Biopharmaceuticals

Biosafety

Monoclonal antibodies (mAbs), fusion proteins

Prolonged plasma halflife, masked immunogenicity

Biosimilars

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NIA delegate-to-EIPG
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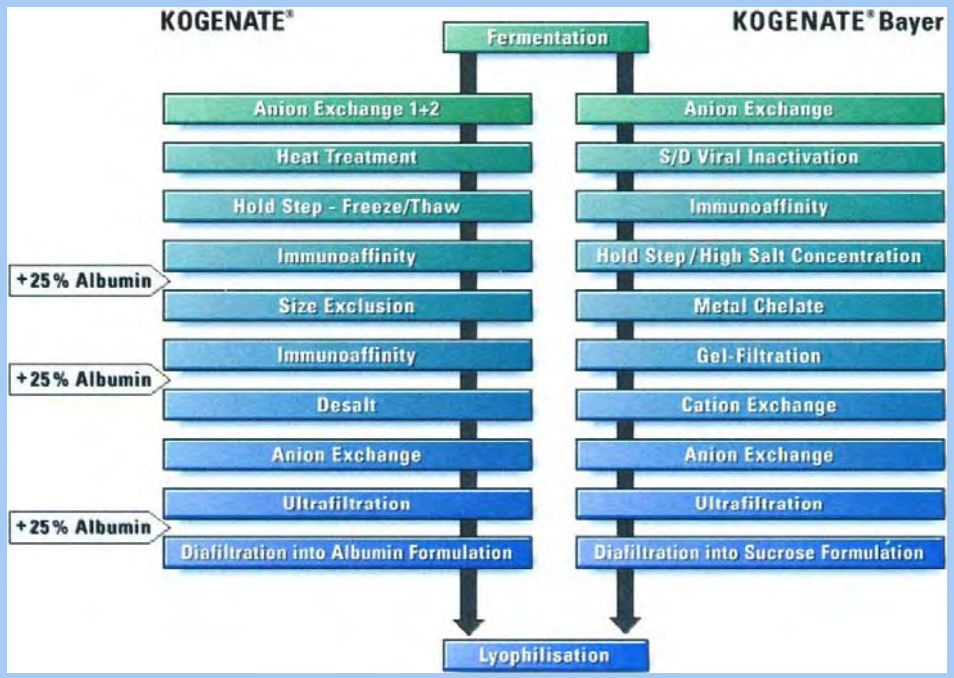
Biosafety



Pharmaceutical Visions 2001:35.

Maerz H et al. Nat Biotechnol 1996;14:651-2.

Removal factor: >5 log reduction for canine parvovirus (naked, 18-26 nm)

Burnouf T, Radosevich M. Haemophilia 2003;9:24-37.

