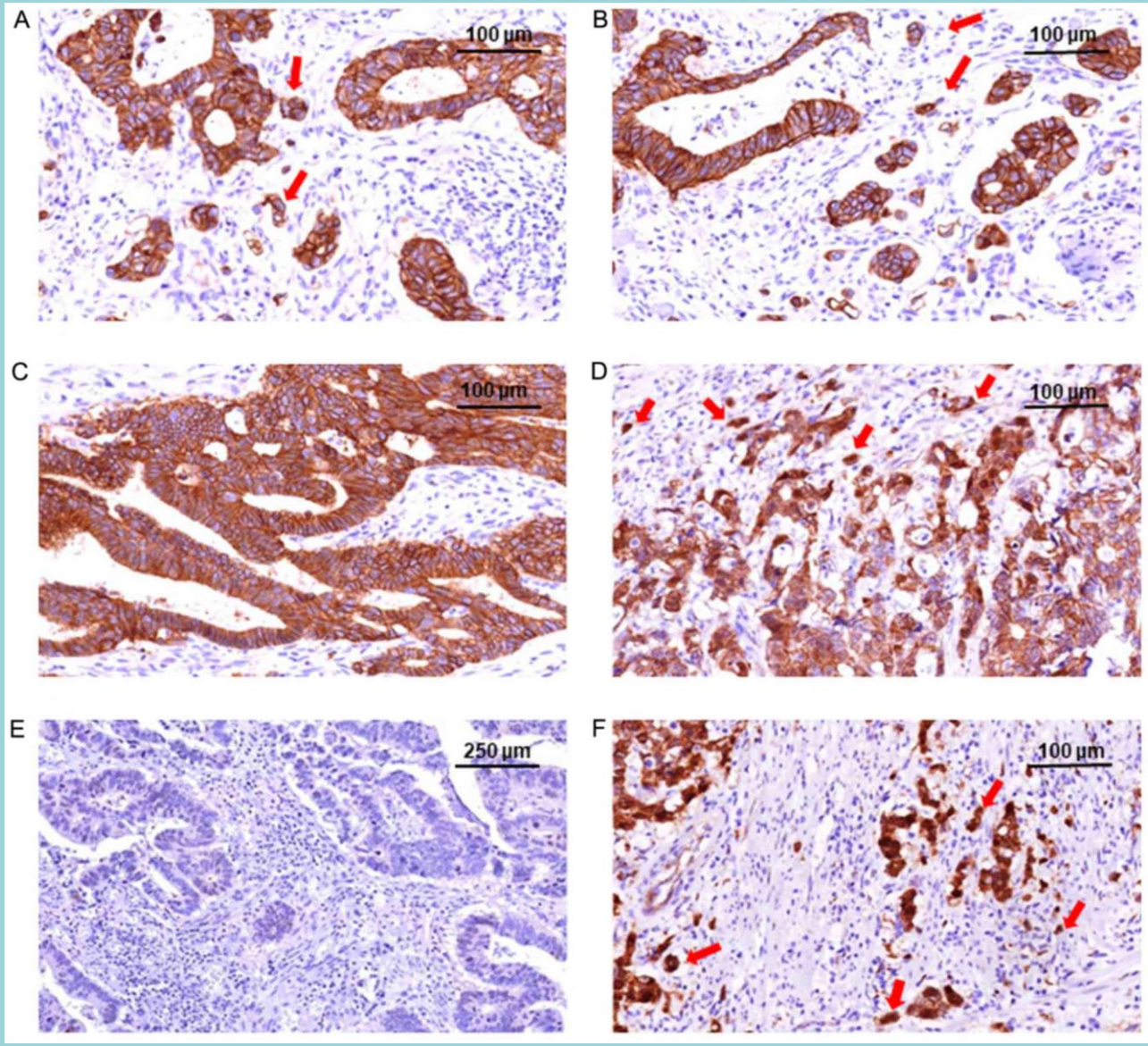
Tumor structural complexity

Tumors are not simply masses of cancer cells. Rather, they are heterogeneous collections of cancer cells (cancer polyclonality) infiltrated with many other cell types (stromal cells)

There are several, totally different tumors insisting on the same organ. They require specific therapeutic approaches

It is therefore necessary to identify them correctly

Tumor structural complexity - biopsies



Tumor structural complexity

Stromal cells and cancer cells communicate within the tumor and can render the tumor edges difficult to identify

Tumors grows initially *in situ*, then can spread (metastasis)

Metastaic development requires several steps of cell de-differentiation, acquired cell mobility and capacity to adhere to other tissues (target specificity)

Part of the necessary information is vehicled by extracellular vesicles

Cancer development

Initiation is the exposure of a cell or tissue to an agent that results in the first genetic mutation

Initiation alone is insufficient for cancer to develop

An initiated cell must go through a process of **clonal expansion** during promotion to become neoplastic: the larger the number of initiated cells, the greater the risk of progressing to cancer (statistically determined risk)

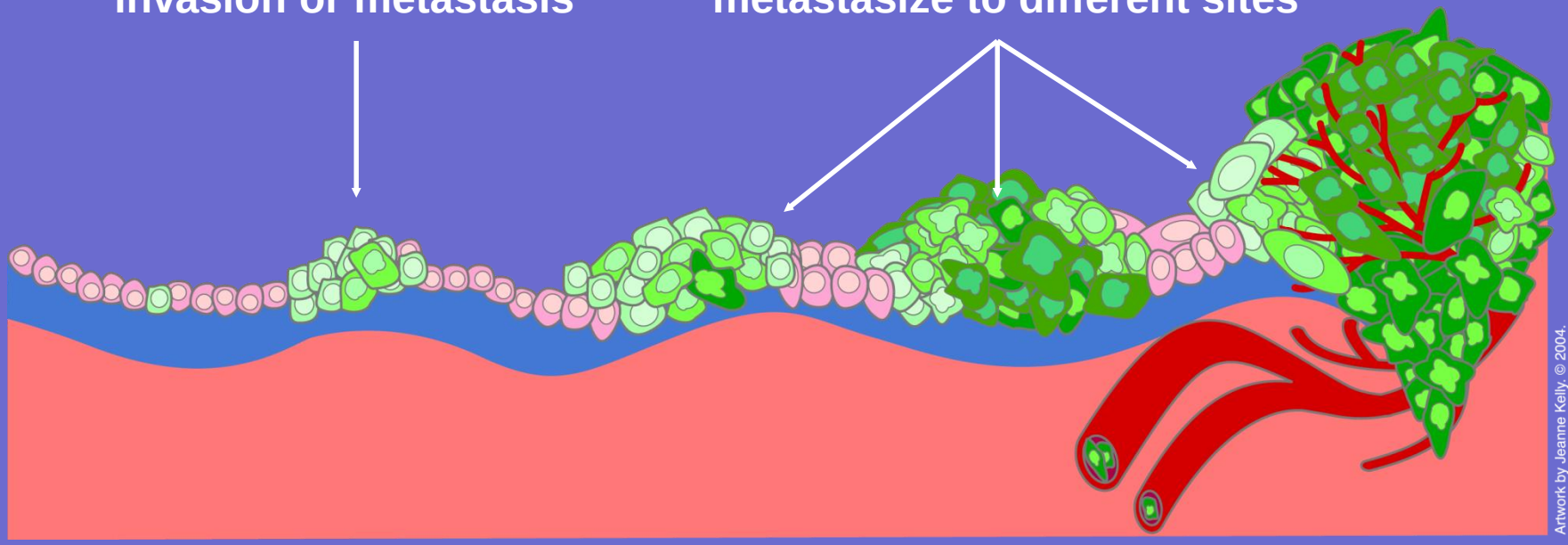
Promotion involves exposure of the initiated cells to a promoting agent. This may allow alterations in the **rate of proliferation**, **additional DNA damage** to occur, leading to further modification, which accelerate gene expression and cellular proliferation

