Anaphylaxis to Immunotherapy/Immunomodulators

WAO

Dec 2103

Chicago

History

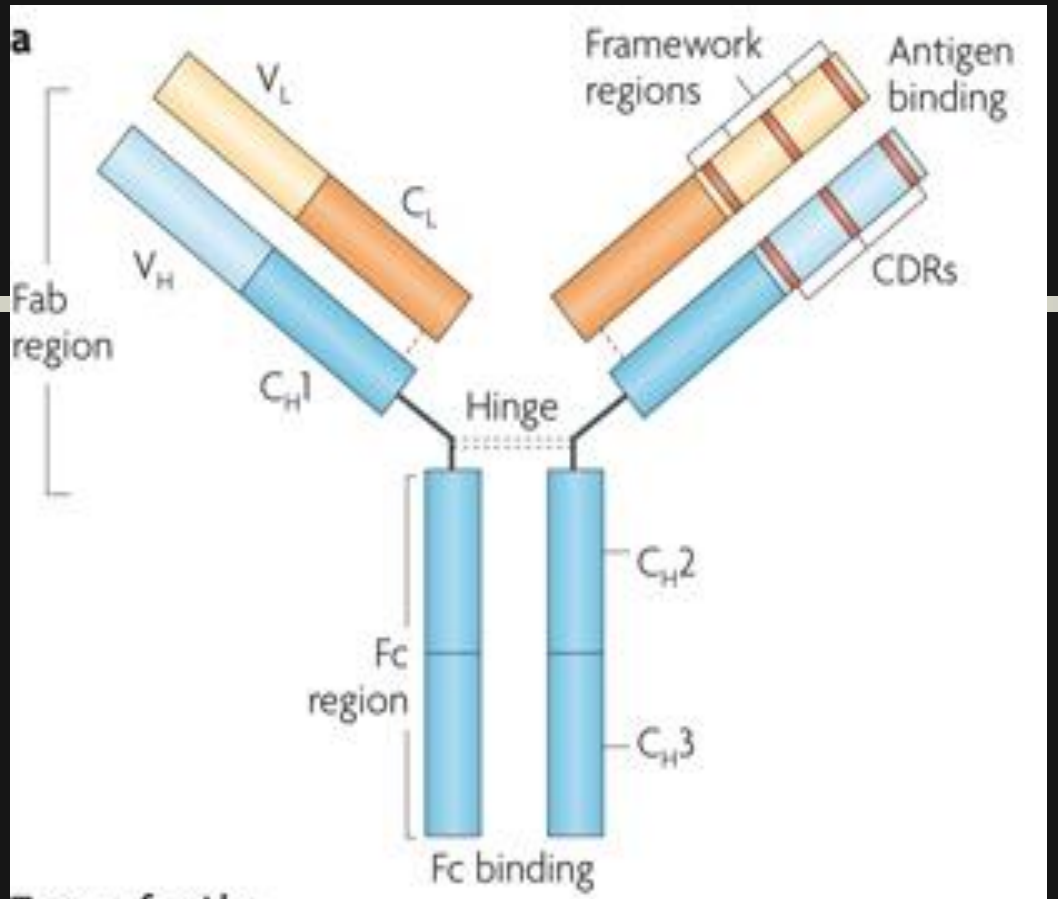
- In 1975, Köhler and Milstein published their seminal manuscript on hybridoma technology enabling the production of mouse monoclonal antibodies (mAbs)
- mouse, chimeric, humanized, to fully human mAbs
- more than 20 mAbs, and more than 150 other mAbs are currently in clinical trials[7].

Nomenclature

- Entirely murine
- Chimeric
- Humanized
- Entirely human

Nomenclature

Murine	Entirely murine amino acids	'o' = mouse e.g. muromonab
Chimeric	Human constant (C) + murine variable (V) regions	'xi' = chimeric e.g. rituximab
Humanized	Murine complementarity determining regions (CDRs)	'zu' = humanized e.g. alemtuzumab
Human	Entirely human amino acids	'u' = human e.g. adalimumab



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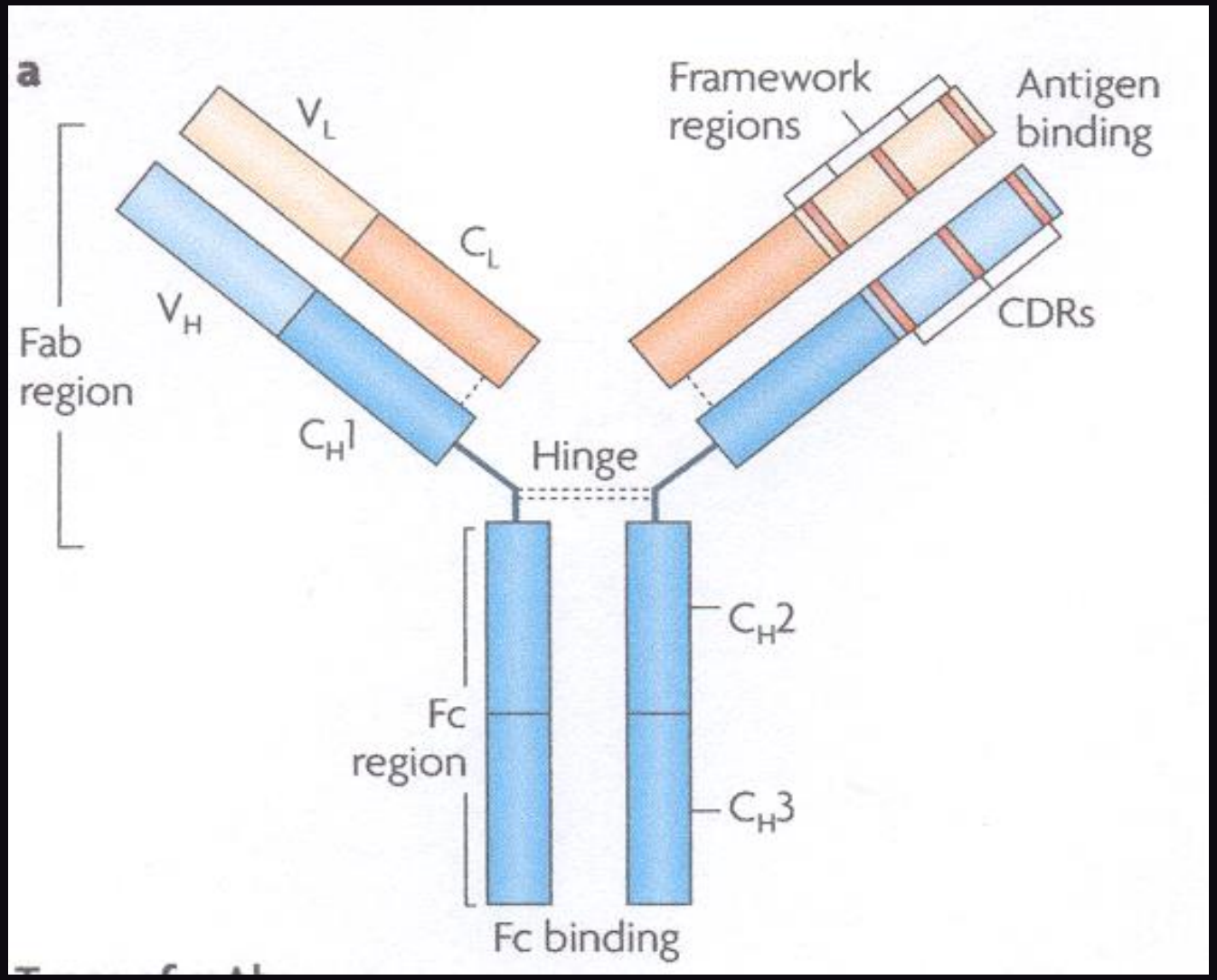

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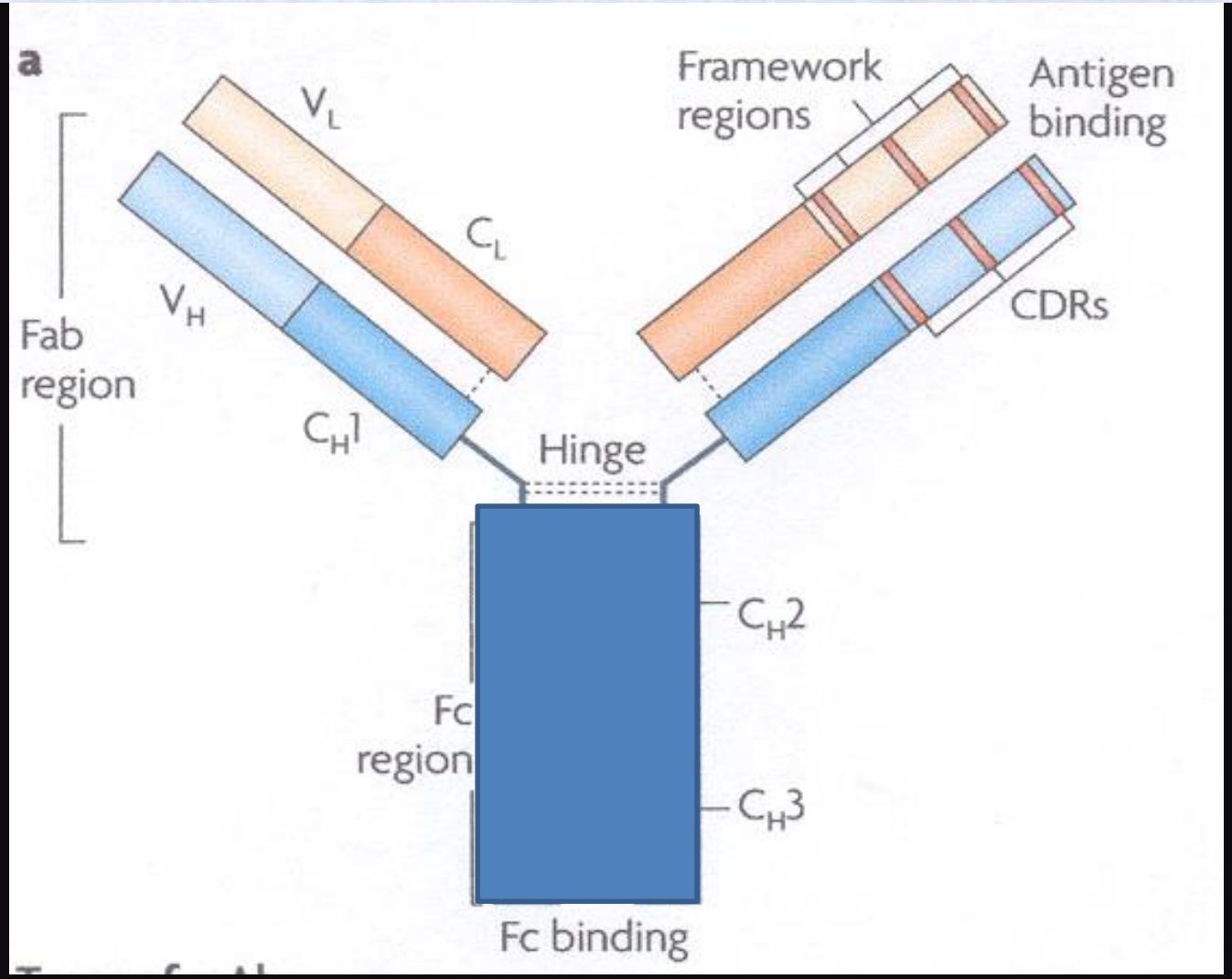
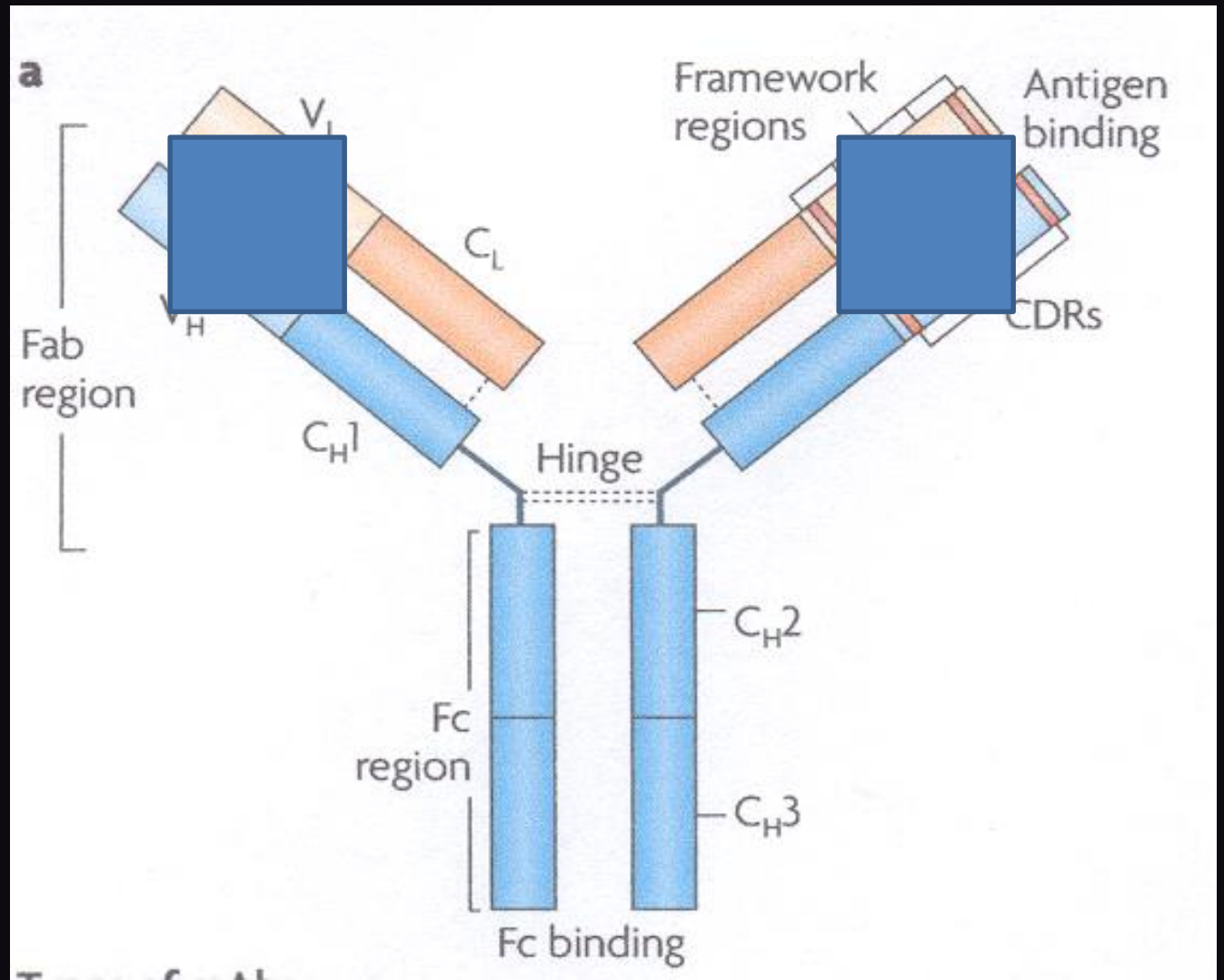


Humanized

Murine complementarity determining regions (CDRs)

