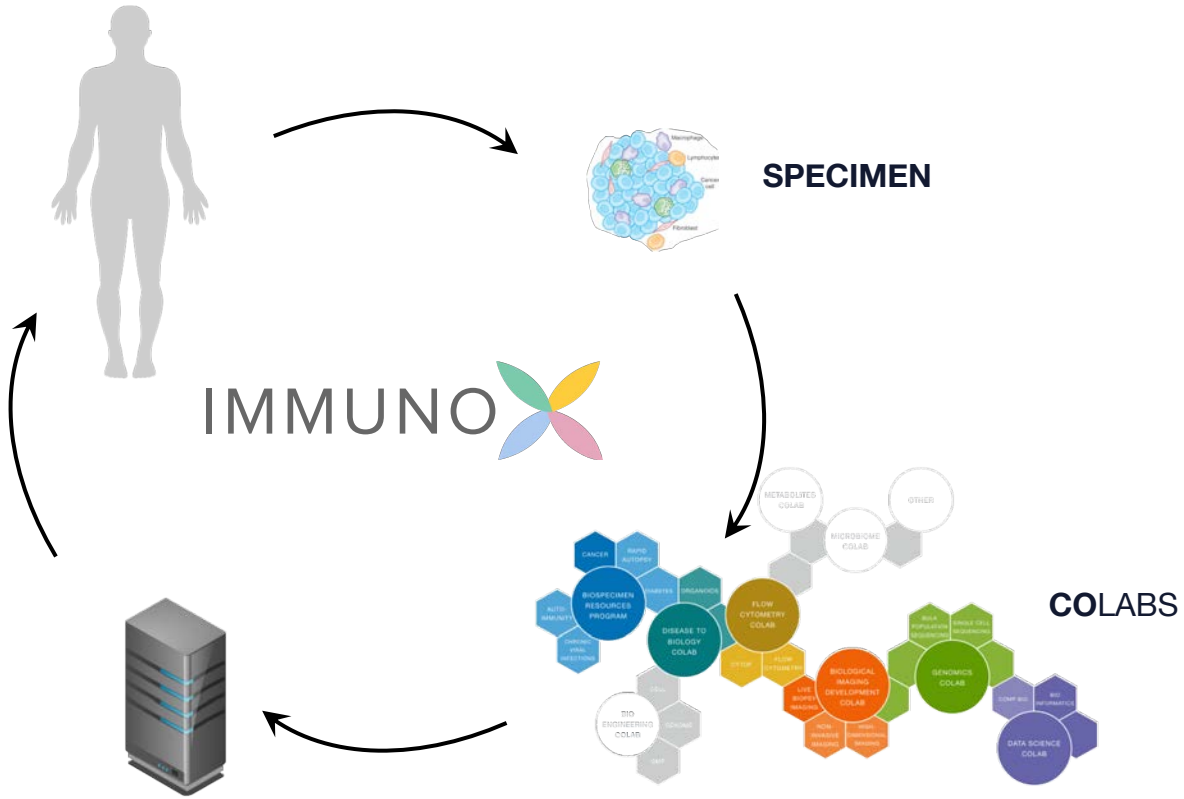
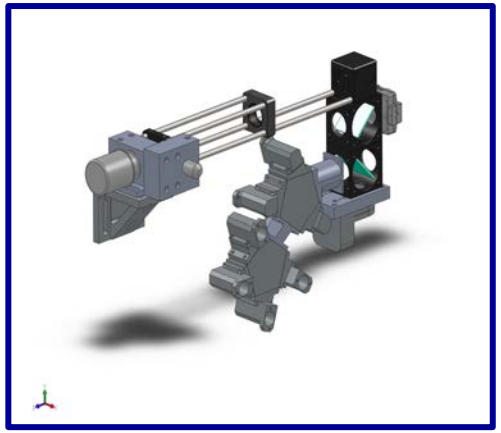
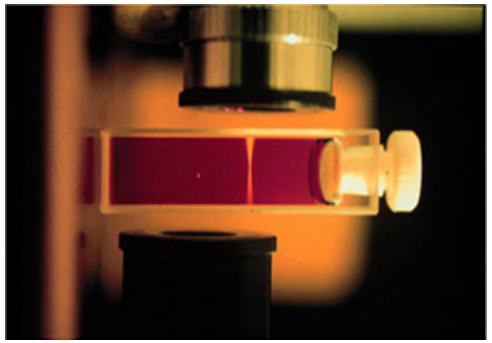
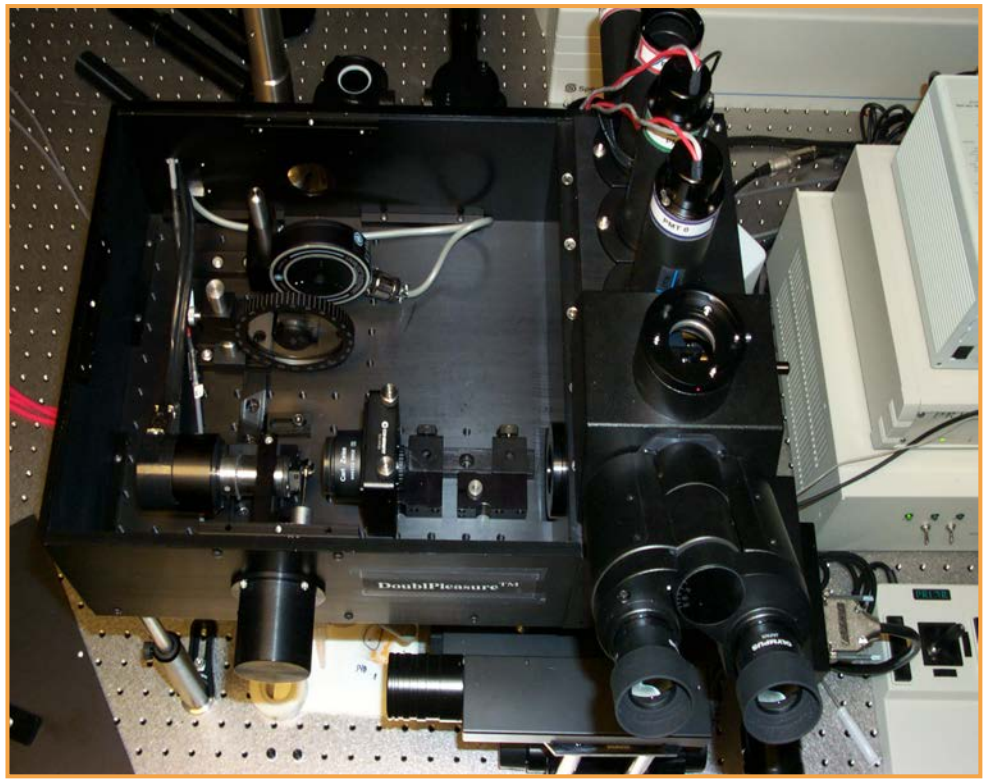
Our Vision for Collaborative Patient-Centric Discovery



Discovery is Sometimes by Looking. High-Resolution View of the Biology







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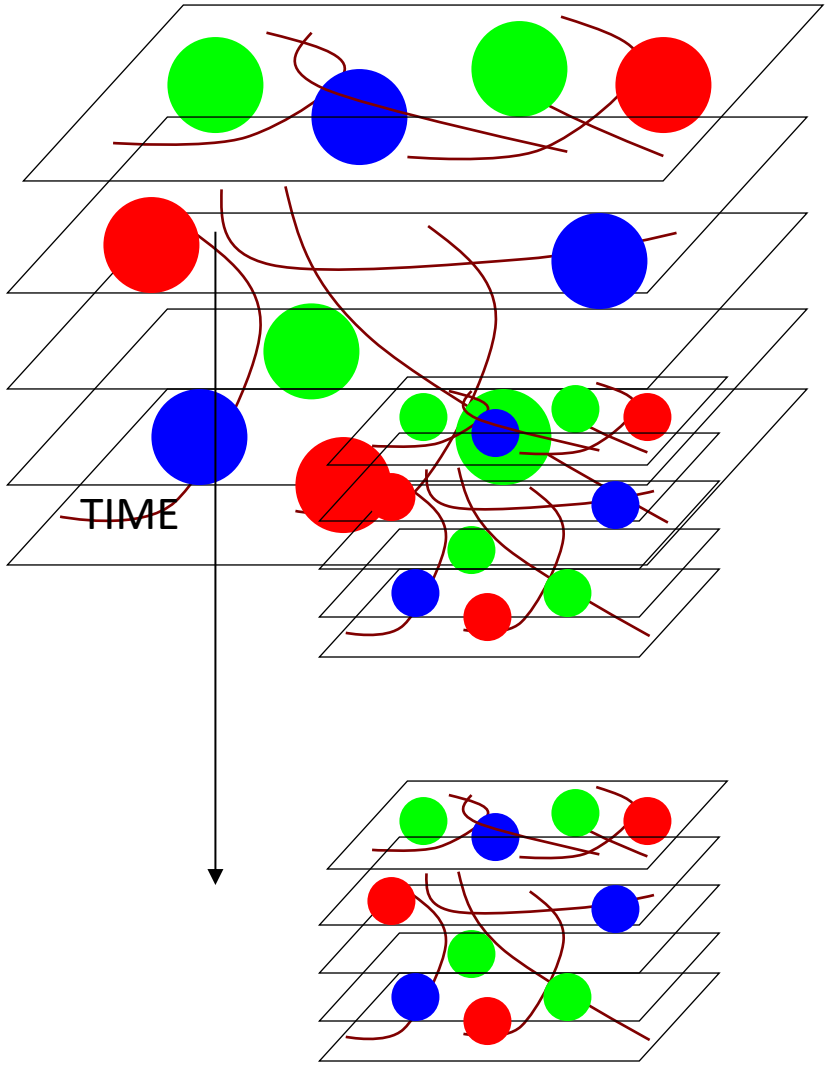
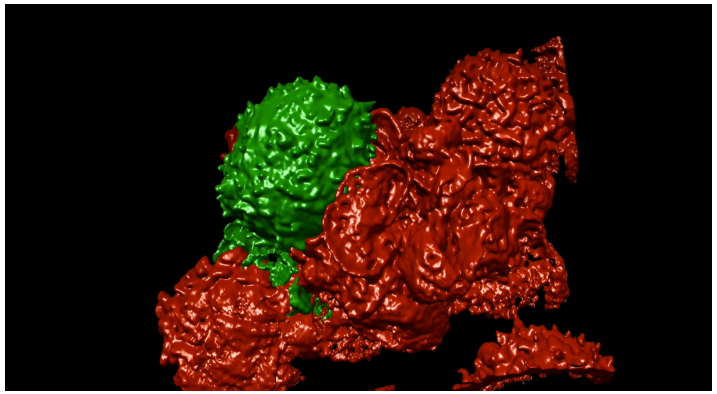
Making Movies



"…like the billowing dancing figures in a brightly lit ballroom that you gaze into from outside in the dark—and from a distance so great that you can no longer hear the music… the turning and twisting movement of the couples seems senseless."