Finally, these initiated and promoted cells grow and **expand** to form a **tumor mass**

Cancer Tends to Involve Multiple Mutations

Benign tumor cells grow only locally and cannot spread by invasion or metastasis

Malignant cells invade neighboring tissues, enter blood vessels, and metastasize to different sites



Time

Mutation inactivates suppressor gene

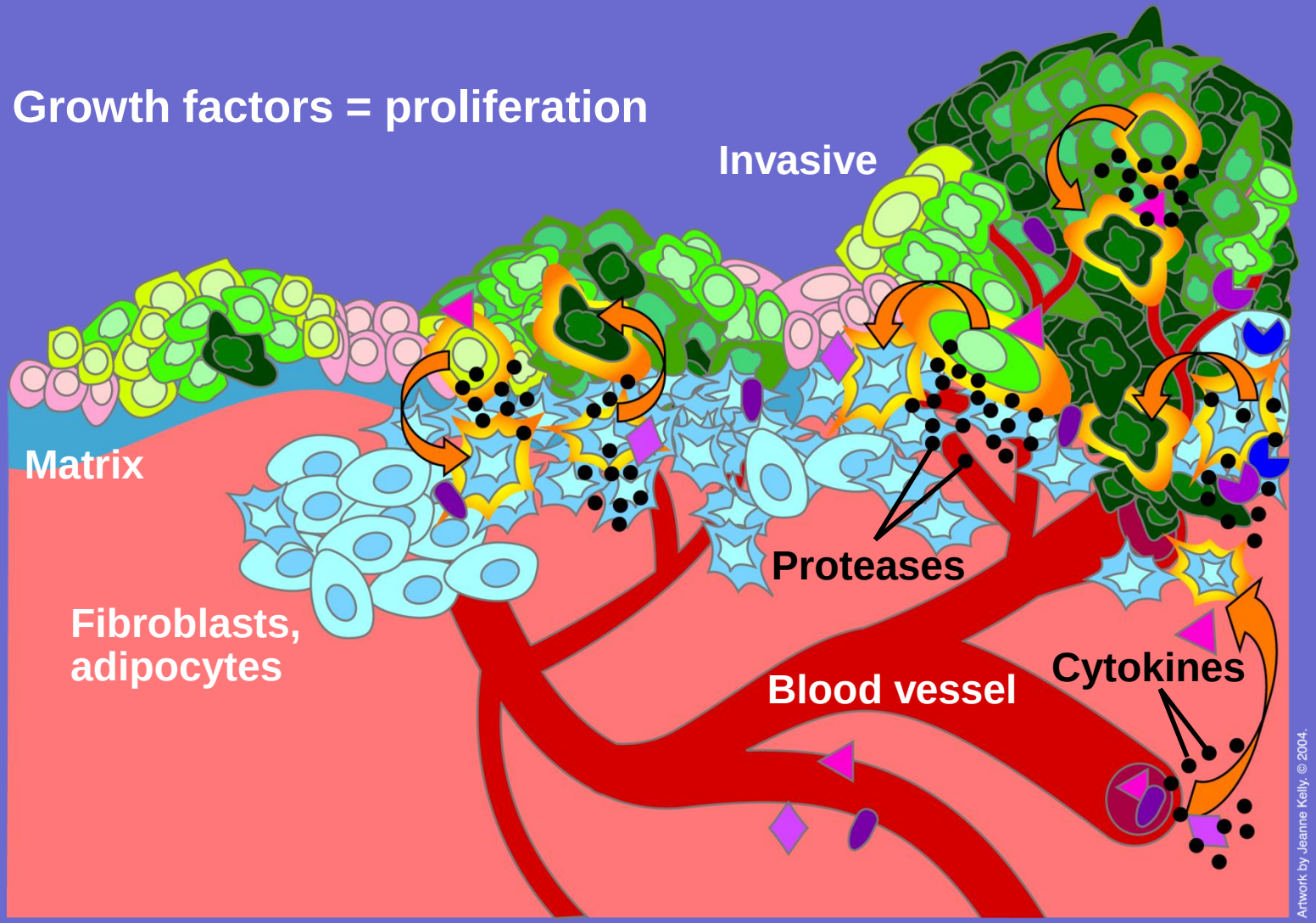
Cells proliferate

Mutations inactivate DNA repair genes

Proto-oncogenes mutate to oncogenes

