



IO17 | Large Scale Bioinformatics for Immuno-Oncology

Signaling pathways in cancer and immune cells

Francesca Finotello, Federica Eduati, and Pedro L. Fernandes

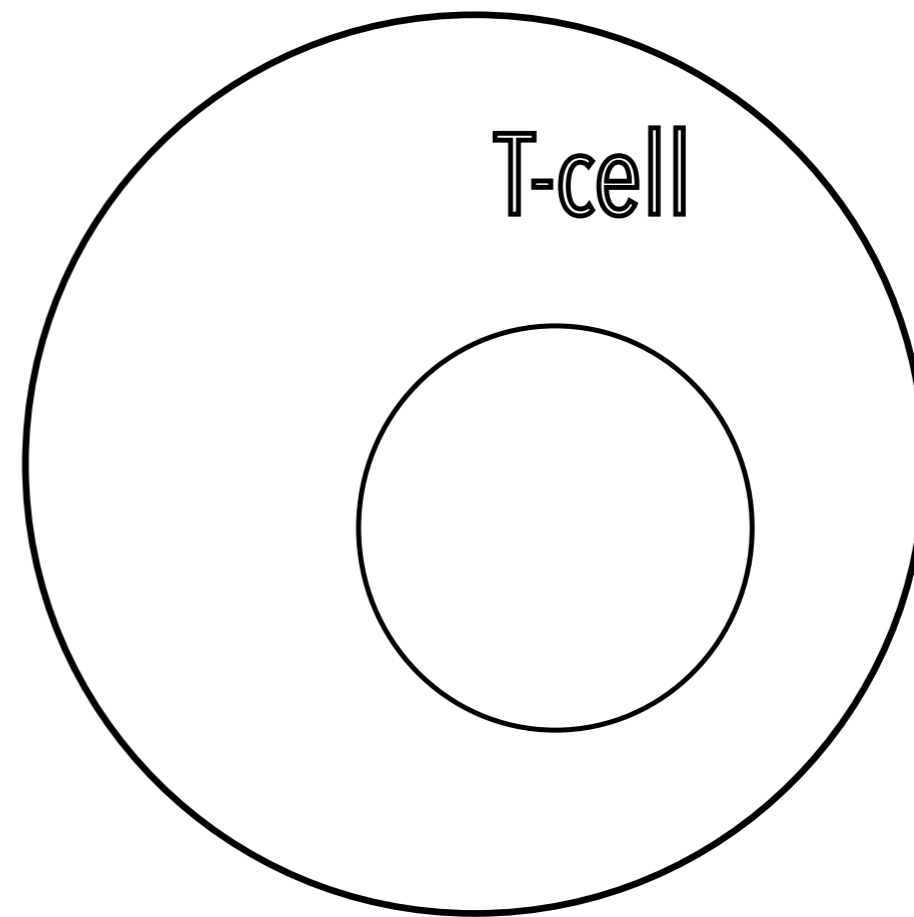
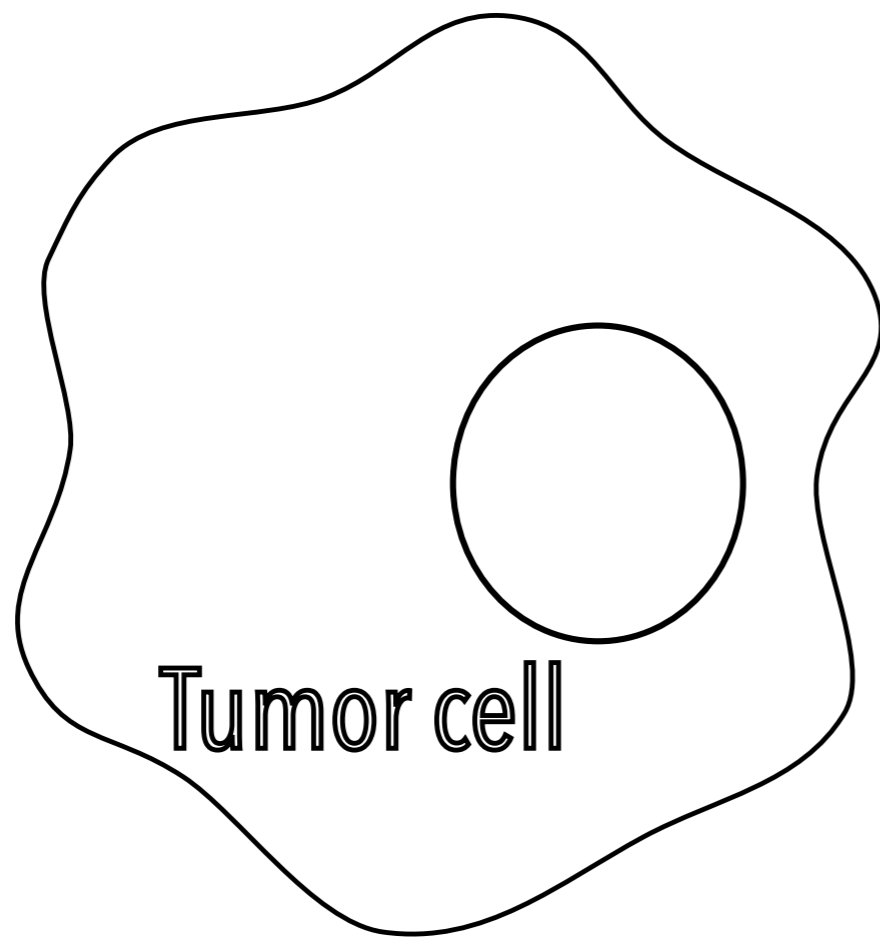
GTPB | The Gulbenkian Training Programme in Bioinformatics
Instituto Gulbenkian de Ciência, Oeiras, Portugal | Sept 19th-22nd, 2017

What are signaling pathways and what is their function?

