2007

International Society for Biological Therapy of Cancer

Cytotoxic Chemotherapy

and

Immunotherapy

Workshop

Cytotoxic Chemotherapy and Immunotherapy

Underlying Concept:

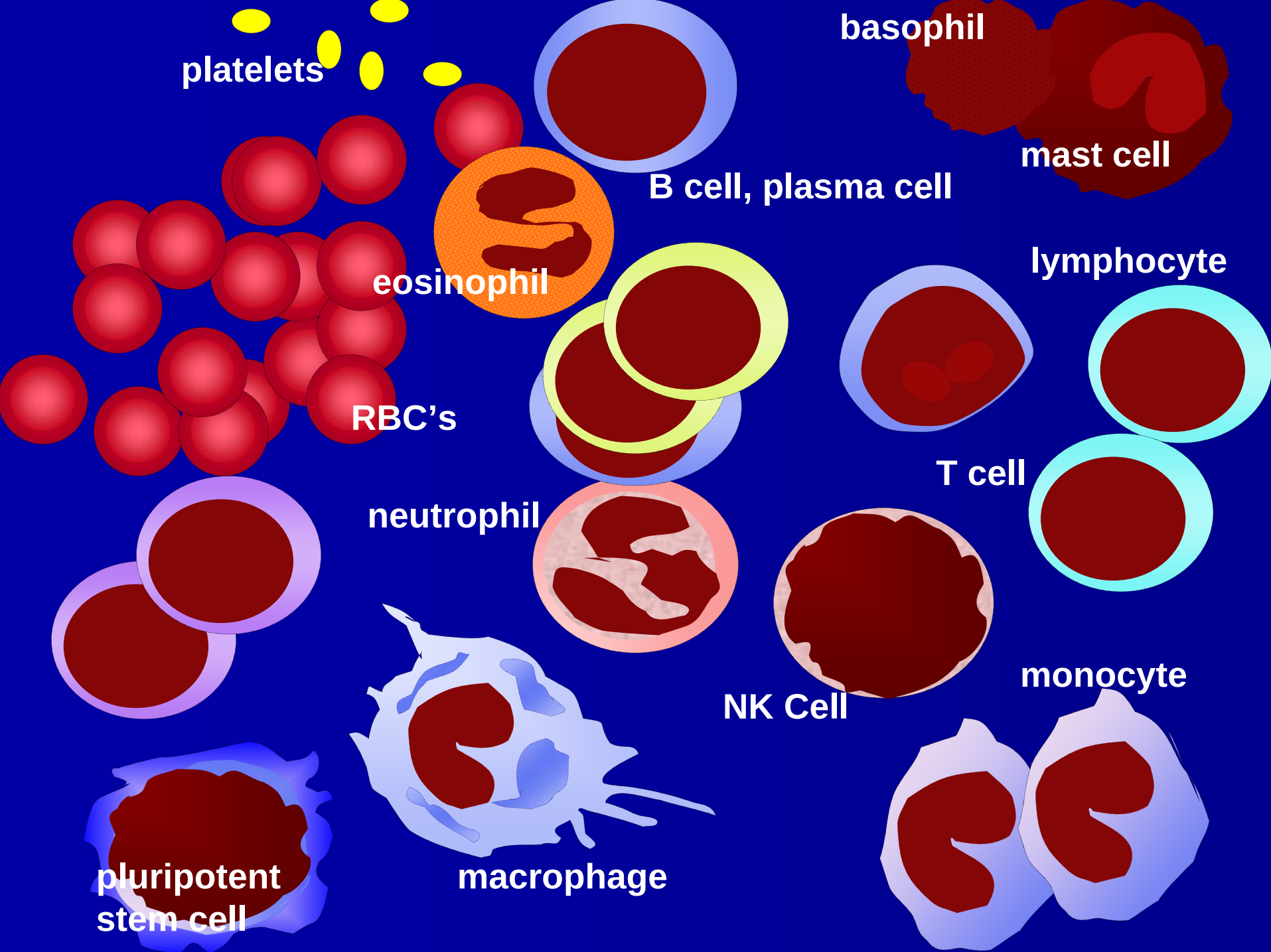
If we can understand the relevant biology, then we can control and direct immune responses with therapeutic intent.

