BARCELONA 2024 ESMO congress

SPECIAL SYMPOSIUM:

TARGETING INNATE IMMUNE SIGNALLING PATHWAYS

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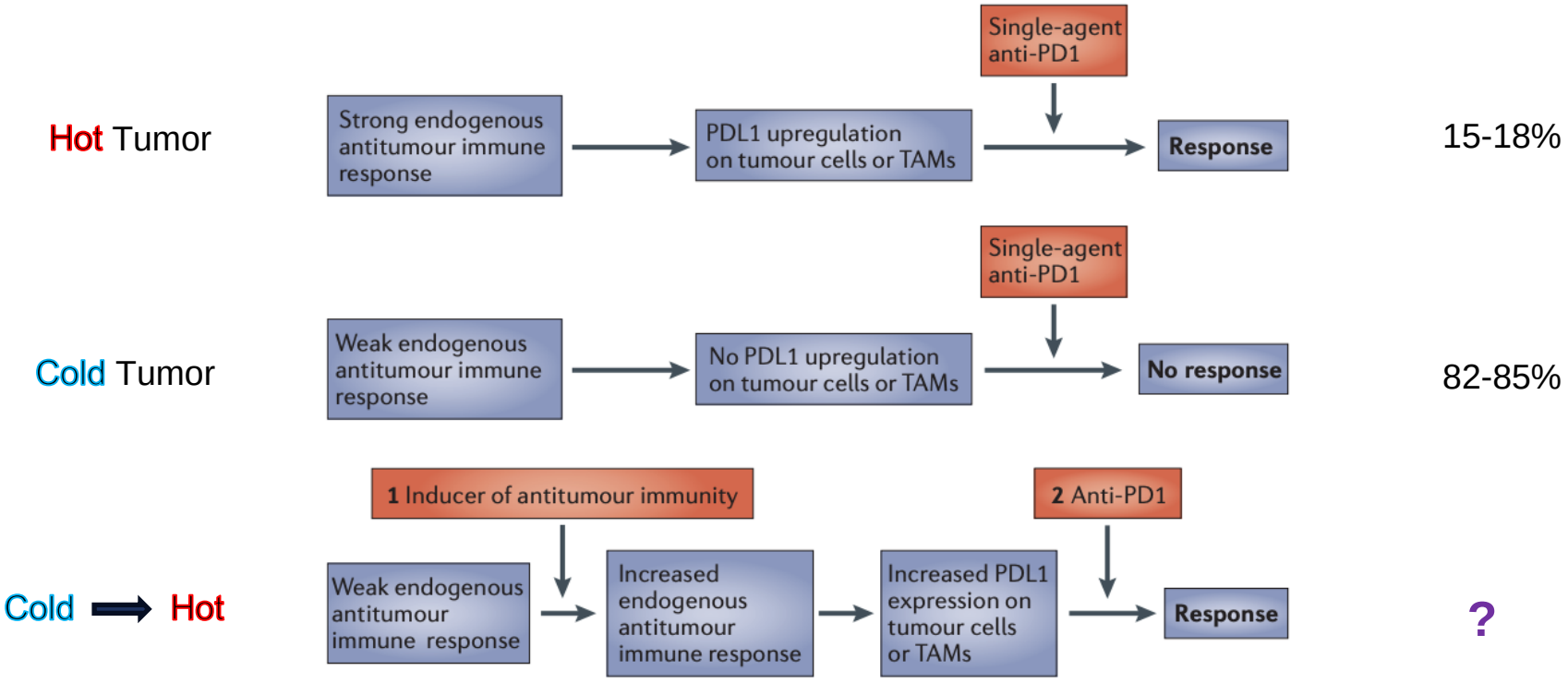
DECLARATION OF INTERESTS

Sara Pai:

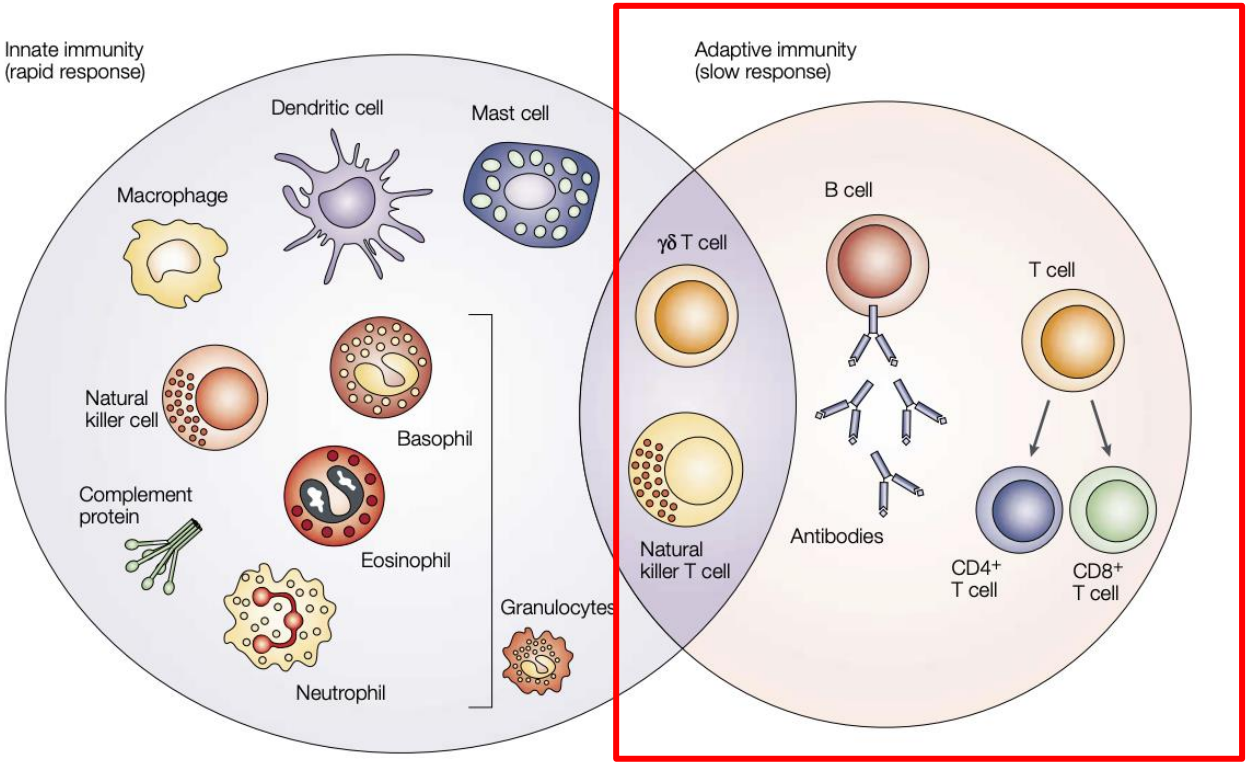
Consultant:	Abbvie, AstraZeneca, Cue Biopharma, G1 Therapeutics, Incendia, Inovio Pharmaceuticals, Merck Sharp & Dohme LLC, Oncolys, Recurrent Respiratory Papillomatosis Foundation, Replimmune, Sensei Bio, Scopus Biopharma
Grant/Research:	Abbvie, AstraZeneca, Cue Biopharma, Sensei, Tesaro
Educational Talks:	Merck Sharp & Dohme LLC
Investigator-Initiated Clinical Trials:	ASTX Pharmaceuticals, AstraZeneca, Cue Biopharma, Eisai, Immune Design, Merck Sharp & Dohme LLC
Editorial Roles:	Senior Editor, *Cancer Research*
Travel Support:	Chan-Zuckerberg Institute, Merck Serono, Recurrent Respiratory Papillomatosis Foundation

