# *"FARMACI INNOVATIVI, BIOTECNOLOGICI E TERAPIE STAMINALI: FARMACOLOGIA, FARMACOTERAPIA E NORMATIVE"*

Roma, 14 aprile 2015

## Biotecnologie: Farmacocinetica

**Cinzia Dello Russo**

# FARMACI BIOLOGICI

## Classificazione funzionale

| | |
|---|---|
| **Group I: protein therapeutics with enzymatic or regulatory activity** | |
| Ia | Replacing a protein that is deficient or abnormal |
| Ib | Augmenting an existing pathway |
| Ic | Providing a novel function or activity |
| **Group II: protein therapeutics with special targeting activity** | |
| IIa | Interfering with a molecule or organism |
| IIb | Delivering other compounds or proteins |
| **Group III: protein vaccines** | |
| IIIa | Protecting against a deleterious foreign agent |
| IIIb | Treating an autoimmune disease |
| IIIc | Treating cancer |
| **Group IV : protein diagnostics** | |

Leader B, Baca QJ, Golan DE. Protein therapeutics: a summary and pharmacological classification. Nat Rev Drug Discov. 2008; 7: 21-39.

# F. BIOLOGICI vs F. TRADIZIONALI

| Biologics | SMs |
|---|---|
| Large MW | Low MW |
| Complex physicochemical properties (e.g. tertiary structure, stability, PTM) | Mostly well defined physicochemical properties |
| Biological production process: heterogeneous | Chemical production process: homogeneous |
| Understanding of ADME still evolving | ADME tools are available/ extensive ADME understanding |
| Usually administered parenterally (IV, SC, and IM) | Oral administration often possible |
| Distribution usually limited to plasma and/ or extracellular fluids | Distribution to any combination of organs/tissues |
| Not metabolized by CYP enzymes; metabolized to peptides or amino acids | Mainly metabolized by CYP enzymes; metabolized to non-active and active metabolites |
| Rapid clearance and short $t_{1/2}$ | Mostly linear PK; non-linearity mainly due to saturation of metabolic pathways |
| High selectivity (affinity/ potency) | Generally less selective |
| Multi-functional: target binding, Fc effector function, FcRn binding | Off-target effects due to non-selectivity |
| PK and PD mechanistically connected (TMDD) | PK usually not driven by PD due to dominance of non-target mediated binding |
| DIs: sparse examples and mostly PD related | DIs: many examples and PK and/or PD related |
| Immunogenicity often observed | Immunogenicity rarely observed |
| Several bioanalytical assays (mostly LBA) | Usually specific chromatographic methods |

**SMs** = small molecules; **MW** = molecular weight; **PTM** = post-translational modifications; **ADME** = absorption, distribution, metabolism, and excretion; **IV** = intravenous; **SC** = subcutaneous; **IM** = intramuscular; **CYP** = cytochrome P450; $t_{1/2}$ = half-life; **FcRn**= neonatal Fc receptor; **PK** = pharmacokinetics; **PD** = pharmacodynamics; **TMDD**= target-mediated drug disposition; **DIs** = drug interactions; **LBA** = ligand binding assays.

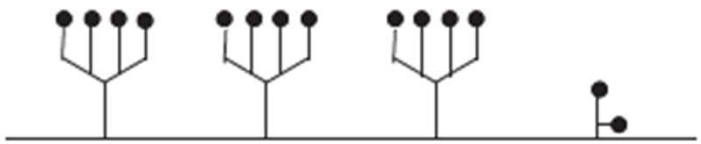
Shi S. Biologics: an update and challenge of their pharmacokinetics. Curr Drug Metab 2014; 15: 271-290.

# MODIFICAZIONI della SEQUENZA AMINOACIDICA

| | | | | | | | | | | AZIONE (ORE) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| SPECIE | Farmaci | Via | $A^{21}$ | $B^{23}$ | $B^{28}$ | $B^{29}$ | $B^{30}$ | $B^{31}$ | $B^{32}$ | Inizio | Picco | Durata |
| **Rapida** | | | | | | | | | | | | |
| Regolare (o Zn cristallina) | ACTRAPID® HUMULIN-R® | SC | Asn | Asn | Pro | Lys | Thr | | | 30-60’ | 2-3 | 6-8 |
| Lispro | HUMALOG® | SC | | | Lys | Pro | | | | 10-15’ | 1-2 | 5-6 |
| Aspart | NOVORAPID NOVOLET® NOVORAPID PENFILL® | SC | | | Asp | | | | | 10-15’ | 1-2 | 5-6 |
| Glulisina | APIDRA® | SC | | Lys | | Glu | | | | ------ | 0.5-1.5 | 1-2.5 |
| **Intermedia** | | | | | | | | | | | | |
| Isofano (NPH)* | HUMULIN N® PROTOPHANE® | SC | | | | | | | | 1-2 | 4-10 | 10-16 |
| Lenta (sospensione Zn-insulina) | MONOTARD® | SC | | | | | | | | 1-3 | 4-12 | 12-18 |
| **Lunga** | | | | | | | | | | | | |
| Ultralenta | ULTRATARD® | SC | | | | | | | | 4-6 | 8-16 | 18-24 |
| Glargine | LANTUS® | SC | Gly | | | | | Arg | Arg | 2-4 | NO | >24 |
| Detemir | LEVEMIR® | SC | | | | Lys-Ac Mir | Del-Thr | | | 2-3 | 6-8 | ≤ 20 |

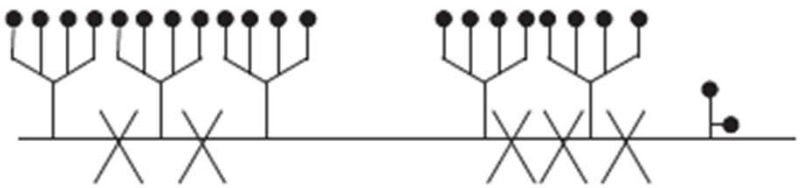
# MODIFICAZIONI POST-TRADUZIONALI: GLICOENGENEERING

**Epoetin**



- 3 N-linked carbohydrate chains
- ≤14 sialic acid residues
- 30 400 Da
- 40% carbohydrate

**Darbepoetin alfa**



- 5 N-linked carbohydrate chains
- ≤22 sialic acid residues
- 37 100 Da
- 52% carbohydrate

Macdougall IC, Eckardt KU. Novel strategies for stimulating Erythropoiesis and potential new treatments for anaemia. Lancet. 2006; 368(9539): 947-953.