'zu' = humanized
e.g. alemtuzumab



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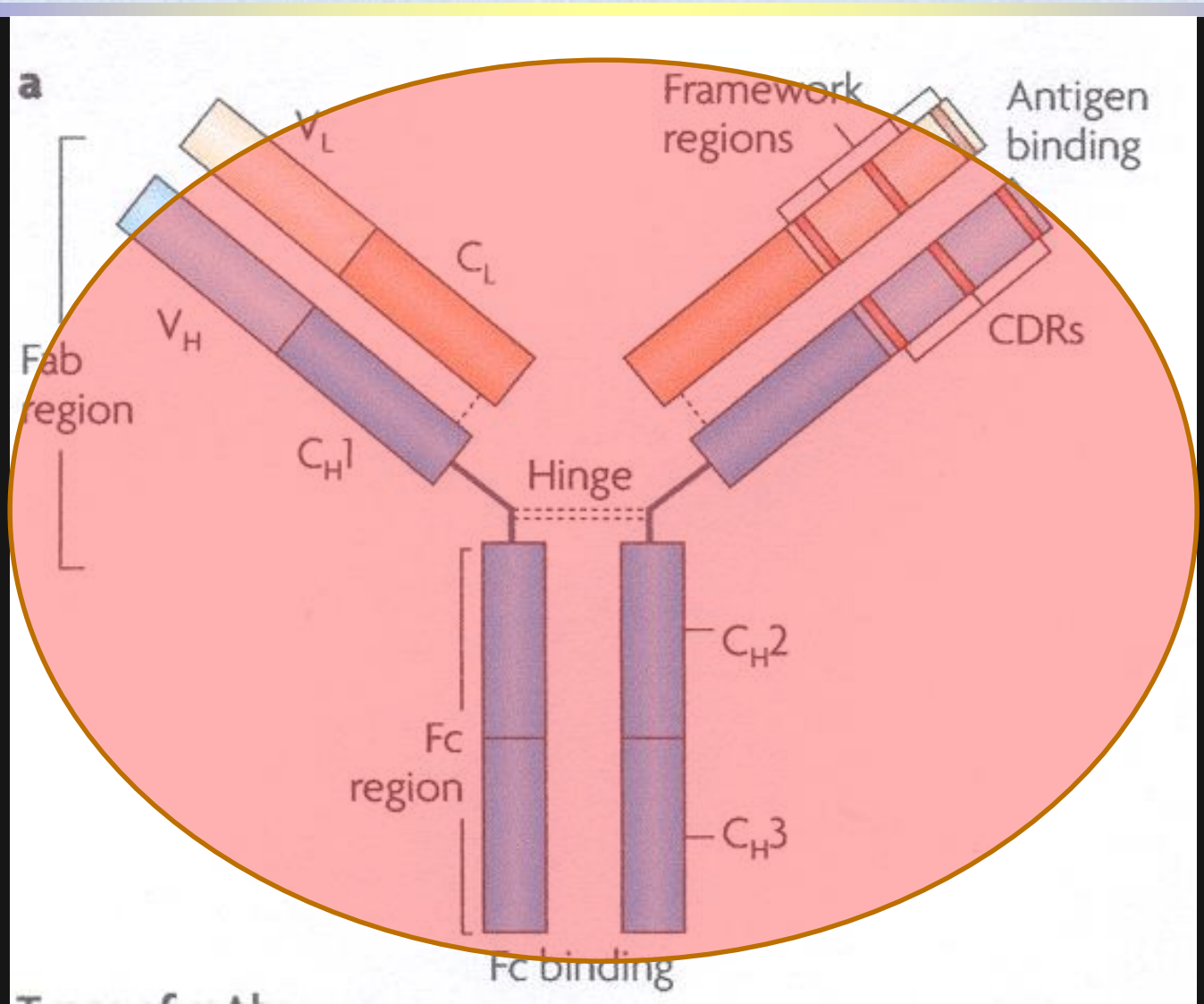

Activities of Monoclonal Antibodies Antagonism and Signalling

- Functions of mAbs, which include antagonism and signalling, are controlled by specific CDRs within the Fab region. Certain mAbs can specifically bind to either a ligand for example, infliximab and omalizumab, or to a receptor, for example, natalizumab and daclizumab — and thereby prevent stimulation.
- By contrast, other mAbs can specifically induce signal transduction by binding to a receptor.TGN1412 is a CD28 superagonist (CD28SA), which means that ligation of the T-cell receptor is not required for T-cell activation.

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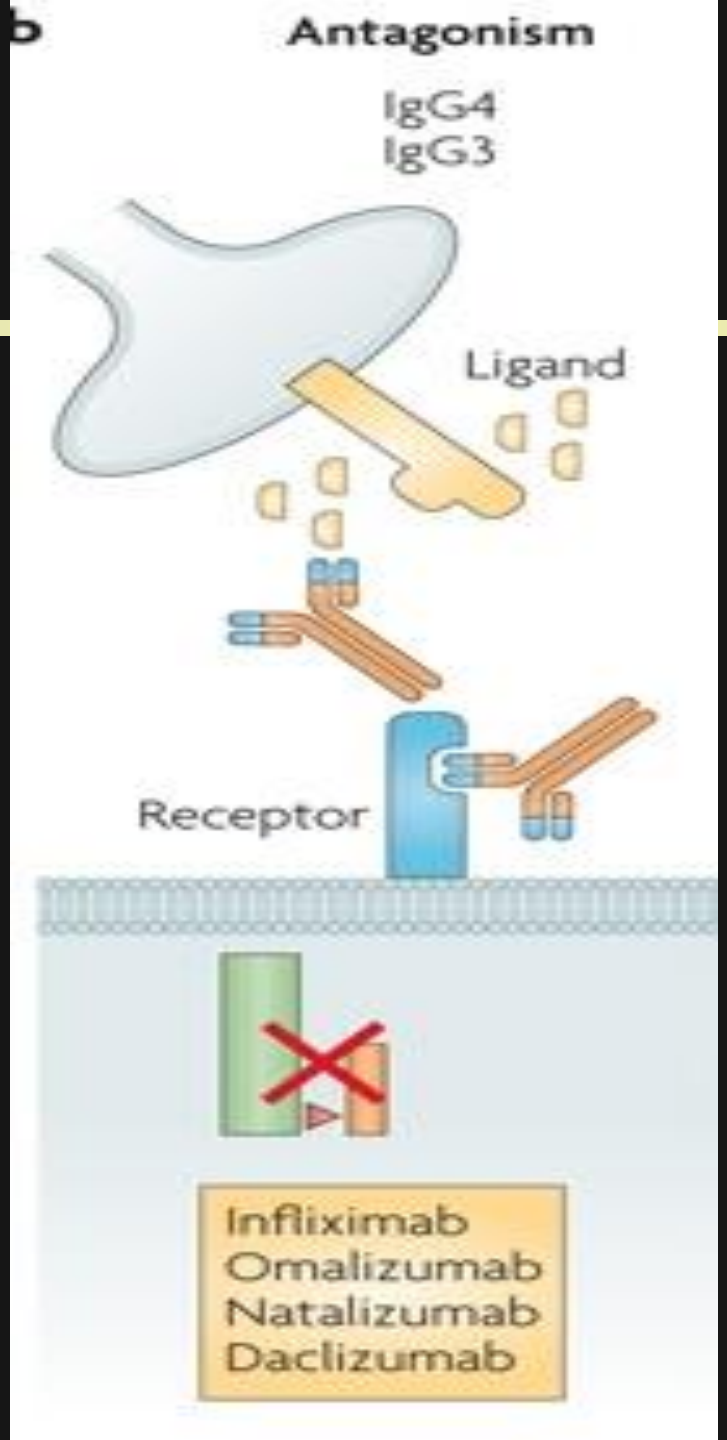
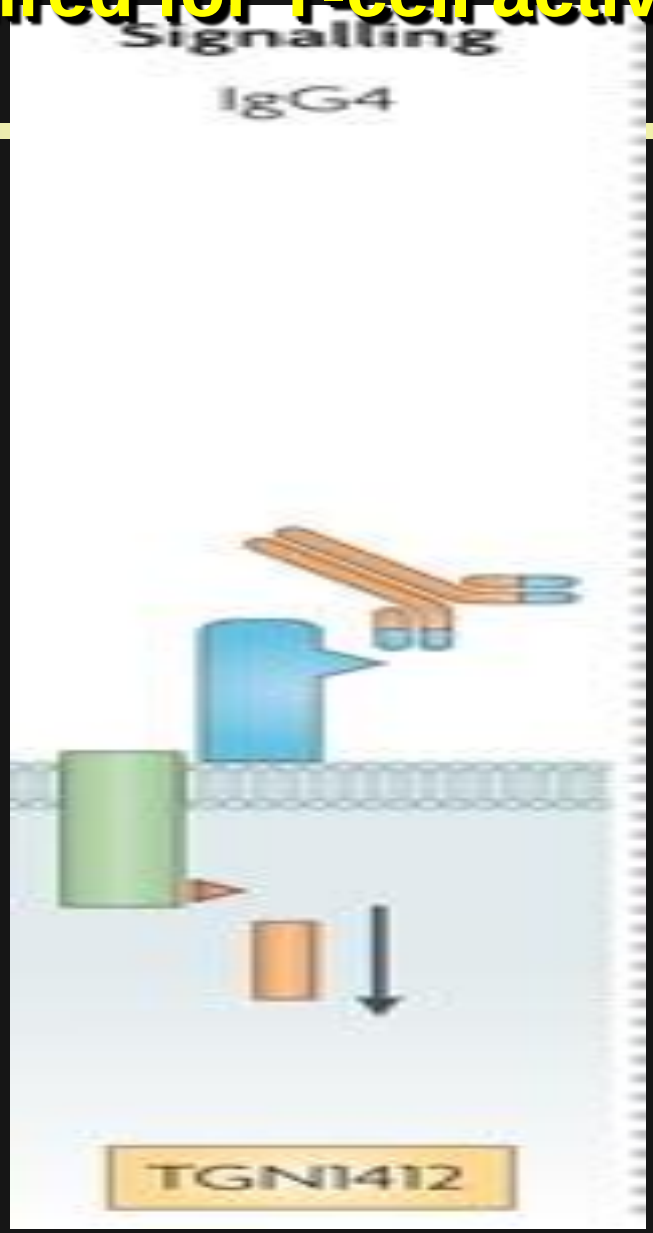


Signalling:TGN1412 is a CD28 superagonist (CD28SA), which means that ligation of the T-cell receptor is not required for T-cell activation



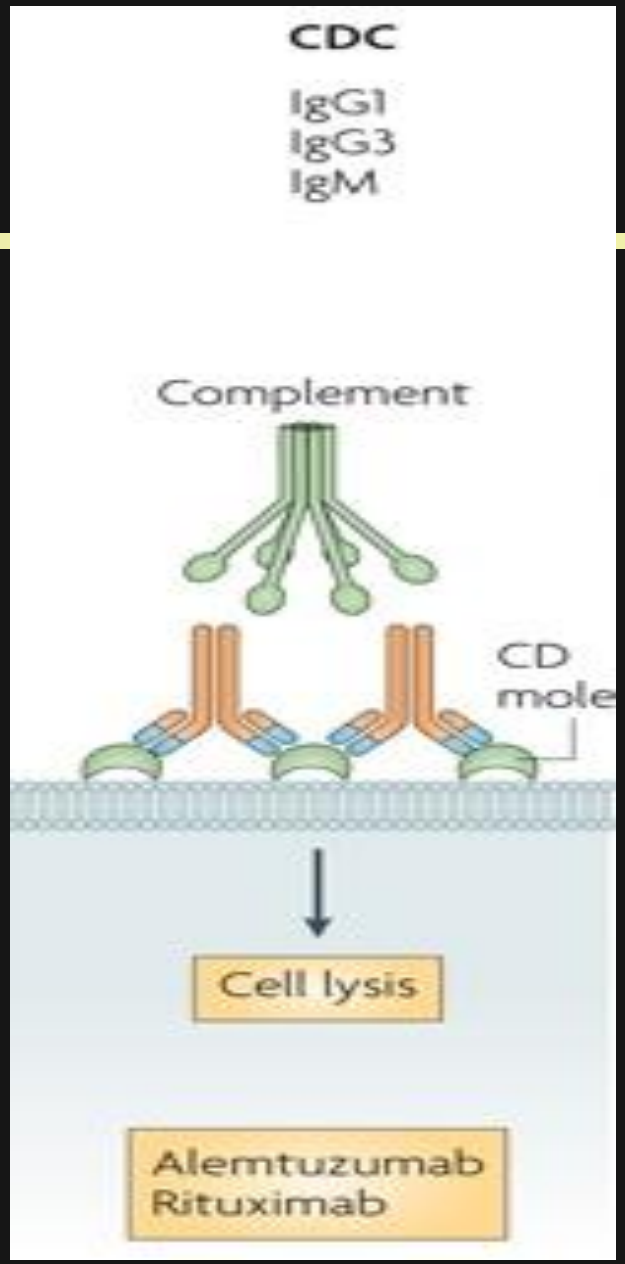
Nature Reviews Drug Discovery 9, 325-338 (April

Activities of Monoclonal Antibodies Actions Controlledby the Fc Region

Functions of mAbs controlled by the Fc region include complement-dependent cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis.

Certain mAbs can lyse cells (for example, T cells or B cells) through complement activation, whereas other mAbs can bind to Fc receptors and mediate cell lysis.

LYSIS



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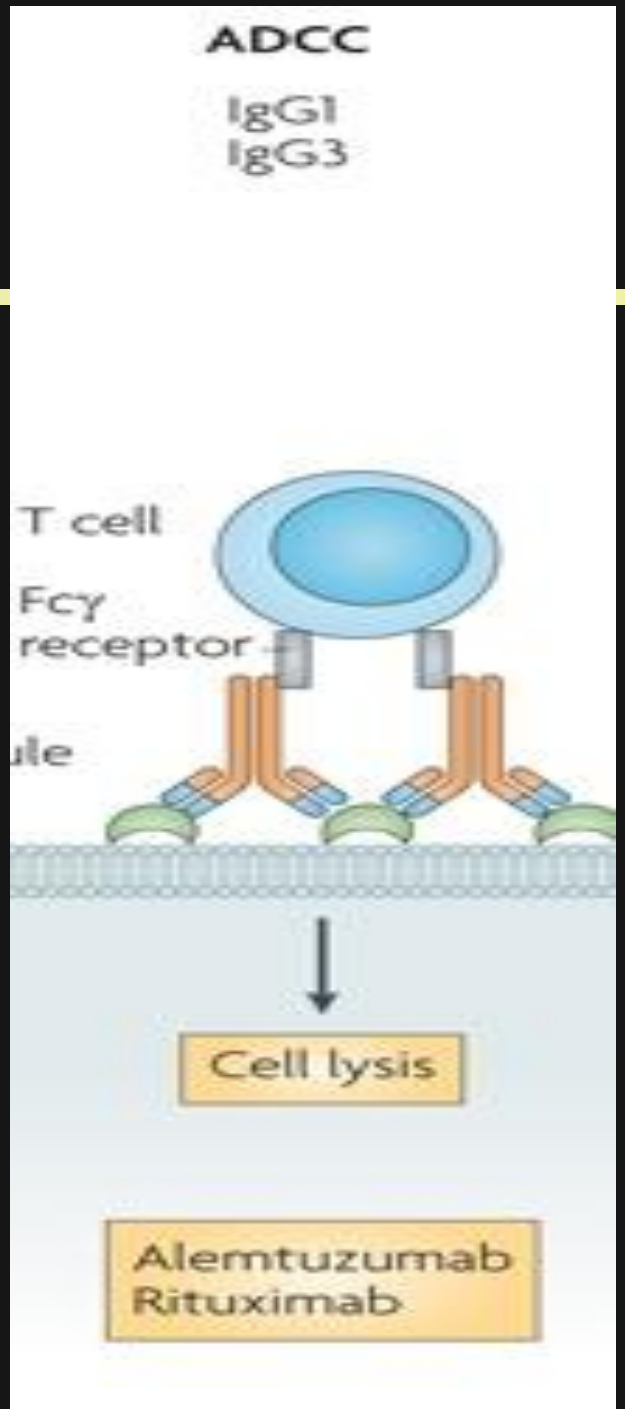


