Molecular Disease Mechanisms

Lecture 5: Cancer and Inflammation

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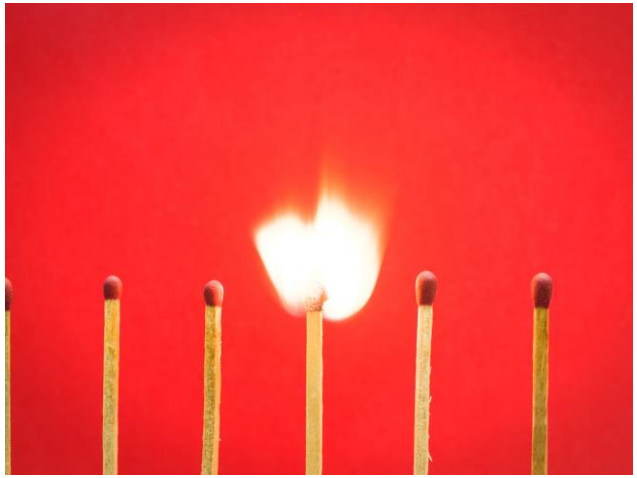
Lecture 5/6, Part 1

CANCER AND INFLAMMATION



After this lecture you will be able to:

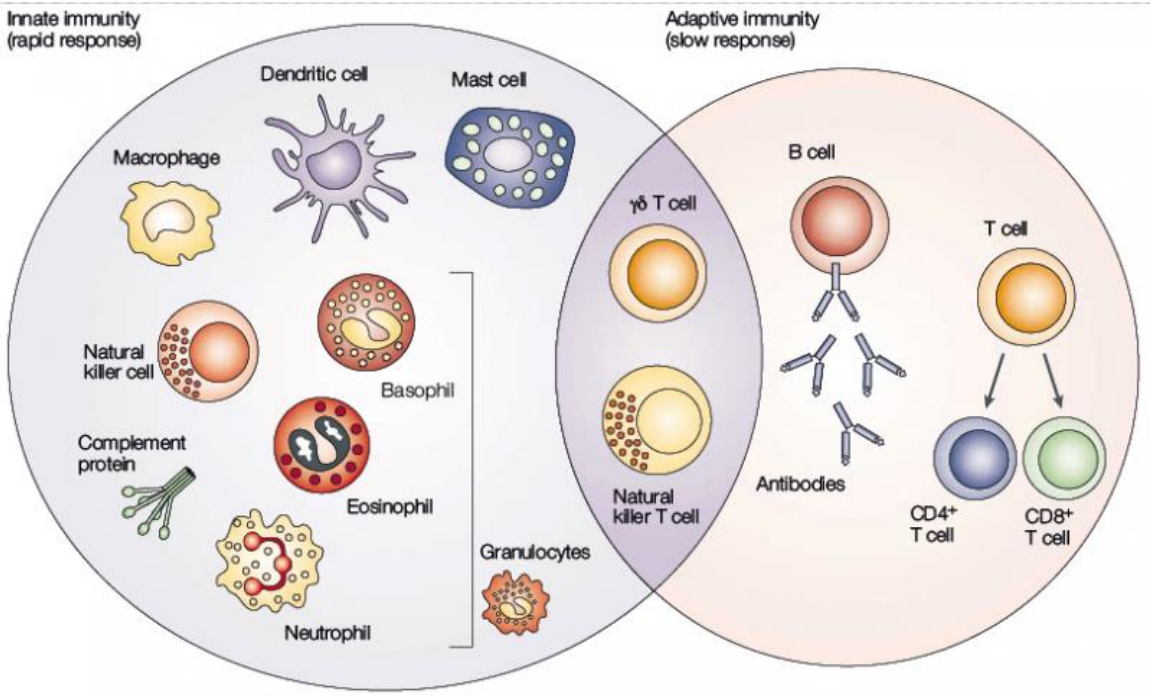
1. Cancer and Inflammation

    Know Inflammation pathways disrupted in cancer

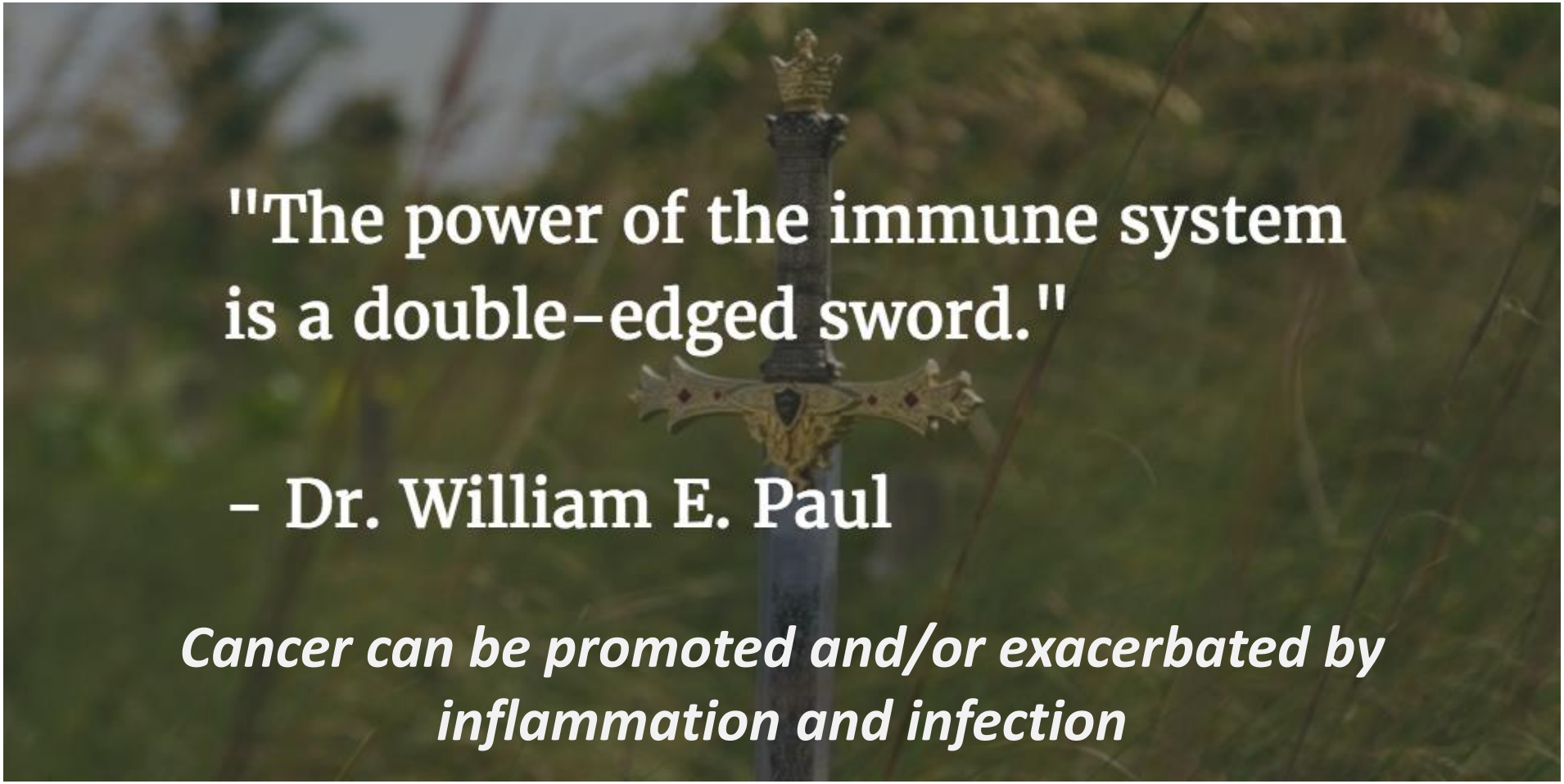
    Understand what is new in cancer immunotherapy

Immune system

- 2 types of defense systems:
  - **Innate**: response after an infection, no prior exposure, does not require the presentation of an antigen, and does not lead to immunological memory
  - **Adaptive**: immune defense later in infection that is highly specific to the pathogen (immunological memory)



