Optimisation des biothérapies

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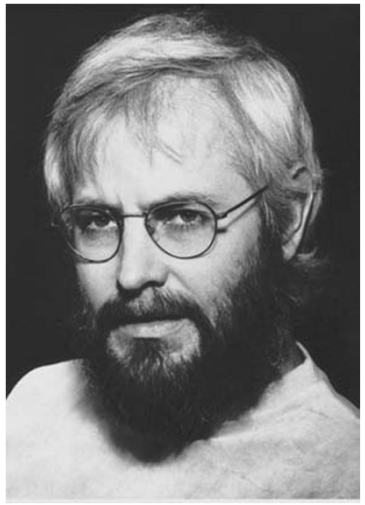
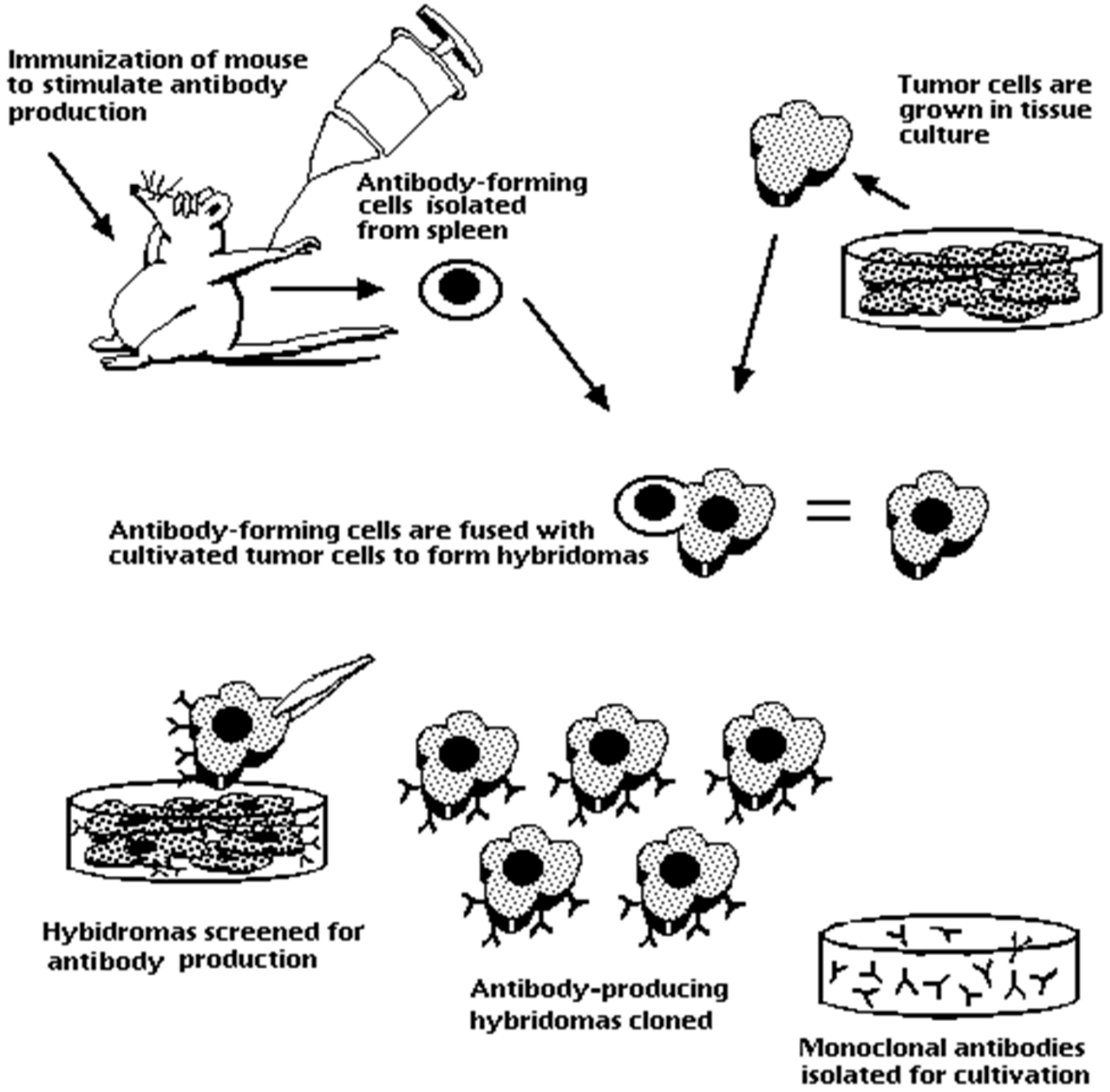
Production d'Ac monoclonaux



Milstein & Kohler 1975



Anticorps monoclonaux

- L'un des outils majeurs des biothérapies est les **anticorps monoclonaux** et leurs dérivés.
- Les Ac monoclonaux sont devenus des outils thérapeutiques de premier plan dans des domaines cliniques très divers
- Le succès de la première génération des Ac monoclonaux a lancé de **nouveaux défis** comme la conception **d'Ac aux activités fonctionnelles optimisées et aux effets secondaires mieux contrôlés**.
- Une nouvelle génération d'Ac est en train d'apparaître
- **Début 2009: 22 Ac monoclonaux sur le marché, plus de 200 évalués dans des essais cliniques**.

Theillaud JL Presse Med 2009

Ac monoclonaux: historique

- 1986: Muromonab-CD3 Ac de souris anti-CD3, prévention du rejet aigu de greffe rénale
- 1994: abciximab Ac chimérique anti-GPIIb-IIIa prévention de la formation du thrombus suite interventions cardio-vasculaires
- 1997: Premier Ac humanisé Daclizumab dirigé contre la chaine alpha du récepteur de l'IL2 (CD25), prévention du rejet aigu d'allogreffe rénale.
- 2002: Premier Ac monoclonal completement humain Adalimumab, anti-TNFα, traitement de la polyarthrite rhumatoïde