Concept of Combinatorial Immunotherapy with ICB



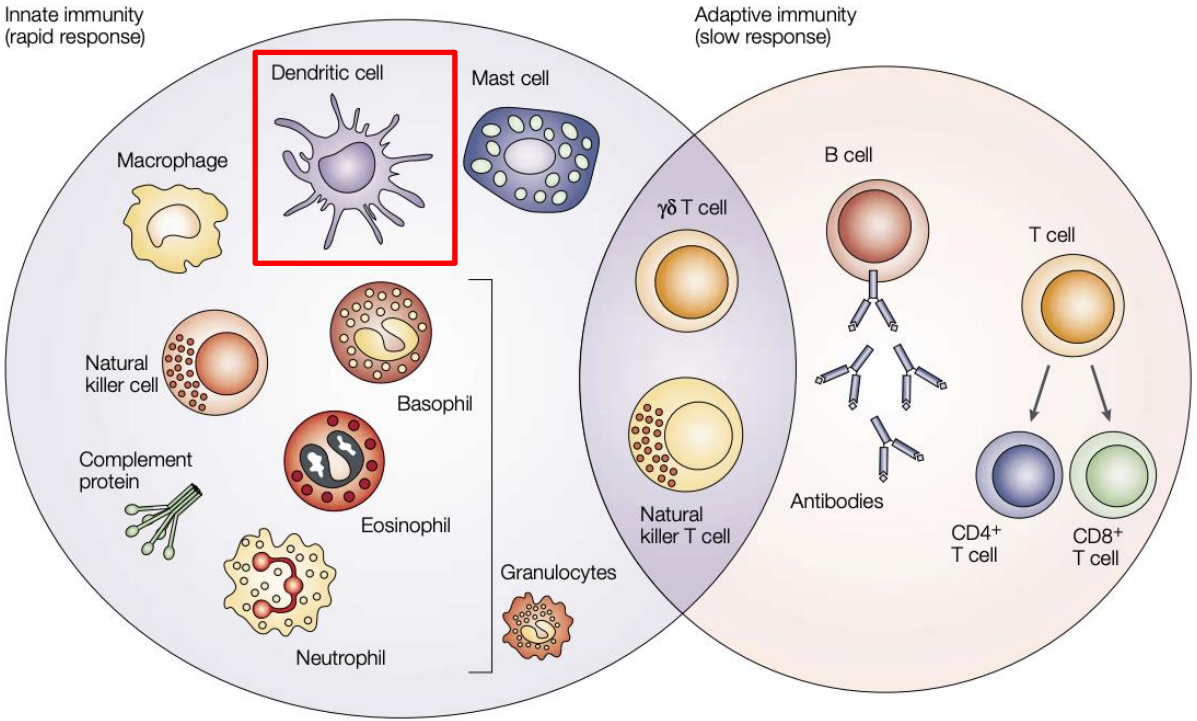
Pardoll DM. *Nature Reviews* April 2012

Innate and Adaptive Immune Response



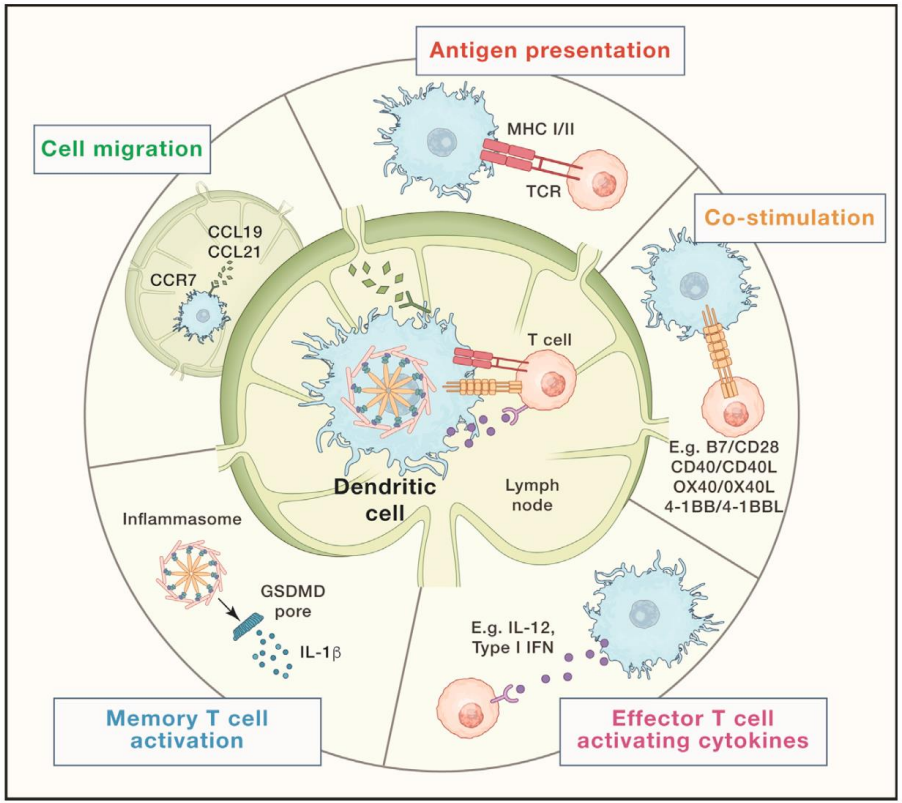
Dranoff G. *Nature Reviews* Jan 2004

Innate and Adaptive Immune Response



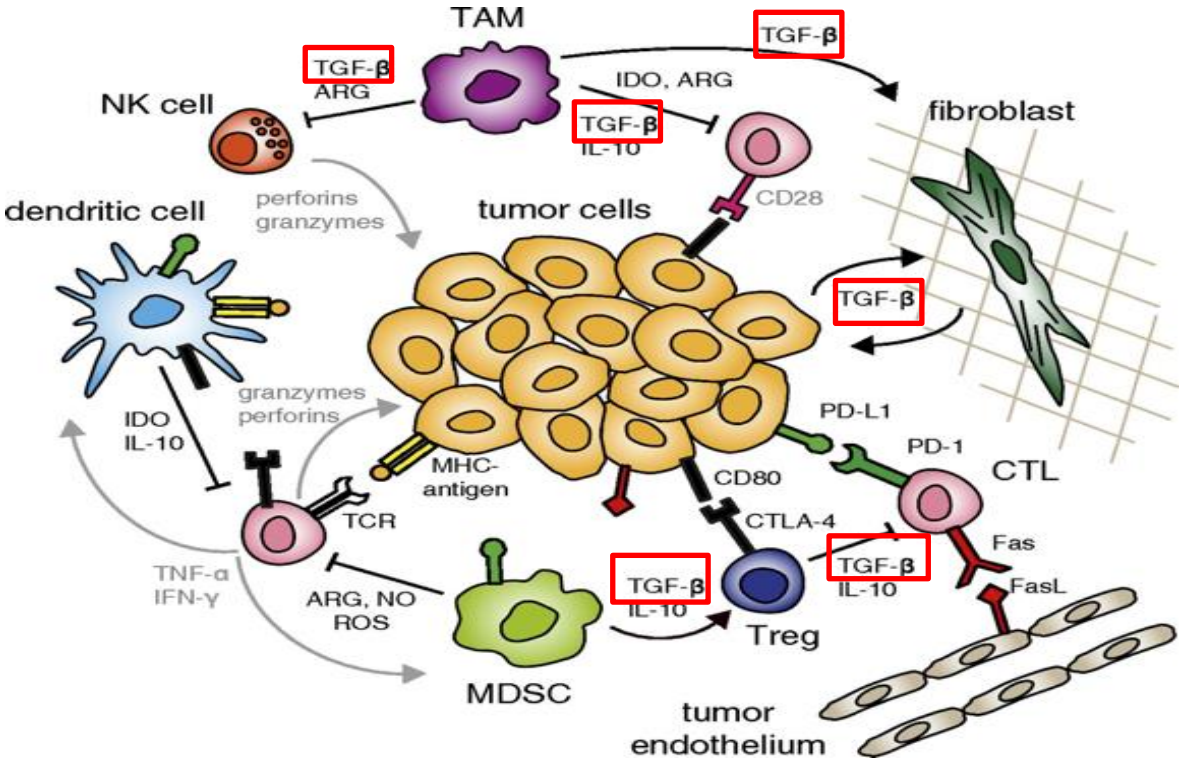
Dranoff G. *Nature Reviews* Jan 2004

Five key activities in DCs needed to stimulate T cells



Cao LL and Kagan JC. *Immunity* Oct 2023

