Immuno-intervention: perspectives thérapeutiques

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Conflicts of interest

- **Consultant**: Actelion, CSL Behring, LFB Biotechnologies, Lilly, Pfizer, Octapharma
  - Financial support to ARMIIC
- **Investigator**: Actelion, CSL Behring, Pfizer
- **Financial support (grants to ARMIIC)**: Actelion, CSL Behring, GSK, LFB Biotechnologies, Pfizer
- **Invited conference**: SOBI, Roche, Actelion, CSL Behring, Octapharma, GSK, LFB Biotechnologies, Pfizer, Lilly, UCB pharma

Clinical use of therapeutic antibodies in autoimmune and inflammatory diseases

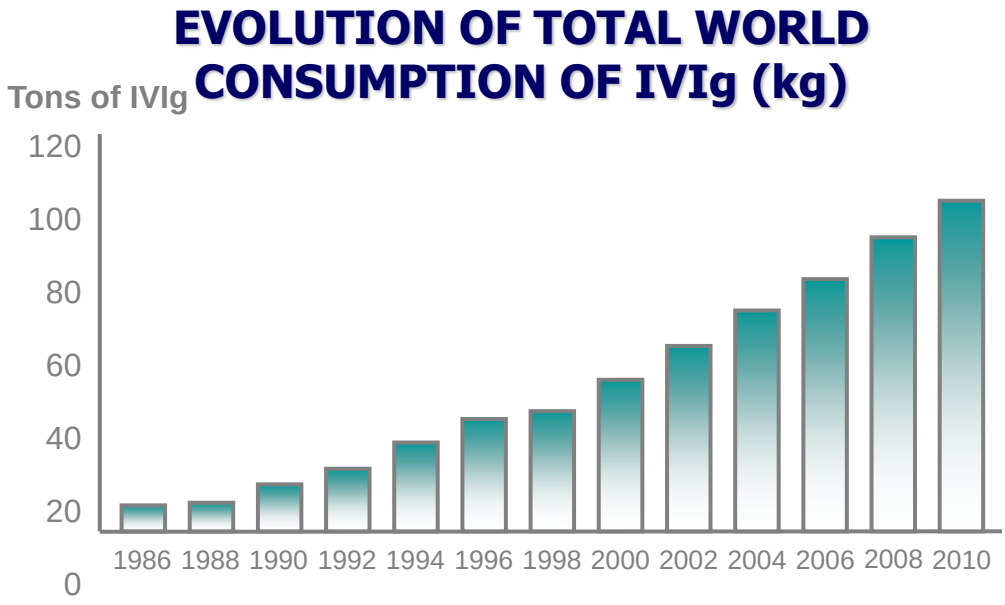
- Intravenous immunoglobulin
  - « Natural » therapeutic antibodies
- Biologics
  - Rheumatoid arthritis: 2000's revolution
  - ANCA-associated vasculitis: another ongoing revolution
  - Systemic lupus erythematosus: still a lot of work to do
  - Multiple sclerosis: efficacy but…

Intravenous immunoglobulin (IVIg)

- Normal human IgG
- Obtained from a pool of plasma of more than 1000 healthy blood donors

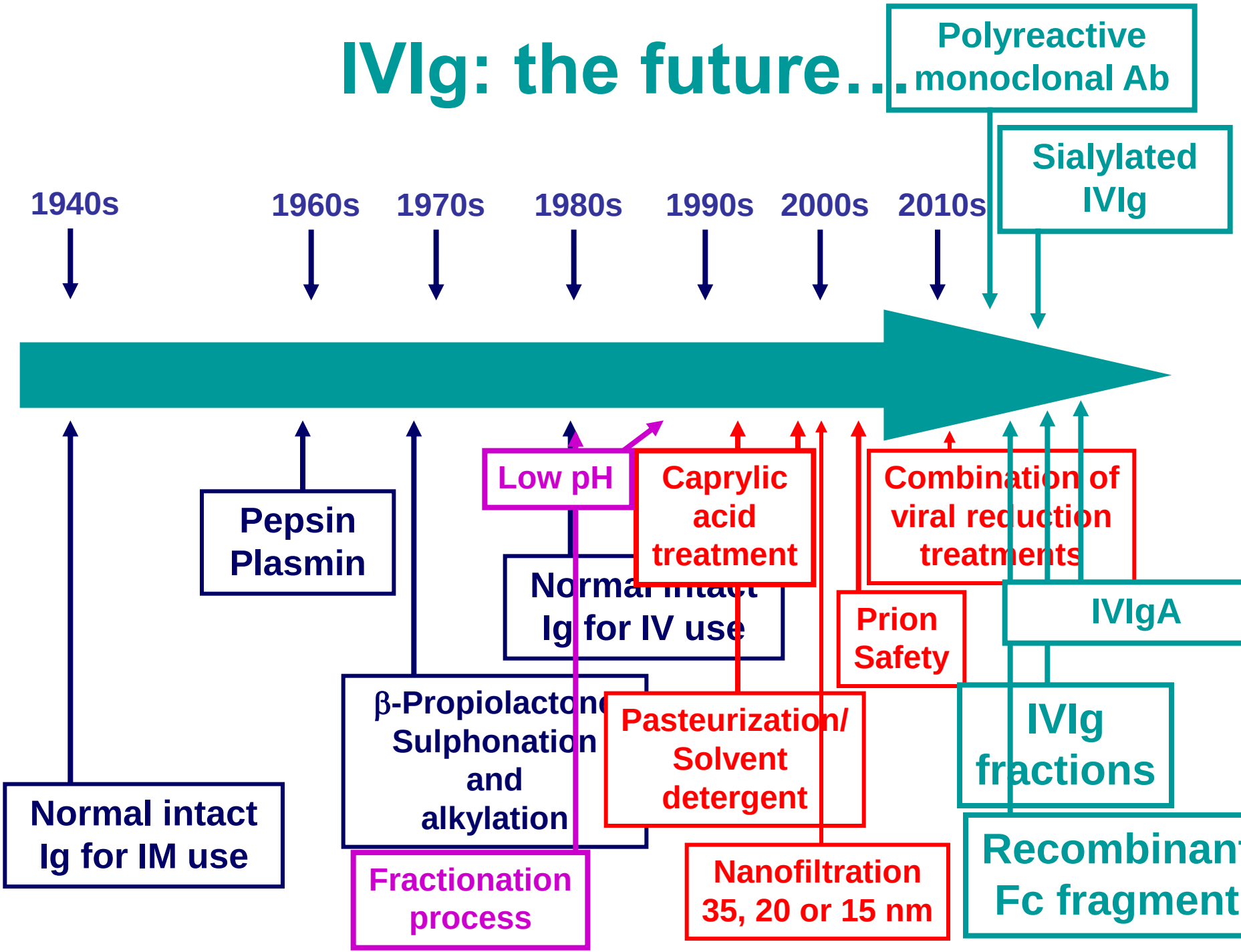
before 1980

- Indications :
  - Substitutive therapy of humoral immune deficiencies
  - Treatment of systemic inflammatory and/or autoimmune diseases



Mouthon L, Hématologie 2005

IVIg: the future…



EMEA guidelines for the preparation of Intravenous immunoglobulin

4th edition - 2002

Plasma : pool > 1000 donnors

Security of the preparation

- **One or more steps to inactivate infectious agents**
- **No transmission of infection**
- **Absence of secondary effects related to products used for virus inactivation**
- **Prekallikreine activator <35 UI/ml**
- **anti-A & anti-B hemaglutinins: absence of agglutination at a dilution of 1/64**

Quality control

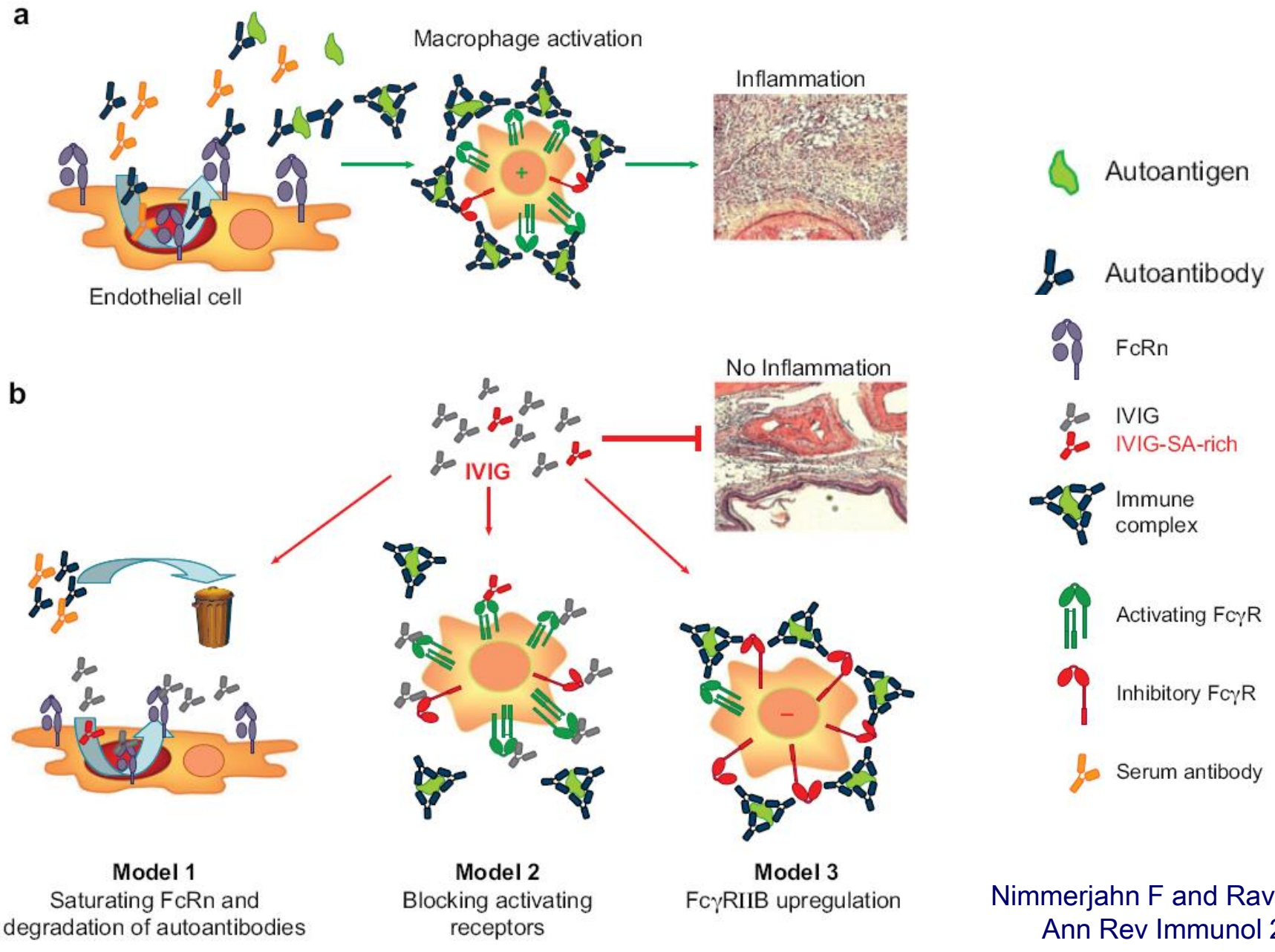
- **Anti-complement activity ≥ 50 %**
- **Total protein content ≥ 90%**
- **monomere/dimere ≥ 90 %**
- **Polymeres/agregates < 3 %**
- **≥ 2 antibodies (viral & bacterial) concentration ≥ 3 times over that of the pool of plasma**
- **distribution of IgG sub-classes identical to that of normal human plasma**
- **functional Fc portion**
- **Anti-HBs Ag Abs : titer > 0,5 UI/g of Ig**

Note for Guidance on the clinical investigation of IVIg

Substitutive therapy	Immunomodulation
- Primary humoral immune deficiencies with hypogammaglobulinemia or agammaglobulinemia :	- Immune thrombocytopenic purpura in children and adults with high risk of bleeding or before surgery
• X-linked agammaglobulinemia / constitutive hypogammaglobulinemia • Common variable immune deficiency • Severe combined immune deficiency • Wiskott Aldrich syndrome	-Guillain-Barré syndrome -Kawasaki disease
- Multiple myeloma and CLL with severe hypogammaglobulinemia and recurrent infections	
Bone marrow allograft	

Note for Guidance on the clinical investigation of human normal immunoglobulin for intravenous administration (IVIg). The European Agency for the Evaluation of Medicinal Products CPMP/BPWG/388/95 rev. 1

Proposed Fc fragment–dependent mechanisms of IVIg activity



Nimmerjahn F and Ravetch JV, Ann Rev Immunol 2008

Nomenclature of monoclonal Abs

Species	Letter	Suffix
Humain	U	umab
mouse	O	omab
Rat	E	
Hamster	E	
Primate	i	
Chimeric	Xi	ximab
Humanized	zu	zumab