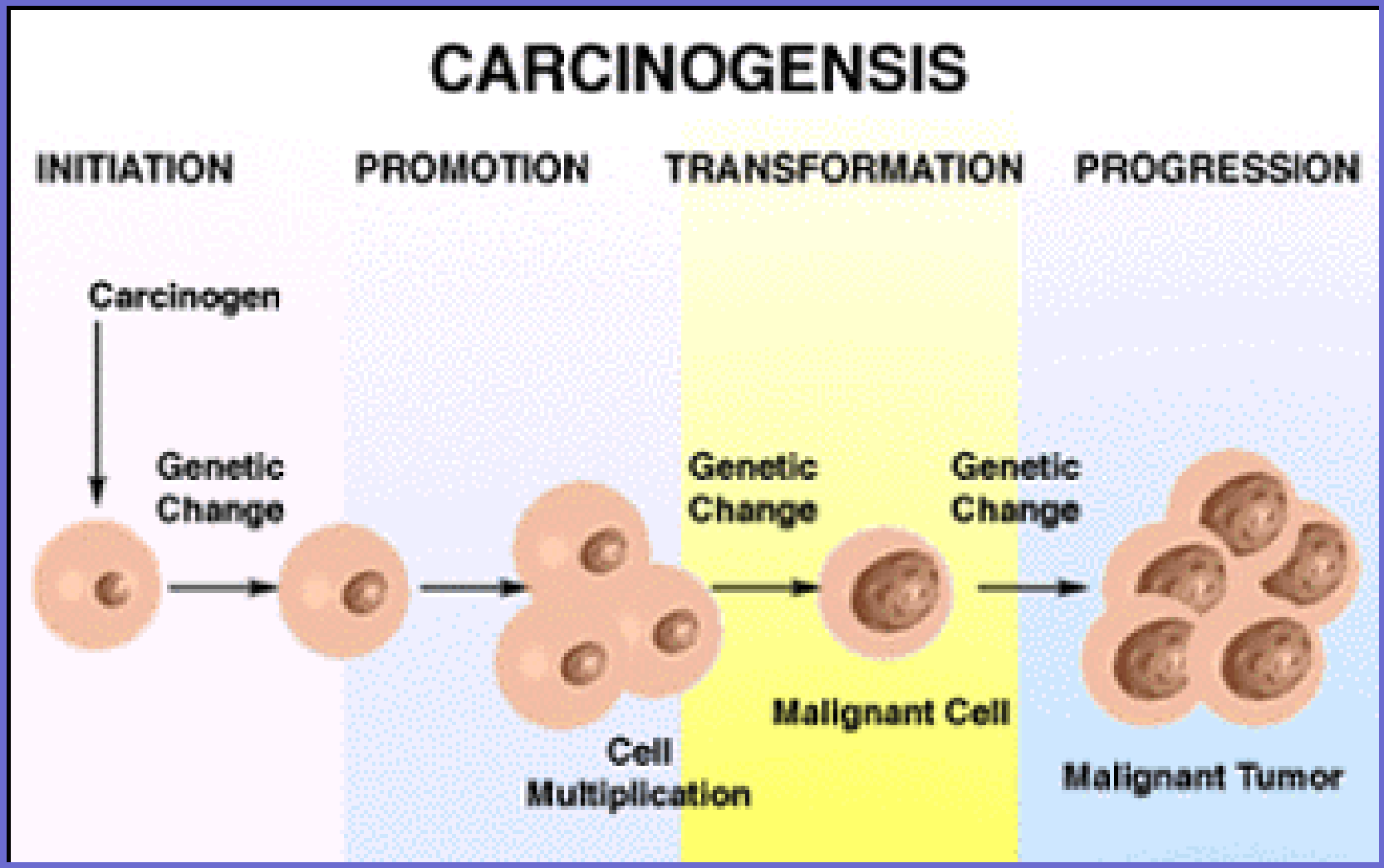
More mutations, more genetic instability, metastatic disease

Cancer Tends to Corrupt Surrounding Environment



Cytokines, proteases = migration & invasion

Stages in cancerogenesis



Cancer and apoptosis

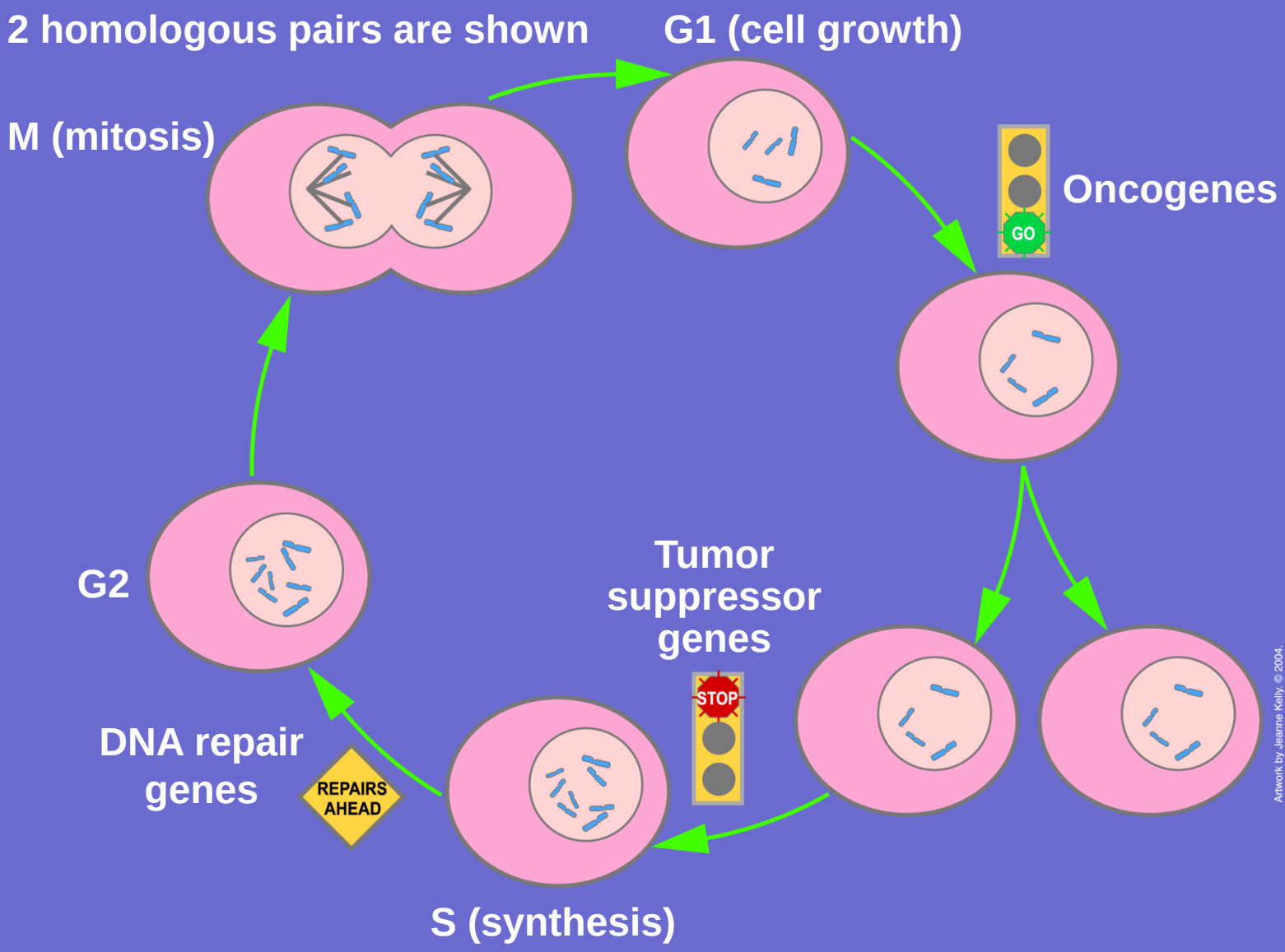
Apoptosis is the tightly regulated process of cell death that controls cell numbers, removes damaged cells, and prevents damaged cells being replicated, thereby maintaining tissue integrity and protecting against cancer

