

Immune response against tumors

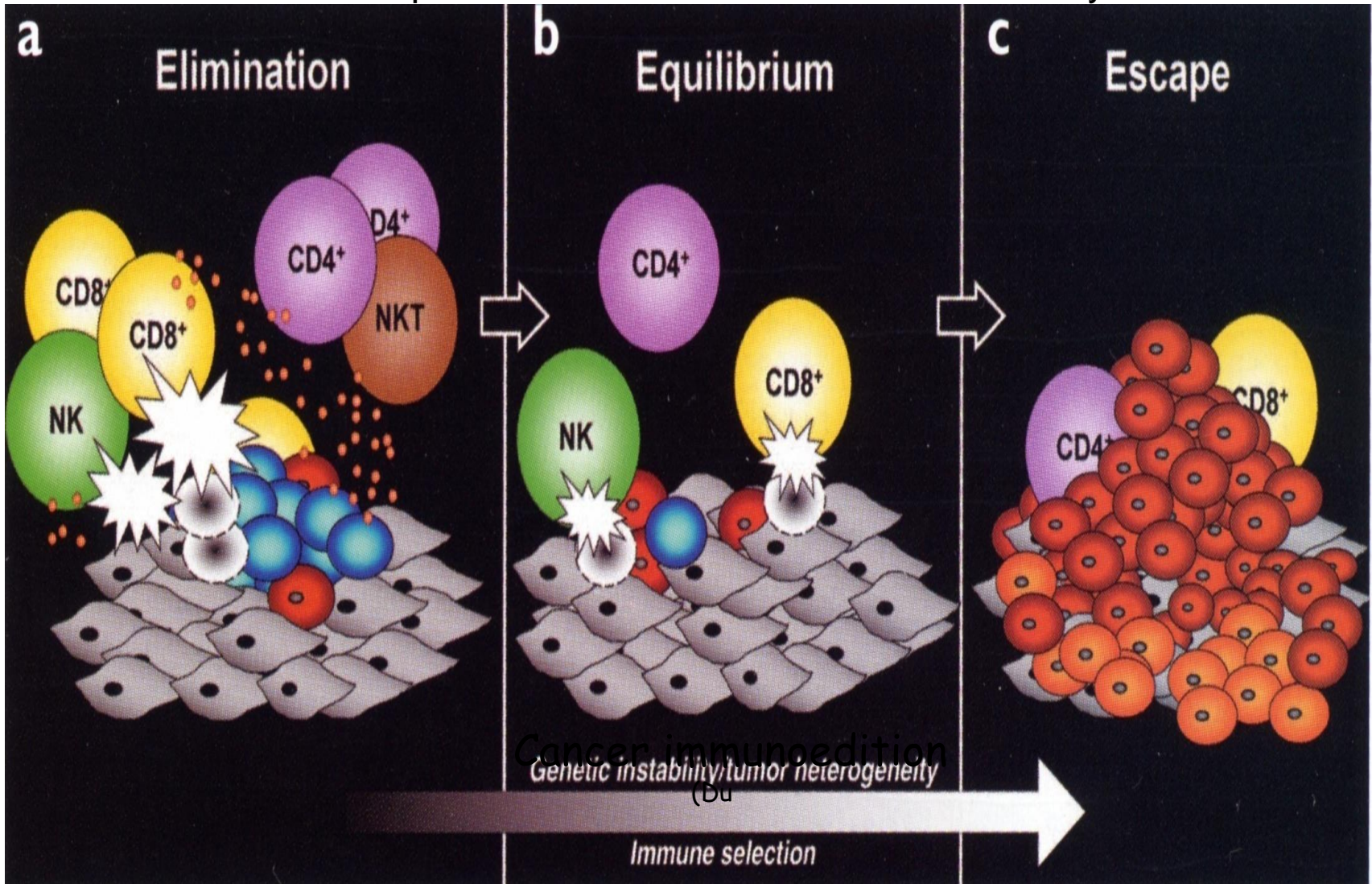
Tumor antigens

- Tumor-specific antigens – new antigens which develop in tumor cells.
- Tumor associated antigens – „normal“ body antigens, but their expression is markedly increased in malignancies (e.g. carcinoembryonic antigens).

Tumor antigens in different types of tumors

- Virus-induced tumors: Antigens are usually virus-specific.
- Carcinogen-induced: no inducer-related specificity of antigens.
- Spontaneous tumors: antigens are usually very variable.

Possible Consequences of Interaction Tumor-Immune System



van Gal, Bruce AT, Ikeda H, Old LJ, Schreiber RD:
Nature Immunology 2002; 3:991-998)

Immune Response to Tumors

- Cytotoxic T-lymphocytes (Tc)
- Natural killer (NK) cells
- Antibody-dependent cellular cytotoxicity (ADCC)
- Activated macrophages
- Role of dendritic cells
- Antibody response – minor importance

Protective Mechanisms of Tumors

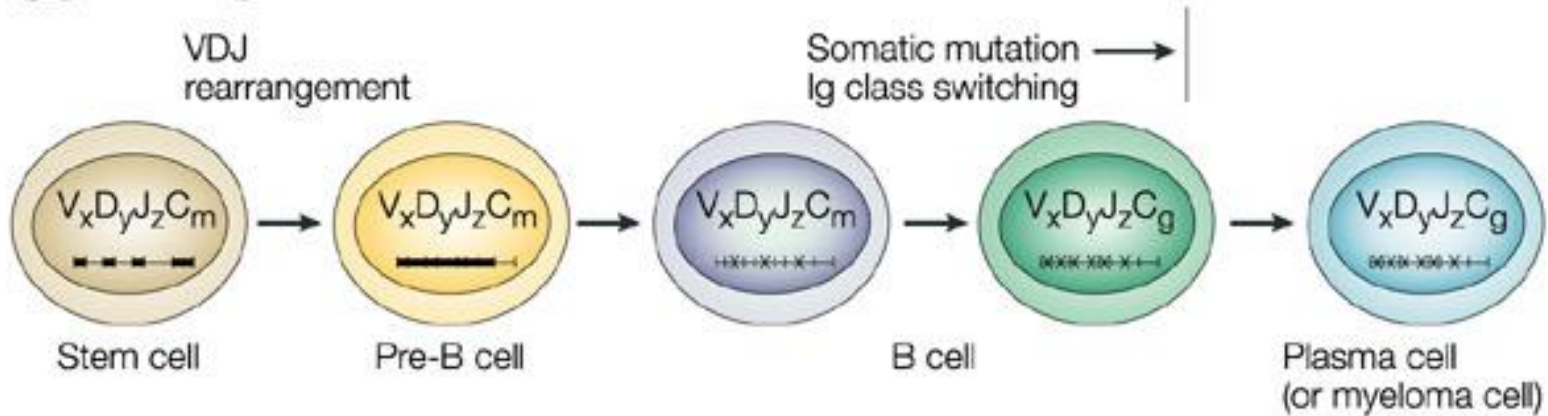
- Low immunogenicity of tumor antigens
- Low expression of HLA I molecules
- Antigenic modulation
- Immunosuppression – prostaglandins, IL-10 and TGF- β like cytokines, stimulation of Ts lymphocytes
- Large tumor mass