Dranoff G. Nat Rev Cancer 2004;4:11-22



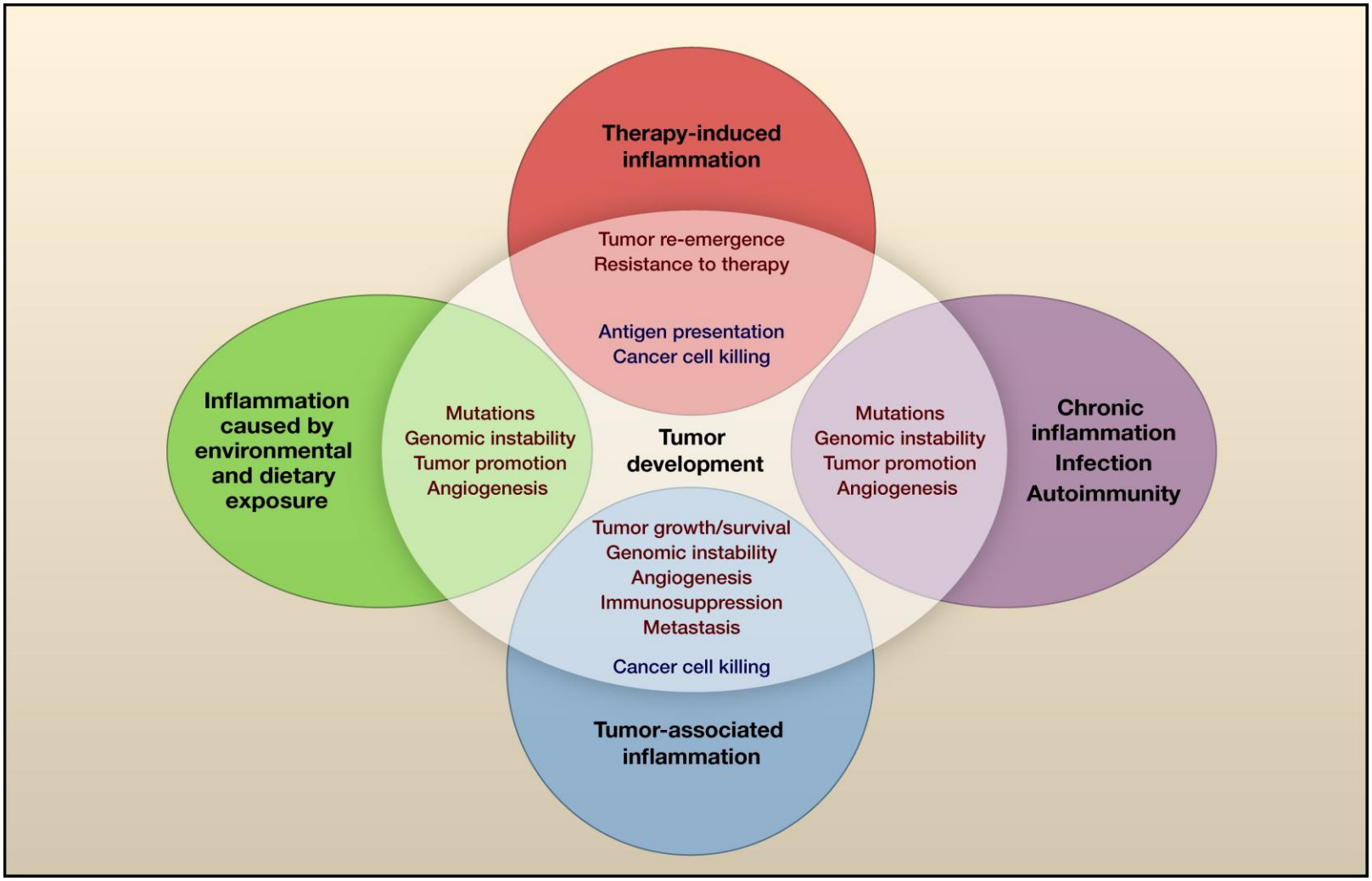
Cancer can be promoted and/or exacerbated by inflammation and infection

Immunity and cancer: a double edged sword

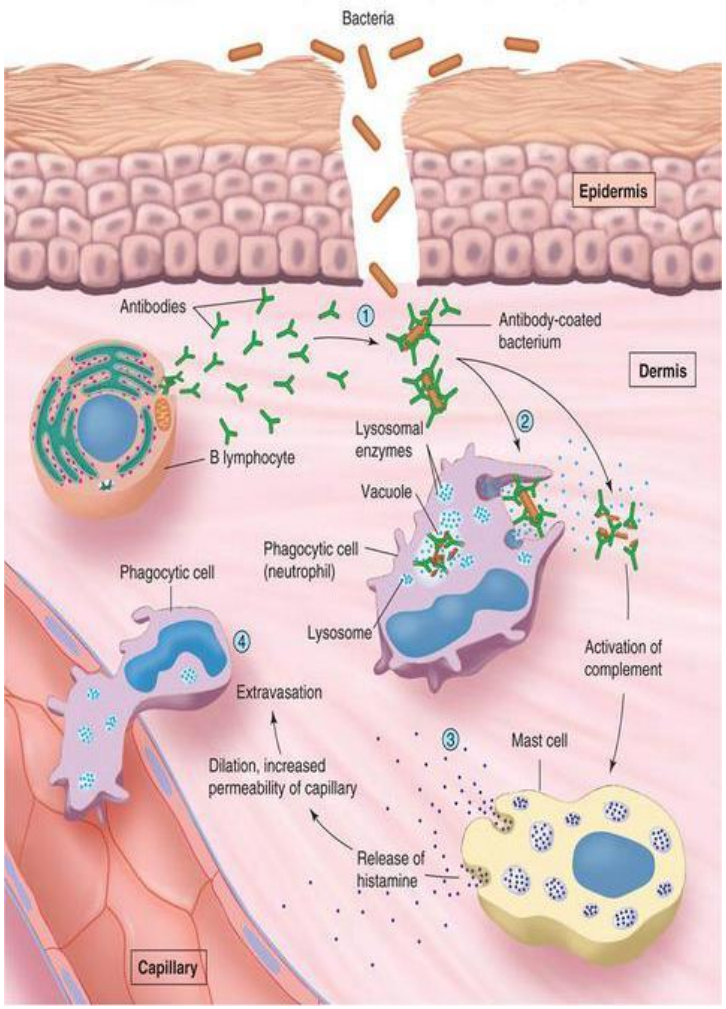
- Tumor cells produce various cytokines and chemokines that attract leukocytes (for growth advantage) as well as to prevent immune cell detection (evade surveillance)

- Chronic inflammation is the problem (vs acute)

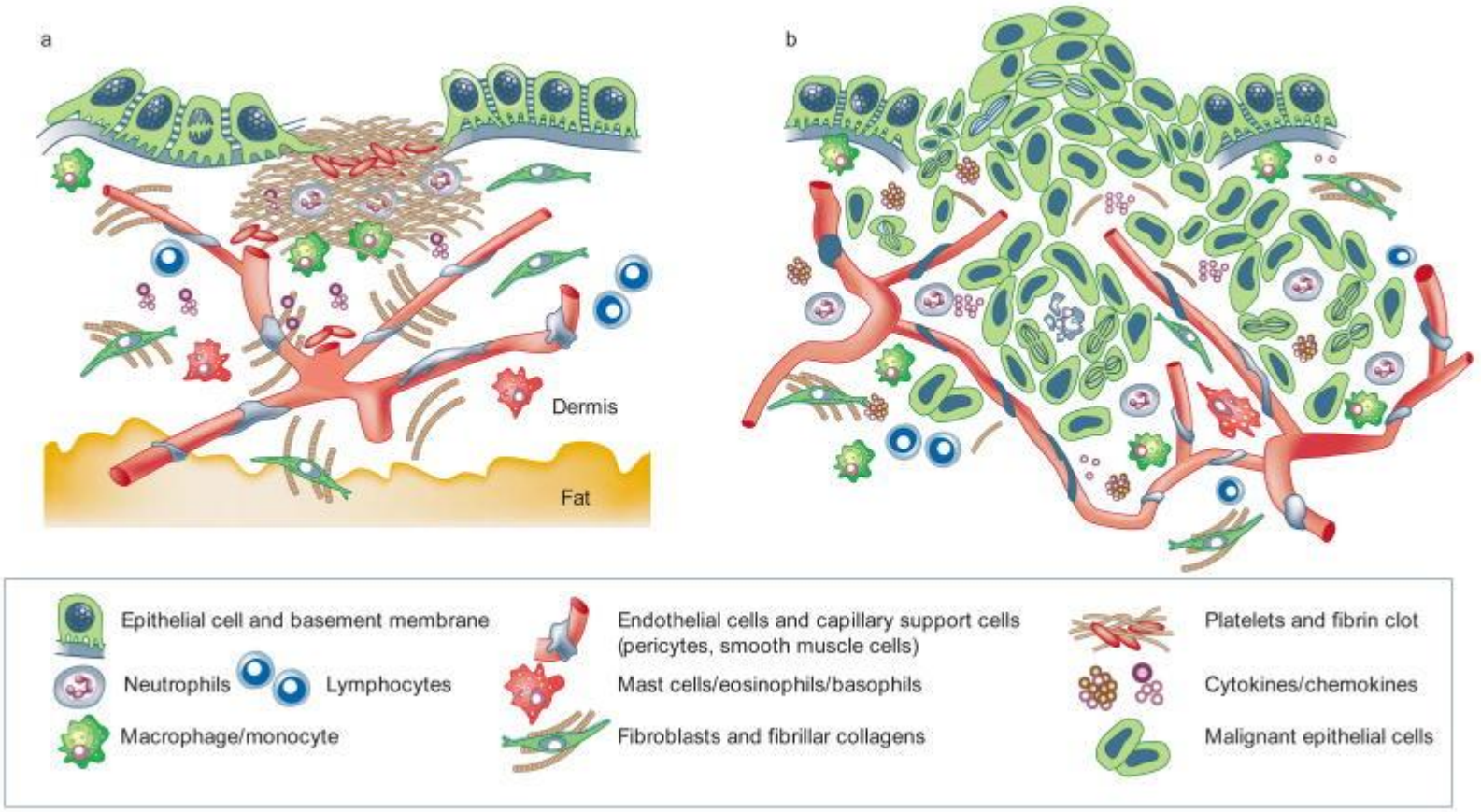
Inflammation has a vital and complex role in driving tumorigenesis



