Immune response against tumors

Tumor antigens

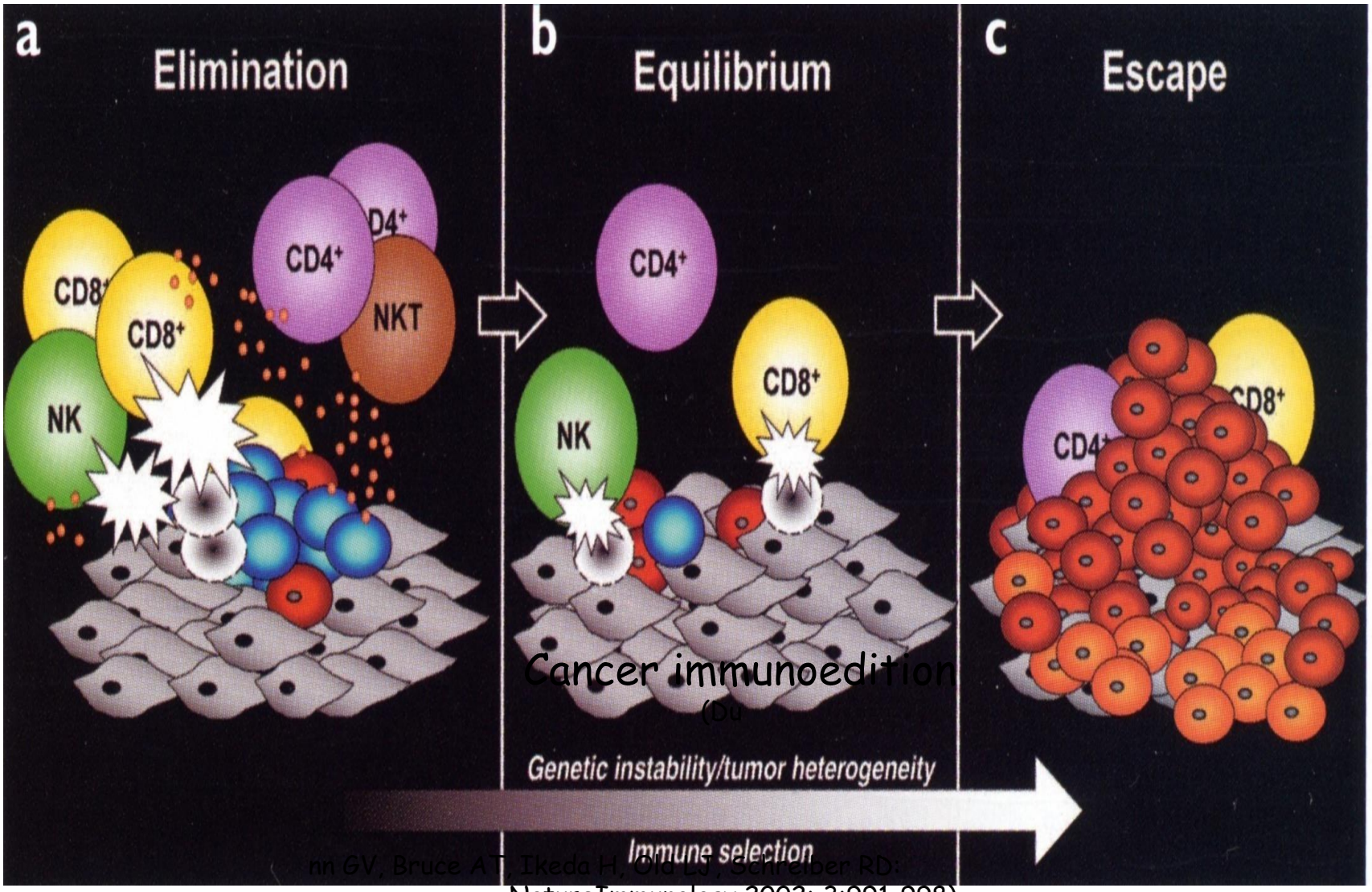
- Tumor-speciphic antigens – new antigens which develop in tumor cells.

- Tumor associated antigens – „normal“ body antigens, but their expression is markedly increased in malignancies:
  - carcinoembryonic antigens -. Levels are increased during cells proliferation – in fetus, during malignancy, but also in another conditions:
    - alfa-feto protein (liver cancer),
    - carcinoembryonic antigen of gastrointestinal tract – mailny colon cancer).
  - Specific prostatic antigen
  - and many others

Tumor antigens in different types of tumors

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

Possible Consequences of Interaction Tumor-Immune Systém (the Rule of 3 E)



Cancer immunoedition

(Du

nn GV, Bruce AT, Ikeda H, Old LJ, Schreiber RD:
NatureImmunology 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