Nomenclature des Ac monoclonaux

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

Rituximab

Ocrelizumab

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

From mouse to human Abs

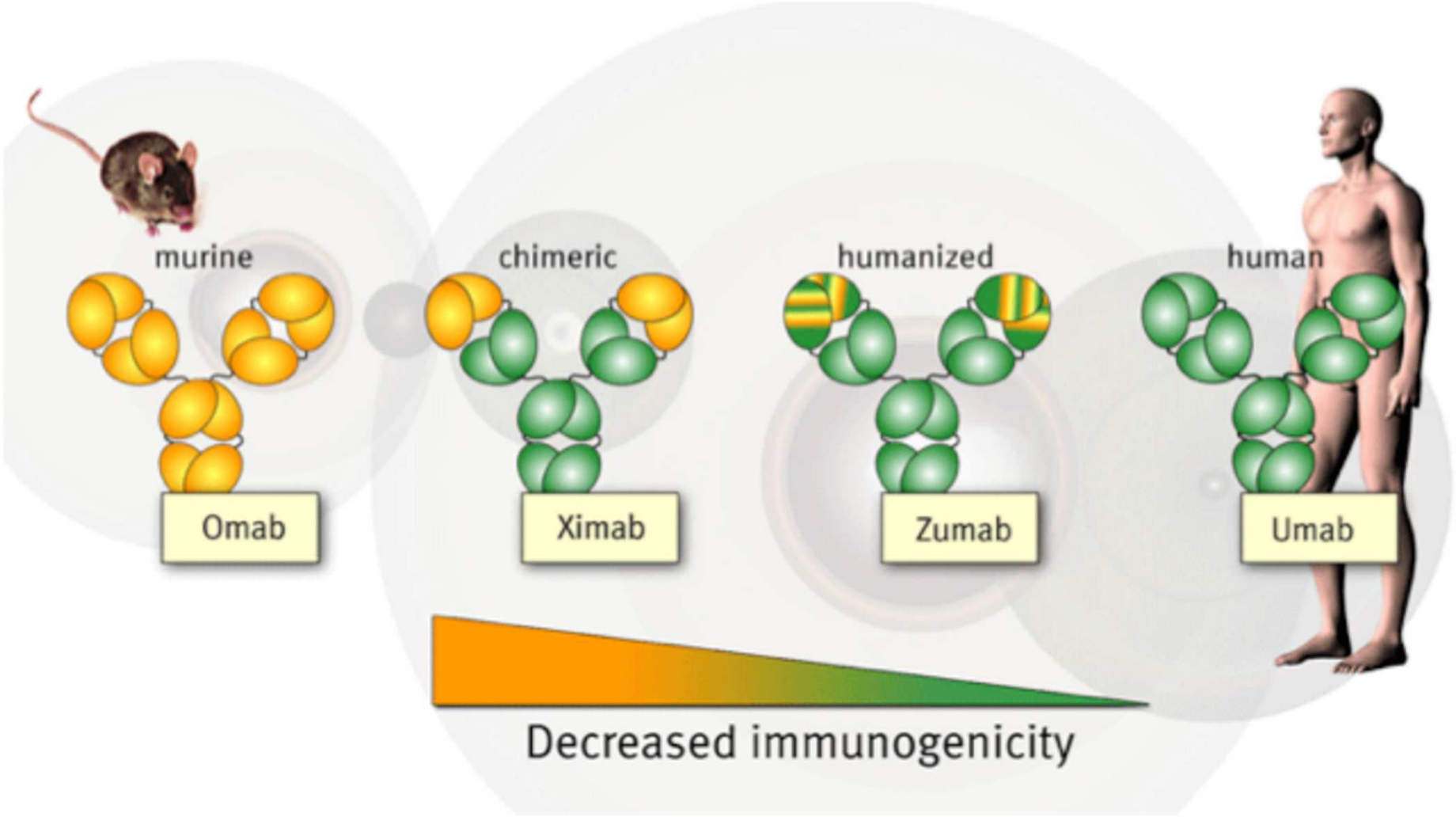


Table I : principales thérapies ciblées biologiques autorisées en France

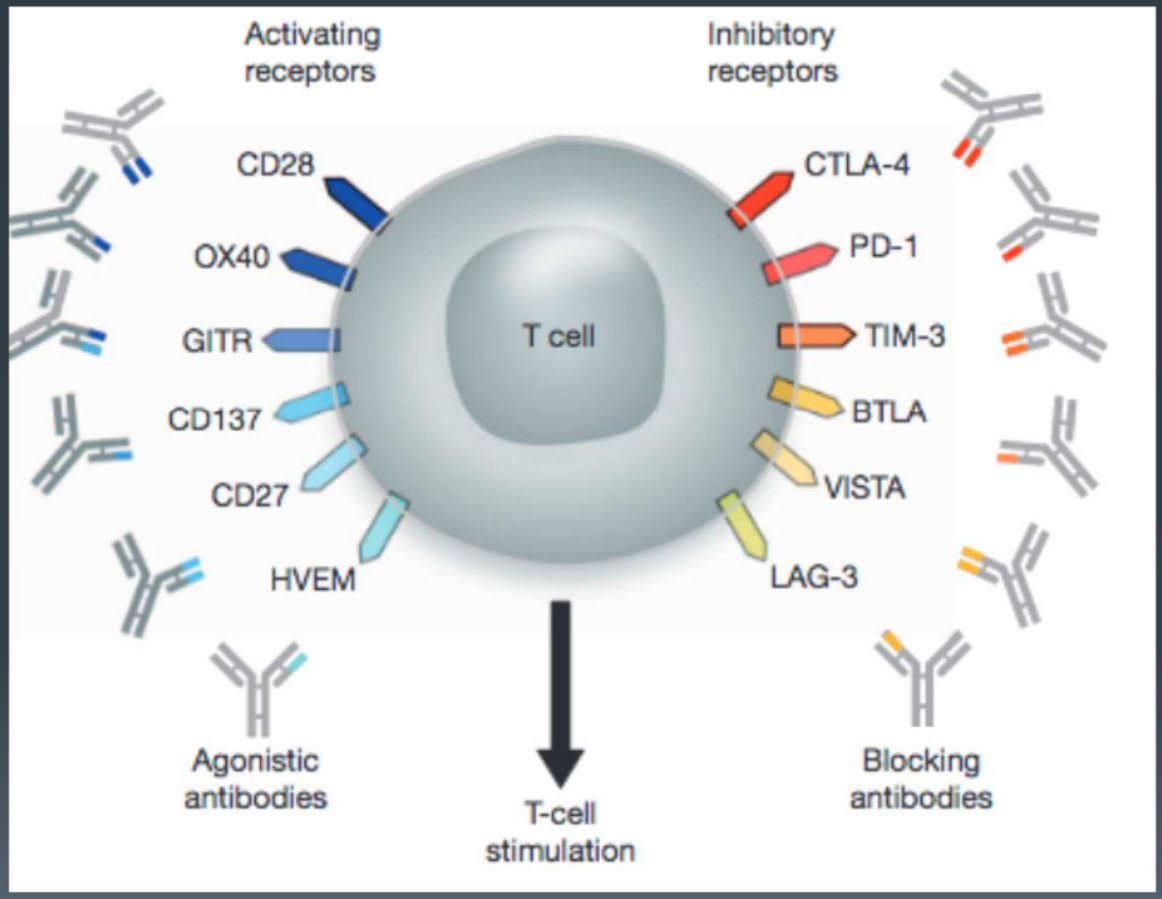
Nom commercial	Substance active	Ligand	Aire thérapeutique	Date d'expiration des brevets[a][b]
Avastin	Bevacizumab	VEGF	OH	2022
Campath/Lemtrada	Alemtuzumab	CD 52	OH, N	2021
Enbrel	Etanercept	TNF-α	R, D	2015
Erbitux	Cetuximab	EGFR	OH	2014
Herceptin	Trastuzumab	HER2	OH	2014
Humira	Adalimumab	TNF-α	R, G, D	2018
Lucentis	Ranibizumab	VEGF	O	2022
Mabthera	Rituximab	CD 20	OH, R	2013
Remicade	Infliximab	TNFα	R, G, D	2015
Roactemra	tocilizumab	IL-6R	R	2017
Simponi	Golimumab	TNF-α	R	2024
Synagis	Palivizumab	VRS	I	2015
Tysabri	Natalizumab	4-intégrine	N	2015
Vectibix	Panitumumab	EGFR	OH	2018
Xolair	Omalizumab	IgE	P	2017
Yervoy	Ipilimumab	CTLA 4	OH	2021

R : Rhumatologie ; G : Gastroentérologie ; D : Dermatologie ; OH : Oncologie/Hématologie ; N : Neurologie ; P : Pneumologie ; I : Infectiologie ; O : Ophtalmologie

[a] Europe

[b] La durée de la période de « protection des données » est de 8 + 2 + 1 ans (Règlement CE n°726/2004, art. 14(11))

The immune checkpoints family

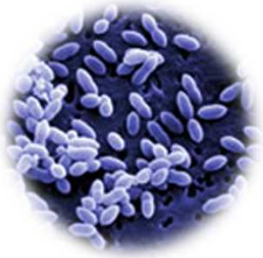


Mellman et al., Nature 2011

Monoclonal antibodies & risk of infection

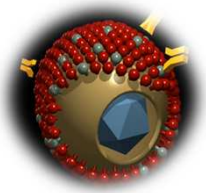
Bacteria

- Adalimumab
- Infliximab
- Certolizumab pegol
- Etanercept
- Abatacept
- Anakinra
- Rilonacept
- Efalizumab
- Alefacept
- Alemtuzamab
- 90Y-ibritumomab Tiuxetan
- Rituximab
- Gemtuzumab ozogamicin
- Bevacizumab
- Cetuximab
- Panitumumab
- Trastuzumab
- Basiliximab
- Daclizumab
- Muromonab
- Abciximab
- Natalizumab
- Palivizumab
- 131I-tositumomab



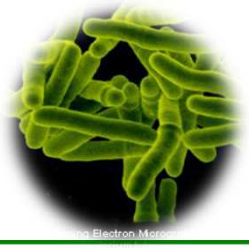
Viruses

- Adalimumab
- Certolizumab pegol
- Infliximab
- Etanercept
- Abatacept
- Alefacept
- Alemtuzamab
- Gemtuzumab ozogamicin
- 90Y-ibritumomab tiuxetan
- Rituximab
- Basiliximab
- Daclizumab
- Muromonab
- Natalizumab
- 131I-tositumomab



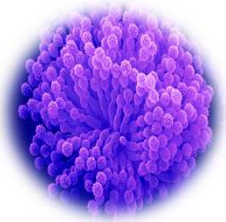
Mycobacteria

- Adalimumab
- Infliximab
- Certolizumab pegol
- Etanercept
- Abatacept
- Anakinra
- Efalizumab
- Alemtuzamab
- Daclizumab
- Rilonacept
- Alefacept
- Daclizumab
- Muromonab
- Natalizumab



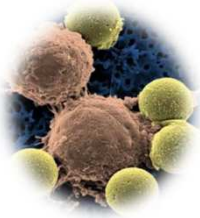
Fungi

- Adalimumab
- Infliximab
- Etanercept
- Abatacept
- Anakinra
- Alemtuzamab
- Bevacizumab
- Basiliximab
- Daclizumab
- Muromonab
- Natalizumab



Parasites

- Adalimumab
- Infliximab
- Etanercept
- Anakinra
- Alemtuzamab
- Basiliximab
- Muromonab
- Natalizumab



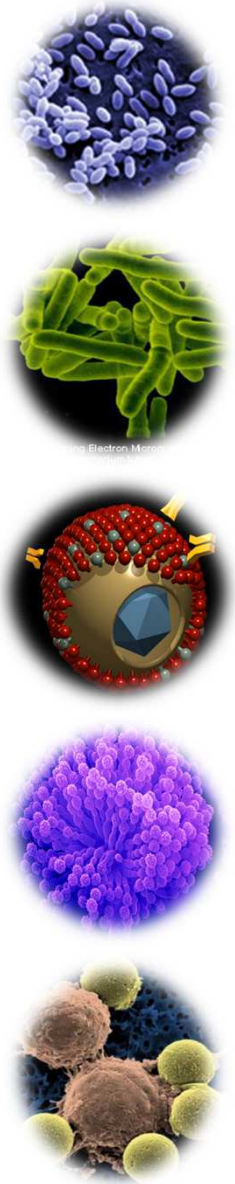
Courtesy JD Chiche

Monoclonal antibodies & risk of infection

Increased risk

Adalimumab
Infliximab
Certolizumab pegol
Etanercept
Abatacept*
Anakinra
Rilonacept
Efalizumab
Alemtuzamab
90Y-ibritumomab tiuxetan
Rituximab
131I-tositumomab
Gemtuzumab ozogamicin
Bevacizumab**
Cetuximab
Panitumumab
Trastuzumab**
Natalizumab

(meta-analysis or postmarketing cases with strong pattern of risk, consistent post hoc phase III RCT analysis)



Approximate level of evidence ?