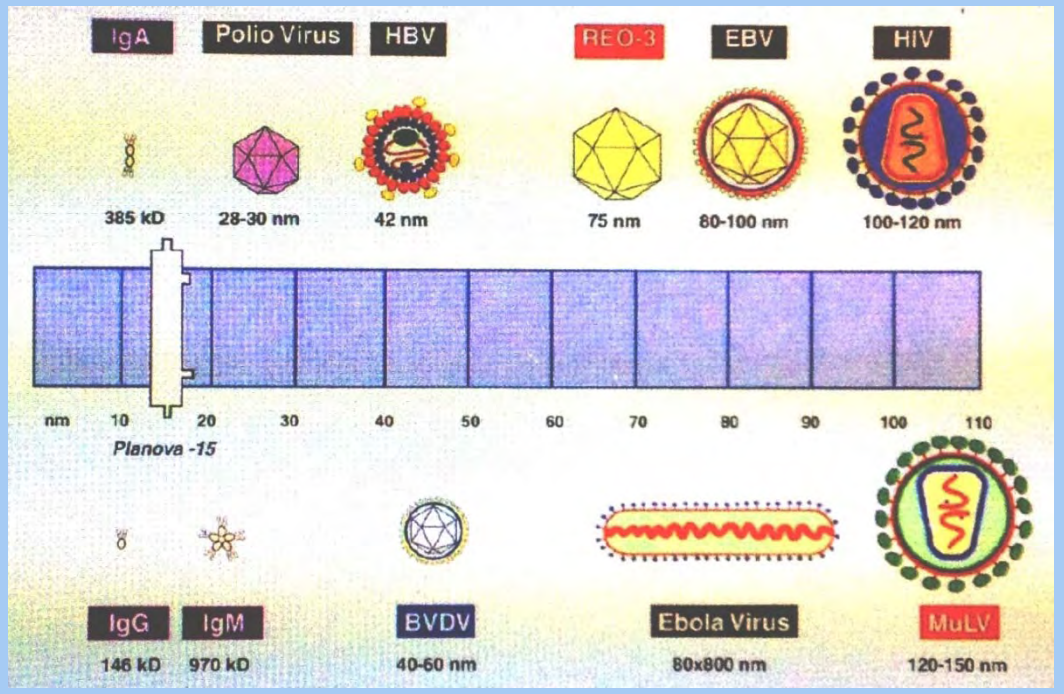
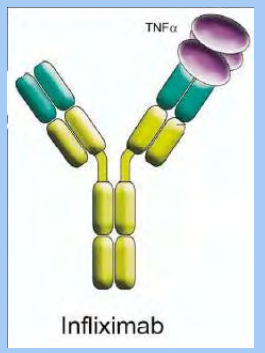
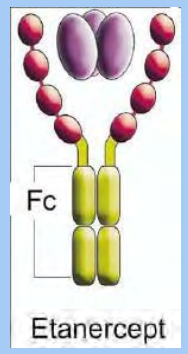
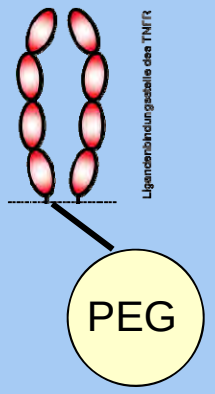


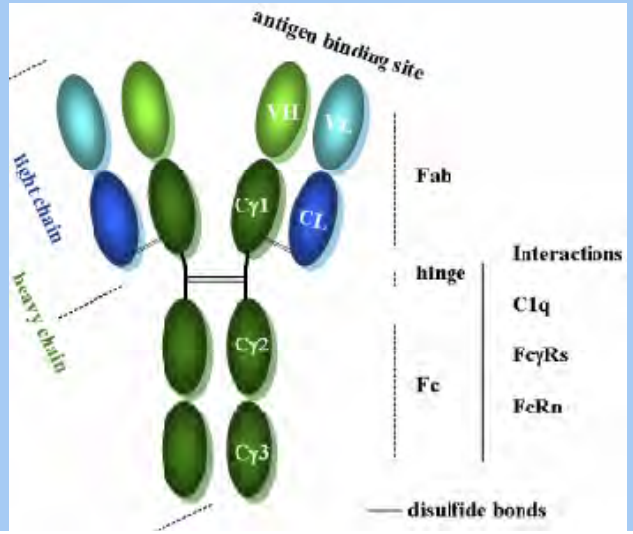
Table 1: Pharmacologic data for several mAbs, a Fab, a PEGylated Fab, fusion proteins* and a PEGylated sc cytokine receptor

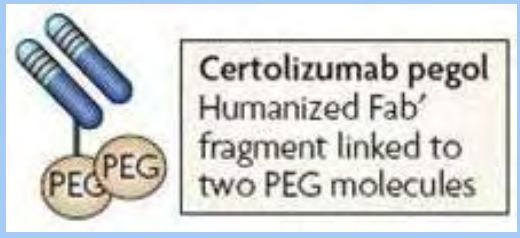
mAb/Fab/FusProt/sCR	$T_{½}$ (plasma)	Immunogenicity	Target; indication
muro**mo**nab-CD3 Orthoclone-OKT3 **M**	18 h	80%	CD3; rejection transplant
abci**xi**mab Reopro **Fab**	20–30 m	6%	GP2b/3a; profylaxis cardiac ischemia
ritu**xi**mab Mabthera **M**	3–17 d	1%	CD20; B-cell lymphoma
infli**xi**mab Remicade **M**	8–10 d	8†-43% RA pat. 61% Crohn pat.	TNFα; RA, M. Crohn
trastu**zu**mab Herceptin **M**	6–28 d	0%	HER2/neu; breast cancer
Alemtu**zu**mab Campath **M**	12 d	2% CLL pat. 63% RA pat.	CD52; CLL
Certoli**zu**mab pegol Cimzia **PEG-Fab**	14 d	8%	TNFα; M. Crohn
abatacept Orencia **FuPr**	13 d	3%	CD80 and -86; RA
etanercept Enbrel **FuPr**	3–5 d	6%	TNFα; RA, psoriasis
pegsunercept **PEG-sCR**	3 d	5%	TNFα; RA
adali**mu**mab Humira **M**	14 d	1†–17%	TNFα; RA
panitu**mu**mab Vectibix **M**	8–16 d	0%	EGFR; solid tumours