Signaling pathways are responsible for the correct functioning of the cells:

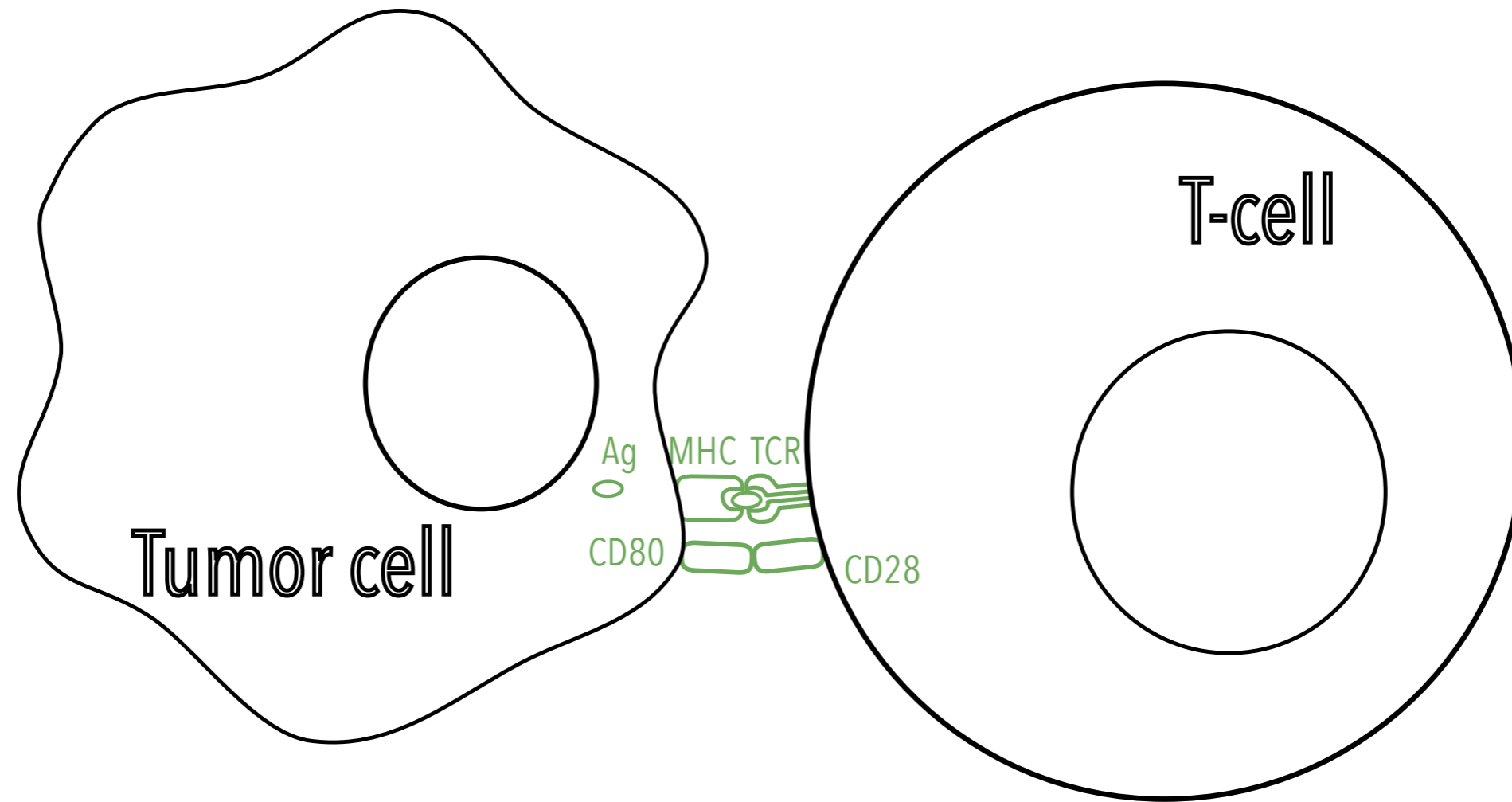
1. extracellular ligands (cytokines, growth factors, ...) bind to cellular receptors
2. the cell responds by processing this signal, through a complex and dynamic signal transduction network
3. information is finally transmitted to the nucleus, where transcription factors regulate the transcriptional response of the cell
4. this process ultimately changes the phenotype of the cell




Cellular communication in immuno-oncology




Cellular communication in immuno-oncology

Antigens are produced by the malfunctioning tumor cells, they are recognised by the T-cell receptor (TCR) and the T-cell is activated. This activatory signal is reinforced by the binding of the CD28 receptor with CD80.

