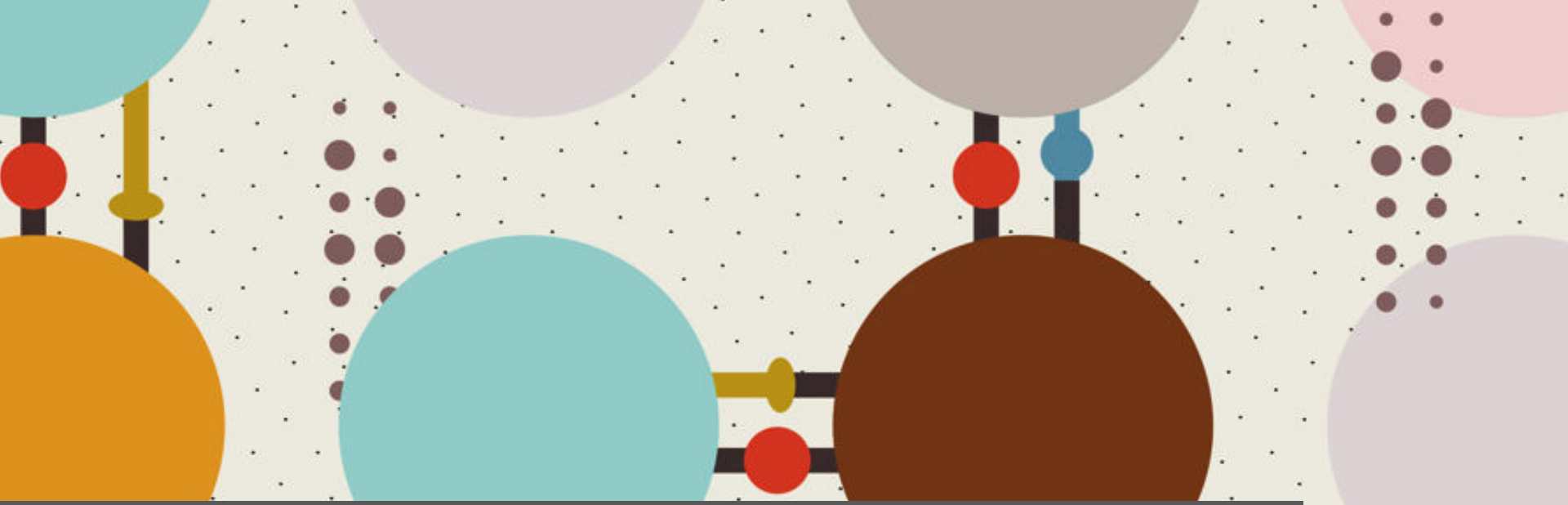

IO17 | Large Scale Bioinformatics for Immuno-Oncology

Introduction: Bioinformatics for Cancer Immunology and Immuno-Oncology

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GTPB | The Gulbenkian Training Programme in Bioinformatics
Instituto Gulbenkian de Ciência, Oeiras, Portugal | Sept 19th-22nd, 2017

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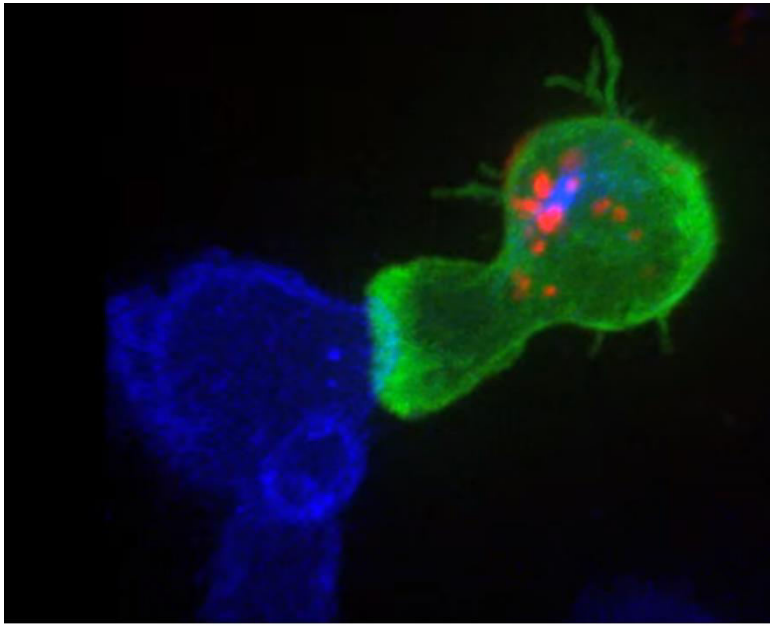
Cancer immunology

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!