# MODIFICAZIONI POST-TRADUZIONALI: GLICOENGENEERING

**Table I.** Some key parameters of erythropoiesis-stimulating agents[20,24,30-37]

| | Epoetin-α | Epoetin-β | Epoetin-ω | Darbepoetin-α |
|---|---|---|---|---|
| Carbohydrate proportion (%) | 40 | 40 | ND | 52 |
| Number of N-linked carbohydrates | 3 | 3 | 3 | 5 |
| Number of sialic acid residues per molecule | ≤14 | ≤14 | ND | ≤22 |
| Proportion of tetra-sialylated carbohydrate residues (%) | 19 | 46 | 21; 50[a] | ND |
| Proportion of isoforms with O-linked carbohydrates (%) | 95 | ND | 60 | ND |
| Half-life (h): | | | | |
| IV route | 4–11 | 8.8–10.4 | ND | 18–25.3 |
| SC route | 19–25.3 | 24 | ND | 48.8 |
| Clearance (IV route) [mL•h$^{-1}$•kg$^{-1}$] | 8.1–8.6 | 7.9 | ND | 2.0 |
| Bioavailability (SC route) [%] | 30–36 | 15–50 | ND | 37 |
| Frequency of administration (×/week) | 1–3 | 0.5[b]–3 | 1–2 | 0.5[b]–1 |
| Relative potency[c]: | | | | |
| thrice weekly | 1 | 1–1.2 | ~1.3 | 3.6 |
| once weekly | 1 | ND | ND | 13–20 |
| Conversion factor | 1 | ND | ND | 200IU : 1μg (up to 433 : 1[d]) |

a Divergent reports.[30,33]

b 0.5×/week = once every 2 weeks.

c As assessed from animal studies.

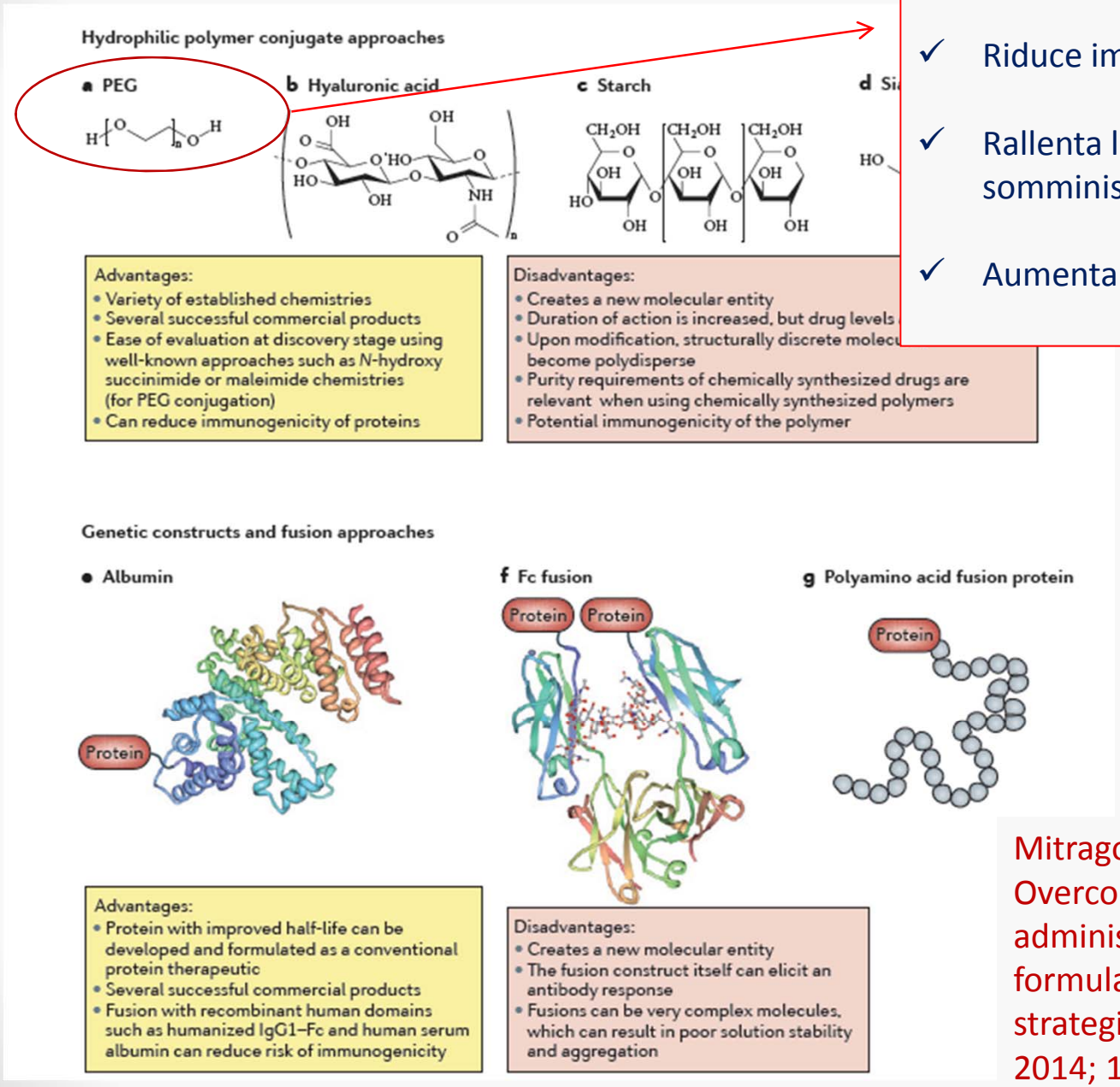
d Depending on dose of epoetin-α (up to 33 999 U/week).