Cytotoxic Chemotherapy

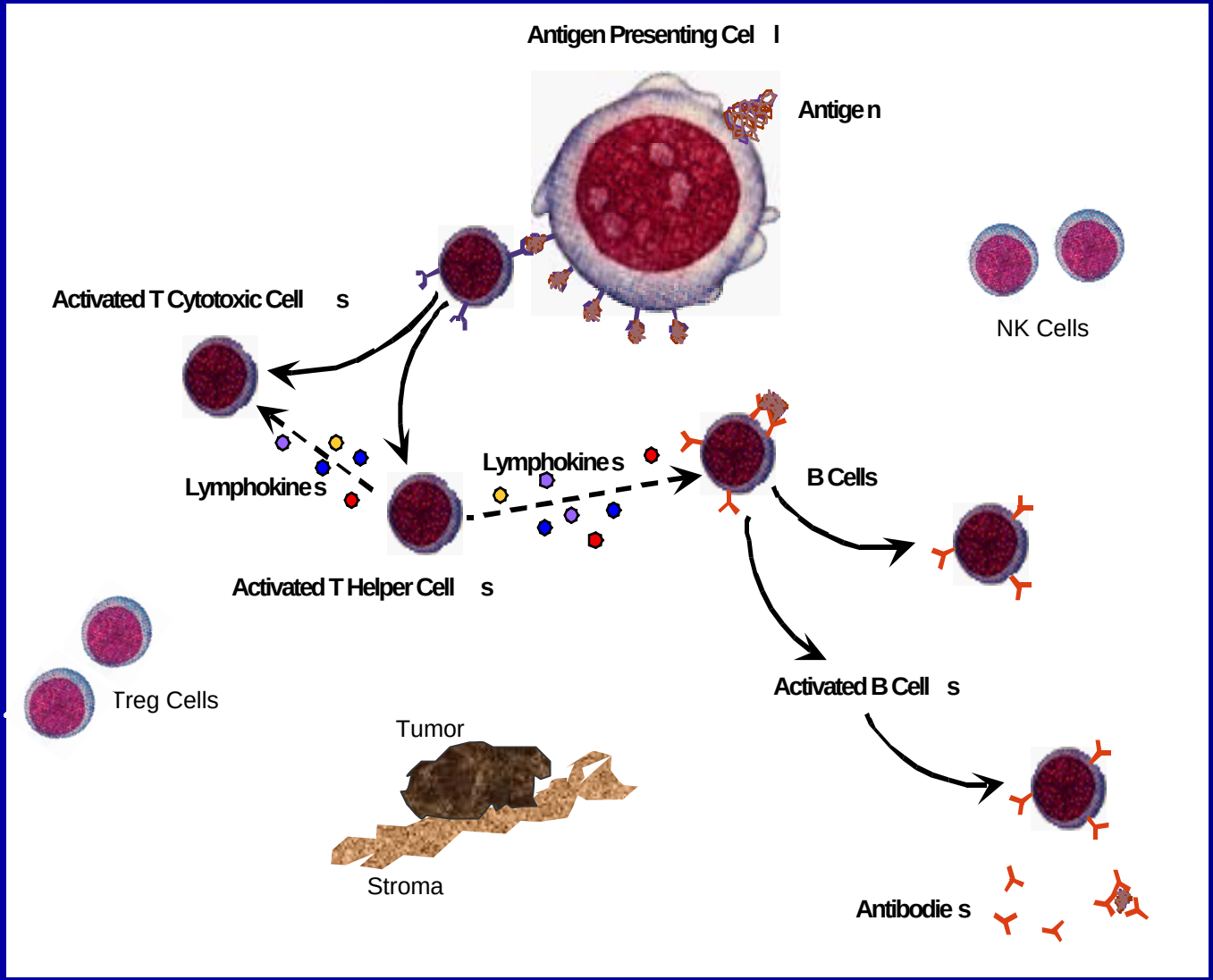
- Differential effects by agent
- "Targeted" therapeutics

Immunotherapy

- Adoptive
- Active
- Combinations


platelets
basophil
mast cell
B cell, plasma cell
eosinophil
lymphocyte
RBC's
T cell
neutrophil
NK Cell
monocyte
pluripotent stem cell
macrophage