Immunodiagnostic of tumours

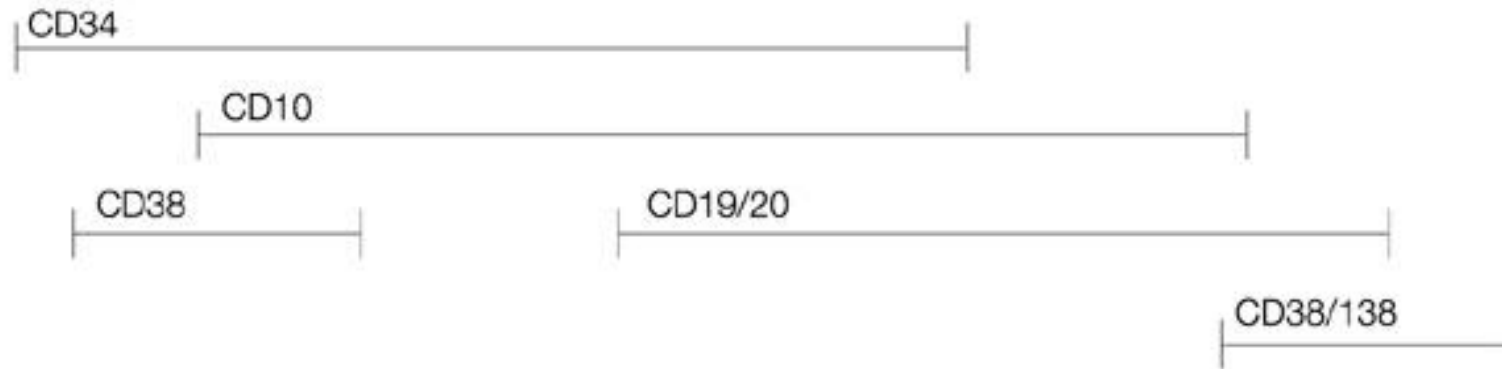
- Detection of tumor associated/specific antigens- if easily detected in plasma/serum – frequently called „oncomarkers“: alpha-feto protein, carcinoembryonic antigens, specific prostatic antigen and many others.....
- Monoclonal gammopathy
- Immunophenotyping of lymphoid malignancies.