**IV** = intravenous; **ND** = no data; **SC** = subcutaneous; ×/**week** = times per week.

Deicher R, Hörl WH. Differentiating factors between erythropoiesis-stimulating agents: a guide to selection for anaemia of chronic kidney disease. Drugs. 2004;64(5):499-509

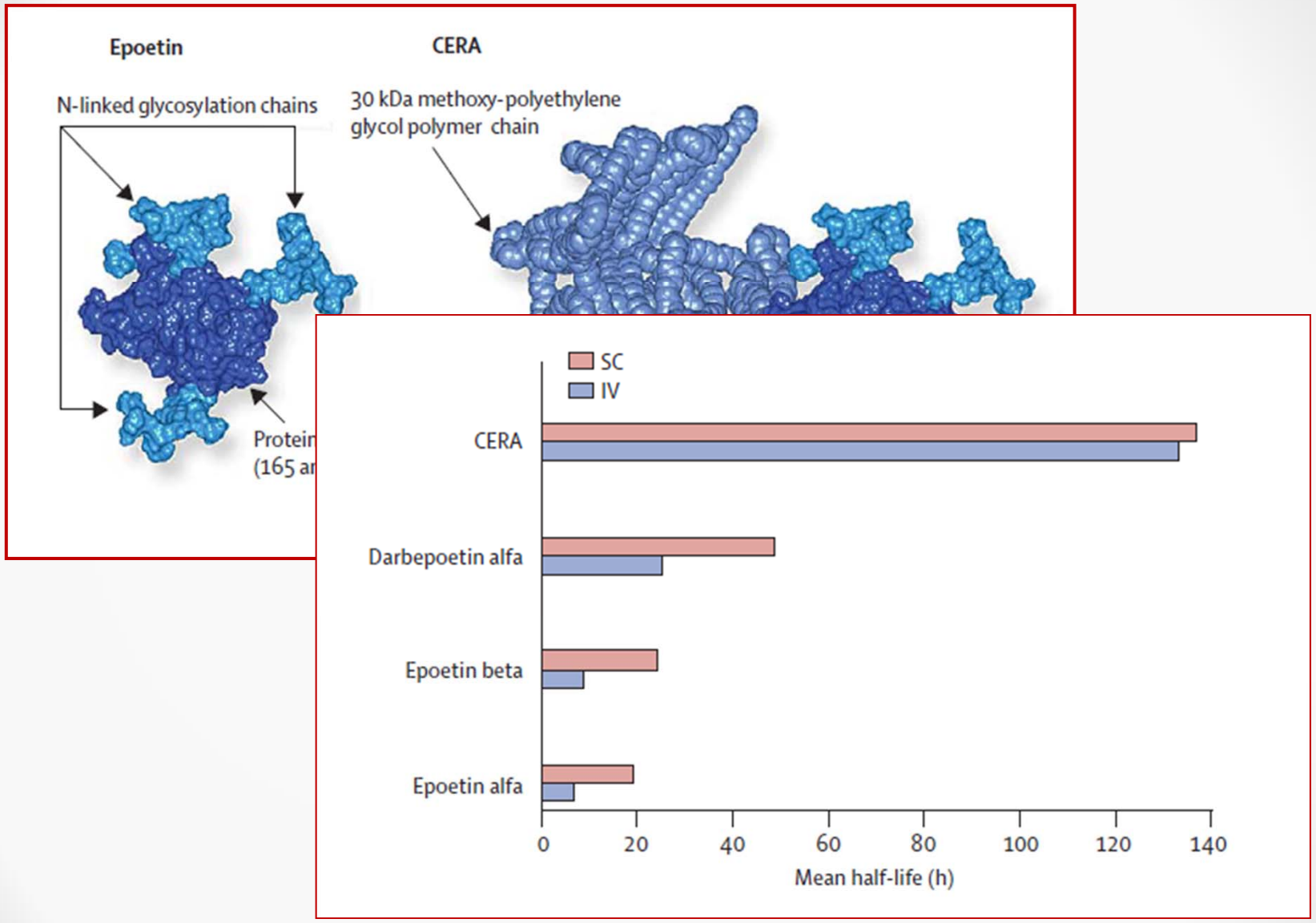
# ALTRE MODIFICAZIONI STRUTTURALI

- ✓ Migliora solubilità e stabilità
- ✓ Riduce immunogenicità e proteolisi
- ✓ Rallenta la clearance dall'organismo, somministrazioni meno frequenti
- ✓ Aumenta gli effetti clinici