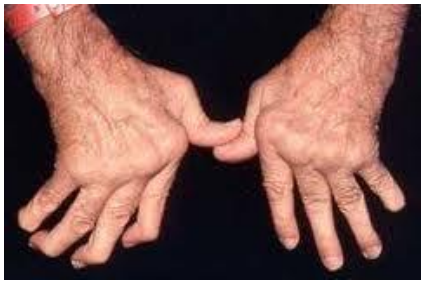
Rituximab

Ocrelizumab

L Mouthon. Livre de l'interne en Médecine Interne. 2007

Polyarthrite rhumatoïde

Biologicals in rheumatoid arthritis

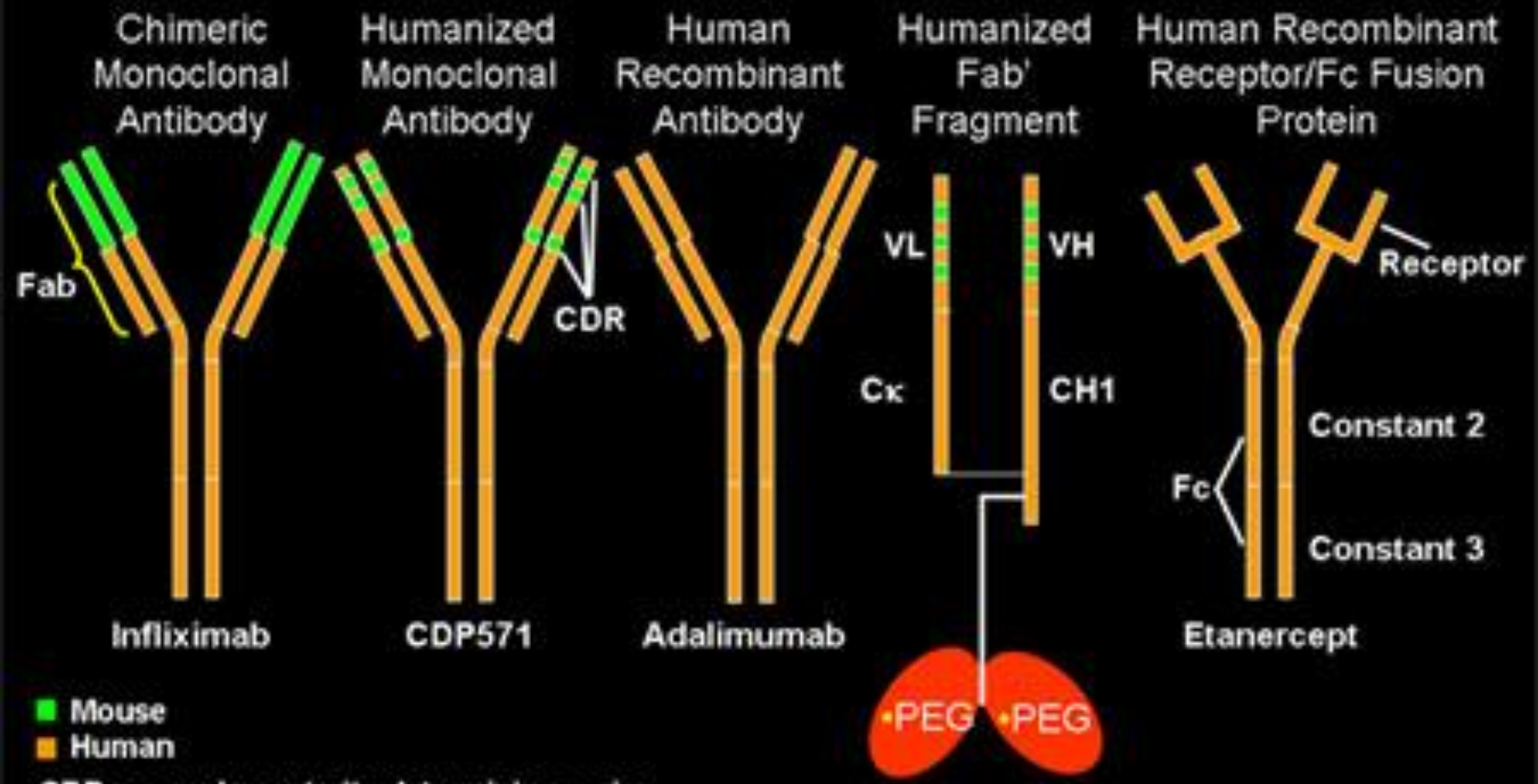


- **TNF-α inhibitors**
  - **Adalimumab: humanised monoclonal antibody against TNF-α**
  - **Certolizumab: Fab fragment of a humanised TNF-α inhibitor monoclonal antibody**
  - **Etanercept: humanised soluble recombinant TNF-α type II receptor-IgG1 fusion protein**
  - **Golimumab: human monoclonal antibody against TNF-α (awaiting NICE appraisal for use in rheumatoid arthritis)**
  - **Infliximab: a chimeric mouse-human monoclonal antibody against TNF-α**
- **Others**
  - **Anakinra: human recombinant interleukin 1 receptor antagonist**
  - **Abatacept: an immunoglobulin and extracellular CTLA4 domain fusion protein that selectively inhibits T cell co-stimulation**
  - **Rituximab: chimeric monoclonal anti-CD20 antibody that depletes B cells**
  - **Tocilizumab: humanised monoclonal anti-interleukin 6 receptor antibody**

*currently licensed for the treatment of RA

Klarenbeek NB et al. BMJ 2010

Anti-TNF-α Protein-Engineered Antibodies And Fusion Proteins



Mouse
Human

CDR = complementarity-determining region.

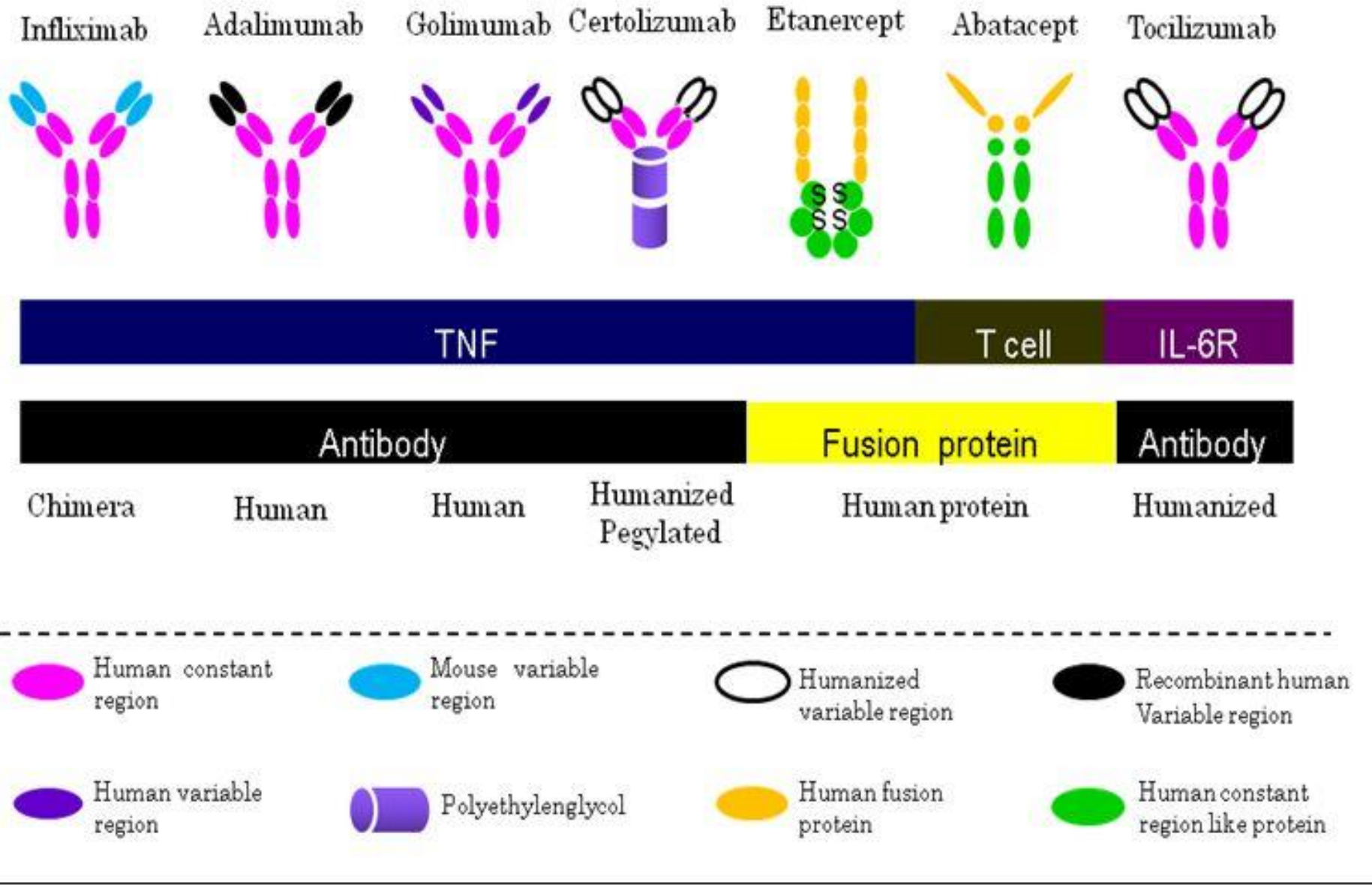
PEG = polyethylene glycol.

Hanauer. *Rev Gastroenterol Disord.* 2004;4(suppl 3):S18.

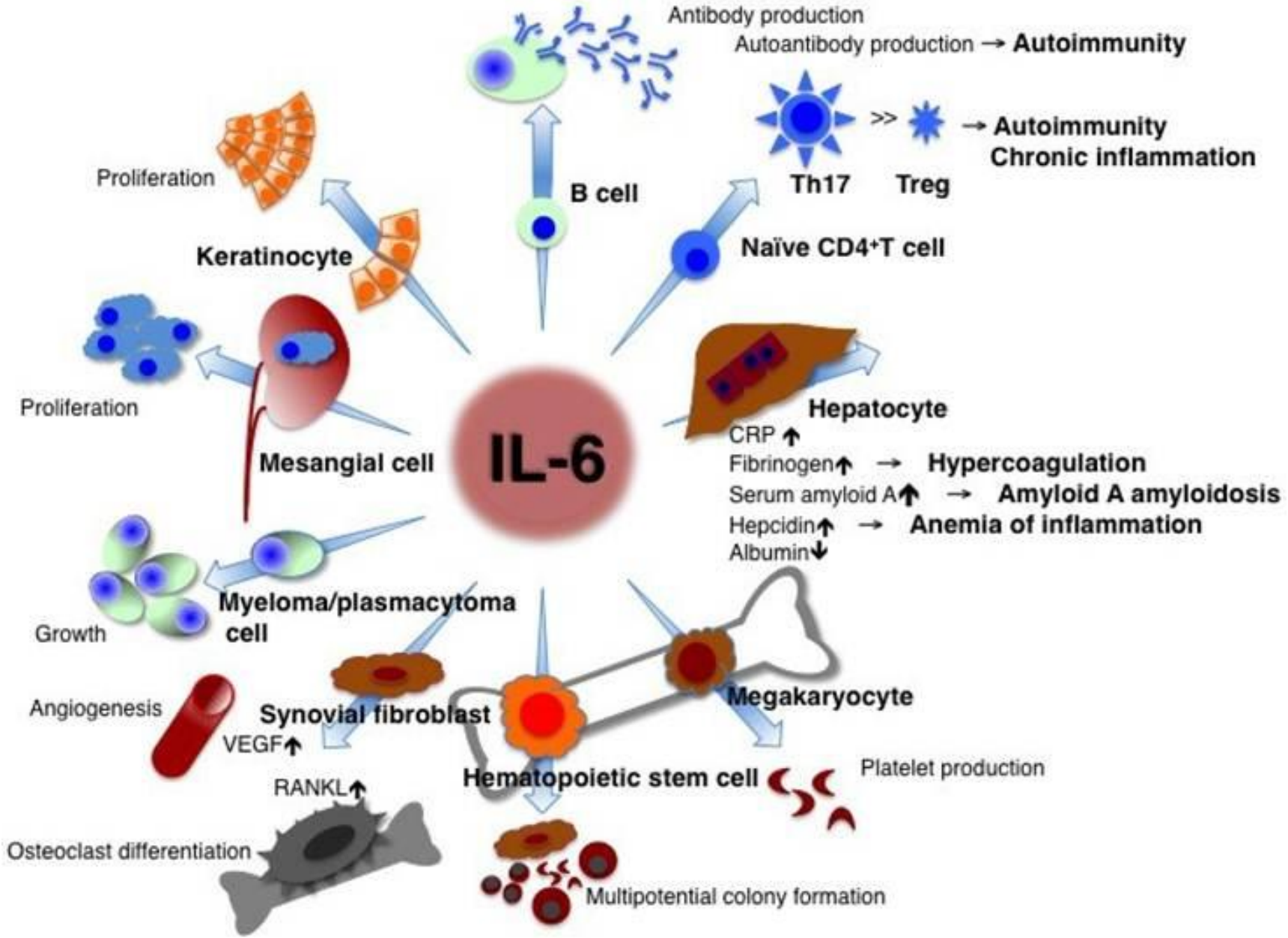
Overall results of biologics versus control