Reactions to Monoclonal Antibodies

- Most reactions to mAbs occur acutely during the infusion
- Symptoms range from mild rigors to anaphylaxis
- Reactions can occur on the initial or repeated exposure(s)
- Skin tests to the offending agent can be negative

Classification of reactions to Immunomodulators

- cytokine release syndromes, interferons (flu-like) or acne-like lesions (anti-epidermal growth factor receptors)
- IgE, IgG, and Tcell
- Cytokine imbalance syndromes
- Immune deficiency
- Miscellaneous (TNF induced heart failure)

Modified from Pichler W.J. Adverse side-effects to biological agents. *Allergy* 2006 ; 61 : 912-920

Classification of reactions to Immunomodulators

- Acute
  - Anaphylactic
  - Serum sickness
  - Tumor lysis syndromes (usually lymphomas/leukemias)
  - Cytokine release syndromes (cytokine storm)

Classification of reactions to Immunomodulators

- **Chronic**

  Progressive multifocal encephalopathy (natulizumab)

  Auto-immune syndromes

  Lupus-like (anti-Tnf)

  Thyroid auto-immune disease **(**alemtuzumab)

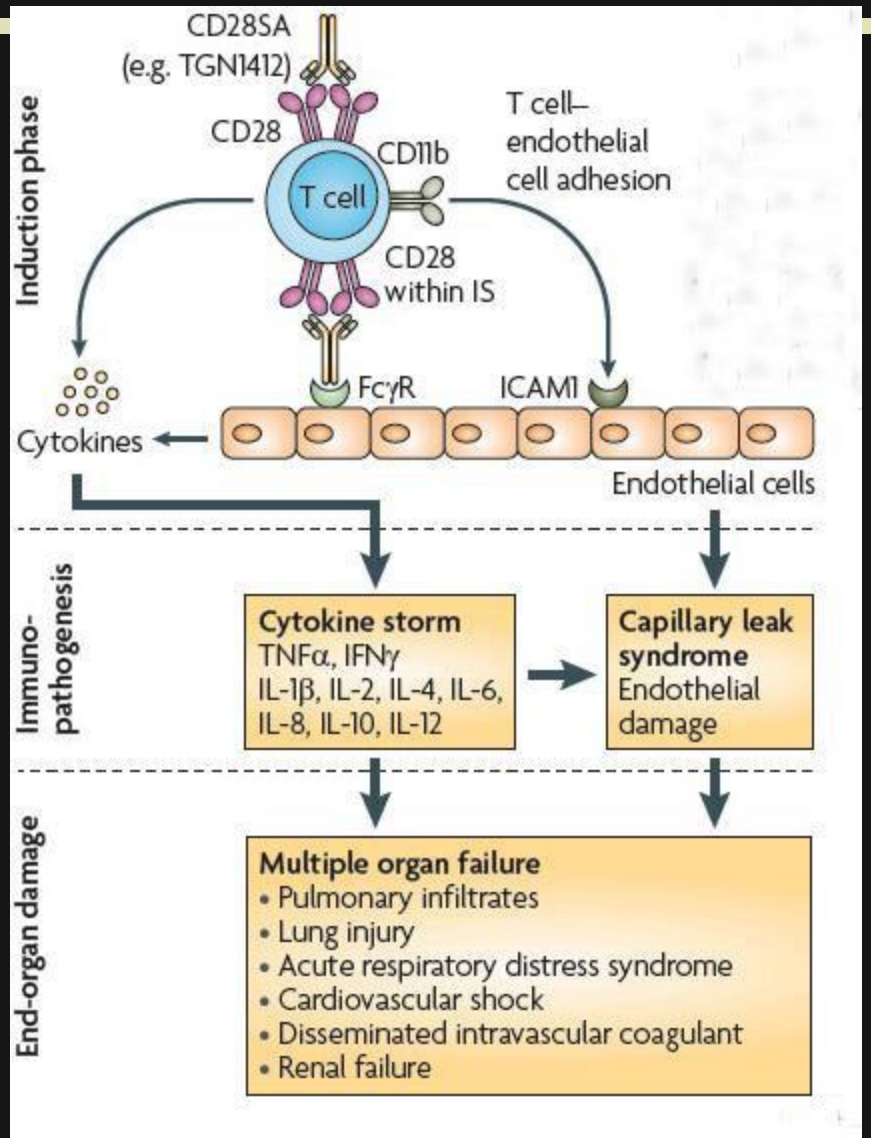
  Auto-immune colitis (ipilimumab)

  Cancer (infliximab)

  Dermatitis (panitumumab)

  Cardiac dysfunction (Trastuzumab)

Cytokine Storm



Tumor lysis syndrome

- **hyperuricemia, hyperkalemia, hyperphosphotemia, hypocalcemia and uremia. Patients may demonstrate one, several, or all of these metabolic abnormalities. Renal failure can follow**

- **Tumors Associated**

ALL, AML, APML

CLL, CML (blast crisis)

NonHodgkins Lymphomas (high grade):

Follicular

Diffuse large cell

Breast cancer

Testicular/Germ cell

Soft tissue sarcomas

Small cell lung cancer

Meduloblastoma

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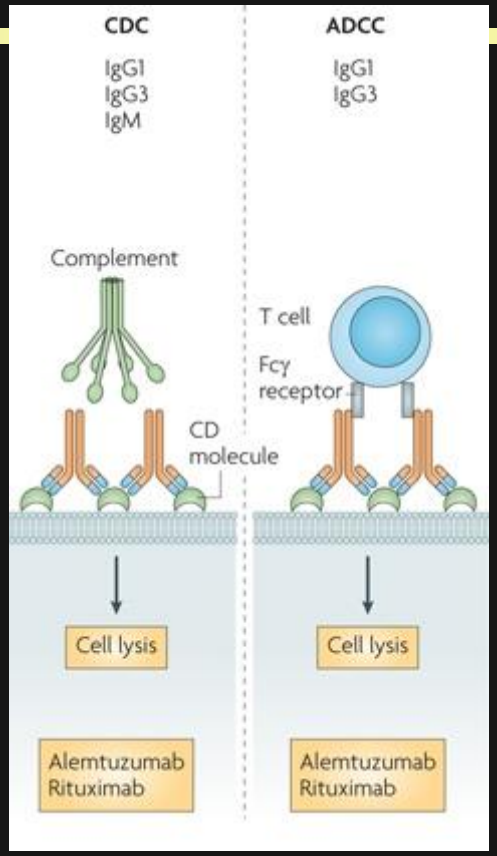

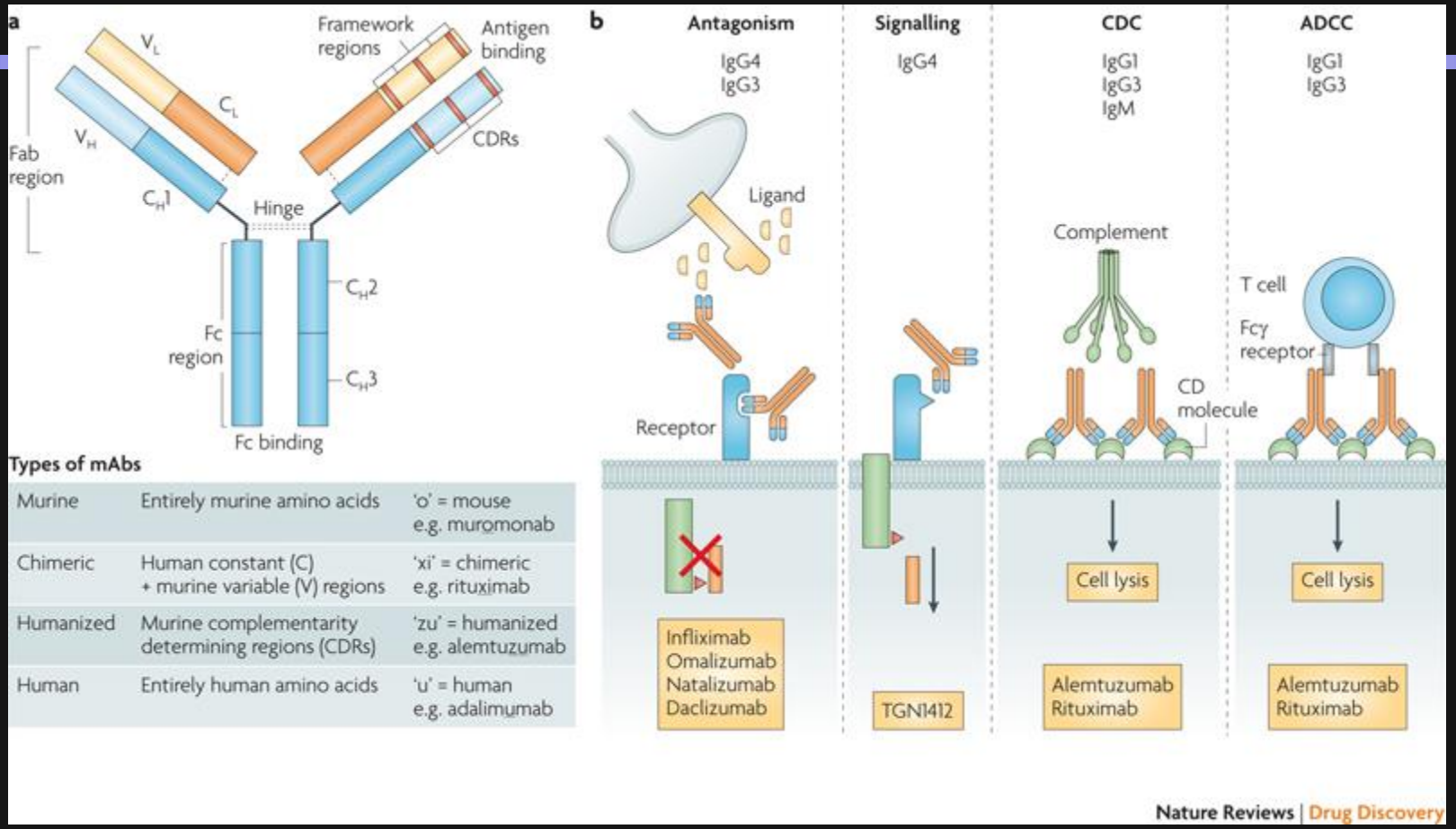

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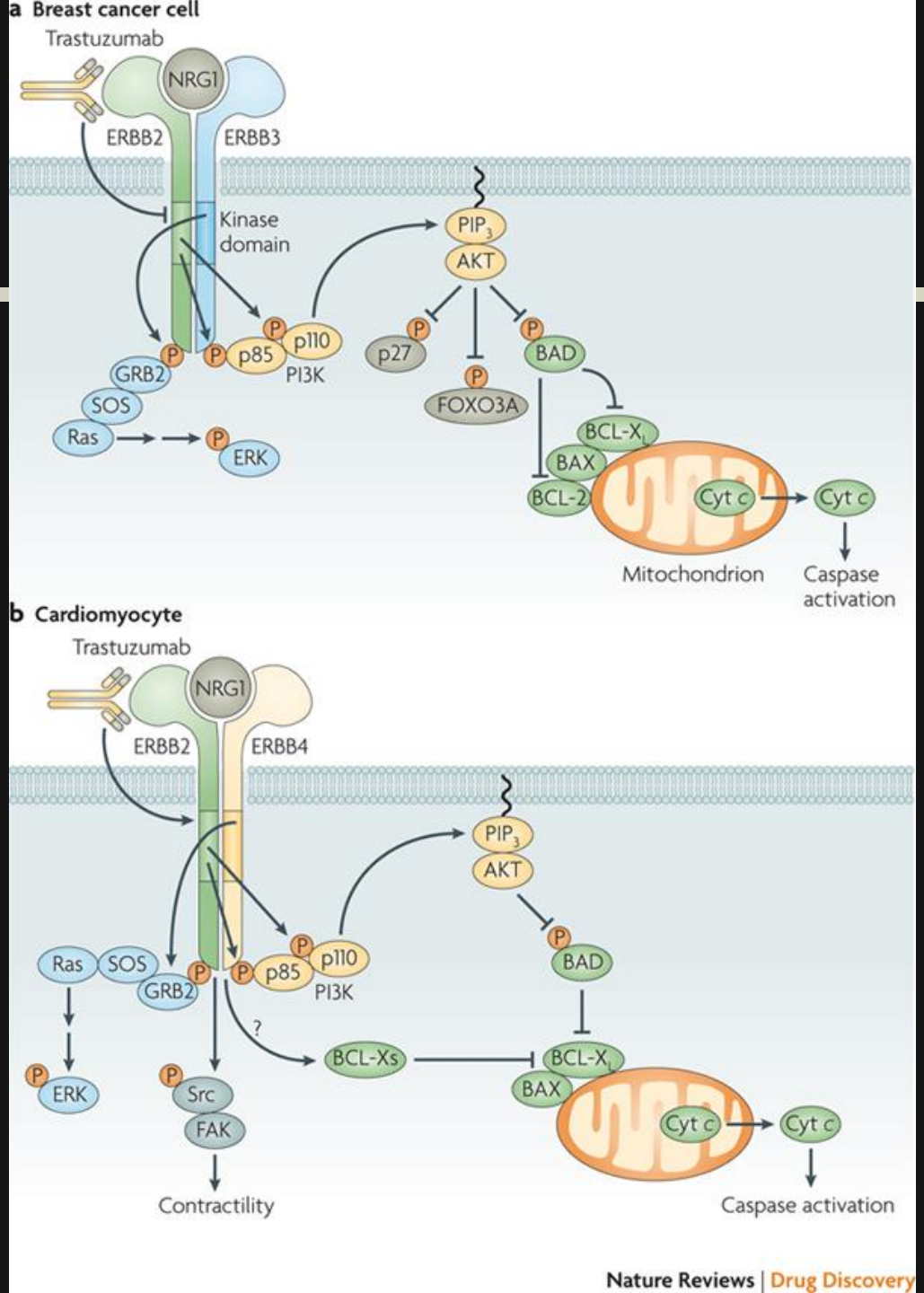