Cellular Responses



Cytotoxic Chemotherapy

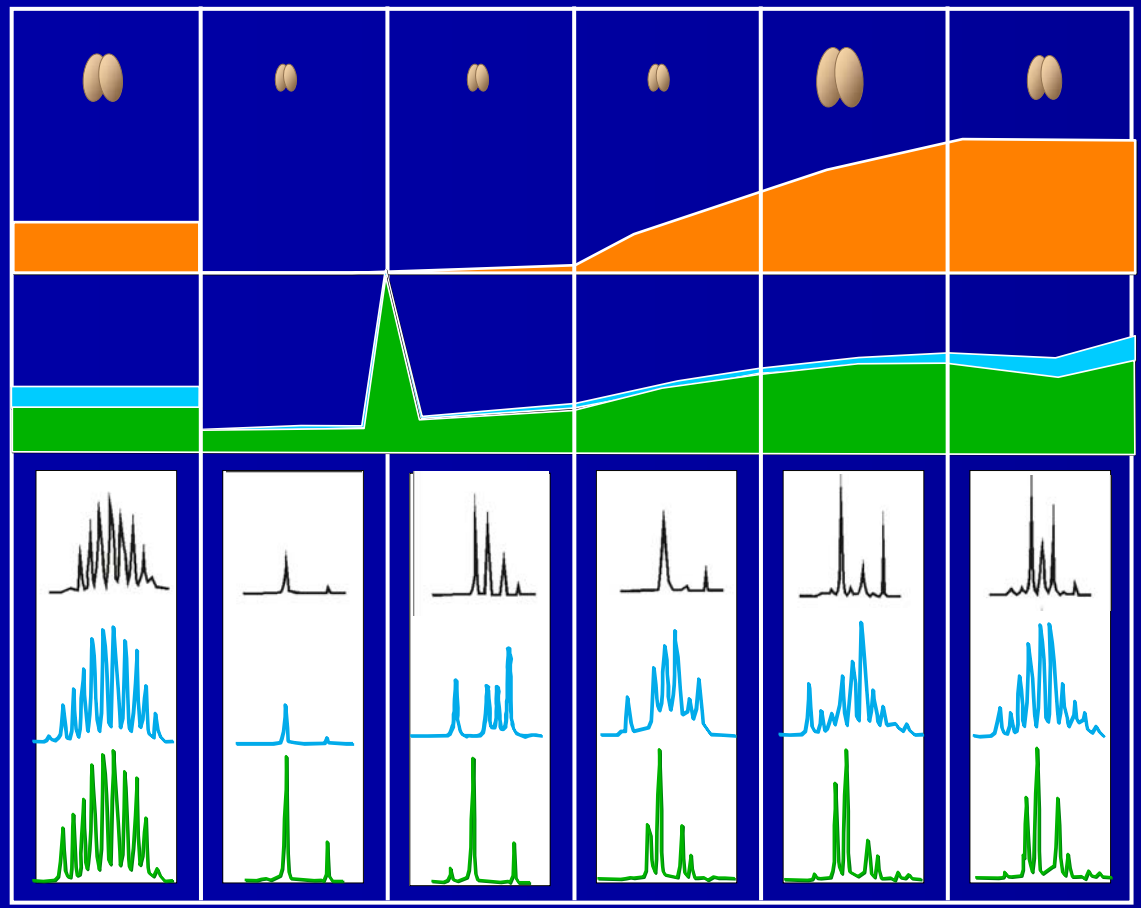
- Lymphoid depletion
- Myelosuppression
- Tissue damage/ breach of membrane integrity
- Damage to lymphoid organs
- Impact on vasculature

Cytotoxic Chemotherapy and Lymphoid Depletion

I. Effector cells

- Differential impact on naïve vs. memory vs. effector populations
- Effect of starting precursor frequency
- Changes in killing capacity, trafficking
- Alterations in cytokine profiles
- Impact of repeated administration: what is optimal frequency and sequence