Outcome	Effect estimate, OR (95% CI)
Serious adverse effects	1.11 (0.94, 1.31)
Serious infections	1.19 (0.94, 1.52)
Total adverse events	1.19 (1.09, 1.30)
Withdrawals due to adverse events	1.32 (1.06, 1.64)
TB reactivation	4.68 (1.18, 18.60)
Lymphoma	0.53 (0.17, 1.66)
Congestive heart failure	0.69 (0.18, 2.69)

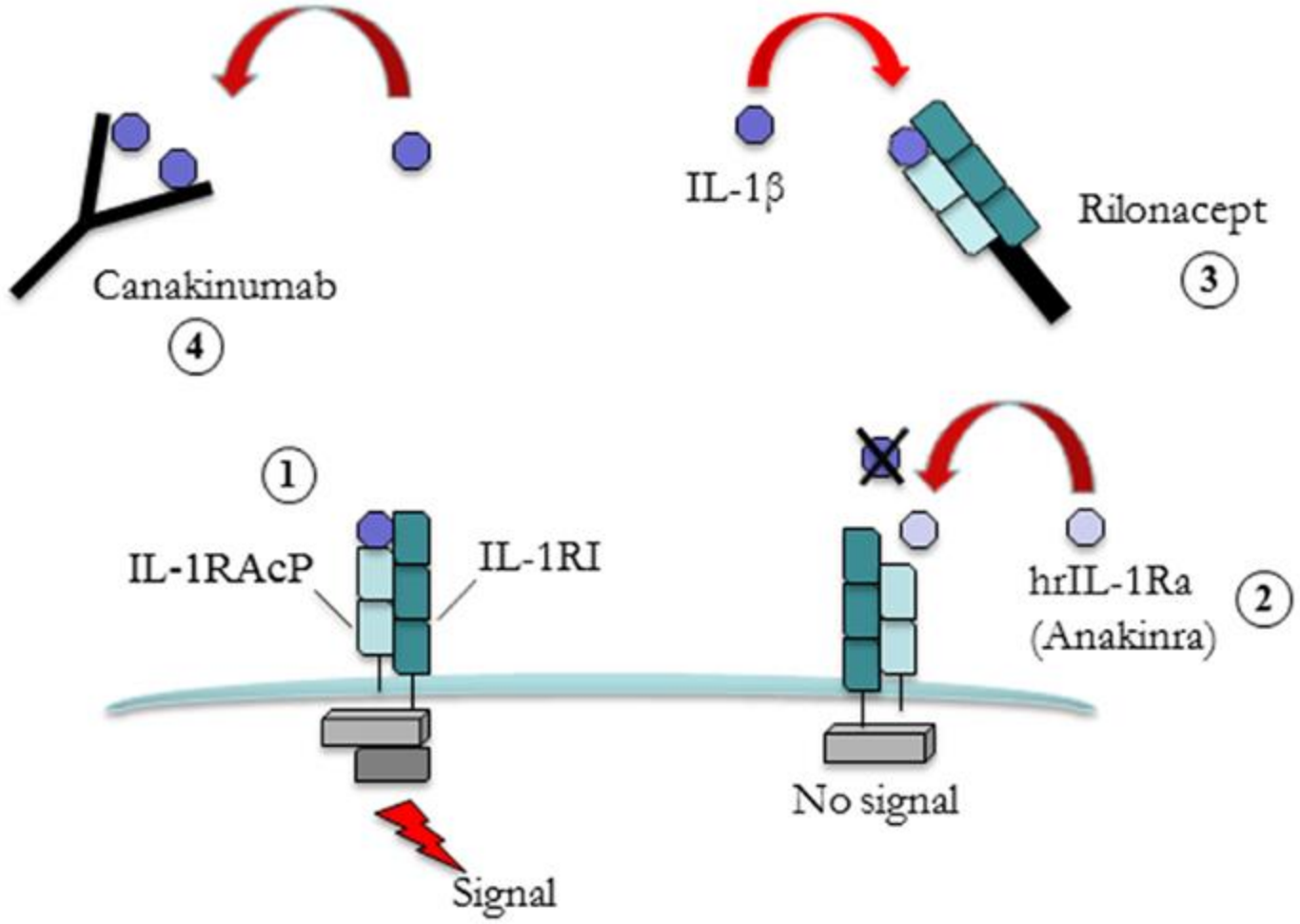
Singh JA *The Cochrane Library* 2011, Issue 2


Infliximab
Adalimumab
Golimumab
Certolizumab
Etanercept
Abatacept
Tocilizumab
S S
S S
TNF
T cell
IL-6R
Antibody
Fusion protein
Antibody
Chimera
Human
Human
Humanized
Pegylated
Human protein
Humanized
Human constant region
Mouse variable region
Humanized variable region
Recombinant human Variable region
Human variable region
Polyethylenglycol
Human fusion protein
Human constant region like protein

IL6 - blockade



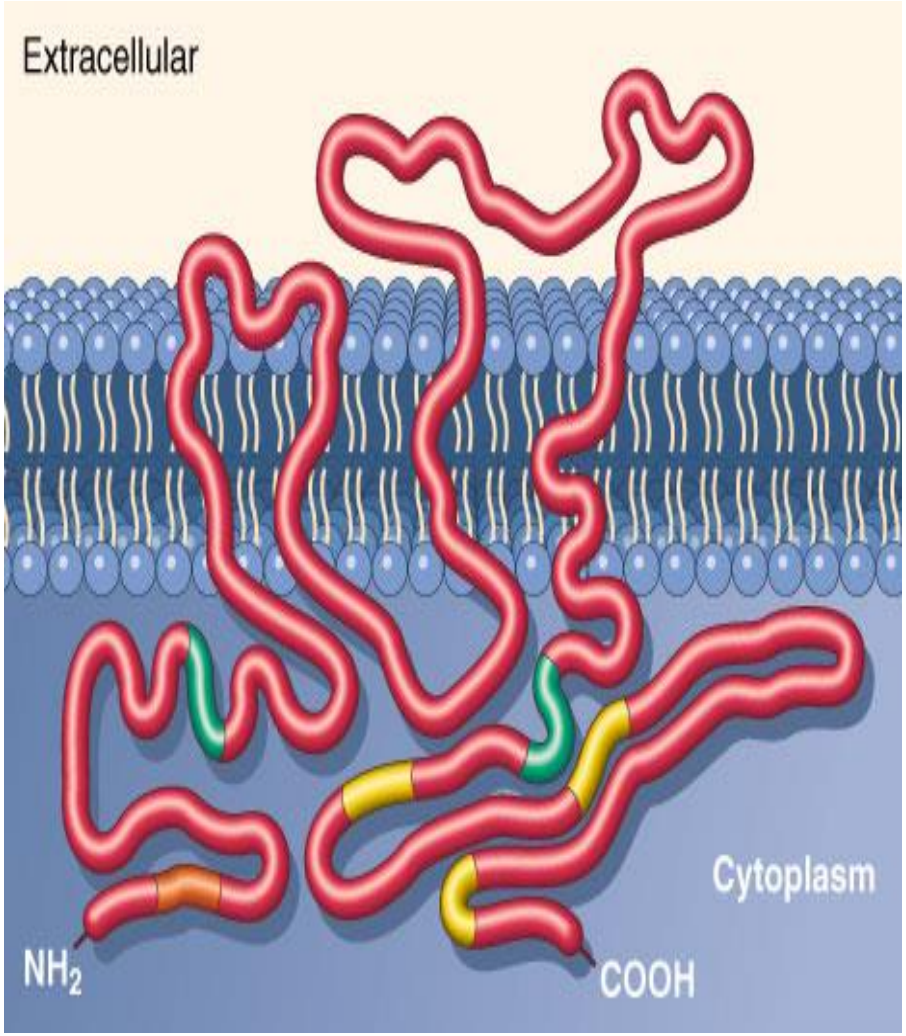
IL1 - blockade



Vascularites ANCA-positives

CD20: molécule de surface spécifique du lymphocyte B

- Phosphoprotéine de 297 aa (33-35 kDa)
- spécifique du LB
- Non exprimée sur:
  - cellules souches
  - Pré-B
  - Cellules dendritiques
  - Plasmocytes
- N'est pas modulée après fixation d'un Ac anti-CD20



Nomenclature des Ac monoclonaux

Espèce	Lettre	Suffixe	
Humain	U	umab	
Souris	O	omab	
Rat	E		
Hamster	E		
Primate	i		
Chimère	Xi	ximab	Rituximab
Humanisé	zu	zumab	Ocrelizumab

L Mouthon. Livre de l'interne en Médecine Interne. 2007

Utilisation du Rituximab dans les pathologies autoimmunes

Autorisation de mise sur le marché
- Polyarthrite rhumatoïde
- Vascularites associées aux ANCA

Études prospectives randomisées positives
- Purpura thrombopénique auto-immune
- Sclérose en plaques
- Vascularites associées aux cryoglobulinémies
- Anémies hémolytiques auto-immunes

Études prospectives randomisées négatives/ne permettant pas de conclure à une efficacité du rituximab
- Polymyosites et dermatomyosites
- Lupus érythémateux systémique
- Syndrome de Gougerot-Sjögren
- Neuropathies périphériques avec anticorps anti-MAG

Études prospectives ouvertes
- Micro-angiopathies thrombotiques
- Auto-anticorps anti-facteur VIII
- Pemphigus vulgaire
- Myasthénie aiguë

Études rétrospectives
- Déficit acquis en facteur Von Willebrand
- Neuromyélite optique (NMO)
- Glomérulonéphrite extra-membraneuse
- Érythroblastopénie auto-immune

ANCA : anticorps anti-cytoplasme de polynucléaire neutrophile ; MAG : glycoprotéine associée à la myéline.

Legendre P, Mouthon L Rev Med Int 2014

ClinicalTrials.gov (10 – 12 – 2014)
Rituximab interventional studies: ongoing

- **347 studies**
- Autoimmune Diseases (n=37)
- Connective Tissue Diseases (n=20)
- Rheumatoid arthritis (n=11)
- ANCA-Associated Vasculitis (n=6)
- Lupus Erythematosus, Systemic (n=6)
- Diffuse Scleroderma (n=3)
- Dermatomyositis (n=1)
- Idiopathic Pulmonary Fibrosis (n=2)
- Idiopathic Thrombocytopenic Purpura (n=2)
- Myasthenia Gravis (n=1)
- Multiple Sclerosis, Chronic Progressive (n=2)
- Multicentric Castleman's Disease (n=1)
- Purpura, Thrombotic Thrombocytopenic (n=1)
- Pulmonary Alveolar Proteinosis (n=1)
- Acquired Hemophilia (n=1)

Du bon usage du Rituximab au cours des maladies auto immunes

- **Autorisation de Mise sur le Marché**
  - Polyarthrite rhumatoïde
  - Vascularites associées aux ANCA

RAVE

197 patients

1 à 3 pulse methylprednisolone

Prednisone + CYC oral, 3 à 6 months + placebo Rituximab	Rituximab 375 X 4 + prednisone + placebo CYC
Azathioprine 12-15 mois	Placebo

Stone JH et al. N Engl J Med 2010; 363: 221-32

RITUXVAS

44 patients

11 patients

33 patients

Prednisone + CYC IV, 3 à 6 months	Rituximab 375 x 4 prednisone 2 bolus CYC
Azathioprine	Nothing

Jones RB et al. N Engl J Med 2010; 363: 211-20

Conclusions

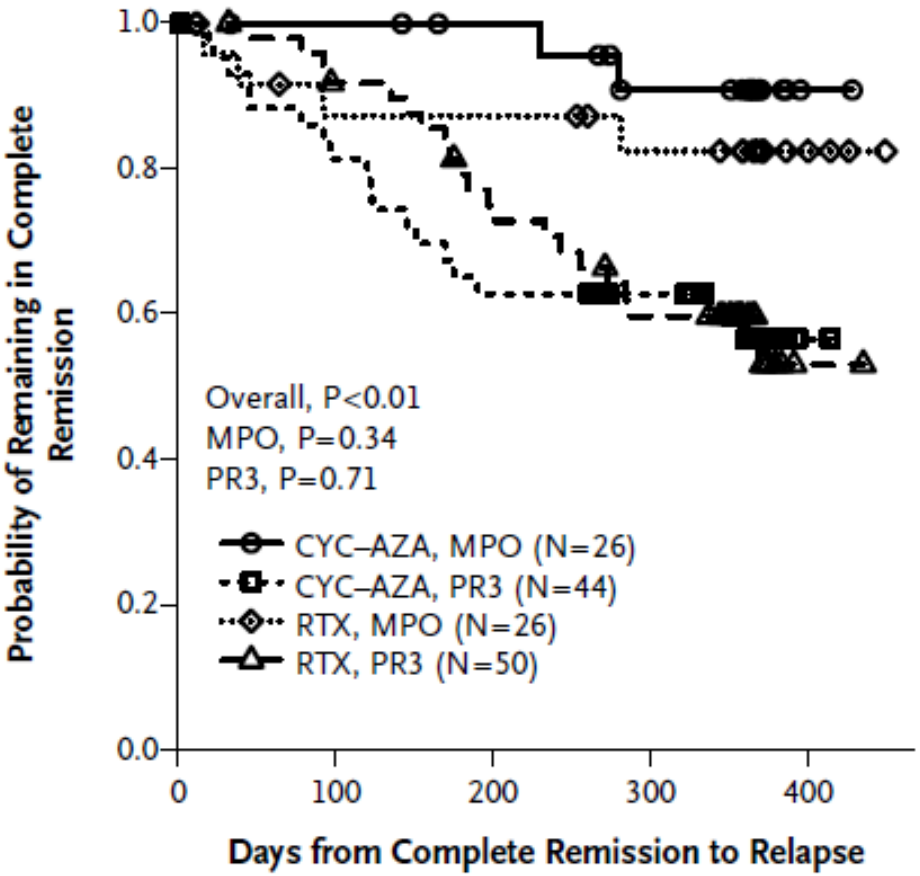
- **Rituximab was as efficient as IV CYC (RITUXVAS) or oral CYC (RAVE) in the induction of remission in ANCA-associated vasculitis.**
- **Adverse events were more frequent than expected under rituximab (as frequent as observed in patients reveiving oral CYC in RAVE).**
- **In RITUXVAS 6/33 patients died in the rituximab arm vs 2/11 in the control group**
- **The results of long term follow up in RAVE should inform us on the duration of remission in patients who received rituximab as an induction treatment and no maintenance therapy.**