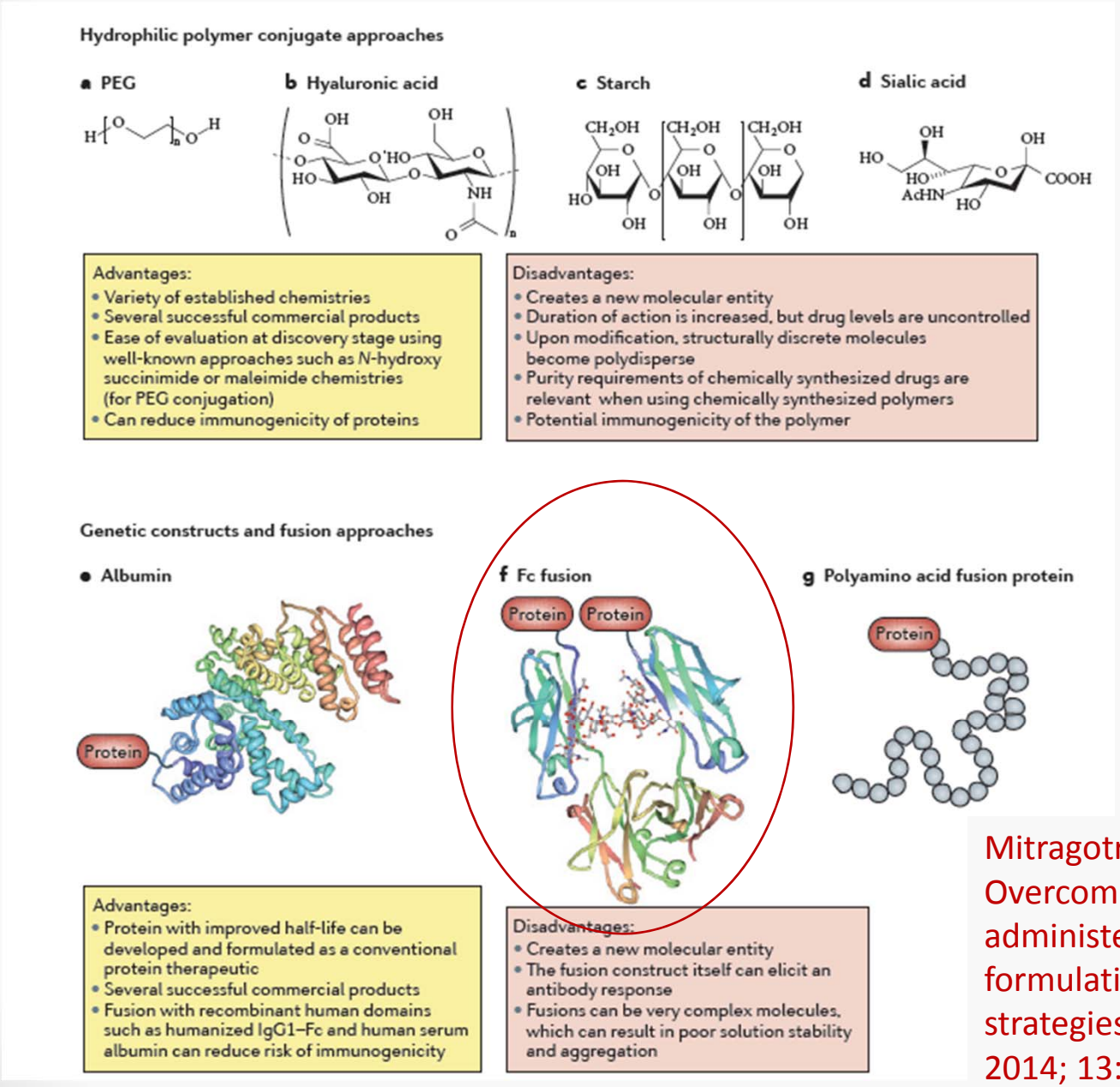

Mitragotri S, Burke PA, Langer R. Overcoming the challenges in administering biopharmaceuticals: formulation and delivery strategies. Nat Rev Drug Discov. 2014; 13: 655-672.

# PEGHILAZIONE DI PROTEINE TERAPEUTICHE




Macdougall IC, Eckardt KU. Novel strategies for stimulating Erythropoiesis and potential new treatments for anaemia. Lancet. 2006; 368(9539): 947-953.

# ALTRE MODIFICAZIONI STRUTTURALI




Mitragotri S, Burke PA, Langer R. Overcoming the challenges in administering biopharmaceuticals: formulation and delivery strategies. Nat Rev Drug Discov. 2014; 13: 655-672.

# Proteine di fusione con la porzione Fc di IgG

| Parent drug | Drug | Indication | Commercial Stage |
|---|---|---|---|
| TNF receptor 2 (TNFR75) | Etanercept (Enbrel) | Rheumatoid arthritis, ankylosing spondylitis, polyarticular juvenile idiopathic arthritis, psoriatic arthritis, plaque psoriasis | Approved 1998 |
| LFA-3 | Alefacept (Amevive) | Severe chronic plaque psoriasis | Approved 2003 |
| CTLA-4 | Abatacept (Orenica) | Rheumatoid arthritis, juvenile idiopathic arthritis, psoriasis | Approved 2005 |
| IL-1R | Rilonacept (Arcalyst) | Cryopyrin-associated periodic syndromes | Approved 2008 |
| Thrombopoietin binding peptide | Romiplostim (NPlate) | Chronic idiopathic thrombocytopenia purpura | Approved 2008 |
| VEGFR 1 + 2 | Aflibercept (Eylea); ziv-aflibercept (Zaltrap) | Wet age-related macular degeneration; metastatic colorectal cancer | Approved 2011, 2012 |
| CTLA-4 | Belatacept (Nulojix) | Prophylaxis of organ rejection in adults receiving a kidney transplant | Approved 2011 |
| Factor IX | rFIXFc (Alprolix) | Hemophilia B | Approved March 2014 |
| Factor VIII | rFVIII-Fc (Eloctate) | Hemophilia A | Approved June 2014 |
| sIL-4R | Altrakincept (Nuvance) | Asthma | Phase III |
| Angiopoietin 1 and 2 binding peptide | Trebananib (AMG386) | Cancer (various) | Phase III |
| B cell activating factor | Blisibimod, A-623 | Systemic lupus erythematosus | Phase III |
| TNFR55 | Lenercept | Rheumatoid arthritis, severe sepsis | Phase III |
| Tumor necrosis factor receptor superfamily member 13B (TACI) | Atacicept | Systemic lupus erythematosus; multiple sclerosis | Phase II/III |
| VEGFR 1 + 2 | KH902 | AMD-associated choroidal neovascularization | Phase II |

Mitragotri S, Burke PA, Langer R. Overcoming the challenges in administering biopharmaceuticals: formulation and delivery strategies. Nat Rev Drug Discov. 2014; 13: 655-672.