Gustav Mahler, on the third movement of his second symphony



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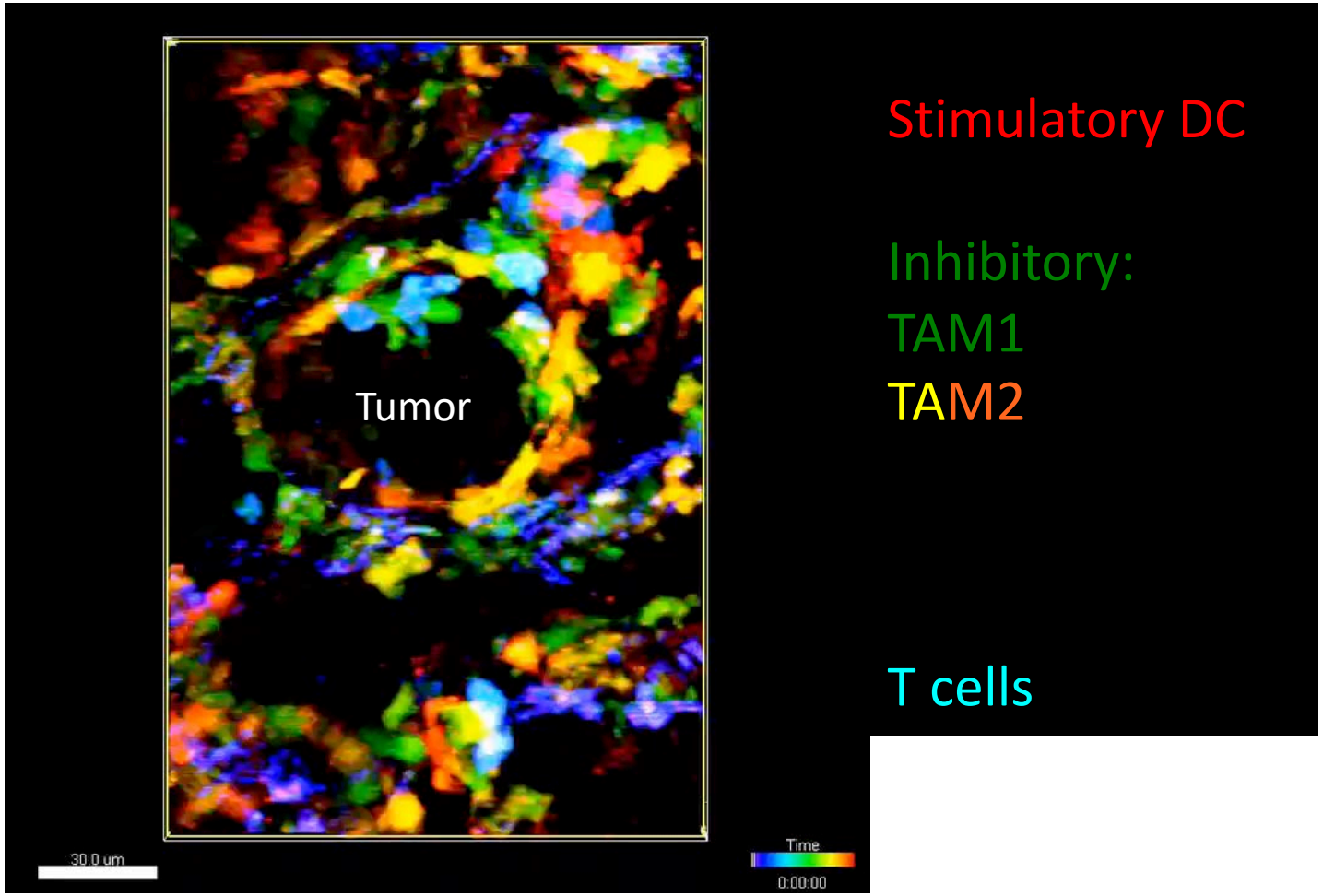
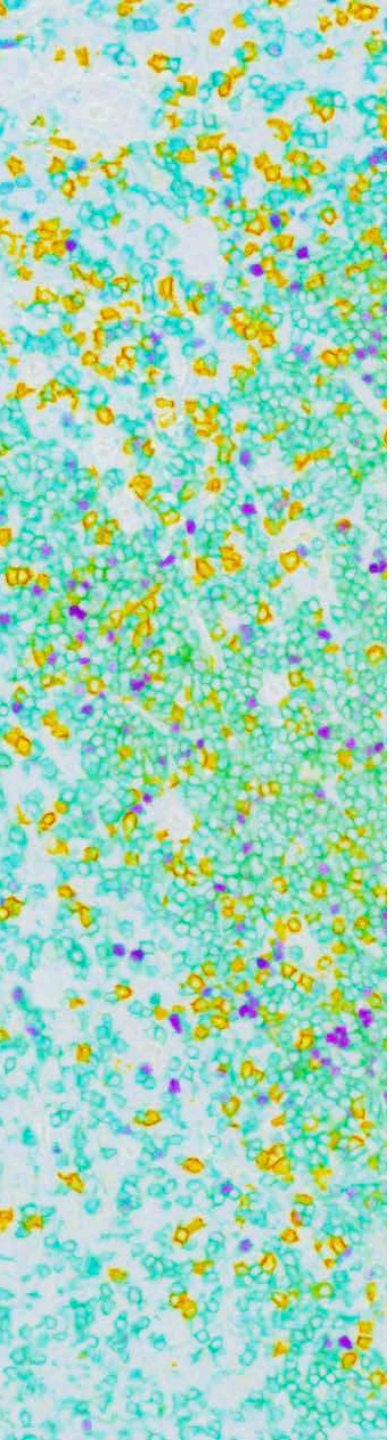
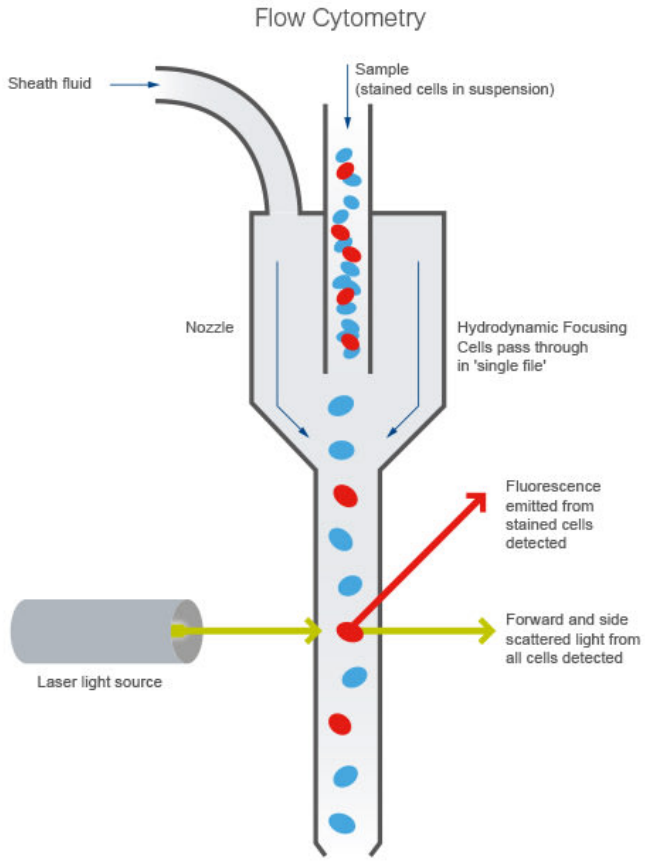
Inhibitory and Stimulatory Immune Landscapes Co-Exist within Cancers