B- cell development

Ig gene changes



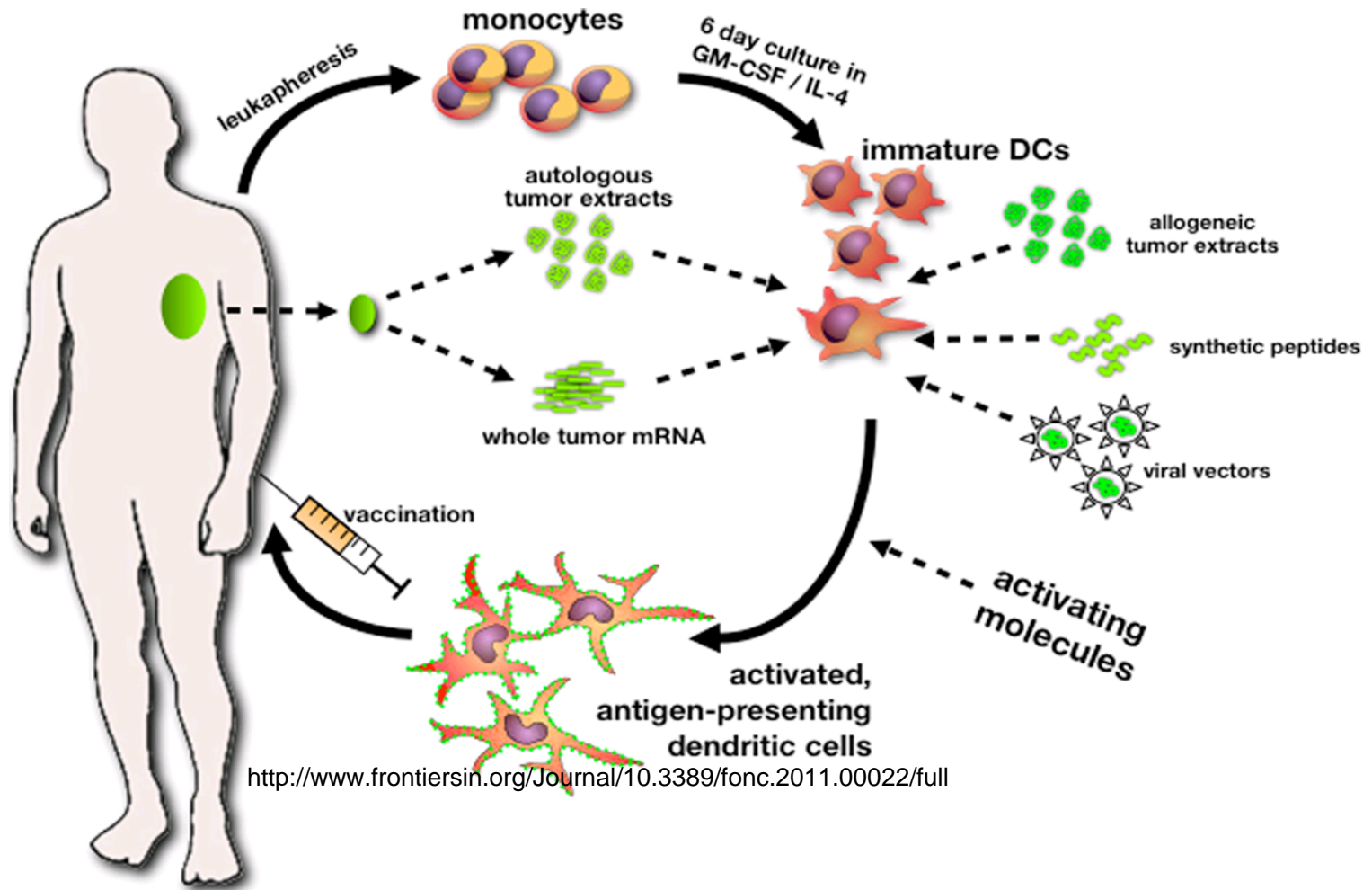
Cell-surface markers



Immunomodulatory treatment of tumors

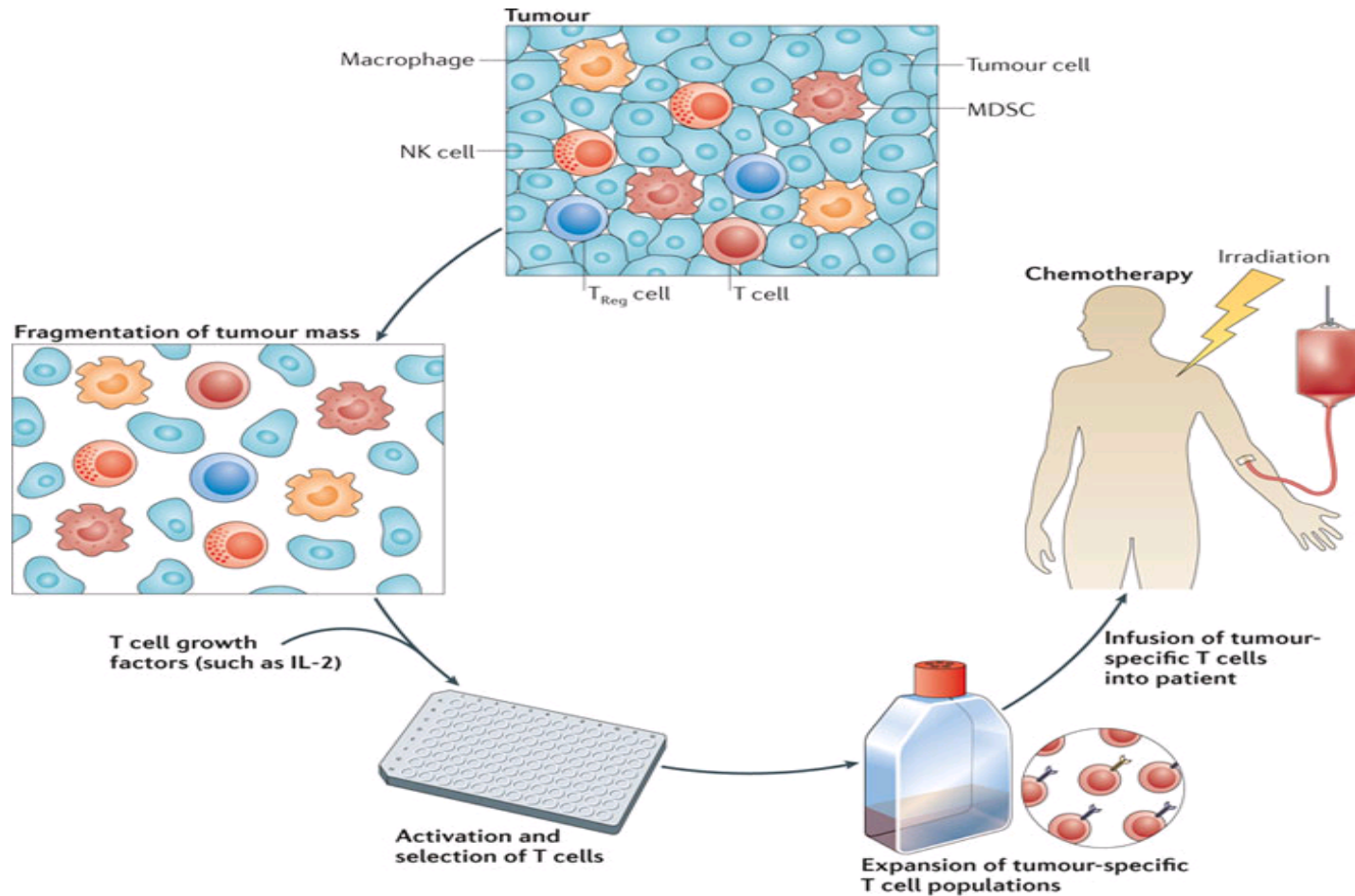
- Adaptive T-cell activation
- Check point (CTLA-4, PD-1) inhibitors (eg. nivolumab, ipilimumab)
- Cytokines – IL-2
- Interferon alpha
- BCG vaccine
- Tumour vaccination:
 - Protective - vaccination against viruses.
 - Therapeutic -mainly using dendritic cells and other approaches
- Monoclonal antibodies
- GVLR (Graft-versus leukaemia reaction) after allogenic HSCT (Hematopoietic stem-cell transplantation).

