



IO17 | Large Scale Bioinformatics for Immuno-Oncology

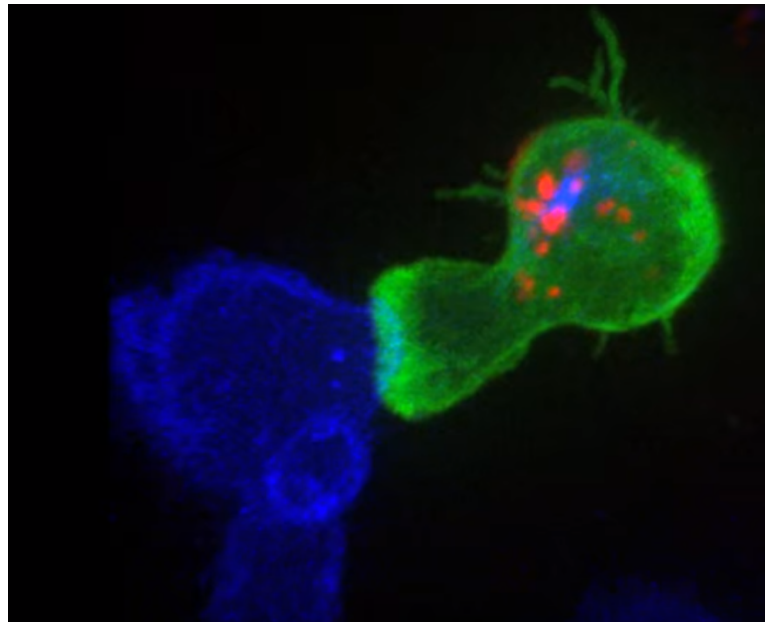
Introduction: Bioinformatics for Cancer Immunology and Immuno-Oncology

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Cancer immunology is a branch of immunology that studies the interactions between the immune system and cancer cells

The immune system can recognize and kill tumor cells!

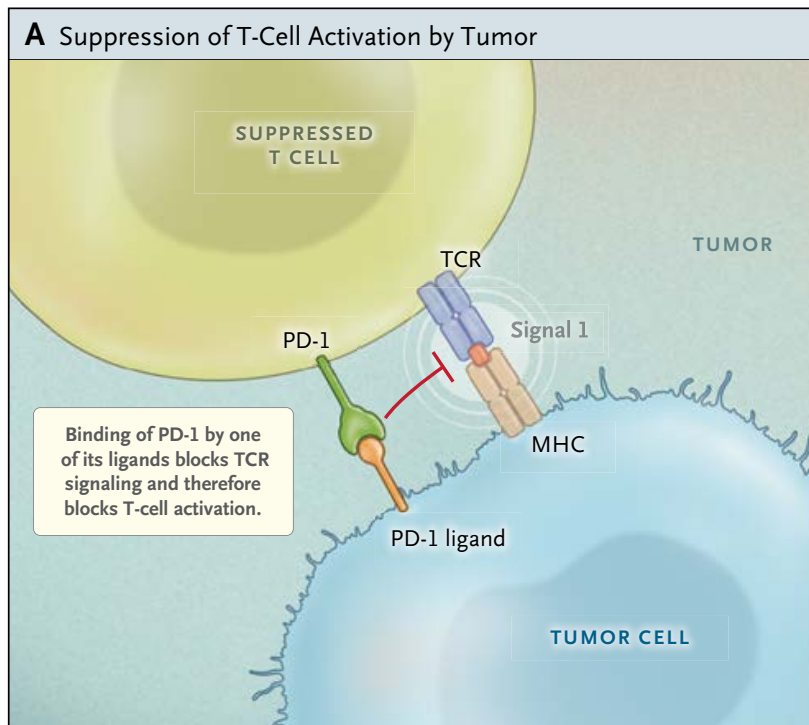


From the YouTube video “**Killer T Cell: The Cancer Assassin**” by Cambridge University
<https://www.youtube.com/watch?v=ntk8XsxVDi0>