# ROMIPLOSTIM

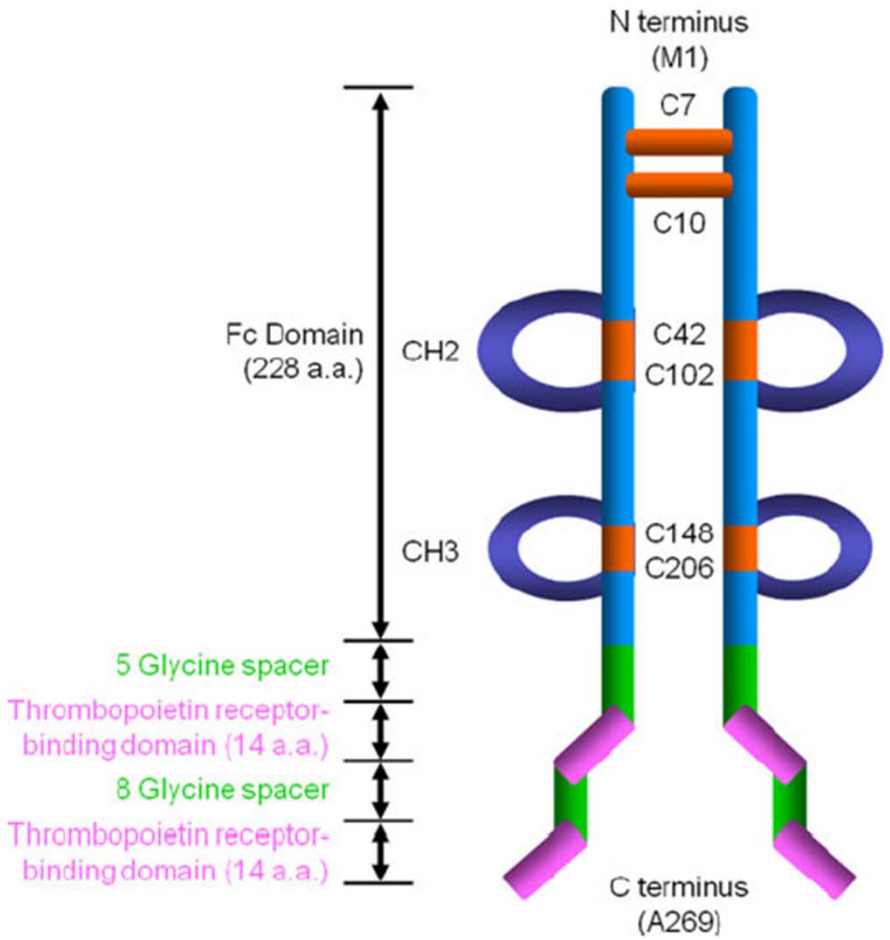


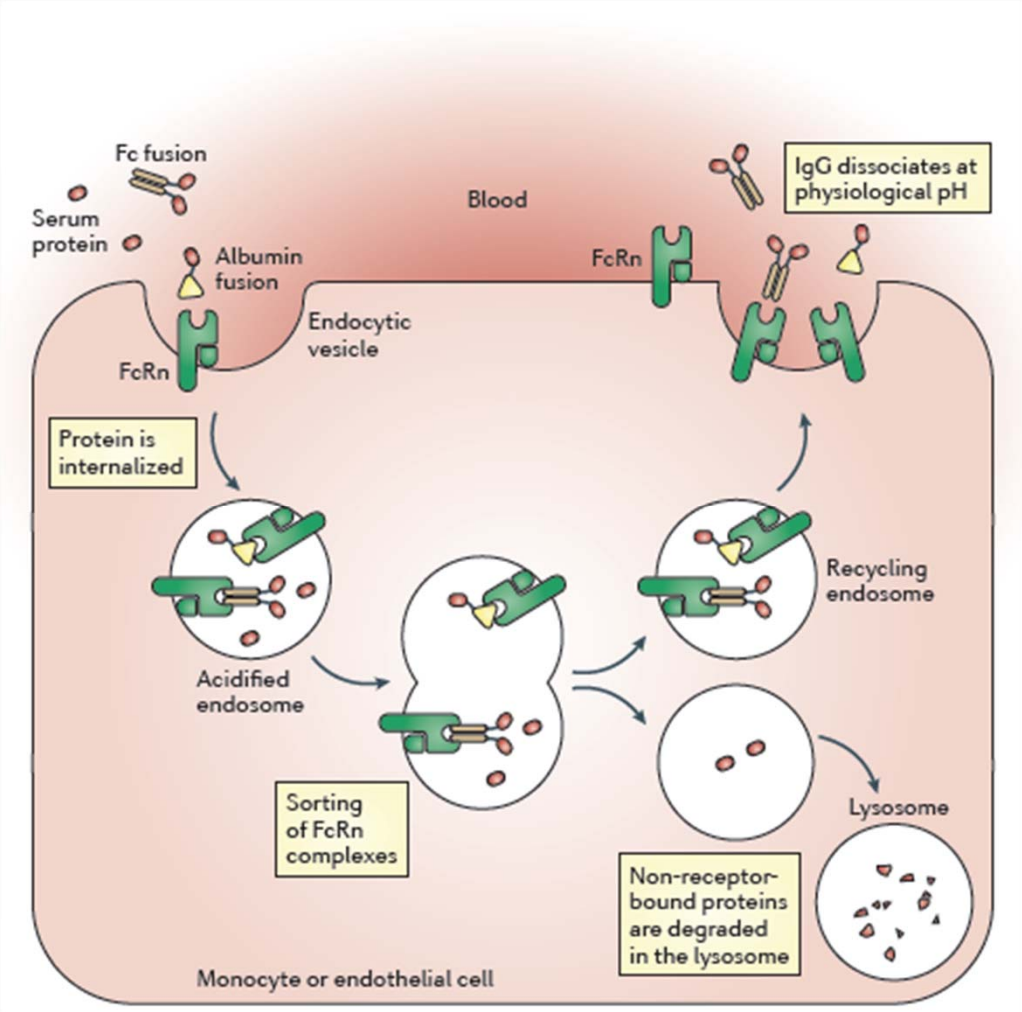

**Fig. 3** Romiplostim structure. Into each arm of the IgG heavy chain are inserted two identical 14-amino acid peptides with the sequence **IEGPTLRQWLAARA** [66]. Glycine linker regions are also shown [66]

Kuter DJ. The biology of thrombopoietin and thrombopoietin receptor agonists. Int J Hematol. 2013; 98:10-23.

**Table 2** Romiplostim: pharmacological aspects [70]

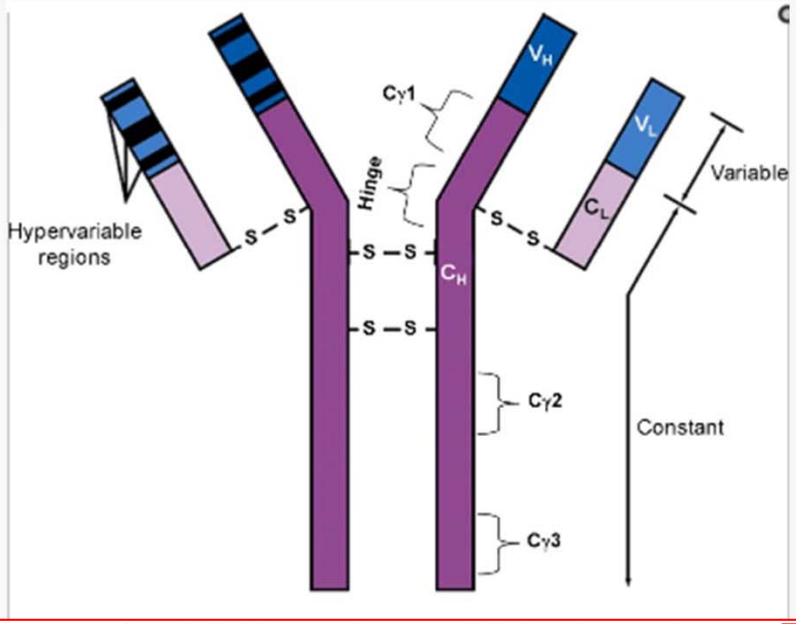
| |
|---|
| Recycled by FcRn on endothelial cells |
| Terminally cleared by reticuloendothelial system |
| T1/2 = 120–140 h |
| Effects of intravenous and subcutaneous (SQ) administration are the same |
| Not formulated for intravenous use |
| No known effect of renal or hepatic dysfunction |
| Not for use in pregnancy |
| Formulation |
| Vials of 250 (375) and 500 (625) µg that are reconstituted with normal saline |
| Dosage in ITP |
| Starting dose: 1 µg/kg SQ weekly |
| Subsequent dose per platelet count: 1–10 µg/kg SQ weekly |

# FcRn: a ‘recycling mechanism’




Mitragotri S, Burke PA, Langer R. Overcoming the challenges in administering biopharmaceuticals: formulation and delivery strategies. Nat Rev Drug Discov. 2014; 13: 655-672.

# STRUTTURA E FUNZIONE degli anticorpi




Bumbaca D, Boswell CA, Fielder PJ, Khawli LA. Physiochemical and biochemical factors influencing the pharmacokinetics of antibody therapeutics. AAPS J. 2012; 14: 554-558.

