Towards biosimilar monoclonal antibodies

Pros and cons

EMEA Workshop
on Biosimilar Monoclonal Antibodies

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Can more complex biologicals be biosimilars?

In principle, the concept of “similar biological medicinal products” applies to any biological medicine.

Guideline CPMP/BWP/437/04

How much do we need to know?

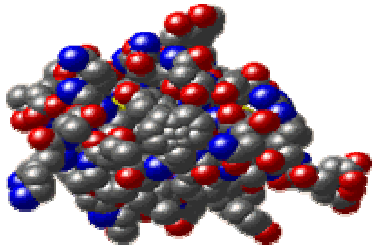
Idea: C. Nick

www.lucky-lions.com

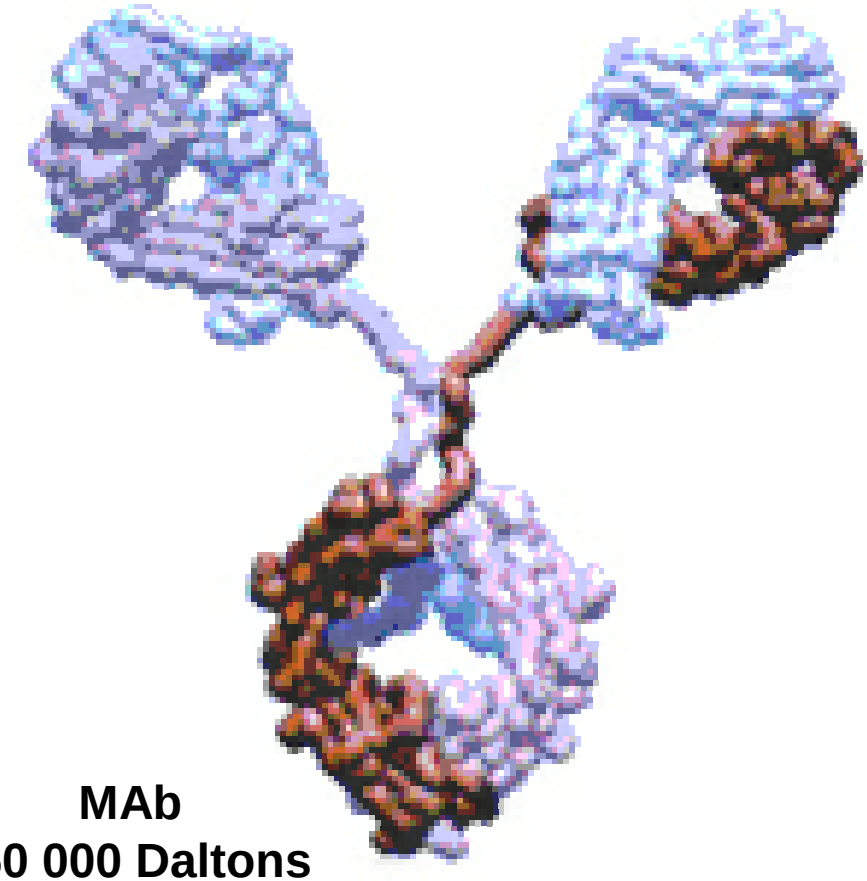
How much „similarity“ do we need?

Why „biosimilar“ (and not „biogeneric“)?

Aspirin
180 Daltons



Insulin
5 700 Daltons



MAb
150 000 Daltons

Why „biosimilar“ (and not „biogeneric“)?

“The process is the product. “

- **Fluctuations in the manufacturing process**
  (e.g., pH, temperature, culture media):

Batch inconsistency
(glycosylation spectra, aggregates)

- **Changes in the manufacturing process**
  (e.g., expression system):

New product?

• „One process – one product“ paradigm

Biotechnological medicinal products are „individuals“

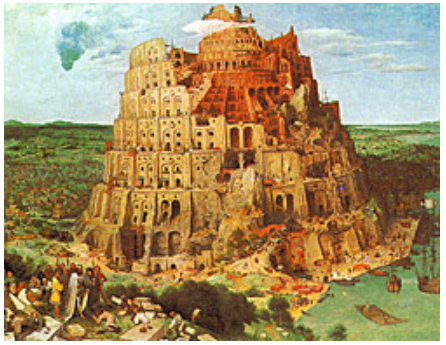
Biotechnological medicinal products are more than the drug substance

Small changes can have high impact

Terminology that matters

Cave terminology!