The inflammatory response

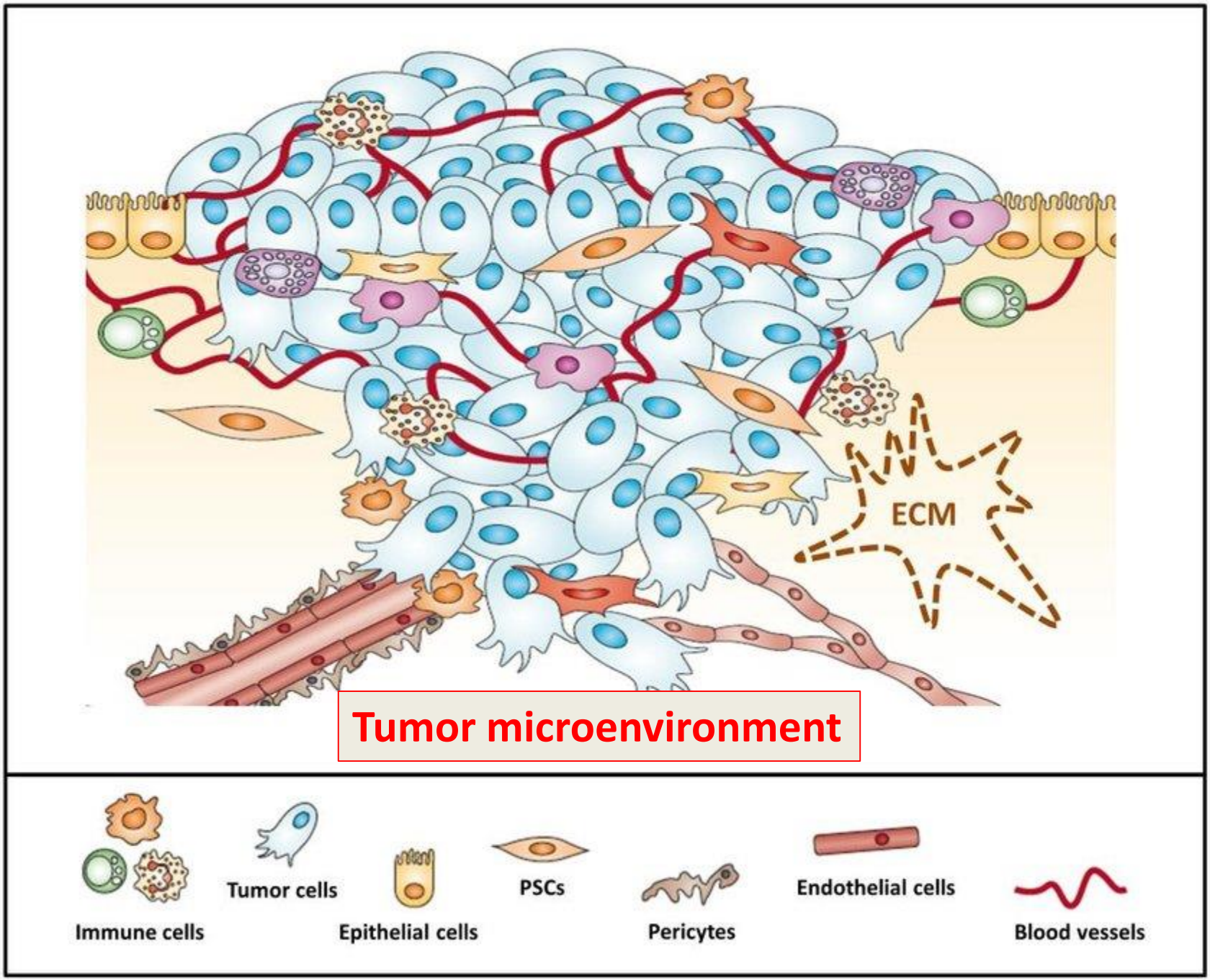


Wound healing vs tumor growth

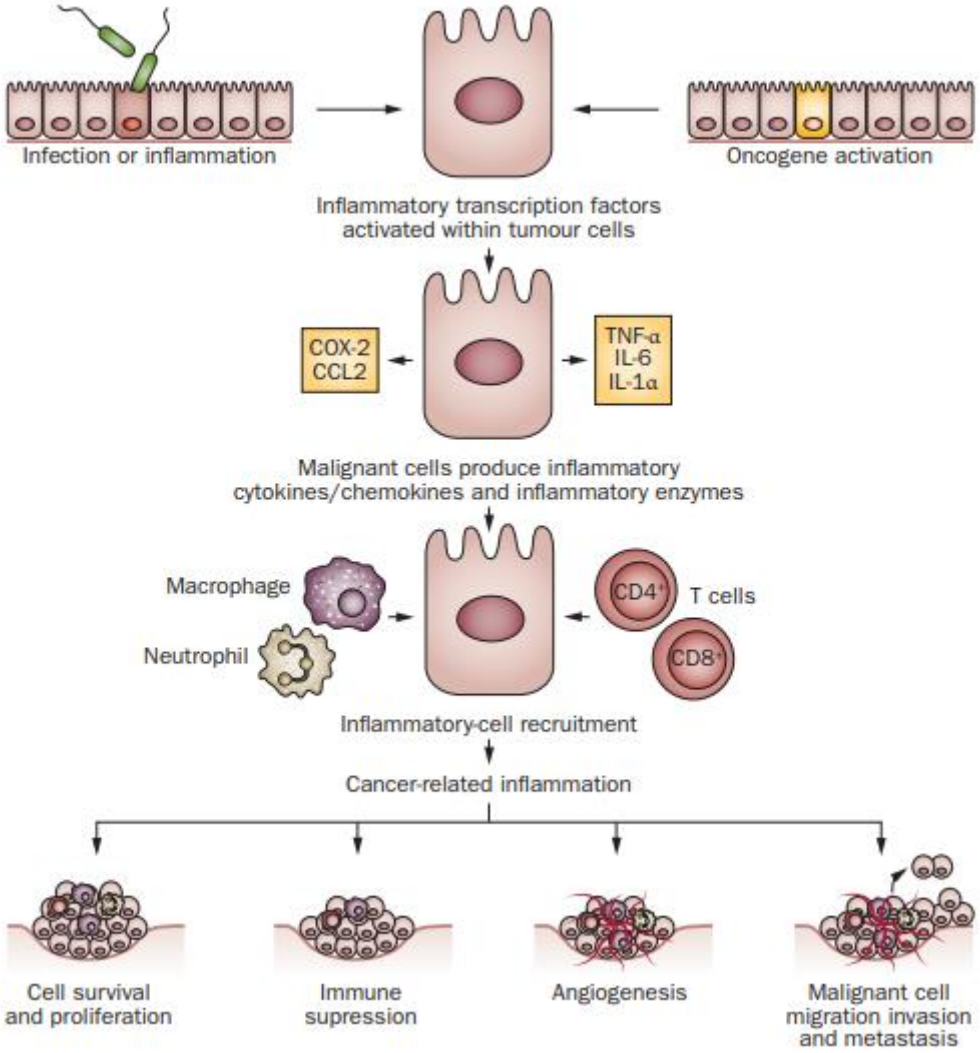


Tumors act as wounds that fail to heal

Nature. 2002 Dec 19; 420(6917): 860–867


ECM
Tumor microenvironment
Immune cells
Tumor cells
Epithelial cells
PSCs
Pericytes
Endothelial cells
Blood vessels