Immune checkpoints: the brakes of the immune system

The major histocompatibility complex (**MHC**) molecules present on the surface of tumor cells can bind and display small peptides called **tumor antigens**

T-cell receptors (**TCR**) can recognize tumor antigens as „non-self“ and initiate an anticancer immune response



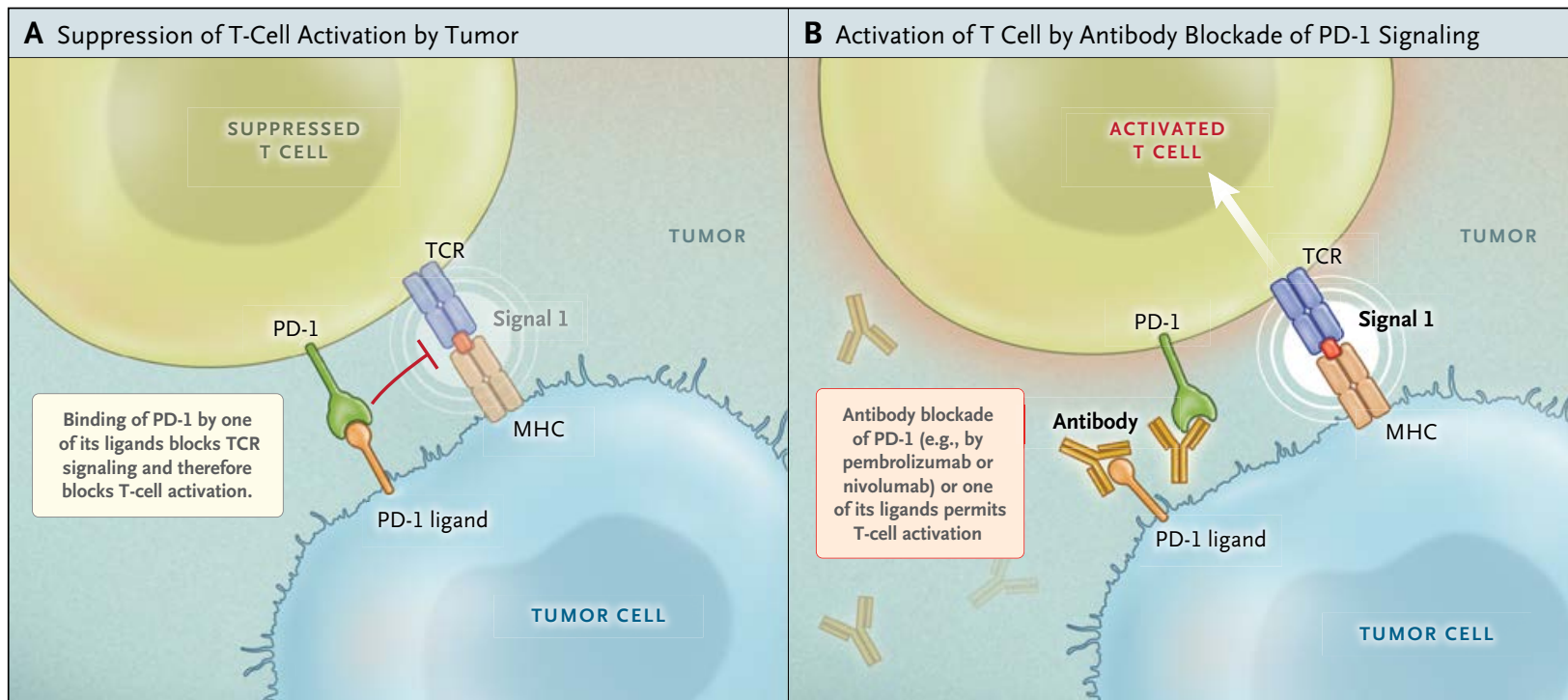
Immune checkpoints (like PD1, PDL1, CTLA4) are inhibitory molecules that modulate the amplitude and duration of immune responses