CD8$^+$ T Cell Depletion and Reconstitution



THYMIC SIZE

TREC

CD8 CELLS
Memory+Activated
Naive

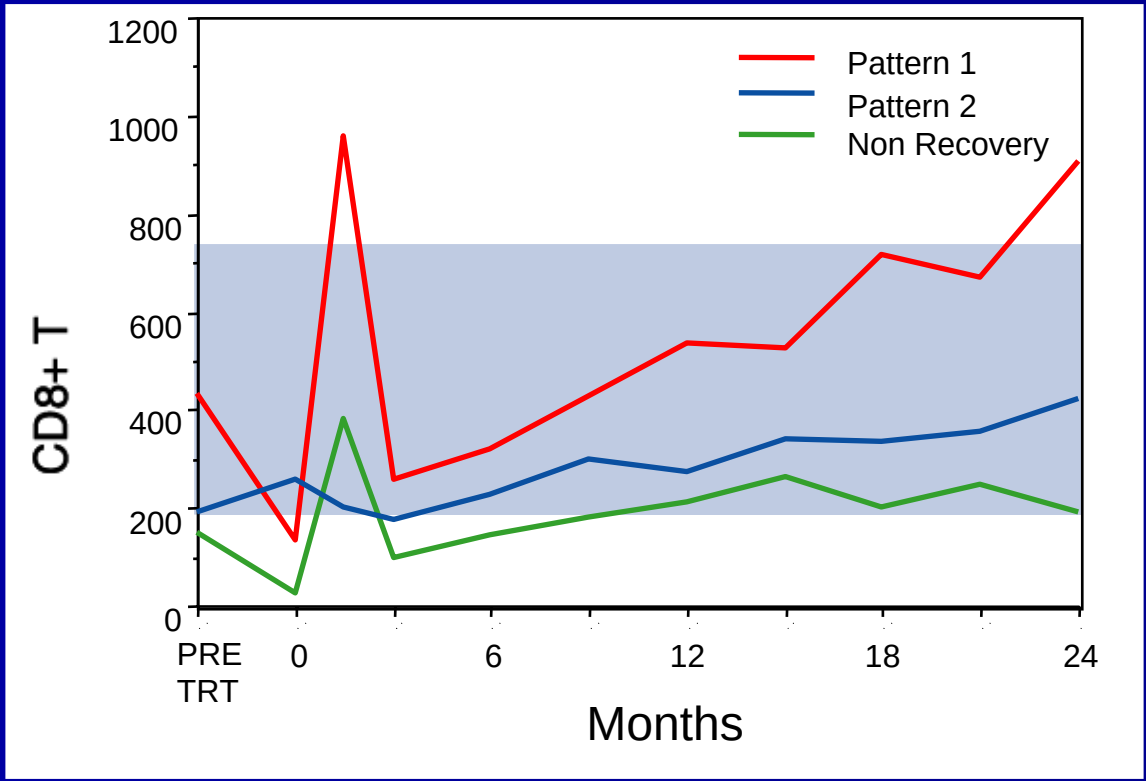
Total

Naive

Activated

Vβ TCR CDR3 Diversity

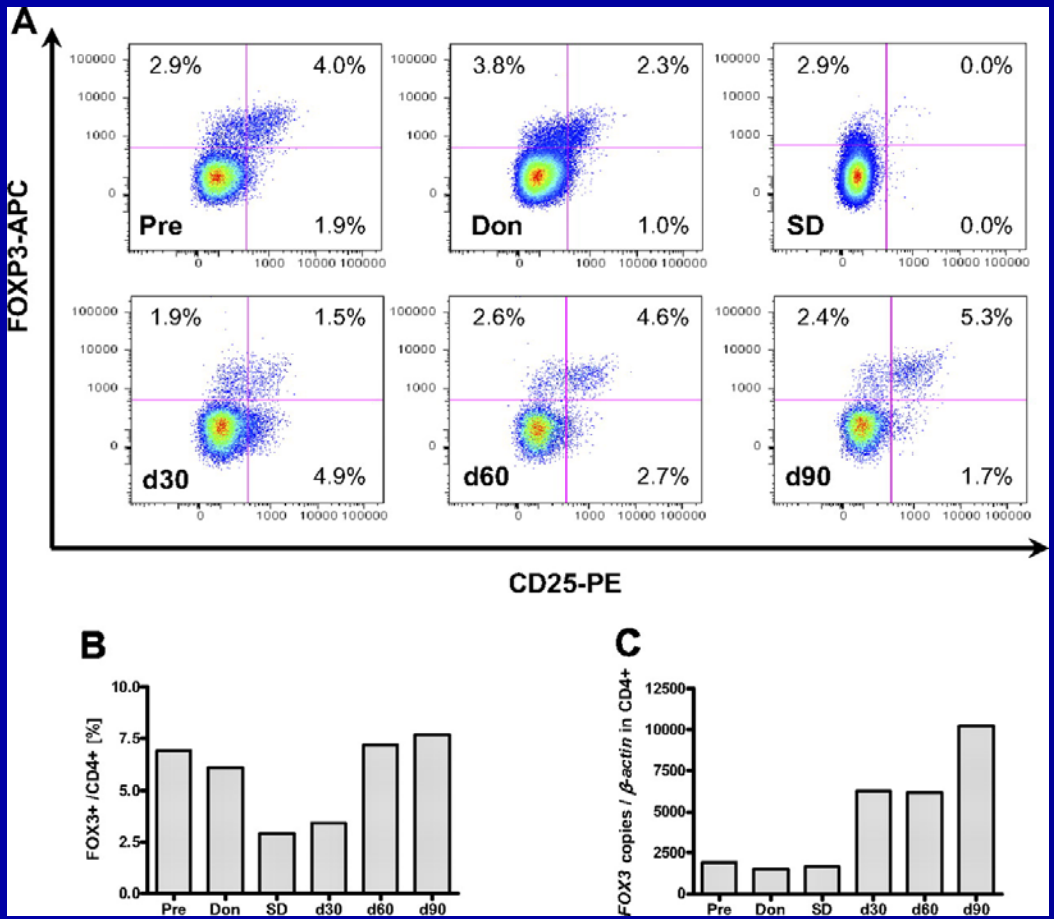
CD8 Recovery Post Chemotherapy Has Two Patterns