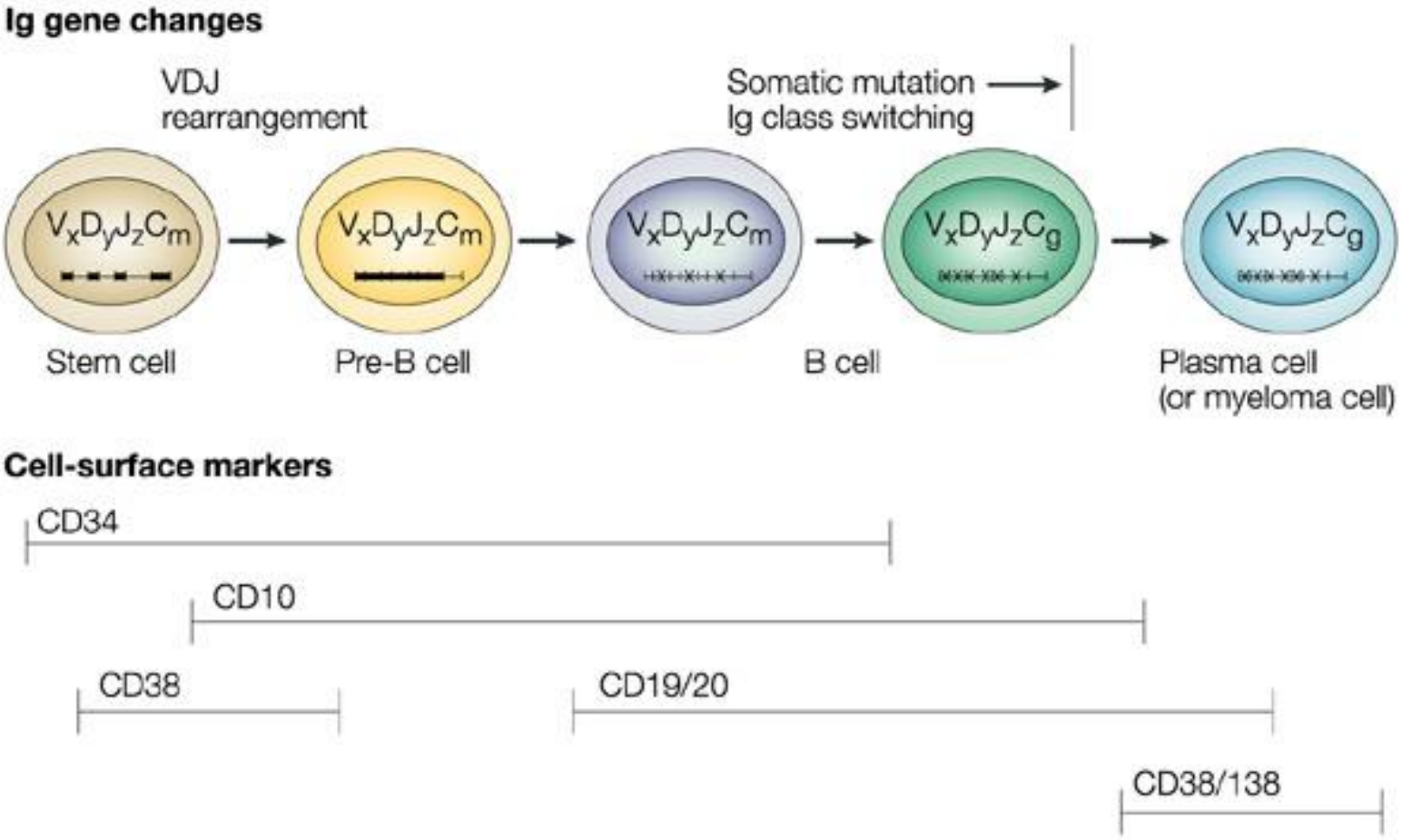
Protective Mechanisms of Tumors

- 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/speciphic antigens- if easily detected in plasma– frequently called „**oncomarkers**“- aplha-feto protein, carcinoembryonic antigen of gastrointestinal tract (CEA); speciphic prostatic antigen and many others…..
- Monoclonal gammopathy
- Immunophenotyping of lymphoid malignancies.