Triggers for apoptosis in normal cells include DNA damage, disruption of the cell cycle, hypoxia, reactive oxygen species, and physical or chemical insult

Cancer cells have acquired mutations in genes regulating apoptosis and therefore can evade apoptotic signals

This avoidance of apoptosis (apoptosis evasion) allows further opportunity for additional mutations to develop

Normal Cell Growth: The Cell Cycle



Cancer and angiogenesis

Tumor cells have high energy requirement

Angiogenesis, the formation of new blood vessels, is essential for the supply of nutrients (glucose) and oxygen to any growing tissue, including tumors

The generation of blood vessels in adults is fairly constant and tightly controlled by a balance of angiogenesis inducers and inhibitors

For a cancer to progress to a larger size, it must acquire the ability to induce angiogenesis

Currently about 35 proteins have been identified as angiogenesis activators or inhibitors

Cancer and immune system

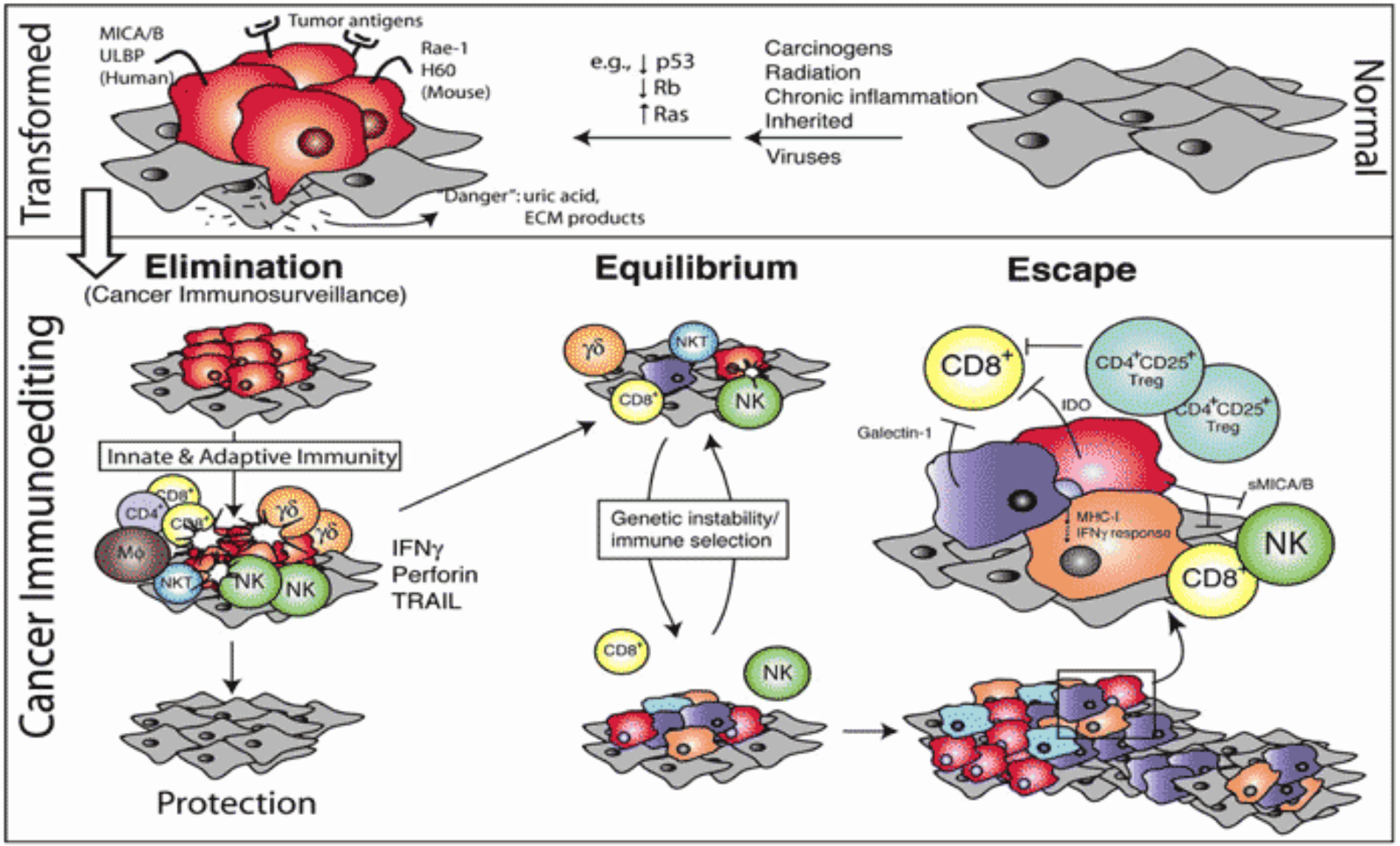
Immune system scavenges constantly abnormal cells, among them cells that could progress to cancer

T cells of the immune system carry out regular checks to find and remove cancerous and pre-cancerous B cells (target cells exposing non-self antigens)