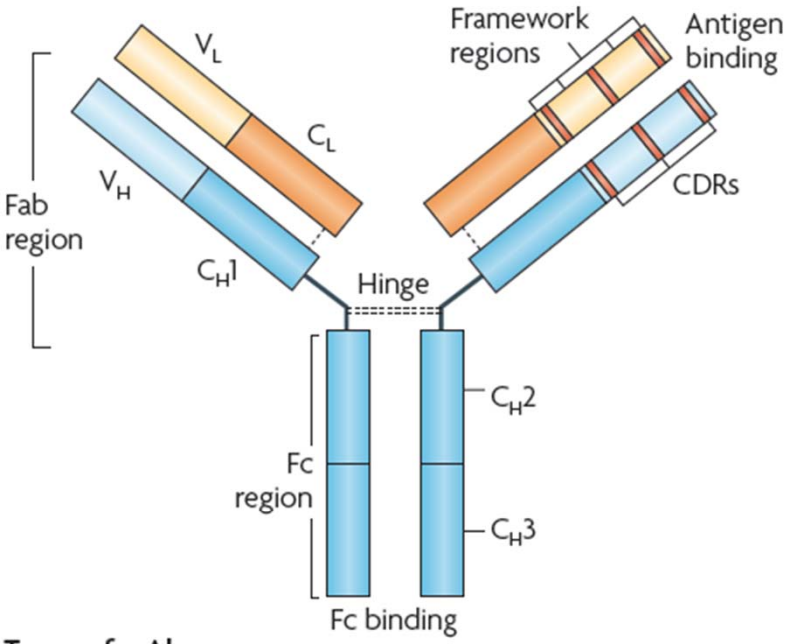
**Table 3.** Characteristics of the Human Immunoglobulin Isotypes*

| | IgA | IgD | IgE | IgG | IgM |
|---|---|---|---|---|---|
| Molecular weight | 160 kDa, 400 kDa | 175 kDa | 190 kDa | 150 kDa | 950 kDa, 1150 kDa |
| Molecular form | Monomer, dimer | Monomer | Monomer | Monomer | Pentamer, hexamer |
| Valence | 2, 4 | 2 | 2 | 2 | 10, 12 |
| Serum concentration (mg/mL) | 1.5–2.6 | 0.04 | 0.0003 | 9.5–12.5 | 0.7–1.7 |
| Serum half-life (days)[a] | 6 | 3 | 2.5 | 23 | 5 |

*Data from Frazer and Capra.[2]
[a]Refers to the average half-lives of human immunoglobulins in normal human subjects.

Lobo ED, Hansen RJ, Balthasar JP. Antibody pharmacokinetics and pharmacodynamics. J Pharm Sci. 2004; 93: 2645-2668.

# ANTICORPI MONOCLONALI (mAbs)



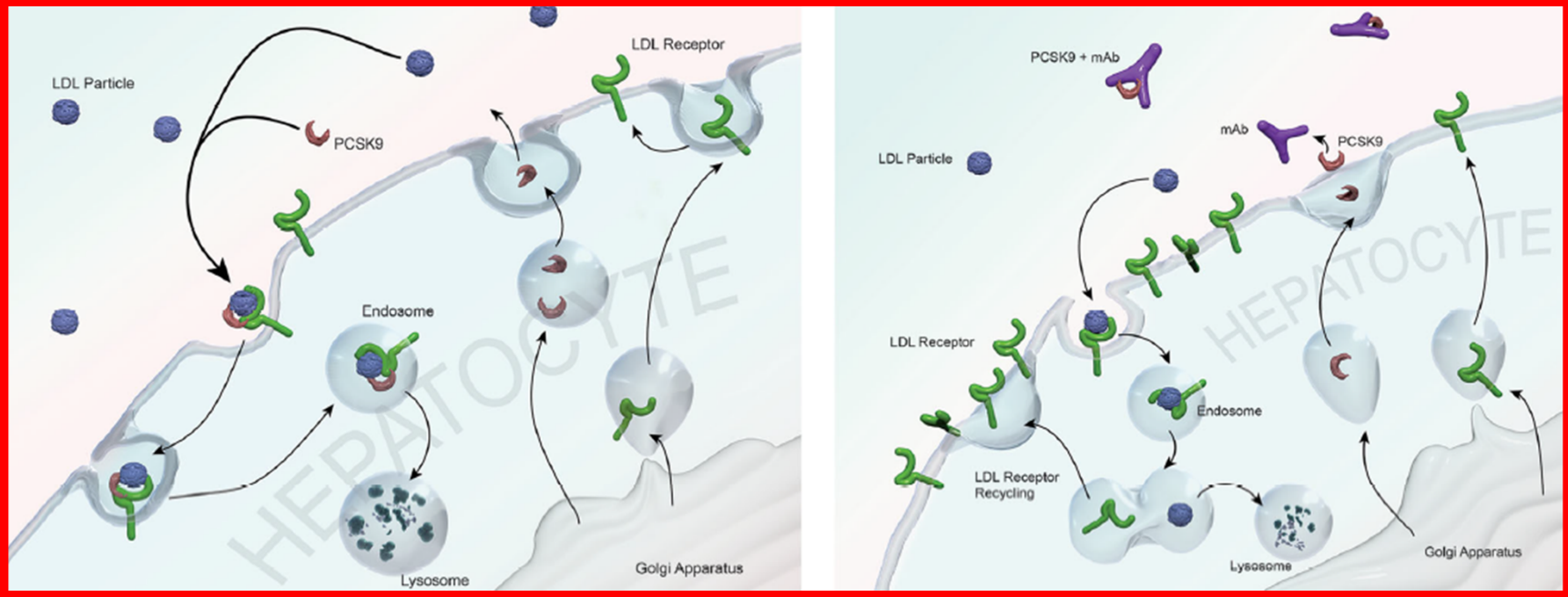

**Types of mAbs**

| | | |
|---|---|---|
| Murine | Entirely murine amino acids | 'o' = mouse<br>e.g. muromonab |
| Chimeric | Human constant (C)<br>+ murine variable (V) regions | 'xi' = chimeric<br>e.g. rituximab |
| Humanized | Murine complementarity determining regions (CDRs) | 'zu' = humanized<br>e.g. alemtuzumab |
| Human | Entirely human amino acids | 'u' = human<br>e.g. adalimumab |

Hansel TT, Kropshofer H, Singer T, Mitchell JA, George AJ. The safety and side effects of monoclonal antibodies. Rev Drug Discov. 2010 Apr;9(4):325-38.