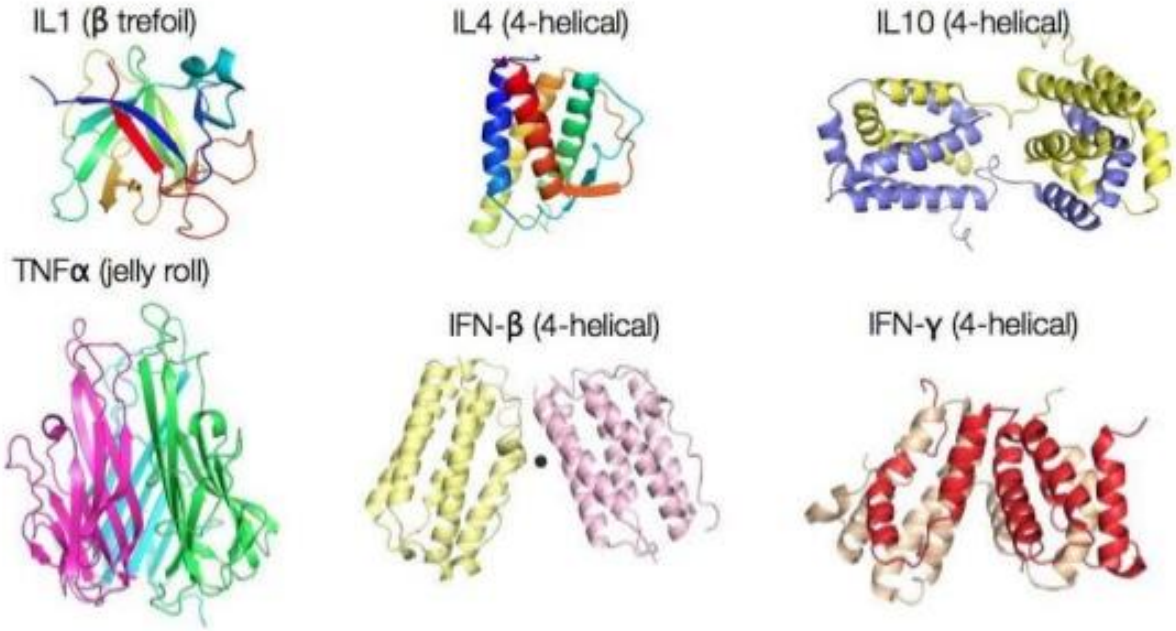
Molecular mechanism of inflammation-induced cancer



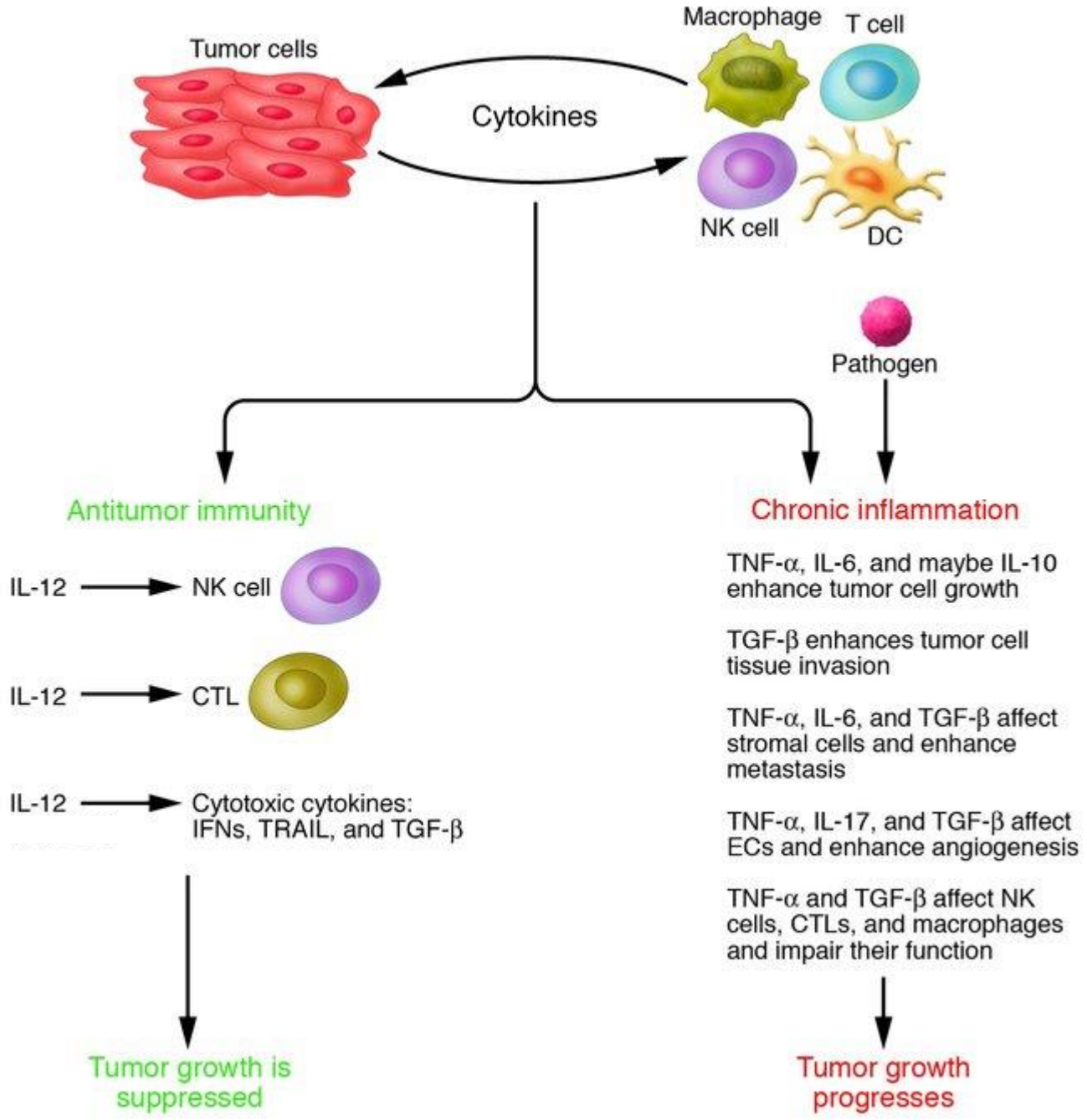
Crusz, S. M. & Balkwill, F. R. Nat. Rev. Clin. Oncol. 12, 584–596 (2015)