B- cell development



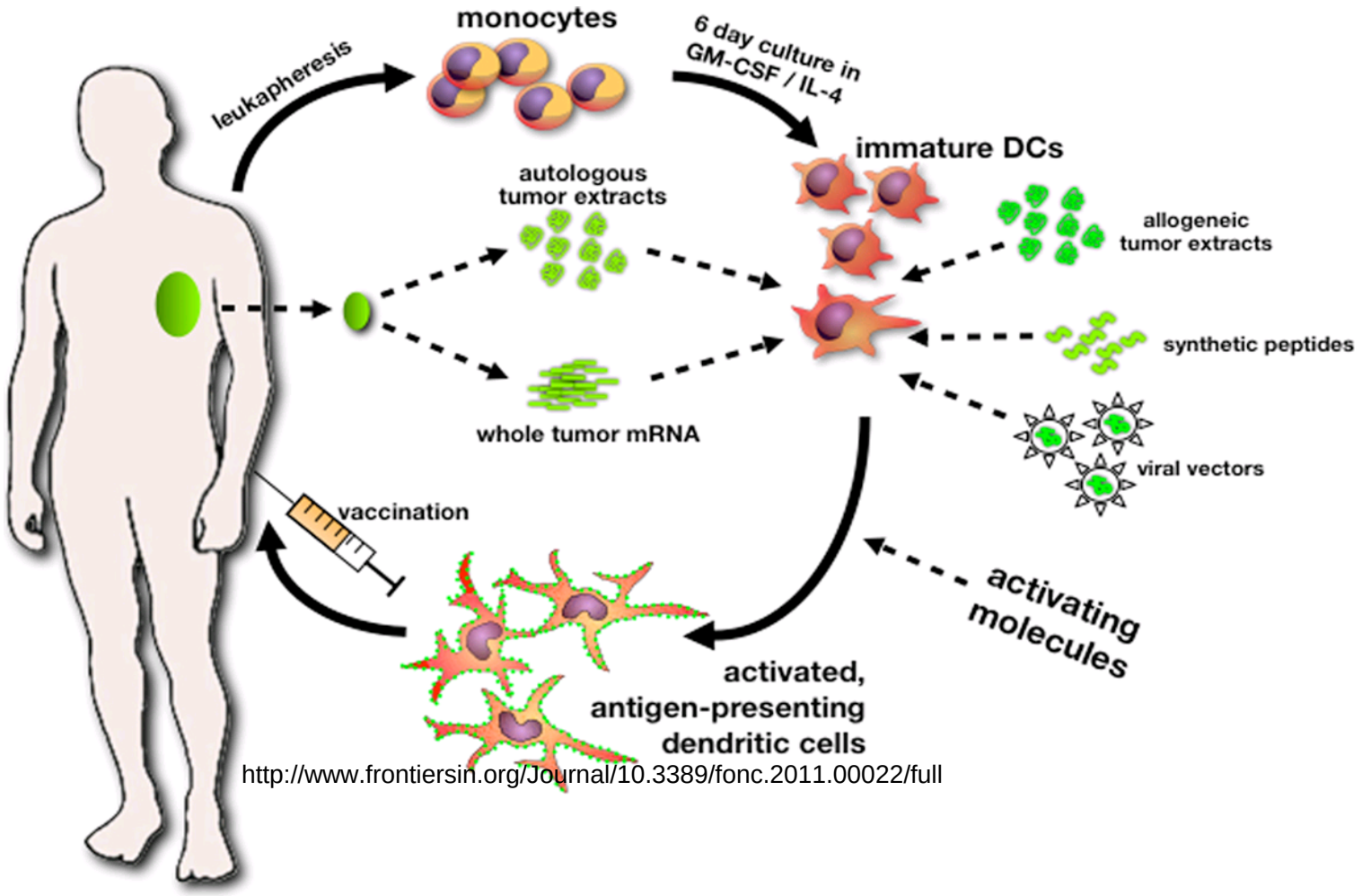
Immunomodulatory treatment of tumors

- Check point (CTLA-4, PD-1) inhibitors (eg. nivolumab, ipilimumab)
- Interferon alpha – lymphatic malignacies
- BCG vaccine – bladder cancer
- Tumour vaccination:

  Protective - vaccination against viruses (papillomavirus, HBV).

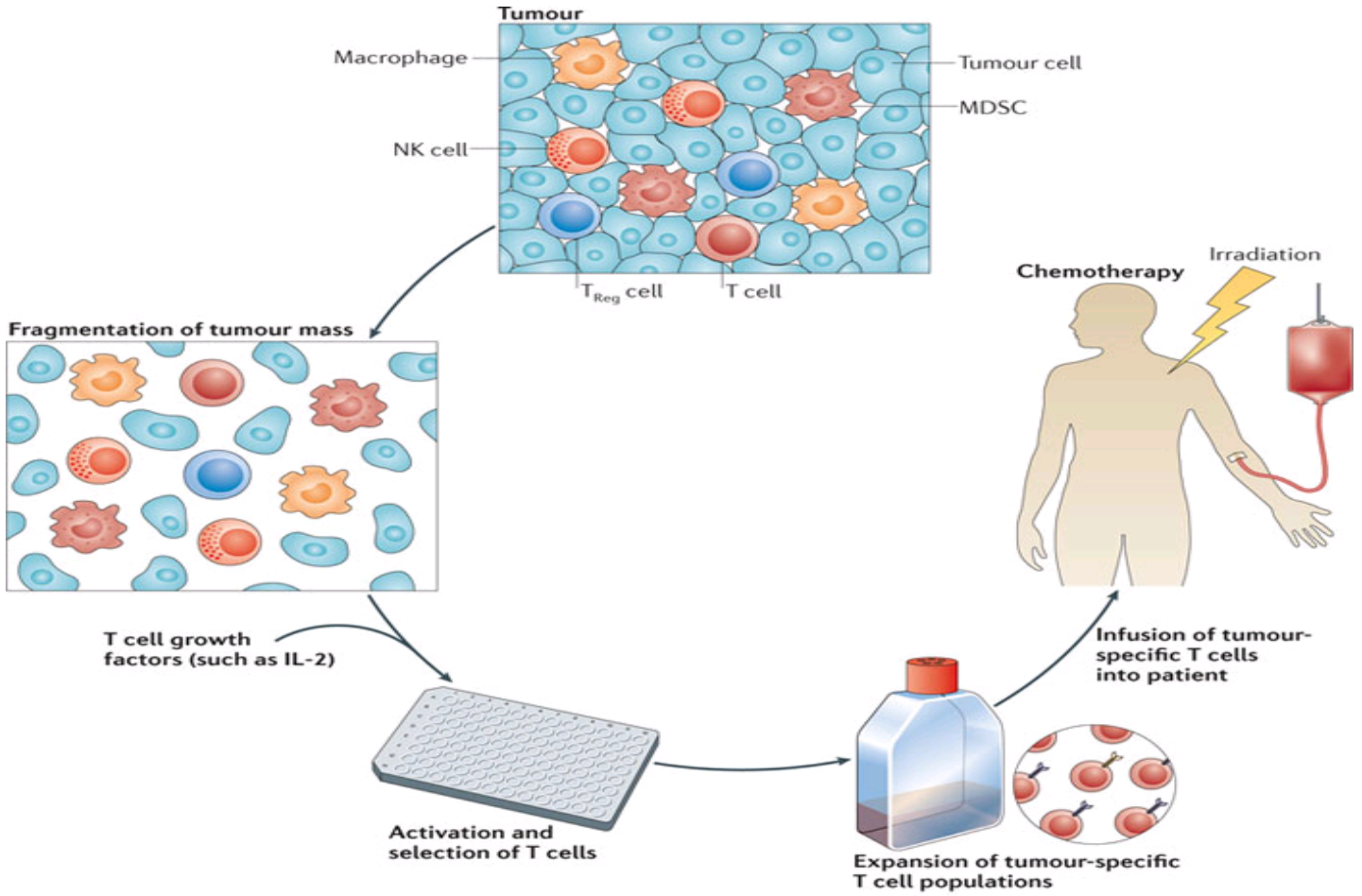
  Therapeutic -mainly using dendritic cells and other approches
- Monoclonal antibodies
- GVLR Graft-versus leukaemia reaction) after allogenic HSCT (Hematopoietic stem-cell transplantation).
- Adaptive T-cell activation by cytokines – (IL-2), including TIL cells