Anderson PJ. Semin Arthritis Rheum 2005;34(Suppl1):19-22

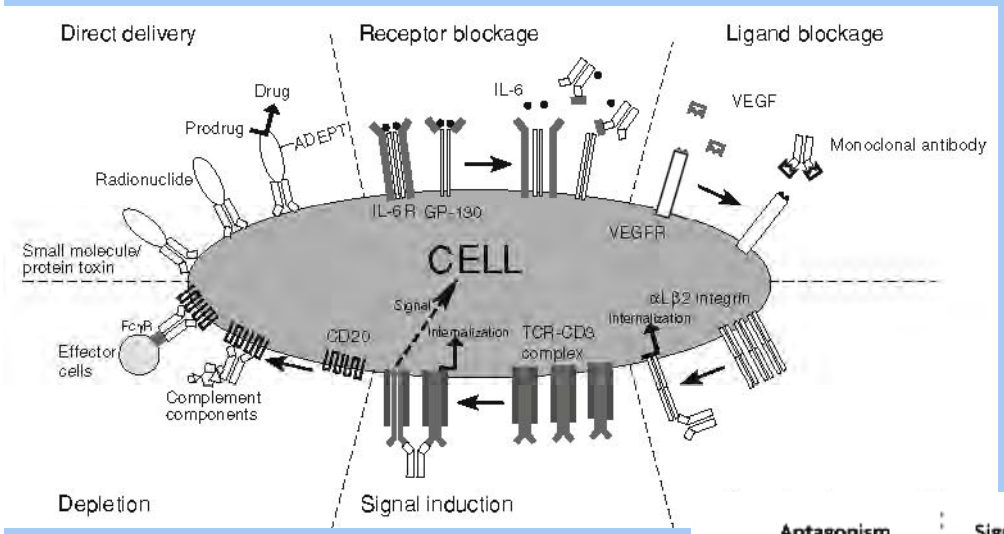
Liu X-y et al. Immunol Rev 2008;222: 9-27

Melmed GY et al. Nat Rev Drug Discov 2008;7:641-2

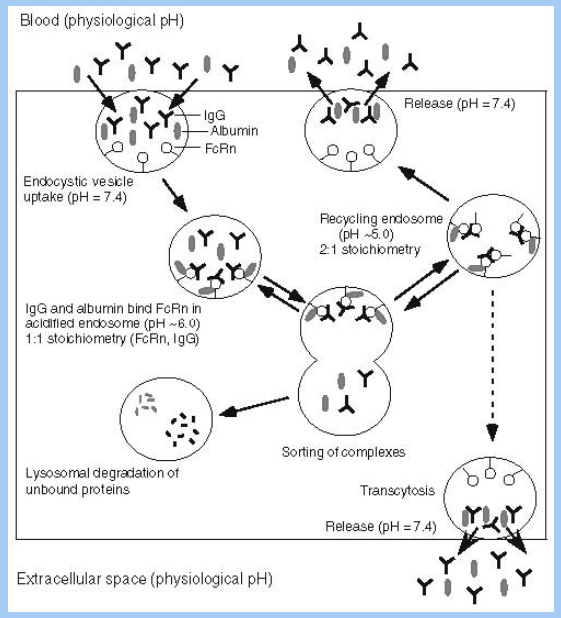
Dingermann Th, Zündorf I. Biotechnol J 2006;1:47-57