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Target	mAb	Type	FDA approval	Indications*	Selected side effects
Platelet glycoprotein IIb/IIIa	Abciximab (ReoPro; Centocor Ortho Biotech, Eli Lilly)	Chimeric antibody fragment: c7E3 Fab	1994	• Prevention of ischaemic cardiac complications of percutaneous coronary interventions and unstable angina	• Hypersensitivity and immunogenicity • Increased risk of bleeding • Thrombocytopaenia
Tumour necrosis factor-α	Adalimumab (Humira; Abbott)	Fully human	2002	• Rheumatoid arthritis • Ankylosing spondylitis • Psoriasis • Psoriatic arthritis • Crohn's disease • Ulcerative colitis	• Infusion reactions and immunogenicity • Hypersensitivity reactions • Immunosuppression and infections (tuberculosis) • Anaemia, leukopaenia and thrombocytopaenia • Worsening heart failure • Malignancy, lymphoma and lympho-proliferative disorders • Elevated liver transaminases • Increased nuclear-specific antibodies
	Certolizumab (Cimzia; UCB)	Humanized pegylated	2008		
	Infliximab (Remicade; Centocor Ortho Biotech)	Chimeric	1998		
CD52 on mature B, T and natural killer cells	Alemtuzumab (Campath; Genzyme)	Humanized	2001	• B cell chronic lymphocytic leukaemia • Graft-versus-host disease • Multiple myeloma • Multiple sclerosis • Vasculitis • Behçet's disease	• Infusion reactions • Hypersensitivity and immunogenicity • CRS • Tumour lysis syndrome • Immunosuppression and opportunistic infections • Cytopaenias: pancytopaenia, lymphopaenia and thrombocytopaenia • Autoimmune haemolytic anaemia • Thyroid disorders • Cardiotoxicity
Interleukin–2 receptor-α on activated lymphocytes	Basiliximab (Simulect; Novartis)	Chimeric	1998	• Prophylaxis of renal transplant allograft rejection	• Severe acute hypersensitivity reactions • CRS and immunogenicity • Immunosuppression and infections • Local skin reactions • Warnings when combined with other immunosuppressives
	Daclizumab (Zenapax; Roche)	Humanized	1997 Discontinued in Europe		
Vascular endothelial growth factor	Bevacizumab (Avastin; Genentech)	Humanized	2004	• Metastatic colorectal cancer • Non-small-cell lung carcinoma • Metastatic breast carcinoma • Metastatic renal carcinoma	• Infusion reactions and immunogenicity • Local complications at tumour site • Arterial and venous thromboembolic events • Haemorrhage • Severe hypertension • Cardiac failure • Reversible posterior leukoencephalopathy syndrome • Slower wound healing and GI perforation
	Ranibizumab (Lucentis; Genentech, Novartis)	Humanized (Fab fragment from bevacizumab)	2006	• Injected intravitreally for neovascular (wet) age-related macular degeneration	• Conjunctival haemorrhage • Intraocular inflammation • Increased intraocular pressure • Retinal detachment • Endophthalmitis
Complement C5	Eculizumab (Soliris; Alexion)	Humanized	2007	• Paroxysmal nocturnal haemoglobinuria	• Meningococcal and *Neisseria* infection • Intravascular haemolysis
CD11a	Efalizumab (Raptiva; Genentech)	Humanized	2003 Recently discontinued	• No longer licensed for chronic plaque psoriasis	• First-dose reaction complex • Immunosuppression • Serious opportunistic infections • PML • Guillain–Barré syndrome, encephalitis, meningitis • Immune haemolytic anaemia • Immune thrombocytopaenia
CD3 antigen on T cells	Muromonab-CD3 (Orthoclone OKT3; Ortho Biotech)	Mouse	1986 (no European Medicines Authority authorization)	• Acute resistant allograft rejection in renal, cardiac and hepatic transplant patients	• Severe acute infusion reactions • Immunosuppression and infections • Immunogenicity • Cardiovascular side effects • Hepatitis
α4 integrin	Natalizumab (Tysabri; Biogen-Idec, Elan Pharmaceuticals)	Humanized	2004	• Highly active relapsing-remitting multiple sclerosis	• Infusion and hypersensitivity reactions • Immunogenicity • PML (0.1%) with immunosuppressives • Hepatotoxicity
Immunoglobulin E (IgE)	Omalizumab (Xolair; Genentech, Novartis)	Humanized	2003	• Severe allergic asthma unresponsive to conventional therapy and with acute exacerbations	• Anaphylaxis (0.1%) • Injection site reactions • Immunogenicity • URTI • Churg–Strauss syndrome (rare)
Fusion protein on RSV	Palivizumab (Synagis; MedImmune)	Humanized	1998	• Prevention of RSV complications in high-risk infants	• Anaphylaxis and apnoea (rare) • Fever, injection site reactions
CD20 on B cells	Rituximab (Rituxan/ Mabthera; Genentech, Biogen Idec)	Chimeric	1997	• Follicular non-Hodgkin's lymphoma • CD20$^+$ diffuse large B cell non-Hodgkin's lymphoma • Autoimmune haematological disorders	• Prominent acute infusion reactions • CRS • Tumour lysis syndrome • Transient hypotension • Immunogenicity • Serum sickness • Severe mucocutaneous reactions • Immunosuppression • Hepatitis B reactivation with fulminant hepatitis • PML • Renal toxicity • Cardiac arrhythmias
EGFR	Panitumumab (Vectibix; Amgen)	Fully human	2006	• Monotherapy for EGFR-positive metastatic colorectal carcinoma with non-mutated (wild-type) *KRAS* after failure of conventional chemotherapy	• Infusion reactions • Skin rashes in most patients (90%) • Diarrhoea (60%), nausea and vomiting • Hypomagnesaemia (2%)
	Cetuximab (Erbitux; Bristol–Myers Squibb, ImClone Systems, Merck Serono)	Chimeric	2004	• EGFR-positive metastatic colorectal cancer • Squamous cell carcinoma of head and neck	• Severe infusion reactions • IgE against oligosaccharide and HAMA • Urticaria and dermatological toxicity • Bronchospasm and pulmonary toxicity • Hypomagnesaemia
	Trastuzumab (Herceptin; Genentech)	Humanized	1998	• ERBB2-positive breast carcinoma	• Hypersensitivity and infusion reactions • Cardiotoxicity with anthracyclines • Skin reactions • Pulmonary toxicity • Hypomagnesaemia
Interleukin-6 receptor	Tocilizumab (Actemra; Roche, Chugai)	Humanized	2009	• Unresponsive active rheumatoid arthritis • Castleman's disease	• Anaphylaxis and anaphylactoid reactions • UTRI • Headache • Serious infections • Abnormal liver function, neutropaenia and lipid deregulation

CRS, cytokine release syndrome; EGFR, epidermal growth factor receptor; ERBB2, also known as HER2/neu; FDA, Food and Drug Administration; GI, gastrointestinal; HAMA, human anti-mouse antibodies; *KRAS*, v-Ki-ras2 Kirsten rat sarcoma viral oncogene homologue; PML, progressive multifocal leukoencephalopathy; RSV, respiratory syncytial virus; URTI, upper respiratory tract infection. *Some of these indications are not currently licensed.

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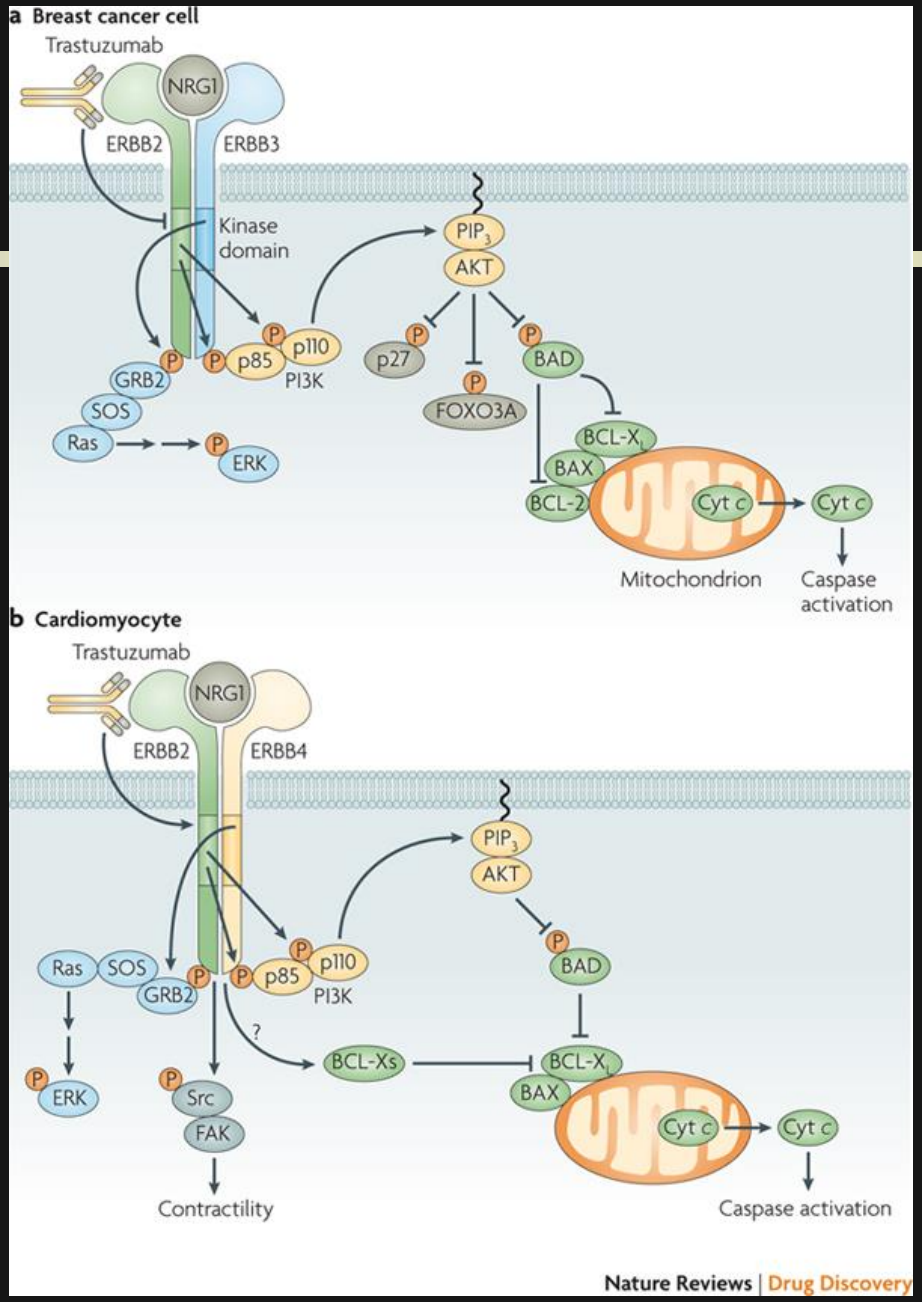
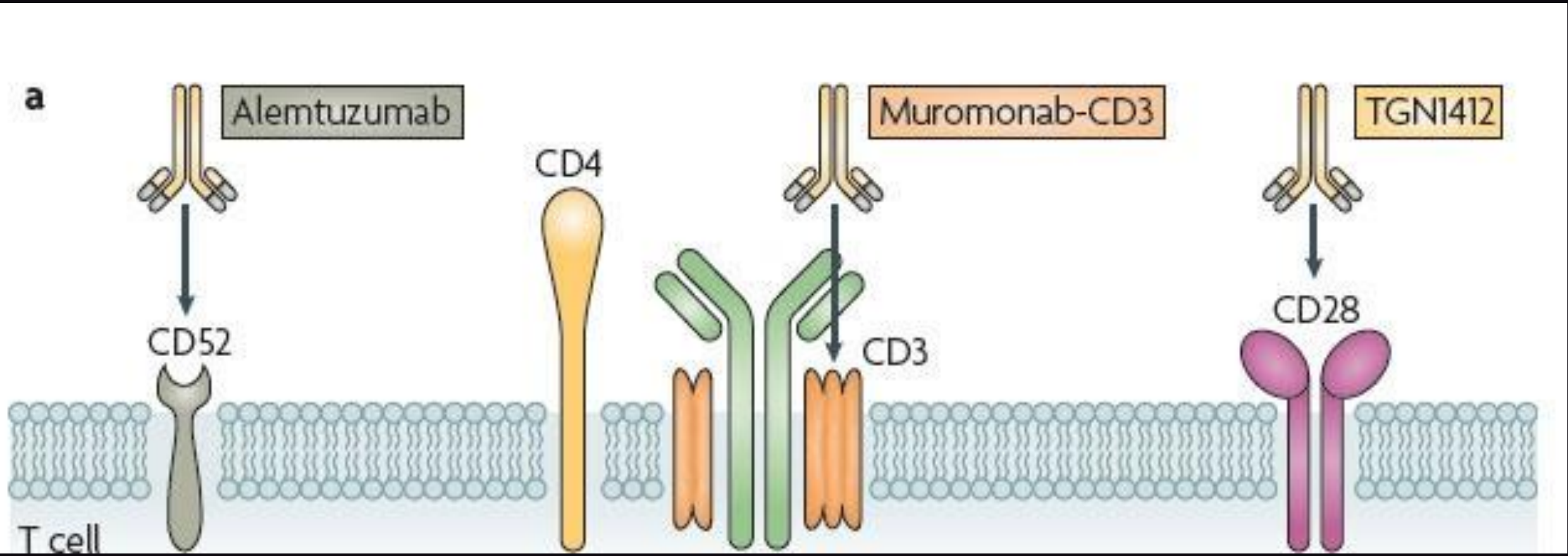


Cytokine storm

- Surface receptors on T cells can cause a cytokine storm when activated by therapeutic monoclonal antibodies (mAbs). Three mAbs that cause cytokine release on infusion in humans are alemtuzumab , muromonab-CD3 and TGN1412. Alemtuzumab recognizes CD52 and causes complement-dependent lysis of lymphocytes. Muromonab targets CD3. TGN1412 is a CD28 superagonist (CD28SA); that is, a co-stimulator molecule contributing to activation of naive T cells.

Cytokine Storm



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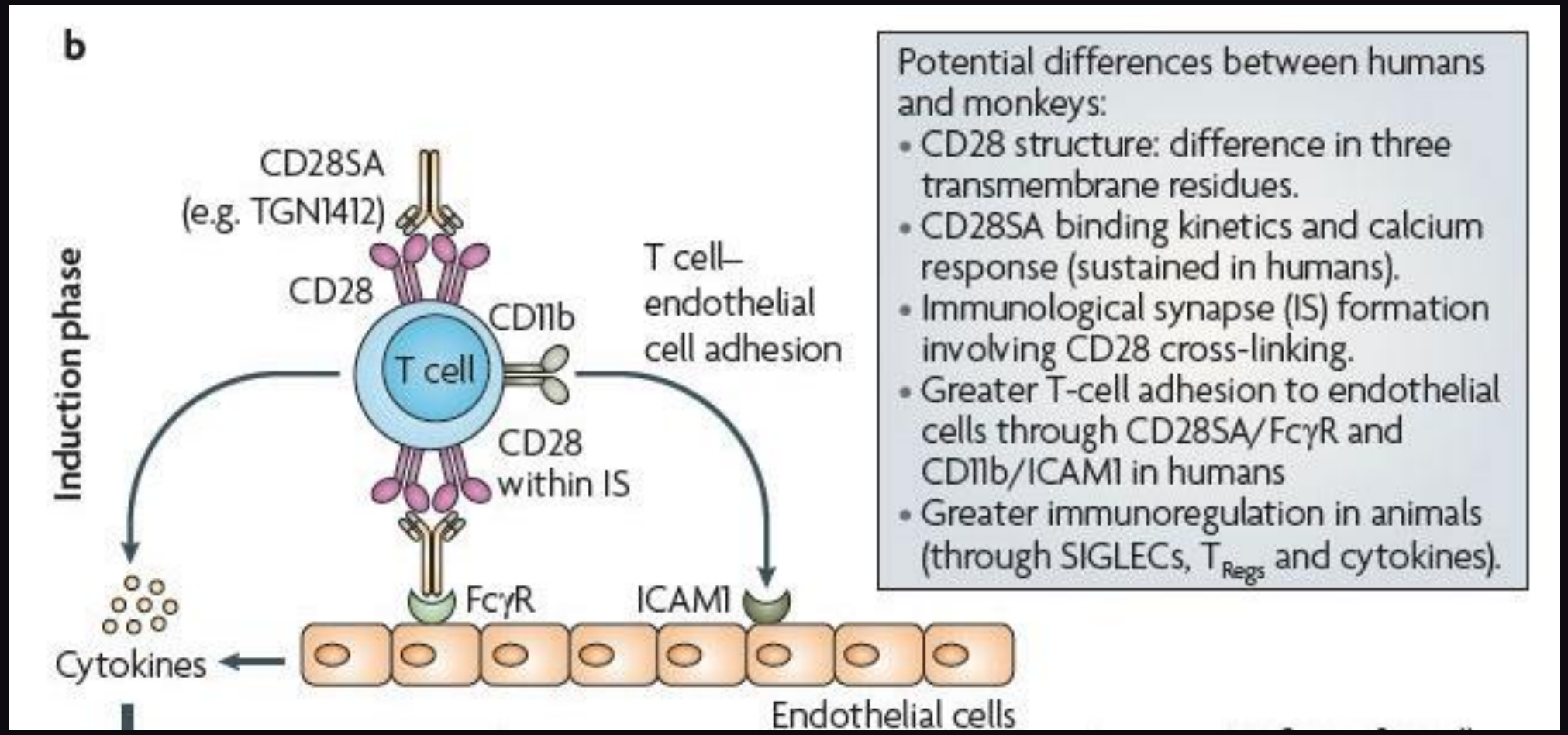
Cytokine Storm