« Long term » efficacy and safety results of the RAVE trial

- **Primary outcome (BVAS/WG and prednisone=0)**
  - **At 6 months 64% RTX vs 53% CYC**
  - **At 12 months 42% RTX vs 38% CYC**
  - **At 18 months 36% RTX vs 31% CYC**
- **Number of flares & number of patients suffering at least one flare did not differ between treatment arms**
- **Relapses more common among PR3-ANCA positive patients than MPO-ANCA positive patients**
- **No difference in adverse events among treatment arms at 18 months**

Specks U et al. NEJM 2013

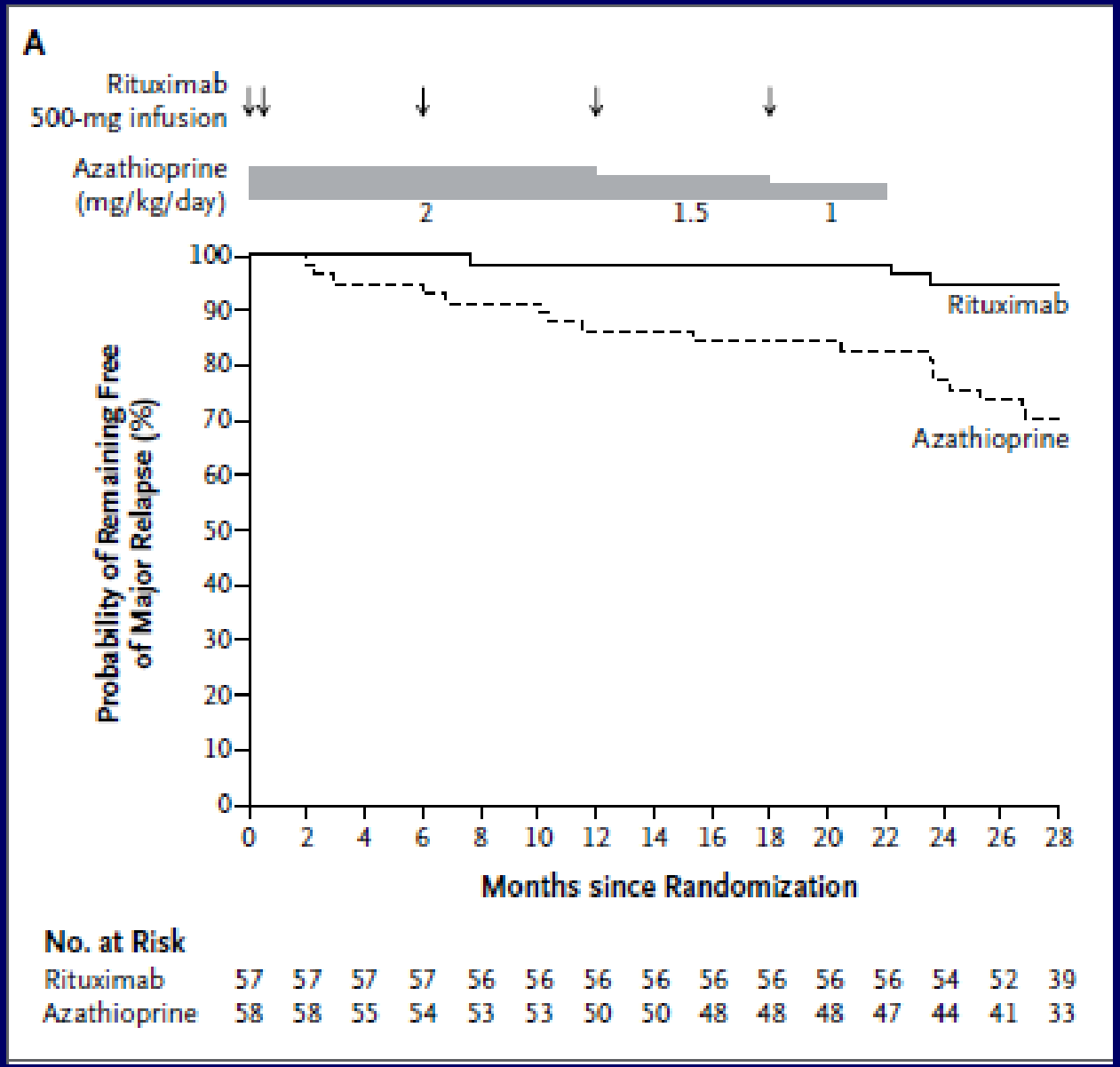
RAVE: Time to first relapse after complete remission according to treatment and baseline type of ANCA



No. at Risk					
CYC–AZA, MPO	26	26	24	19	2
CYC–AZA, PR3	44	36	28	25	2
RTX, MPO	26	21	21	18	4
RTX, PR3	50	45	35	28	2

Specks U et al. NEJM 2013

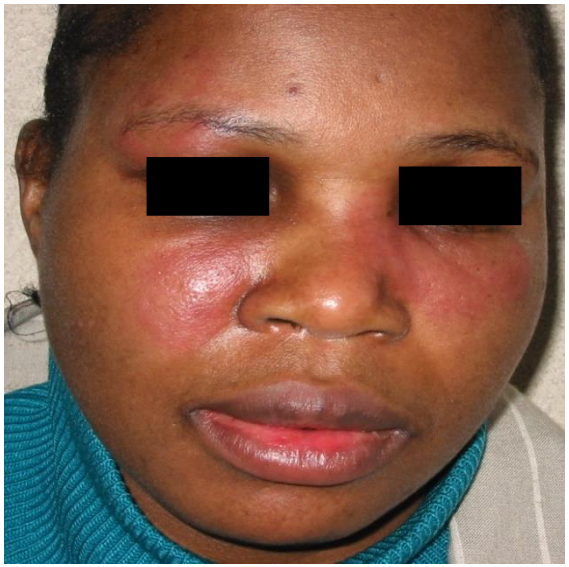
MAINRITSAN

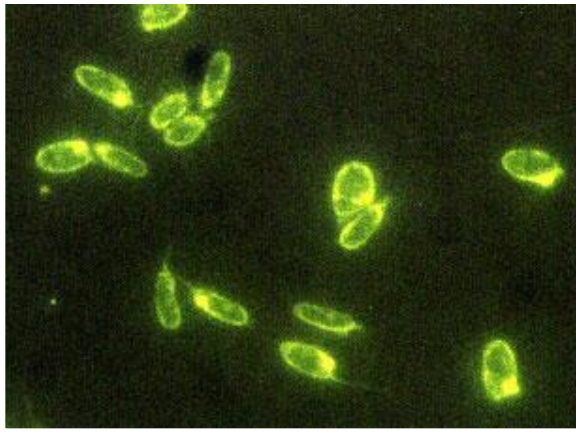


Guillevin L et al. NEJM 2014

Lupus systémique

Classification criteria for SLE (ARA 1982)*





- Malar rash
- Discoid lupus
- Photosensitivity
- Oral or nasal ulcers
- Non erosive arthritis ≥ 2 peripheral joints
- Pericarditis, pleuresis
- Protéinuria ≥ 0,5 g/d
- Seizure or psychosis
- Hemolytic anemia or

Leucopenia < 4000/µl on two occasions *or*
Lymphopenia < 1500/µl on two occasions or
Thrombocytopenia < 100000/µl

- LE cells or

anti-native, double strand DNA or
Anti-Sm *or*
Positive VDRL (negative TPHA) on two occasions at six months intervals

- Abnormal ANA titer in the absence of drug

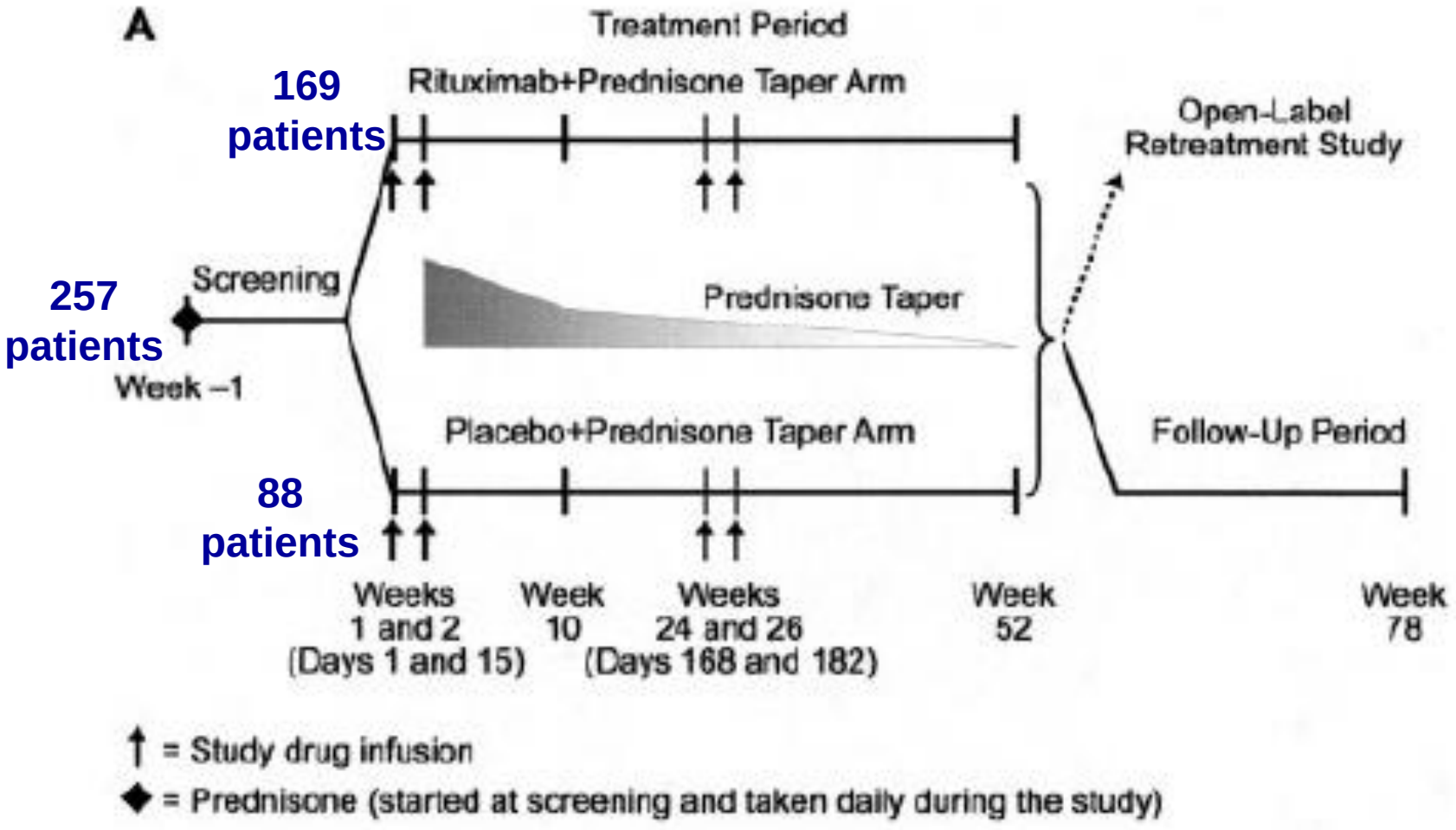
4 criteria simultaneous/successive to assess the diagnosis of SLE (sensitivity and specificity of 96%).