Cytokines

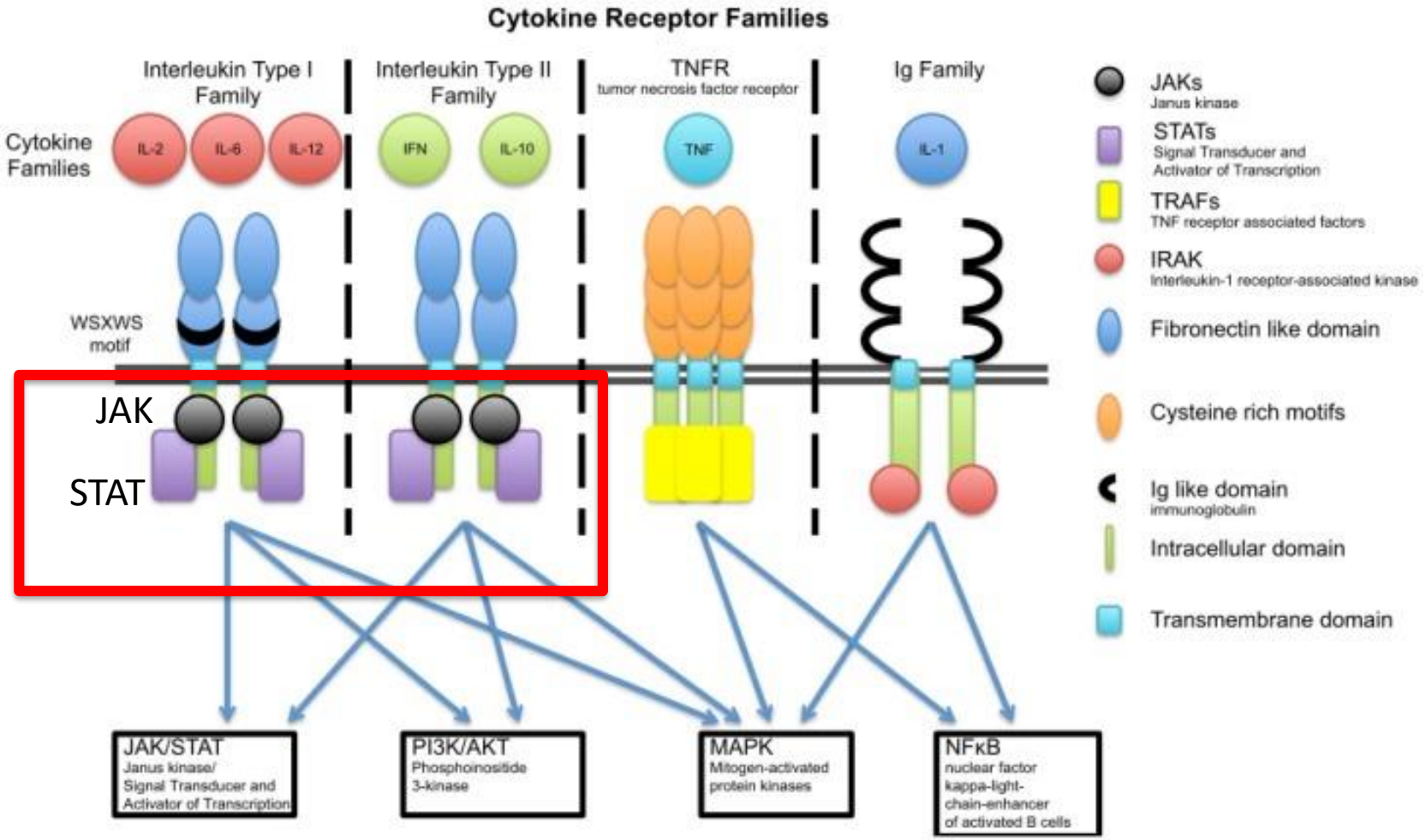
- Broad category of small proteins (~5–20 kDa) important in cell signaling
- Cytokines include chemokines, interferons (IF), interleukins (IL), lymphokines, and tumor necrosis factors (TNF)



The cytokine players in cancer

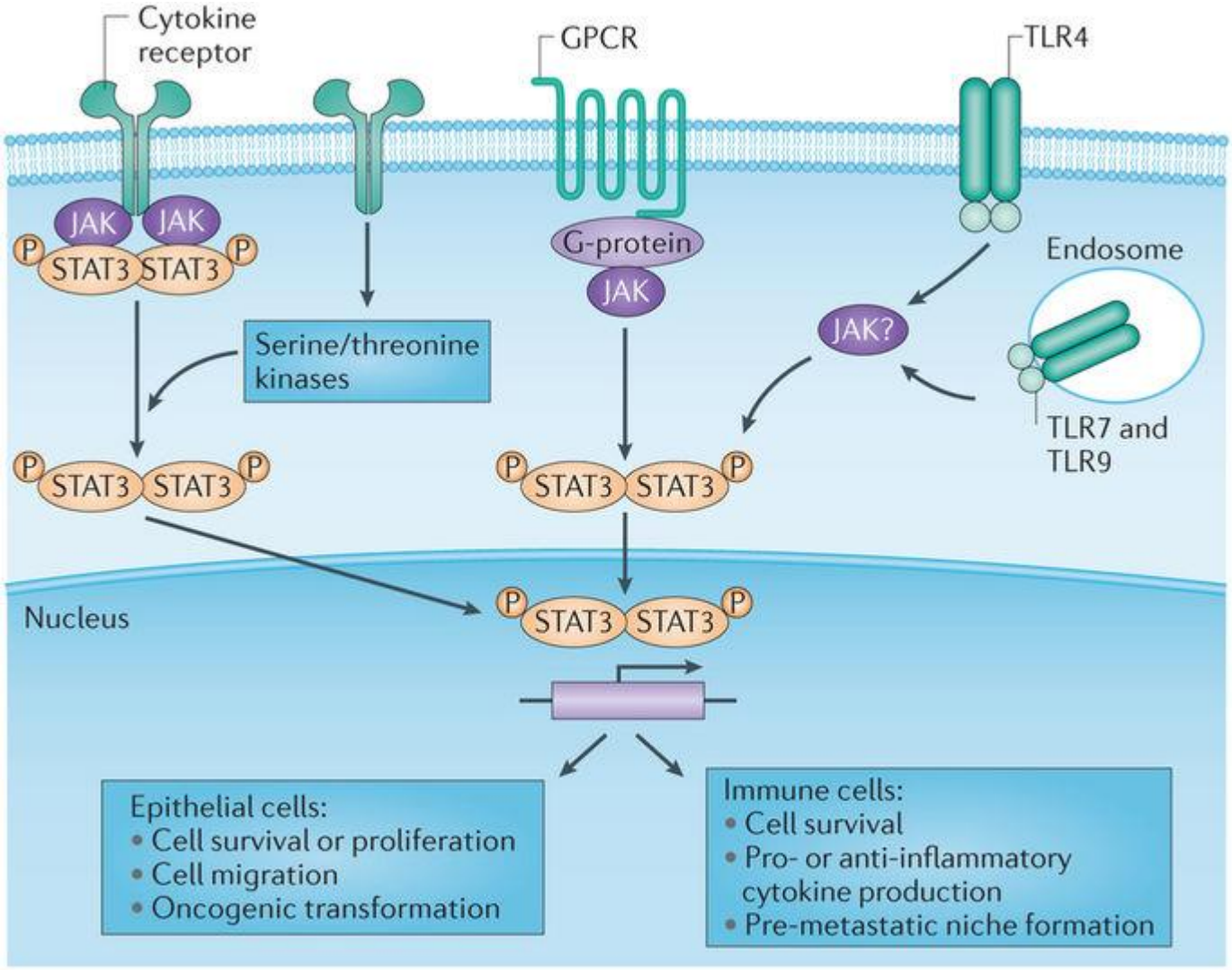


Cytokine receptors



https://openi.nlm.nih.gov/detailedresult.php?img=PMC3645662_ijms-14-06720f2&req=4