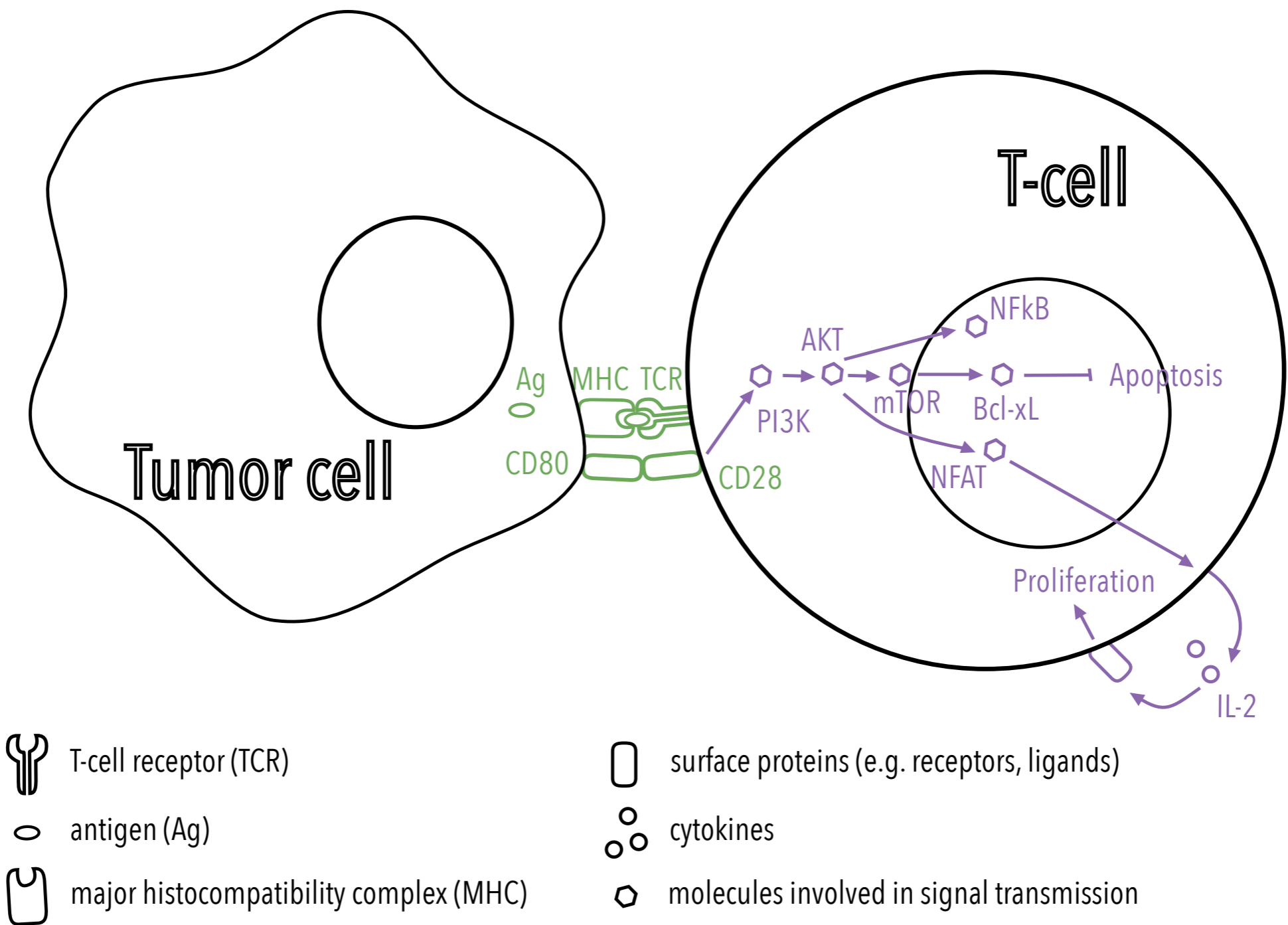


-  T-cell receptor (TCR)
-  antigen (Ag)
-  major histocompatibility complex (MHC)

 surface proteins (e.g. receptors, ligands)

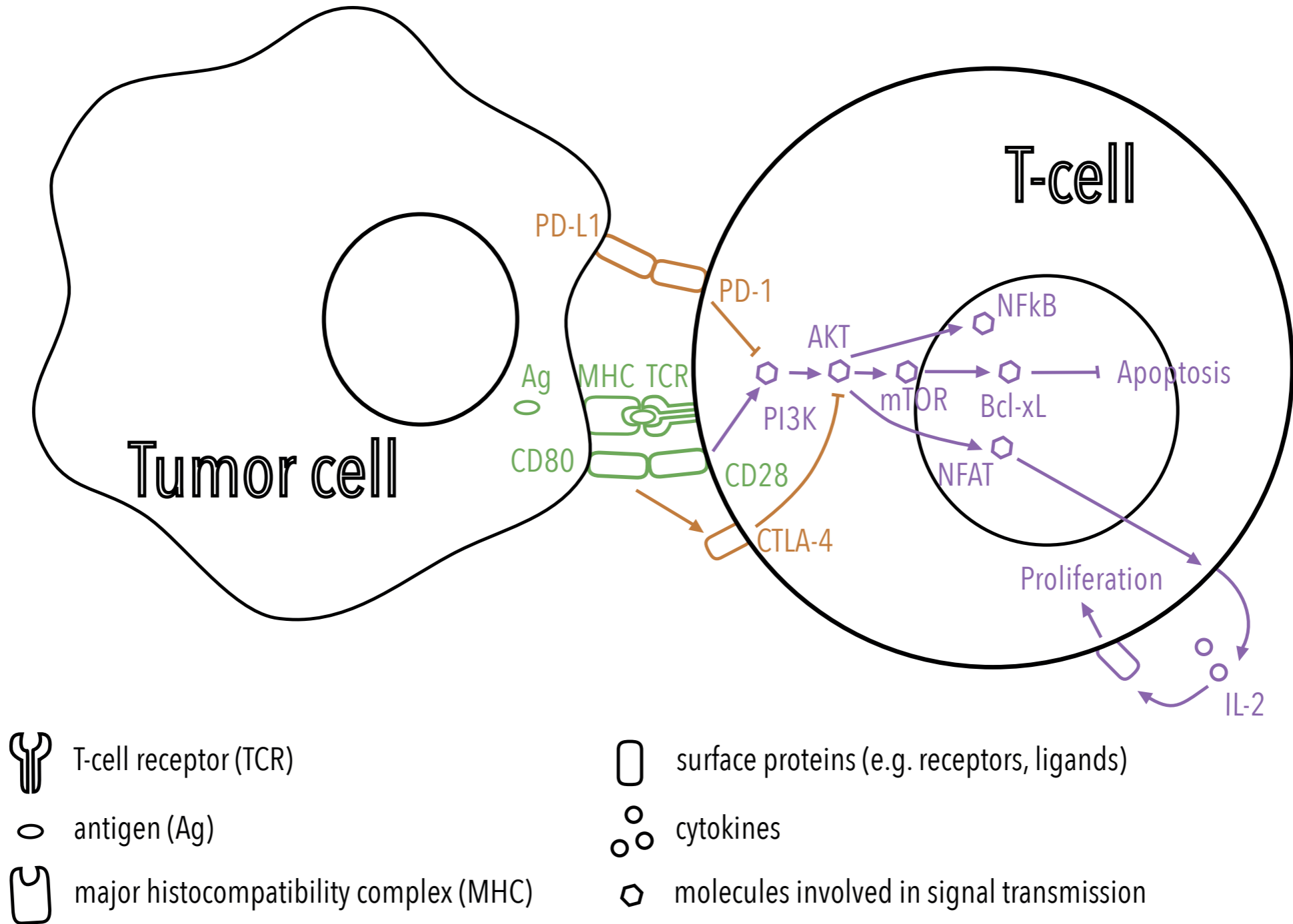
Cellular communication in immuno-oncology

TCR signaling leads to increased survival, differentiation and proliferation of T-cells through production of growth cytokines such as IL-2 and to the inhibition of apoptosis.