Complex Tumor Microenvironment



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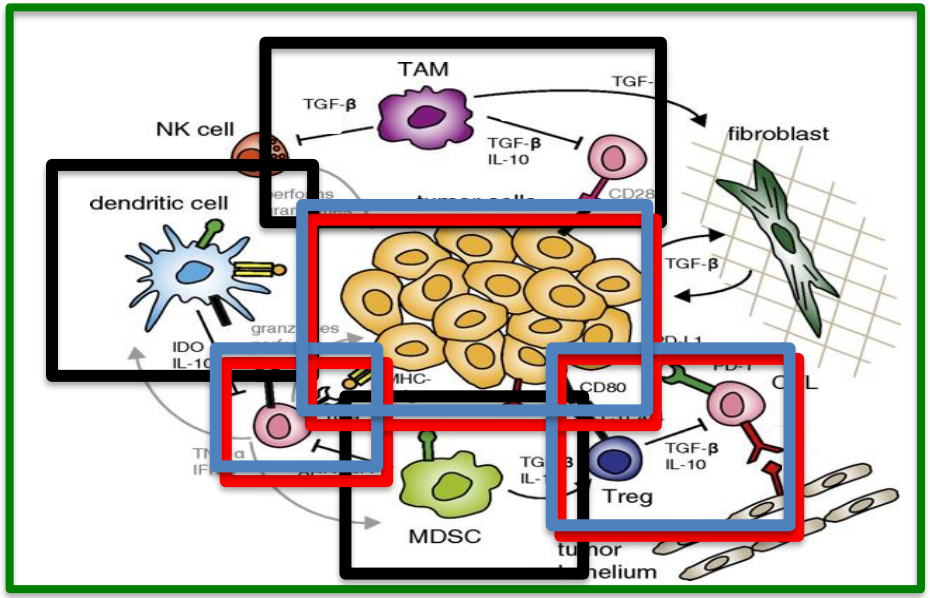
Developing Combinatorial Strategies to Overcome Immune Resistance in Head and Neck Squamous Cell Carcinoma (NIH P01CA240239)



Specific Aim 1: Uncover both intrinsic and extrinsic mechanisms of immune resistance in HNSCC patients

Specific Aim 2: Develop rationale, novel combinatorial strategies that translate into clinically meaningful responses