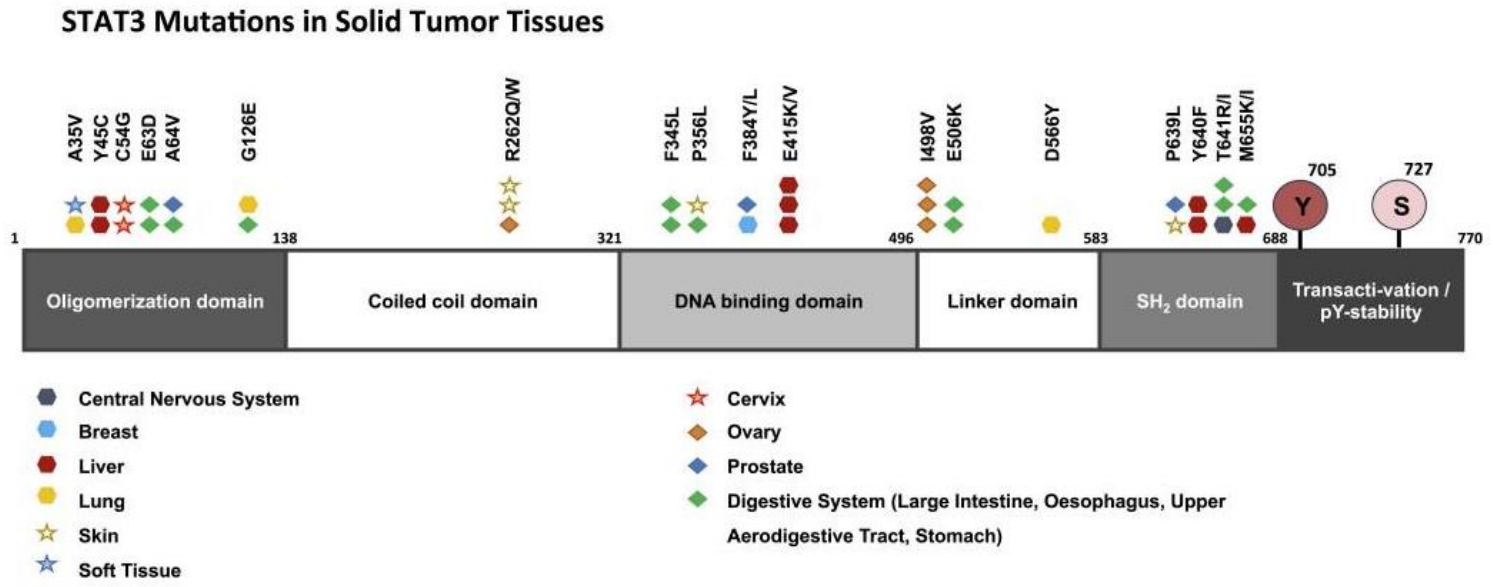
Activation of JAK-STAT3 in cancer

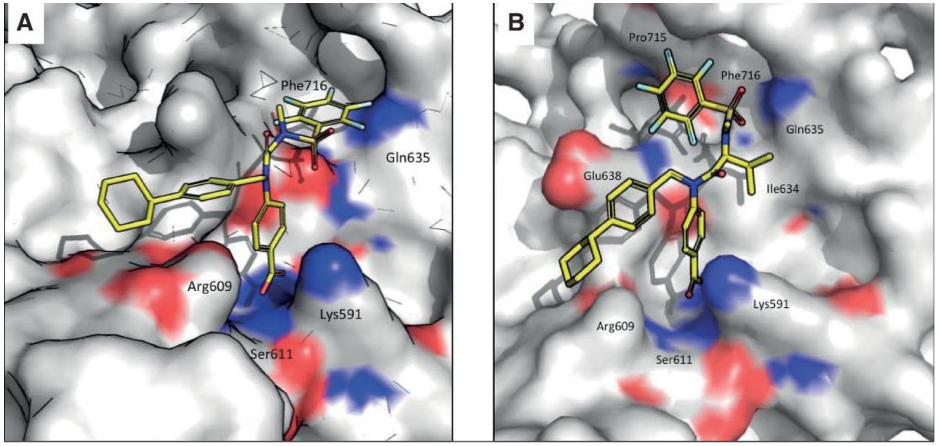


https://www.youtube.com/watch?v=dnnsqiDjAgM

Nature Reviews | Cancer

STAT3 mutations and inhibition

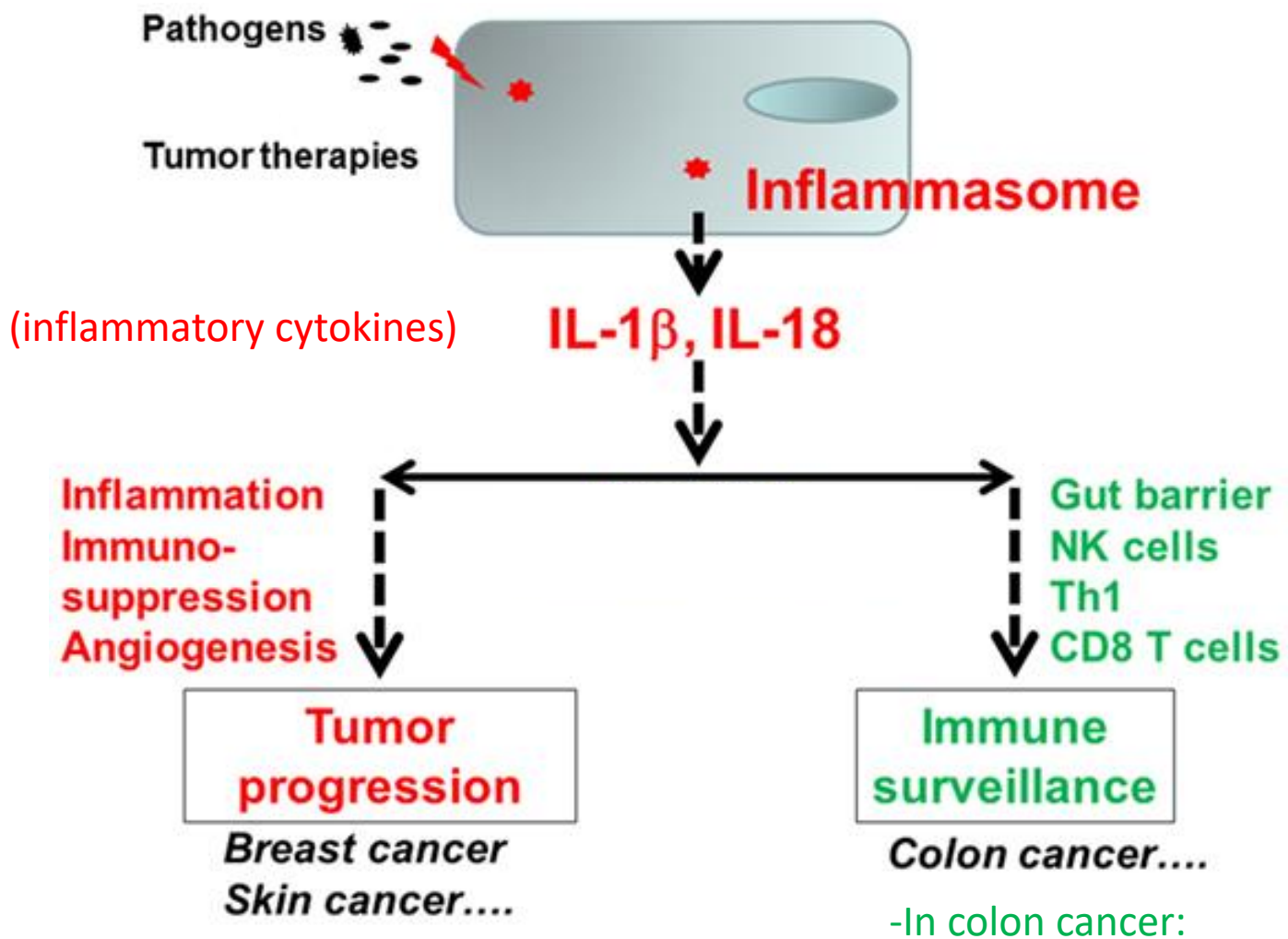




Applying Small Molecule Signal Transducer and Activator of Transcription-3 (STAT3) Protein Inhibitors as Pancreatic Cancer Therapeutics -> Binding to the SH2 domain of STAT