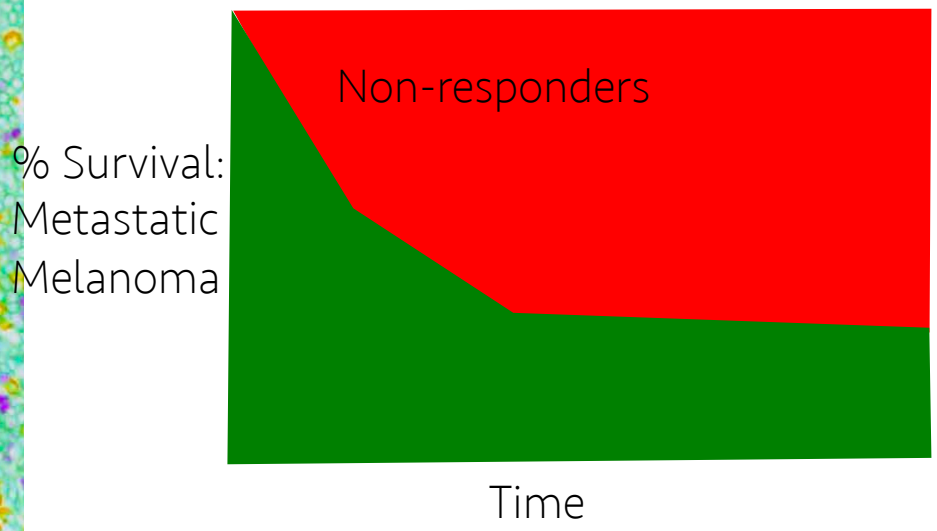


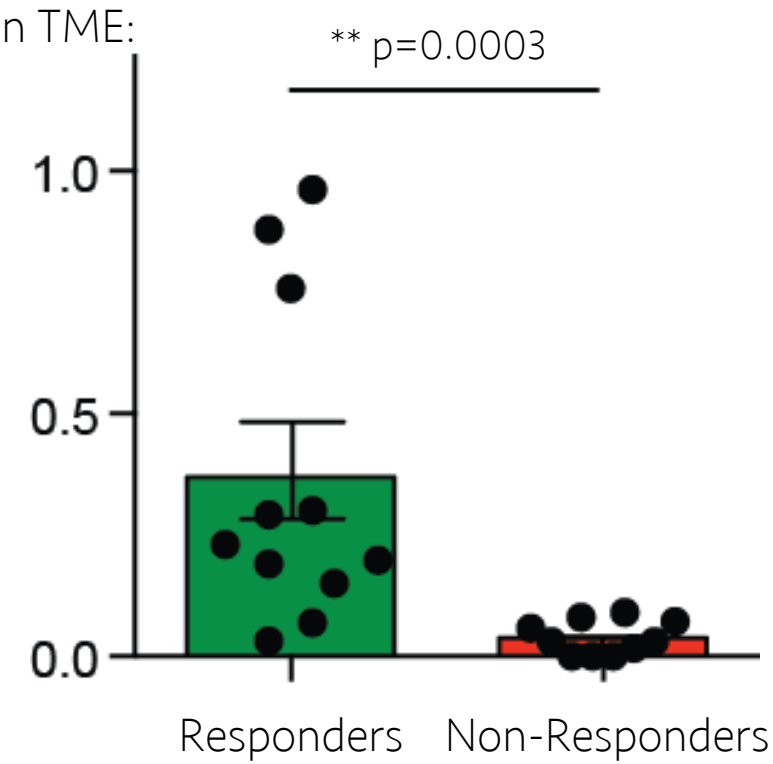


FLOW CYTOMETRY:
COUNTING AND MEASURING CELLS FROM TISSUES



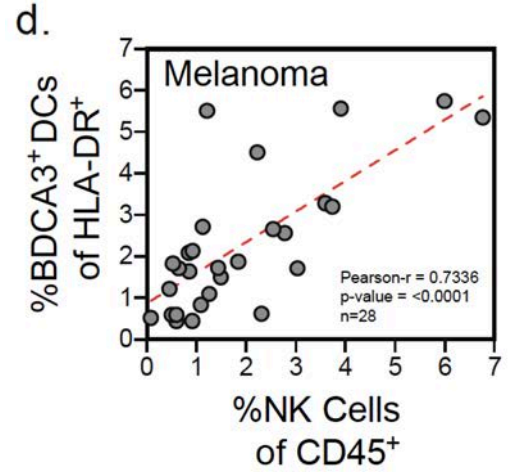
What Class of Immune System You Have Matters

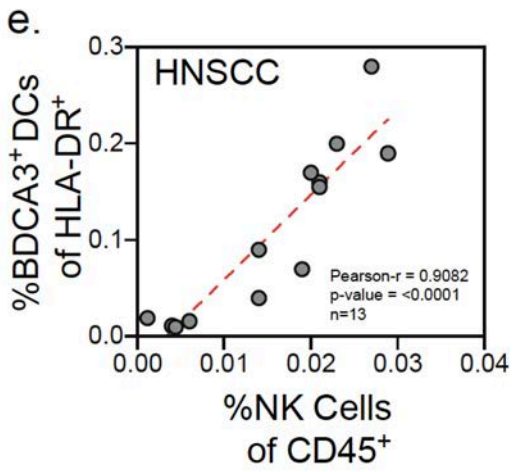




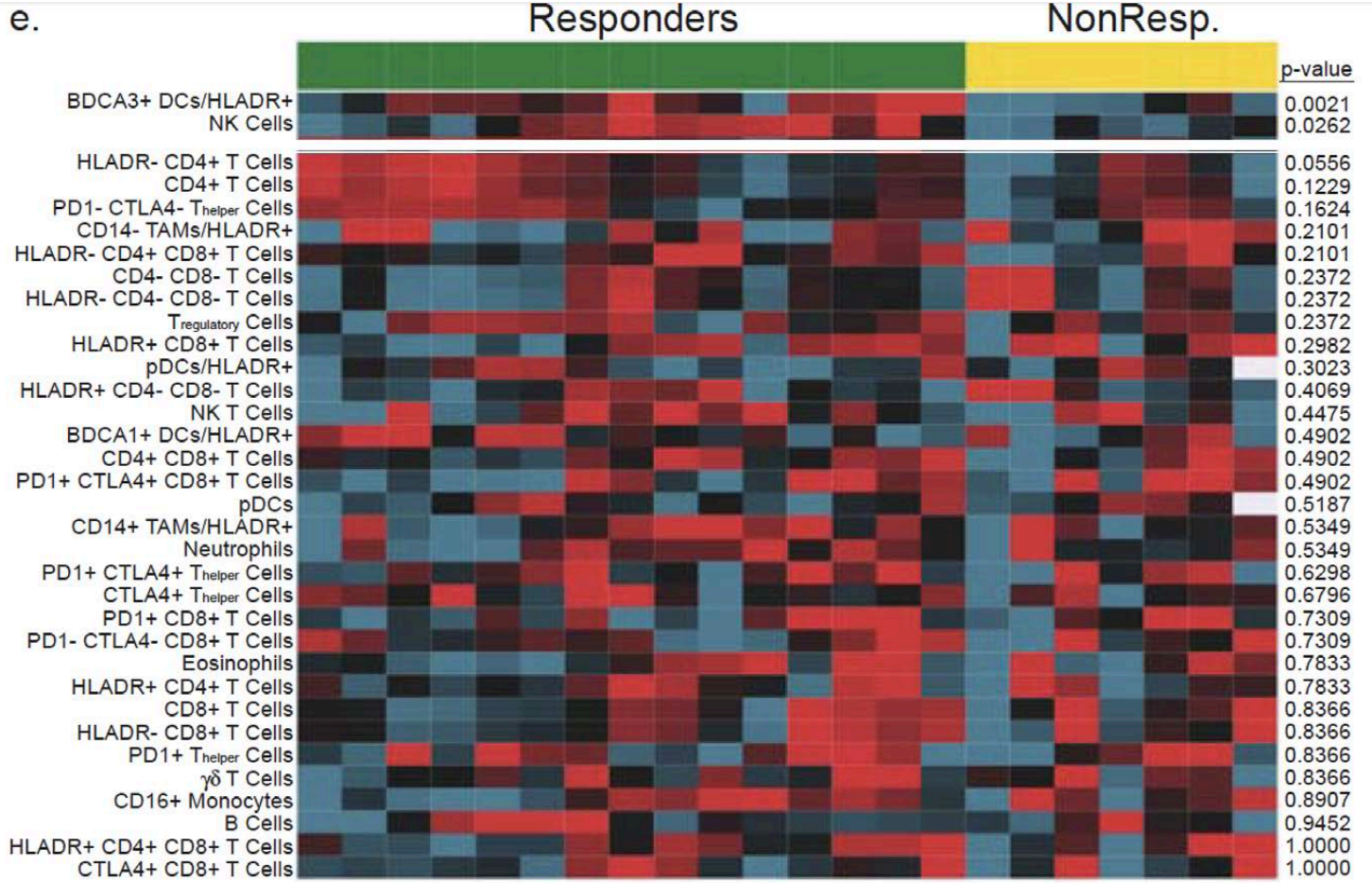
Responders to checkpoint inhibition different cellular allies

NK and cDC1 numbers are tightly linked and are correlated with response to Checkpoint Blockade