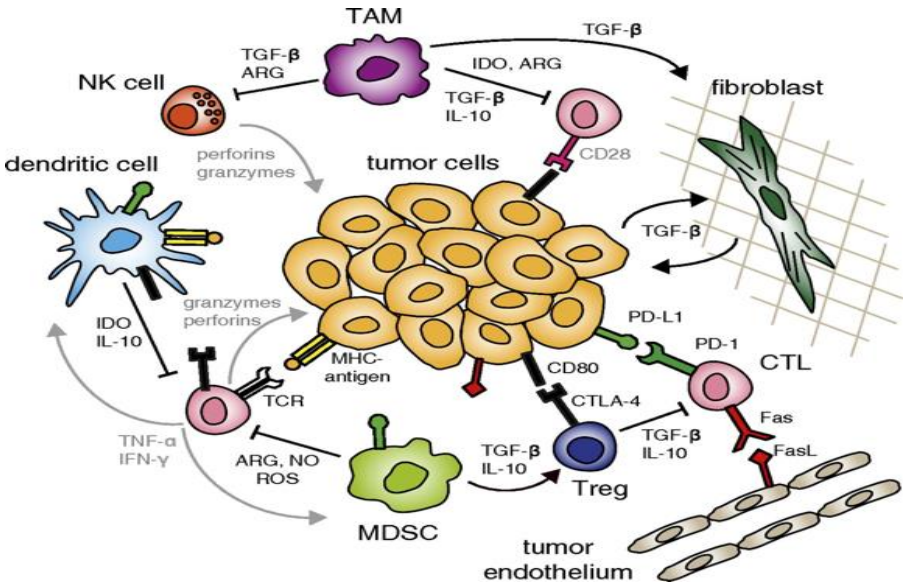
Project 1: Improving antigenicity through epigenetic reprogramming (Pai)

Project 2: Redirecting pre-existing anti-viral immunity to HNSCCs with APECs (Mempel)

Project 3: Myeloid-lymphoid cell crosstalk in HNSCC therapy (Pittet)

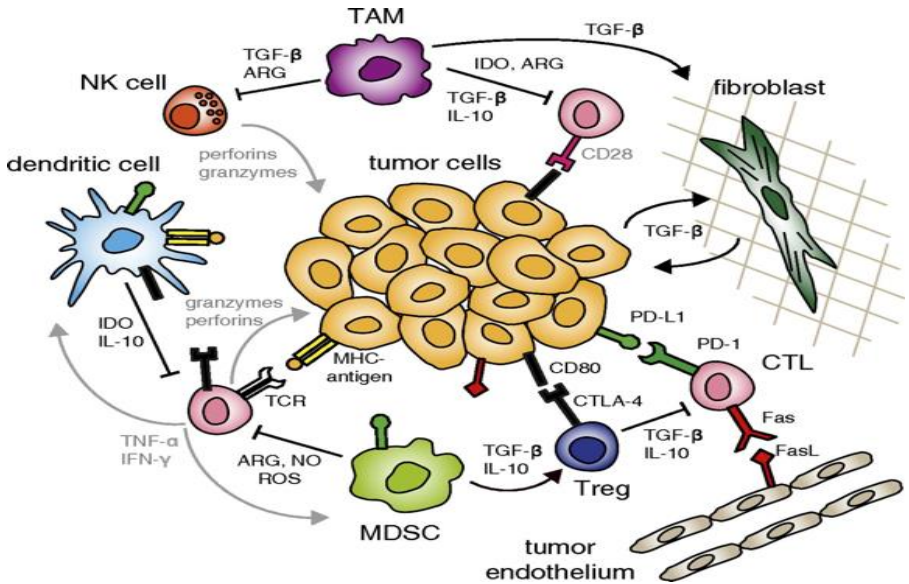
ESMO 2024 867MO

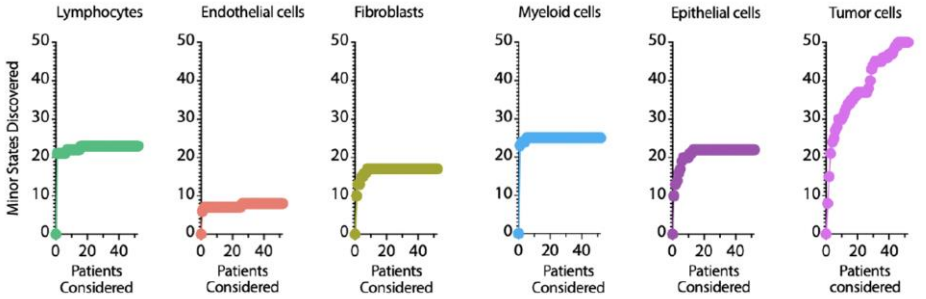
Despite a Complex Tumor Microenvironment…



Bill R et al. *Science* Aug 2023

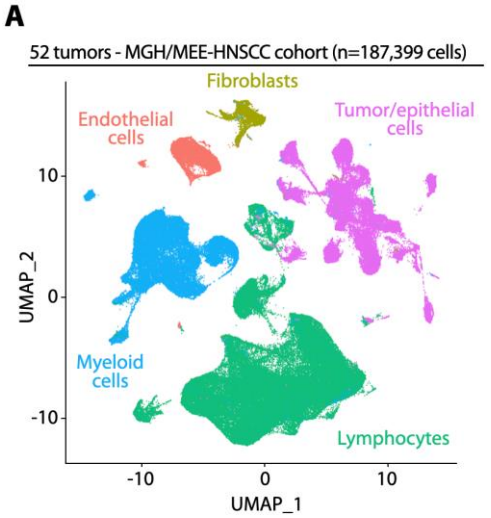
Our Immune System is Uniform Across Individuals