Adapt treatment to disease severity

- **Skin and joint involvement**
  - hydroxychloroquine
  - NSAID
  - topical corticosteroids
  - low dose oral CS
  - Never use immunosuppressants
- **Pleuritis, pericarditis**
  - hydroxychloroquine (Plaquénil)
  - NSAID
  - CS 0,5 mg/kg
  - No immunosuppressants
- **Visceral involvement**
  - hydroxychloroquine (prevention of relapses)
  - High dose CS (1 mg/kg)
  - Eventually pulse MP
  - Immunosuppressants
  - anti-CD20, plasma exchanges…

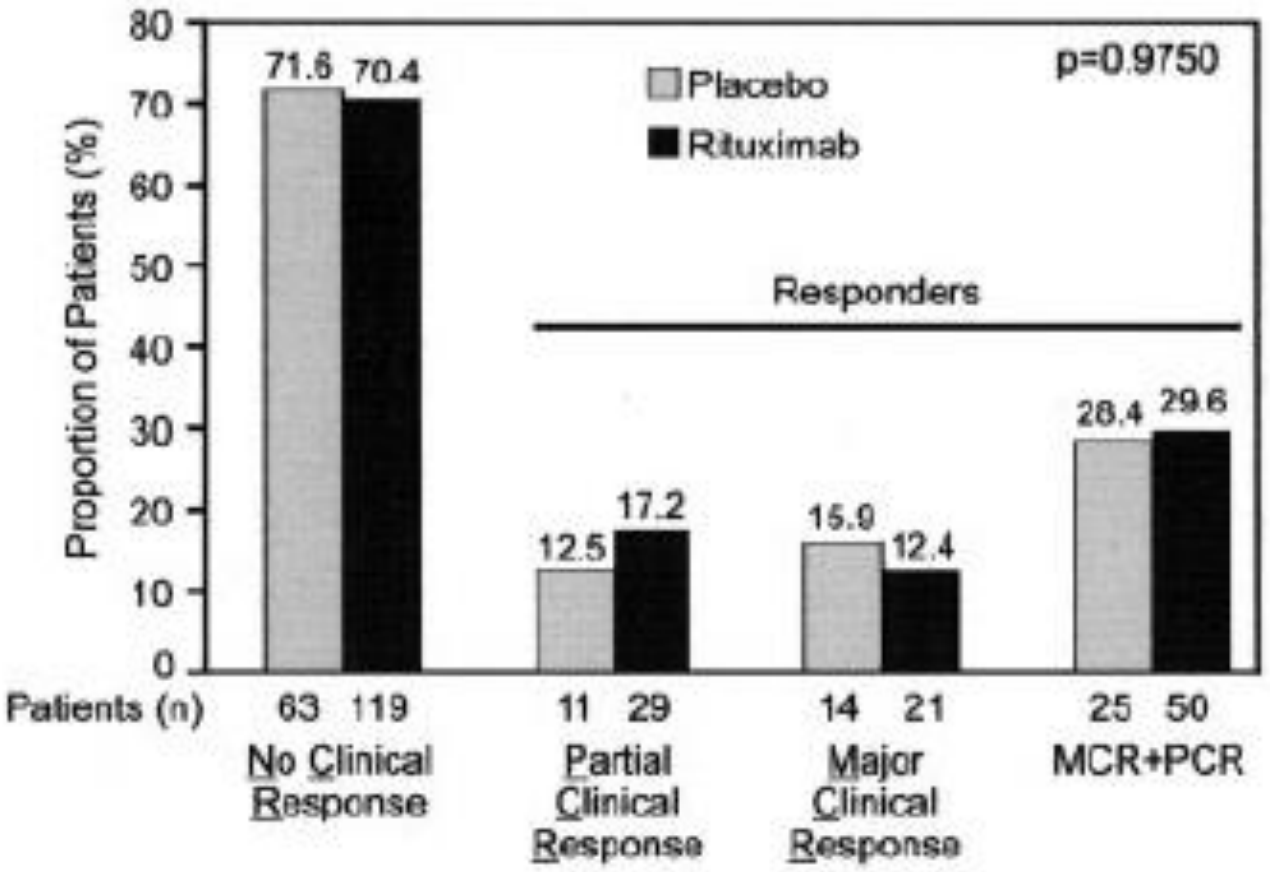
EXPLORER (I)

Efficacy of rituximab in moderately to severely active SLE



Merrill JT Arthritis Rheum 2010

Proportion of patients experiencing a major clinical response (MCR), a partial clinical response (PCR), and no clinical response (NCR) at 52 weeks



Merrill JT Arthritis Rheum 2010

A Study to Evaluate the Efficacy and Safety of Rituximab in Subjects With ISN/RPS Class III or IV Lupus Nephritis (LUNAR)

- Phase III, randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of rituximab in combination with MMF compared with placebo in combination with mycophenolate mofetil (MMF) in subjects diagnosed with ISN/RPS 2003 Class III or IV Lupus Nephritis.

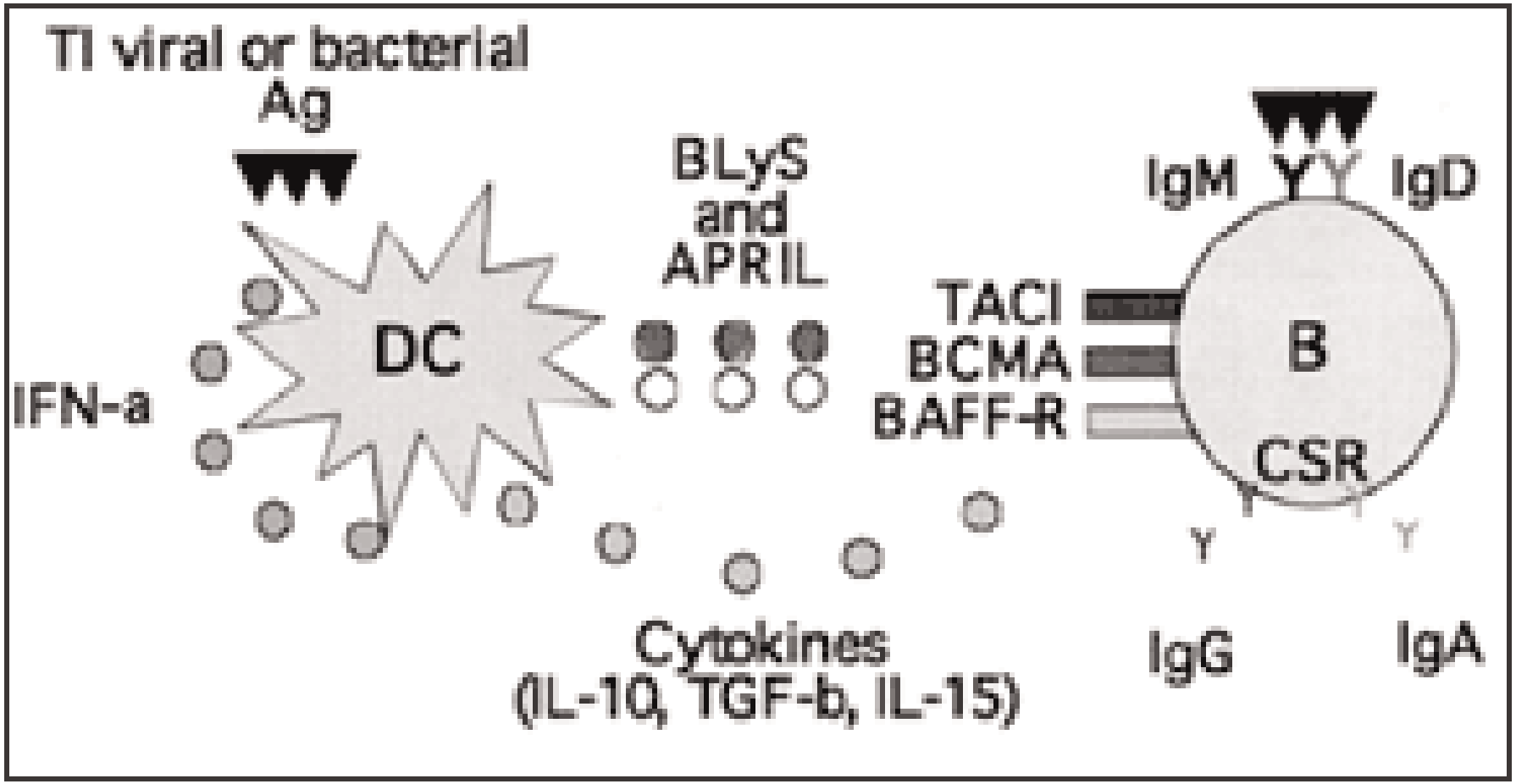
B-cell-depletion therapy in SLE--what are the current prospects for its acceptance?

Favas C, Isenberg DA.

Nat Rev Rheumatol. 2009 Dec;5(12):711-6.

- The failure of rituximab, a monoclonal antibody that induces B-cell depletion, to meet its primary and secondary end points in trials of nonrenal SLE (EXPLORER) and renal (LUNAR) lupus nephritis has been disappointing given the success reported in many open-label studies. Concluding that B-cell-depletion therapy is not effective in SLE seems rather extreme.
- Further analysis of the as-yet unpublished results and their comparison with data from published studies might provide insight into whether B-cell depletion will eventually be accepted as a useful approach for the treatment of SLE.

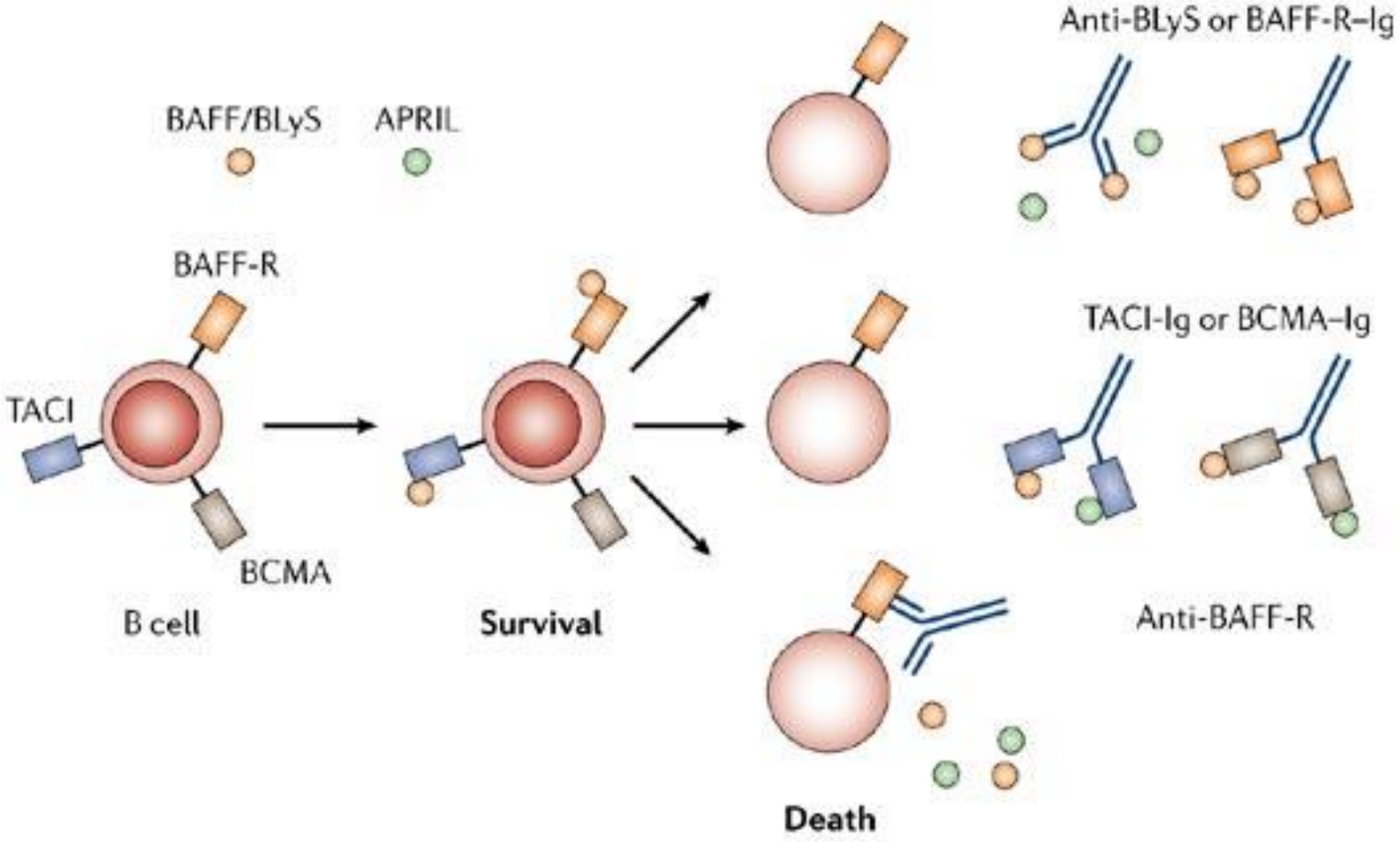
B lymphocyte stimulator (BLyS)



Litinskiy et al. Nat Immunol. 2002; 3:822-9

Les autres anti-B

- Ac monoclonal anti-CD20 humanisé
- Ac monoclonal anti-CD22 (epratuzumab)
- Ac monoclonal anti-BAFF (BLyS): Lymphostat B
- BR3-Fc (BAFF-Fc)
- TACI-Fc
- Alemtuzumab (anti-CD52): Campath-1H



Nature Reviews | Drug Discovery

Benlysta (belimumab): anti-BAFF in SLE

- Seropositive SLE patients (ie, antinuclear antibody positive and/or anti-DNA positive) without active nephritis or active central nervous system disease were enrolled in two phase II/III studies (BLISS-52 and BLISS-76) and treated with placebo, 1 mg/kg of anti-BAFF, or 10 mg/kg of anti-BAFF.
- Primary endpoint: SRI (SLE Responder Index),
- Both studies showed superiority of the 10 mg/kg dose to placebo at 12 months (56.7% of patients have shown improvement when treated with a 10 mg/kg dose of belimumab in addition to standard treatment as opposed to 43.6% improvement under standard treatment and placebo).
- Benlysta (belimumab): agreement US FDA (july 2011).