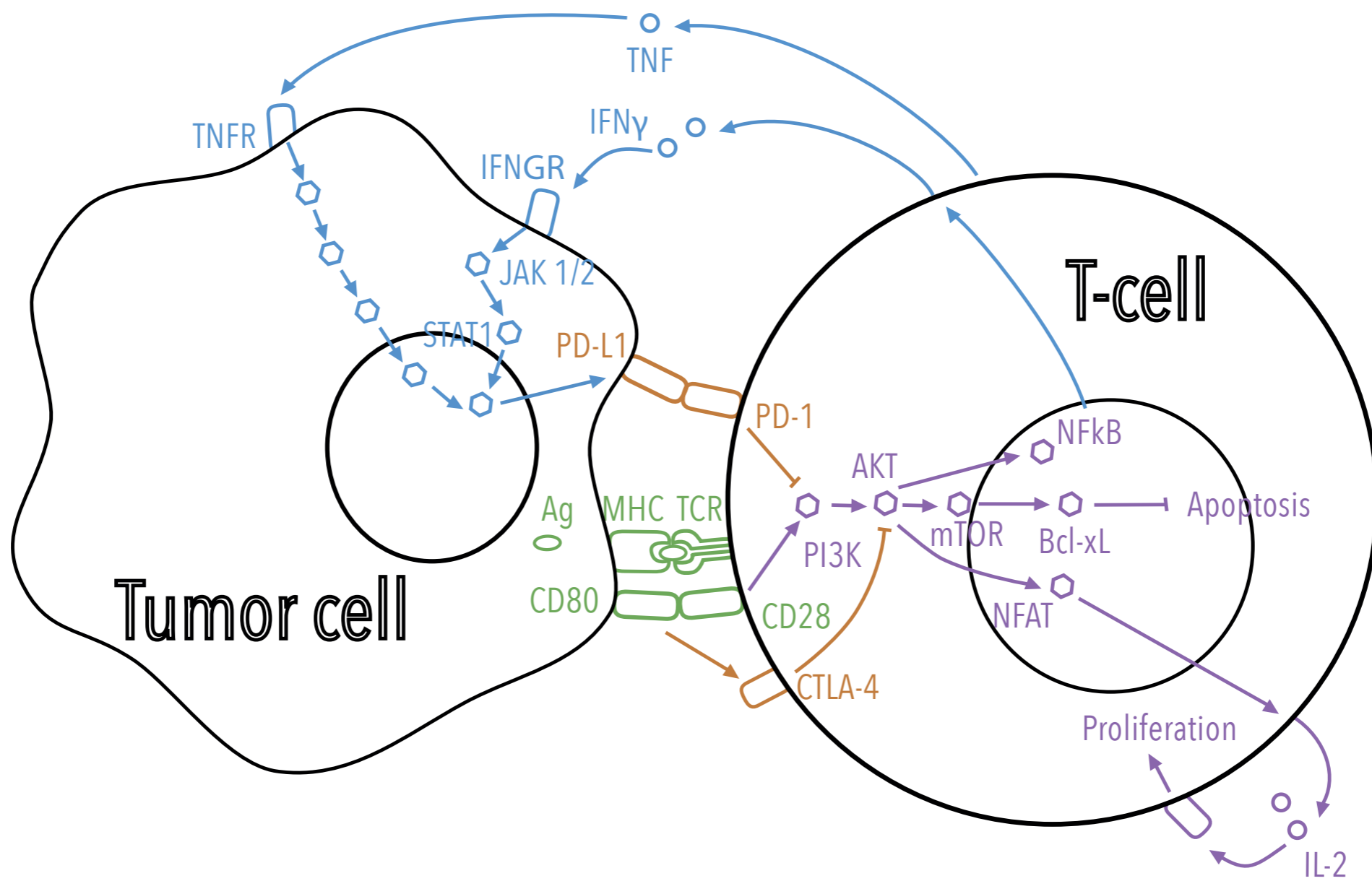
Cellular communication in immuno-oncology







PD-1 and CTLA-4 are check-points responsible of suppression of the immune system. Binding of PD-L1 to PD-1 transmits an inhibitory signal that reduces the proliferation of these T cells and can induce apoptosis. CTLA-4 is a CD28 homolog with much higher binding affinity for CD80.