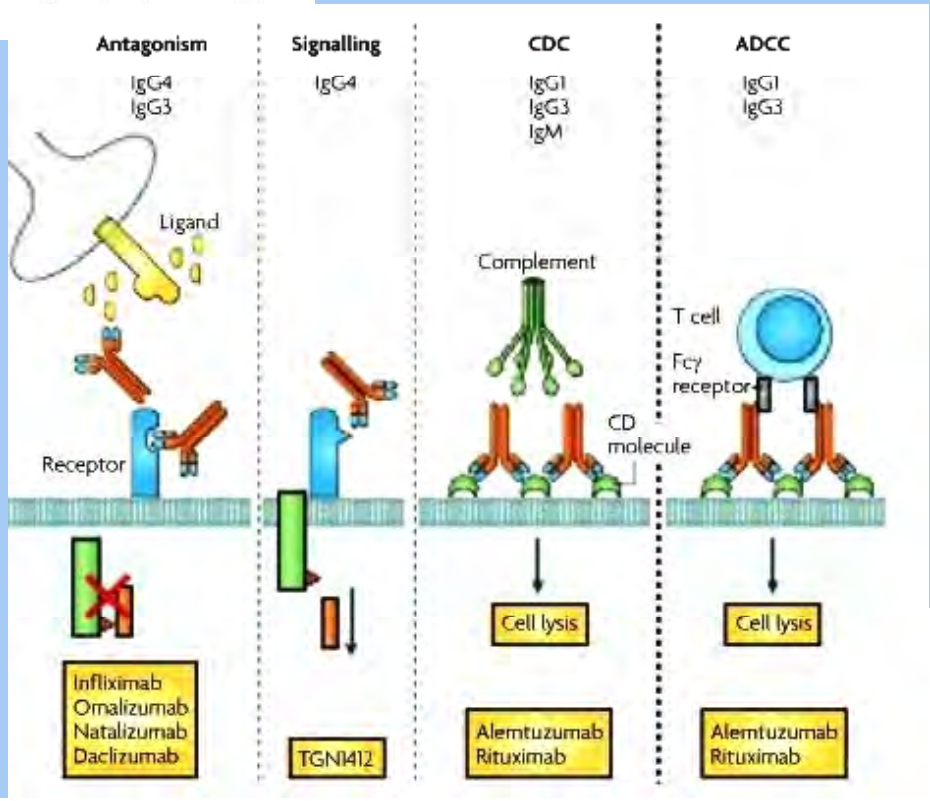
Wafelman AR. EJHP Practice 2011;17:30-5

mAbs pharmacodynamics



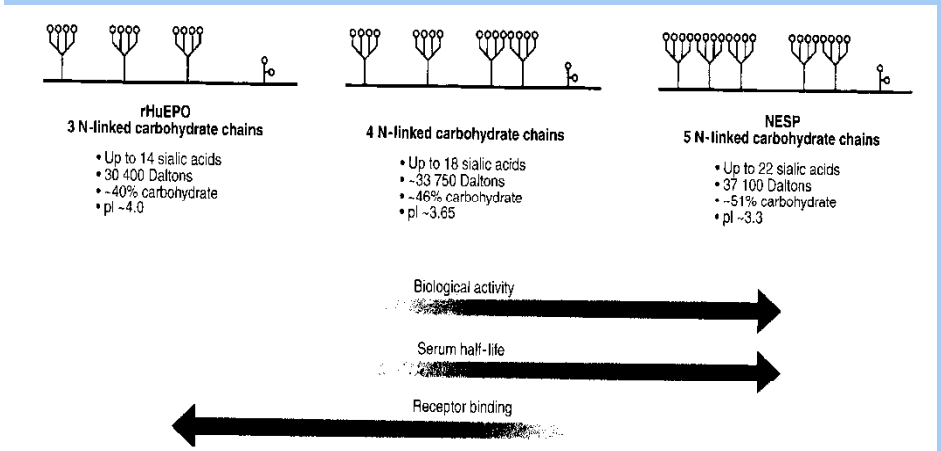
Dostalek M et al. Clin Pharmacokinet 2013;52:83-124
Hansel TT et al. Nat Rev Drug Discov 2010;9:325-38





Prolonged halflife/masked immunog..