Wallace DJ *et al. Arthritis Care Res (Hoboken)* 2009 ; **62** : 580 – 1 .
Petri M *et al*. *Arthritis Rheum* 2010;**62**:S190 (abstract).

Only three drugs were FDA-approved for the treatment of SLE:

Prednisone

Aspirin

Hydroxychloroquine

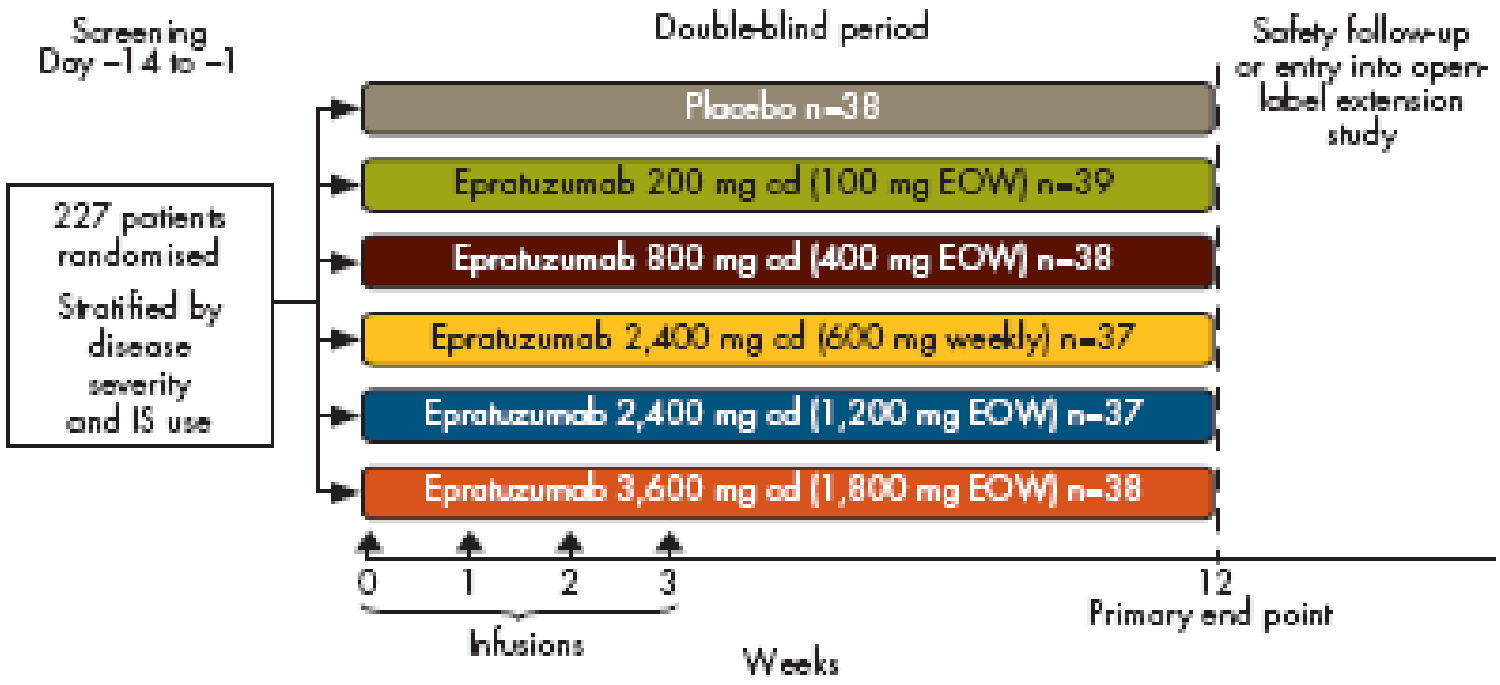
Belimumab efficacy is 'mild' but market potential still great: anticipating us approval of the first lupus drug since 1957.

Weintraub B. BioDrugs. 2011 Jun 1;25(3):203-5.

EMBLEM: epratuzumab (anti-CD22) in SLE

Wallace DJ et al. 2010 (abstract) EULAR

Figure 1. EMBLEM™ study groups and design

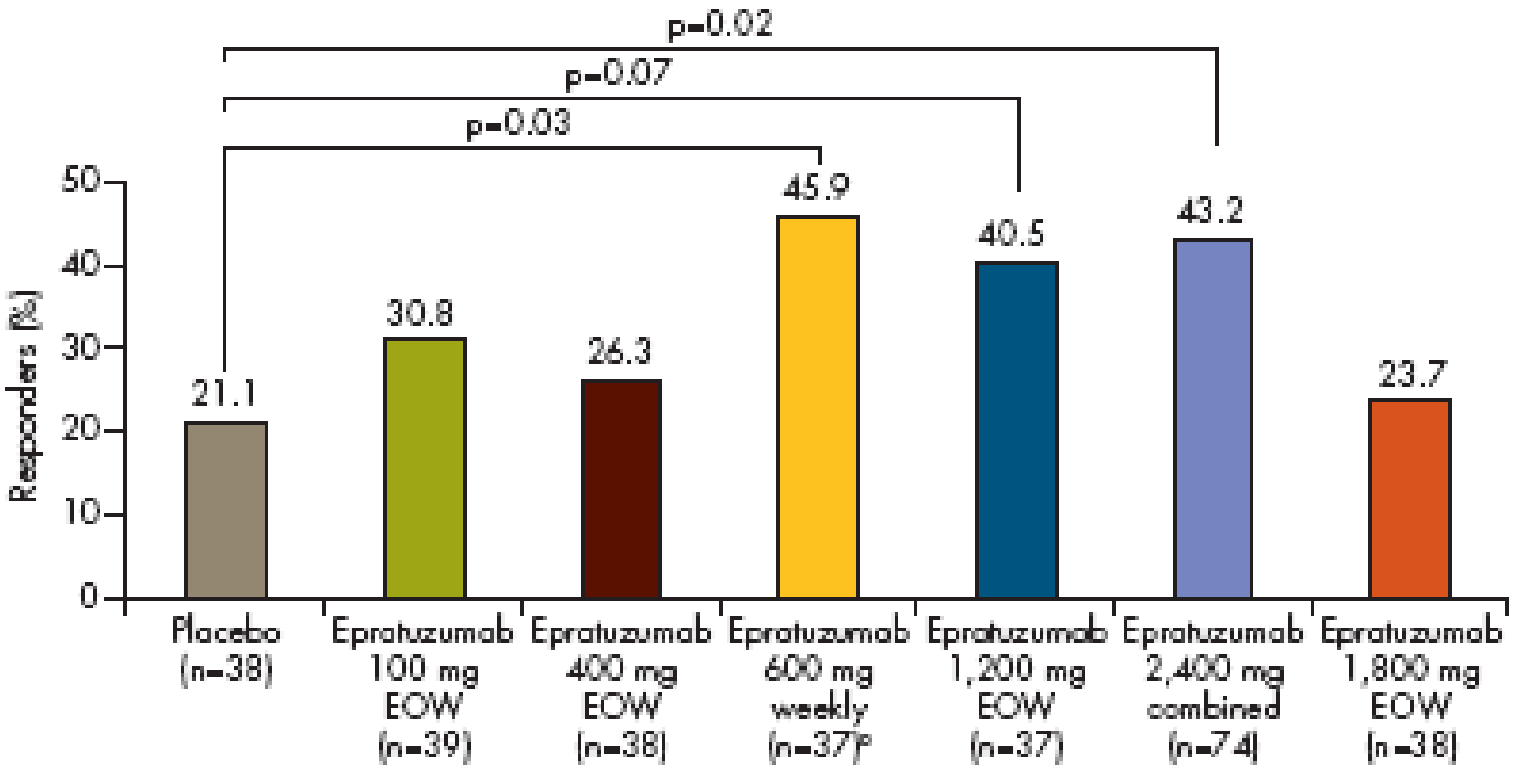


cd = cumulative dose; EOW = every other week; IS = Immunosuppressants.

EMBLEM: epratuzumab (anti-CD22) in SLE

Wallace D.J et al. 2010 (abstract) EULAR

Figure 3. Combined responder index rate at Week 12 (ITT population)



*2 patients randomised but never received drug.
In the primary analysis, subjects who prematurely terminated treatment were classified as non-responders (NRI).
p Value for all 6 treatment arms for overall treatment effect assessed in primary analysis = 0.148.
p Values were not adjusted for multiple comparisons.

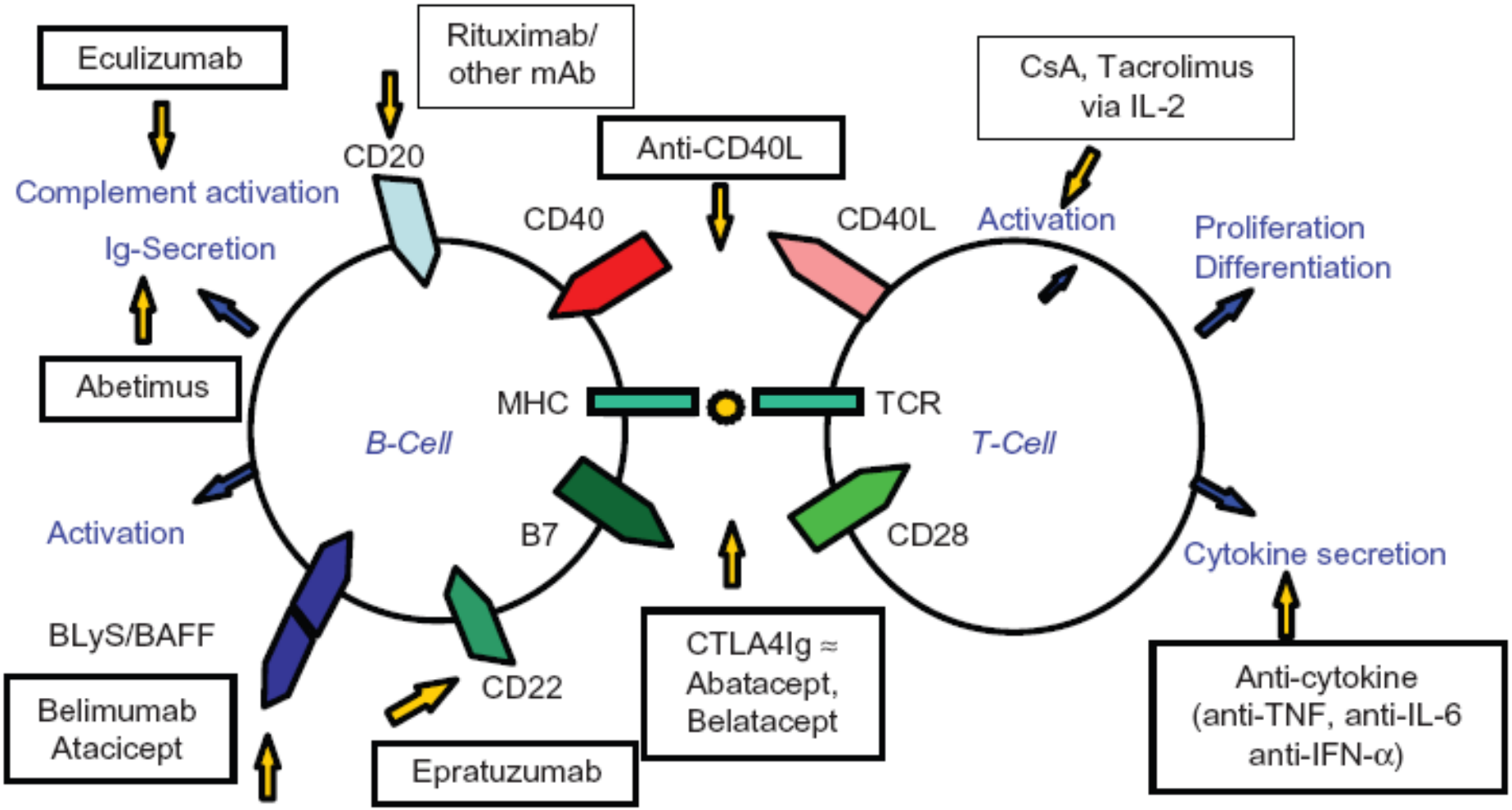
There is a need for cost-benefit studies

« Biologics »

« Old drugs »

The exemple for systemic lupus erythematosus…….