- TGN1412 can directly causes cytokine release by cross-linking CD28 causing the formation of an immunological synapse on T cells, and binding of CD28SA to Fcγ receptors on endothelial cells and other leukocytes. Activation of CD28 also causes upregulation of adhesion molecules such as CD11b which can then bind to intracellular adhesion molecule 1 (ICAM1) on endothelial cells. T cell–endothelial complexes have the capacity to cause amplified cytokine production and local endothelial damage. Hence, the cytokine storm and neutrophil infiltration could mediate the capillary leak syndrome with resultant multiple organ failure

Cytokine Storm



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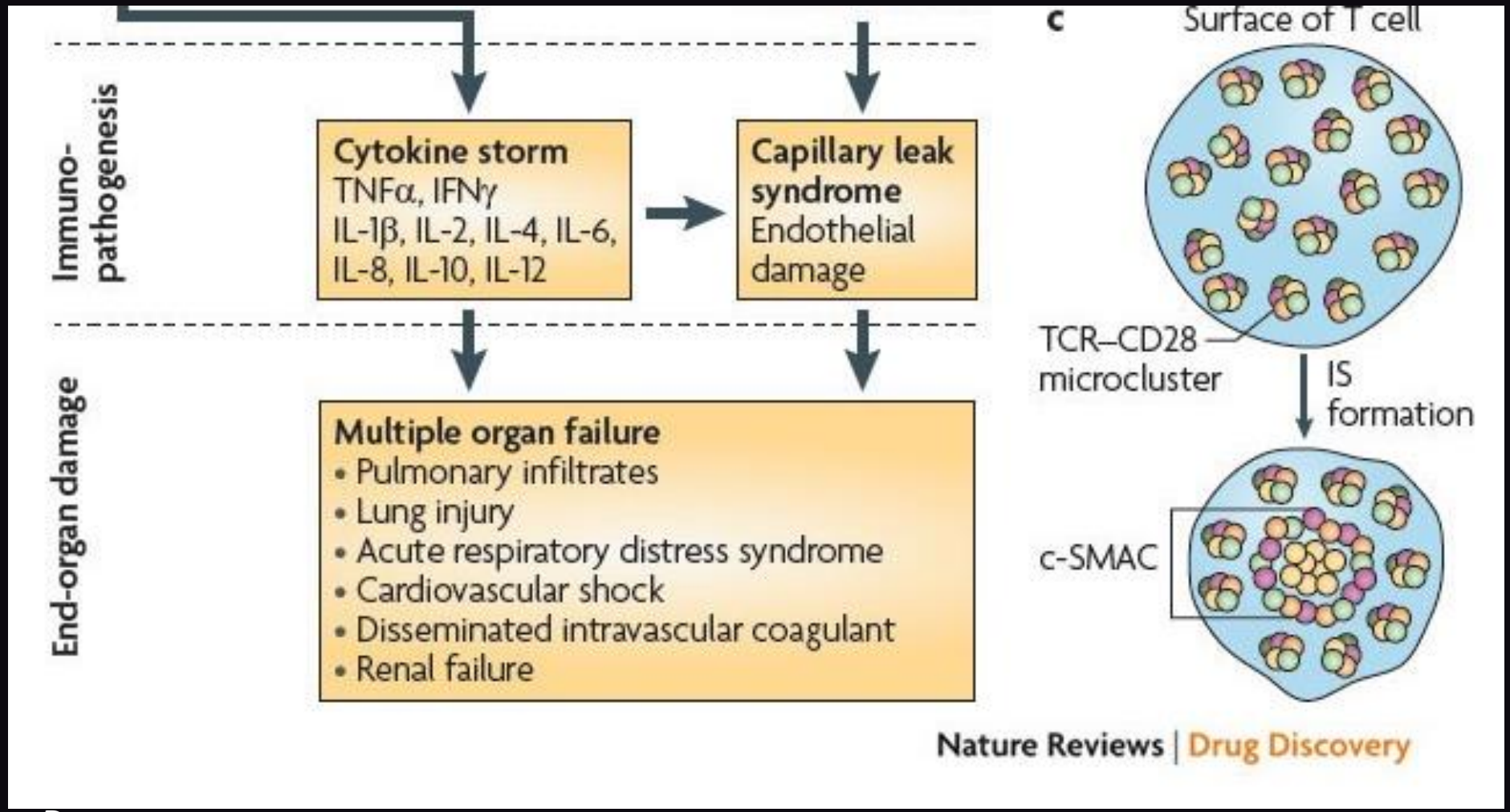
- **The Immune Synapse forms on the T-cell plasma membrane, in which the five components of the TCR–CD28 microcluster aggregate to form a central supramolecular activation cluster (c-SMAC). The latter consists of a core of TCR and CD3 molecules, surrounded by a ring of CD28 molecules with associated protein kinase Cθ, which causes sustained T-cell activation.**

Cytokine Storm



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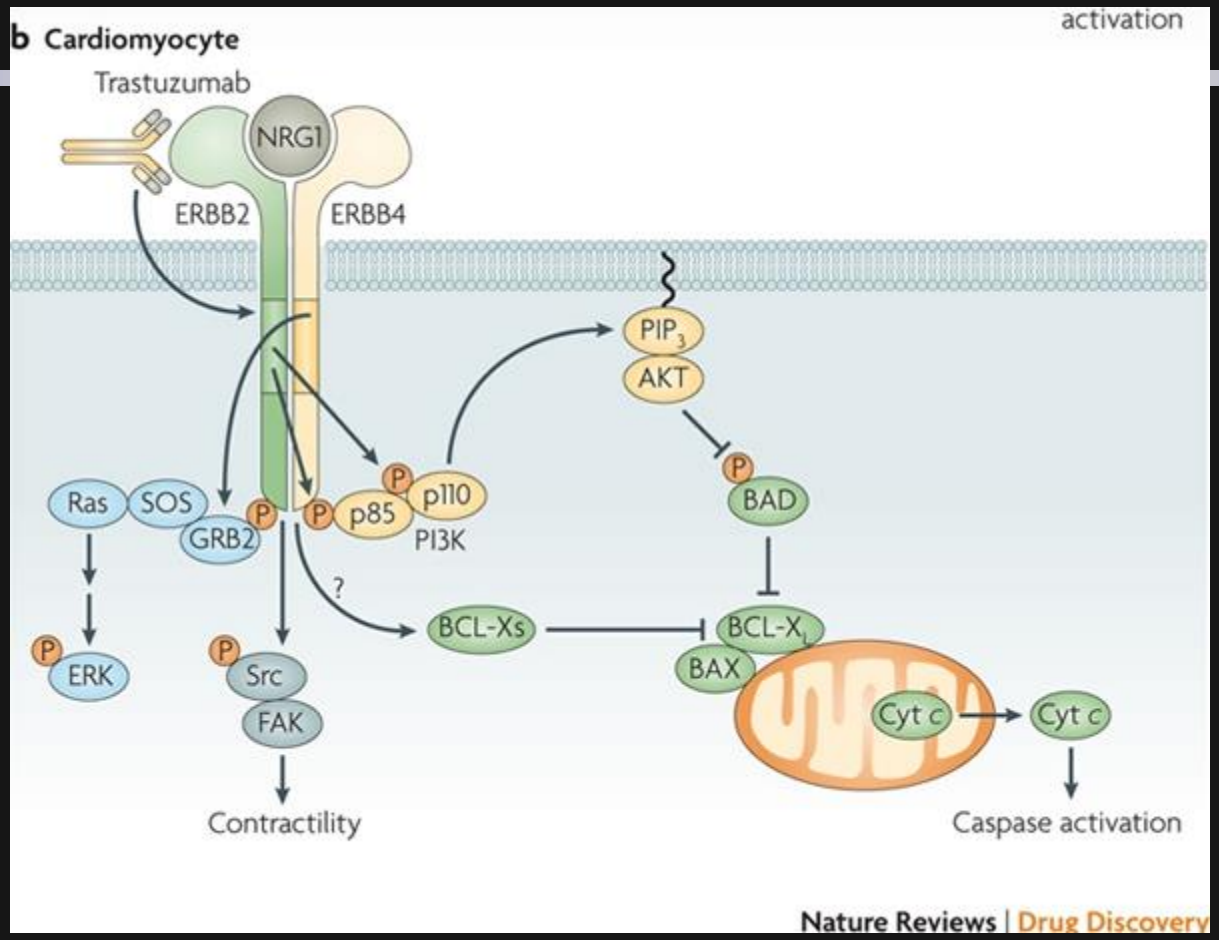

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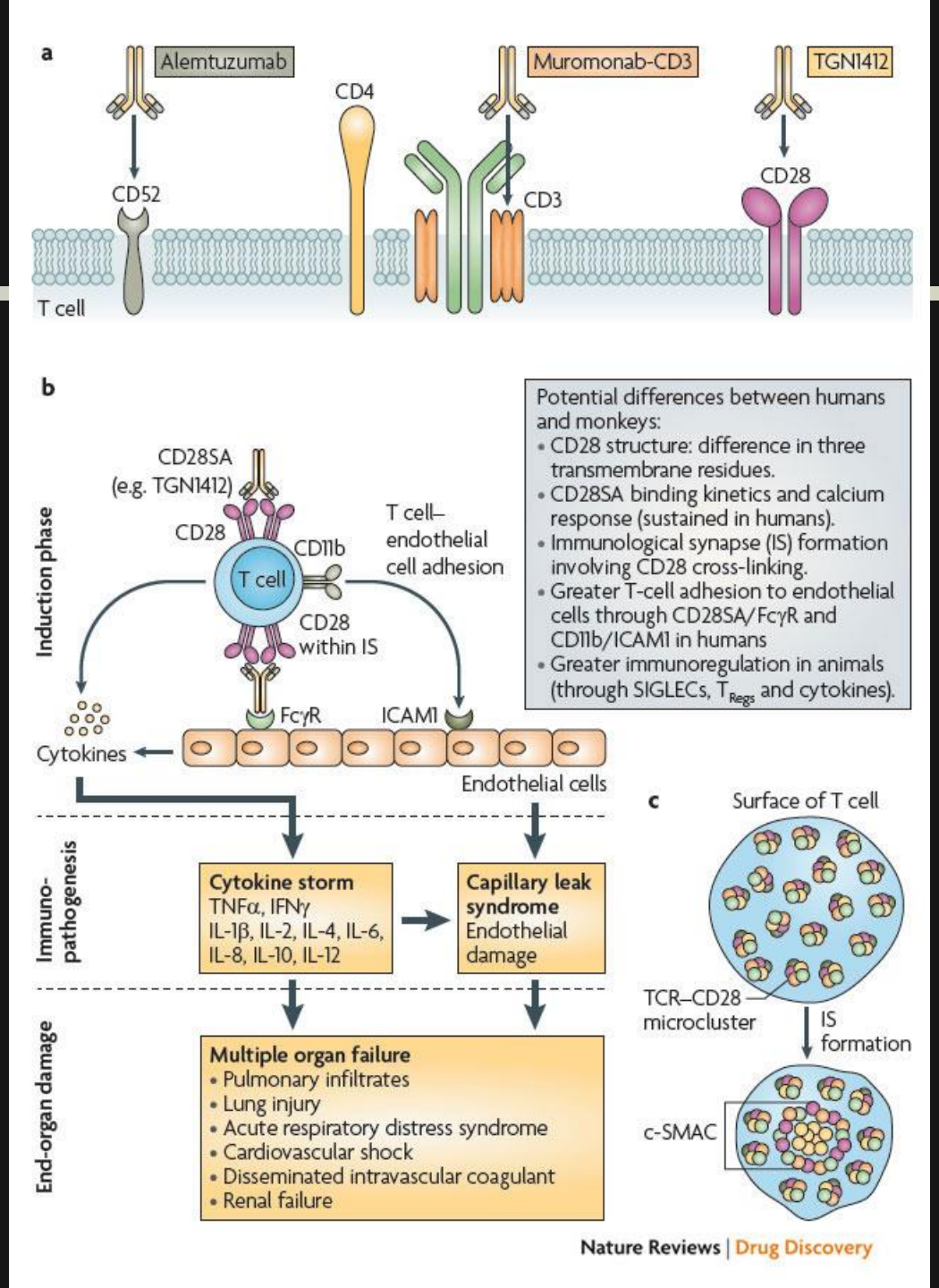

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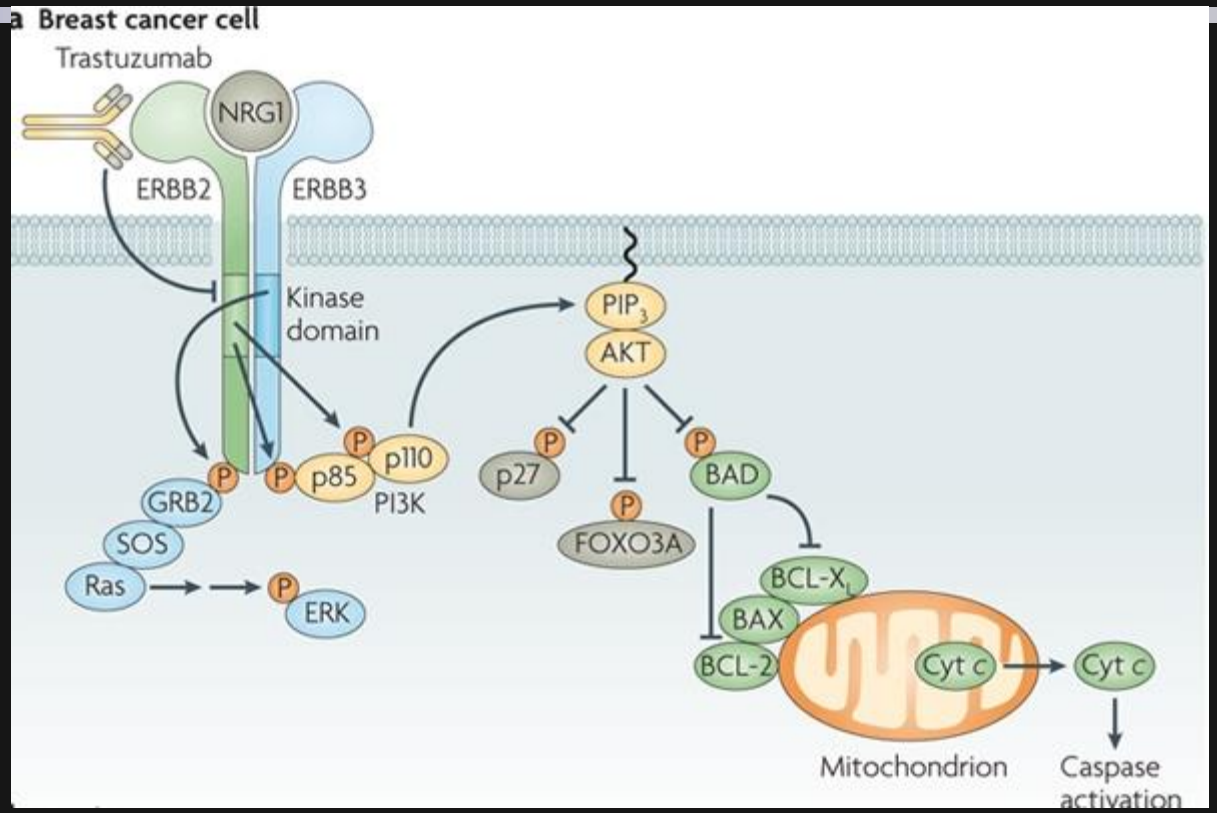