Antitunour vaccines



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

TIL – tumor infiltrating lymphocytes

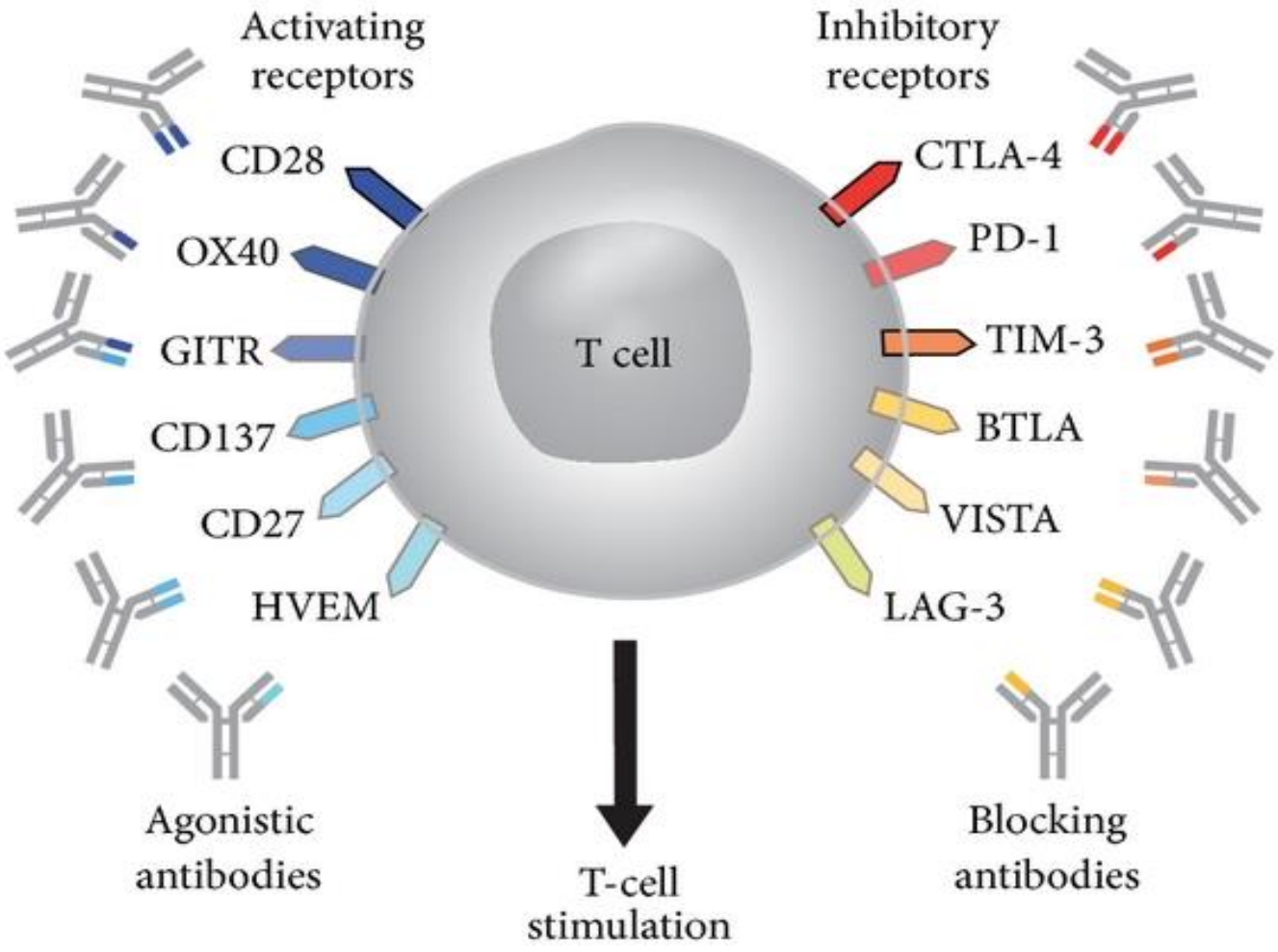


http://www.nature.com/nri/journal/v12/n4/fig_tab/nri3191_F1.html

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

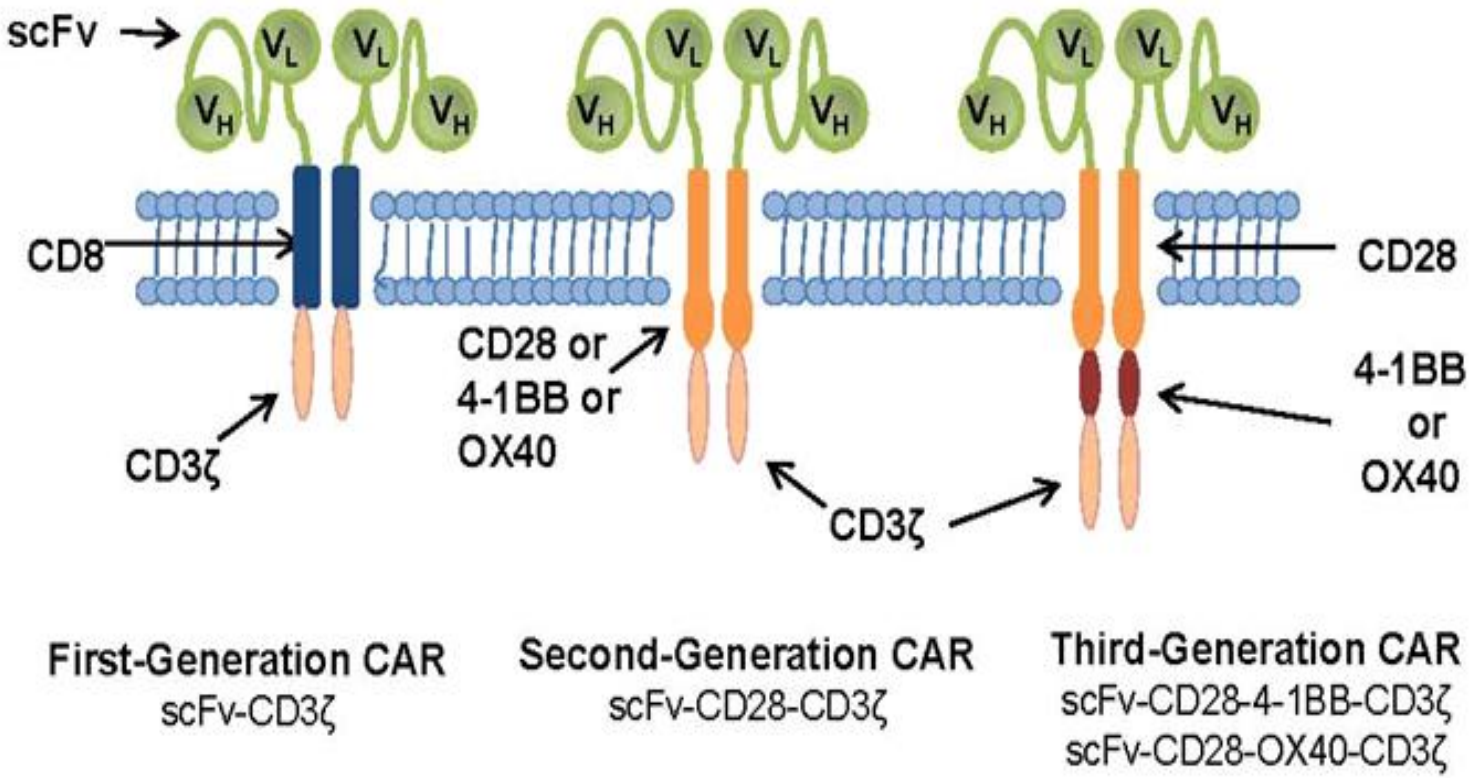


https://www.hindawi.com/journals/scientifica/2013/857519.fig.001.jpg

Other approaches

- Blockade of BTK (Burton's tyrosine kinase, necessary for B-cells development) – ibrutimib
- 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