Patients—profiled pre-treatment with anti-PD1



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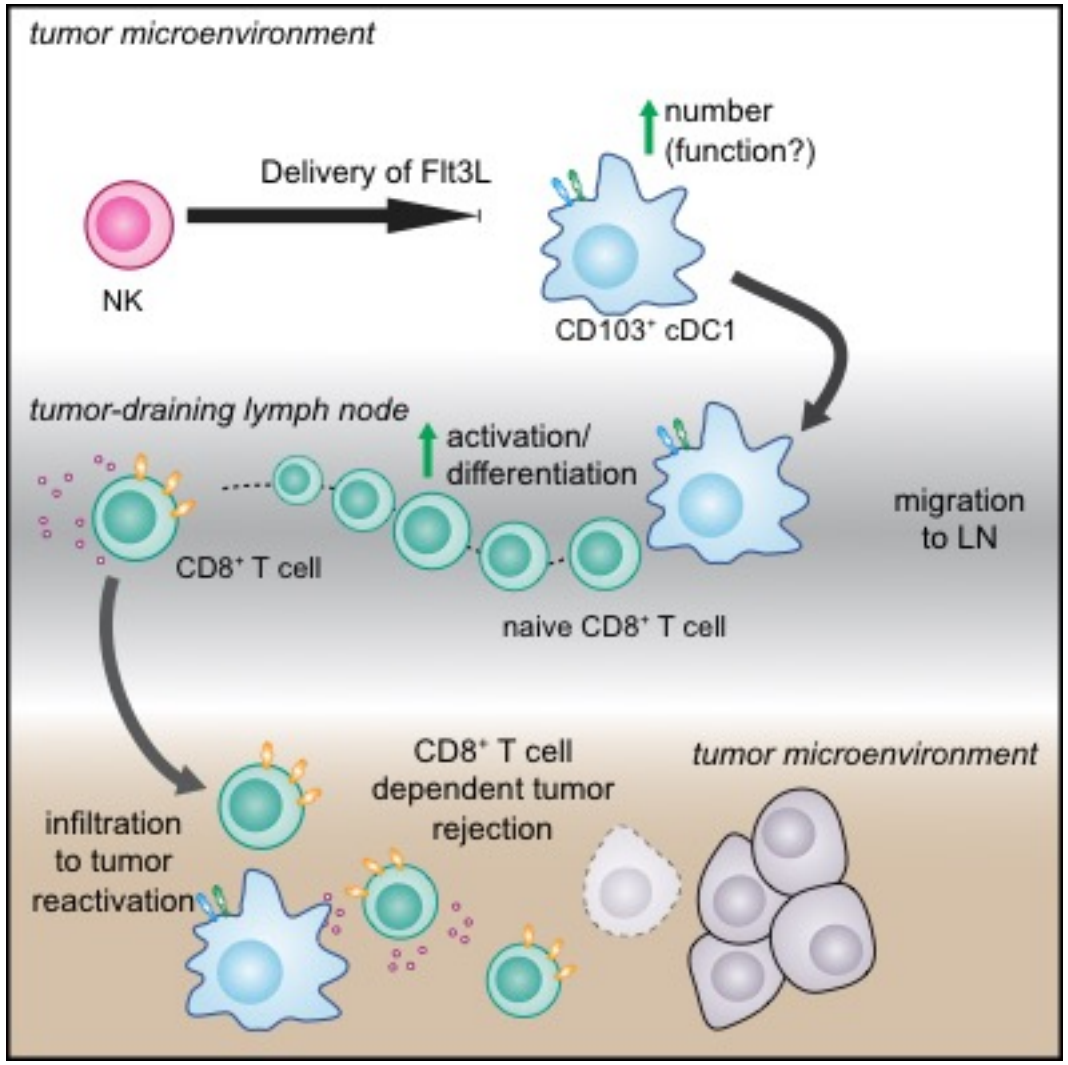
Archetypes Of Immune Systems in Tumors-Generally



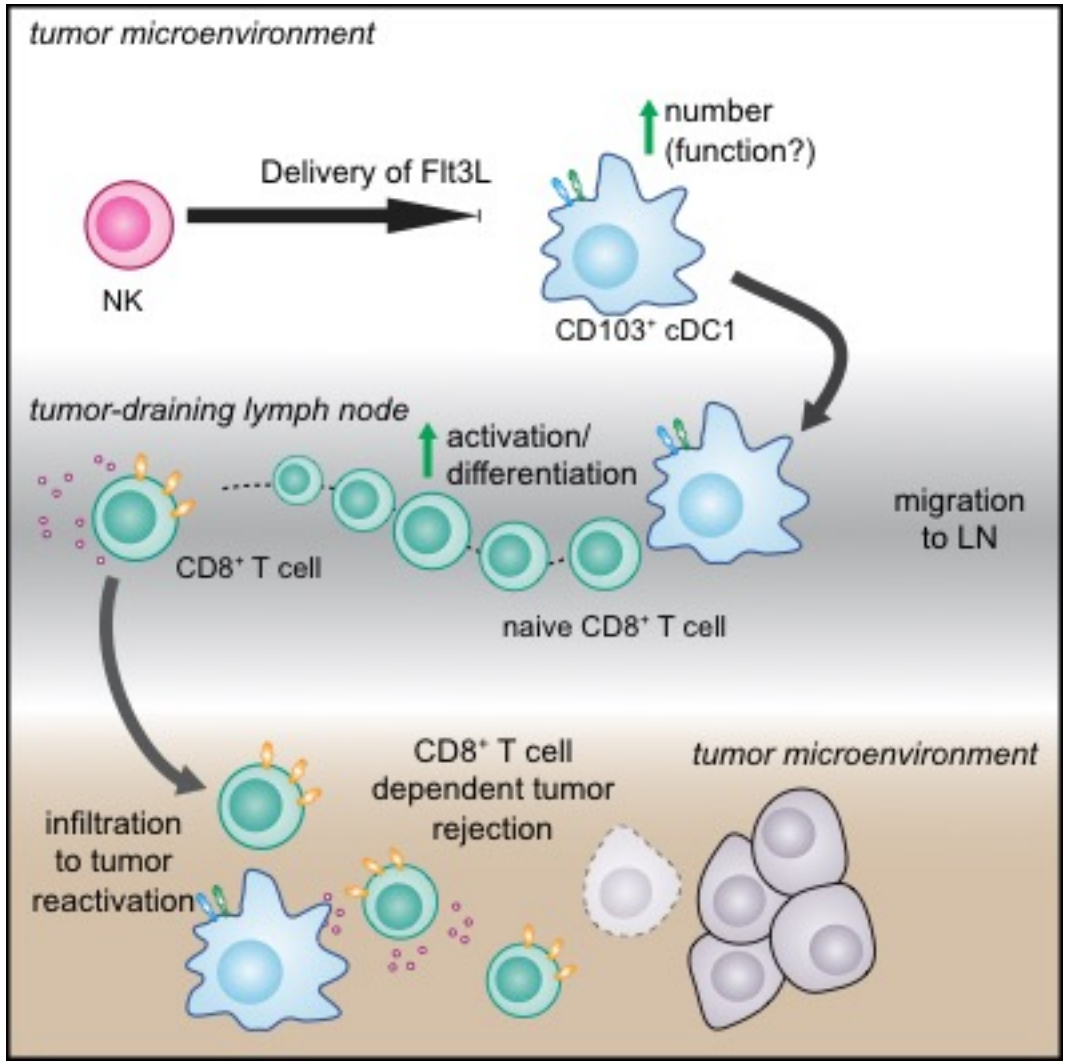
Archetype here defined as:
Collections of cells in linked states, across tissue types, typically following an evolutionary design

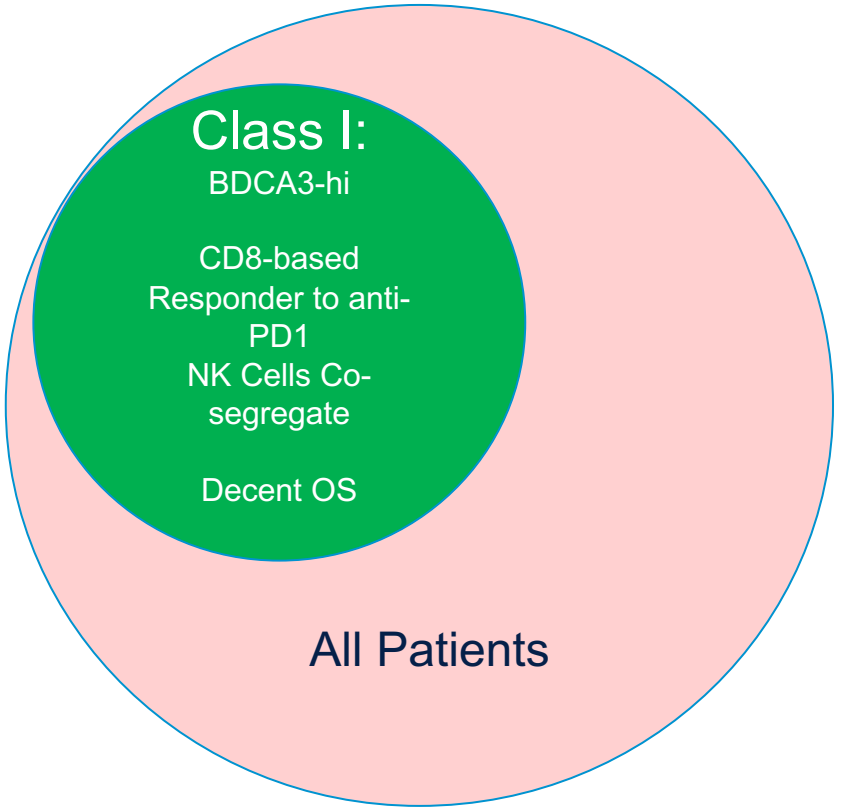
CD8 T cells
cDC1 Dendritic Cells
NK Cells

Are all part of a key ‘Archetype’ of responsiveness to tumors

Nature Med 2018

Archetypes Of Immune Systems in Tumors-Generally





A "Better" Immune System in Human Cancer

This partnership appears to define a 'better' immune system that harnesses CD8 immunity that is more receptive to Checkpoint Blockade.