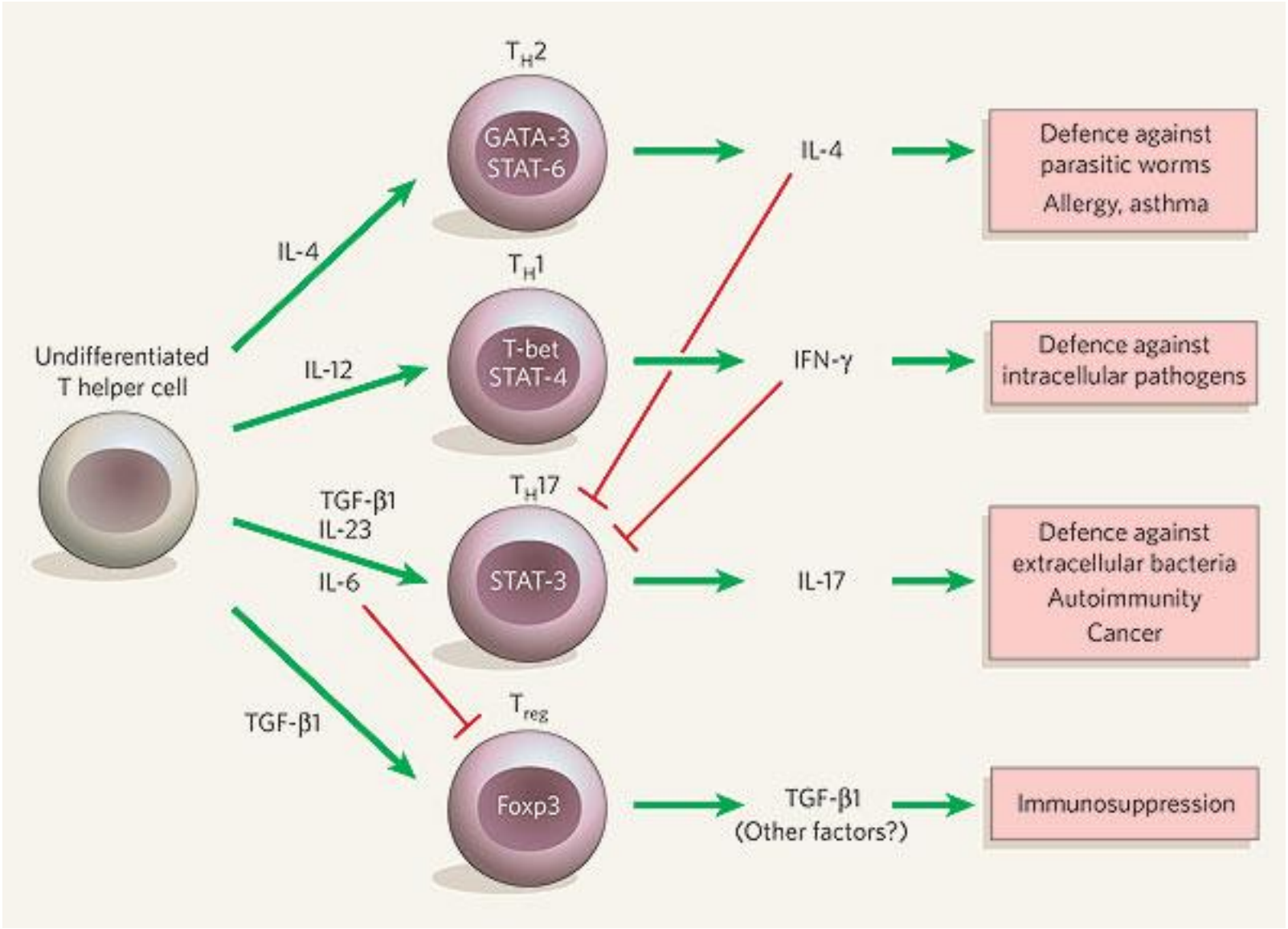
Potential future targets and relevant drugs in connection with B-cells and T-cells in the management of SLE



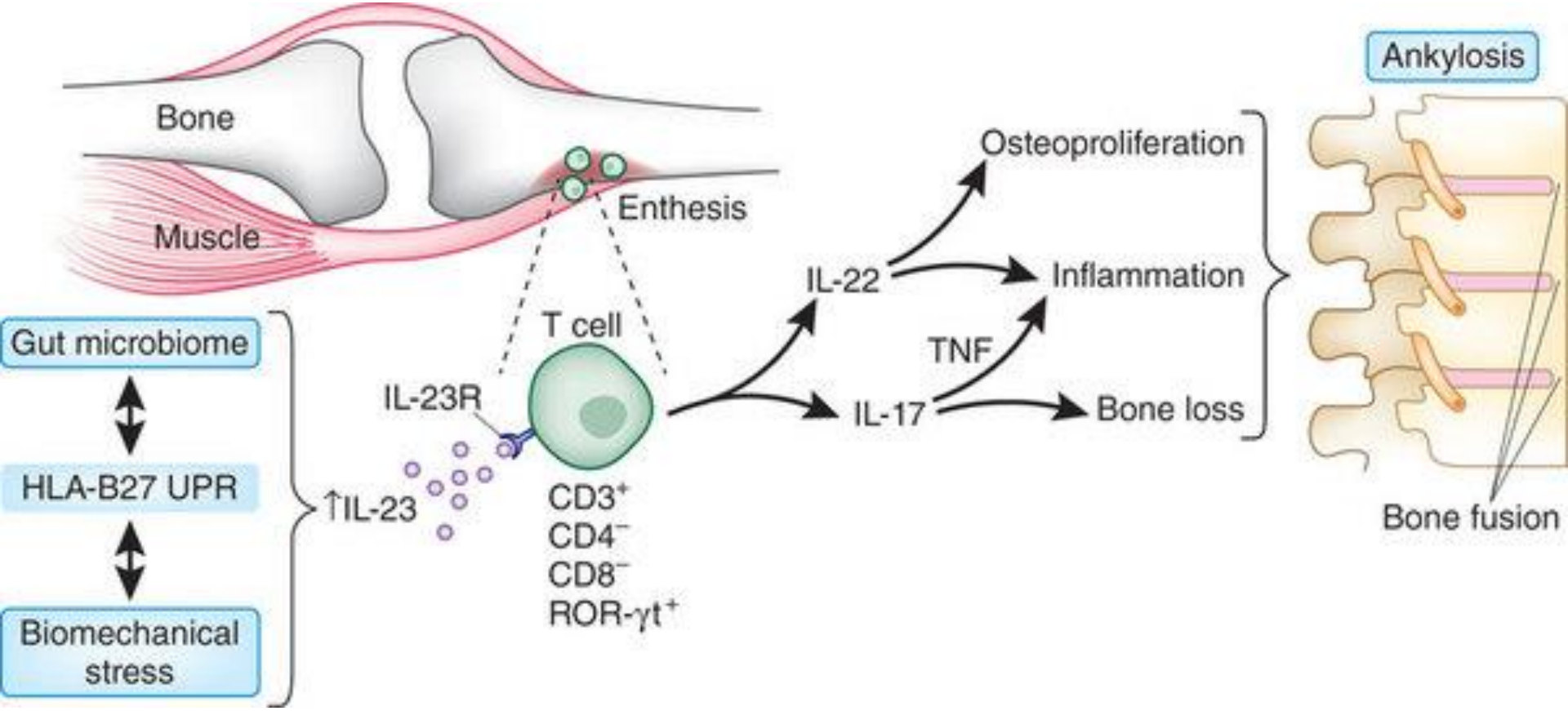
Haubitz M. Biologics: Target & therapy 2010