Pieter Bruegel der Ältere (1525/1530-1569)
The Tower of Babel, 1563



- **Biosimilar mAb**
  - Similarity of active substance
  - Aim is to establish similarity to licensed product
  - Same indications (but not necessarily all)

- **2nd generation mAb**
  - Different active substance
    (Humira® is not a biosimilar to Remicade®!)
  - Stand-alone development, might however be comparative
  - Can be different indications
  - *(would these be the „follow-on“ biologicals?)*

Monoclonal antibodies – a success story

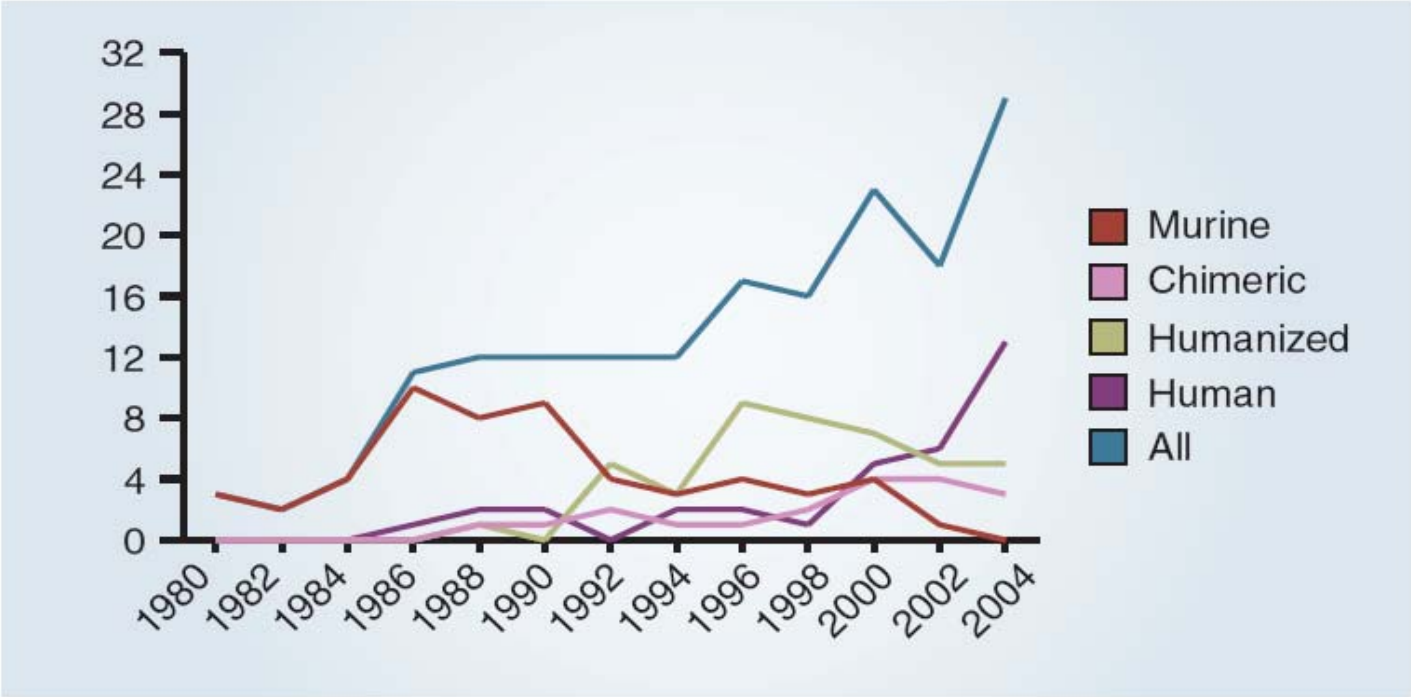


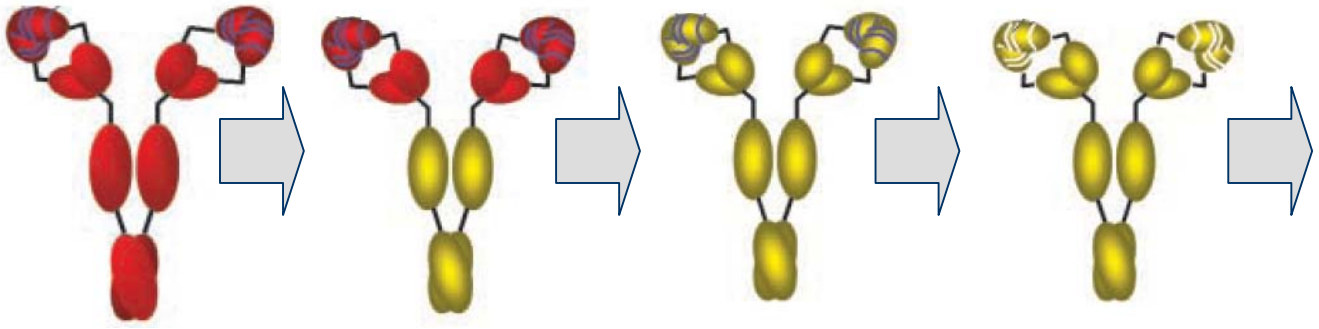
Figure 1 Number of therapeutic mAbs entering clinical study per year (1980–2004). Data are presented as two-year moving averages.