Tumor cells can exploit these molecules to send inhibitory signals to the immune system and suppress anticancer immune responses

Cancer immunotherapy with checkpoint blockers

Cancer immunotherapy supports the body's own immune system in the fight against cancer

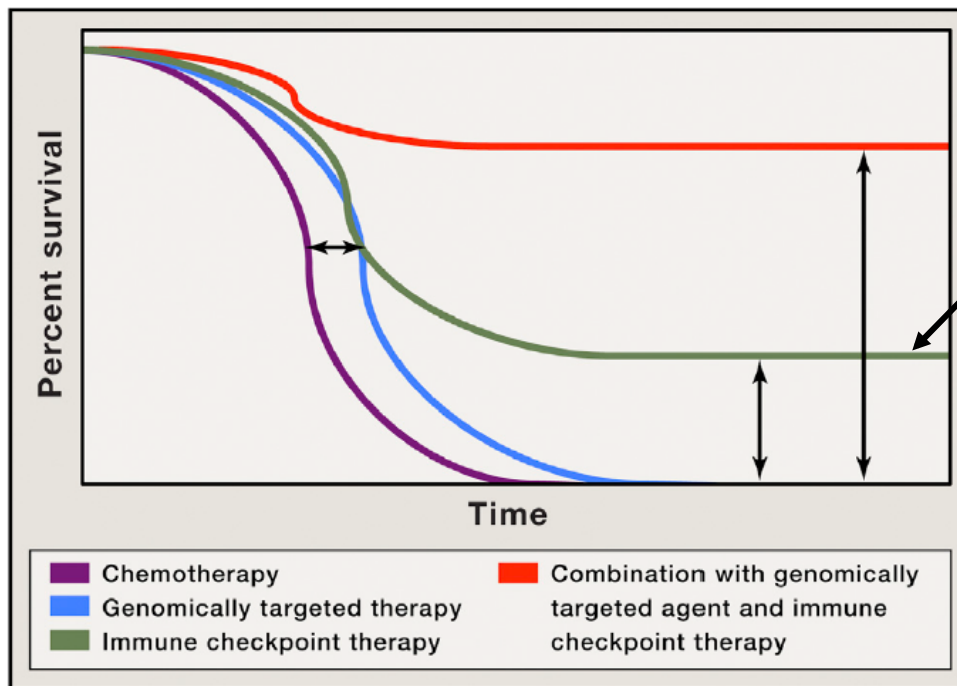
Immunotherapy with **checkpoint blockers** (monoclonal antibodies that block immune checkpoints) can release the “brakes” of the immune system and elicit effective anticancer immune responses



The paradigm shift of Immuno-Oncology

Immuno-Oncology has moved the focus (and therapy) from the tumor to the immune system

Immunotherapies with checkpoint blockers have shown remarkable clinical effects and are approved for different advanced cancers worldwide