Moderate risk

Alefacept
Basiliximab
Daclizumab
Muromonab

(most post hoc phase III RCT analysis & postmarketing studies show risk or trend to risk)

Possible risk

Abciximab
Omalizumab
Palivizumab

(case reports & trend toward increased infection but inconsistent in big RCTs, reported cases with confounders, or theoretical risk)

Courtesy JD Chiche

Fusion proteins (X-Fc)
in inflammation / auto-immunity /ophtalmology / oncology

- etanercept (Enbrel®), Fc IgG1, ECDp75 of TNFα-RII, 1998
- alefacept (Amevive®), Fc IgG1, ECD LFA3 (CD2 ligand), 2003
- abatacept (Orencia®), Fc IgG1, ECD CTLA-4 (B7.1 and B7.2 ligand), 2005
- rilonacept (Arcalyst®), Fc IgG1, ECD IL1β-R/IL1β-RAcP, 2008
- romiplostim (Nplate®), Fc IgG1, peptidomimetic of thrombopoïetin (TPO), 2008
- belatacept (Nulojix®), Fc IgG1, ECD CTLA-4 (B7.1 and B7.2 ligand) (PM: 92 kDa, 2 a.a. #/abatacept), 2011
- aflibercept (Eylea®, Zaltrap®), ECD VEGF-RI (indication: AMD, CRC), 2011

NB: pegsunercept, pegylated ECDp55 of TNFα-RI, development discontinued after Phase II in 2007

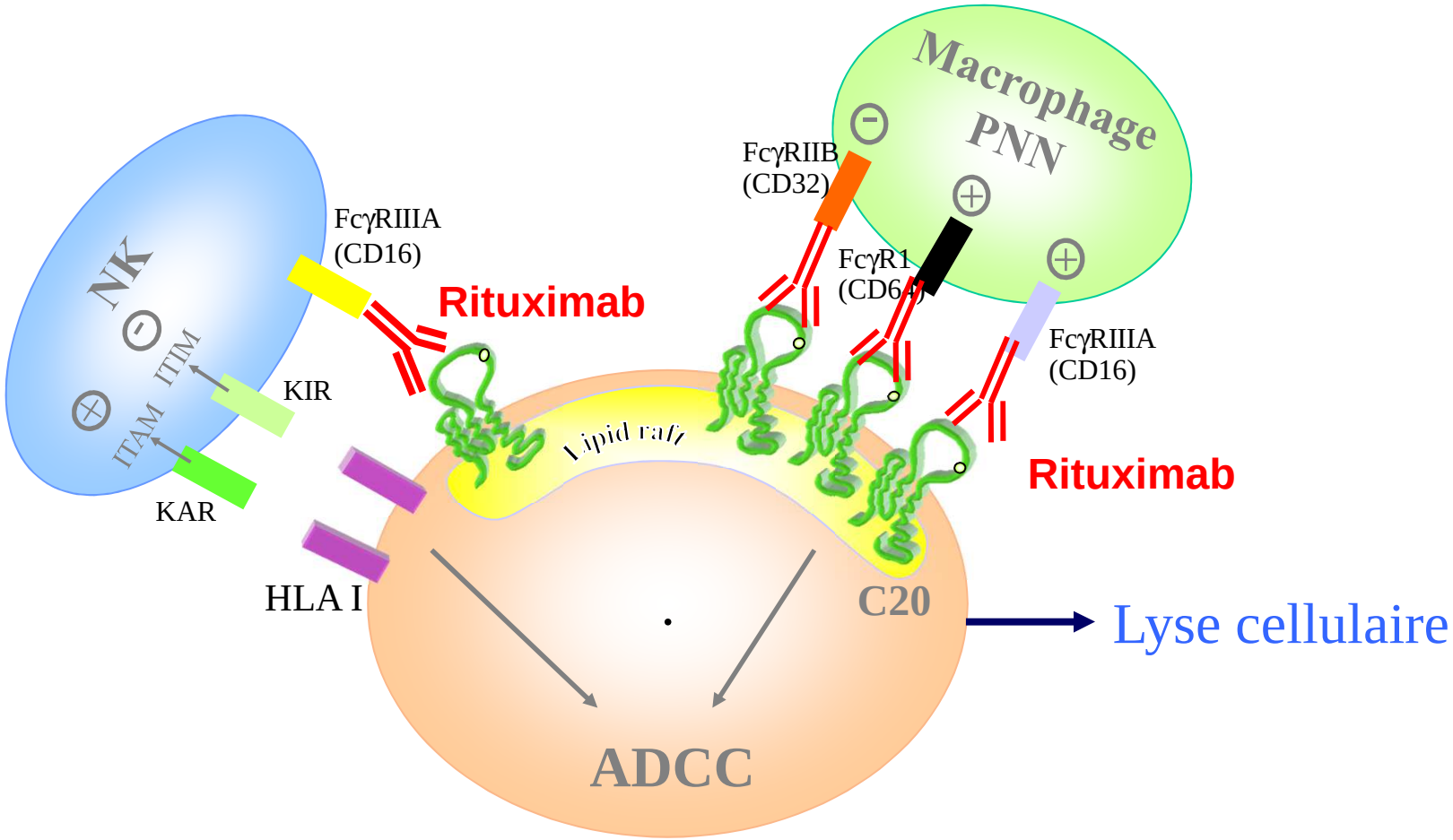
NB: anakinra (KINERET®) = recombinant IL1-RA (unglycosylated), 2002

** July 2014*

Mechanisms of action of therapeutic antibodies

- **Cible les médiateurs de l'inflammation**
  - **Cytokines**
  - **Cellules de l'immunité**
  - **Cellules tumorales**
- **Cible une molécule particuliere : CD**
- **Entraine une apoptose de la cellule cible**
- **ADCC**
- **Neutralisation spécifique de l'antigène/molécule**
- **Inactivation d'un récepteur cible par fixation directe**
- **Inactivation d'un récepteur cible par création d'un récepteur soluble**
- **Vecteur de thérapies ciblées**
-
- **Opsonisation**
- **Activation du complément**