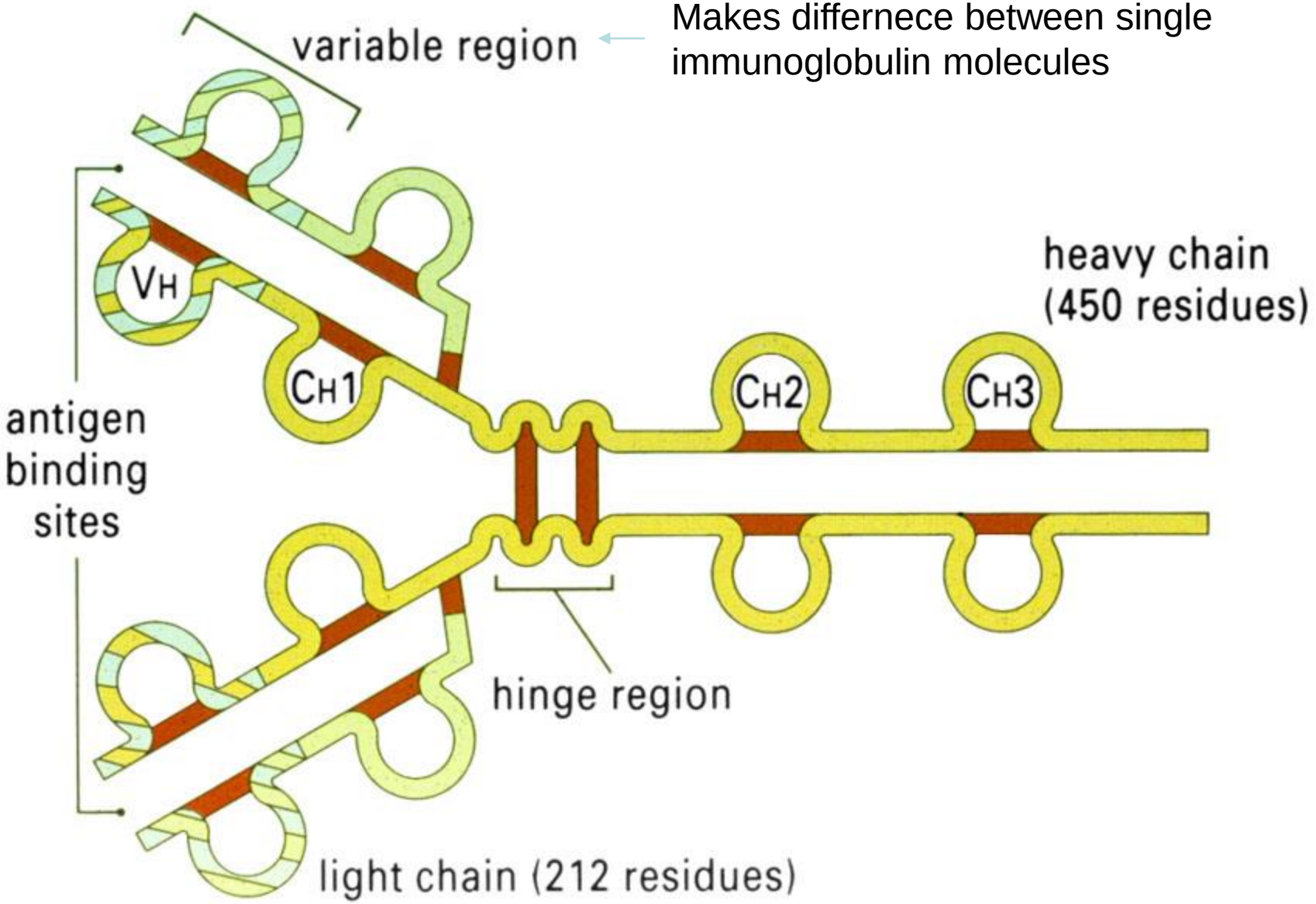


http://www.discoverymedicine.com/Jae-H-Park/2010/03/30/adoptive-immunotherapy-for-b-cell-malignancies-with-autologous-chimeric-antigen-receptor-modified-tumor-targeted-t-cells/