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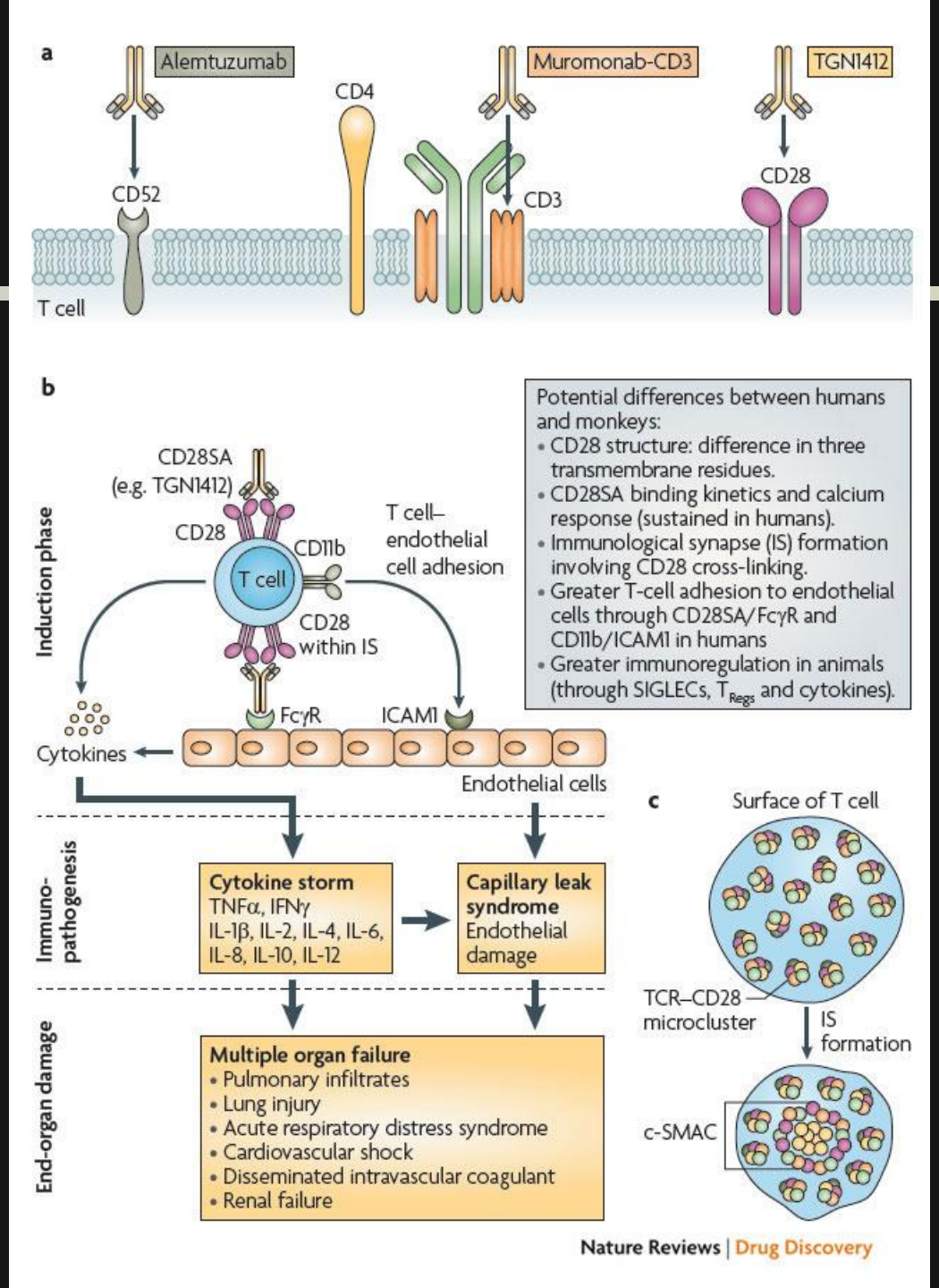
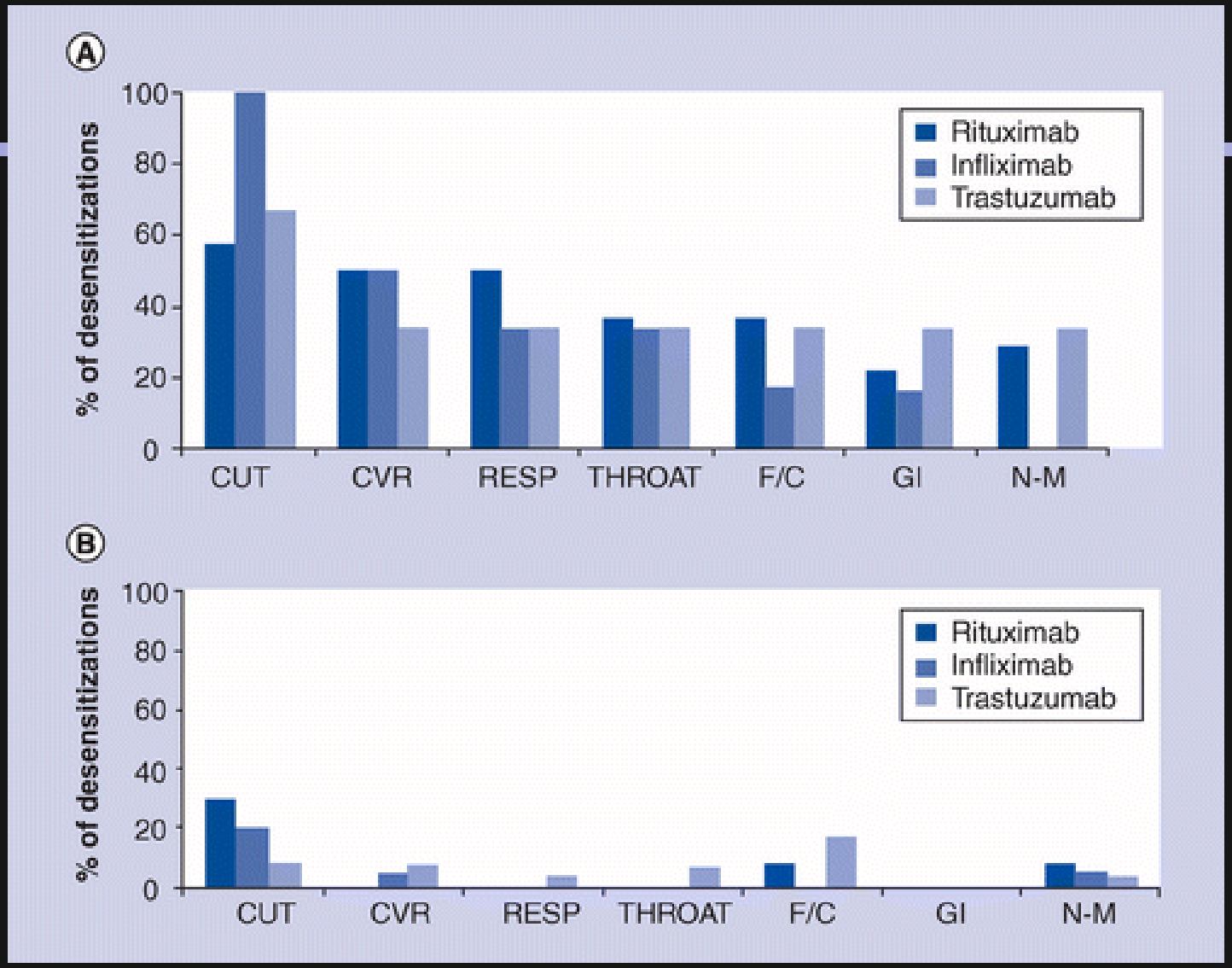


Before Desensitization

After Desensitization



*J. Allergy Clin. Immunol.*124,1259–1266 (2009).

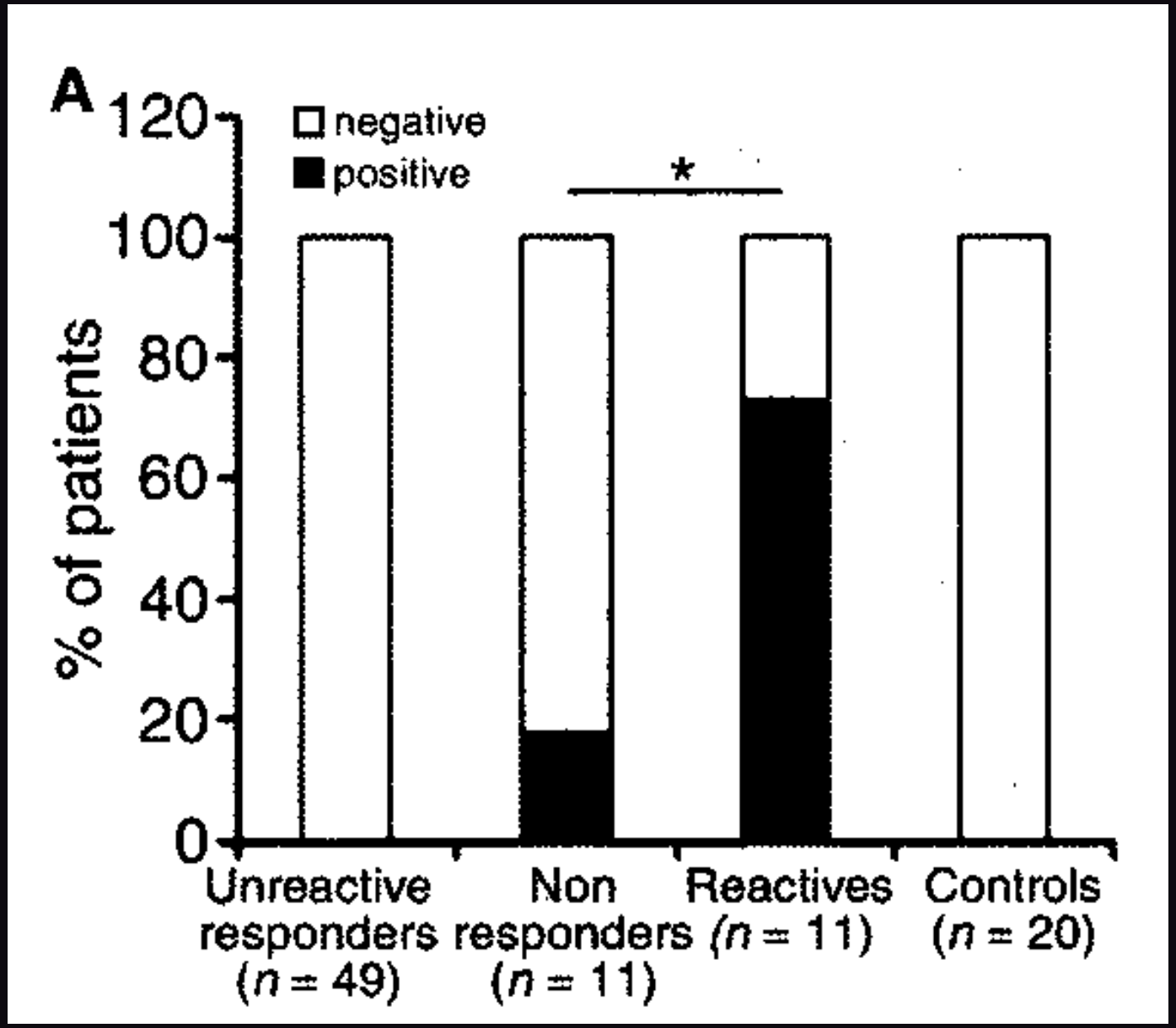
Anaphylaxis to Monoclonals

- Cetuximab
- Natalizumab
- Toclizumab
- Basilixumab
- Anti-TNF
- Abciximab
- Alemtizumab
- Basiixumab

Anti infliximab antibodies in reactors and non reactors

- 11 reactors, 60 non reactors
- Assessed for antibodies to infliximab
- Inconsistent findings but in some reactors antibodies to infliximab were detected

Allergy 2010 65:657



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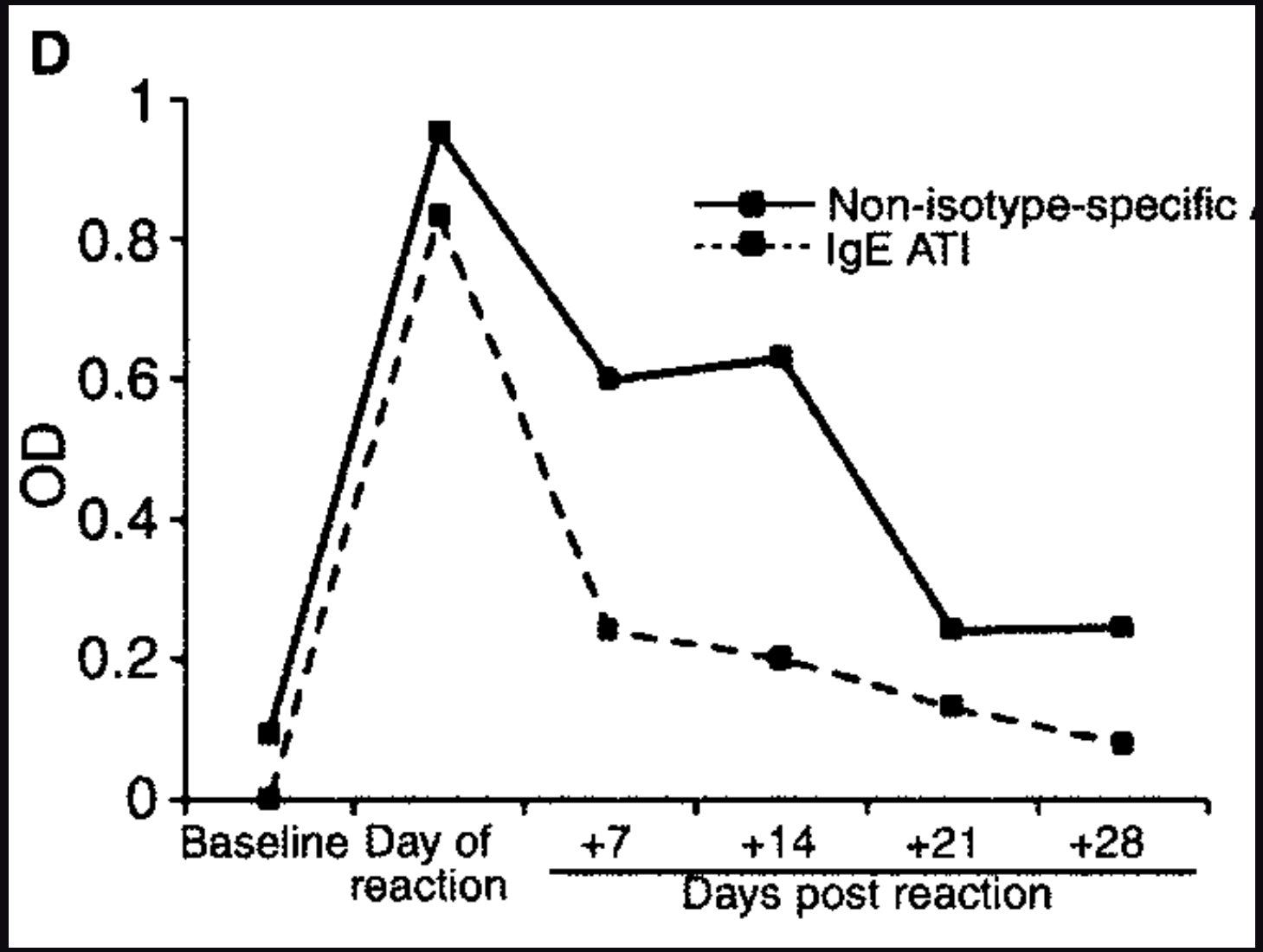