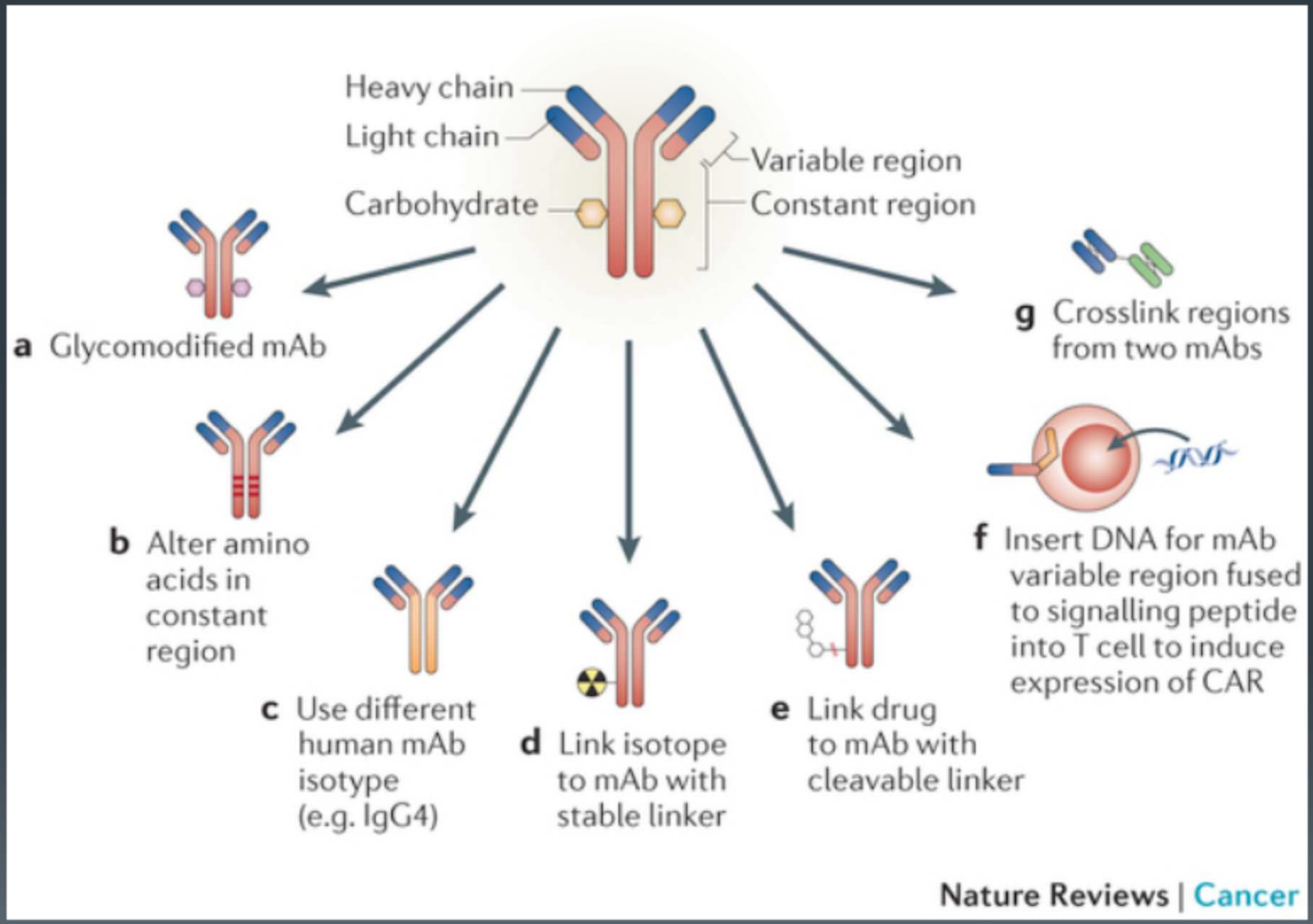
Rituximab: ADCC



ADCC: Cytotoxicité cellulaire dépendant des Ac

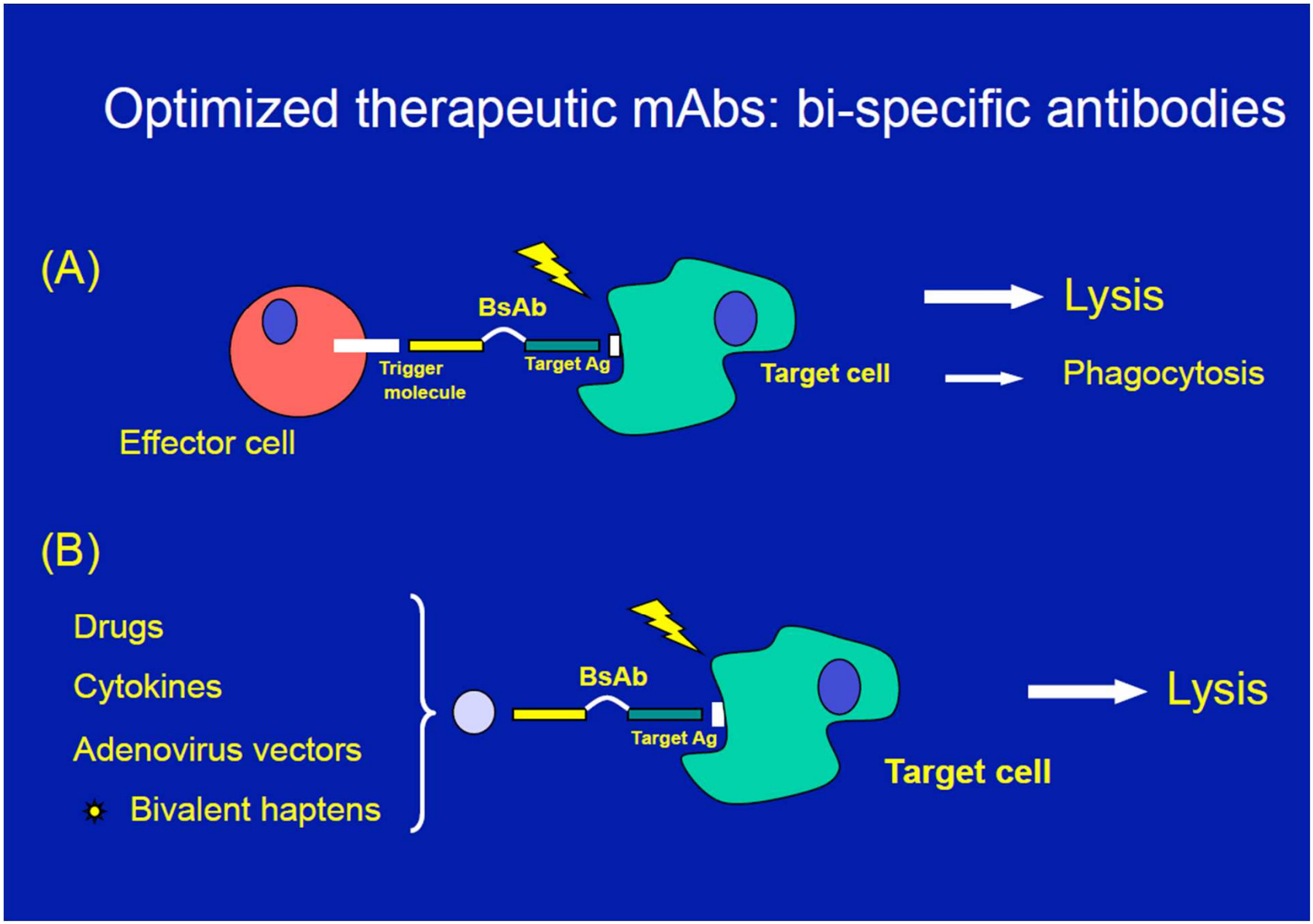
Anderson et al. *Biochem Soc Trans* 1997;25:705-8.
Clynes et al. *Nat Med* 2000; 6:443-6.

Optimization of therapeutic mAbs

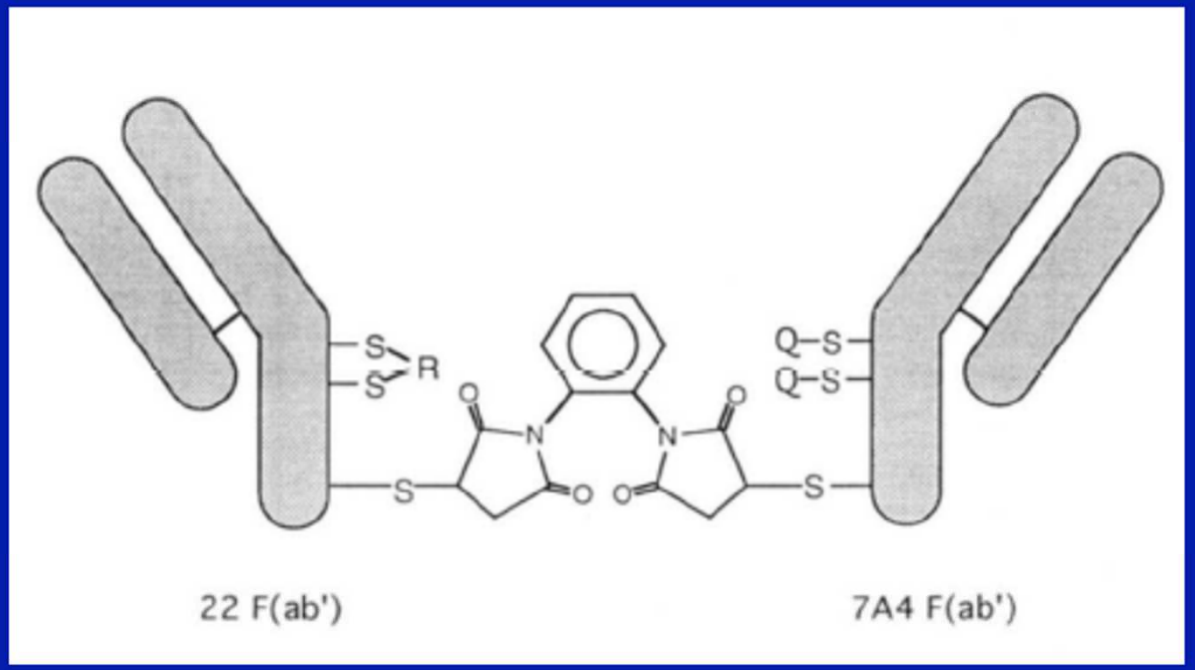


Weiner, Nature reviews Cancer, 2015

Optimized therapeutic mAbs: bi-specific antibodies



Bispecific Ab: 1. Biochemical engineering (example: MDX-260, anti-CD64 /anti-G_{D2})

