# Monoclonal antibody biosimilars: robustness of products vs clinical experience

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## Disclosure

Håkan Mellstedt has received honoraria from Abbvie, Amgen, Bio-Sweden, Boeringer-Ingelheim, Hospira, Roche and research grants from Merck GmBH.

Håkan Mellstedt has served on ad hoc SAB for Abbive, Amgen, Boeringer-Ingelheim, Hospira

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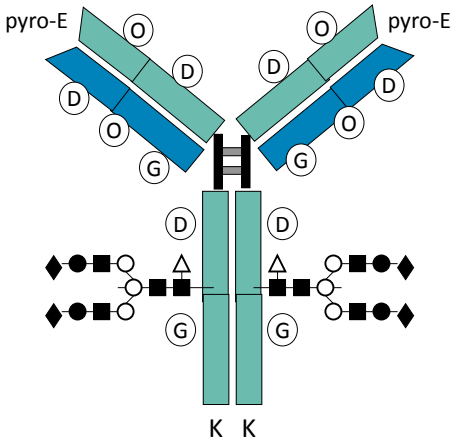
# The structure of monoclonal antibodies is highly complex

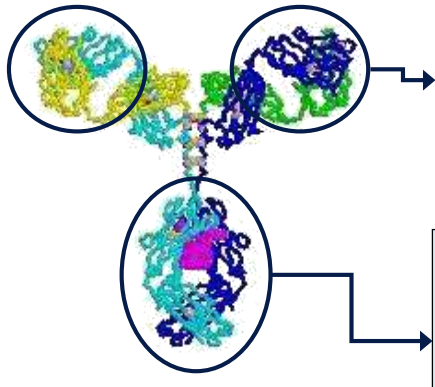



$(9600)^2 \approx 10^8$
potential variants

- Pyro-Glu (2)
- Deamidation (3 x 2)
- Methionine oxidation (2 x 2)
- Glycation (2 x 2)
- High mannose, G0, G1, G1, G2 (5)
- Sialylation (5)
- C-term Lys (2)
- 2 x 6 x 4 x 4 x 5 x 5 x 2 = 9600

**Adapted from:** ***Steven Kozlowski; FDA***

# Monoclonal antibodies: Multifunctional molecules



**Fab region**

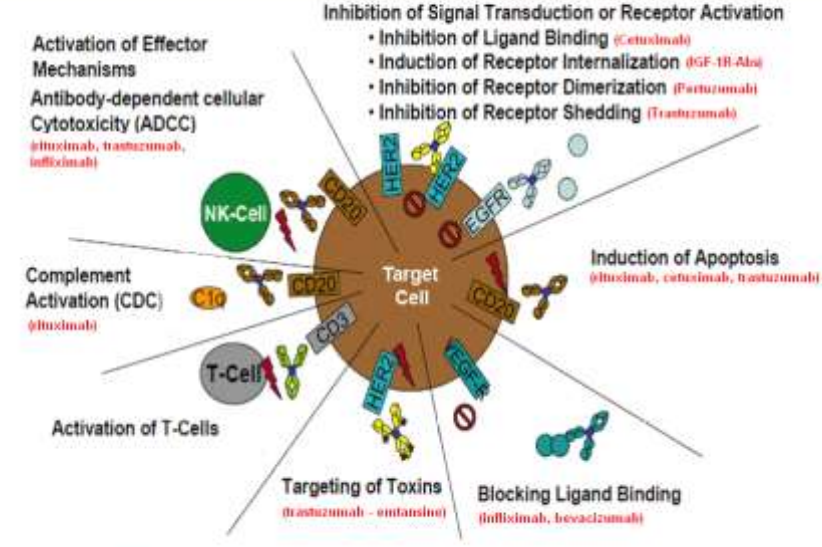
Selected for optimum target-mediated effects (light chain and heavy chain variable binding domains)

**Fc region**

- Different isotypes with different effector functions
- Contains 2 glycosylation sites (1 in each of the 2 chains)