Antitumour vaccines



<http://www.frontiersin.org/Journal/10.3389/fonc.2011.00022/full>

TIL – tumor infiltrating lymphocytes

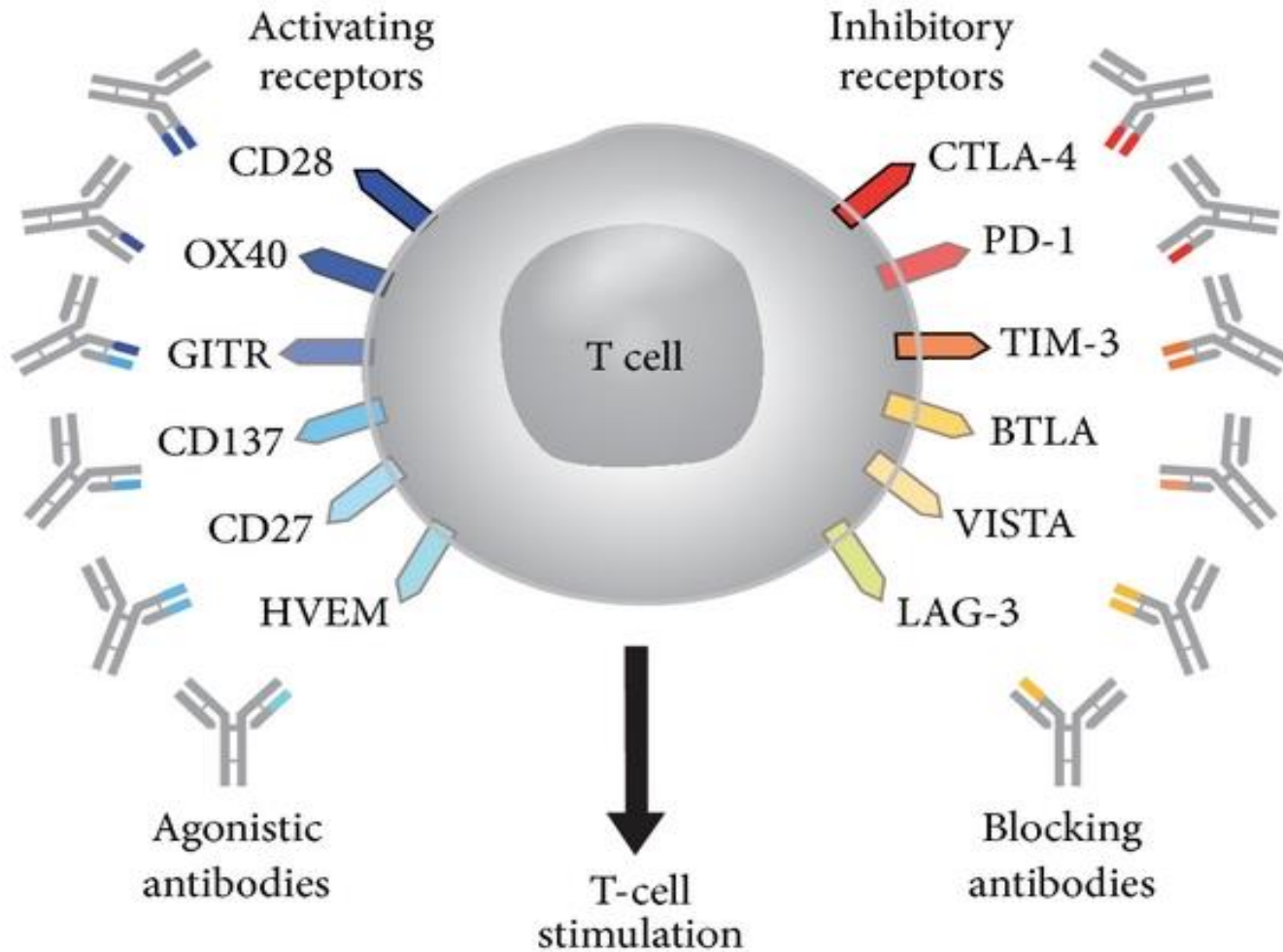


http://www.nature.com/nri/journal/v12/n4/fig_tab/nri3191_F1.html

Monoclonal Antibodies in Oncology

- Anti-CD20 (rituximab) directed against malignant B-cells.
- Anti-CD52 – T-cell lymphoma, chronic lymphatic leukemia
- Monoclonal antibodies against receptors for growth factors: ERBB2(HER 2 receptor) epidermal grow factor...
- Monoclonal antibodies against negative check points of T-cells – PD-1, CTLA-4

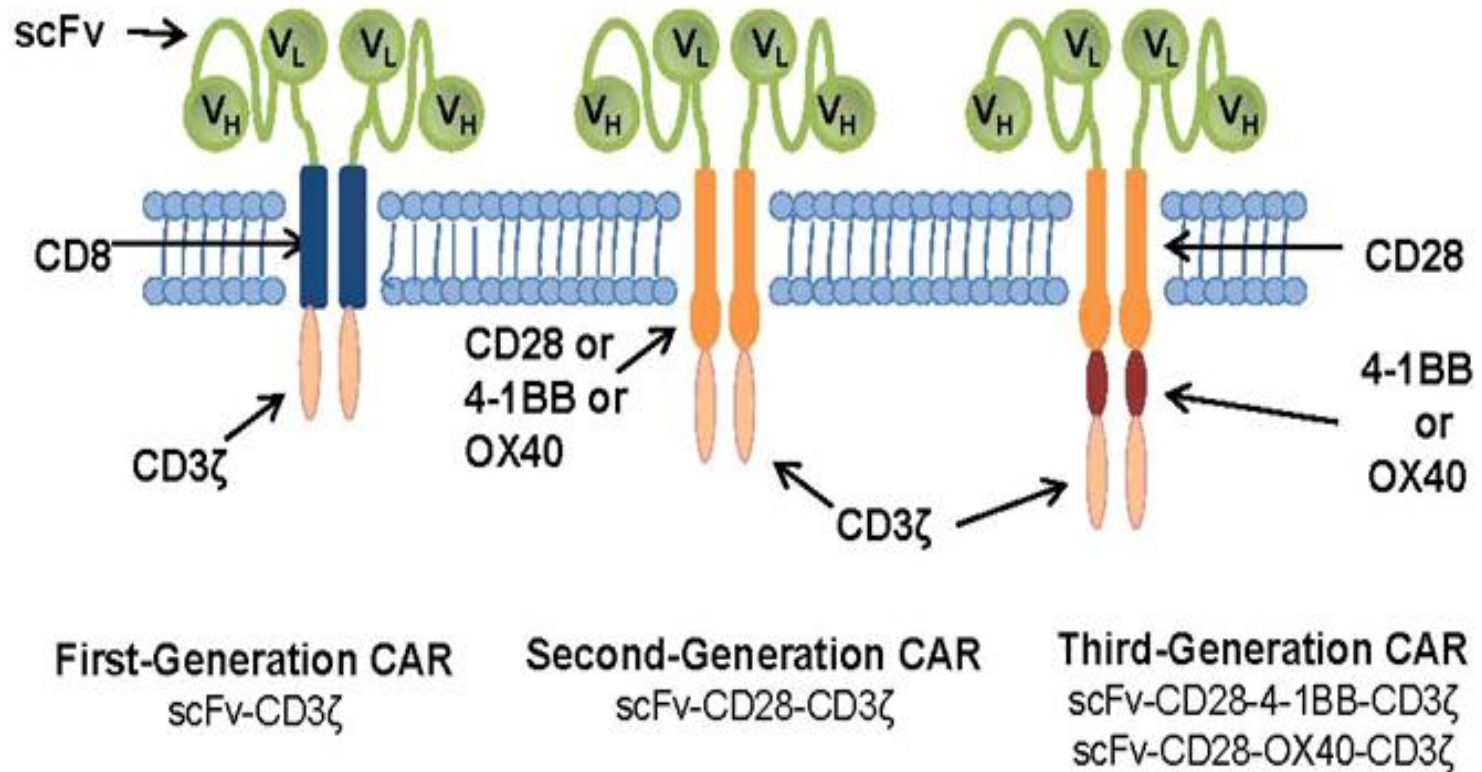
Checkpoint blockers



Other approaches

- Blockade of BTK (Burton's tyrosine kinase, necessary for B-cells development) – ibrutinib
- Blockade of the intracellular signalling pathways (e.g. kinase inhibitors)
- CAR chimeric antigen receptor T cells – antigen specific part of monoclonal antibody attached to T-receptor intracellular chain + other stimulatory molecules.