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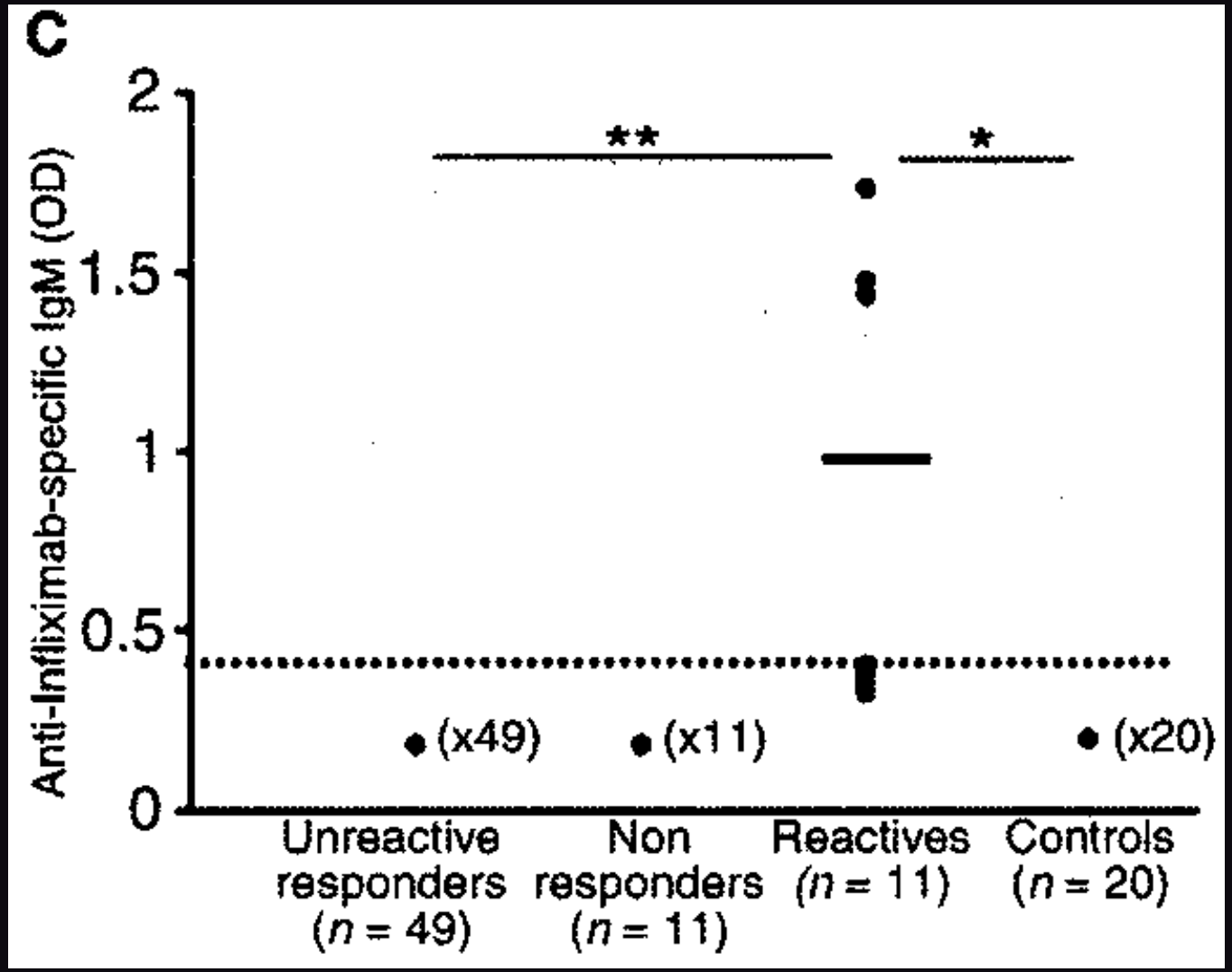

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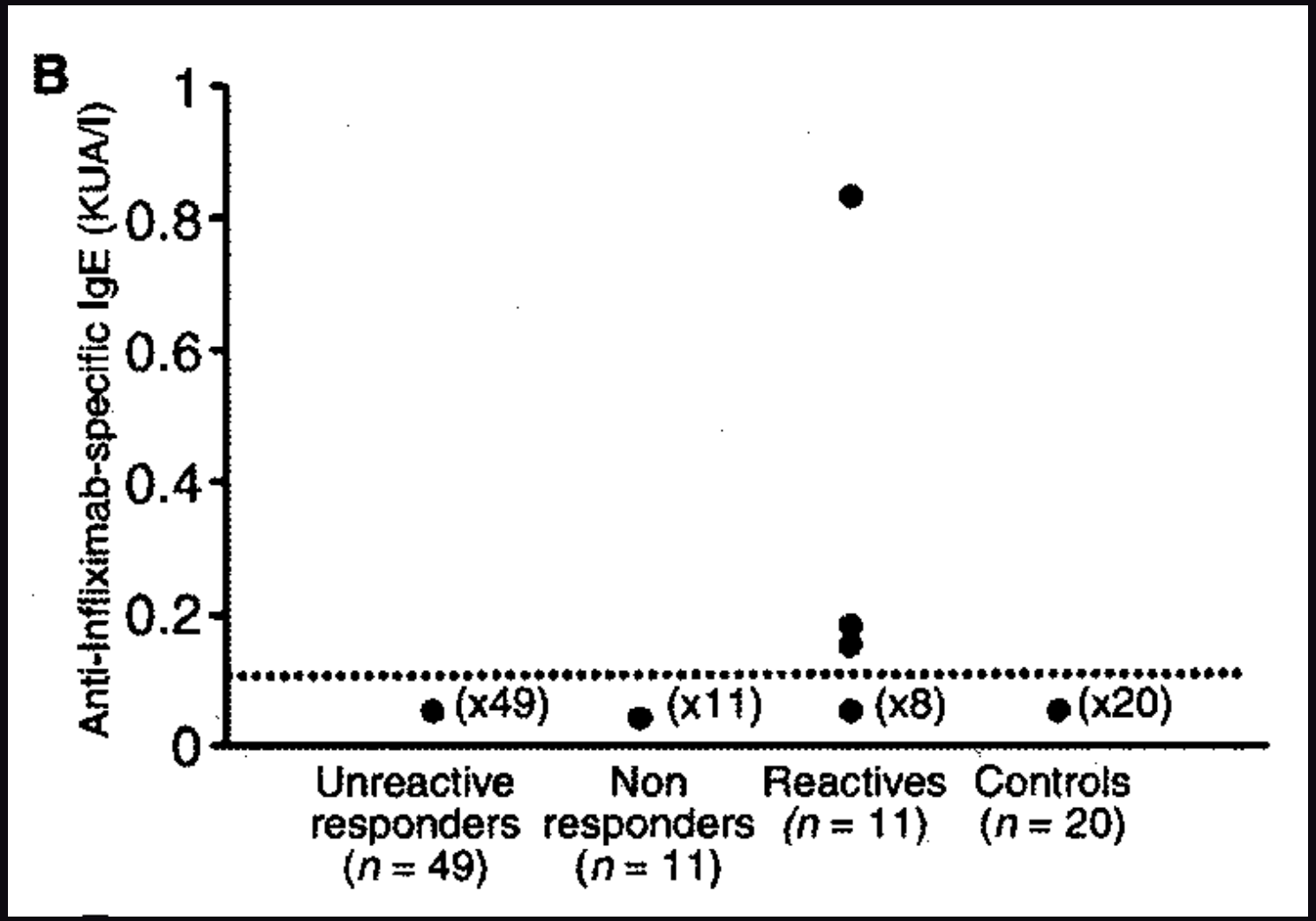
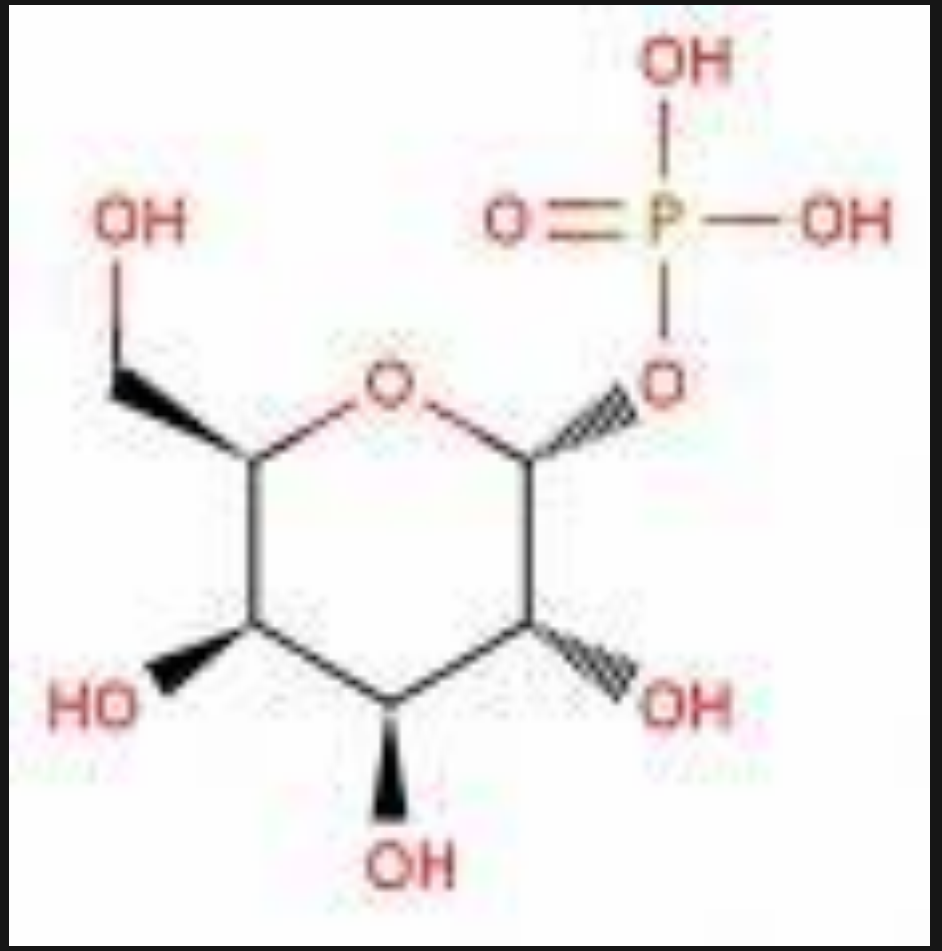
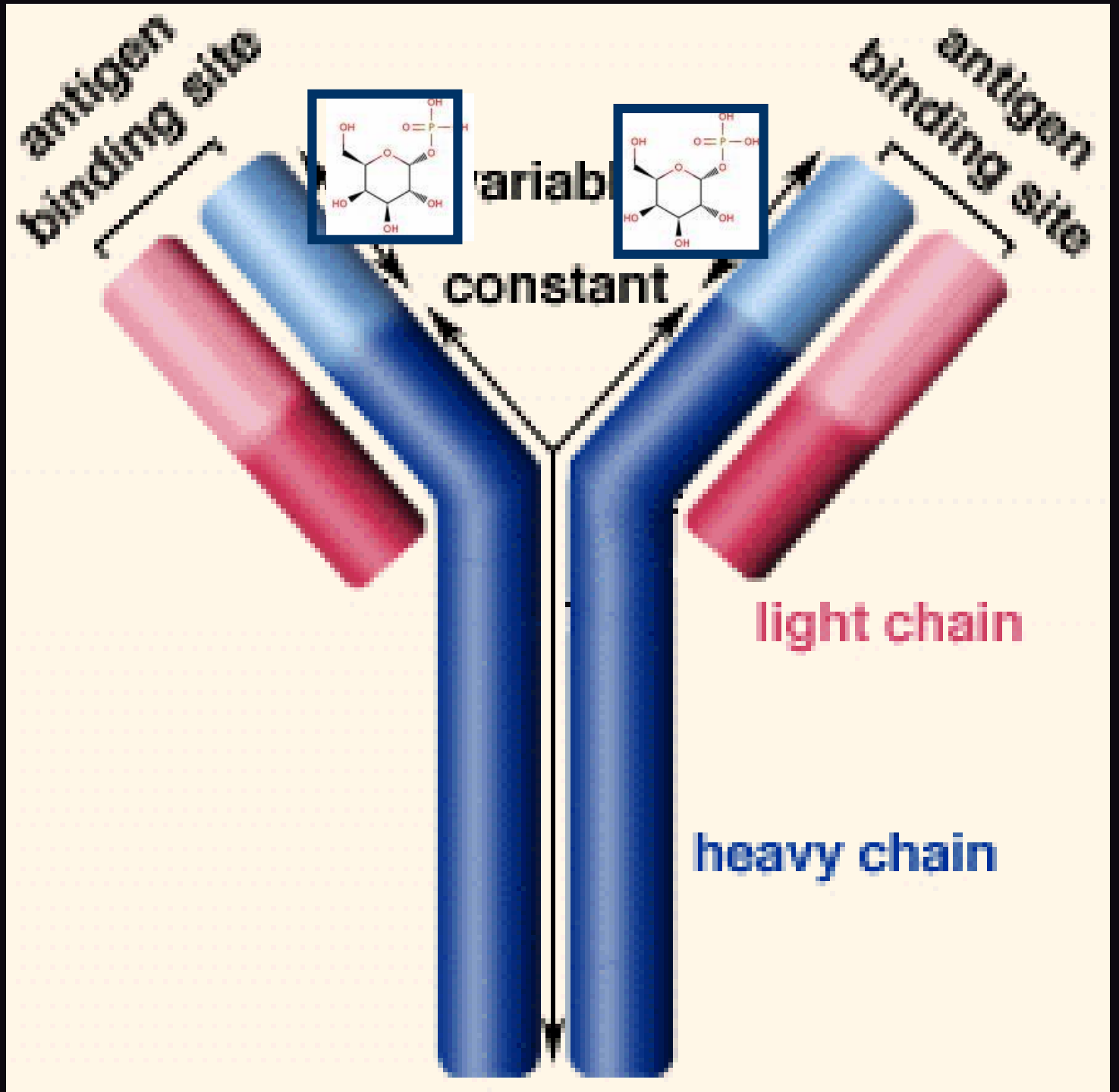