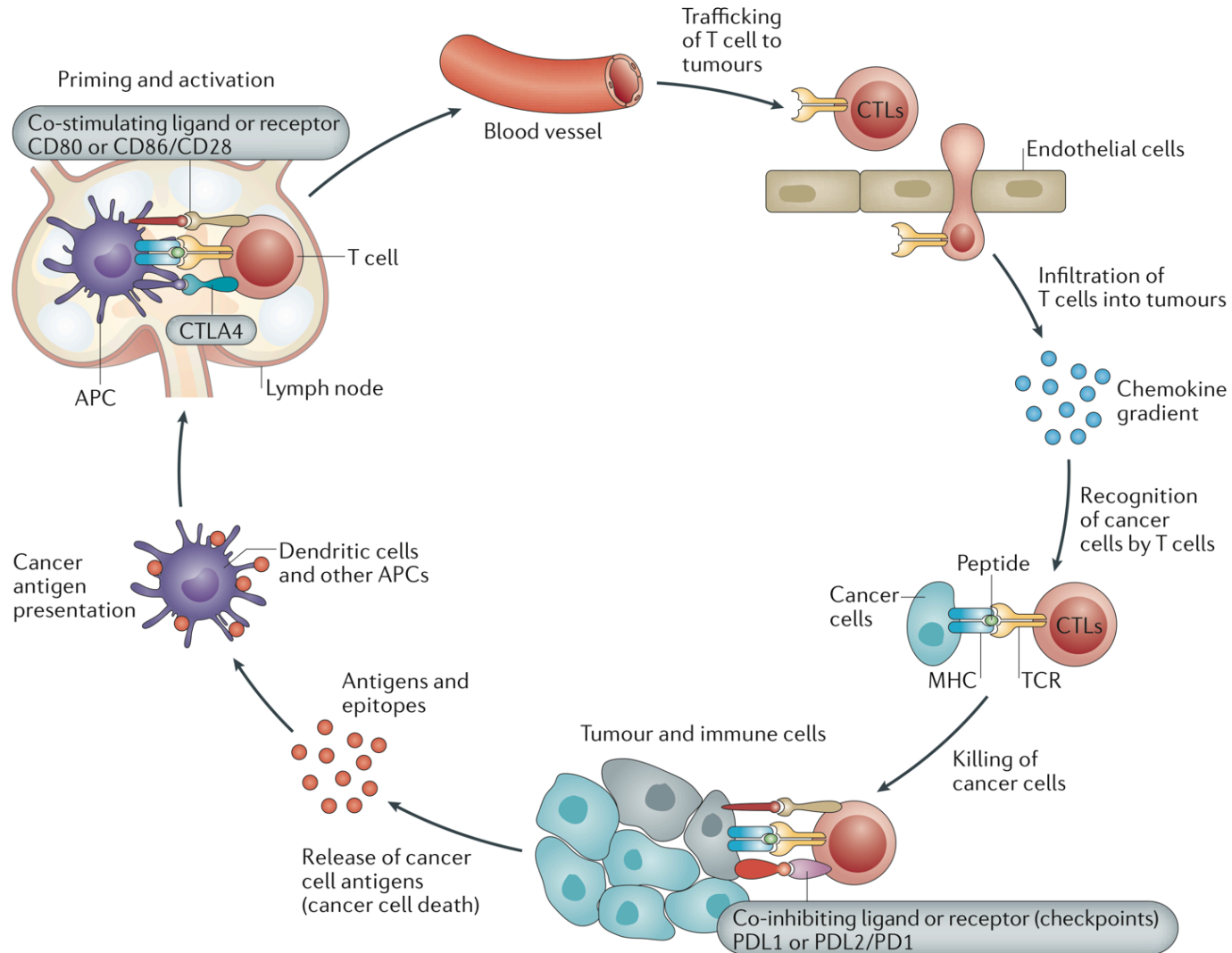
Durable responses are obtained only in a fraction of patients

Needs:

- Understand the mechanisms of resistance
- Identify biomarkers (monitor and predict)
- Design combination therapies