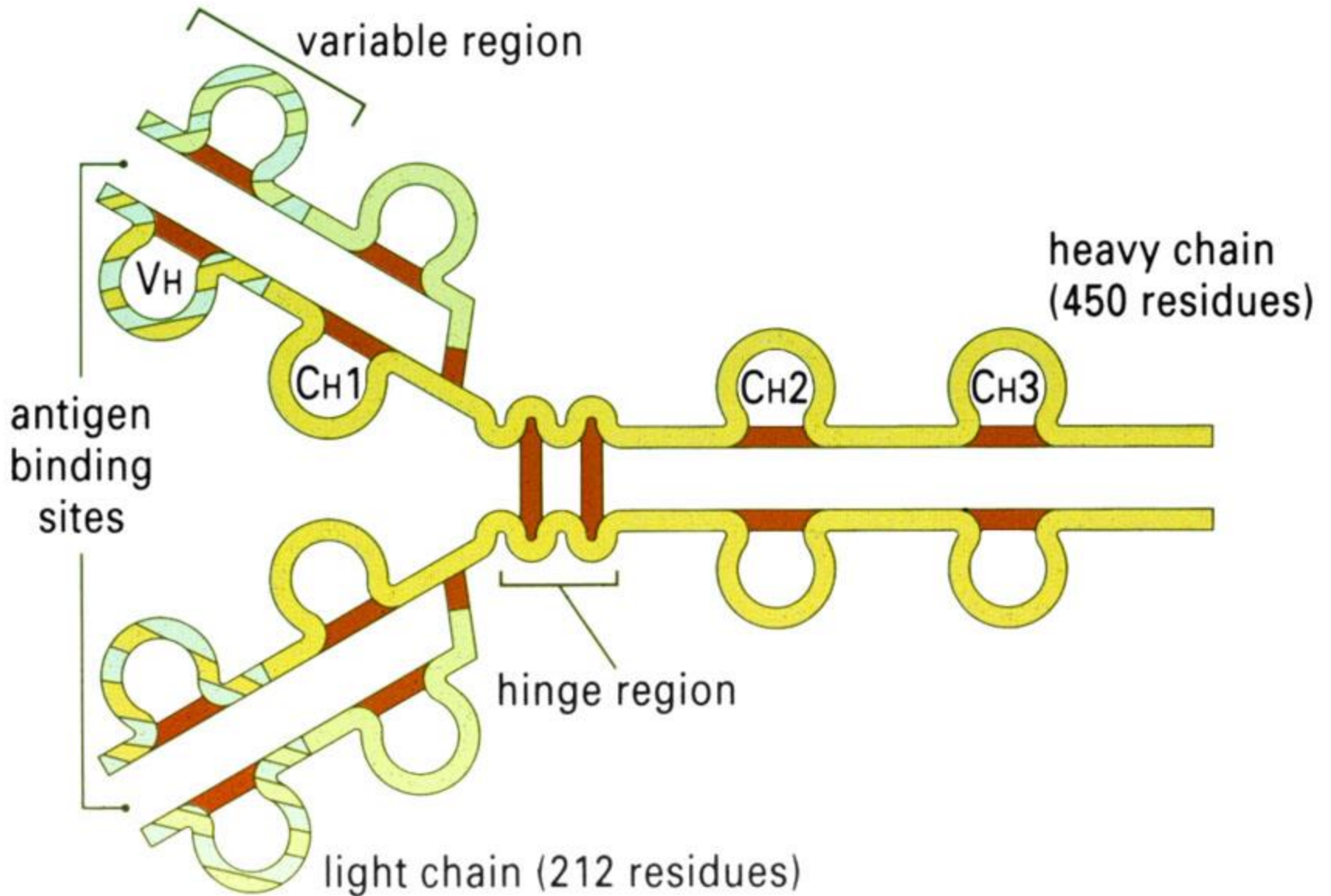
CAR



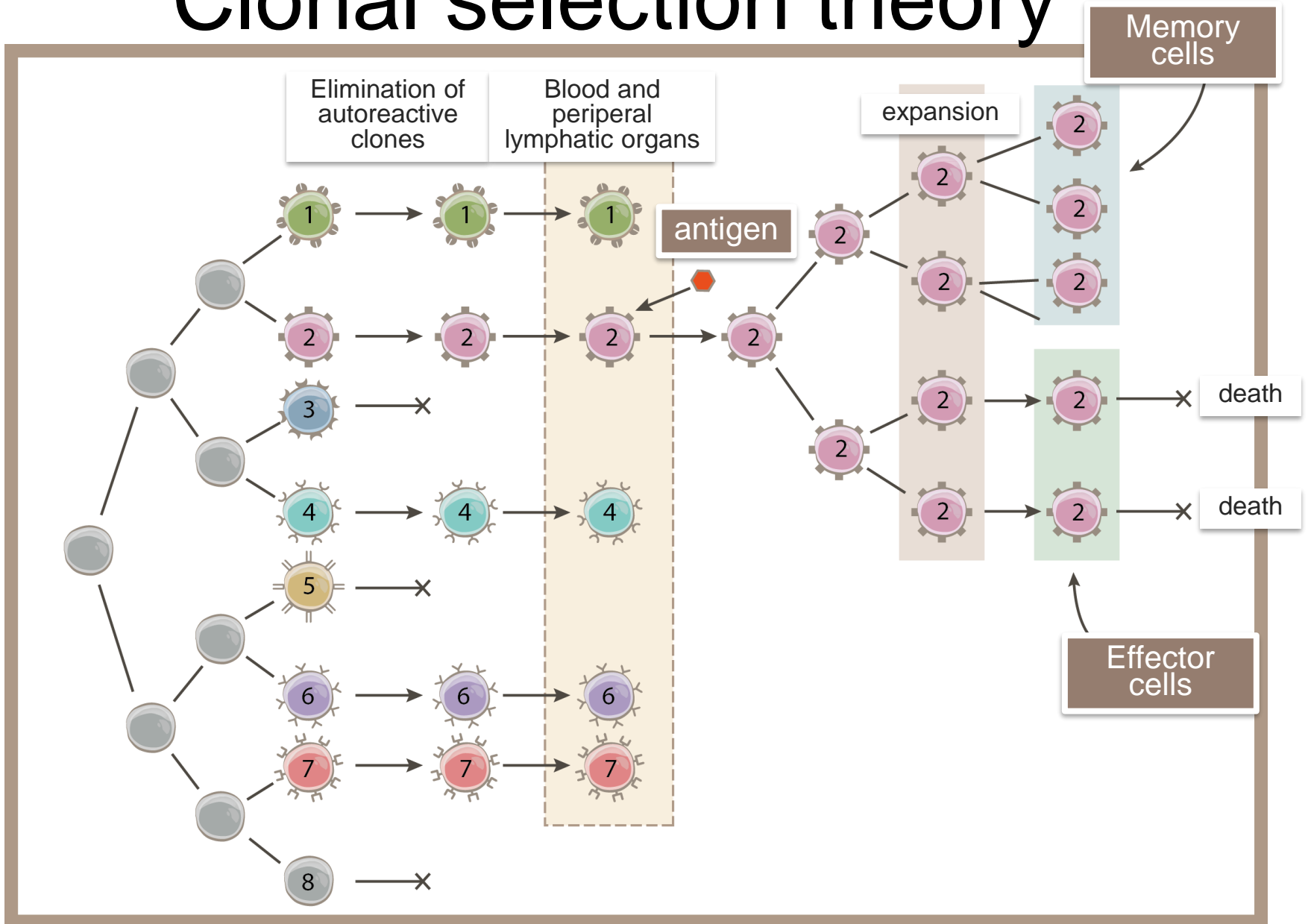
<http://www.discoverymedicine.com/Jae-H-Park/2010/03/30/adoptive-immunotherapy-for-b-cell-malignancies-with-autologous-chimeric-antigen-receptor-modified-tumor-targeted-t-cells/>