# AREE TERAPEUTICHE

## Anticorpi anti PSCK9




Rodriguez, Knowles JW. PCSK9 inhibition: current concepts and lessons from human genetics. Curr Atheroscler Rep. 2015 Mar;17(3):487

# Modalità di somministrazione

**Table I.** Summary of approved therapeutic monoclonal antibodies (mAbs) [as at 27 May 2010]

| Generic name | Therapeutic class | Targets | Route of administration | US FDA/European Medicines Agency approval | mAb type |
|---|---|---|---|---|---|
| Ibritumomab tiuxetan | Non-Hodgkin's lymphoma | CD20 | IV | 2002/2004 | Murine $IgG_2$ |
| Infliximab | Crohn's disease<br>Rheumatoid arthritis | TNFα | IV | 1998/1999 | Chimeric $IgG_1$ |
| Muromonab-CD3 | Organ transplantation | CD3 | IV | 1986/– | Murine $IgG_2$ |
| Natalizumab | Multiple sclerosis | $\alpha_4$-integrin | IV | 2004/2006 | Humanized $IgG_4$ |
| Ofatumumab | Chronic lymphocytic leukaemia | CD20 | IV | 2009/2010 | Human $IgG_{1K}$ |
| Omalizumab | Asthma | IgE | SC | 2003/2005 | Humanized $IgG_1$ |
| Palivizumab | Respiratory syncytial virus infection | RSV gpF | IM | 1998/1999 | Humanized $IgG_1$ |
| Panitumumab | Metastatic colorectal carcinoma | EGFR | IV | 2006/2007 | Human $IgG_2$ |
| Ranibizumab[a] | Macular degeneration | VEGF-A | IVT | 2006/2007 | Humanized $IgG_1$ |
| Rituximab | Non-Hodgkin's lymphoma<br>Rheumatoid arthritis | CD20 | IV | 1997/1998 | Chimeric $IgG_1$ |
| Tocilizumab | Rheumatoid arthritis | IL-6 receptor | IV | 2010/2009 | Humanized $IgG_1$ |
| Tositumomab (I-131) | Non-Hodgkin's lymphoma | CD20 | IV | 2003/– | Murine $IgG_2$ |
| Trastuzumab | Breast cancer | HER2/neu | IV | 1998/2000 | Humanized $IgG_1$ |
| Ustekinumab | Plaque psoriasis | IL-12/23 | SC | 2009/2009 | Human $IgG_1$ |

a Fab fragment.

b Efalizumab was withdrawn from the market voluntarily in 2009 by the manufacturer.

**EGFR** = endothelial growth factor receptor; **EpCAM** = epithelial cell adhesion molecule; **gp** = glycoprotein; **HER** = human epidermal growth factor receptor; **IL** = interleukin; **IM** = intramuscular; **IP** = intraperitoneal; **IV** = intravenous; **IVT** = intravitreal; **RSV** = respiratory syncytial virus; **SC** = subcutaneous; **TNFα** = tumour

Keizer RJ, Huitema AD, Schellens JH, Beijnen JH. Clinical pharmacokinetics of therapeutic monoclonal antibodies. Clin Pharmacokinet. 2010; 49: 493-507.

# S.C. vs I.V.

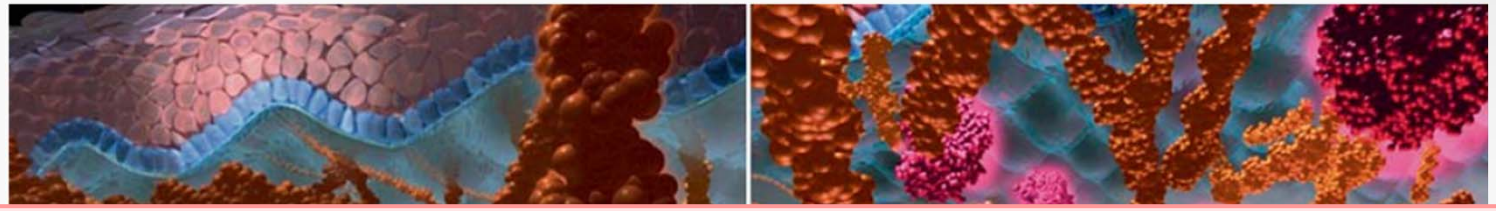
**Table 1** Advantages and disadvantages of subcutaneous and intravenous administration.

| Administration form | Advantages |
|---|---|
| s.c. | ▸ shorter clinic/office visits for the patient<br>▸ optimised use of resources<br>▸ self-administration is possible<br>▸ less invasive than i. v. administration |
| i.v. | ▸ suitable for substances that can cause irritations<br>▸ suitable for drugs that must be administered in larger volumes |

| Administration form | Challenges |
|---|---|
| s.c. | ▸ pain-free administration of larger fluid volumes<br>▸ minimisation of adverse events at the injection site<br>▸ guarantee of good absorption and bioavailability<br>▸ administration of exact doses requires practice |
| i.v. | ▸ requires trained personnel in special infusion settings<br>▸ handling of port system (e.g., central port, Hickman catheter, PICC)<br>▸ placement of a peripheral cannula<br>▸ longer clinic/office stays than with s.c. administration<br>▸ risk of systemic infections |

Jackisch C, Müller V, Maintz C, Hell S, Ataseven B. Subcutaneous Administration of Monoclonal Antibodies in Oncology. Geburtshilfe Frauenheilkd. 2014; 74: 343-349.

# TESSUTO SOTTOCUTANEO



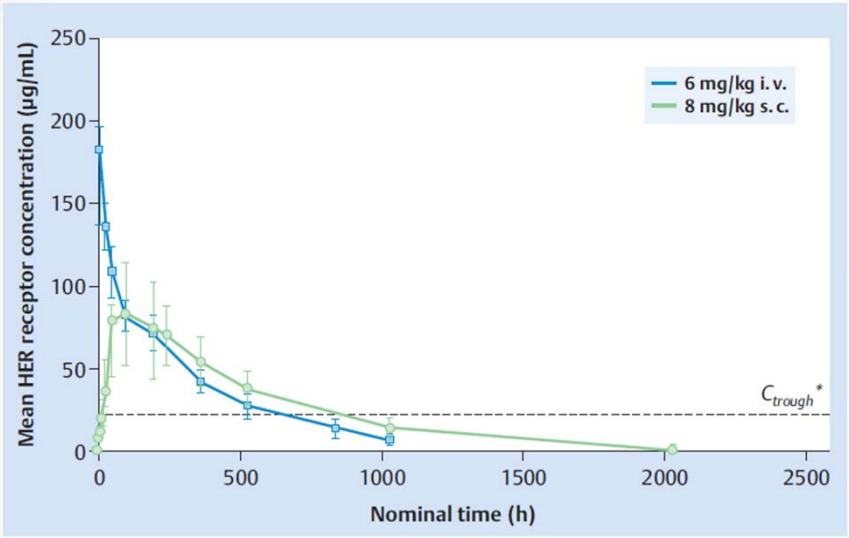
## APERTURA TRANSITORIA DELLA MATRICE EXTRACELLULARE

ENHANZE TECHNOLOGY: rHuPH-20 (human hyaluronidase PH-20)