**All parts contribute to the efficacy and safety in a cooperative way**

## Antibodies have different modes of actions



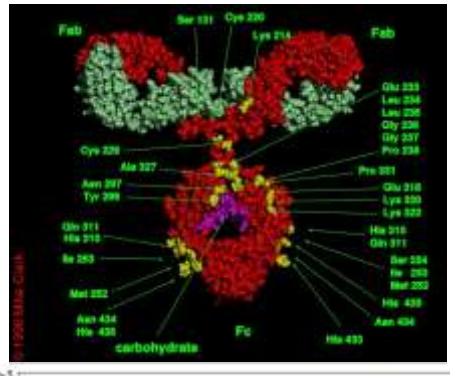

Modified from: Hasmann M, et al. (2009)

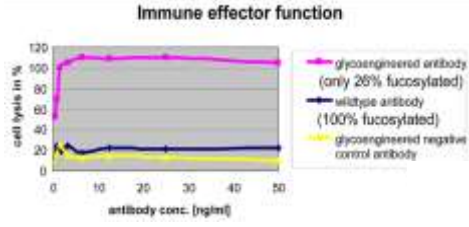
## Small Glycosylation Differences May Have Significant Effects on Immune Effector Functions

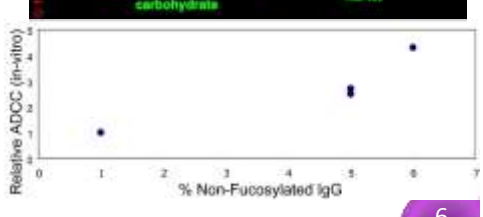
Both amino acid sequence and glycosylation pattern of $C_H2$ influence FcR binding and ADCC activity

The presence or absence of one fucose residue can affect the biological activity (killing of target cells via ADCC)

Even very small differences in fucosylation may have significant effects on in vitro ADCC

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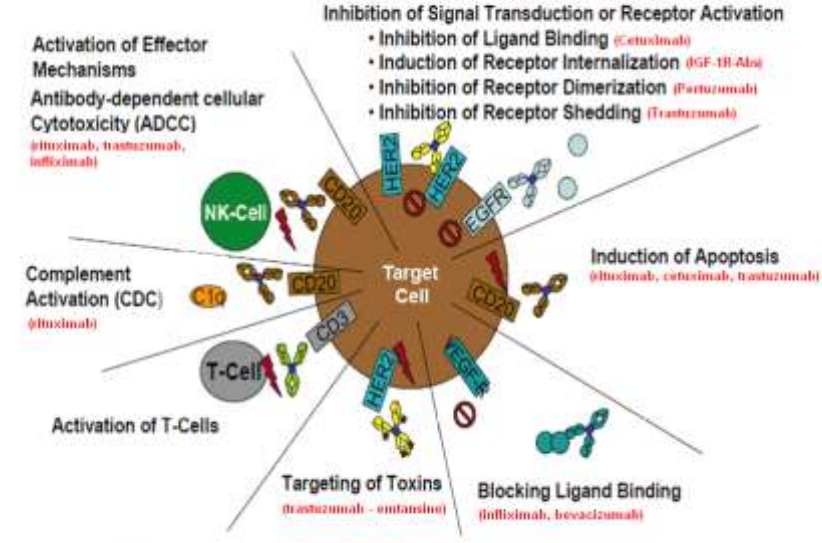
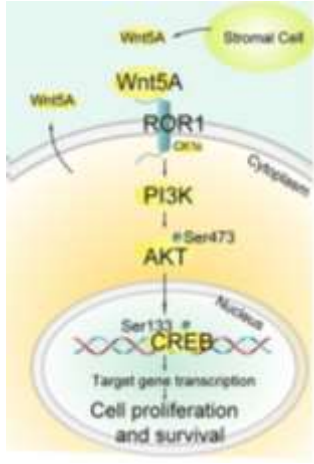
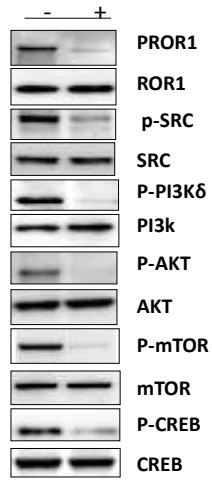
# Antibodies have different modes of actions