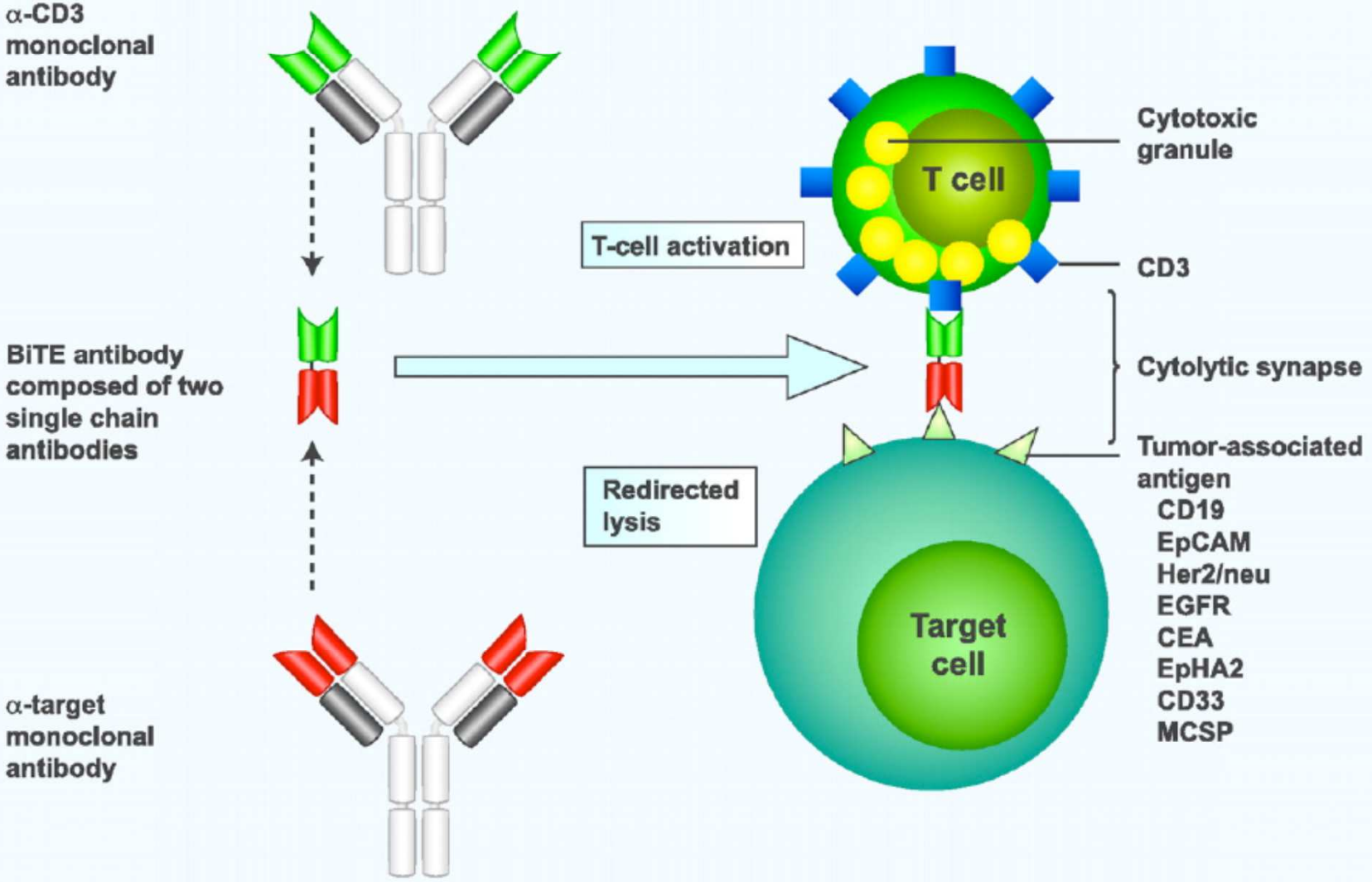


Q represents N-ethyl succinimidyl; R, O-phenylenedissuccinimidyl

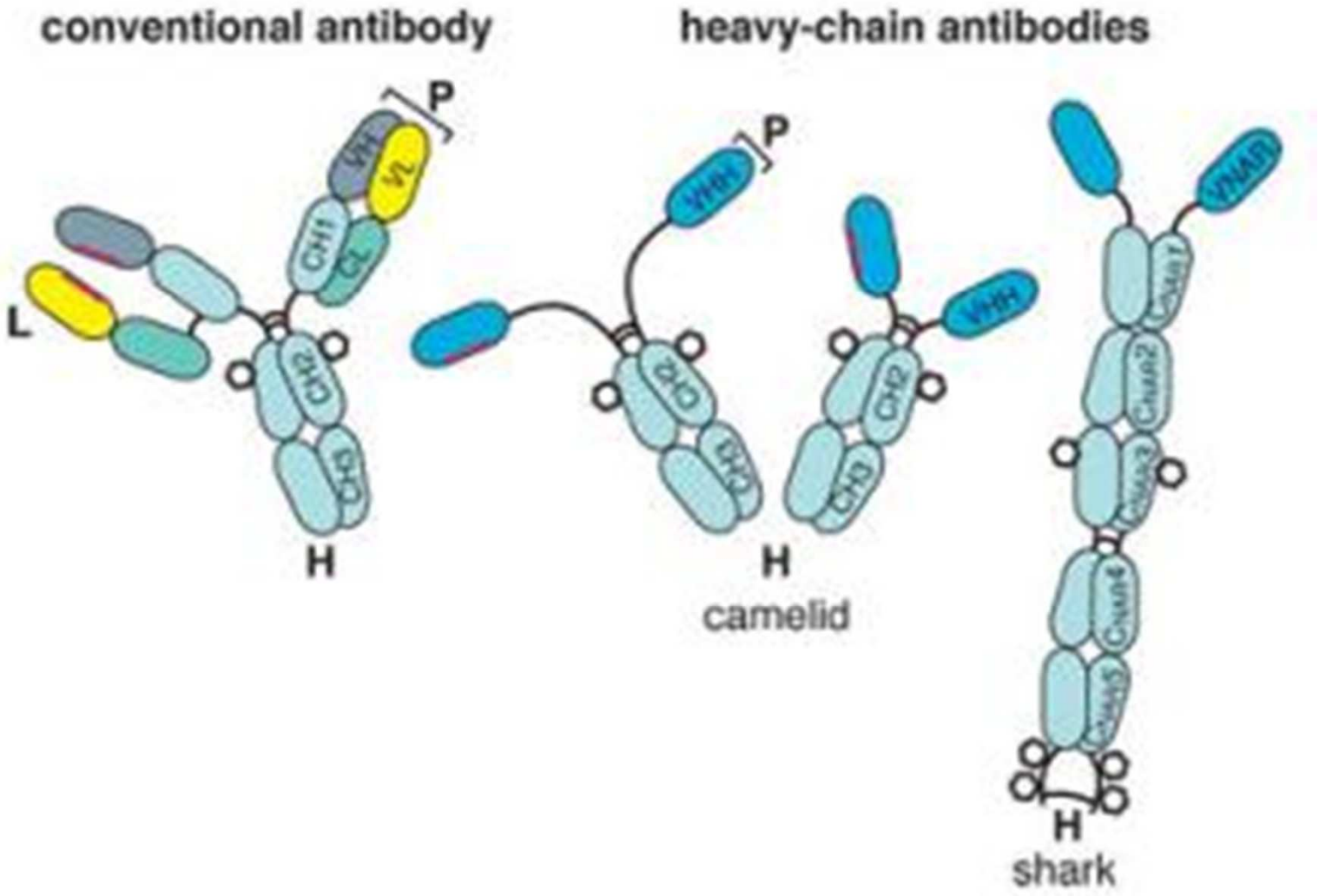
(Michon et al., *Blood,* 86, 1124, 1995)

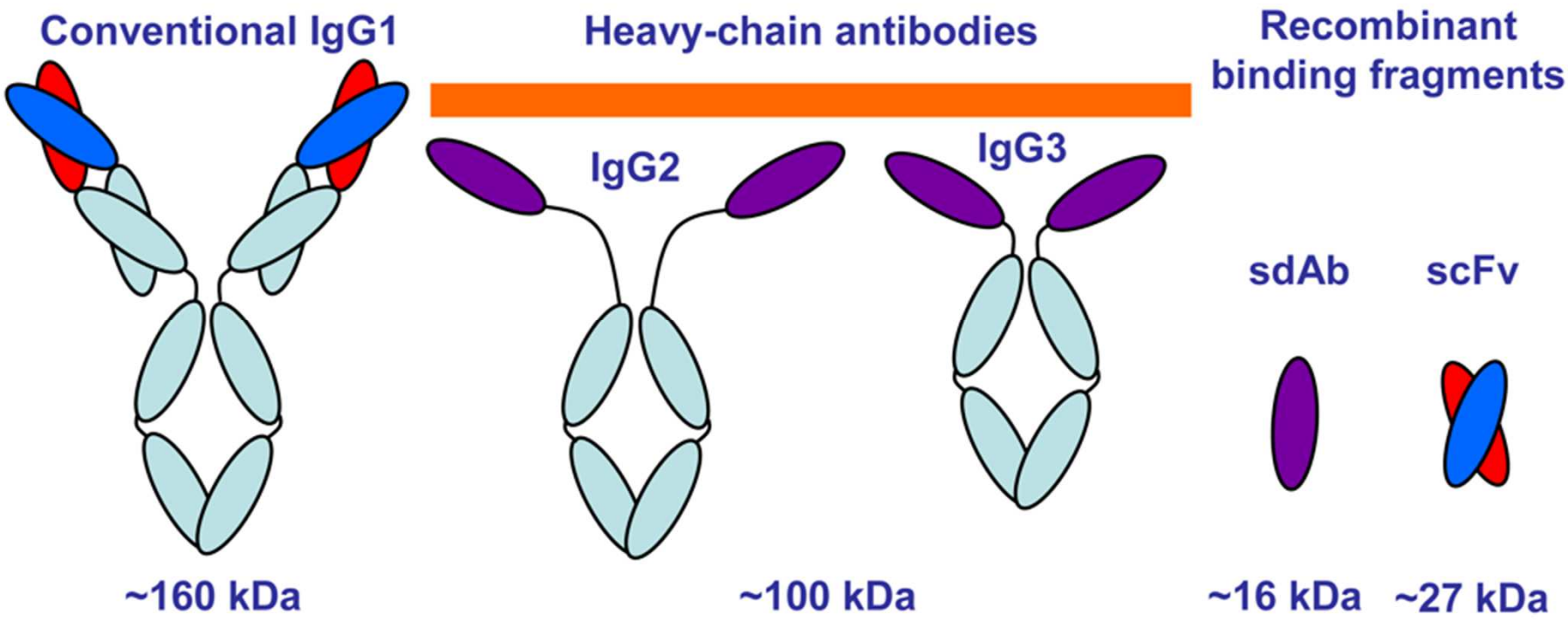
Alternative molecular formats and therapeutic applications for bispecific antibodies