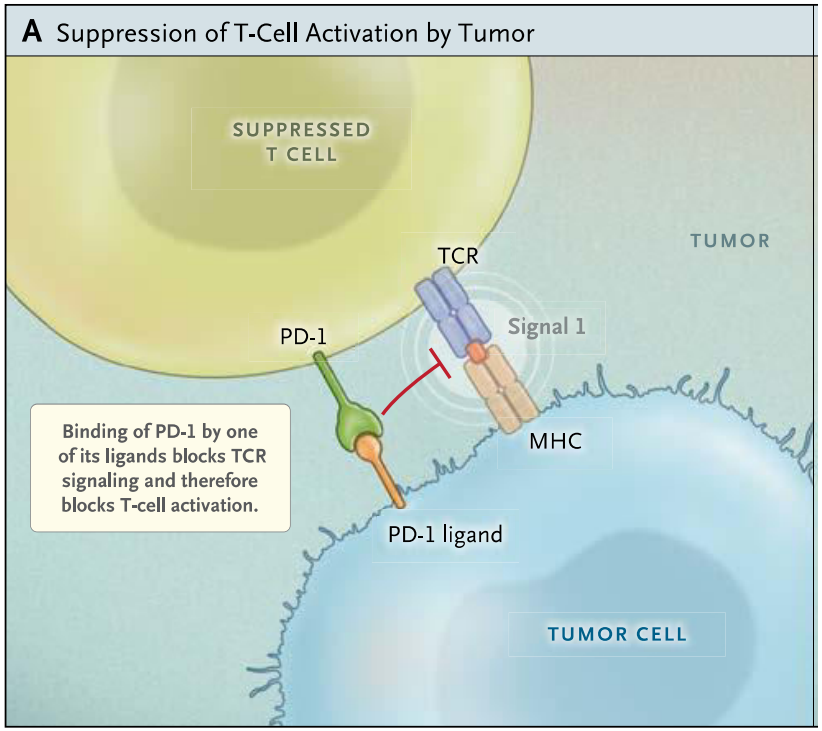


From the YouTube video "**Killer T Cell: The Cancer Assassin**" by Cambridge University
https://www.youtube.com/watch?v=ntk8XsxVDi0

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



A Ribas, N Engl J Med, 2015

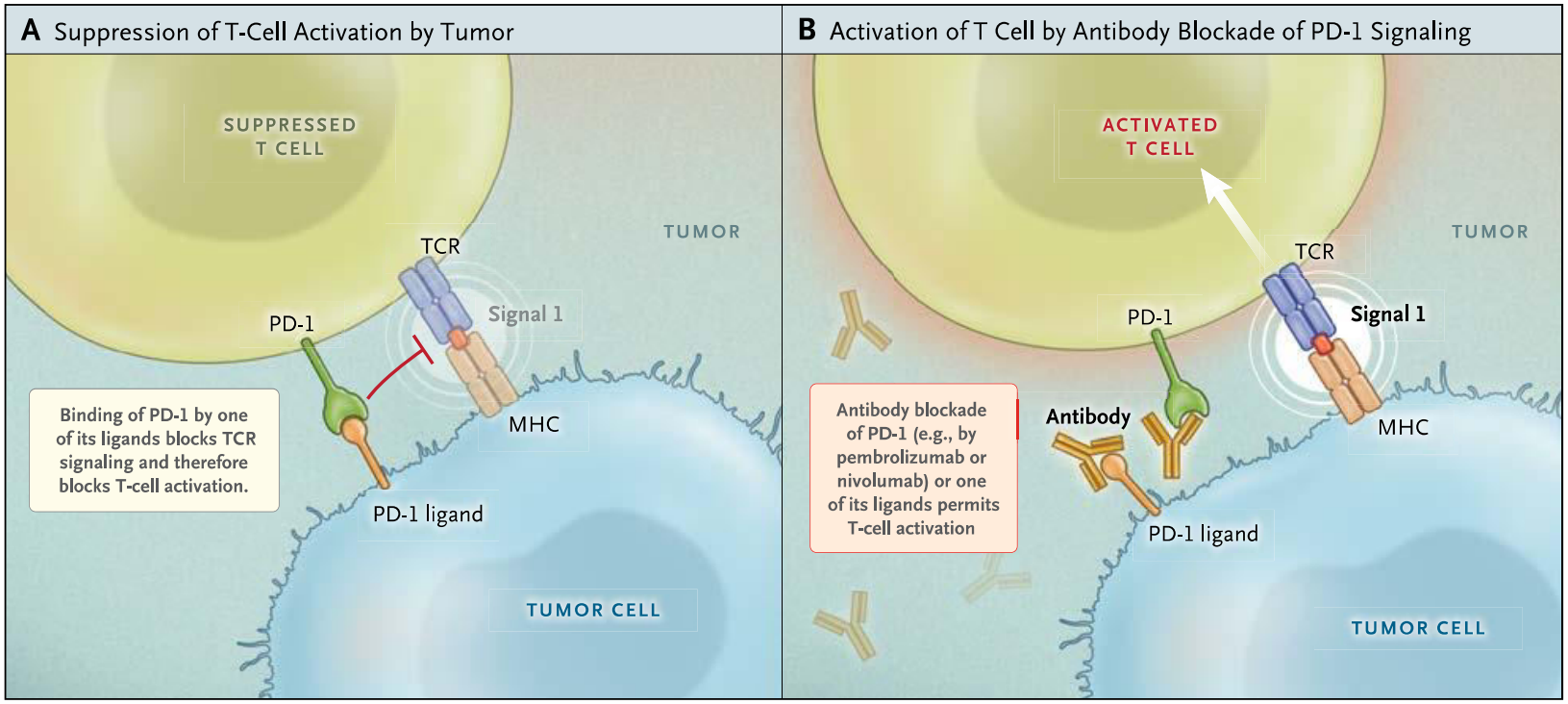
Immune checkpoints (like PD1, PDL1, CTLA4) are inhibitory molecules that modulate the amplitude and duration of immune responses