Front Immunol. 2017; 8: 1132

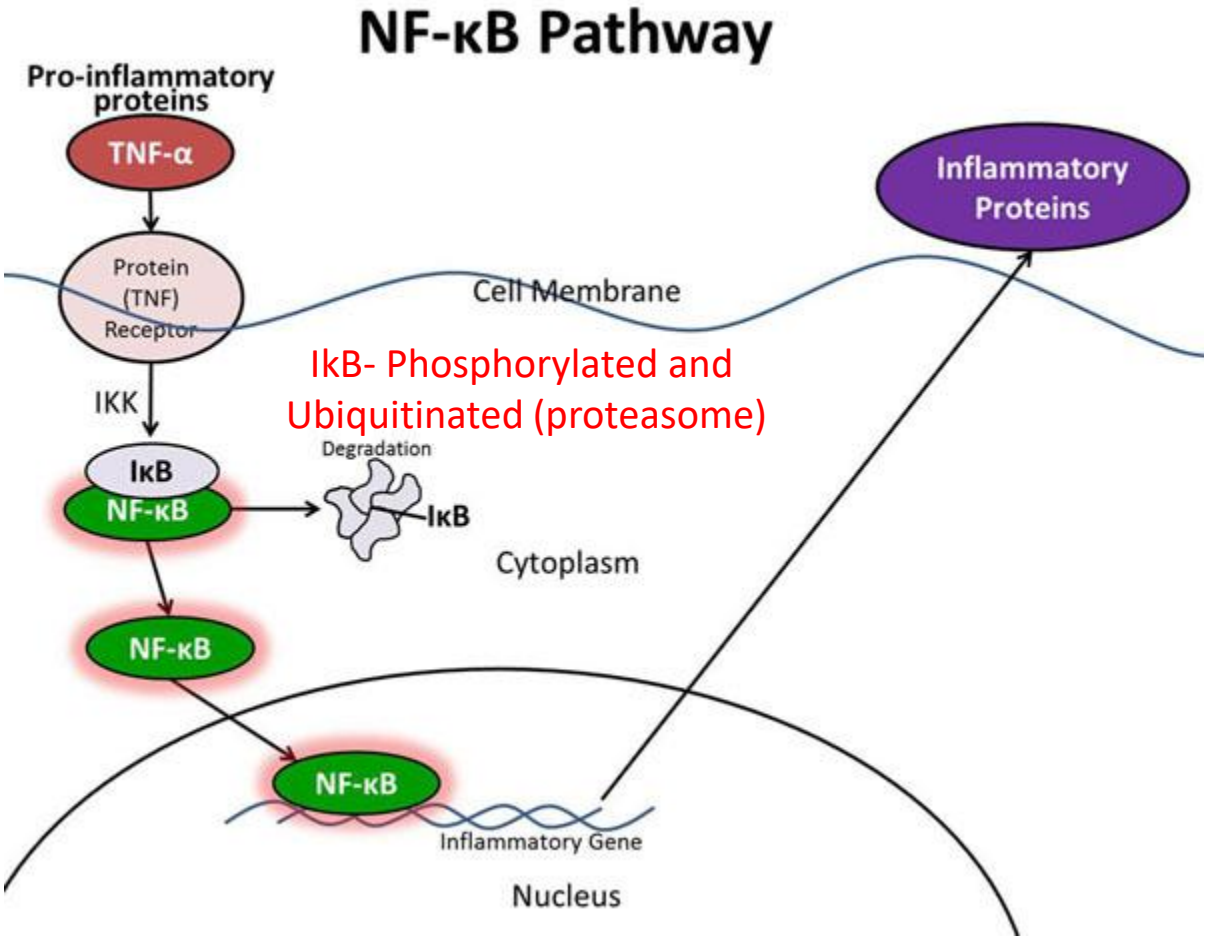
Inflammasome and cancer



-In Breast Cancer:
IL-1β induces tumor growth

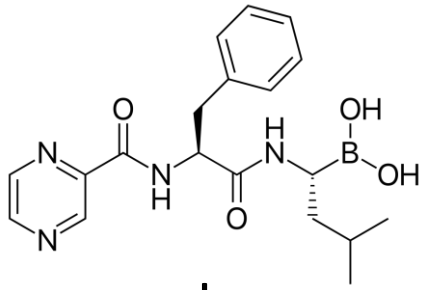
-In colon cancer:
IL-18 induces tumor surveillance

Inflammation triggers NF-kB pathway

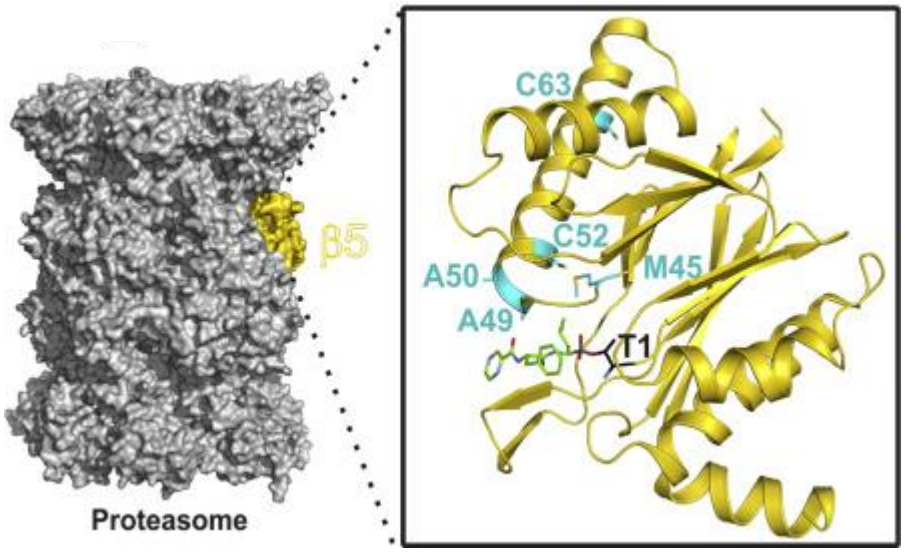


https://sites.google.com/a/googlesciencefair.com/science-fair-2012-project-ahjzfnnjawvuy2vmywlyltiwmtjydwssb1byb2ply3qyv5pida/research/nf-kb-inflammatory-pathway

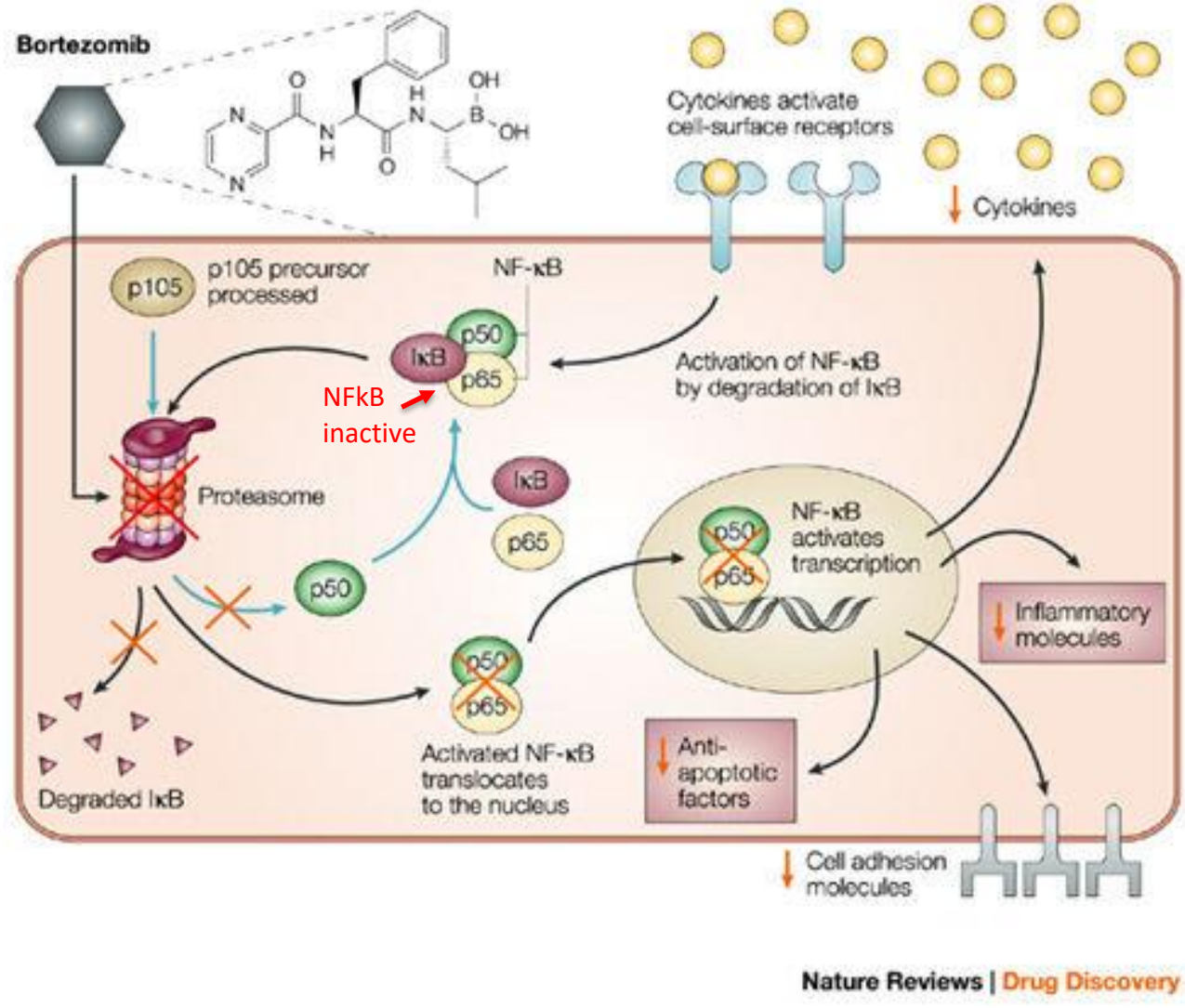
Bortezomib



- Bortezomib - the first proteasome inhibitor anticancer drug
- Treatment of relapsed and refractory multiple myeloma (hard cancer to treat)
- mechanism - suppression of the NF-κB signaling pathway resulting in the down-regulation of its anti-apoptotic target genes
- Bortezomib is a reversible inhibitor of the proteasome
- The boronic acid group can bind and complex to the active site of threonine hydroxyl group (β5-subunit) and block the chymotrypsin-like activity of the proteasome