Pegfilgrastim (Neulasta) showed in a clinical trial—with in total 296 breast cancer patients on combination chemotherapy—in a SC dose of 100 µg/kg once per chemocycle of 21 days, a significant lower percentage of neutropenic patients with fever, 9% vs 18%, as compared to filgrastim (Neupogen) in a SC dose of 5 µg/(kg*day). Curran MP, Goa KL. Pegfilgrastim. Drugs. 2002;62:1207-13.



Egrie JC, Browne JK. Br J Cancer 2001;84(Suppl1):3-10.

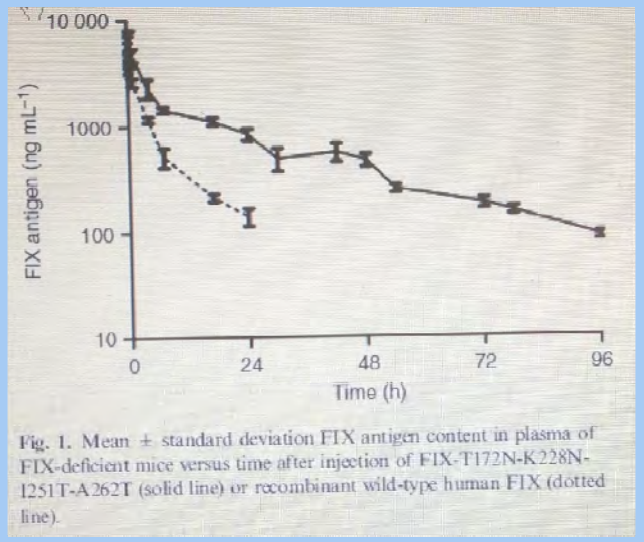


Fig. 1. Mean ± standard deviation FIX antigen content in plasma of FIX-deficient mice versus time after injection of FIX-T172N-K228N-I251T-A262T (solid line) or recombinant wild-type human FIX (dotted line).

Bolt G et al. J Thromb Haemost 2012;2397-8.

Hyperglycosylation

Alternatively, a recent R & D and pre-clinical paper on a **fusion protein of EPO and a hybrid human Fc**—aiming at prolonged activity—is promising. The Fc comprises IgD and IgG4 domains, thus avoiding ADCC and CDC. Im SJ et al. PLoS ONE 2011;6(9):e24574.

Paradigm shift ahead

REVIEW

BIOTECHNOLOGY and BIOENGINEERING

Glycans-By-Design: Engineering Bacteria for the Biosynthesis of Complex Glycans and Glycoconjugates

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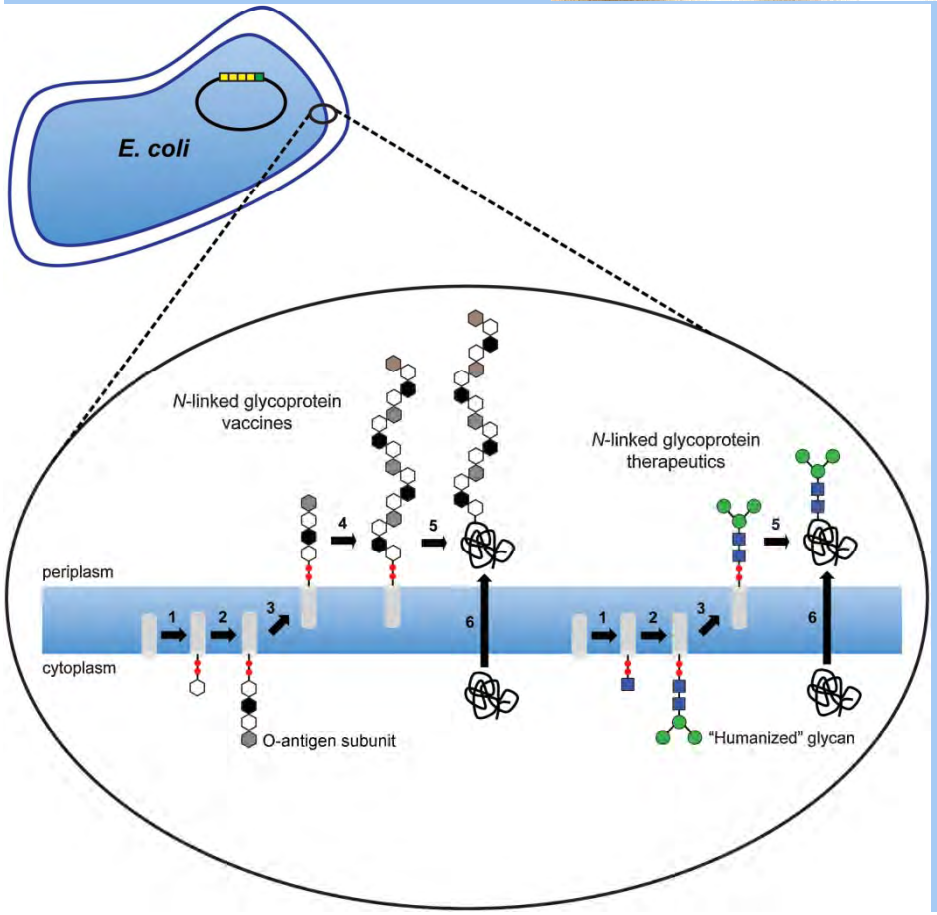