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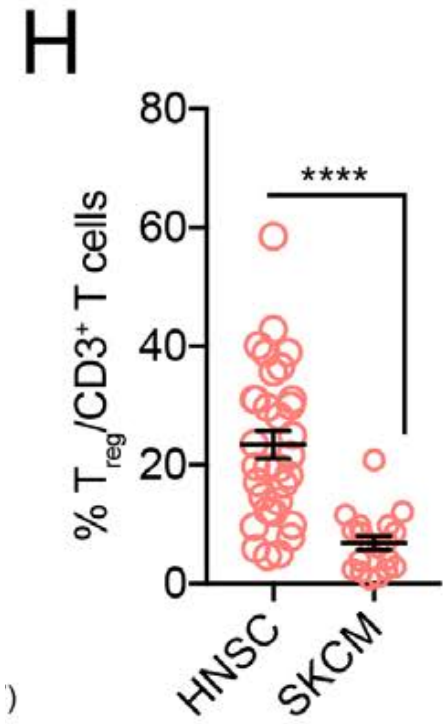
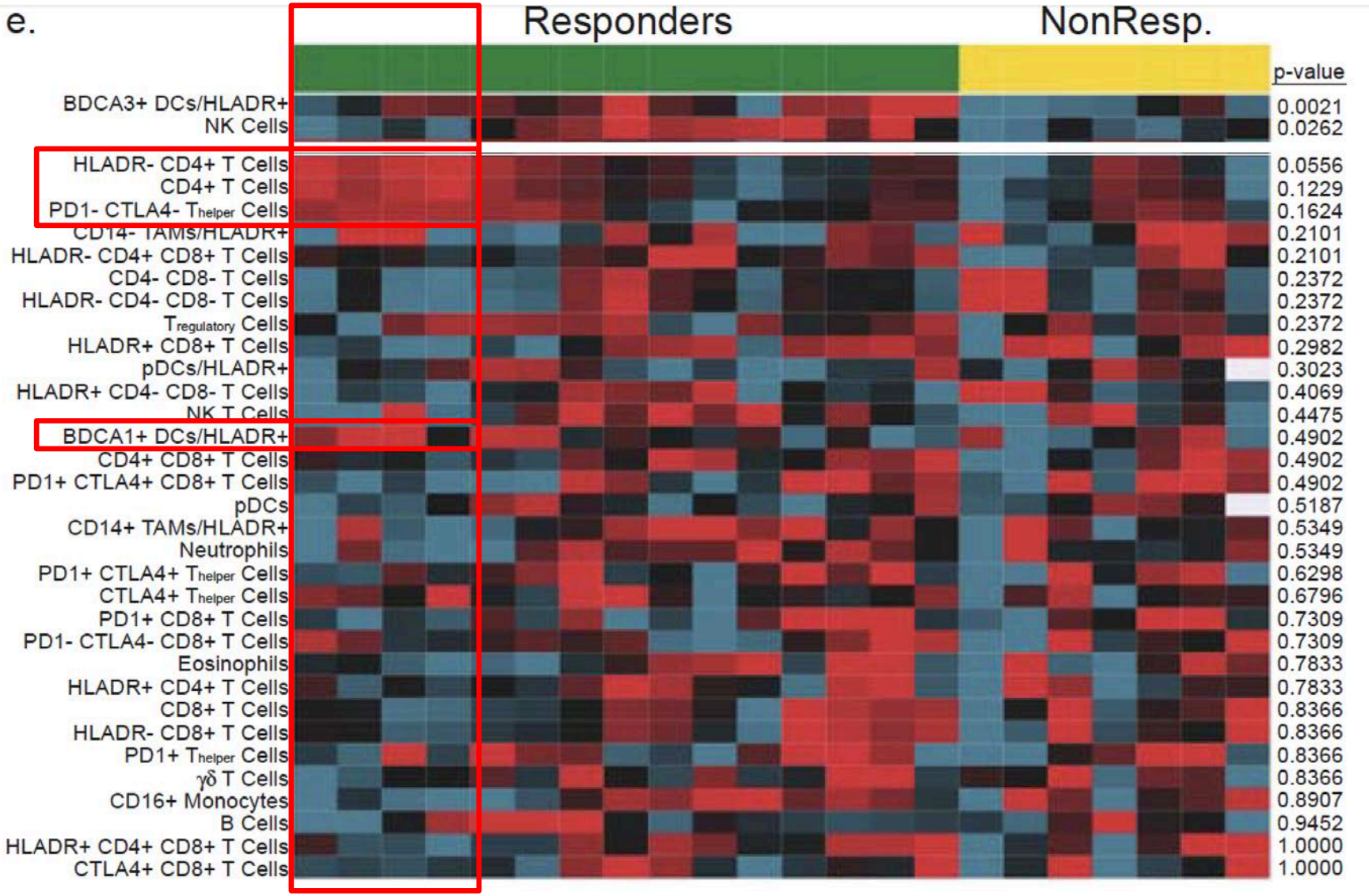
KRUMMELLab

A CD4-Enhanced Class of Melanoma Patients Also Can be Checkpoint Responders.

Patients—profiled pre-treatment with anti-PD1





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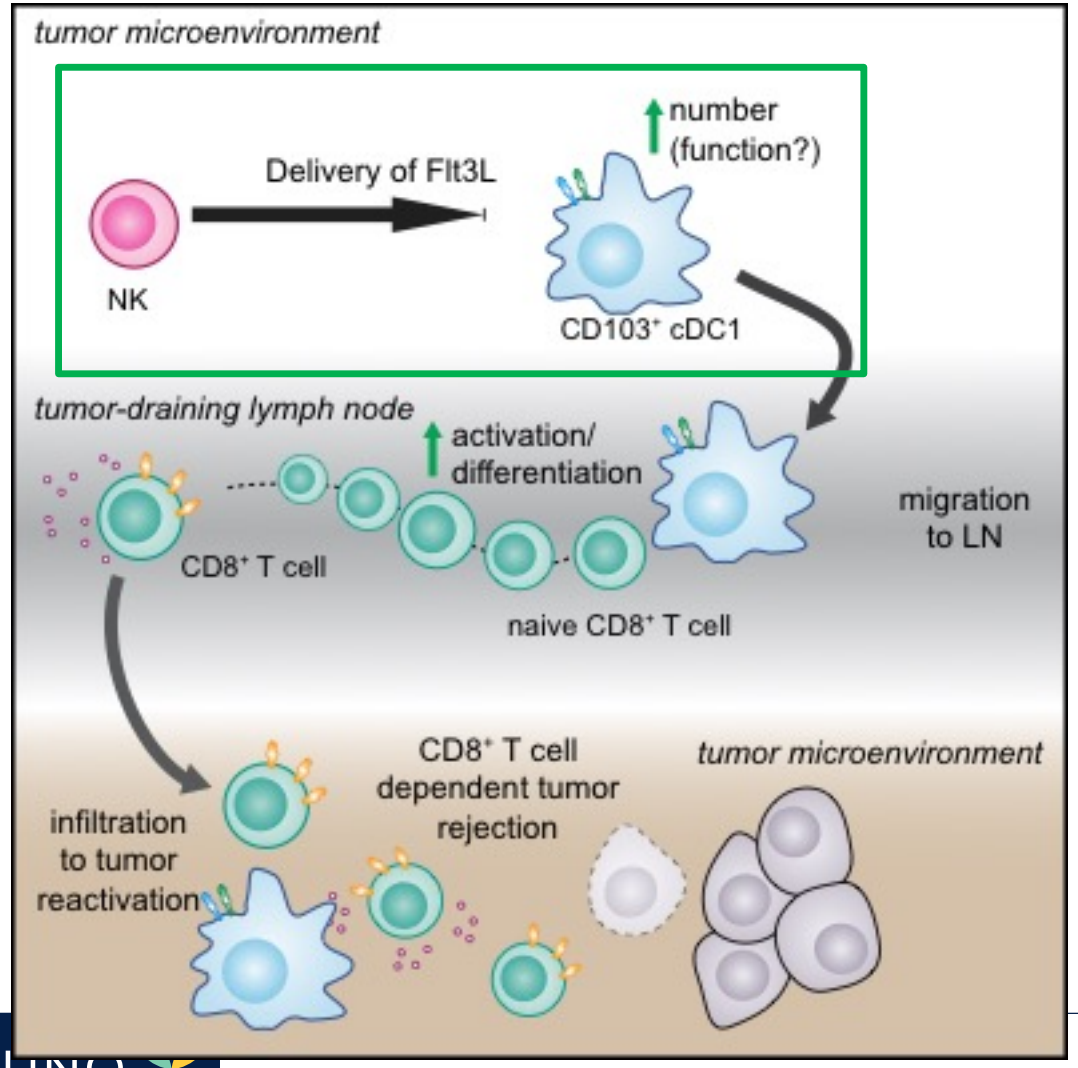
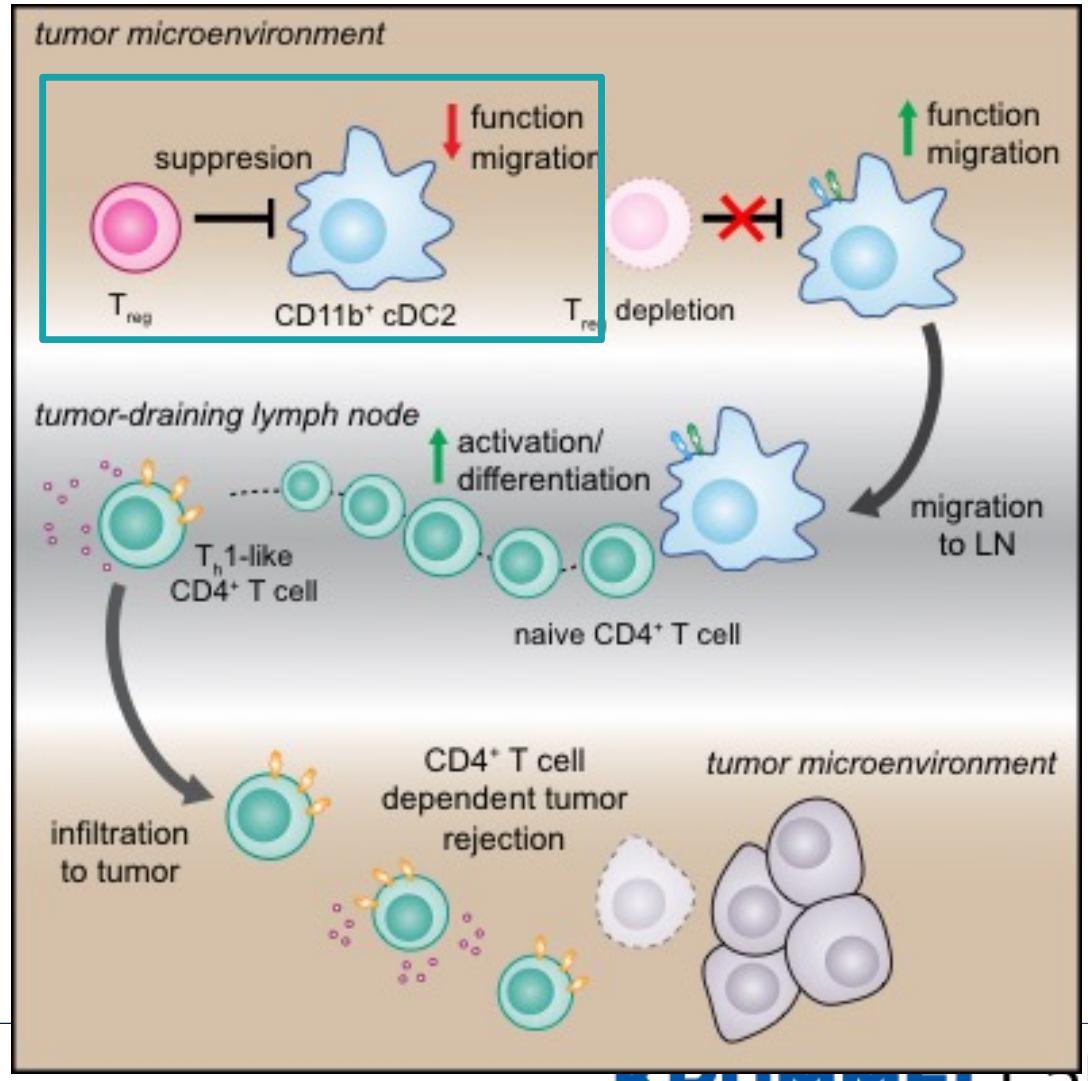
Tumoral Immunity Axes