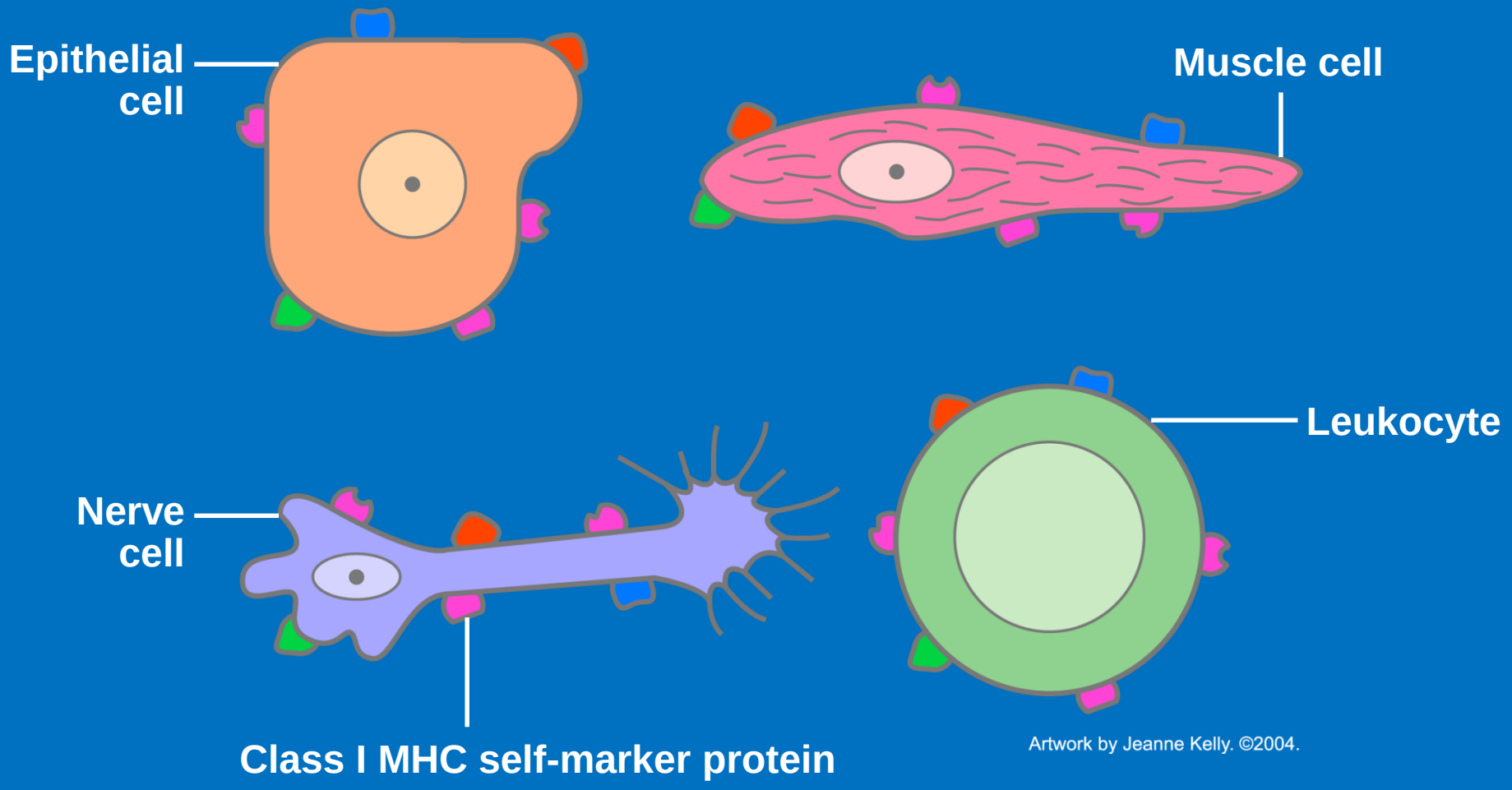
Tumour cells acquire the capacity to escape immune system checks (cancer cells manage to be recognized as "self")

There are strategies to reactivate the immune system against tumor cells (recognized as "non-self"), for instance by inhibiting the immune check-points