ABSTRACT: There is an urgent need for new tools that enable better understanding of the structure, recognition, metabolism, and biosynthesis of glycans as well as the production of biologically important glycans and glycoconjugates. With the discovery of glycoprotein synthesis in bacteria and functional transfer of glycosylation pathways between species, *Escherichia coli* cells have become a tractable host for both understanding glycosylation and the underlying glycan code of living cells as well as for expressing glycoprotein therapeutics and vaccines. Here, we review recent efforts to harness natural biological pathways and engineer synthetic designer pathways in bacteria for making complex glycans and conjugating these to lipids and proteins. The result of these efforts has been a veritable transformation of bacteria into living factories for scalable, bottom-up production of complex glycoconjugates by design.

Biotechnol. Bioeng. 2013;xxx: xxx–xxx.

KEYWORDS: glycosylation; glycolipids; glycoproteins; glycome; glycoengineering; glycosyltransferase; oligosaccharyltransferase; lipopolysaccharides; sugar nucleotides; *Escherichia coli*

Biosimilars

Weise M et al. Blood 2012;120:5111-7 Working Party Similar Biological Medicinal Porducts (BMWP) of CHMP, European Medicines Agency:

The type and extent of clinical data requirements for biosimilars vary…a repetition of the entire development program of the reference product is scientifically not necessary and could even be considered unethical.

Similar ≠ identical: increased level of phosphorylated high mannose-type structures in a biosimilar EPO-α as compared to reference, was accepted because applicant could prove that these are common glycoforms on proteins in human plasma.

Immunogenicity may be influenced by (patient-), (disease-), or product- (AW: formulation components, aggregation) related factors.

Extrapolation of efficacy data to other indications only when mechanism of action is the same. Extrapolation of immunogenicity only from high-risk to low-risk patients: e.g. from s.c. to i.v.

Traceability (adverse effects) is the main argument against automatic substitution. Start with biosimilars in naïve patients.

Further reading

Wafelman AR. Biopharmaceuticals, Characteristics and examples. EJHP Practice 2011;17: 30-5.

Dostalek M et al. Pharmacokinetics, Pharmacodynamics and Physiologically-Based Pharmacokinetic Modelling of mAbs. Clin Pharmacokinet 2013;52:83-124.

Brinks V et al. Quality of Original and Biosimilar Epoetin Products. Pharm Res 2011;28: 386-93.

Ebbers H et al. Interchangeability, immunogenicity and biosimilars. Nat Biotechnol 2012;30:1186-90.

Singh SK. Impact of Product-Related Factors on Immunogenicity of Biotherapeutics. J Pharm Sci 2011;100:354-87.

Hansel TT. The safety and side effects of monoclonal antibodies. Nat Rev Drug Discov 2010;9:325-38.

Haller CA et al. Safety Issues Specific to Clinical Development of Protein Therapeutics. Clin Pharmacol Ther 2008;84:624-7.

Muller PY et al. Safety Assessment and Dose Selection for First-in-Human Clinical Trials with Immunomodulatory mAbs. Clin Pharmacol Ther 2009;85:247-58.

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