Reichert J et al: Monoclonal antibody successes in the clinic. Nature Biotechnol.23(9): 1073 (2005)

Evolution of monoclonal antibodies

Evolution of monoclonal antibodies („-mab“):

= murine
= human



Murine mAb	Chimaeric mAb	Humanized mAb	Fully Human mAb
„-omab“	„-iximab“	„-zumab“	„-umab“
Arcitumomab (CEA-Scan®) (1996)	Infliximab (Remicade®) (1999)	Trastuzumab (Herceptin®) (2000)	Adalimumab (Humira®) (2003)

New constructs
- bispecific antibodies
- diabodies
- single chain fragments
- engineered Fc mAbs
- conjugated mAbs
- ...

Immunogenicity

We have experience!

Table 1 US and EU therapeutic mAb approvals to date

Generic	Company/location	Trade	Description	Therapeutic category	Approval date
Muromonab-CD3	Johnson & Johnson New Brunswick, New Jersey	Orthoclone OKT3	Murine, IgG2a, anti-CD3	Immunological	06/19/86 (US)
Abciximab	Centocor	ReoPro	Chimeric, IgG1, anti-GPIIb/IIIa; Fab	Hemostasis	12/22/94 (US)
Rituximab	Genentech	Rituxan	Chimeric, IgG1κ, anti-CD20	Oncological	11/26/97 (US) 06/02/98 (EU)
Daclizumab	Hoffmann-La Roche Basel	Zenapax	Humanized, IgG1κ, anti-CD25	Immunological	12/10/97 (US) 02/26/99 (EU)
Basiliximab	Novartis Basel	Simulect	Chimeric, IgG1κ, anti-CD25	Immunological	05/12/98 (US) 10/09/98 (EU)
Palivizumab	MedImmune Gaithersburg, Maryland	Synagis	Humanized, IgG1κ, anti-respiratory syncytial virus	Anti-infective	06/19/98 (US) 08/13/99 (EU)
Infliximab	Centocor	Remicade	Chimeric, IgG1κ, anti-tumor necrosis factor (TNFα)	Immunological	08/24/98 (US) 08/13/99 (EU)
Trastuzumab	Genentech	Herceptin	Humanized, IgG1κ, anti-HER2	Oncological	09/25/98 (US) 08/28/00 (EU)
Gemtuzumab ozogamicin	Wyeth Madison, New Jersey	Mylotarg	Humanized, IgG4κ, anti-CD33; immunotoxin	Oncological	05/17/00 (US)
Alemtuzumab	Genzyme Cambridge, Massachusetts	Campath-1H	Humanized, IgG1κ, anti-CD52	Oncological	05/07/01 (US) 07/06/01 (EU)
Ibritumomab tiuxetan	Biogen Idec	Zevalin	Murine, IgG1κ, anti-CD20; radiolabeled (Yttrium 90)	Oncological	02/19/02 (US) 01/16/04 (EU)
Adalimumab	Abbott Deerfield Park, Illinois	Humira	Human, IgG1κ, anti-TNFα	Immunological	12/31/02 (US) 09/1/03 (EU)
Omalizumab	Genentech	Xolair	Humanized, IgG1κ, anti-IgE	Immunological	06/20/03 (US)
Tositumomab-I131	Corixa Seattle	Bexxar	Murine, IgG2aλ, anti-CD20; radiolabeled (Iodine 131)	Oncological	06/27/03 (US)
Efalizumab	Genentech	Raptiva	Humanized, IgG1κ, anti-CD11a	Immunological	10/27/03 (US) 09/20/04 (EU)
Cetuximab	Imclone Systems New York	Erbitux	Chimeric, IgG1κ, anti-Epidermal growth factor receptor	Oncological	02/12/04 (US) 06/29/04 (EU)
Bevacizumab	Genentech	Avastin	Humanized, IgG1, anti-vascular endothelial growth factor	Oncological	02/26/04 (US) 01/12/05 (EU)
Natalizumab[a]	Biogen Idec	Tysabri	Humanized, IgG4κ, anti-α4-integrin	Immunological	11/23/04 (US)