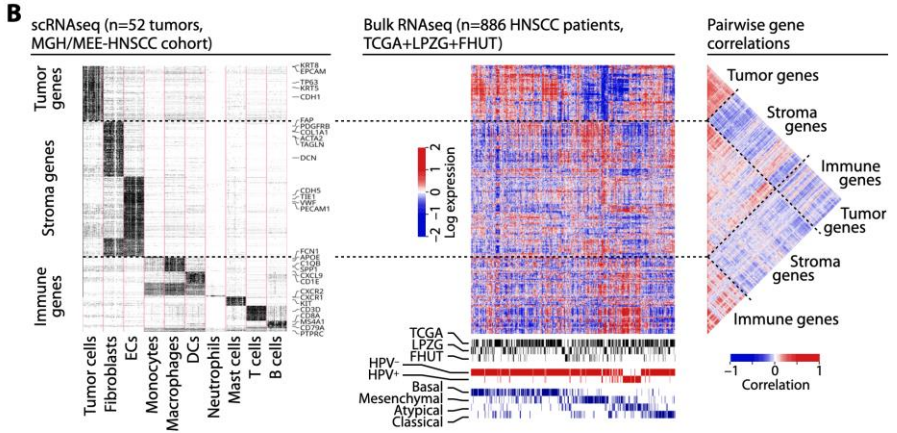




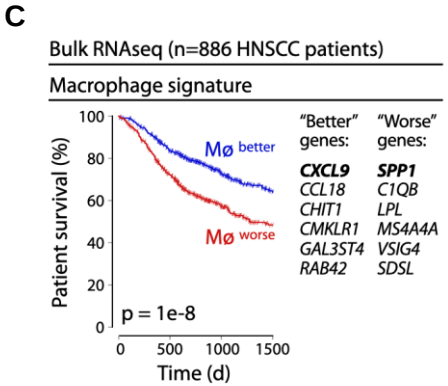
Bill R et al. *Science* Aug 2023

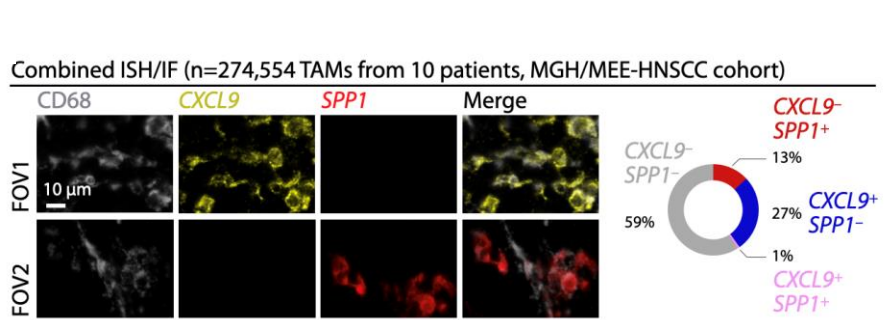
CXCL9:SPP1 polarity of TAMs is a major contributor to the clinical outcome of HNSCCs





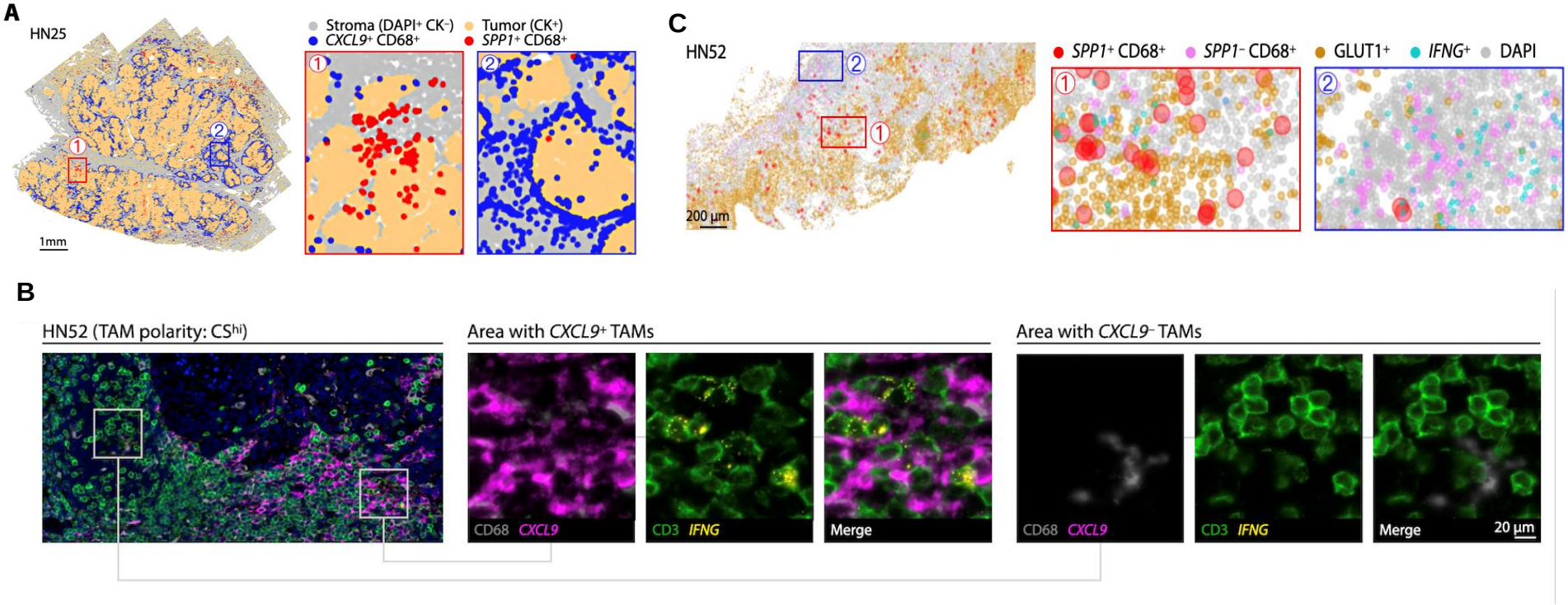
Genes with a fold-change > 3 relative to the next cell type identified for each major cell type.