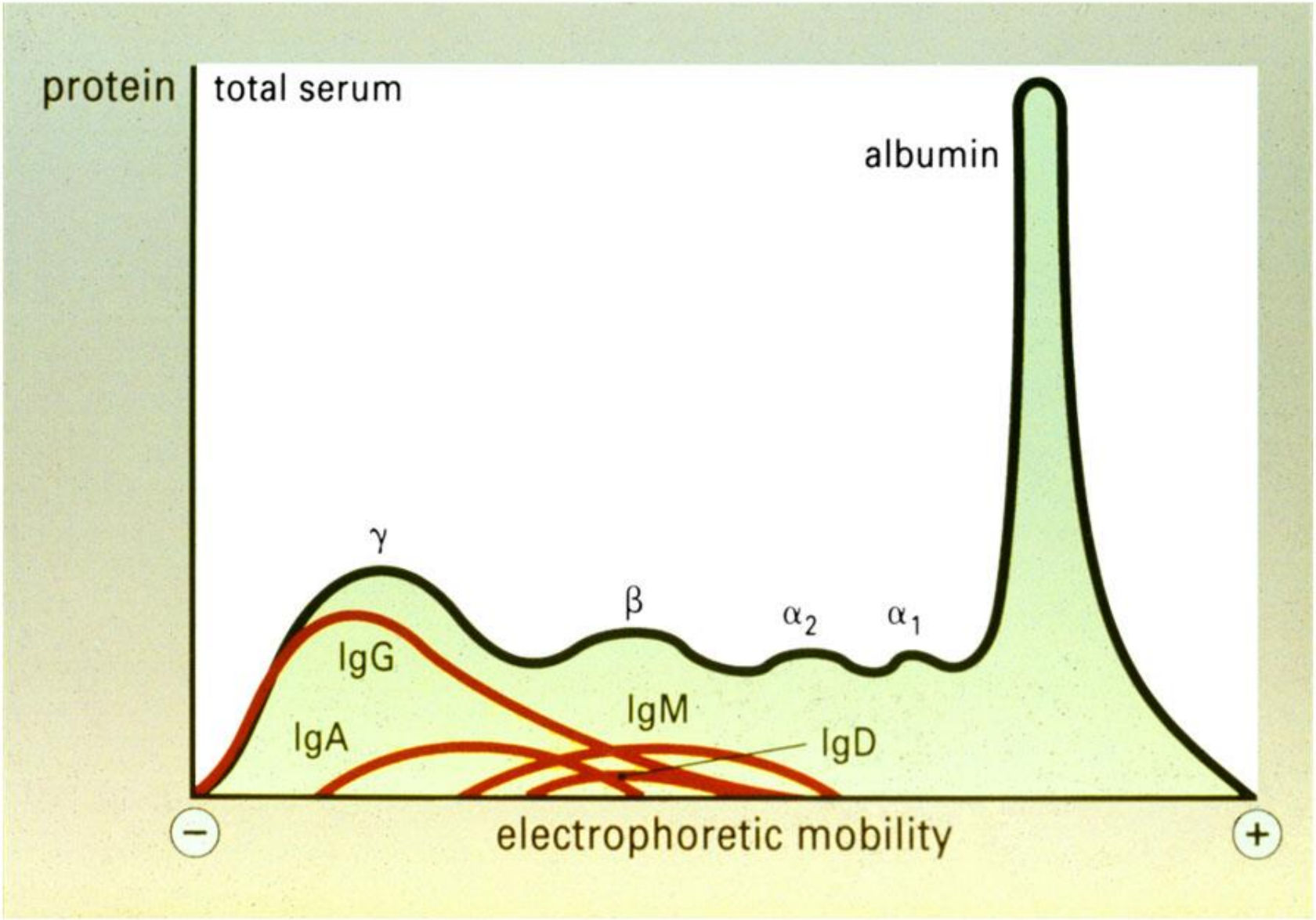
Monoclonal gammopathy and myeloma

The basic structure of IgG1

Makes differnece between single immunoglobulin molecules

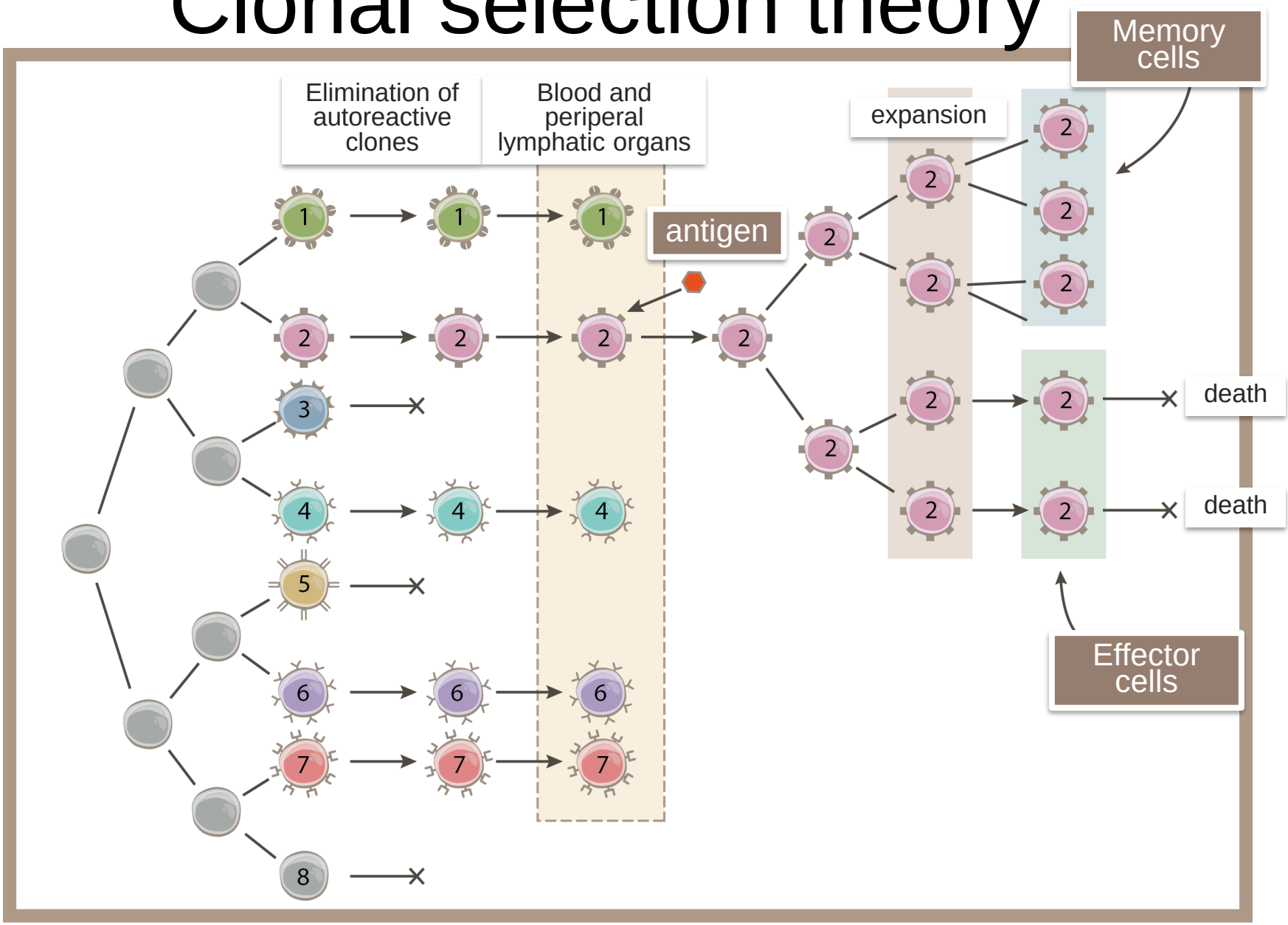


Distribution of the major human immunoglobulins



From: I. Roit et al: Slide atlas of Immunology. 3rd. edition