CD8 Responses

Nature Med 2018

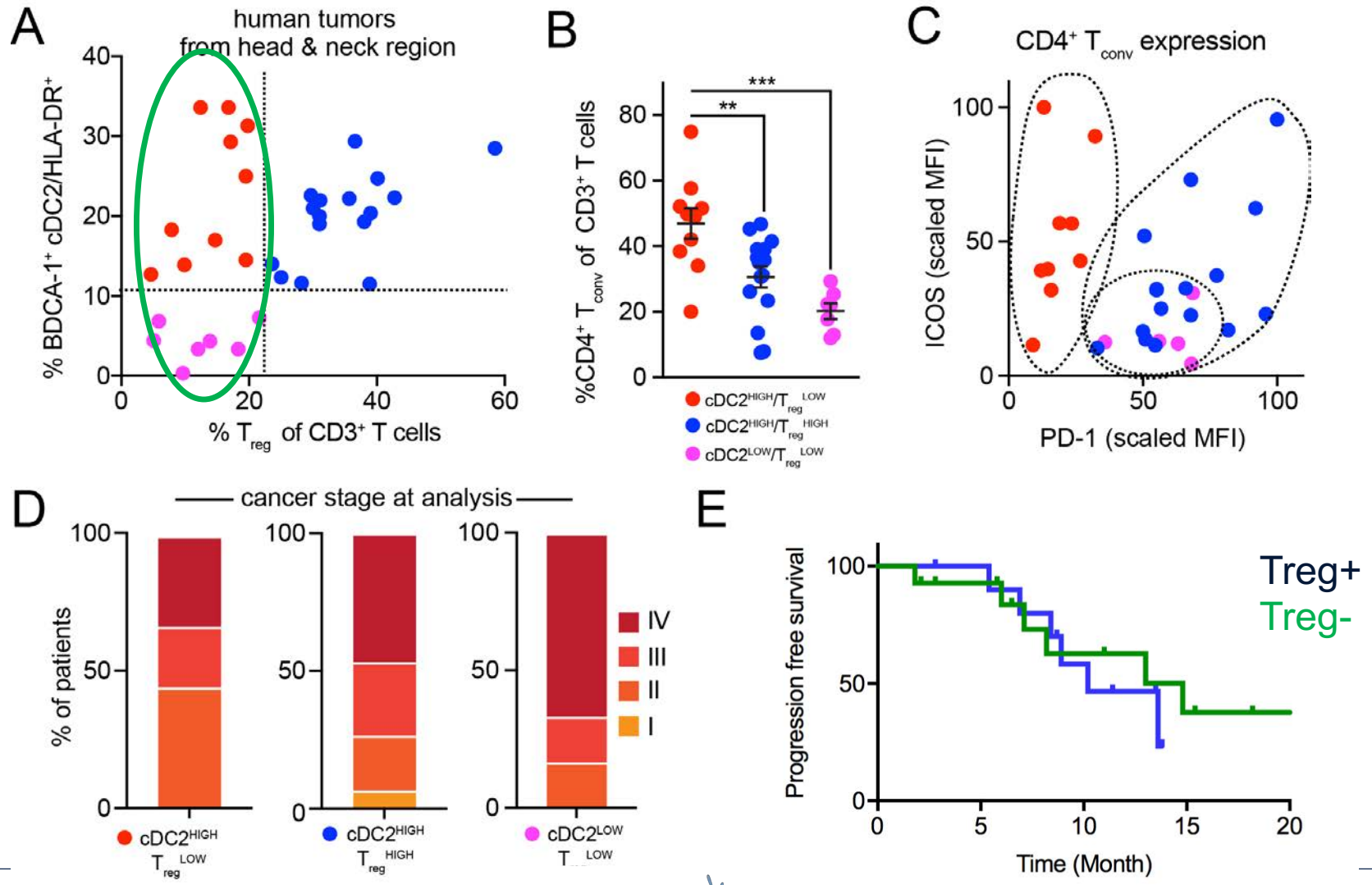


CD4 Responses



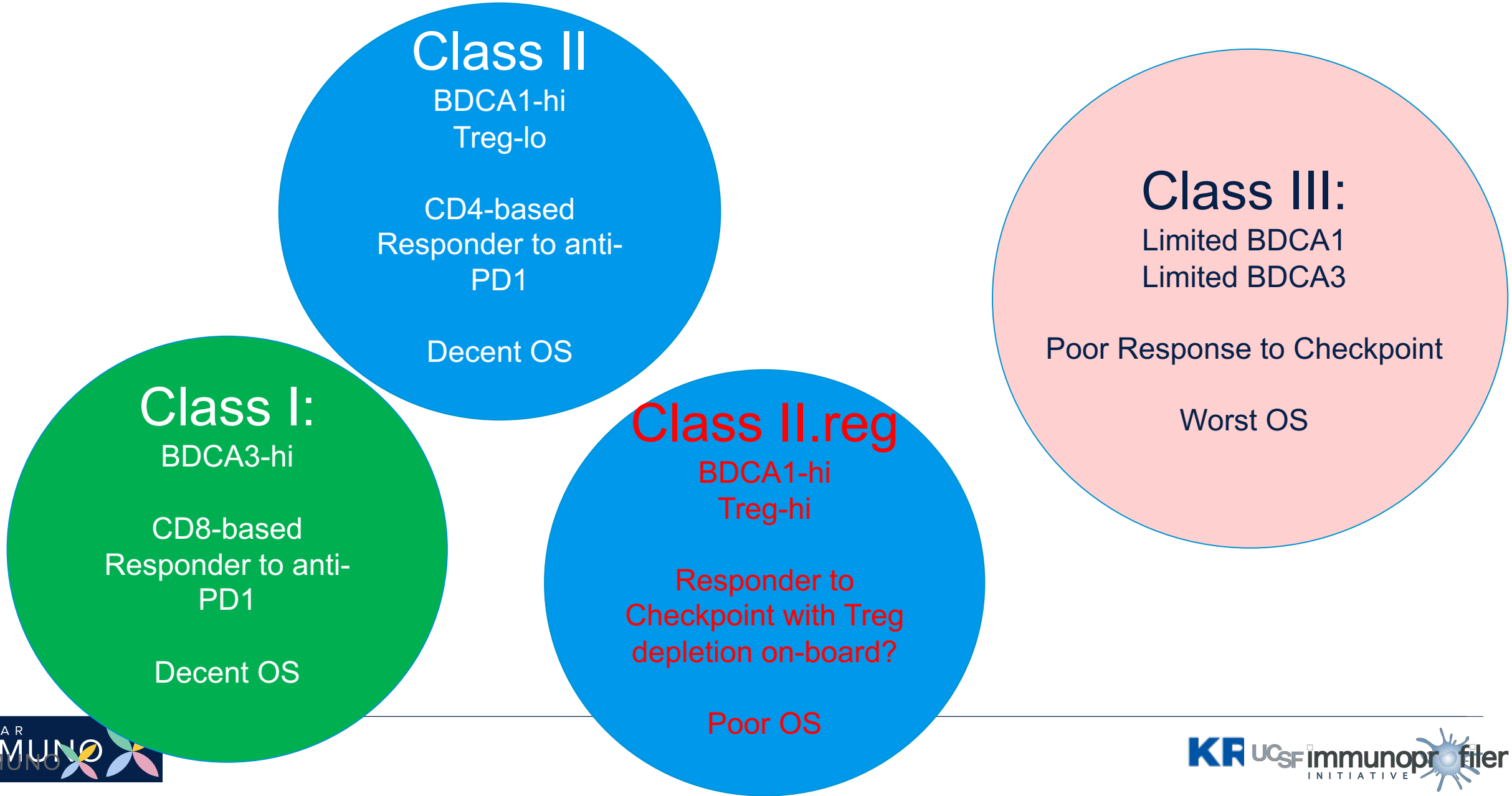
Ce

The **Paired presence of Treg, together with cDC2 numbers classifies patients with a ‘better ‘ CD4 Response**