Tumour and immunity

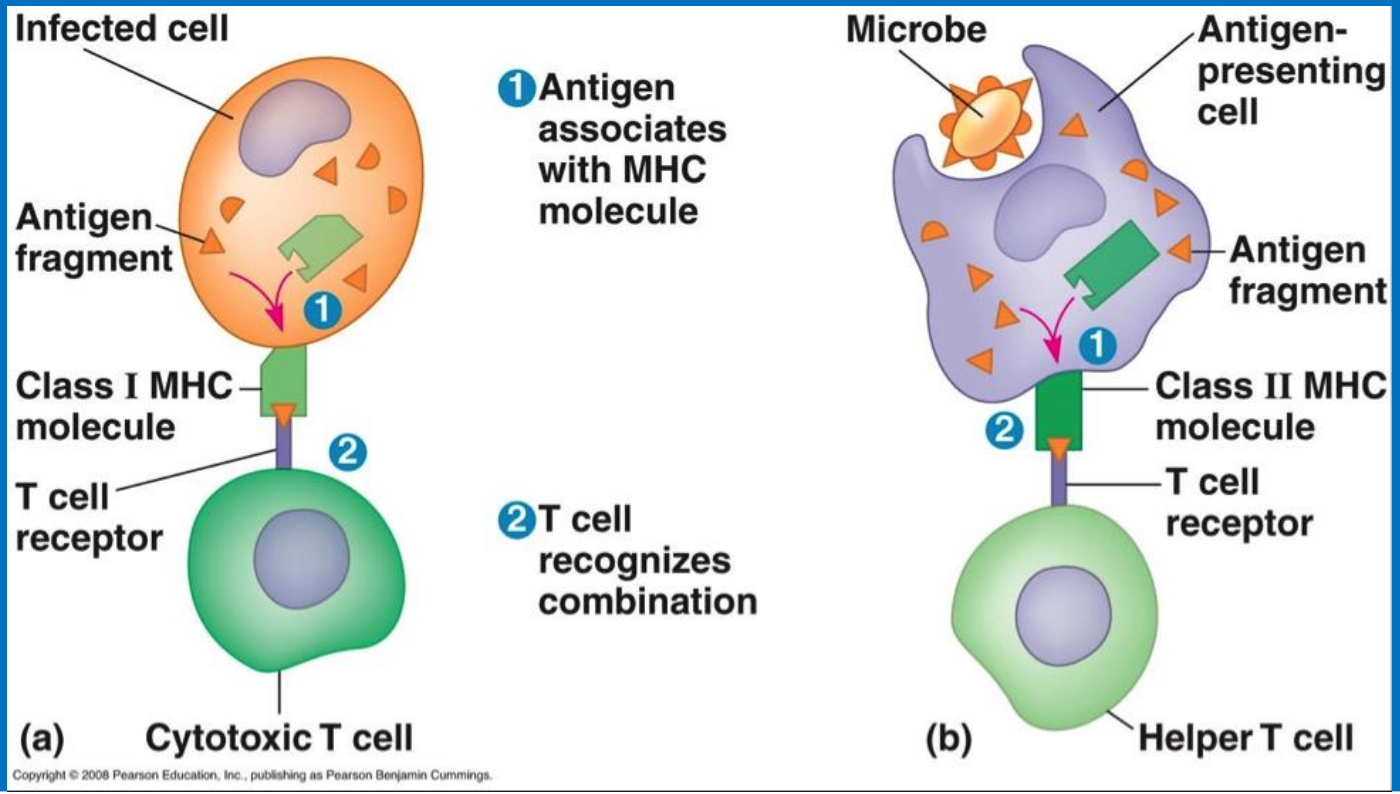


Markers of Self - major histocompatibility complexes

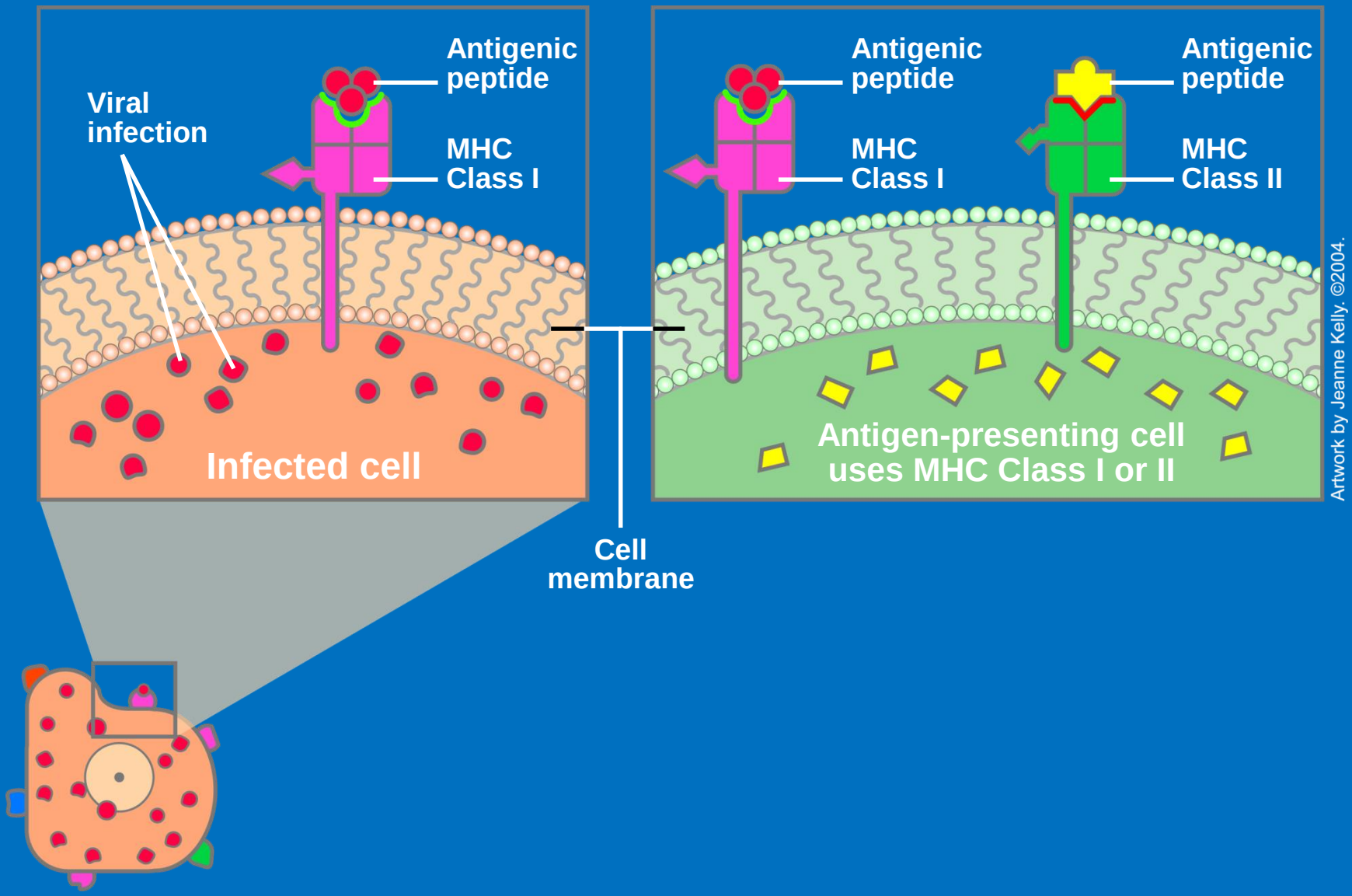


Degradation of pathogen proteins

- The peptides originated from proteasome degradation of pathogen proteins are displayed at the cell surface by the major histocompatibility complex class I and II (MHC) proteins
- This process plays a critical role in the function of the adaptive immune system