Modified from: Hasmann M, et al. (2009)

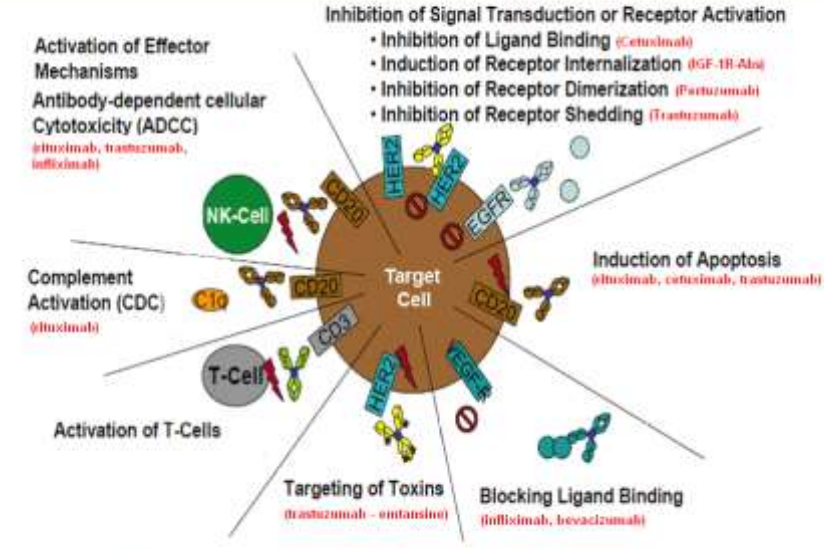
## Anti-ROR1 MAb (Kancera) - intervened in the non-canonical Wnt signaling pathway




Amir DaneshManesh et al, Brit J Hematol, 2014 Nov 19. doi: 10.1111/bjh.13228

## Antibodies have different modes of actions

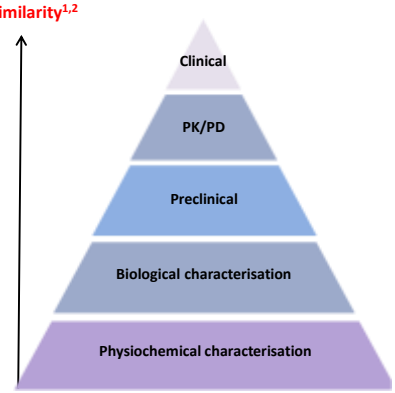



Modified from: Hasmann M, et al. (2009)

## Principles of biosimilarity

**Stepwise approach**

**Demonstration of Biosimilarity[1,2]**




Entire biosimilar process is built on a solid foundation of **extensive** analytical characterization which is **robustly assessed**

Principles of biosimilar comparability exercise are based on the evaluation of the impact of changes in the manufacturing process (ICH Q5E)[2]

1. EMA website. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000408.jsp Accessed 01 July 2013.
2. ICH Q5E: Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process. Available at: http://www.fda.gov/OHRMS/DOCKETS/98fr/2004d-0118-gdl0001.pdf. Accessed 01 July 2013.

# Typical physiochemical biosimilarity exercise

**Primary Structure**
Peptide map
Amino acid sequence
Total mass analysis
Disulfide bonds
Free sulfhydryls

**Higher Order Structure**
FTIR
Far UV
Near UV
DSC

**Purity**
SE-HPLC
CE-SDS
SDS-PAGE
AUC
MALS
Deamidation
Oxidation

**Potency**
Binding affinity (ELISA/SPR)
Cell based assay
Apoptosis
ADCC
C1q binding
CDC
FcγRI binding
FcγRII binding
FcγRIII binding
FcRn binding

**Glycosylation**
N-linked glycans
Oligosaccharide profile
Monosaccharide analysis
Sialic acid analysis

**Charge variants**
Cation exchange HPLC
Ion exchange HPLC

Biosimilars Testing Services. Available at: http://www.intertek.com/pharmaceutical/biopharmaceutical-research/biosimilars/ Accessed 01 July 2013.