Cellular communication in immuno-oncology

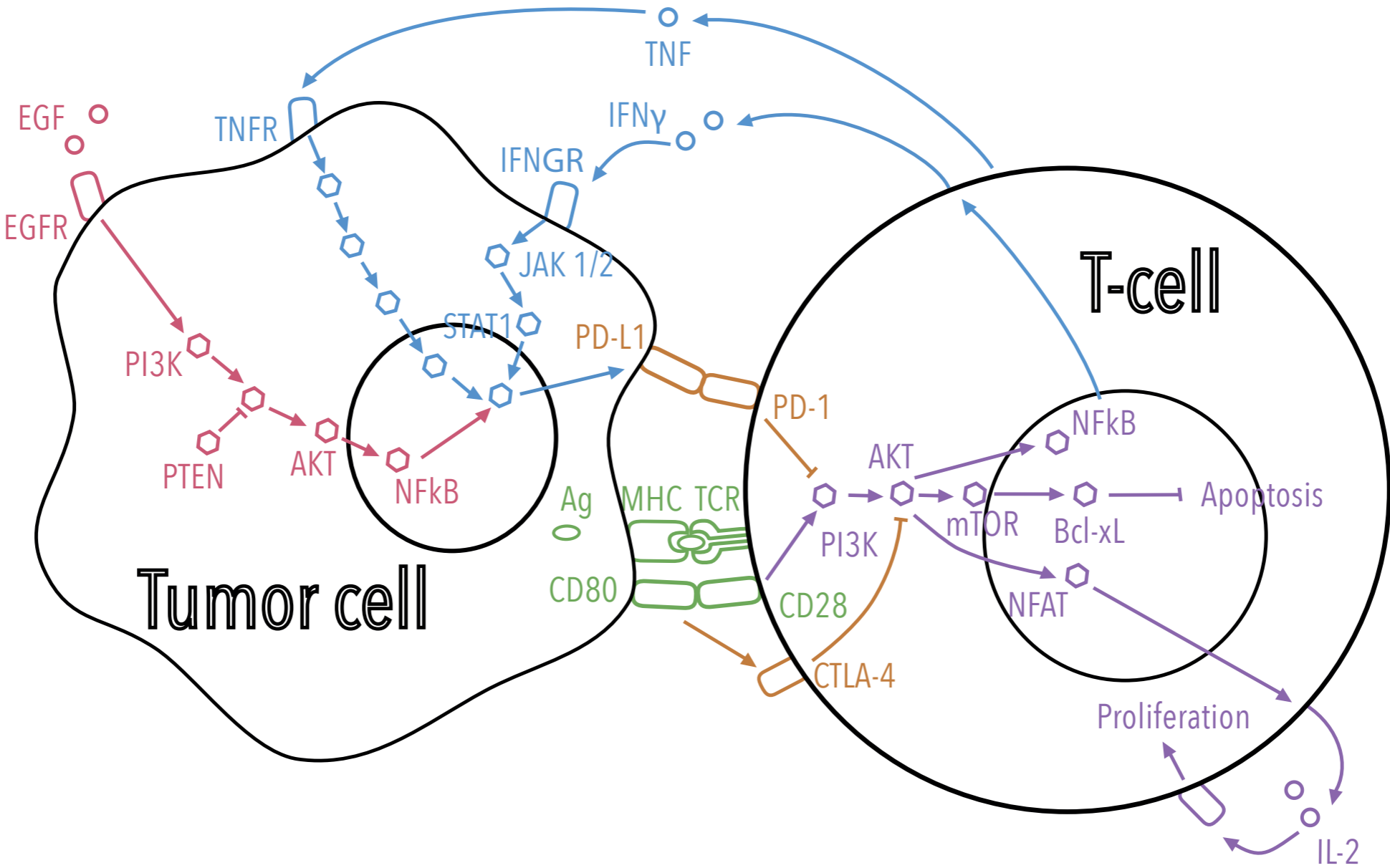
“Adaptive immune resistance”: tumor protects itself by inducing PD-L1 in response to IFN- γ (and/or TNF- α) produced by activated T cells









-  T-cell receptor (TCR)
-  antigen (Ag)
-  major histocompatibility complex (MHC)
-  surface proteins (e.g. receptors, ligands)
-  cytokines
-  molecules involved in signal transmission

Cellular communication in immuno-oncology

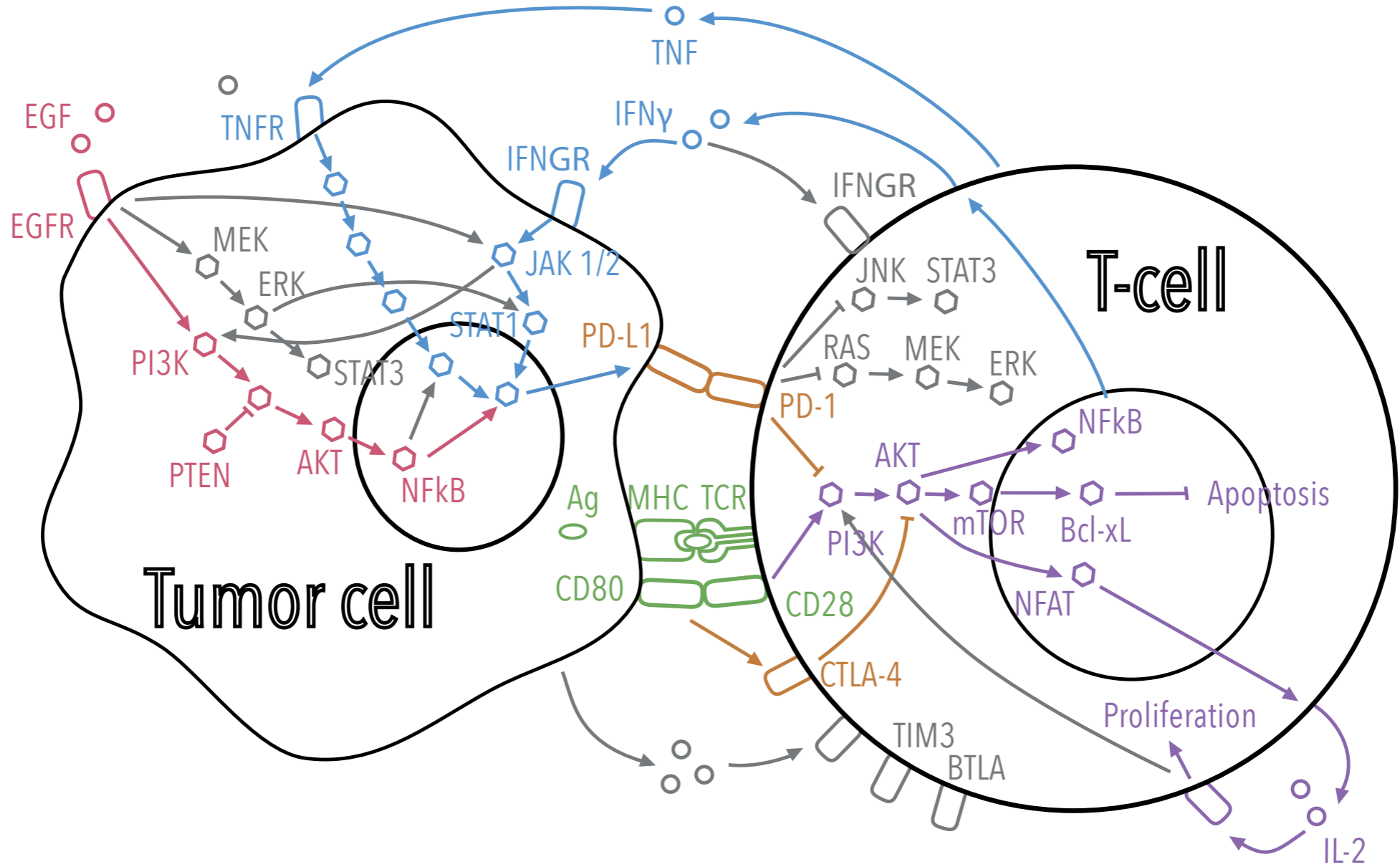
“Inherent immune resistance”: PD-L1 is also regulated by oncogenes, e.g. loss of tumor suppressor PTEN function increases PD-L1 expression and causes immunoresistance.