Markers of Self versus non-Self: Major Histocompatibility Complex

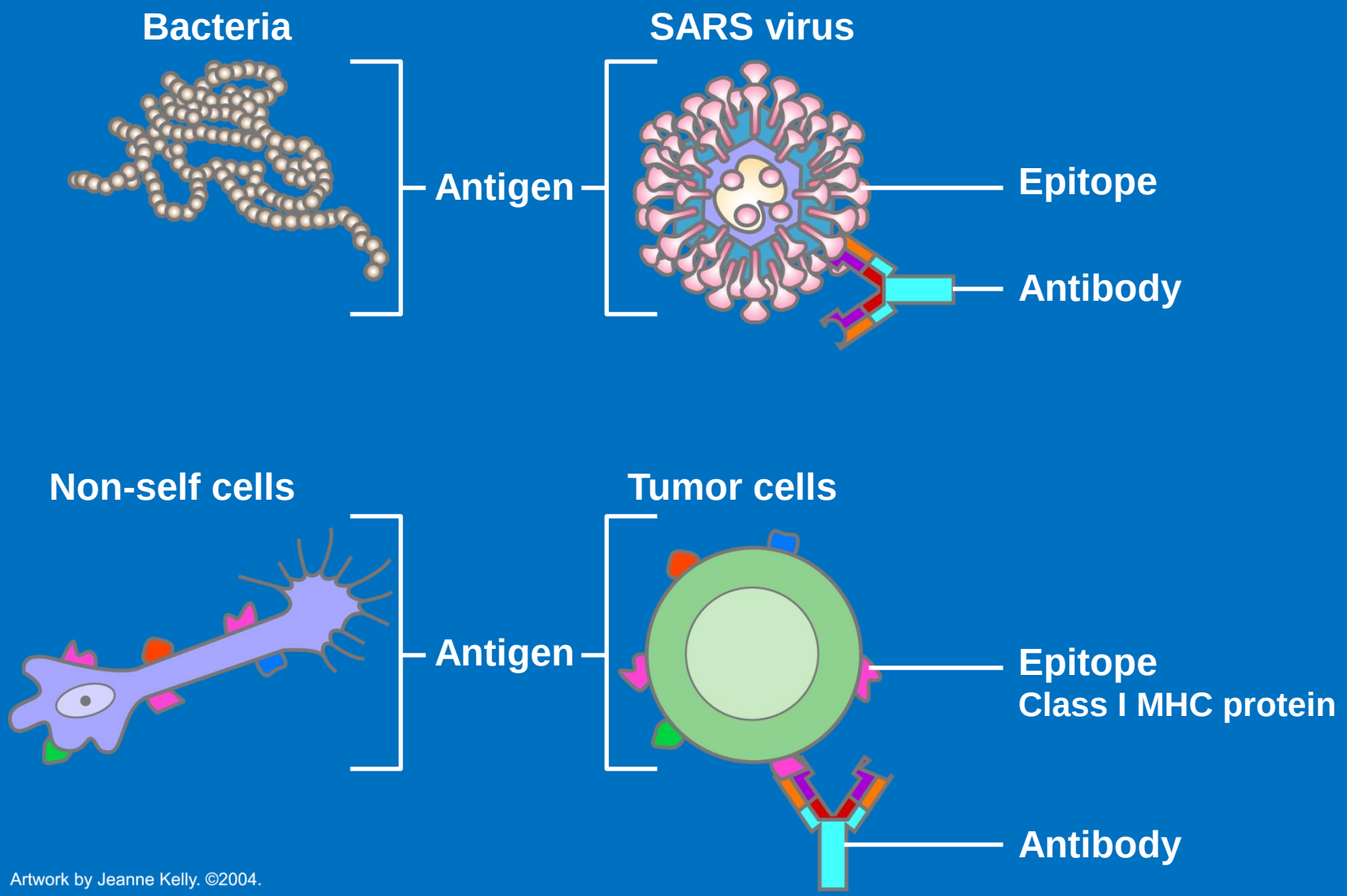


Markers of Non-Self: tumor-specific and tumor-associated antigens

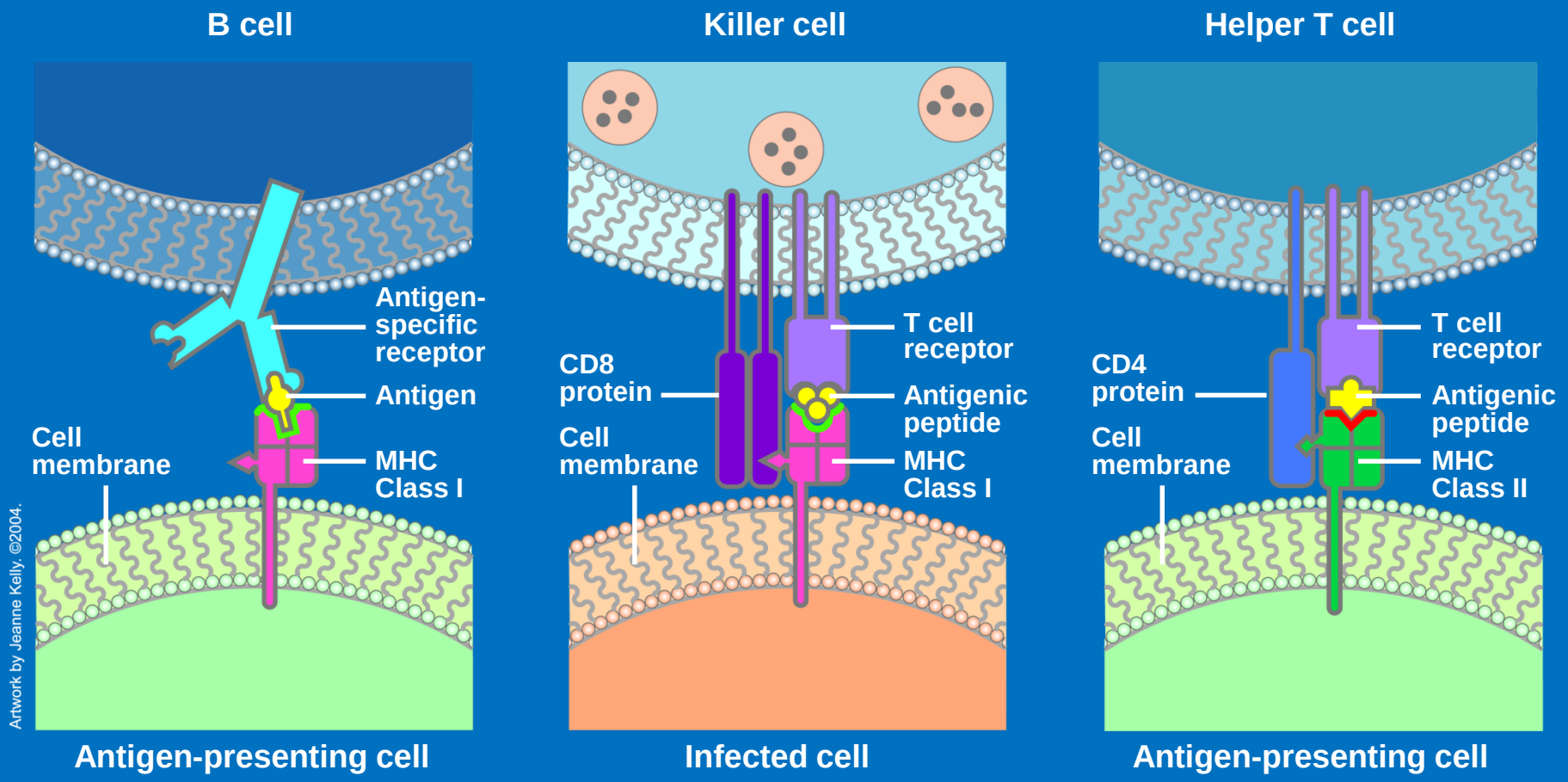
Tumor specific antigens: present exclusively on tumor cells as a consequence of mutations and metabolism modification

Tumor associated antigens: expressed also in self tissues such as testis or placenta. They do not need to be involved in oncogenesis but are usually promoting growth and development (in physiological conditions)