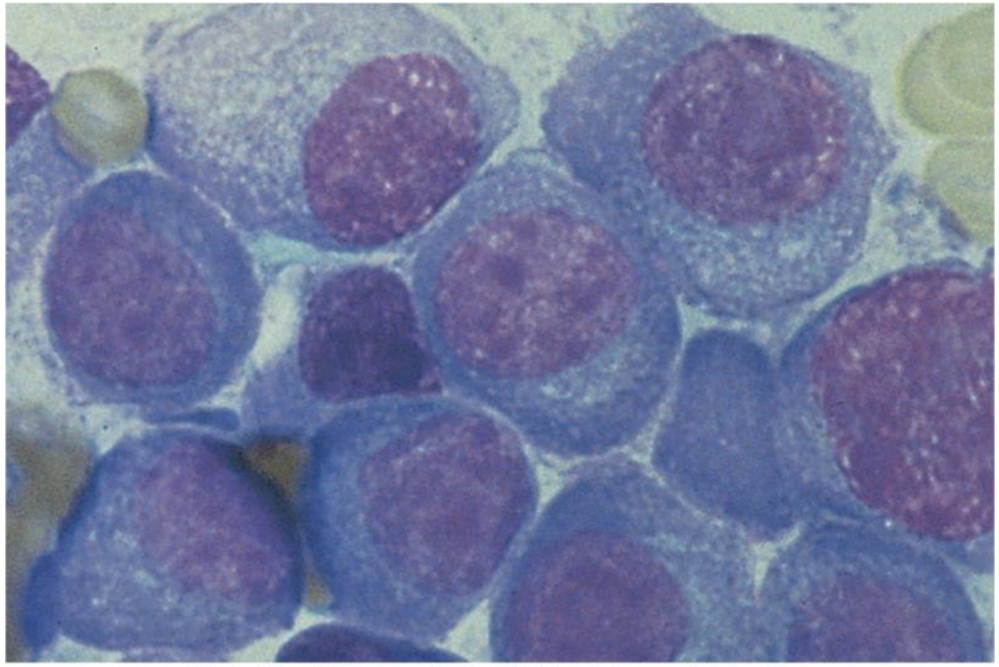
Clonal selection theory



Myeloma

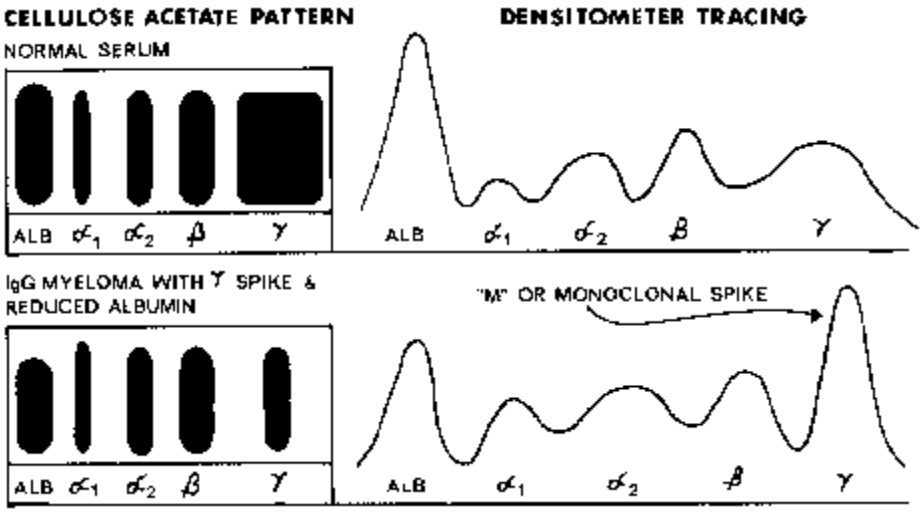
- Tumor that evolves from plasma cells
- Paraprotein (monoclonal gammopthy) in serum
- Increase in plasma cells in bone marrow
- Kidney failure
- Pathologic fractures
- Secondary immunodeficiency