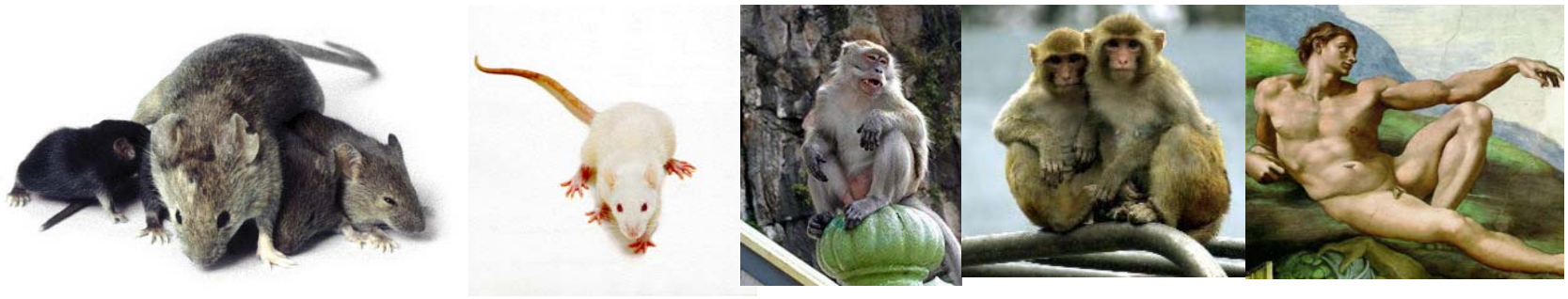
See **Box 1** for methodology.

[a]Voluntary suspension of natalizumab marketing announced February 28, 2005.

Reichert J et al: Monoclonal antibody successes in the clinic. Nature Biotechnol.23(9): 1073 (2005)

Non-clinical testing: A question of relevance

Central aspect: biotechnological products are species-specific.



A relevant species is one in which the test material is pharmacologically active due to the expression of the receptor or an epitope (in the case of monoclonal antibodies)*.

*NfG on preclinical safety evaluation of biotechnology derived pharmaceuticals (CPMP/ICH/302/95; ICH S6)

Relevant species for licensed mAbs described

Potency assays are available

Product	Specificity	Potency assay	Comments
Avastin (Bevacizumab)	Anti-VEGF	**anti-proliferation bioassay** (inhibition of rhVEGF-induced proliferation of Human Umbilical Vein Endotheliae Cells HUVEC). (relative number of viable cells, quantified by fluorescence)	Assay chosen as drug substance release test based on its sensitivity (ability to detect significant changes in the activity), robustness, precision (RSD<10%) and accuracy (98-102%)
Simulect (Basiliximab)	Anti-CD25	**Inhibition of binding** of radiolabelled IL-2 to IL-2 receptor expressed on T-lymphocytes (and thus inhibition of lymphocyte proliferation)	
Synagis (Palivizumab)	Anti-RSV	**In vitro:** RSV Microneutralisation Assay, RSV Fusion Inhibition Assay, BIAcore Analysis **In vivo potency:** Reduction of RSV titre in the lungs of infected cotton rats	Comparison of different predecessor products with palivizumab during development
Tysabri (Natalizumab)	Anti-α4-integrin	**In vitro assay:** Ability to bind α4-integrins and block its interaction with its co-receptor.	
Xolair (Omalizumab)	Anti-IgE	**Inhibition of binding:** Ability of omalizumab to inhibit binding of IgE to its receptor	Shown to correlate to the inhibition of release of histamine

Current methodology: Increasing sensitivity

- **Physicochemical characterisation, e.g.**
  - » **Capillary electrophoresis with laser-induced fluorescence detection (CE-LIF)**
  - » **Mass spectrometry techniques (e.g., MALDI-TOF)**
  - » **Nuclear magnetic resonance**
- **Antigen-antibody interaction, e.g.**
  - » **Surface plasmon resonance**
- **Secondary structure detection, e.g.**
  - » **Circular dichroism in near- and far-UV spectra**
- **Combination of methodologies, e.g.**
  - » **liquid chromatography combined with mass spectrometry**
    (e.g. Beck, A. et al, J Chromatogr B Analyt Technol Biomed Life Sci. 819(2): 203-218 (2005))

Licensed mAbs: Efficacy and safety

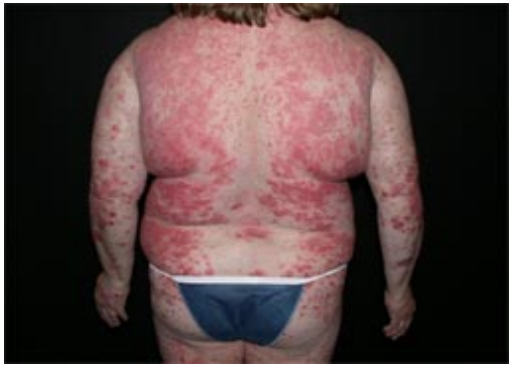
- **For example: Remicade® (Infliximab) (anti-TNFα)**