The anticancer immune response

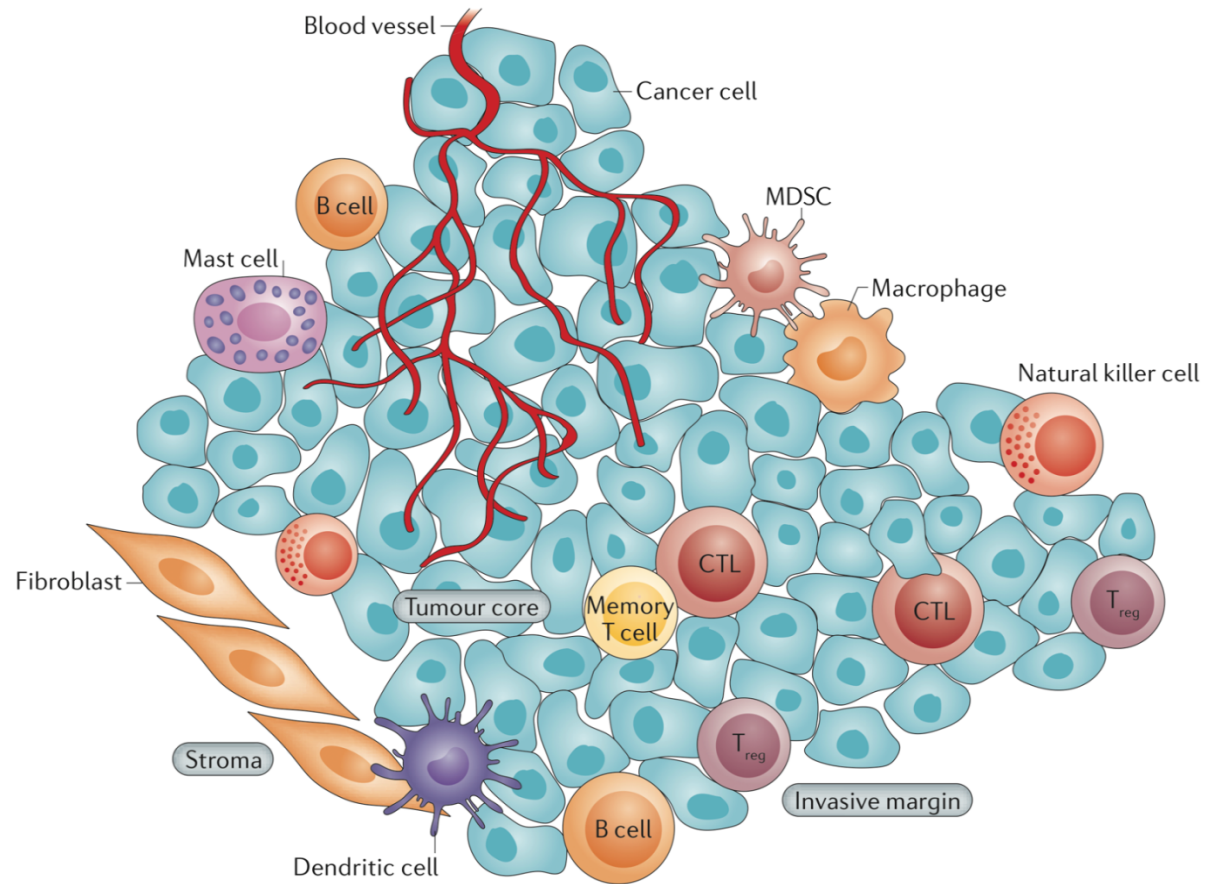
Effective anticancer immune responses require a series of stepwise events:



The immune contexture of human tumors

- Various immune cell types
- Pro- or anti-tumorigenic roles

E.g. regulatory CD4⁺ T (T_{reg}) cell → immunosuppressive



Immune cells influence tumor progression and response to therapy

Bionformatics tools for the analysis of the tumor-immune interface

The paradigm-shift in cancer treatment and research has been mirrored in bioinformatics and data analysis

Large-scale tumor data (especially from Next-Generation Sequencing) can be used to extract also **immunological features**, like:

- Tumor (neo)antigens
- Tumor-infiltrating immune cells

And to derive insights on the interplay between tumor and immune cells and the role of the immune system in tumor progression and response to therapy