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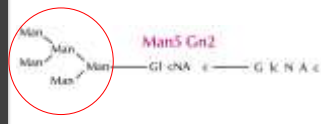
# Comparability of pharmaceutical quality determining functional characteristics

- Similarity of functional aspects deduced from comparability of corresponding quality attributes

- N- Glycosylation


- Amounts of nonfucosylated oligosaccharides → Antibody-Dependent Cell-Mediated Cytotoxicity
- Portion of G2 glycan → Complement Dependent Cytotoxicity




- Content of high mannose oligosaccharides → PK profile (clearance)

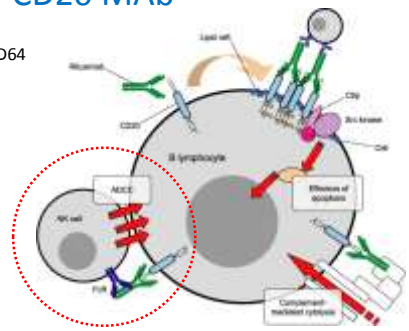
- Aggregate Levels  → Immunogenicity

*Goetze et al. High-mannose glycans on the Fc region of therapeutic IgG antibodies increase serum clearance in humans. Glycobiology. 2011 Jul;21(7):949-59*
*Peipp et al. Antibody fucosylation differentially impacts cytotoxicity mediated by NK and PMN effector cells. Blood. 2008 Sep 15;112(6):2390-9.*
*Eon-Duval et al. Quality attributes of recombinant therapeutic proteins: an assessment of impact on safety and efficacy as part of a quality by design development approach. Biotechnol Prog. 2012 May-Jun;28(3):608-22.*
*Shields et al. Lack of fucose on human IgG1 N-linked oligosaccharide improves binding to human Fcgamma RIII and antibody-dependent cellular toxicity. J Biol Chem. 2002 Jul 26;277(30):26733-40*

**Bernd Liedert, CDMA**

# A higher level of resolution – ADCC Antibody-Dependent Cell-Mediated Cytotoxicity as exemplified by anti-CD20 MAb

- Mediated by effector cells including NK cells, granulocytes and macrophages: Interactions with CD16 (FcγRIII), CD32 (FcγRII), CD64 (FcγRI)
- CD16 has an allelic variation
- CD16 homozygous for valine at 158 (VV) has a higher affinity for Rituximab (IgG1) than does CD16 with phenylalanine at that position (VF or FF)



- In FL (monotherapy) and DLBCL (CHOP combi) patients carrying the VV genotype have a better clinical response than patients that are VF or FF
- But: Predictivity of CD16 polymorphisms not clear for
  CLL: reduced expression of CD20 on the neoplastic CLL cells ?
  FL treated with Rituximab plus CHOP: Negative impact of chemo on NK activity ?

*Cartron et al. Therapeutic activity of humanized anti-CD20 monoclonal antibody and polymorphism in IgG Fc receptor FcgammaRIIIa gene. Blood 2002;99(3):754–8.*
*Farag et al. Fc gamma RIIIa and Fc gamma RIIa polymorphisms do not predict response to rituximab in B-cell chronic lymphocytic leukemia. Blood 2004;103(4):1472–4.*
*Carlotti et al. FcgammaRIIIA and FcgammaRIIA polymorphisms do not predict clinical outcome of follicular non-Hodgkin's lymphoma patients treated with sequential CHOP and rituximab. Haematologica 2007;92(8):1127–30*



# Clinical efficacy in oncology – Monoclonal antibodies

Compared with growth factors, mAbs are more complex[1]