Monoclonal gammopathy and myeloma

The basic structure of IgG1



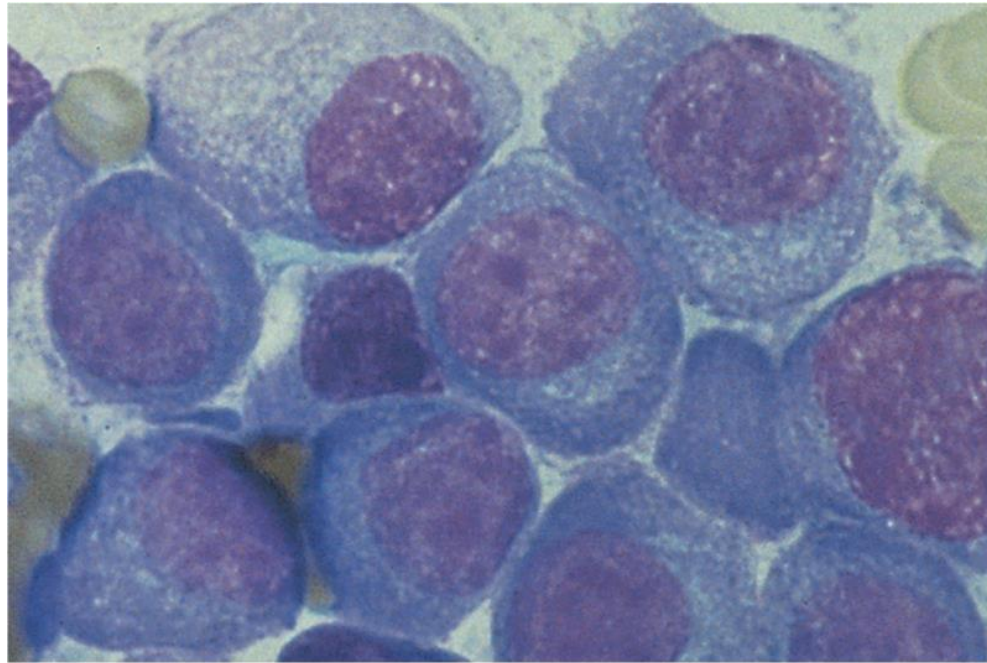
Clonal selection theory



Myeloma

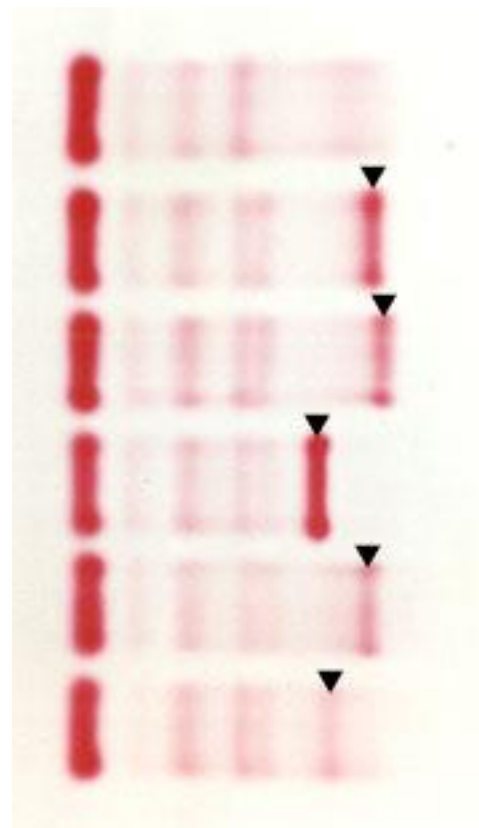
- Tumor that evolves from plasma cells
- Paraprotein (monoclonal gammopathy) in serum
- Increase in plasma cells in bone marrow
- Kidney failure
- Pathologic fractures
- Secondary immunodeficiency

Myeloma cells



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Electrophoresis of human serum