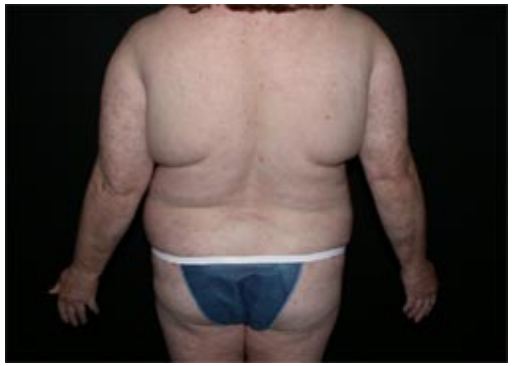
- **Licensed indications:**
  - **Rheumatoid arthritis**
  - **Adult Crohn‘s disease**
  - **Paediatric Crohn‘s disease**
  - **Ulcerative colitis**
  - **Ankylosing spondylitis**
  - **Psoriatic arthritis**
  - **Psoriasis**

http://www.emea.europa.eu/humandocs/Humans/EPAR/remicade/remicade.htm

Licensed mAbs: Efficacy and safety

- **For example: Moderate to severe psoriasis**





Before treatment **After treatment**

Summary of PASI response and PGA score at Weeks 10, 24 and 50. EXPRESS.

	Placebo → Infliximab 5 mg/kg (at week 24)	Infliximab 5 mg/kg
Week 10		
n	77	301
≥ 90% improvement	1 (1.3%)	172 (57.1%)[a]
≥ 75% improvement	2 (2.6%)	242 (80.4%)[a]
≥ 50% improvement	6 (7.8%)	274 (91.0%)
PGA of cleared (0) or minimal (1)	3 (3.9%)	242 (82.9%)[ab]
PGA of cleared (0), minimal (1), or mild (2)	14 (18.2%)	275 (94.2%)[ab]

http://www.emea.europa.eu/humandocs/Humans/EPAR/remicade/remicade.htm

Licensed mAbs: Efficacy and safety

- **Safety data in 2005:**

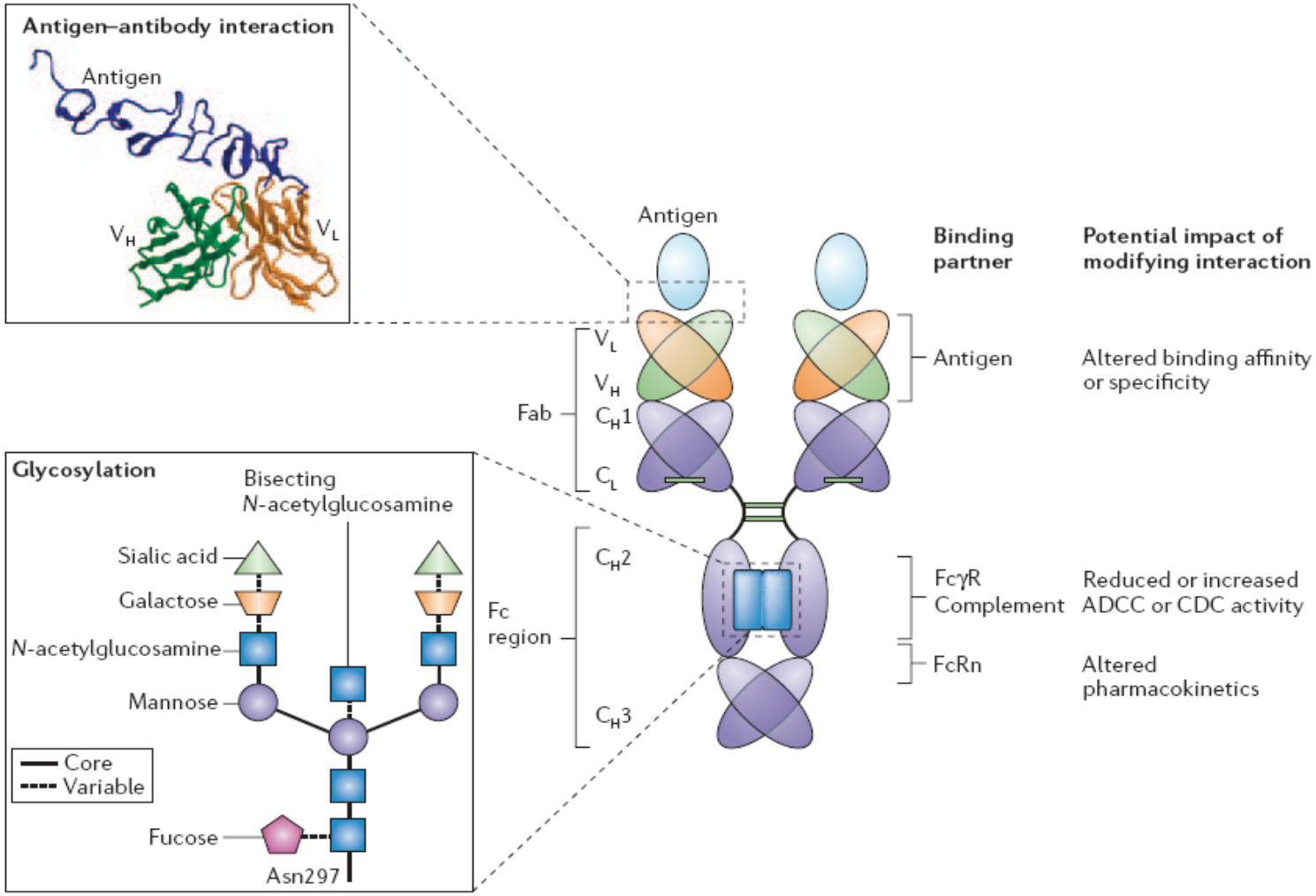
  - **TREAT-Registry (only patients with Crohn‘s disease)** (Crohn’s **T**herapy **R**esource **E**valuation and **A**ssessment **T**ool registry)
    - 6290 patients, 3235 of them treated with Remicade
    - Ca. 25.000 Infusions