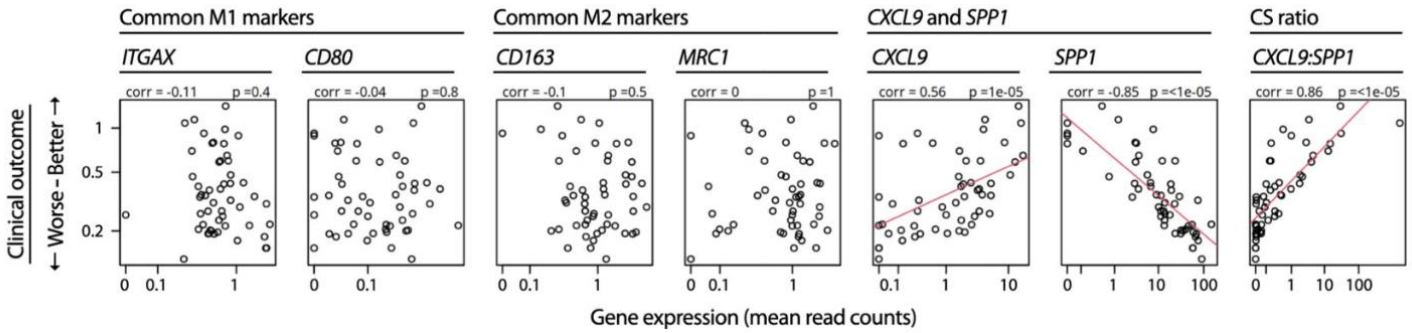
Bill R et al, *Science*, Aug 2023

IFN-g Increases CXCL9+ TAM whereas Hypoxia Increases SPP1+ TAM Polarity

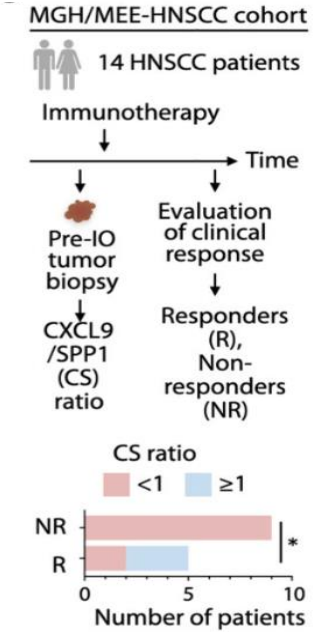


Bill R et al. *Science* Aug 2023

CXCL9/SPP1 (C/S) Ratio is a Better Biomarker of Clinical Outcome than M1/M2 Markers

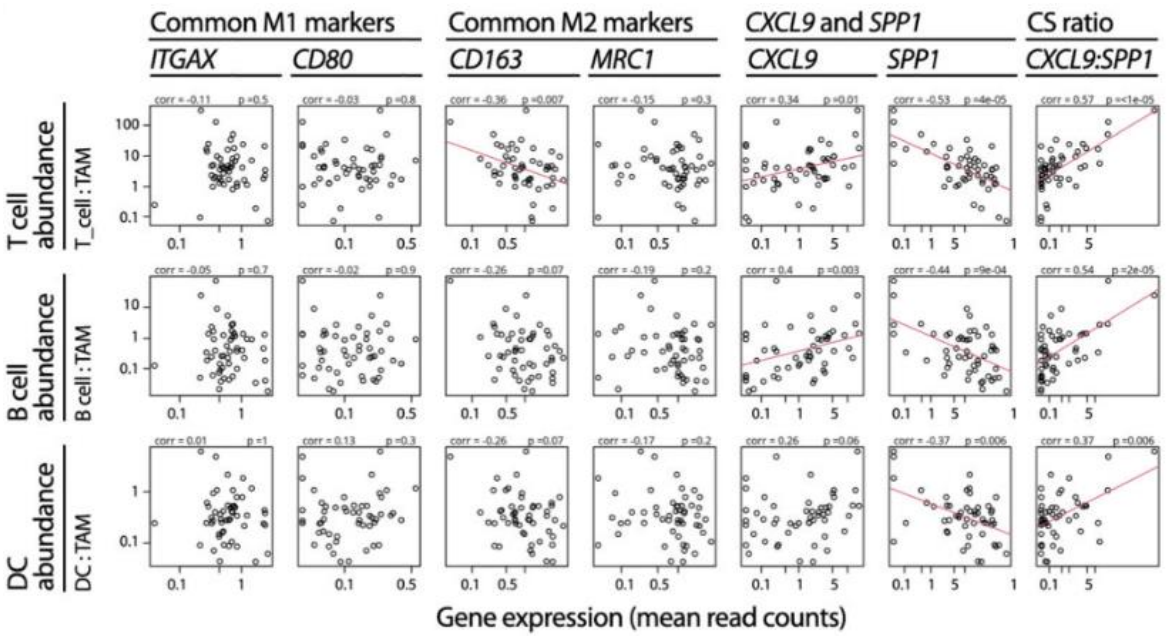


Scatter plots show lack of correlations between the common M1/M2 markers



Bill R et al. *Science* Aug 2023

CXCL9:SPP1 Tumor-associated Macrophage Polarity Determines the Broader TME



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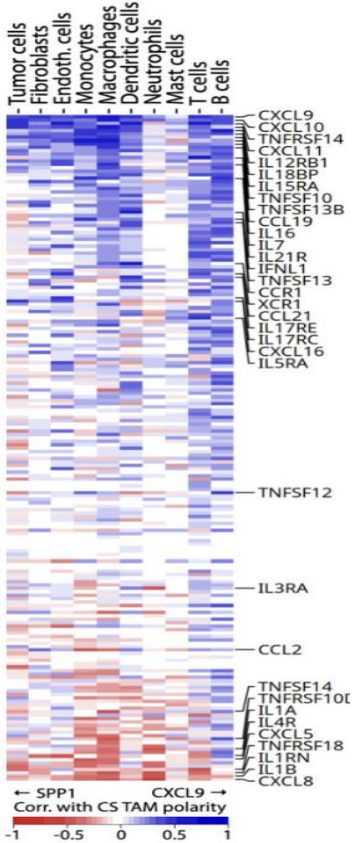
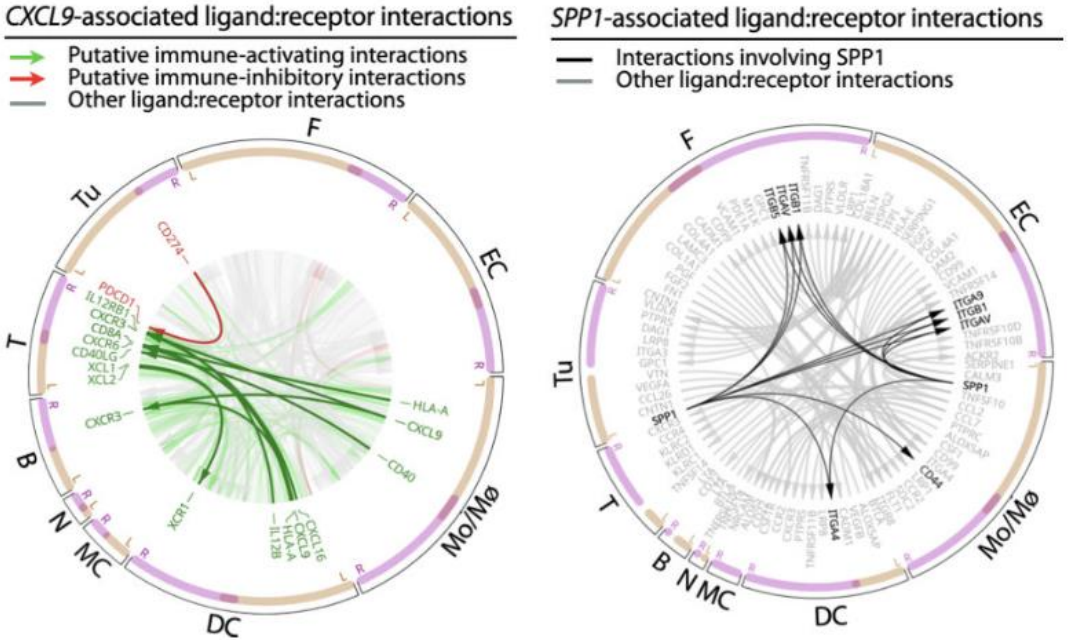
Cytokines and Ligand:Receptor Pairs associated with CXCL9:SPP1 Tumor-associated Macrophage Polarity