Bispecific T-cell Engager Antibodies (BiTEs)

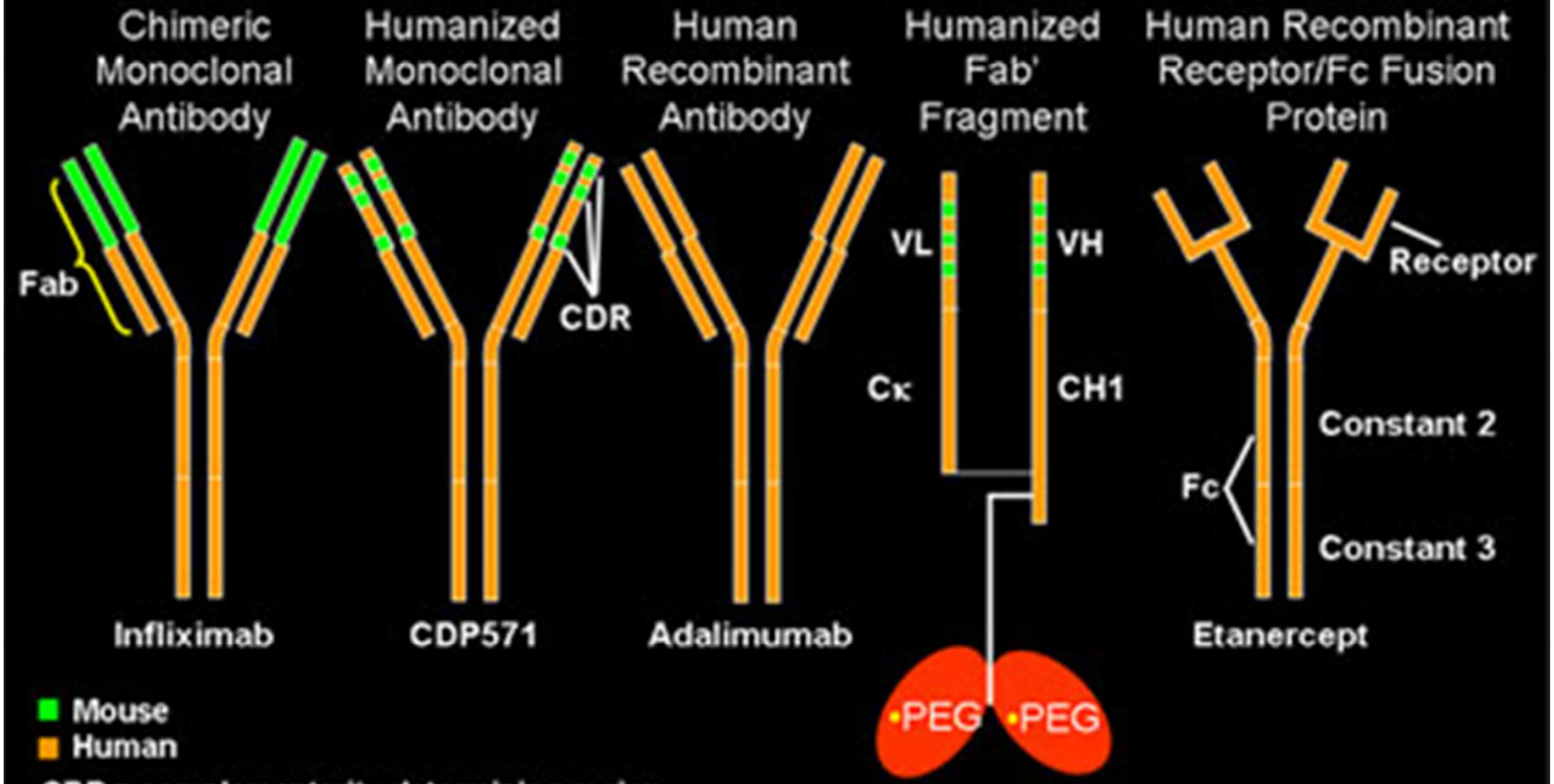


Camelid and Shark heavy chain antibodies




Conventional IgG1
Heavy-chain antibodies
Recombinant binding fragments
IgG2
IgG3
sdAb
scFv
~160 kDa
~100 kDa
~16 kDa
~27 kDa

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



CDR = complementarity-determining region.

PEG = polyethylene glycol.

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

Optimized therapeutic monoclonal antibodies

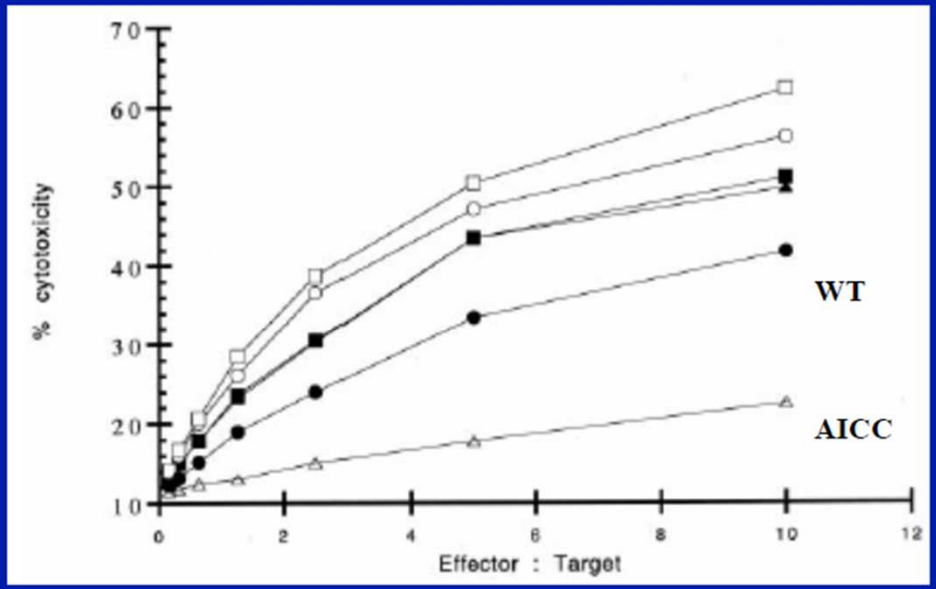
- Screening of Fc mutations
- Change in Fc glycosilation

Design of IgG1variants with improved binding to FcγRIIIA and ADCC

Strategy: site-directed mutagenesis of all solvent-exposed residues in the CH2 and CH3 domains of IgG1 (anti-HER2/Neu, Herceptin®)

Mutants >WT (↗ FcγRIIIA binding)*

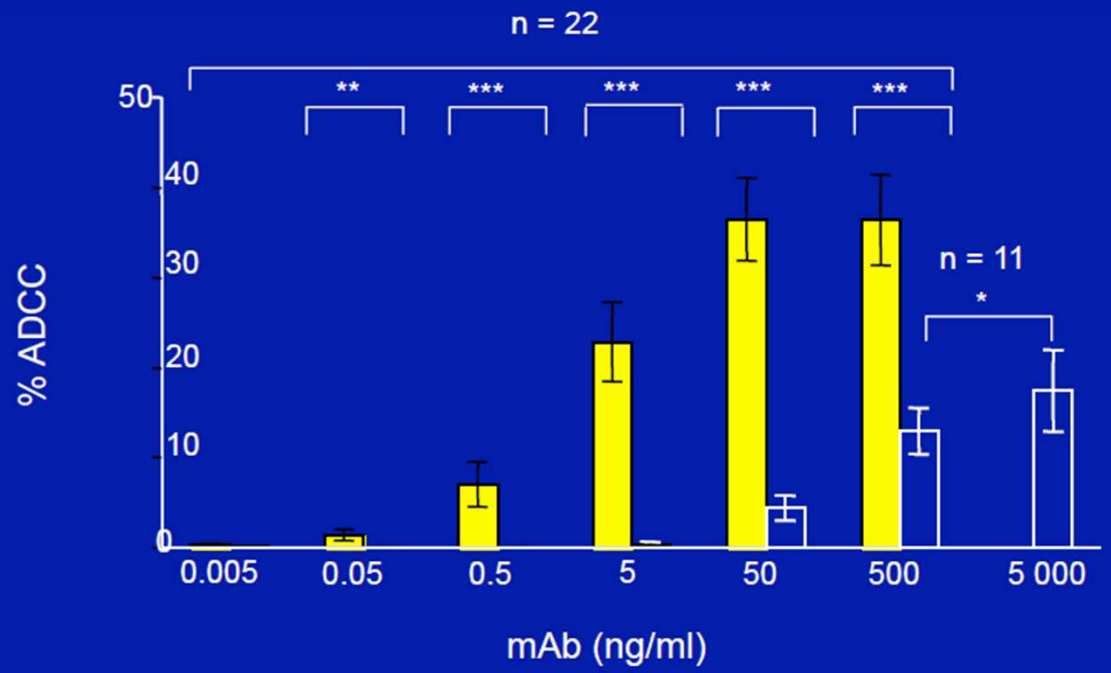
T256A
K290A
S298A (in the binding site of the Fc:FcγRIIIA crystal)
E333A
K334A
A339T
S298A/E333A
S298A/K334A
S298A/E333A/K334A