  - **Cumulative safety data (August 1998 – August 2004):**
    - 1.350.000 Patient years
    - 576.000 Patients

Toward biosimilar mAbs

…and Con‘s

Complexity of monoclonal antibodies



Carter PJ: Potent antibody therapeutics by design, Nature Rev Immunol 6, 343 (2006)

Glycosylation of mAbs

REPORTS

Anti-Inflammatory Activity of Immunoglobulin G Resulting from Fc Sialylation

Yoshikatsu Kaneko,* Falk Nimmerjahn,* Jeffrey V. Ravetch†

Immunoglobulin G (IgG) mediates pro- and anti-inflammatory activities through the engagement of its Fc fragment (Fc) with distinct Fcγ receptors (FcγRs). One class of Fc-FcγR interactions generates pro-inflammatory effects of immune complexes and cytotoxic antibodies. In contrast, therapeutic intravenous gamma globulin and its Fc fragments are anti-inflammatory. We show here that these distinct properties of the IgG Fc result from differential sialylation of the Fc core polysaccharide. IgG acquires anti-inflammatory properties upon Fc sialylation, which is reduced upon the induction of an antigen-specific immune response. This differential sialylation may provide a switch from innate anti-inflammatory activity in the steady state to generating adaptive pro-inflammatory effects upon antigenic challenge.

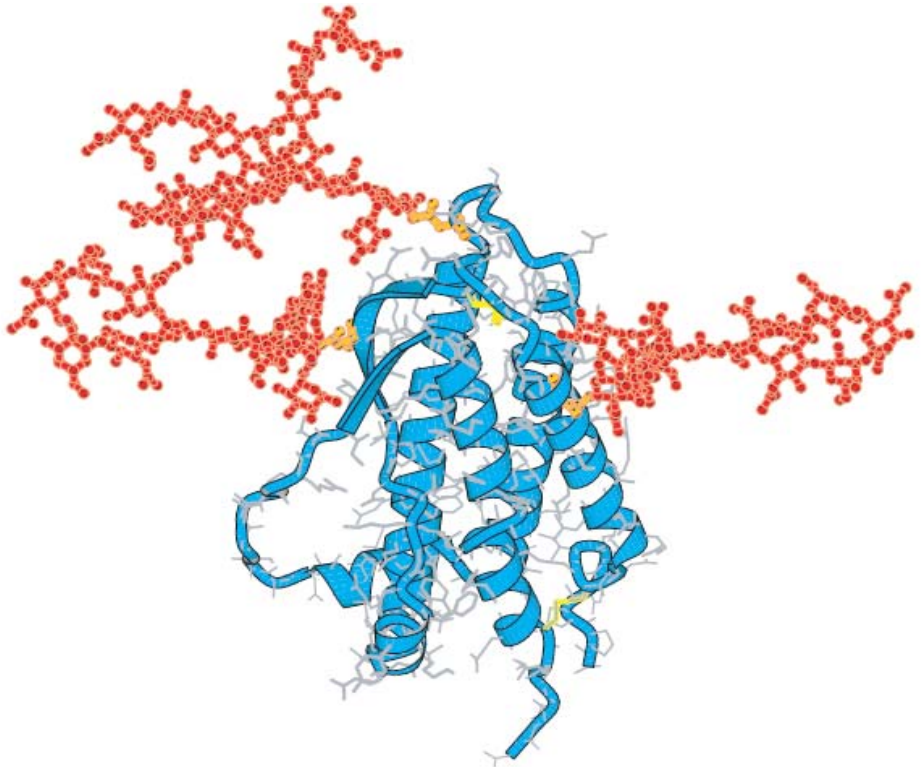
4 AUGUST 2006 VOL 313 **SCIENCE** www.sciencemag.org