-  T-cell receptor (TCR)
-  antigen (Ag)
-  major histocompatibility complex (MHC)
-  surface proteins (e.g. receptors, ligands)
-  cytokines
-  molecules involved in signal transmission

Cellular communication in immuno-oncology

A number of other pathways and cross-talks between pathways are involved in the regulations of both Tumor cells and T-cells and affects the transduction of signals responsible for communication between tumor and immune cells.



-  T-cell receptor (TCR)
-  antigen (Ag)
-  major histocompatibility complex (MHC)
-  surface proteins (e.g. receptors, ligands)
-  cytokines
-  molecules involved in signal transmission

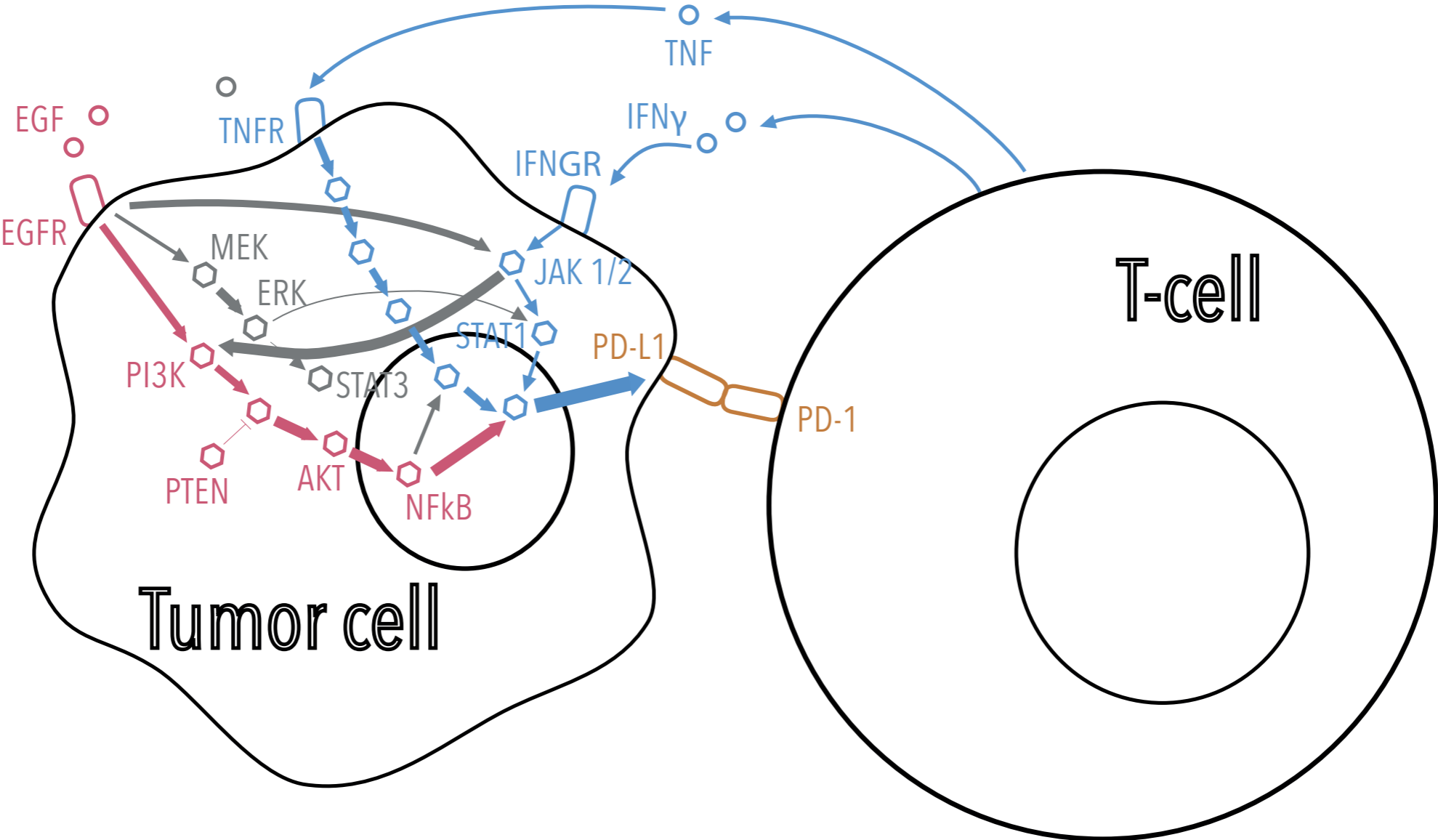
Why studying signaling pathways in immuno-oncology?