- Similarities and comparability to the innovator biologicals will be more difficult to assess

Which endpoints should be evaluated for mAbs?

| | mAbs |
|---|---|
| Clinical endpoints | • ORR according to guideline.<br>• PFS more reliable. |

- Which patient population?
  - The most sensitive (efficacy, safety, immunogenicity)

ESA, erythropoiesis-stimulating agent; ANC; absolute neutrophil count; Hb, haemoglobin

1. Mellstedt H. *Future Oncol* 2010;6:1065–1067. 2. EMA annex to guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical Issues - Guidance on biosimilar medicinal products containing recombinant granulocyte-colony stimulating factor. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003955.pdf. 3. EMA annex to guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues - Guidance on similar medicinal products containing recombinant erythropoietins. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/04/WC500089474.pdf.

# Phase I/IIb Trial Comparing Herceptin and its Biosimilar CT-P6 in MBC: Results

- **Multicenter trial: Korea, Russia, Ukraine, Latvia, Serbia**

| Parameter | Treatment | N | Geometric mean | % CV | Ratio (%) | 90% CI | *P* value |
|---|---|---|---|---|---|---|---|
| $AUC_{SS}$ (µgh/mL) | CT-P6 | 48 | 32,000 | 43.5 | 104.57 | 93.64, 116.78 | .5029 |
| | Herceptin | 49 | 30,600 | 30.9 | | | |
| $C_{trough\ SS}$ (µg/mL) | CT-P6 | 51 | 19.5 | 37.0 | 101.35 | 87.94, 116.82 | .8754 |
| | Herceptin | 49 | 19.2 | 39.6 | | | |

**Conclusions of the study:**

- **CT-P6 demonstrated equivalent PK profile to Herceptin**
- **CT-P6 well tolerated with a comparable safety profile to Herceptin**
- **(infusion-related reaction, cardiotoxicity, and infection)**

Im Y, et al. Presented at 13th St Gallen International Breast Cancer Conference; 13-16 March 2013; St Gallen, Switzerland. Poster 268.

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# Biosimilar monoclonal antibodies in oncology

Randomized first line study in metastatic breast cancer combining trastuzumab biosimilar (CT-P6) and paclitaxel

| MAb | No. of patients | ORR | TTR (months) | TTP (months) |
|---|---|---|---|---|
| Innovator trastuzumab | 231 | 62% | 1.38 | 12.5 |
| | | *NS* | *NS* | *NS* |
| Biosimilar trastuzumab | 244 | 57% | 1.38 | 11.1 |

Im et al. *J Clin Oncol* 2013;31(suppl): Abstr 629.

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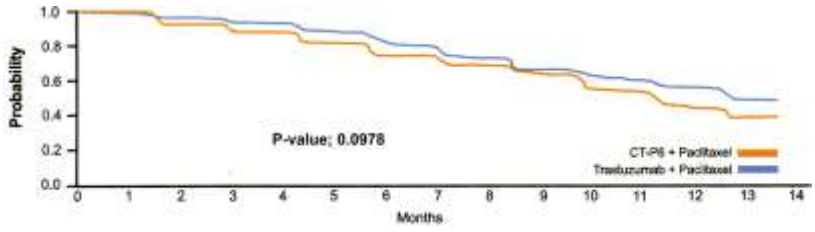
## Kaplan Meier plots of time to progression in the responder group of trastuzumab/paclitaxel compared to CT-P4 paclitaxel




Im et al, ASCO 2013, Chicago, USA poster

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## Key principles for extrapolation of indications (I)

- Clinical experience with the reference product
- Mechanism(s) of action/active site(s) of the active substance in each indication (including its degree of certainty)
- The degree to which the functional moieties of the molecule can be analytically characterized and compared
- Differences in the safety/immunogenicity profile between the therapeutic indications
- Acceptable clinical safety profile must have been established for the biosimilar