Glycosylation

Commercial interest grows in glycan analysis

Cormac Sheridan, Dublin

VOLUME 25 NUMBER 2 FEBRUARY 2007 NATURE BIOTECHNOLOGY

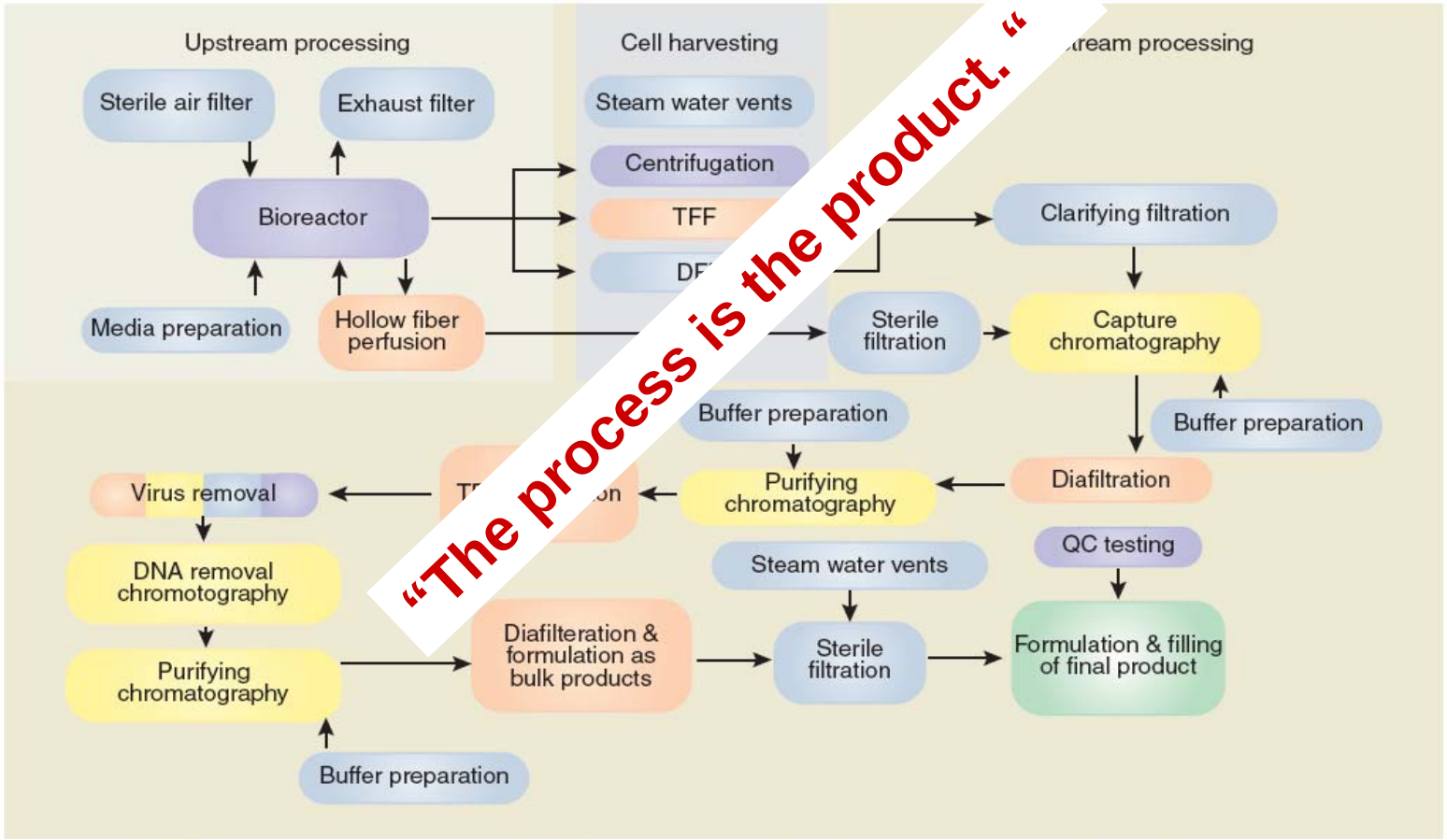


Courtesy of M.R. Wormald and R.A. Dwek, Oxford Glycobiology Institute, and P.M. Rudd, NIBRT

Molecular model of erythropoietin with complex N-linked glycans at sites N24, N38 and N83. The glycan-protein linkages are likely to exhibit considerable flexibility; the structure shown is just one possible conformation.