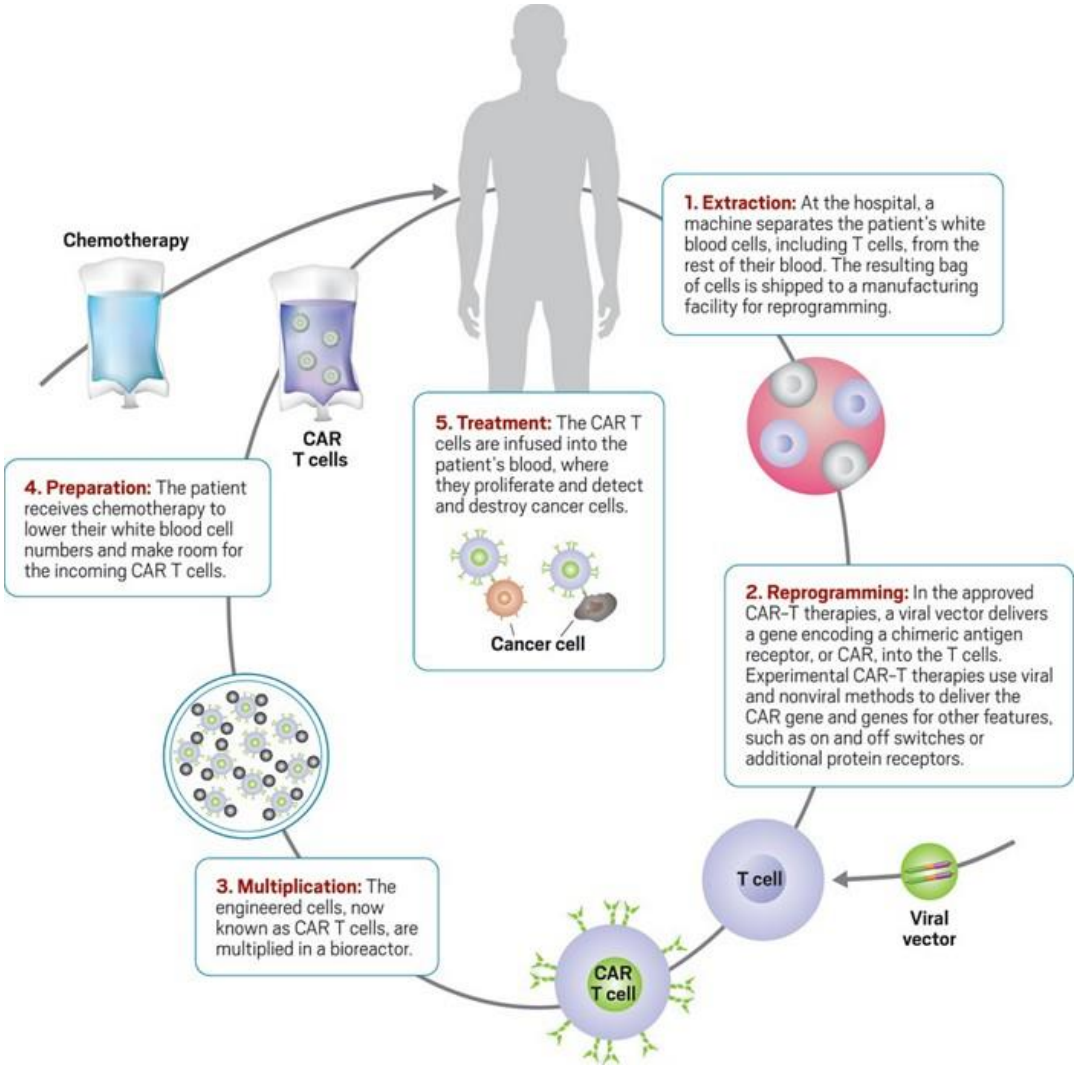
Proposed mechanism of action



NF-kB involved in B cell maturation - (Bortezomib treats B cell malignancies)

What's new in cancer immunotherapy?

- Immunotherapy treatment uses a person's immune system to fight cancer. This can be done in a couple of ways:
  - Stimulating your own immune system to attack cancer cells
  - Administering immune system components, such as man-made immune system proteins
- CAR-T : (chimeric antigen receptor T cell therapy) - Engineering patients' immune cells to treat their cancer



https://www.youtube.com/watch?v=mXADrg_ckhI

ONCOLOGY

CAR-T cancer immunotherapy took off

Two personalized immune-cell therapies came to the market, and more are likely on the way

Ryan Cross

C&EN, **2017**, *95* (48), pp 44–44 | December 4, 2017

August 2017 FDA approved 2 CAR-T therapies

An IV bag of Kymriah, the one-time, $475,000 CAR-T immunotherapy treatment from Novartis, contains a patient's genetically engineered T cells. (Credit: Novartis)

Challenges with CAR T-cell therapy

- Dosing: No uniform consensus on the dose. Small dose infusions may not obtain the ideal curative effect; large dose infusions can increase cytokine release syndrome and tumor lysis syndrome.
  - Traditional drugs are **ephemeral**—they begin to break down as soon as they enter the bloodstream—CAR-Ts are a **living therapy** that multiplies exponentially once the cells spot their cancer target in the blood
- Toxicity: *Kymriah and Yescarta both come with warnings for cytokine release syndrome, a severe, body-wide immune reaction after injection of the drug. "It's not an exaggeration to say that it almost kills you before it helps you"*
- Treatment: approved for only a small subset of cancers
  - Kymriah: treats people up to 25 years old with acute lymphoblastic leukemia of B-cell origin who are resistant to treatment or have relapsed twice (~100 cases/yr).
  - Yescarta treats large B-cell lymphoma in adults after two other treatments have failed (estimated to help ~7,500 people/yr).
- Price: Kymriah's (Novartis) one-time cost of $475,000 and Yescarta's (Kite Pharma) price tag of $373,000 – This is only for the living therapy, not hospital stays etc…

https://www.futuremedicine.com/doi/10.2217/imt.15.129

CAR-T 2.0

Controlling CAR-T: How scientists plan to make the engineered T cell therapy safer, and work for more cancers

CAR T-cell therapy works wonders for some cancer patients. For others, it is a death sentence. To make the revolutionary therapy work for more people, scientists must devise better ways to control it

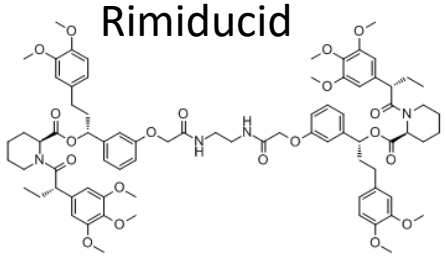
by Ryan Cross

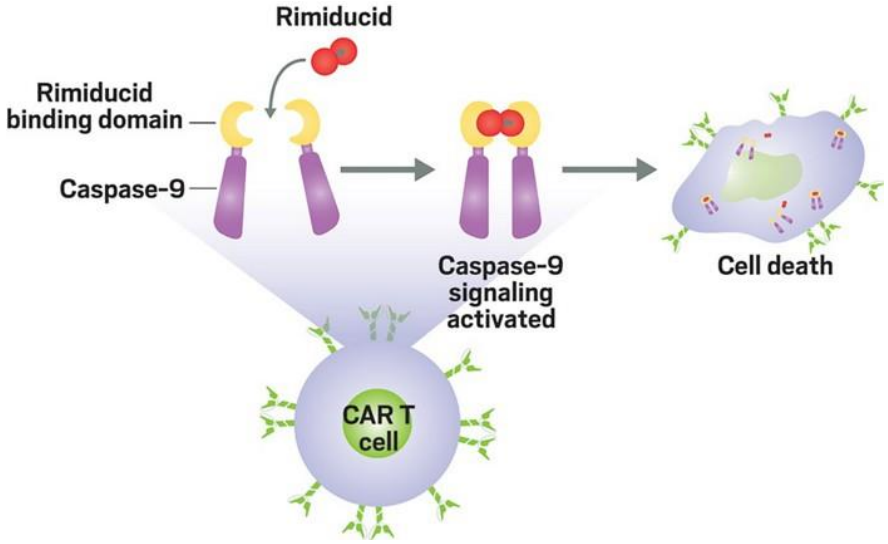
MAY 7, 2018 | APPEARED IN VOLUME 96, ISSUE 19

May 7, 2018 issue

- Brain swelling commonly occurs with CAR-T cell therapy (>12 patients have died so far)
- Making a kill switch:
  - two engineered proteins located inside the CAR T cell that dimerize when exposed to a small-molecule drug called rimiducid.
  - Rimiducid activates a protein called caspase-9, which kick-starts the process of CAR T-cell suicide.

Rimiducid





https://cen.acs.org/pharmaceuticals/oncology/Controlling-CAR-T-scientists-plan/96/i19