Weise M et al, Blood online October 8, 2014: doi10.1182/blood-2014-06-583617

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## Key principles for extrapolation of indications (II)

- Increased immunogenicity of the biosimilar must have been reasonably excluded
- Extrapolation of immunogenicity is only possible from high to low risk patient populations and clinical settings (e.g., from SC to IV route of administration or from immunocompetent to immunocompromised patients, but normally not vice versa)
- Additional tests or studies may be needed to further support extrapolation, e.g. relevant pharmacodynamic parameters and/or specific functional assays reflecting the pharmacological action(s) of the molecule; **clinical studies using outcome endpoints are usually less sensitive to detect potential differences between the biosimilar and the reference product**
- **TOTALITY OF THE EVIDENCE OF BIOSIMILARITY DERIVED FROM THE COMPARABILITY EXERCISE**

Weise M et al, Blood online October 8, 2014: doi10.1182/blood-2014-06-583617

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## Acceptability of biosimilar infliximab by gastroenterologists


SPECIAL ARTICLE

ECCO position statement: The use of biosimilar medicines in the treatment of inflammatory bowel disease (IBD)

Silvio Danese [a,*], Fernando Gomollon [b,**] on behalf of the Governing Board and Operational Board of ECCO

### 6. Conclusion

The overall position of ECCO is that the use of most biosimilars in patients with IBD will require testing in this particular patient population, with comparison to the appropriate innovator product. Although wider access to appropriate use of biological therapy in IBD and potential direct cost savings are important, rigorous testing is necessary in patients with IBD to ensure that appropriate efficacy and safety standards are met. Final clinical decisions should always be made on an individual basis, taking into account both circumstances of the individual patient and prescribing physician.

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## Comments on Extrapolation of Biosimilars

- Epoetin has a simple mechanism of action. Tested in a sensitive population. Extrapolation to oncology/hematology accepted.
- G-CSF has a simple mechanism of action. Extrapolation to certain indications still a matter of debate. Biosimilar G-CSF for mobilization of PBSC in healthy donors.
- Monoclonal antibodies complex MOA. Intensive debate among rheumatologists and oncologists/hematologists. Infliximab approved for all indications in Europe, Korea, Japan but not for IBD in Canada. What will happen with rituximab and trastuzumab is unclear.

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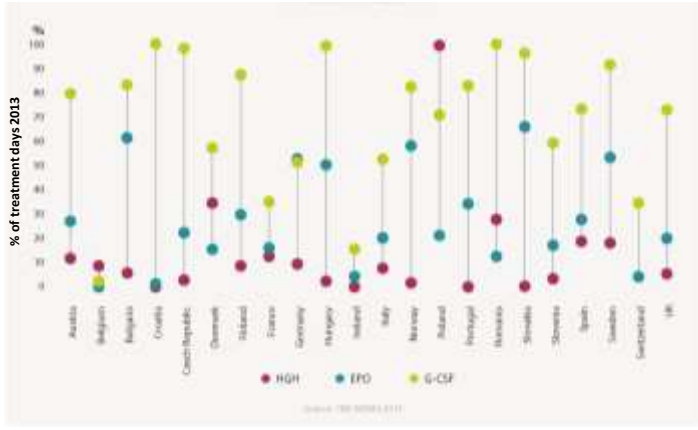
## Biosimilar Filgrastim Market Penetration




**Average up-take in Europe 2013, 90%.** (Igngatovic. www.datamonitorhealthcare.com)

www.imshealth.com/Assessing biosimilar uptake and competition in European markets 2014

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## Executive summary of monoclonal antibody biosimilars for health care providers

- The mode of action of monoclonal antibodies is multifactorial depending on the antibody and indication . The contribution of each function to the totality of the effect of a monoclonal antibody is not fully established.
- The monoclonal antibody product is pre-clinically highly well characterized using the latest advances in biotechnology.
- A rigorous approval process has been applied.
- Limited clinical information at approval with regard to clinical efficacy, immunogenicity and extrapolated indications.

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