(from Shields et al., *J. Biol. Chem.*, 276, 6591, 2001)

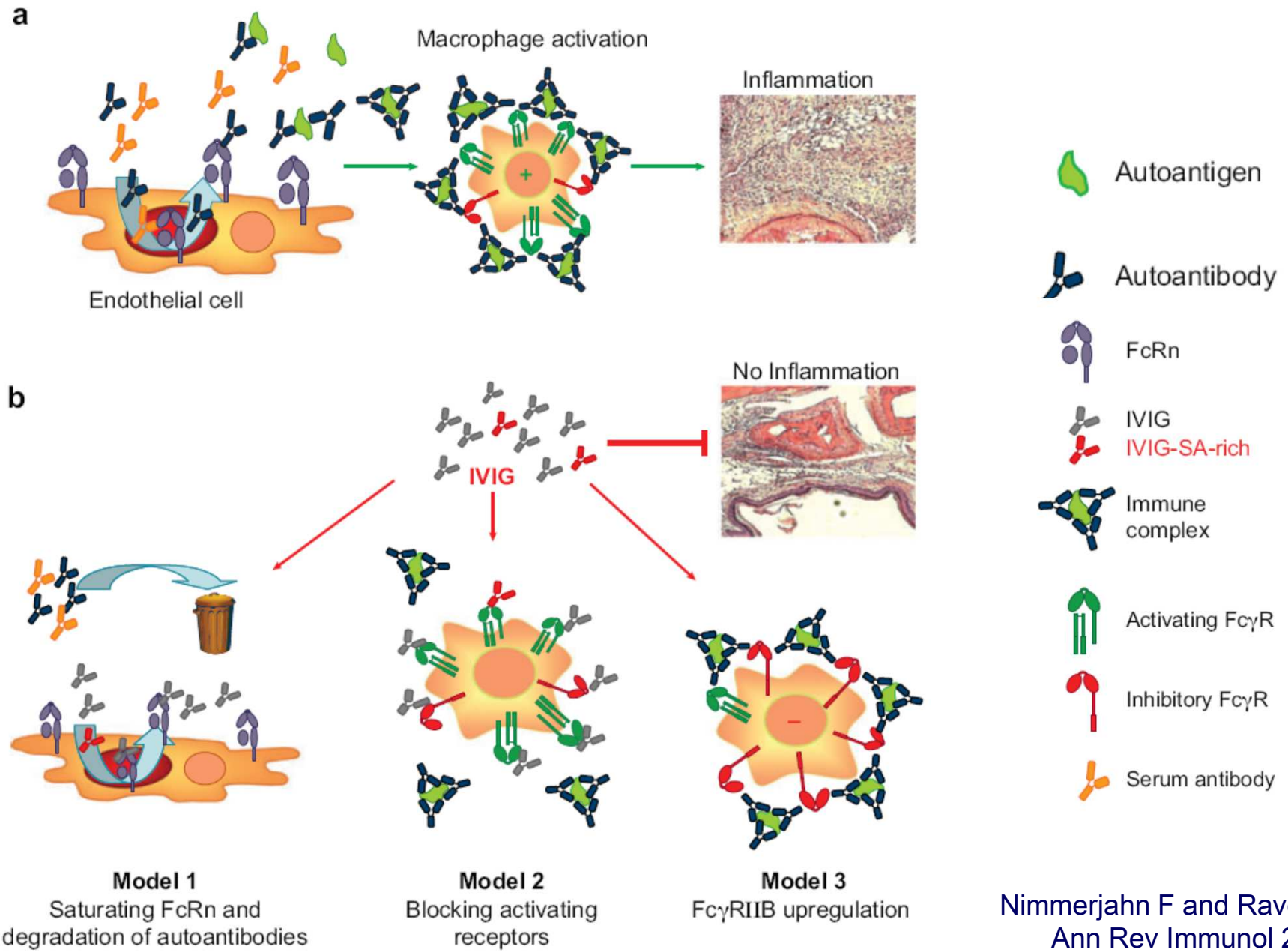
* Eu numbering

EMAB-6 (LFB), a low-fucose chimaeric human IgG1, strongly kills B-CLL cells in vitro as opposed to rituximab



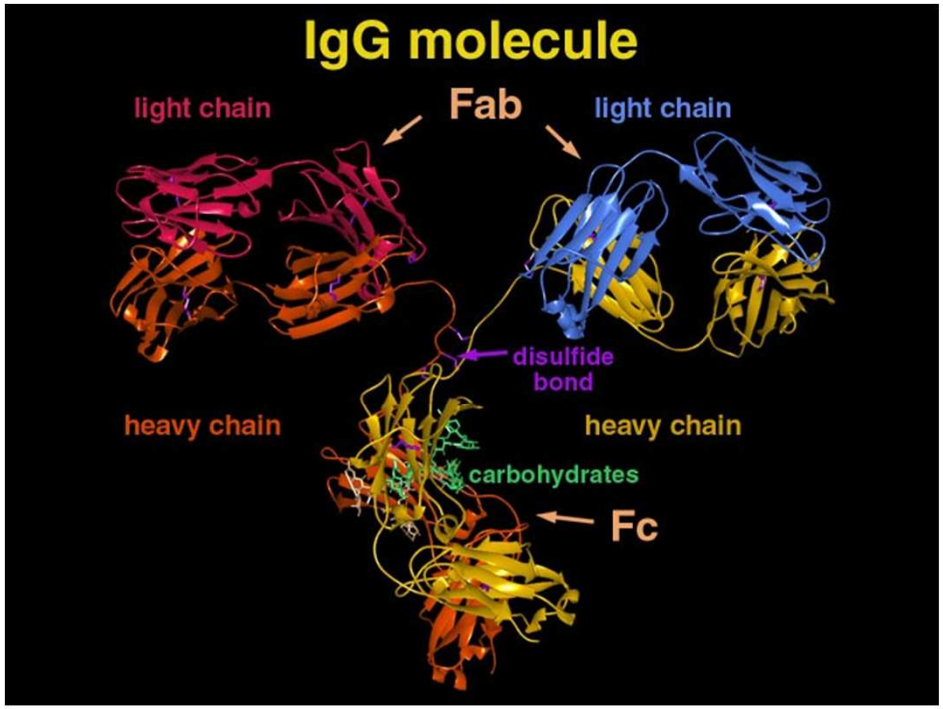
de Romeuf et al, *British J Hæmatol*, 140, 653, 2008

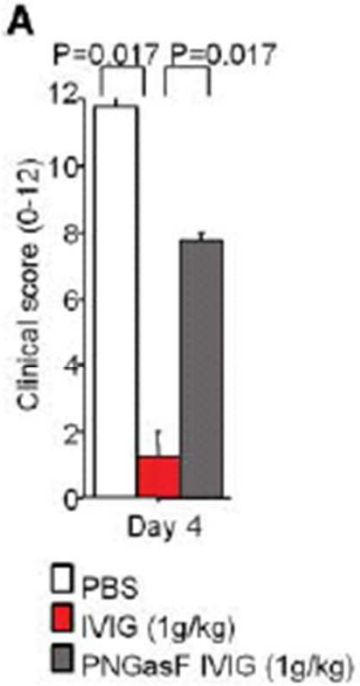
Proposed Fc fragment–dependent mechanisms of IVIg activity

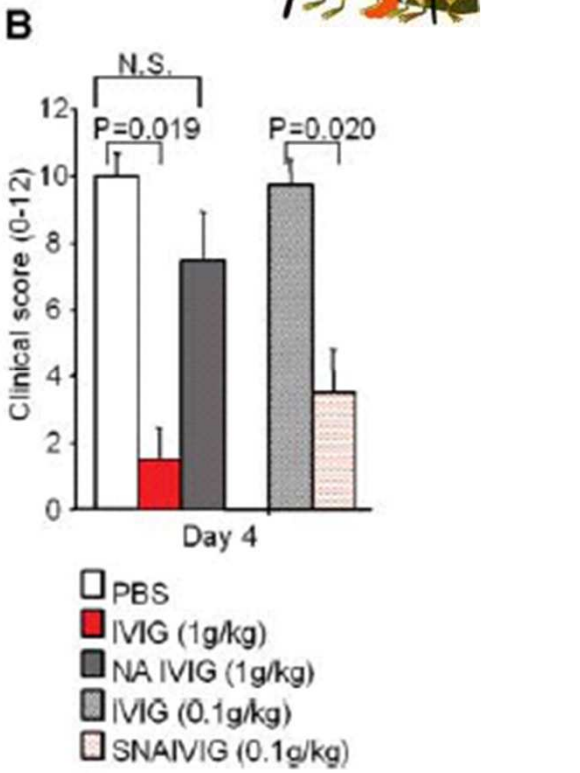


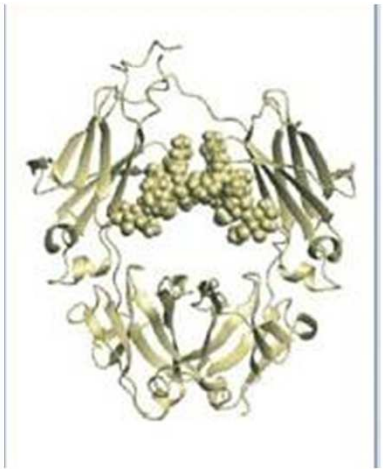
Nimmerjahn F and Ravetch JV, Ann Rev Immunol 2008