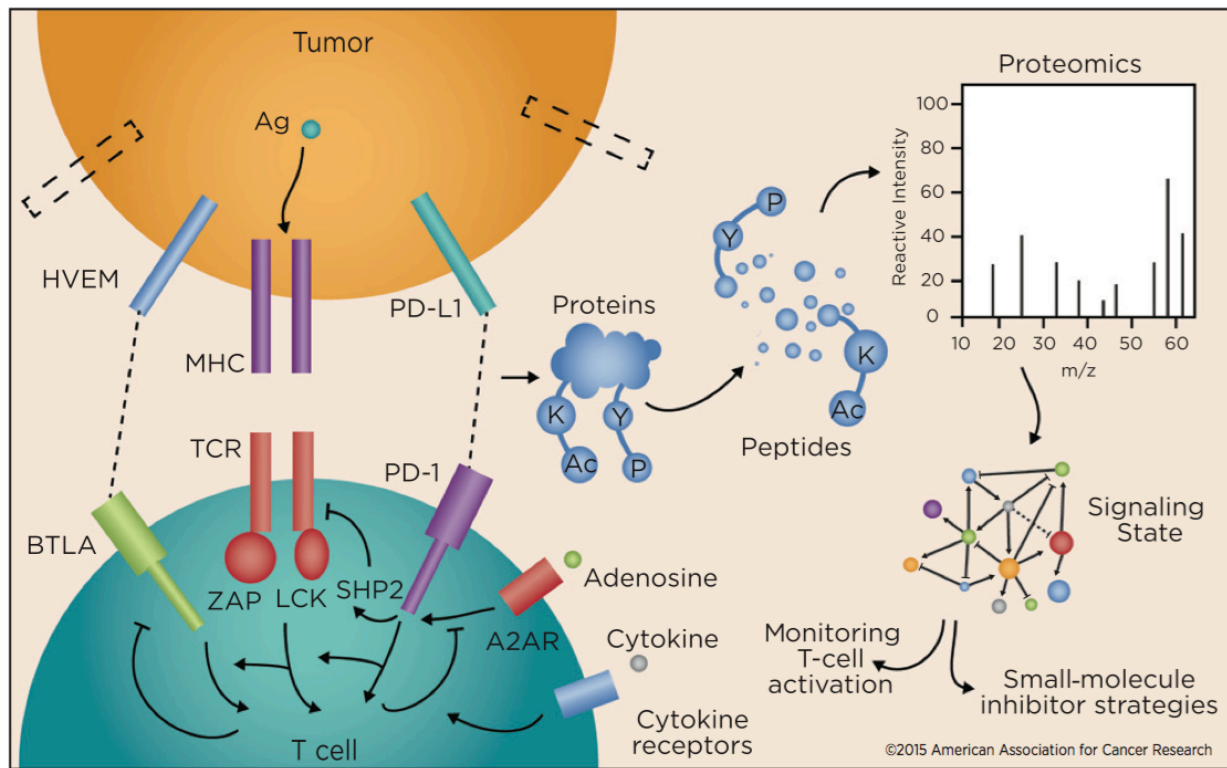
→ address the urgent needs of Immuno-Oncology:

- Understand the **mechanisms of resistance** (Lack of tumor antigens? No infiltration of CD8+ T cells? Presence of immunosuppressive cells?)
- Identify **biomarkers** (Tumor neoantigens/immune cell types to predict or monitor response to immunotherapy)
- Design **combination (immuno)therapies**

Importance of signaling pathways in Immuno-Oncology

Activation state of an antitumor effector T-cell in a tumor depends on the sum of all stimulatory and inhibitory signals it receives.