Mechanistic understanding of signalling pathways in immuno-oncology can help to:

1. understand deregulations
2. suggest possible therapeutic targets
3. understand mechanisms of resistance
4. suggest combinatorial therapies

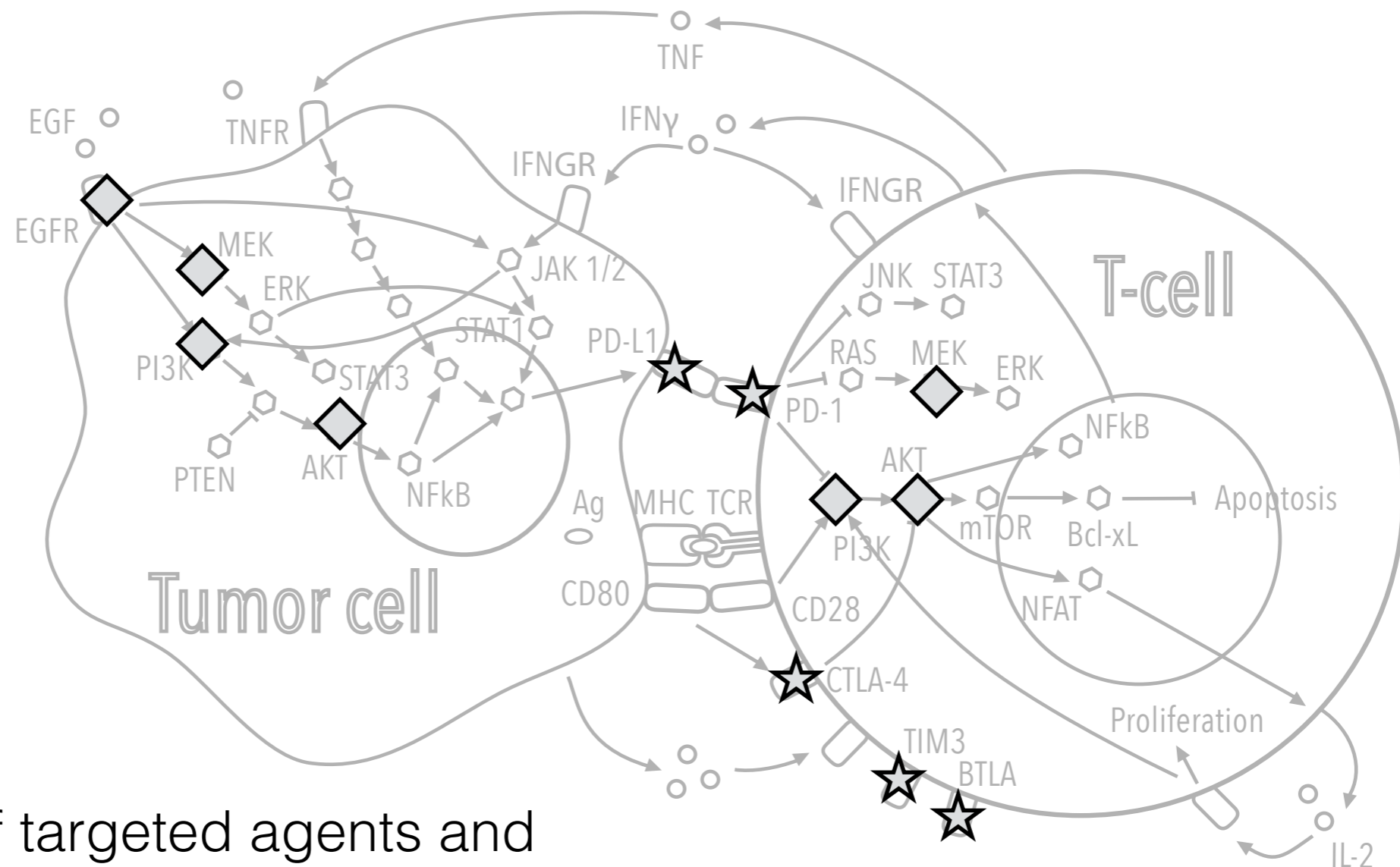
1. Pathways deregulations in cancer

Cancer is caused by gene mutations that affect cellular signaling pathways, ultimately changing the phenotype of the cell and leading to an abnormal growth into a tumor and metastasis.



2. Possible therapeutic targets

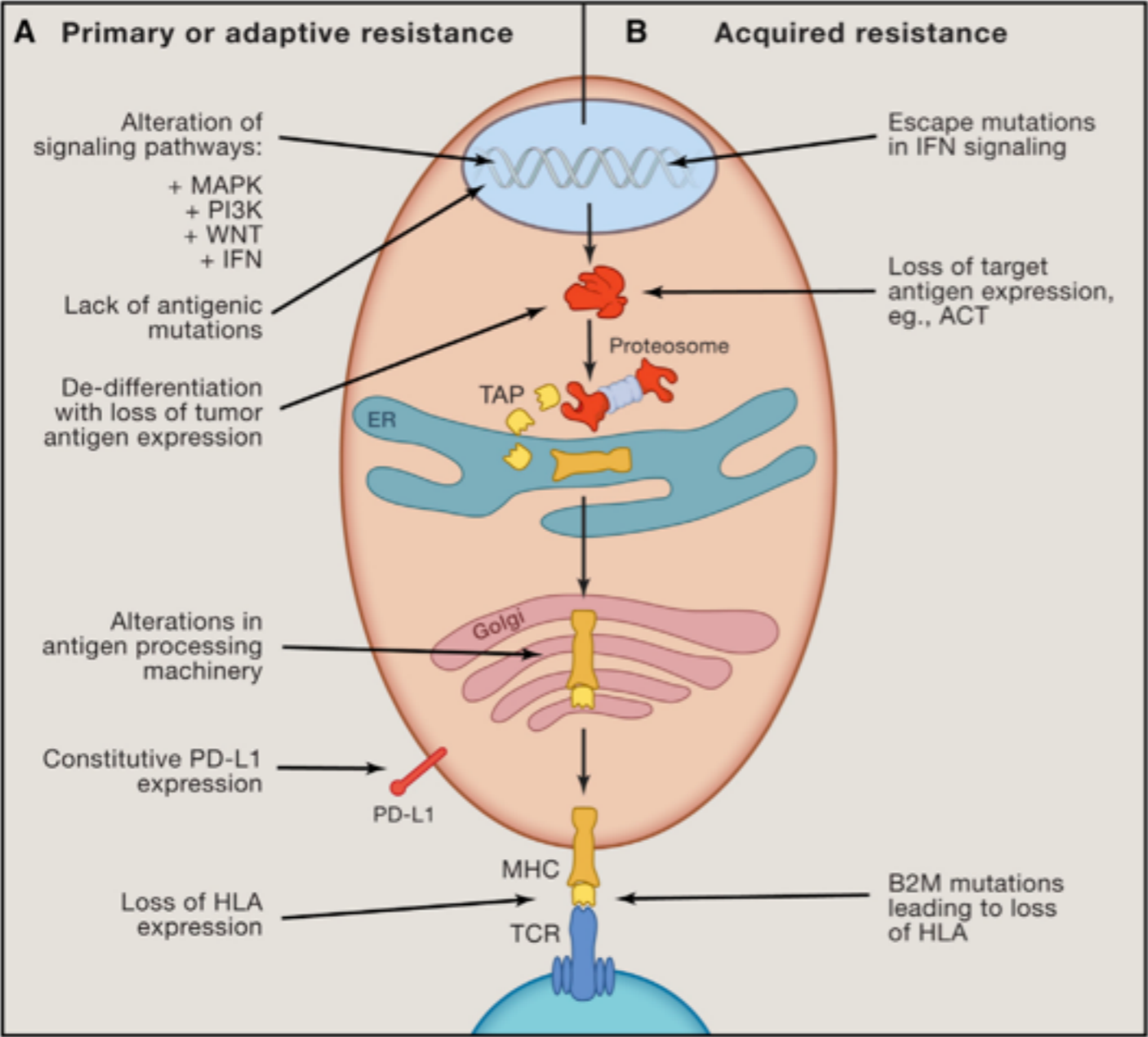
- ◆ **Targeted agents:** chemical compounds acting on key components of the pathways (e.g. kinase inhibitors).
- ☆ **Checkpoint inhibitors:** inhibitors of immune checkpoints aimed at unleashing an immune system response.