1. **Early expansion**
2. **Thymic production of naïve cells**
3. **Neither**

Cytotoxic Chemotherapy and Immunotherapy

II. T Regulatory Cells



Don = Donor
SD = CD25-depleted lymphocyte product

Percentages displayed represent the fraction of positive cells in CD4+ cells.

(B) Total fraction of FOXP3+ cells in CD4+ cells.

(C) Foxp3 mRNA expression in CD4-selected cells expressed

Mielke, S. et al. Blood 110:1689-1697, 2007.

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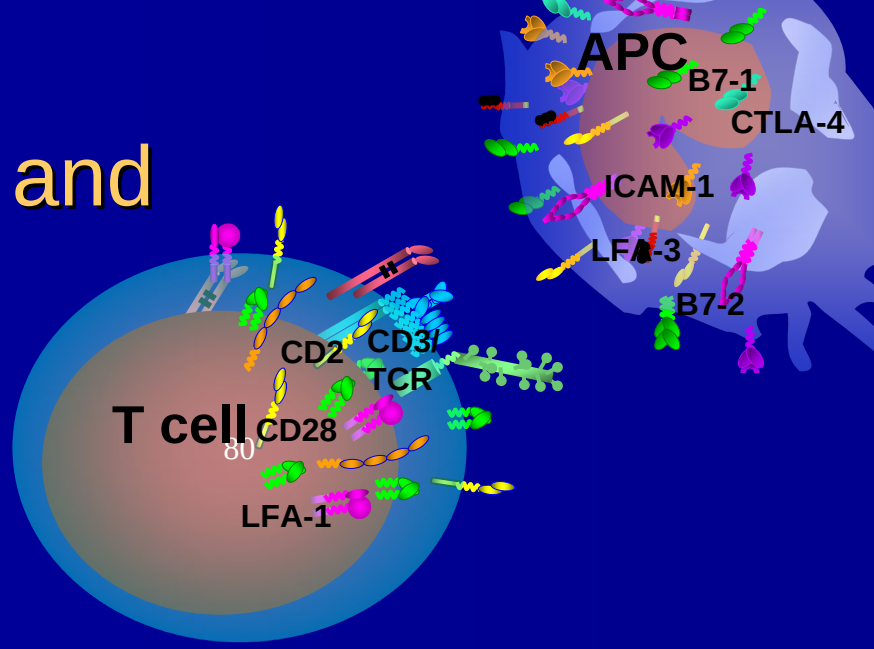


Antigen presentation

- Direct cytotoxic effects of chemotherapy
- APC repopulation
- APC activation
- Implications for timing of immunotherapy active and adaptive
- As a strategy in immunotherapy