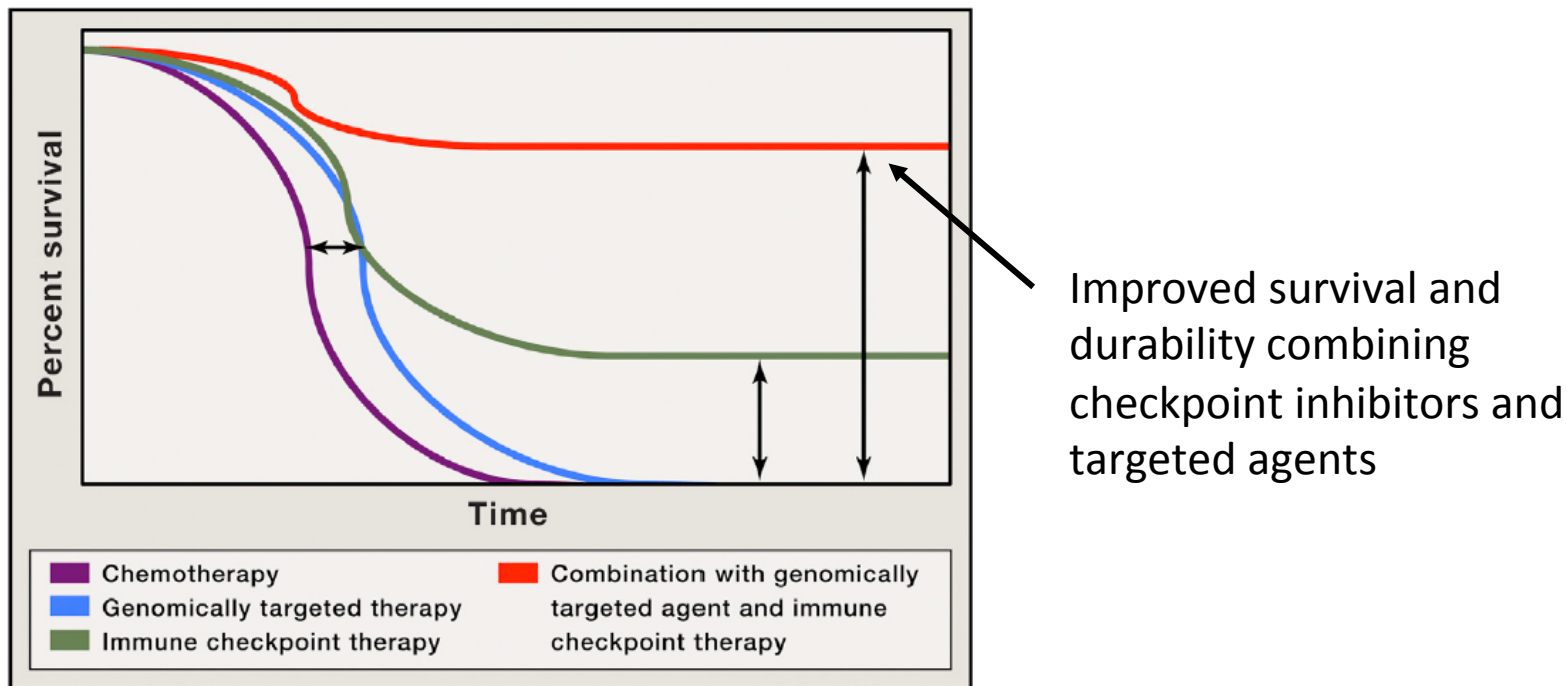
Cellular response to external **stimuli** as well as to **drugs** is mediated by **complex signaling pathways** both in the tumor and in the immune T-cell.



Mechanism-based design of combinatorial therapy

There are hundreds of clinical studies on combinations of **checkpoint inhibitors** and **targeted agents** (targeting signaling proteins).

Mechanistic understanding of how signaling components work and interact can help to gain biological insights, understand mechanisms of resistance, design optimal (combinatorial) therapies.



Hands-on activities to get familiar with:

- Assembly of a pipeline to predict set of neoantigens from RNA-seq and mutational data
- Quantification of tumor-infiltrating immune cells from expression data using deconvolution
- Implementation of Boolean model of signaling pathways using proteomics data

Course material available on the GitHub repository:

<https://github.com/FFinotello/Immuno-Oncology>

All slides and data can be downloaded from:

<https://github.com/FFinotello/Immuno-Oncology/blob/master/Program.md>