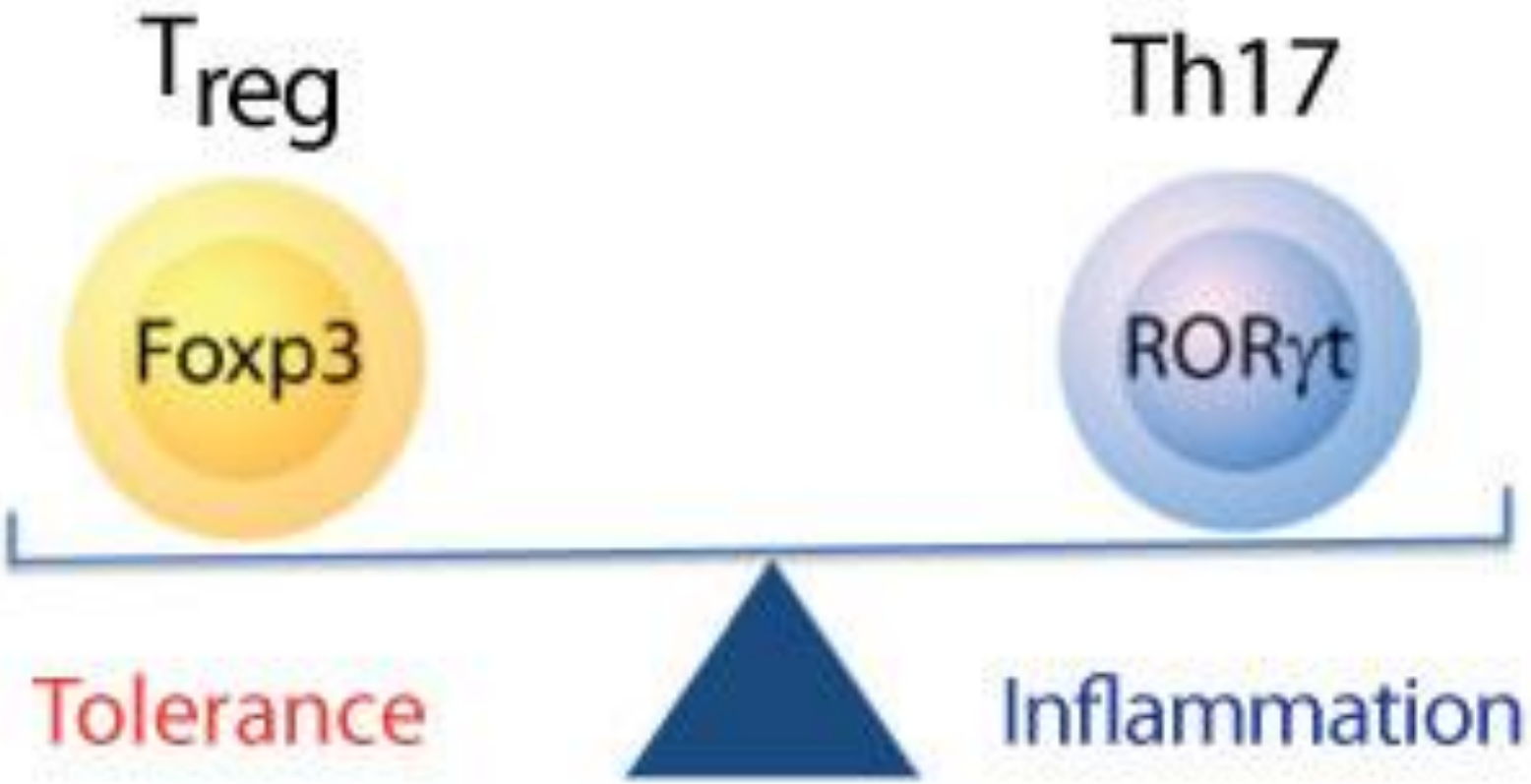
Spondyloarthrites

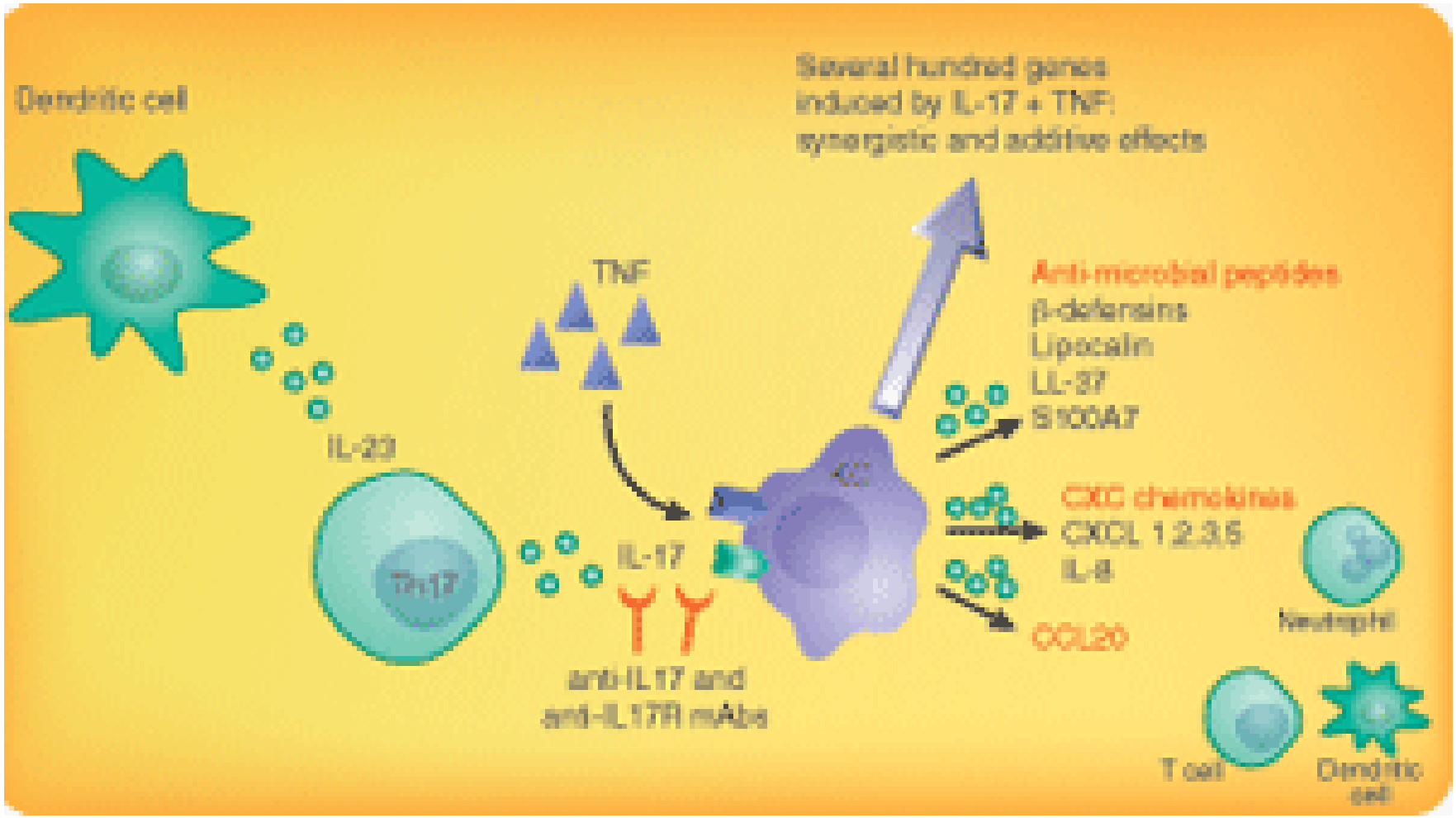
Cytokines et différentiation des lymphocytes T helper



Spondyloarthritis




Treg
Th17
Foxp3
RORγt
Tolerance
Inflammation


Several hundred genes
induced by IL-17 + TNF:
synergistic and additive effects
Dendritic cell
TNF
IL-23
Th17
IL-17
anti-IL17 and
anti-IL17R mAbs
Anti-microbial peptides
β-defensins
Lipocalin
LL-37
S100A7
CXC chemokines
CXCL 1,2,3,5
IL-8
CCL20
Neutrophil
T cell
Dendritic
cell

Sclérose en plaques et Natalizumab

Progressive Multifocal Leukoencephalopathy Complicating Treatment with Natalizumab and Interferon Beta-1a for Multiple Sclerosis

Kleinschmidt-DeMasters BK & Tyler KL.
N Engl J Med 2005;353:369-74.

- A 46-year-old woman with relapsing–remitting multiple sclerosis died from progressive multifocal leukoencephalopathy (PML) after having received 37 doses of natalizumab (300 mg every four weeks) as part of a clinical trial of natalizumab and interferon beta-1a.

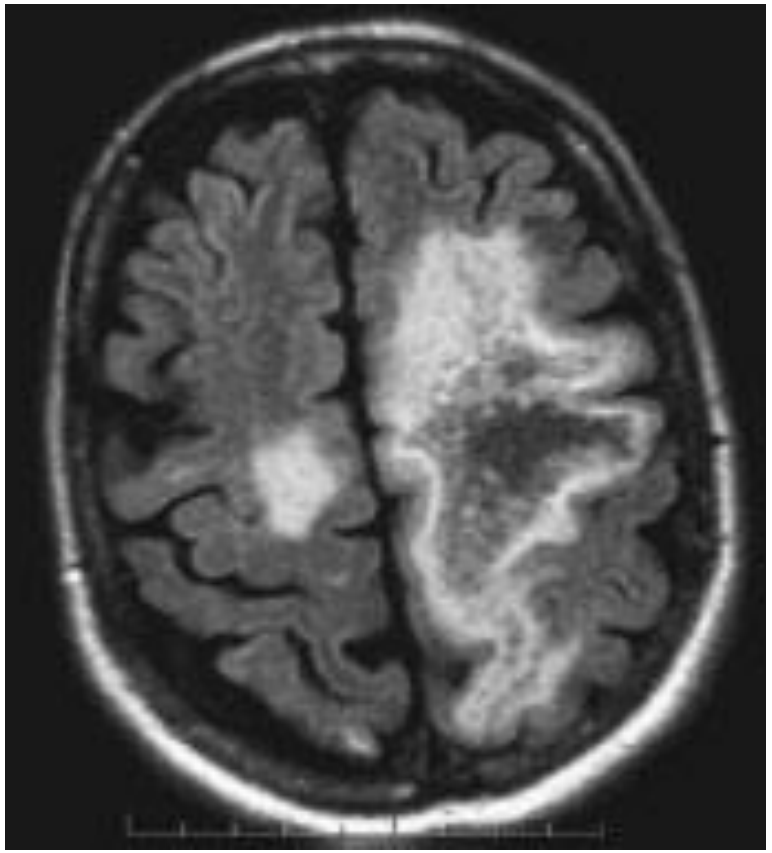
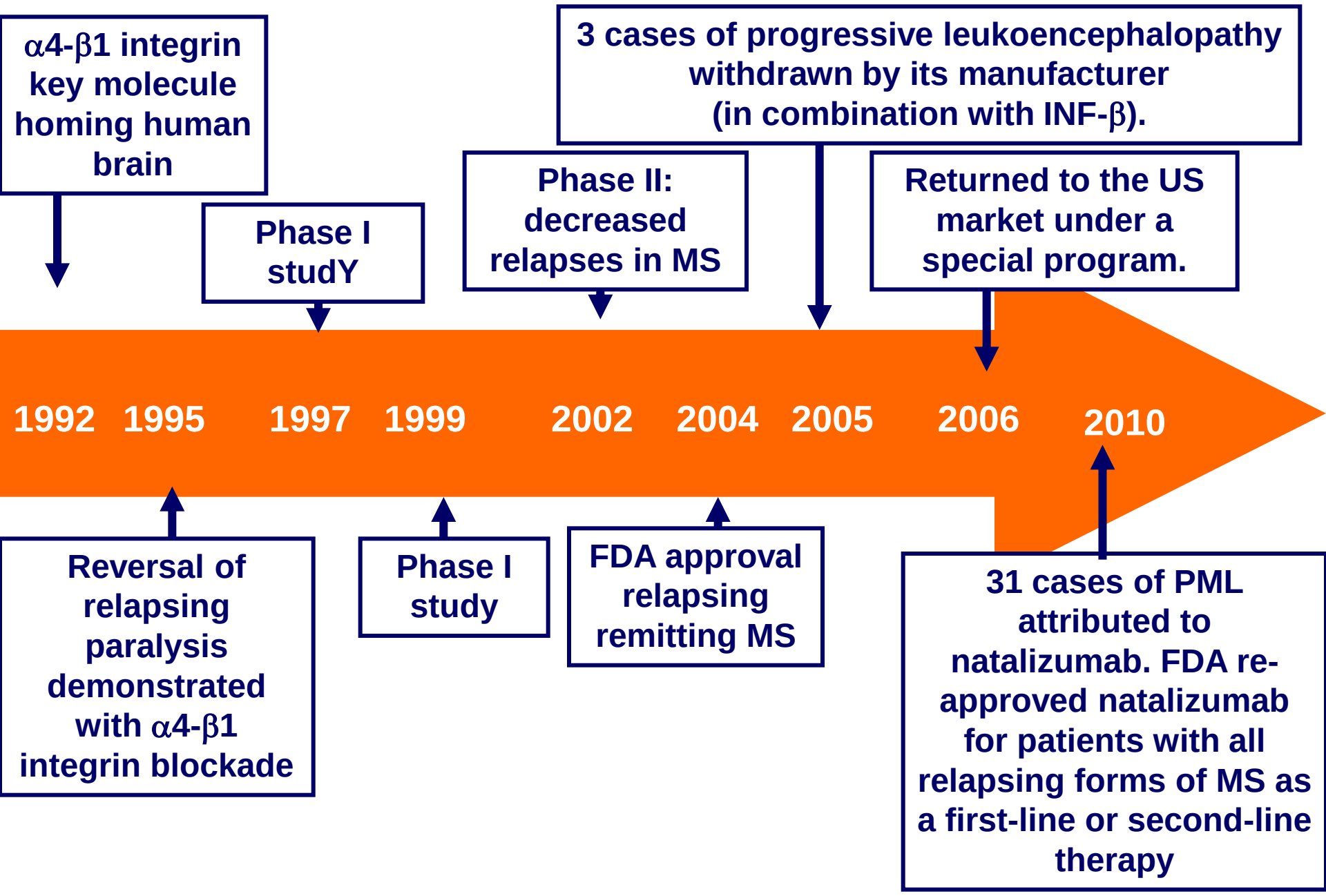


Table 1. Doses and Timing of Treatments for Multiple Sclerosis.

Treatment*	Treatment Interval
Interferon beta-1a, 30 μg IM	February 2000–January 2005
Methylprednisolone, 500 mg IV twice daily	March 16–20, 2001 December 15–19, 2004 January 5–9, 2005
Natalizumab, 300 mg IV every 4 weeks	April 12, 2002–January 18, 2005

Discovery and development of natalizumab

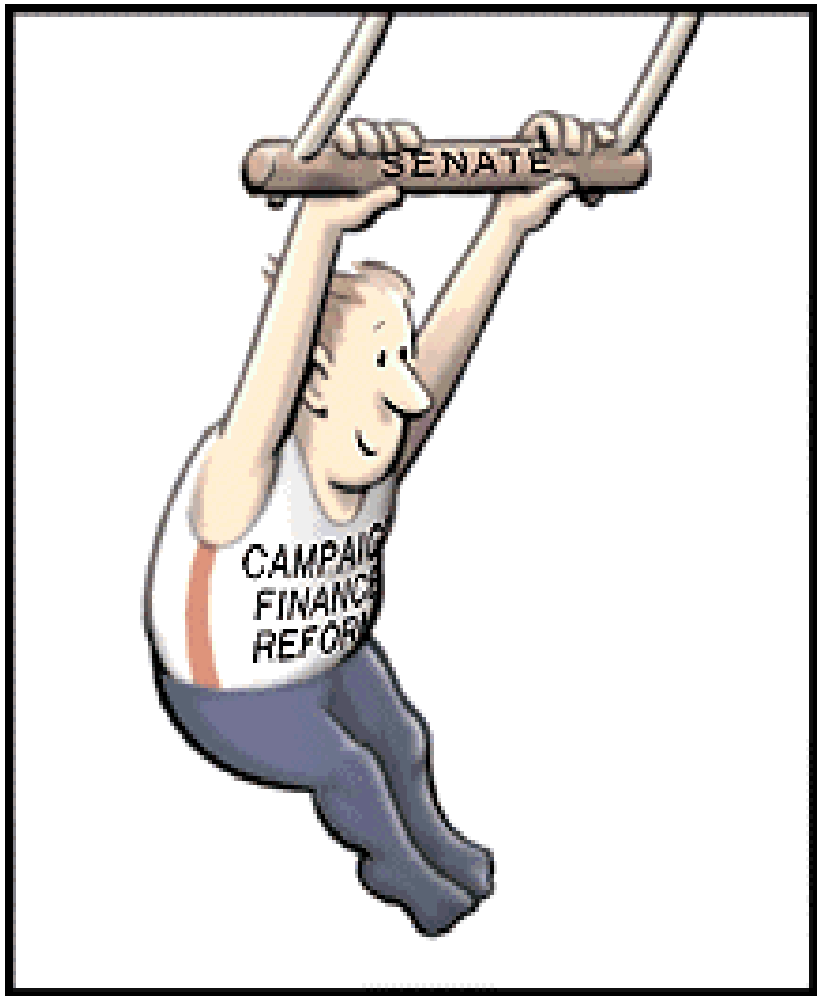


Ocrelizumab (anti-CD20)

- **Ocrelizumab** had reached Phase III clinical trials for rheumatoid arthritis and systemic lupus erythematosus, and Phase II for multiple sclerosis and hematological cancer.
- In March 2010, Roche announced the suspension of clinical trials in rheumatoid arthritis and lupus erythematosus. This step followed excess deaths due to opportunistic infections.
- Development for multiple sclerosis continues

Conclusions

- **Large number of biologics available, new generations coming up**
- **Biologics: revolution in the treatment of rheumatoid arthritis**
- **Cost-benefit studies are necessary**
- **Improve efficacy: increase immunosuppression**
- **From the use of biologics we learn from the pathophysiology of autoimmune diseases**
- **New treatments: new risks**



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