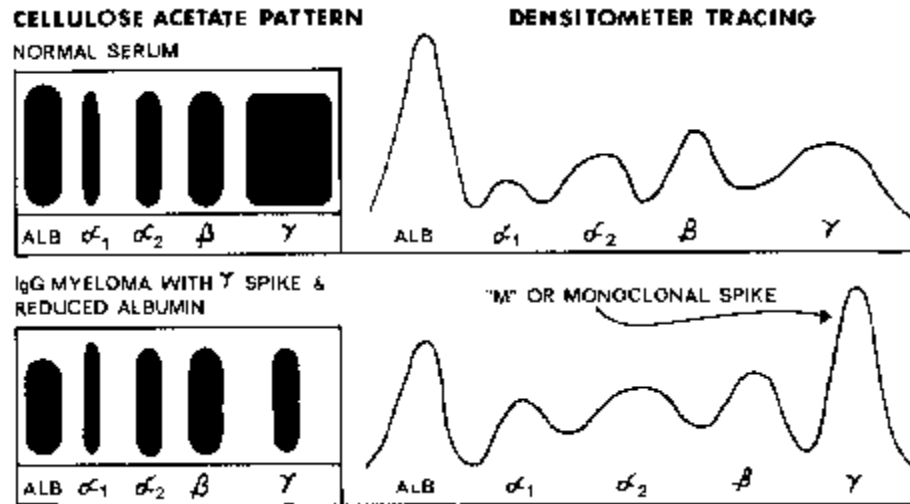


Normal serum

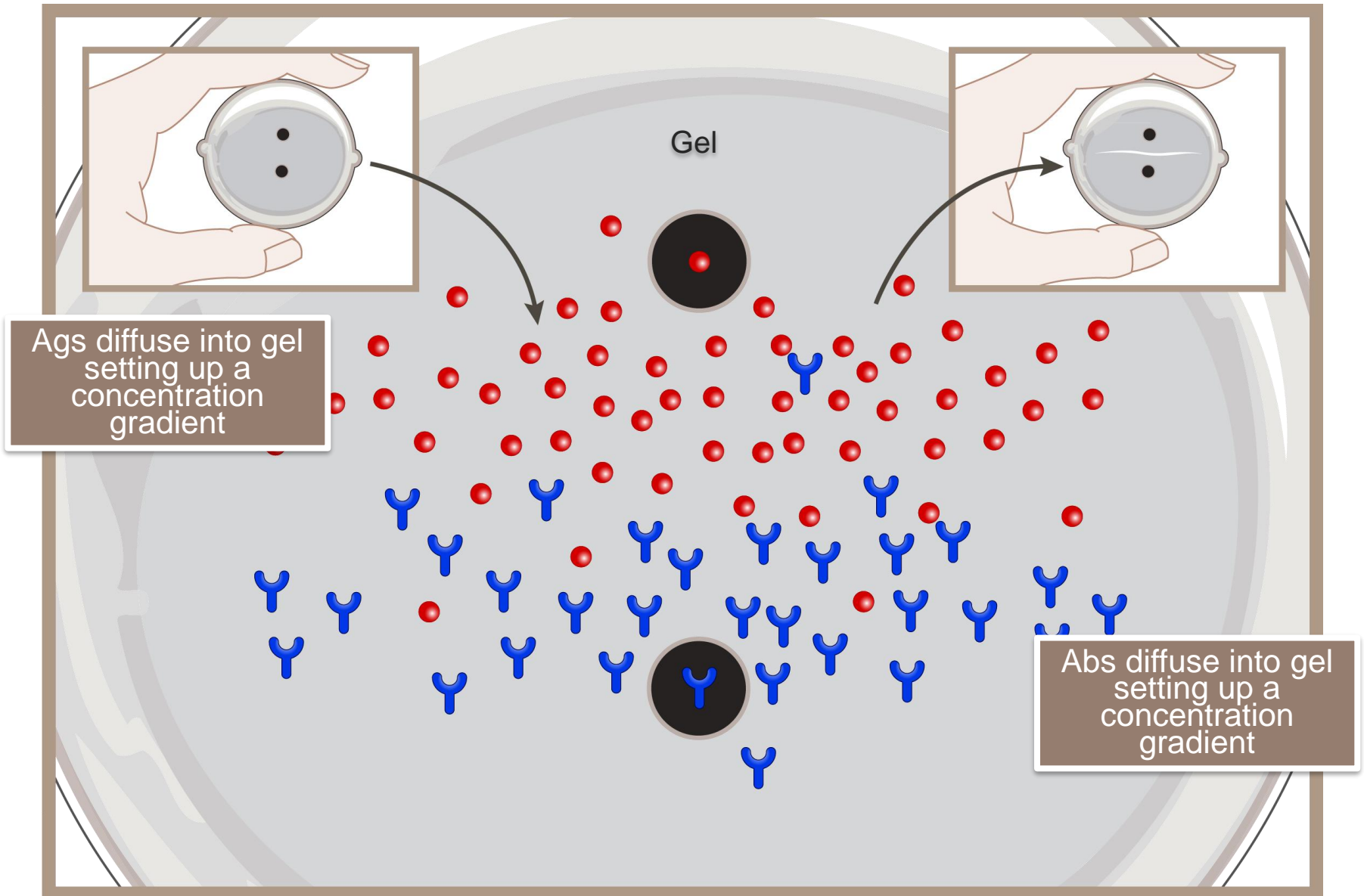
Paraproteins

Electrophoresis

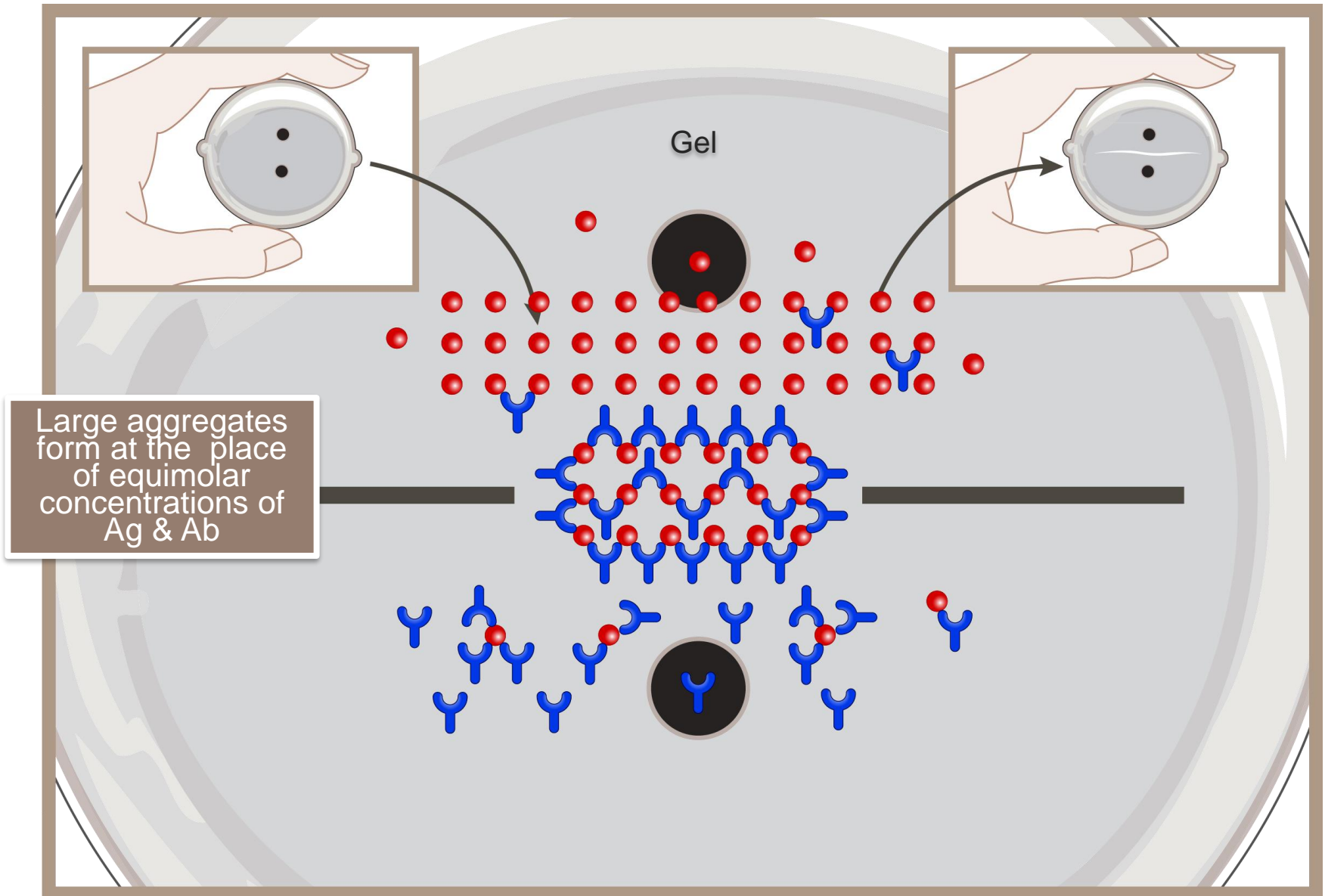
- paraprotein



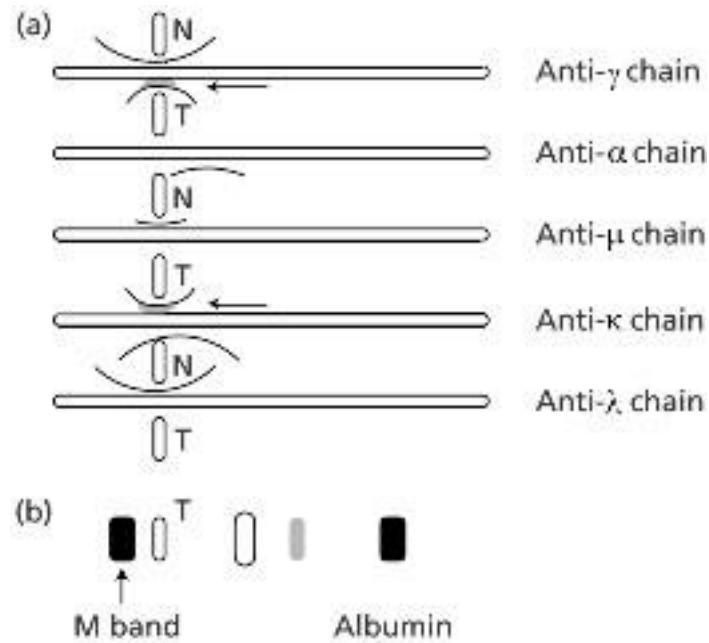
Immunodiffusion-I



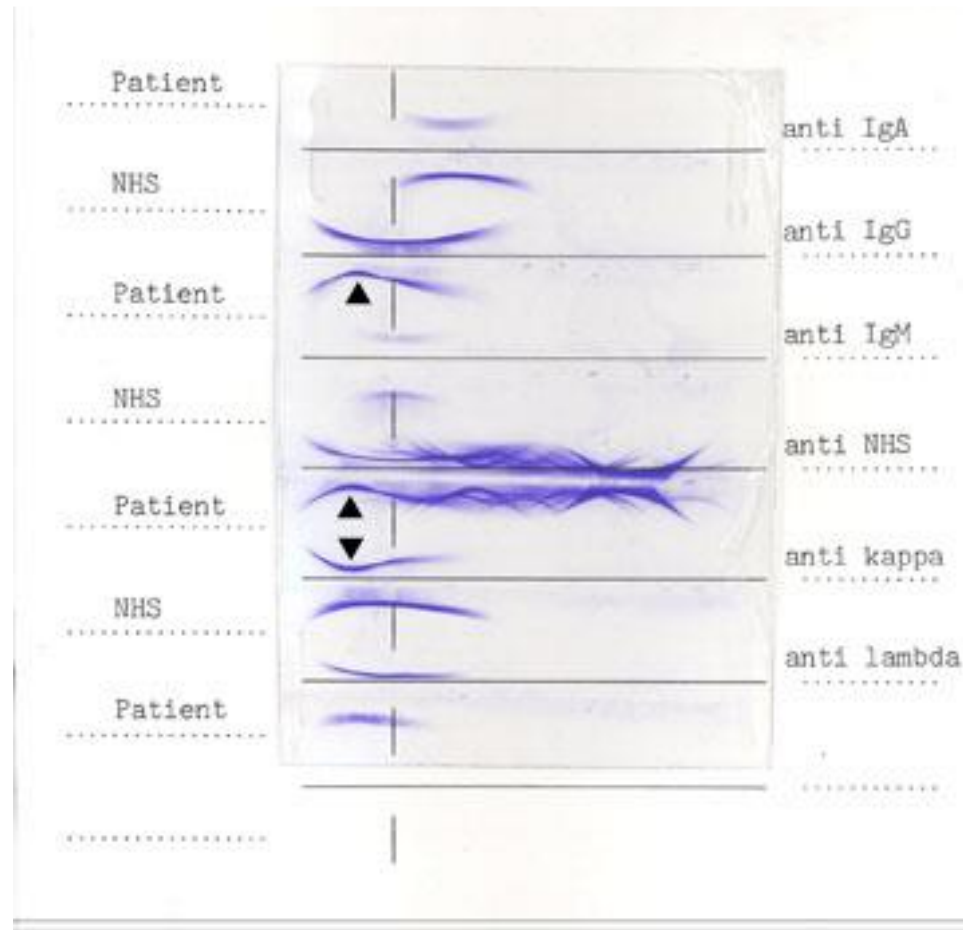
Immunodiffusion - II



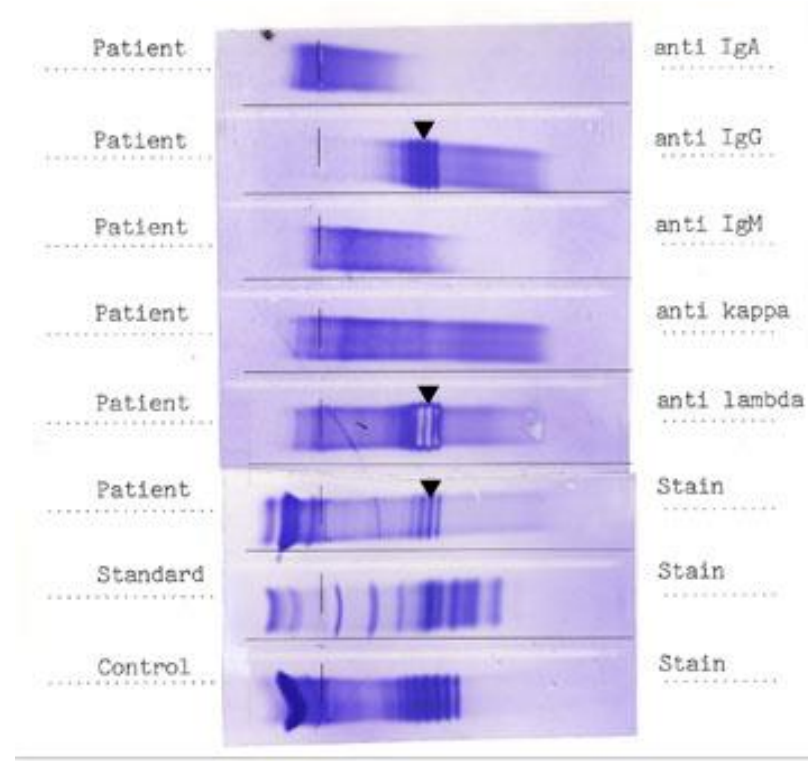
Imunoelectrophoresis



Imunoelectrophoresis



Imunofixation (antisérum IgG Lambda)



Paraproteins

- Monoclonal immunoglobulins in human serum.
- Malignant – in myeloma
- Benign – mainly in old people, patients with chronic inflammation, idiopathic (MGUS – monoclonal gammopathy of unknown significance)
- Detected by immunoelectrophoresis, immunofixation