Complexity of monoclonal antibodies

Typical antibody manufacturing process



Carson KL. Flexibility – The guiding principle for antibody manufacturing. Nature Biotechnol 23(9): 1054 (2005)

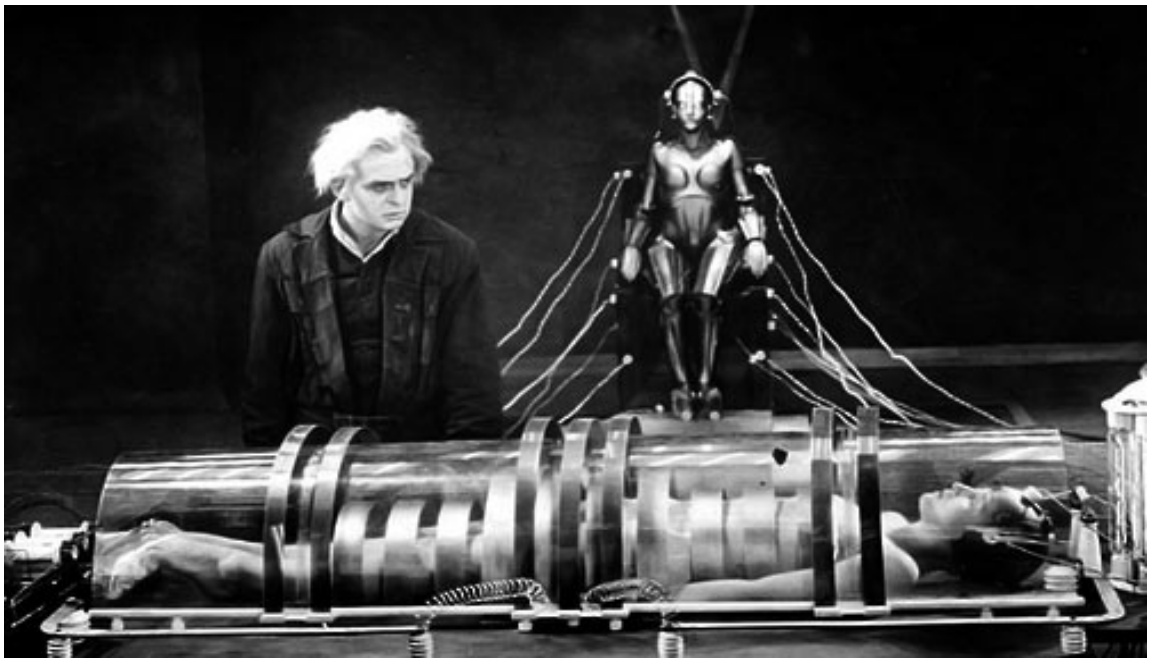
Current methodology: Increasing sensitivity

- Physicochemical characterisation.
  - » Capillary electrophoresis wi[illegible]nduced fluorescence detection (CE-LIF)
  - » Mass spectrometry te[illegible]s (e.g., MALDI-TOF)
  - » Nuclear magnetic r[illegible]ce
- Antigen-antibody i[illegible]on, e.g.
  - » Surface plas[illegible]sonance
- Secondary s[illegible]e detection, e.g.
  - » Circu[illegible]roism in near- and far-UV spectra
- Comb[illegible] of methodologies, e.g.
  - » [illegible]chromatography combined with mass spectrometry

(e.g. [illegible], A. et al, J Chromatogr B Analyt Technol Biomed Life Sci. 819(2): 203-218 (2005))

Are these sensitive enough?

Biosimilar mAbs: Signs or fiction?



Are obviously approaching?!

EMEA Workshop

- Philosophy: Open discussion on pros and cons of biosimilar mAbs
- Possibility and feasibility
- No conclusion (yet)…
  …but scientific evolution
- Questions as a starting point
- Focussed presentations, not meant to be exhaustive, but to initiate discussions.
- If issues come up that are important, but do not fit to the topic of session: Move to end of workshop (where there should be time)

The floor is yours!