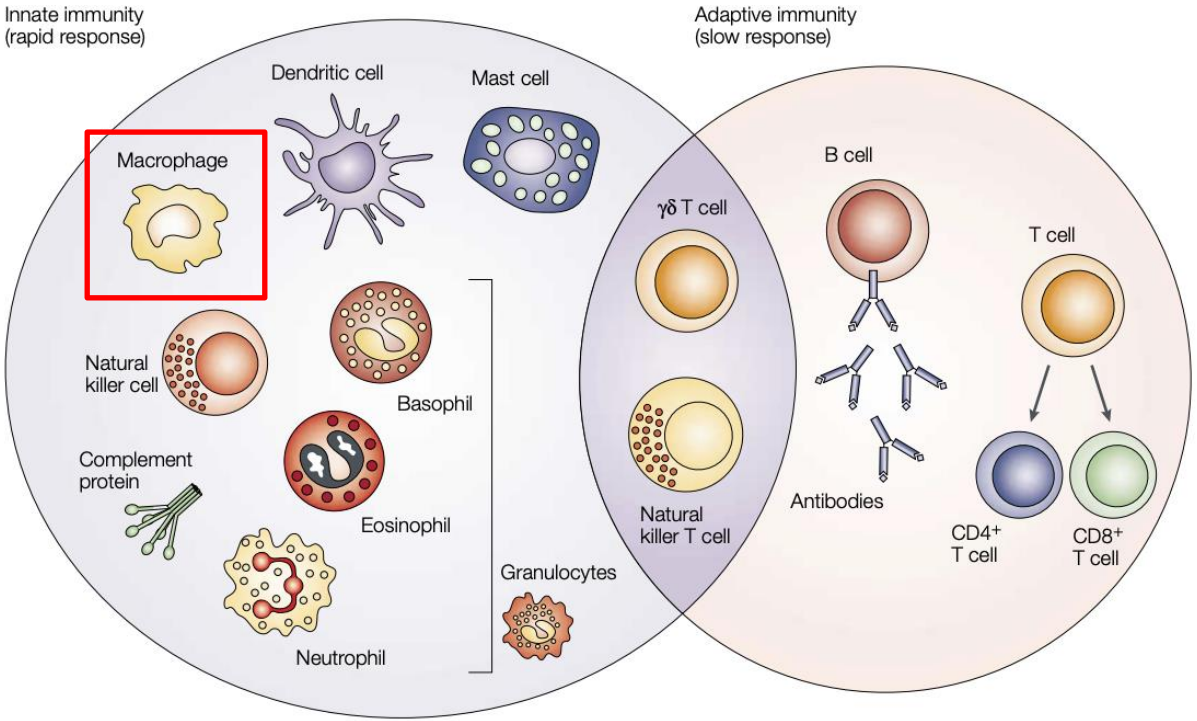
Circos Plots



Bill R et al. *Science* Aug 2023

Innate and Adaptive Immune Response Programs

CXCL9/SPP1 (C/S) Tumor-associated Macrophages



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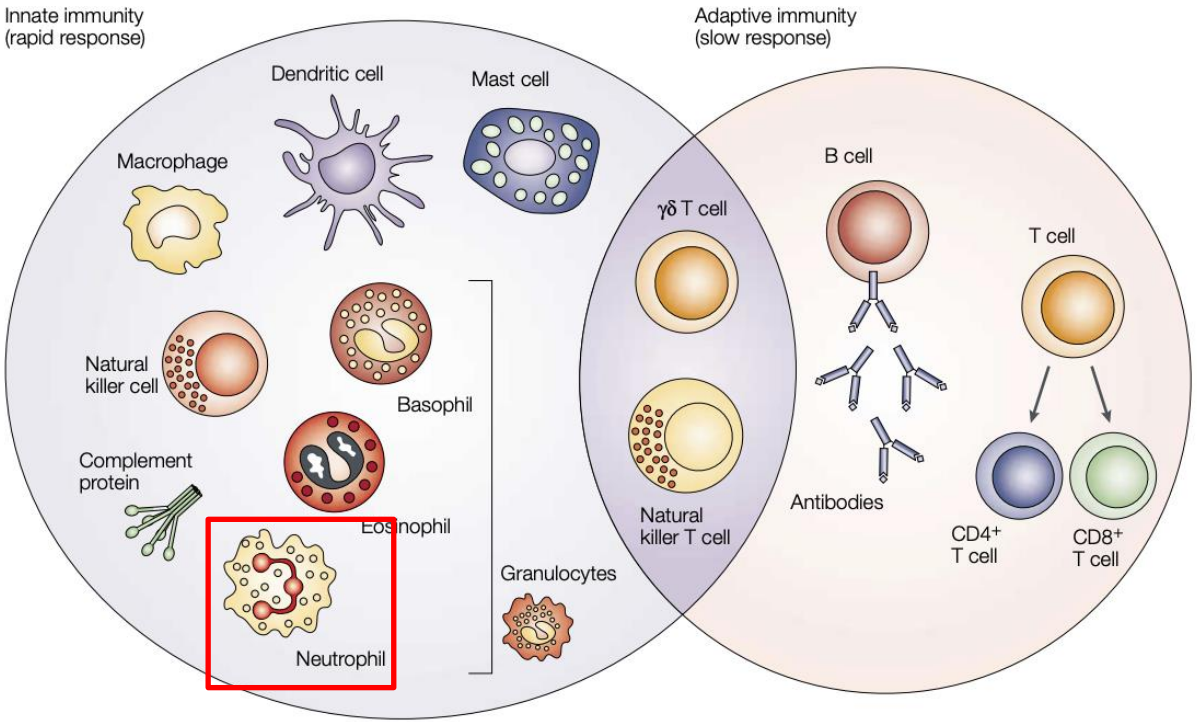
Innate and Adaptive Immune Response