Few examples of targeted agents and checkpoint inhibitors used in immune-oncology

3. Mechanisms of resistance

Often tumors either do not respond to therapy or initially respond to therapy but later relapse.



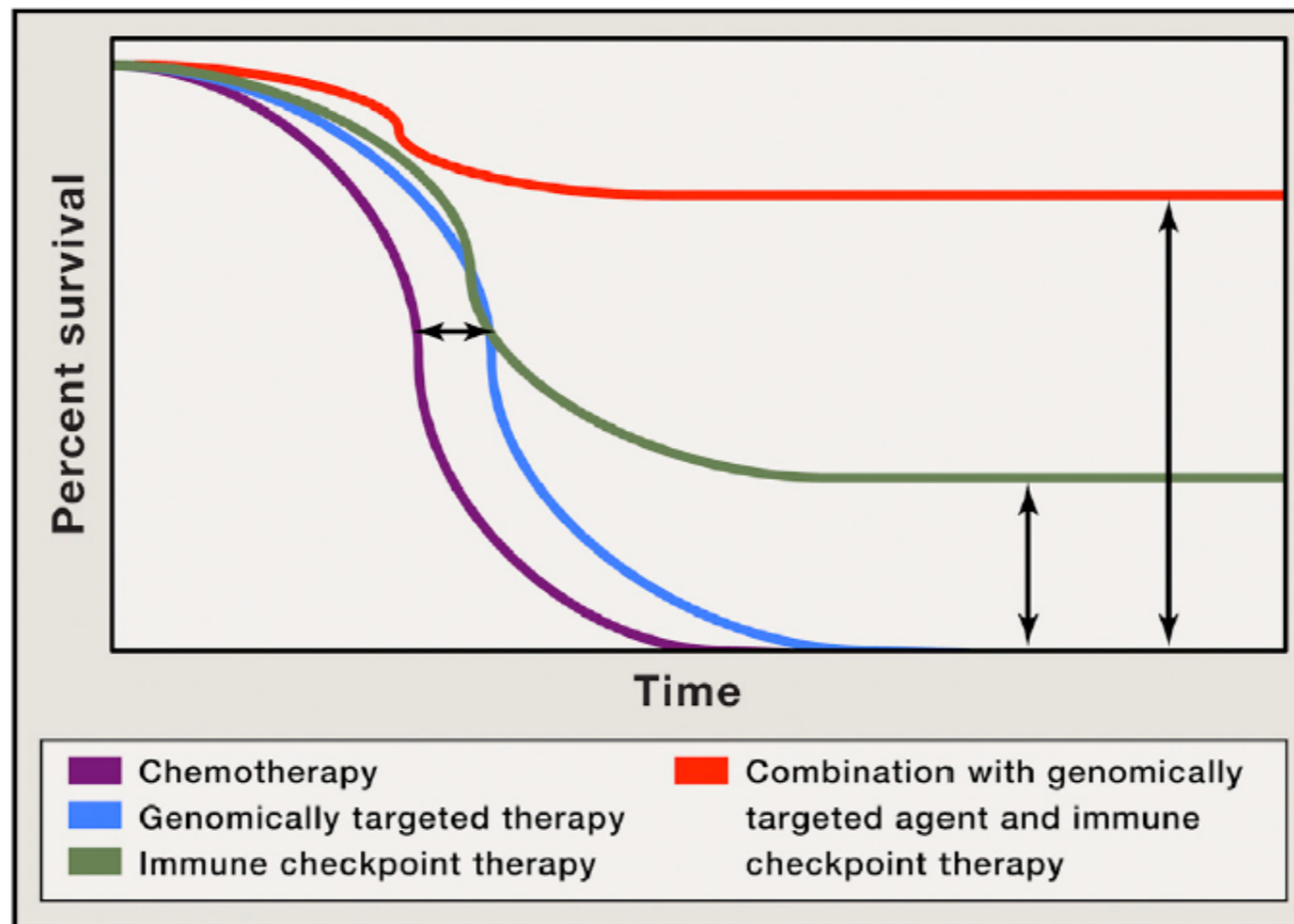
P Sharma, et al., Cell, 2017

4. Suggest combinatorial therapies

Combinatorial therapy can help to overcome resistance and reduce toxicity

In the context of targeted therapy acting on pathways, pairwise combinations can be:

- between 2 checkpoint inhibitors
- between 2 targeted agents
- between 1 checkpoint inhibitor and 1 targeted agent (acting either on the cancer or immune T-cell)



P Sharma and JP Allison, Cell, 2015