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

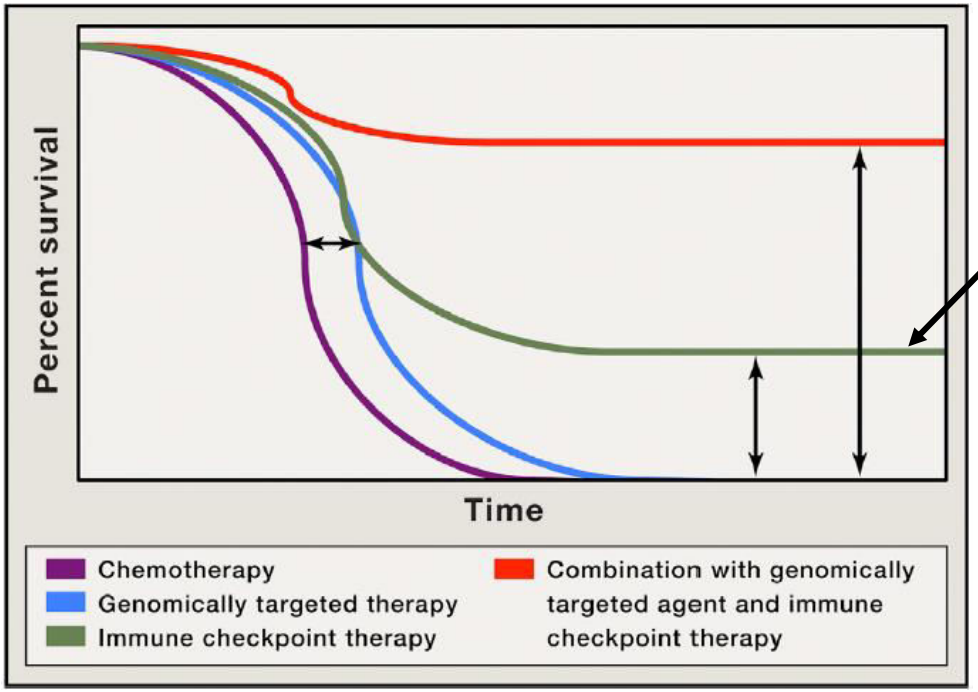


A Ribas, N Engl J Med, 2015

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

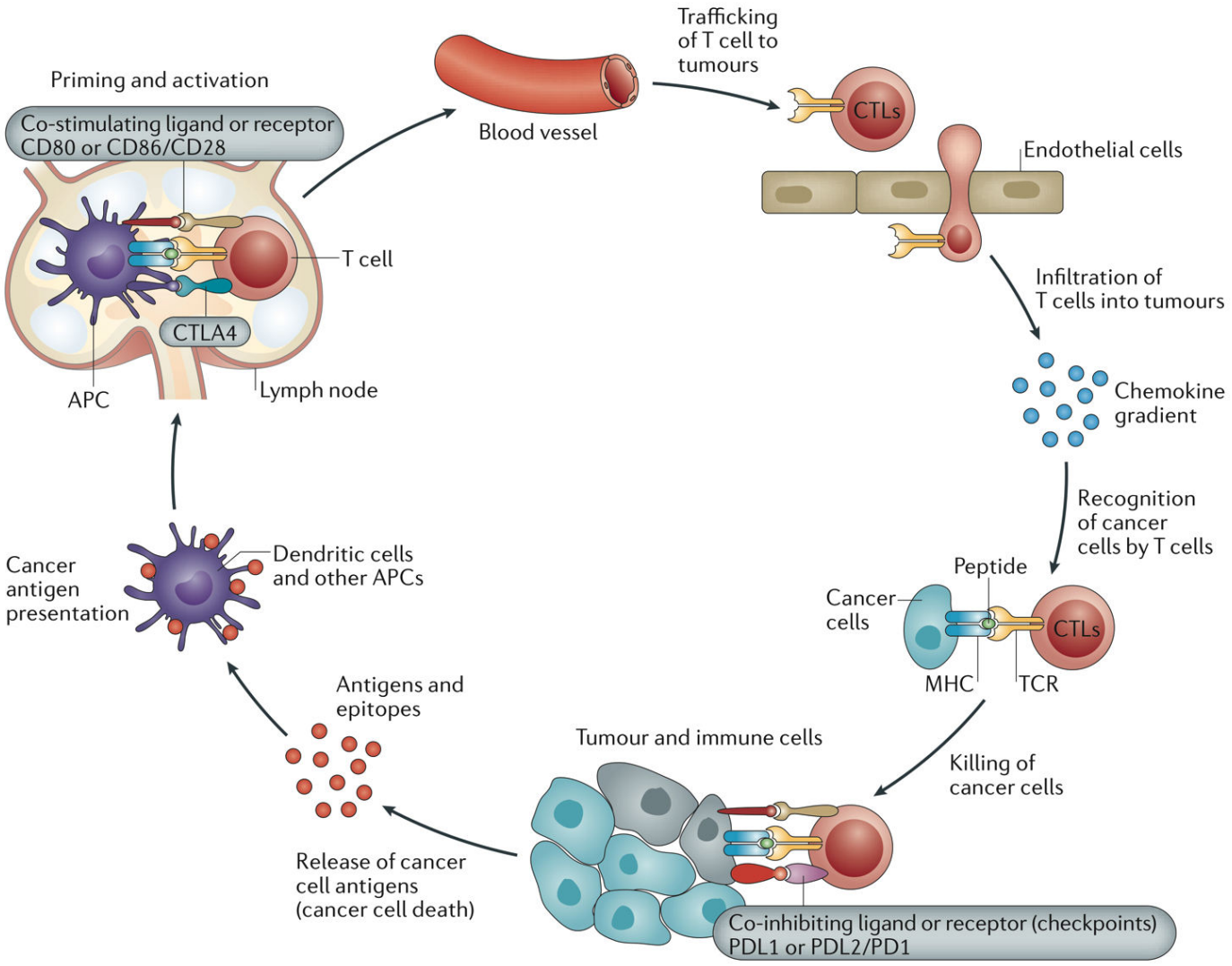
Needs:

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

P Sharma and JP Allison, Cell, 2015

The anticancer immune response

Effective anticancer immune responses require a series of stepwise events:

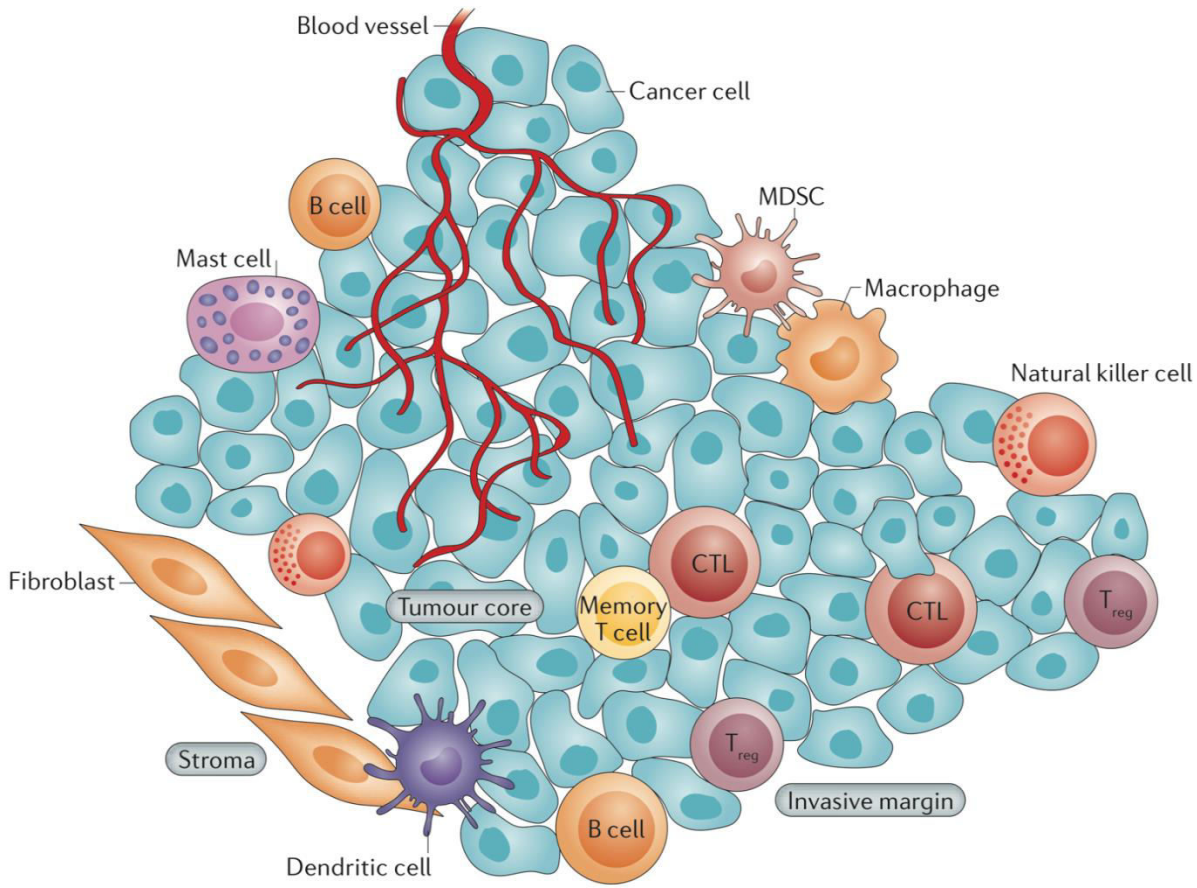


H Hackl*, P Charoentong*, F Finotello* et al., Nature Reviews Genetics, 2016

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

H Hackl*, P Charoentong*, F Finotello* et al., Nature Reviews Genetics, 2016

Bionformatics for Immuno-Oncology

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

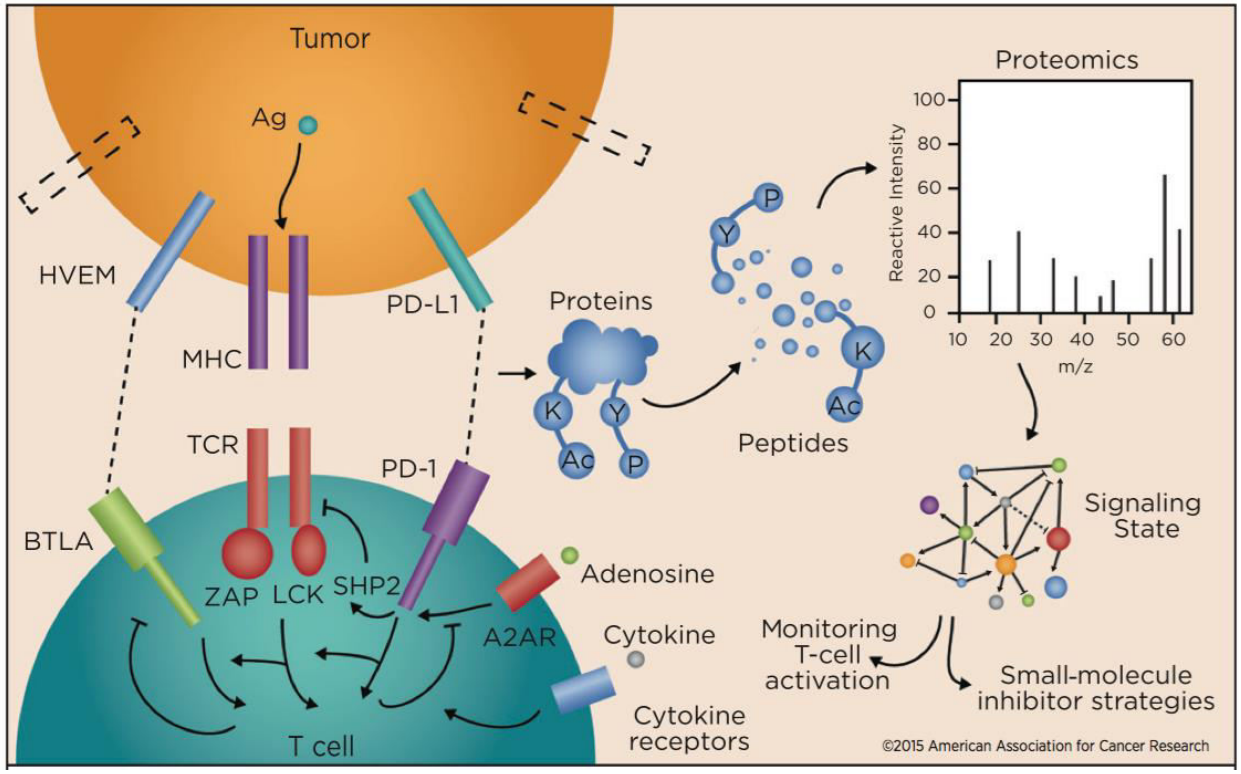
Bioinformatics can help to address the urgent needs of Immuno-Oncology:

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

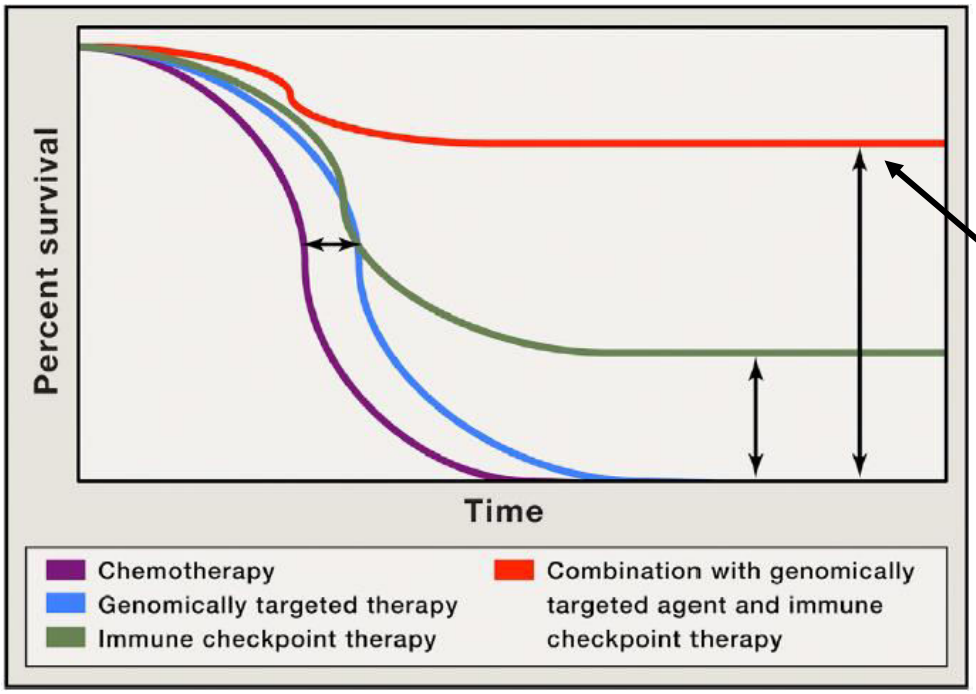


EB Haura et al., Cancer Immunology Research, 2015

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.



Improved survival and durability combining checkpoint inhibitors and targeted agents

P Sharma and JP Allison, Cell, 2015

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Hands-on activities to get familiar with:

- Assembly of computational pipelines for the prediction of neoantigens from RNA-seq and mutational data
- Application of deconvolution algorithms for the quantification of tumor-infiltrating immune cells from expression data
- Implementation of Boolean models 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