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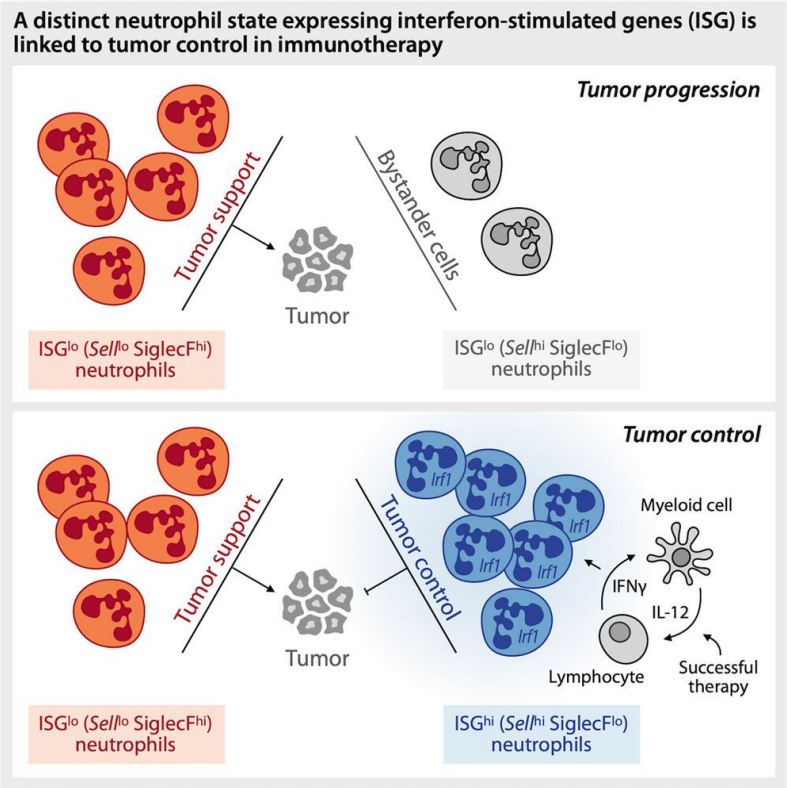
Distinct Neutrophil States Exist



- Neutrophils can accumulate in tumors during successful immunotherapy
- Immunotherapy expands a distinct neutrophil state with an IFN-stimulated gene signature
- The neutrophil response requires IFN-g and IL-12 from BATF3-dependent DCs
- ISG^{hi} ($Sell^{hi}$ $SiglecF^{lo}$) neutrophil response is associated with better outcomes

Gungabeesoon et al, *Cell* March 2023 186:1448-1464

Conclusions

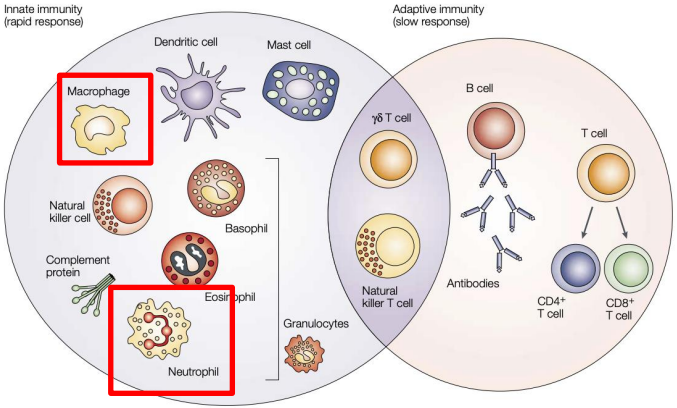
Innate immunity is the first line of defense against infection and/or cancer and can be harnessed to support adaptive immune responses.

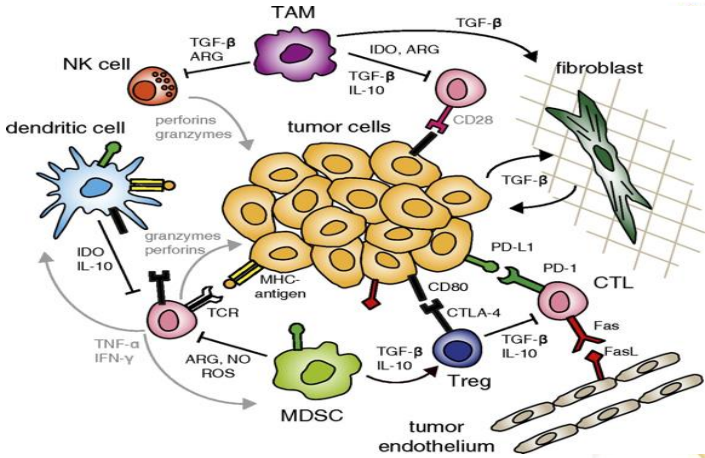
Cells of the innate immune system are abundant yet complex with multiple molecular identities.

Targeting single molecule(s) within the innate signaling pathway(s) may be met with limited success based on the intricate soluble and cellular interactions within the tumor microenvironment.

Unveiling relevant innate immune programs may yield successful future targets.

CXCL9/SPP1 TAM polarity is associated with improved clinical outcomes and response to immunotherapy





National Institute of Health/National Cancer Institute
Head and Neck Cancer Program Project Grant (P01 CA240239)

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Director, Head and Neck Pathology, Massachusetts Eye and Ear

Thorsten Mempel, M.D., Ph.D

Associate Director, Center for Immunology and Inflammatory Dis

Cellular immunology; T cell repertoire; Tregs; chemokines

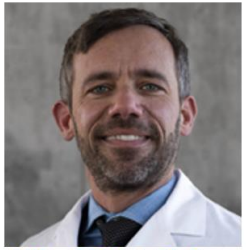
Sara Pai, M.D., Ph.D.

Director, Translational Head & Neck Cancer Research

Cancer vaccines, HPV, head and neck cancer

Benjamin Judson, M.D., M.B.A.

Chief, Otolaryngology-Head and Neck Surgery, Head and Neck Cancer



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Cancer immunotherapy, lymphocyte and myeloid cell biology

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David Rimm, M.D., Ph.D.

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