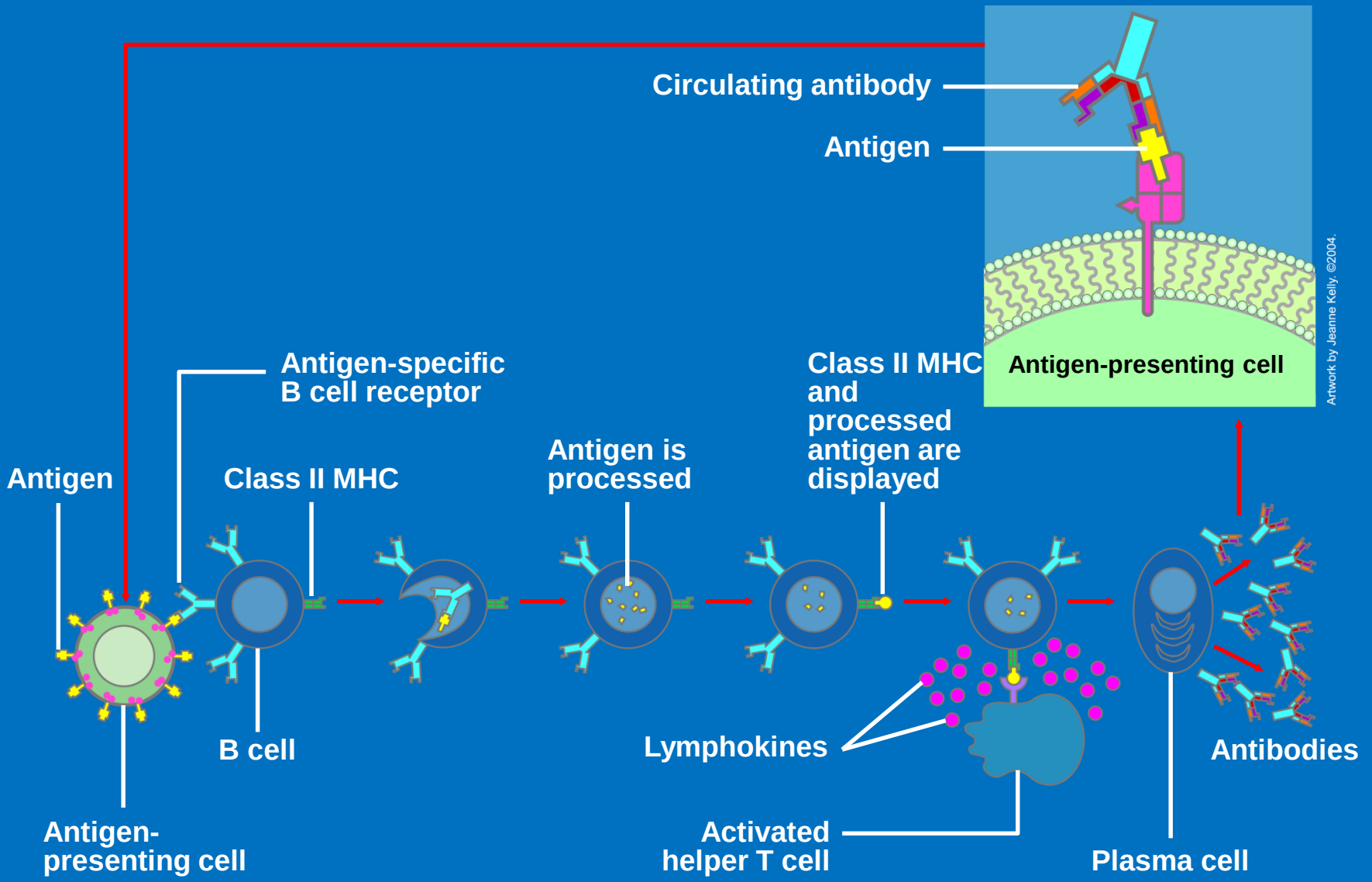
Markers of Non-Self



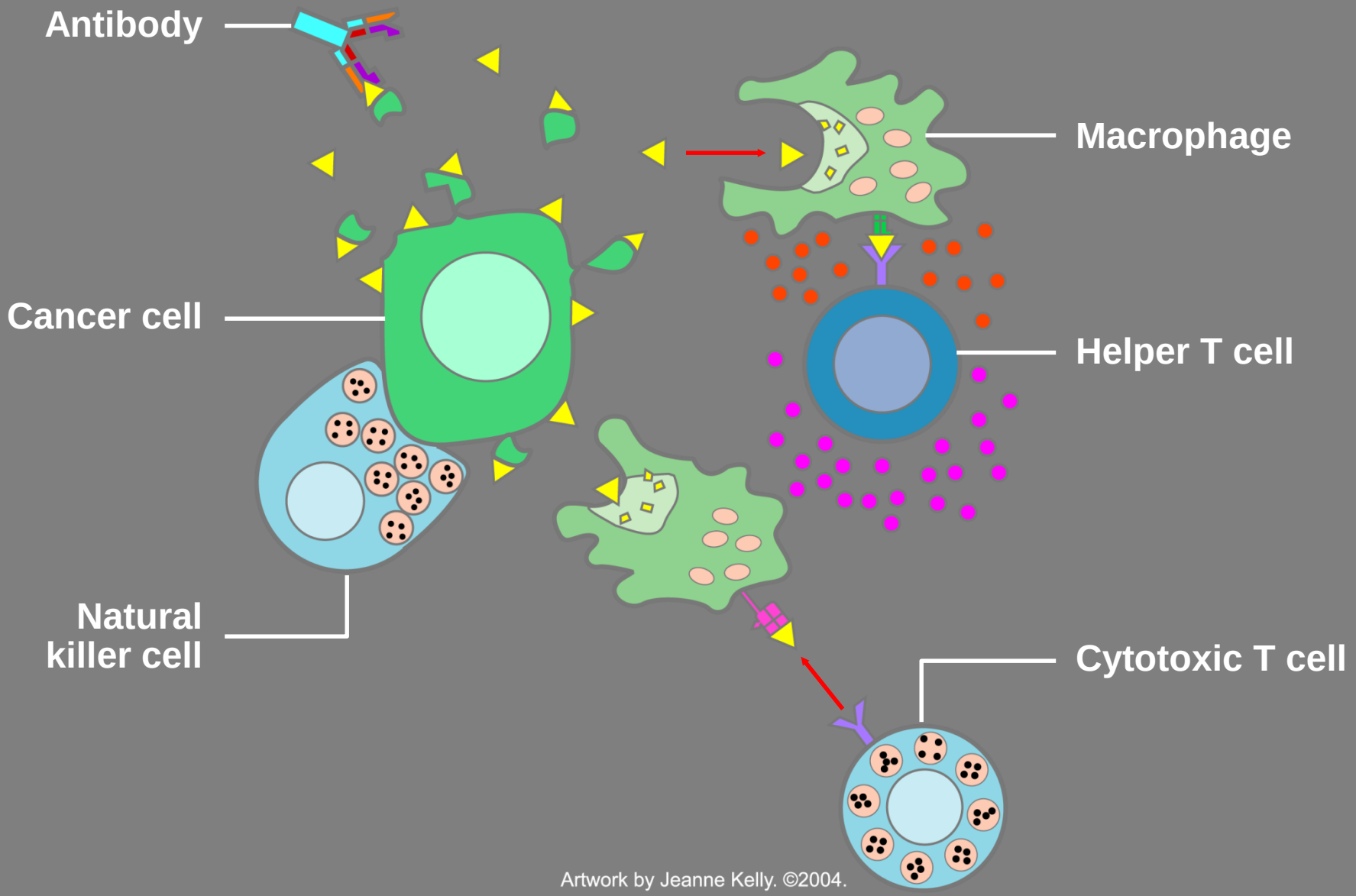
Antigen Receptors



Activation of B Cells to Make Antibody



Immunity and Cancer



Regulatory T Cells (Treg)

The immune response is crucial to control disfunctions, but its activity must be modulated to avoid autoimmunity