Allergy 2010 65:657

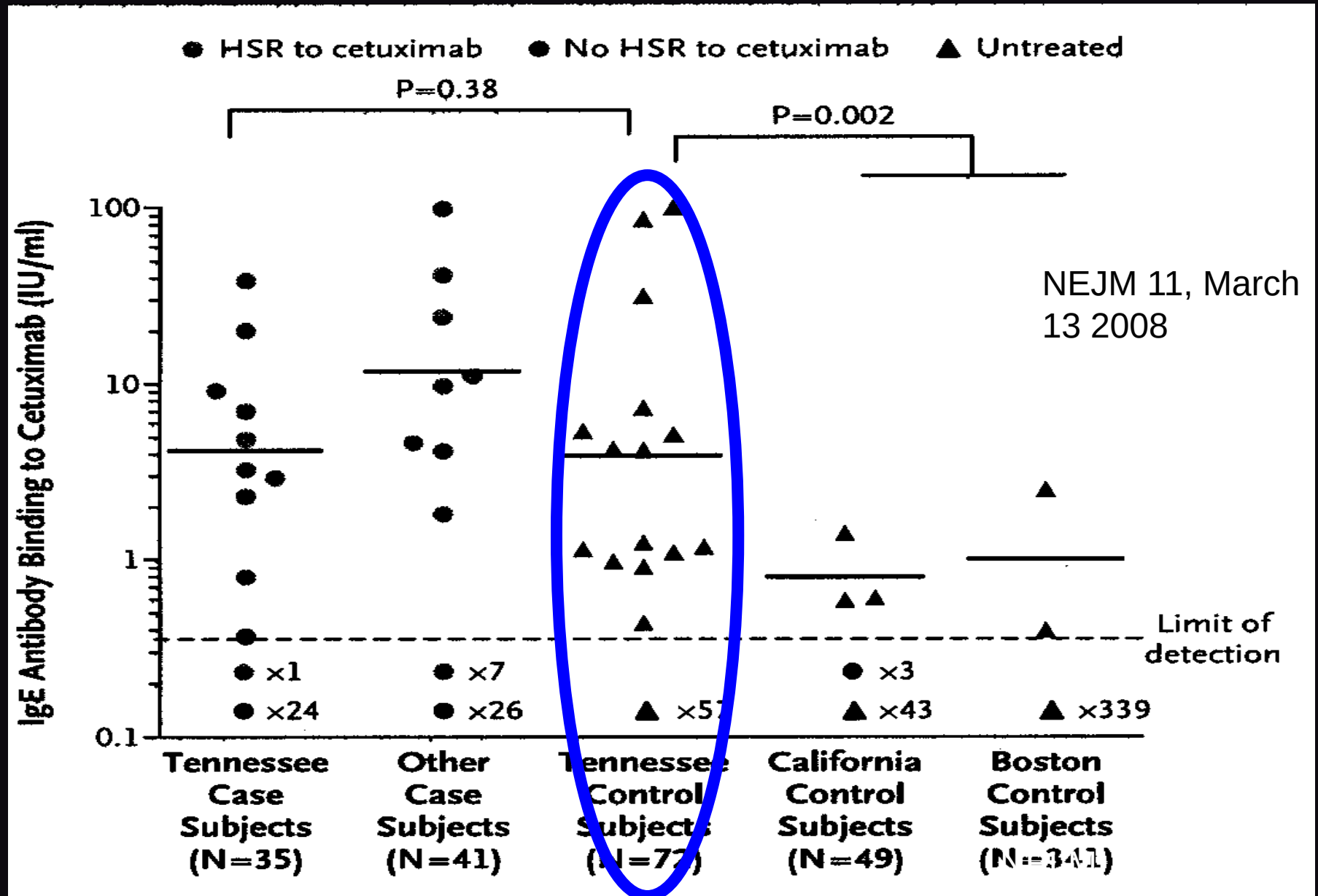
Galactose-α-1,3-Galactose

- Found on the fab segment of cetuximab
- Found in non primate mammals
- Humans have natural IgG ab against
- Is major antigen preventing transplants
- Anaphylaxis pork, beef




antigen binding site
variable
constant
antigen binding site
light chain
heavy chain

Ige anti-Galactose



NEJM 11, March 13 2008

Delayed anaphylaxis, angioedema, or urticaria after consumption of red meat in patients with IgE antibodies specific for galactose-α-1,3-galactose

24 patients with delayed reactions after meat

Negative prick tests to commercial antigens

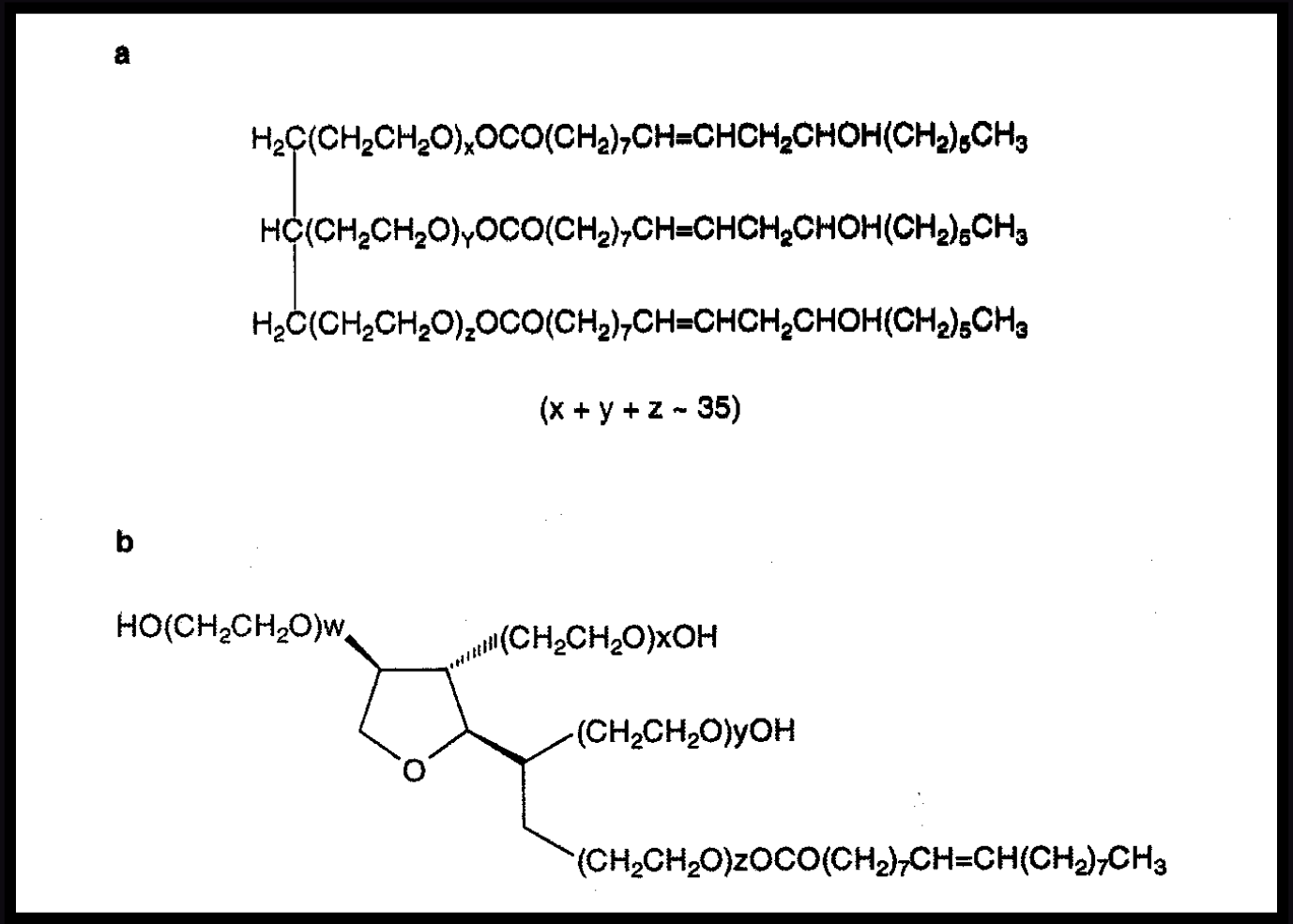
Positive prick, ID to fresh meat

Positive for IgE anti gal-gal

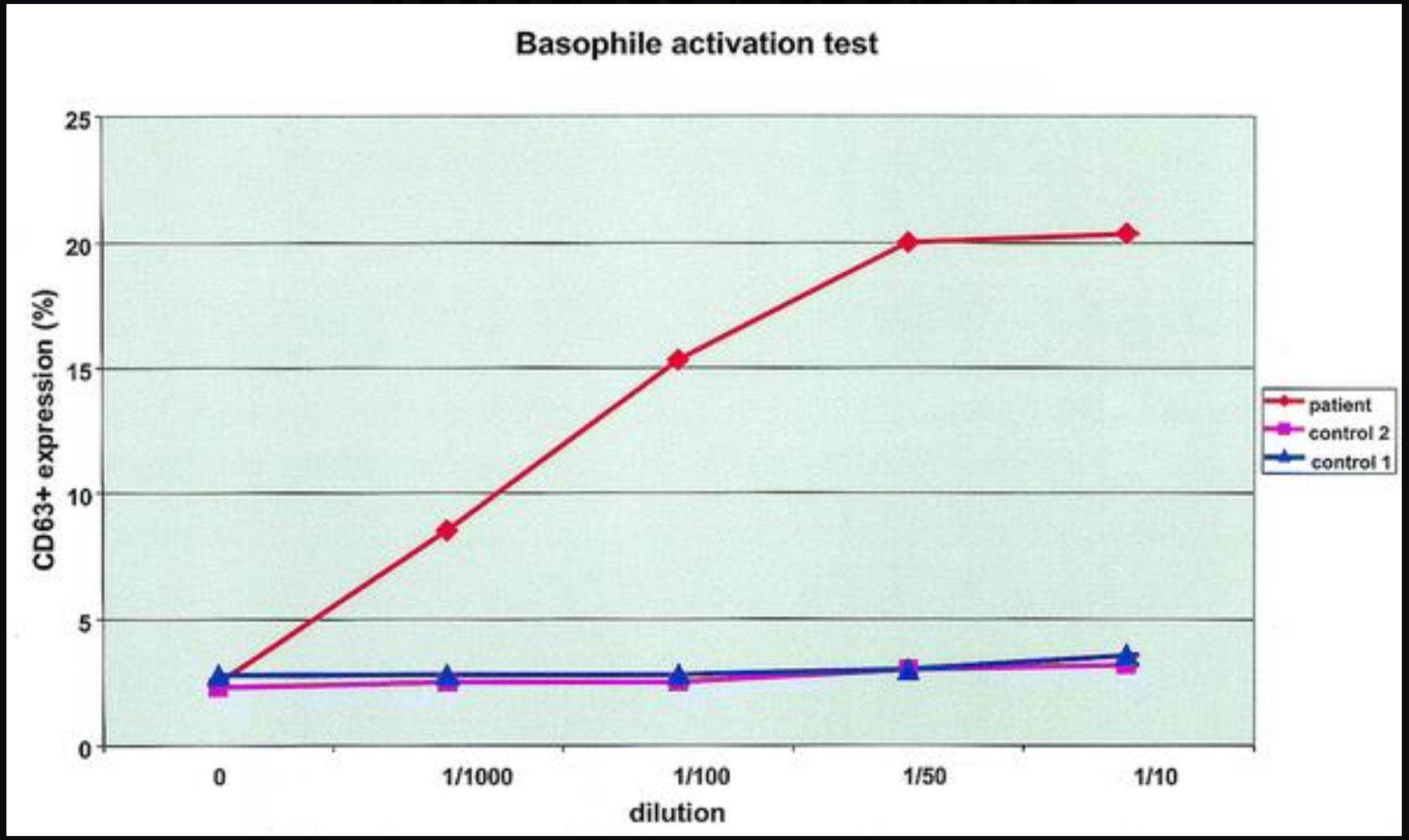
JACCI 123: 426-433, 2009

Tween and Chremophor

Polysorbates and Chremophor



Polysorbate activates basophils



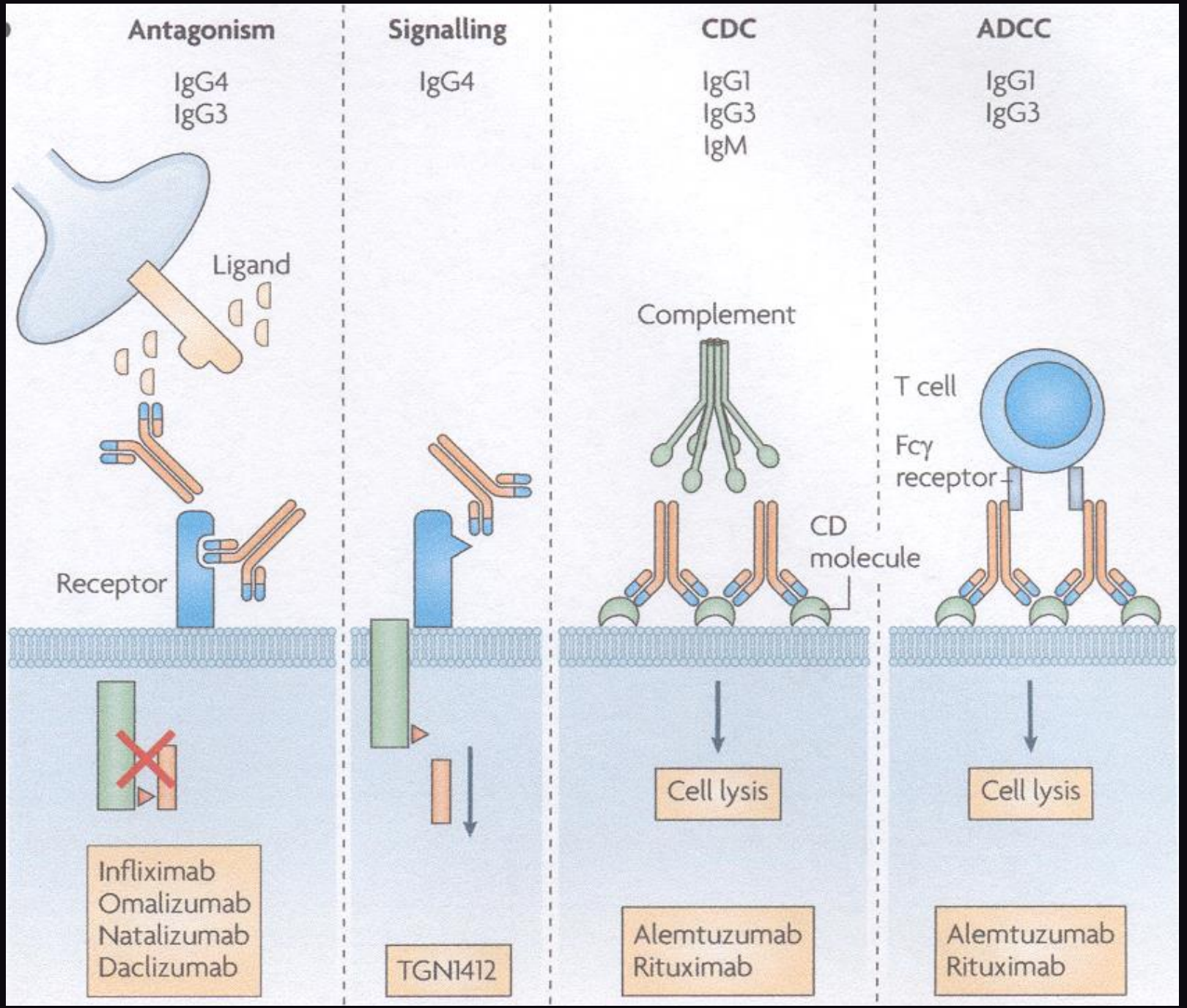
Annals of Allergy, Asthma and Immunology
2005, vol. 95, no. 6, pp. 593 -8 599

Differences between older and younger E.D pts

- The study included 220 patients. Food was the most common Food was the most frequently suspected cause of anaphylaxis for patients younger than 50 or 65 years but was much less common in patients 50 or 65 years or older .

- Cardiovascular symptoms were more likely to occur in older patients

- Patients 50 or 65 years or older were less likely to be dismissed home directly from the ED and were less likely to be prescribed self-injectable epinephrine (≥50 years old,


Antagonism
IgG4
IgG3
Ligand
Receptor
Infliximab
Omalizumab
Natalizumab
Daclizumab
Signalling
IgG4
TGN1412
CDC
IgG1
IgG3
IgM
Complement
CD molecule
Cell lysis
Alemtuzumab
Rituximab
ADCC
IgG1
IgG3
T cell
Fcγ receptor
Cell lysis
Alemtuzumab
Rituximab