Myeloma cells

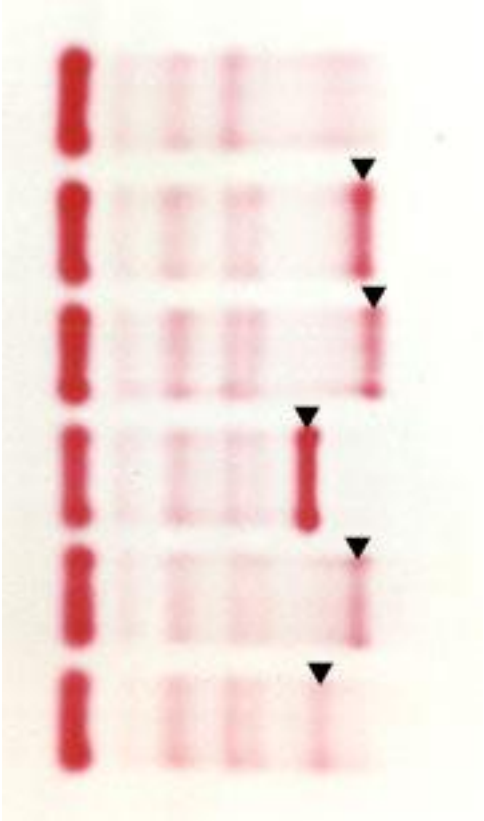


Electrophoresis

- paraprotein



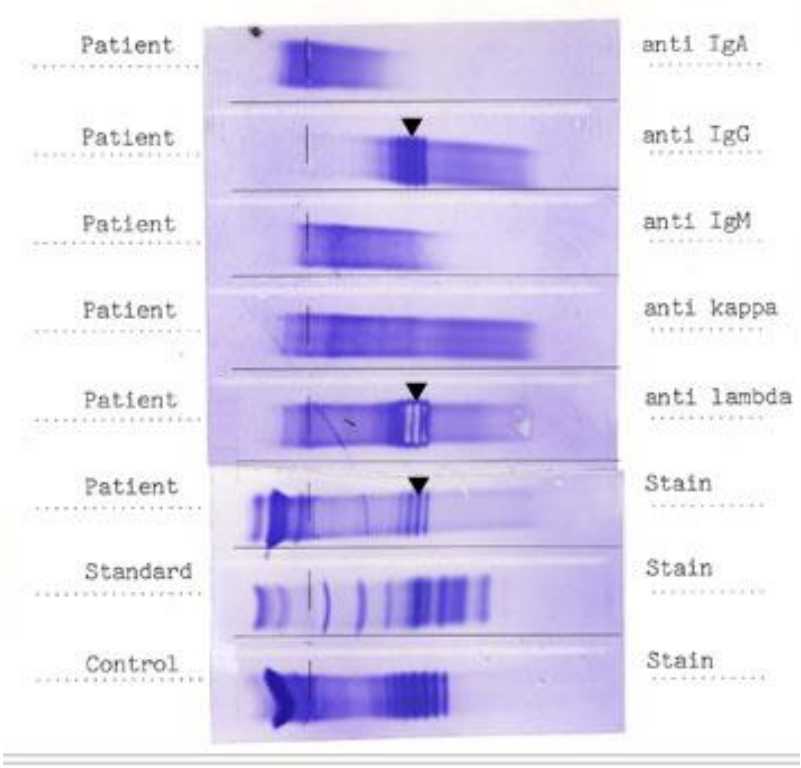
Electrophoresis of human serum



Normal serum

Paraproteins

Imunofixation
(antisérum IgG Lambda)



Paraproteins

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