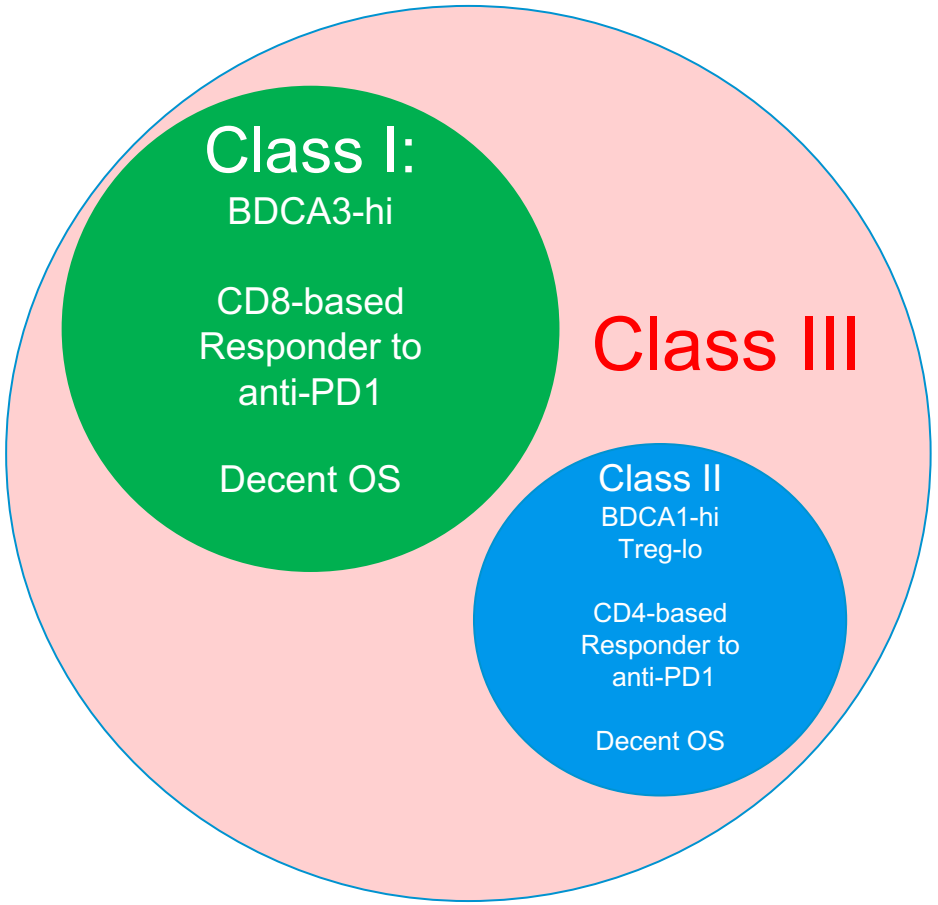


Binnewies, Cell, 2019

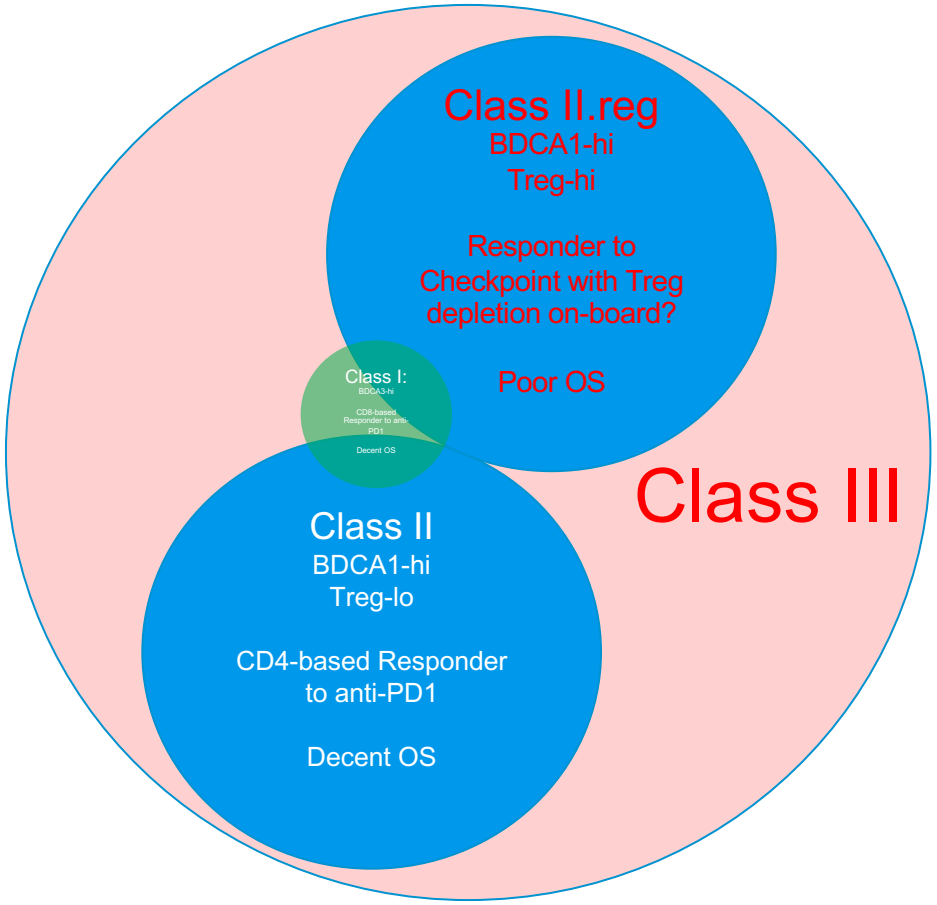
Archetypes Of Immune Systems in Tumors-Generally