Cytotoxic Chemotherapy and Immunotherapy

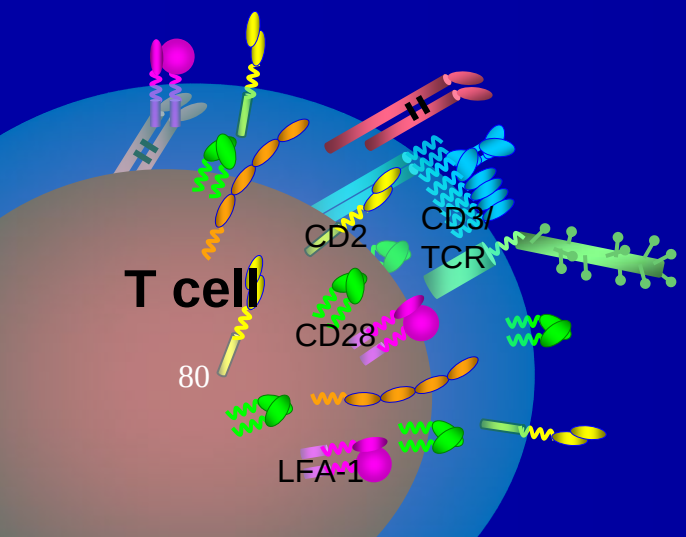
Tumor microenvironment

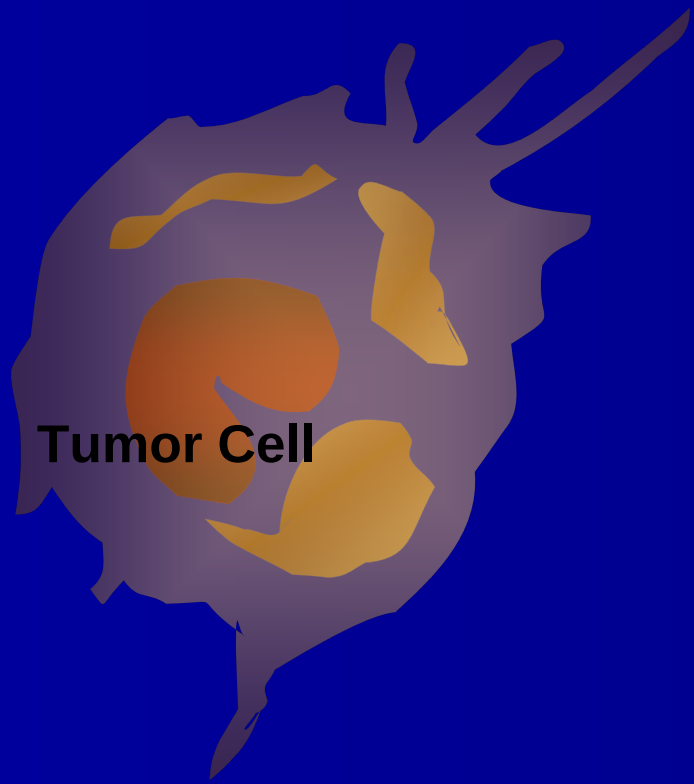
- Approaches to study
- How is the stroma repopulated by infiltrating cells
- Role in access by effector cells

Cytotoxic Chemotherapy and Immunotherapy

Effects on Tumor

- Antigen expression and liberation
- Tolerance





Cytotoxic Chemotherapy and Immunotherapy

Cellular Homeostasis

- Can lymphocyte count (or IL-7/ IL-15 levels) guide individualized therapy?
- Does it matter which drugs achieve lymphopenia?
- Does telomere shortening affect strategies?
- What is the therapeutic role of cytokines?

T Cell Homeostasis

I. T Cell Maintenance

II. T Cell Production (Regeneration)

Immunotherapy During T Cell Lymphopenia

I. Generation of T cell response in vivo

A. Tumor vaccines → issue of T cell production

II. Infusion of T cell populations derived ex vivo

A. Adoptive immunotherapy → issue of T cell maintenance

T Cell Maintenance: Role of Cytokines

Niche 1	Naïve $CD4^+$ T cells	**IL-7**
	Naïve $CD8^+$ T cells	
Niche 2	Central memory $CD8^+$ T cells	**IL-15**
	Activated $CD8^+$ T cells	
	Memory CD4+ T cells	**Unknown**

Global Questions in Immunotherapy

For both vaccines and adoptive therapy:

- Sequence and timing probably matter
- How to integrate multiple cycles
- For each drug, distinct biological dose response curves regarding impact on host immunity.
- Need for indicies that can be measured in real-time to guide decisions regarding immunotherapy in the setting of chemotherapy.

Cytotoxic Chemotherapy and Immunotherapy

The Interface