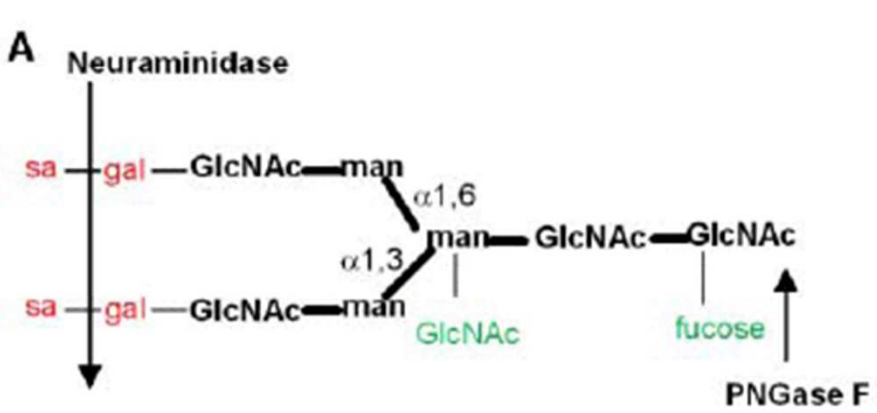
The anti-inflammatory activity of IVIg requires sialic acid







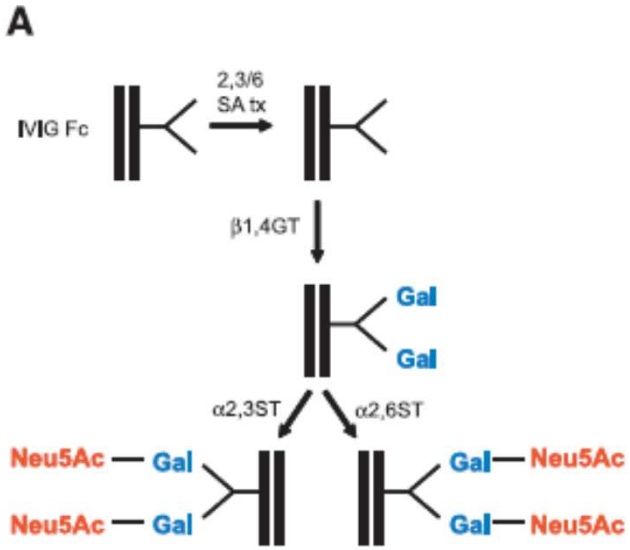


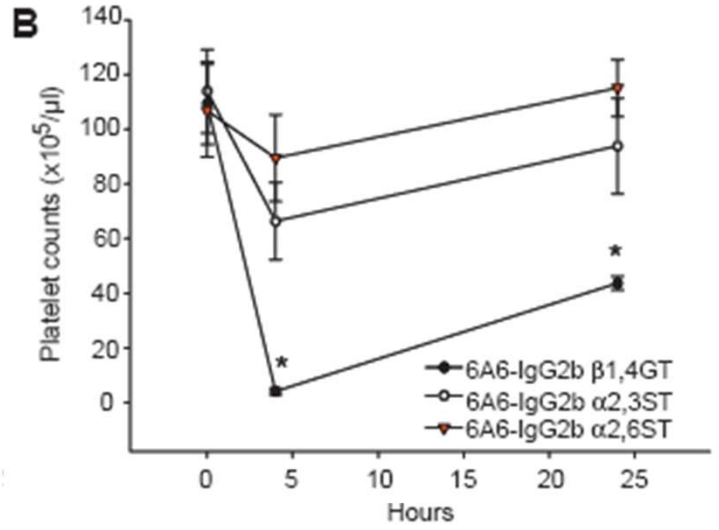


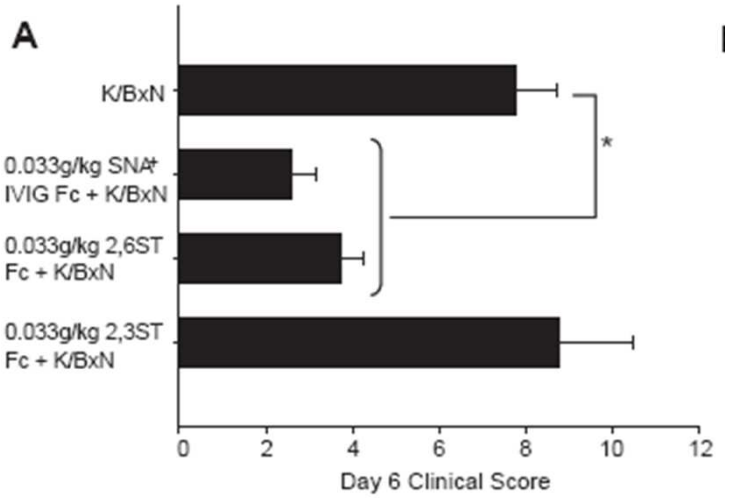
Kaneko Y, Science 2006

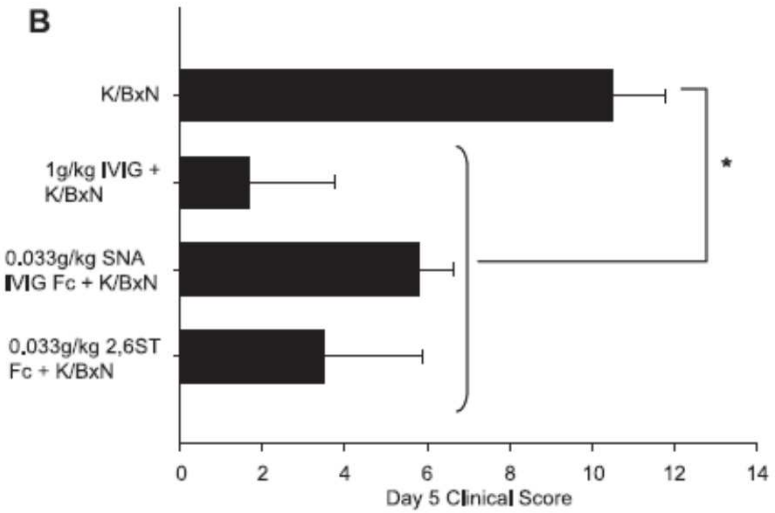
Recapitulation of IVIg Anti-Inflammatory Activity with a Recombinant IgG Fc

Anthony RM. Science 2008









Biosimilars: some definitions

Biosimilar [1]: biologic whose active ingredient is similar and not strictly identical to the reference biologic. The production process of a Biologic generally uses an host-cell or a living organism. Thus, it can generate structural and functional modifications of the final product.

The BPCI Act includes an abbreviated approval pathway for biological products shown as being biosimilars to or interchangeable with a reference product already approved by the FDA [section 351(k) of the «Public Health Service Act»].

=> *which degrees of structural and functional similarities* ?

[1] Defined by the FDA as «a biological product that is highly similar to an already approved biological product, notwithstanding minor differences in clinically inactive components …»

Scientific issues associated with Biosimilars: EMA statements

"Studies[1] have shown Remsima to have a comparable quality, safety and efficacy* profile to Remicade (infliximab)." It refers to requirements indicated in the EMA Guidelines:

-A biosimilar demonstrates similarity to the reference medicinal product in terms of **quality characteristics**, biological activity, safety and efficacy based on a comprehensive comparability exercise

-demonstration of comparability with the reference medicinal product using appropriate physico-chemical and *in vitro* biological tests, non-clinical and clinical studies.

=> non-clinical studies [2]: pharmaco-toxicological [3] assessment

=> clinical studies: pharmacokinetic, pharmacodynamic (bioequivalence), and **efficacy** studies (therapeutic equivalence).

⇒ clinical **safety** and pharmacovigilance studies: clinical safety studies and risk management plan with special emphasis on studying the immunogenicity of the biosimilar

[1] Studies should be done with an appropriate number of batches

[2] "A decision then made as to the extent of what, if any, *in vivo* work will be required"

[3] "Do not refer to a complete repeated dose toxicity study, but rather an in-life evaluation of safety parameters such as clinical signs, body weight and vital functions"

Scientific issues associated with biosimilars (mAbs)

- Sequence identity and postranslational modifications (glycosylation and a.a. modifications)
- Epitope binding (affinity)

- In vitro functional activity[1] (neutralization, signal transduction, antibody-dependent cell cytotoxicity (ADCC), complement-dependent cytotoxicity…)

- In vivo PK and PD (bioavailability)

- Formulation (stability, solubility, aggregation)

- Immunogenicity

[1] The concentration-activity/binding relationship between the biosimilar and the reference medical product should be assessed with a range of concentrations where differences are most sensitively detected