Archetypes Of Immune Systems in Tumors-By Indication

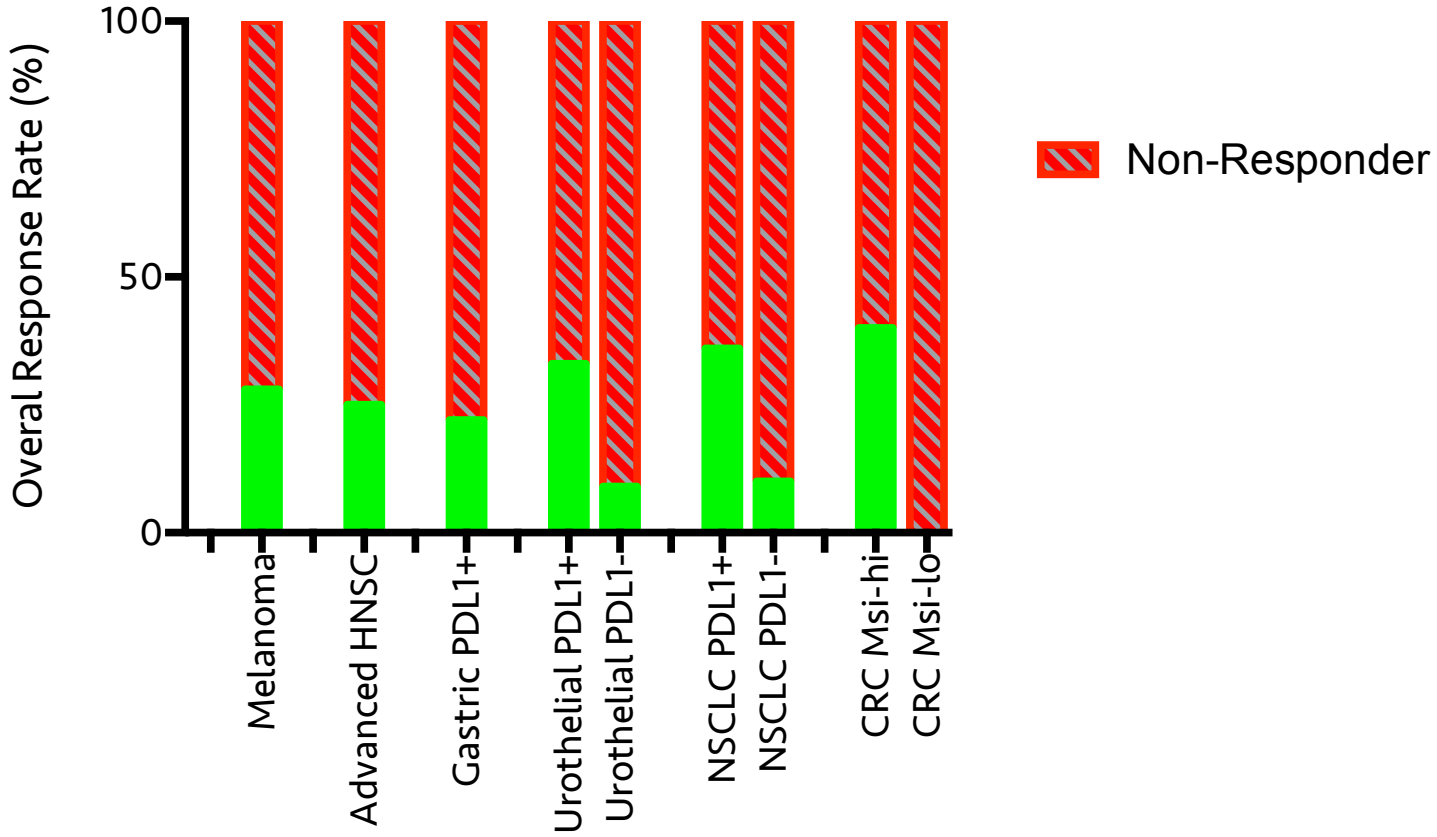


Melanoma

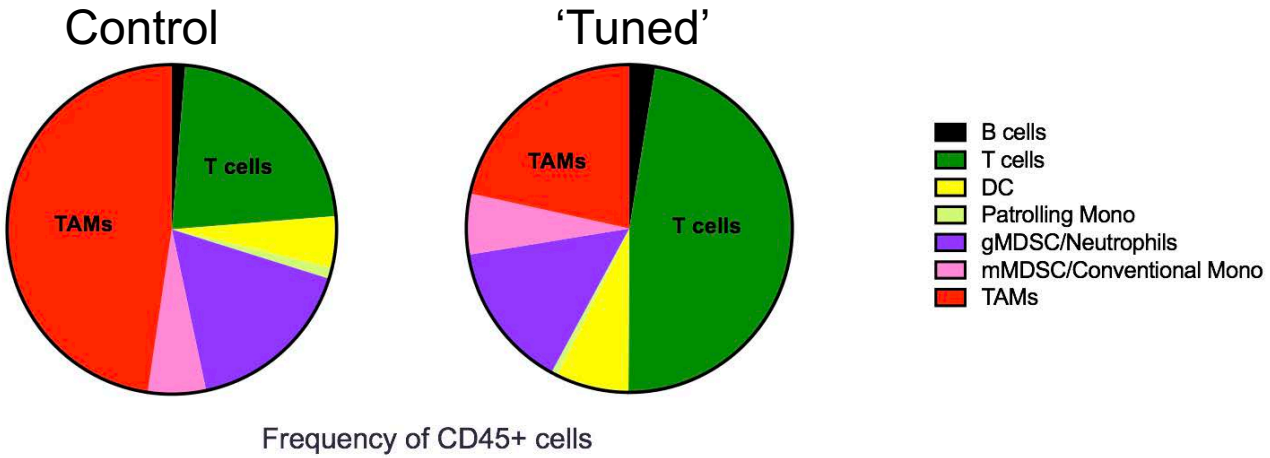


HNSC

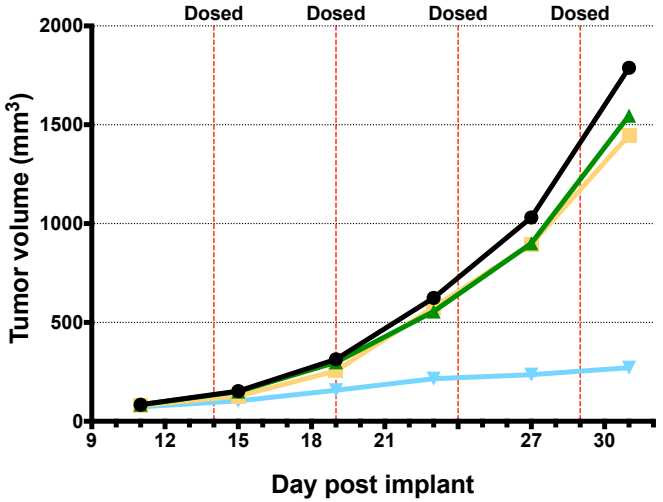
What to do for the Non-responders?



The Next Generation of Cures: Modulate the Biology of Type II Patients…



Frequency of CD45+ cells



Control
Checkpoint Blockade
'Tuned'
'Tuned'+Checkpoint Blockade

PIONYR IMMUNOTHERAPEUTICS

UCSF

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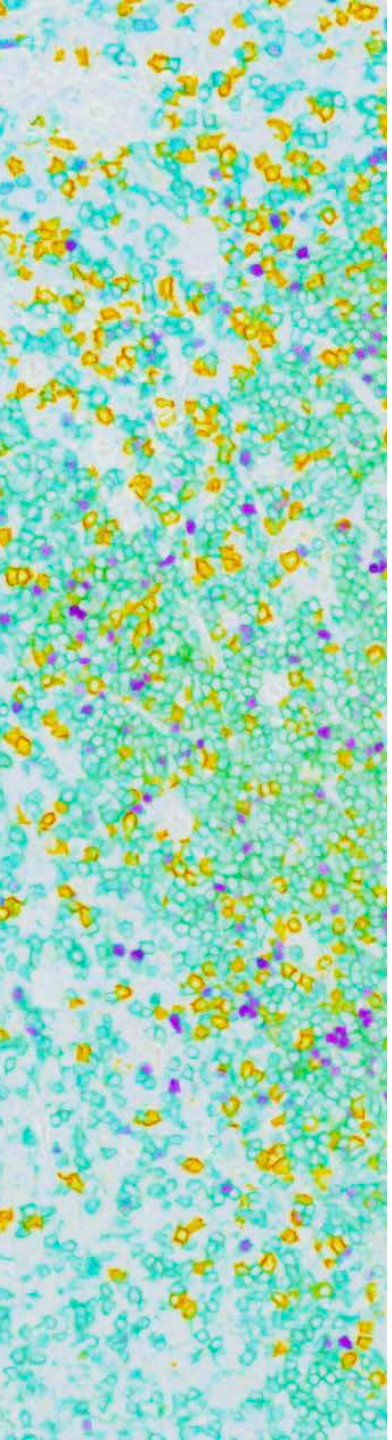
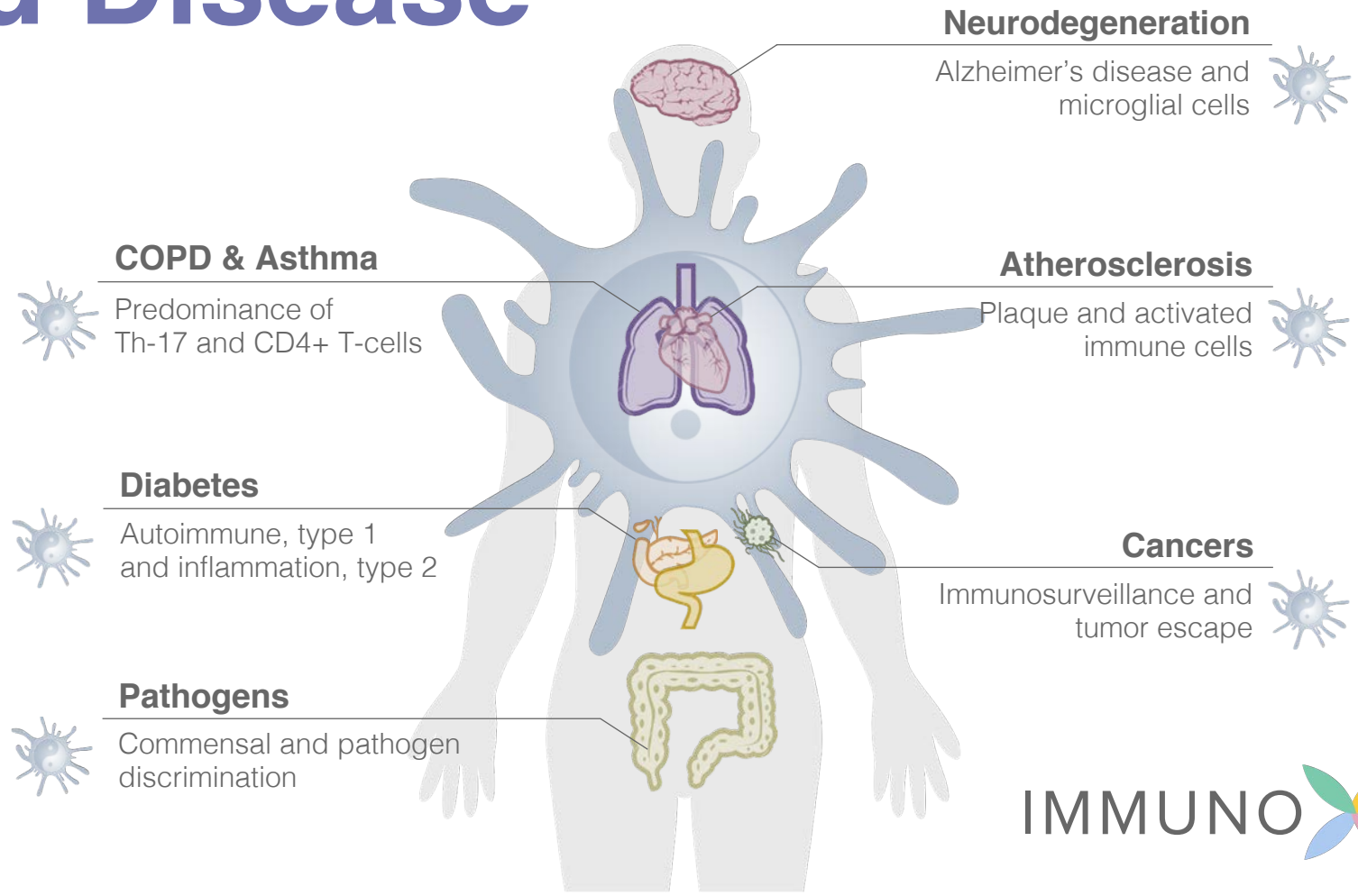


The Immune System and Disease



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