- ✓ Somministrazione di volumi > 2 mL  senza disconfort/dolore
- ✓ Riduzione degradazione di F. Biologici
- ✓ Aumento di biodisponibilità
- ✓ Riduzione reazioni nel sito di iniezione

Jackisch C, Müller V, Maintz C, Hell S, Ataseven B. Subcutaneous Administration of Monoclonal Antibodies in Oncology. Geburtshilfe Frauenheilkd. 2014; 74: 343-349.

# SOMMINISTRAZIONE S.C. di mAb in oncologia: TRASTUZUMAB




| | Cohort 1: HMVs, IV | Cohort 2: Patients, IV | Cohort 3: HMVs, SC | Cohort 4: HMVs, SC | Cohort 5: HMVs, SC | Cohort A: Patients, SC | Cohort B: Patients, SC |
|---|---|---|---|---|---|---|---|
| n | 6 | 6 | 6 | 6 | 6 | 20 | 20 |
| Dose, mg/kg | 6 | 6 | 6 | 10 | 8 | 8 | 12 |
| $C_{max}$, µg/mL | 150 (14.4) | 185 (42.9) | 66.8 (11.4) | 102 (17.2) | 82.0 (11.3) | 88.4 (33.3) | 151 (58.6) |
| $t_{max}$, h[a] | 1.65 (1.60-24.0) | 3.00 (1.55-24.0) | 156 (96.0-216) | 132 (96.0-216) | 96.0 (96.0-216) | 97.1 (47.9-217) | 96.1 (24.5-241) |
| $AUC_{0-\infty}$, µg·d/mL | 1610 (303) | 1800 (250) | 1350 (320) | 2500 (515) | 1960 (244) | 2090 (638) | 3550 (982) |
| $t_{1/2}$, h | 254 (32.2) | 244 (69.2) | 227 (55.9) | 240 (34.4) | 236 (43.9) | 241 (48.1) | 270 (80.1) |
| $C_{day22}$, µg/mL | 25.6 (12.1) | 27.5 (7.45) | 31.6 (12.0) | 51.4 (15.8) | 39.4 (5.48) | 37.8 (10.4) | 60.8 (22.0) |

Abbreviations: HMVs, healthy male volunteers; IV, intravenous; SC, subcutaneous; SD, standard deviation.
[a]Median (min-max).

Wynne C, Harvey V, Schwabe C et al., Comparison of subcutaneous and intravenous administration of trastuzumab: a phase I/Ib trial in healthy male volunteers and patients with HER2-positive breast cancer. J Clin Pharmacol. 2013; 53: 192-201.

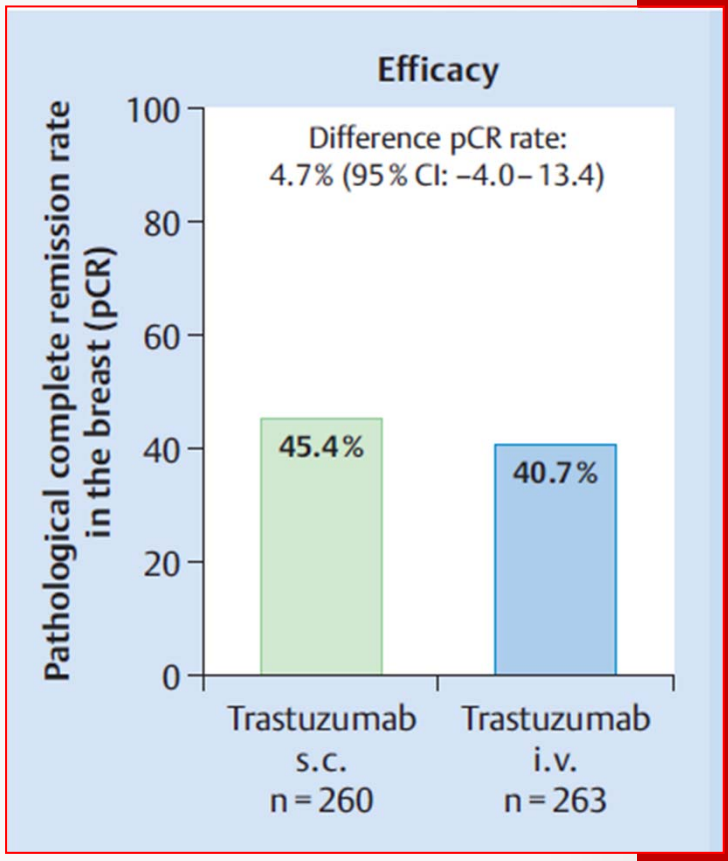
# TRASTUZUMAB S.C.: fixed-dose regimen

## Neoadjuvant/adjuvant setting

| | Intravenous trastuzumab (n=235) | Subcutaneous trastuzumab (n=234) |
|---|---|---|
| **Primary pharmacokenetic endpoint** | | |
| $C_{trough}$ predose cycle 8 | | |
| Mean (µg/mL; SD) | 57·8 (30·3) | 78·7 (43·9) |
| Geometric mean (µg/mL; percentage coefficient of variation)* | 51·8 (52·5%) | 69·0 (55·8%) |
| **Secondary pharmacokinetic endpoints** | | |
| Patients >20 µg/mL at predose cycle 8 | 232 (98·7%) | 227 (97·0%) |
| Mean (SD) $C_{max}$ at cycle 7 (µg/mL)† | 221 (118·0) | 149 (64·8) |
| Mean (SD) $T_{max}$ at cycle 7 (days)‡ | 0·05 (0·04) | 4·12 (2·91) |
| Mean (SD) $AUC_{0\text{-}21\,days}$ (µg/mL×day) | 2056 (598) | 2268 (875) |
| Geometric mean $AUC_{0\text{-}21\,days}$ (µg/mL×day; percentage coefficient of variation)§ | 1978 (29·1%) | 2108 (38·5%) |

$AUC_{0\text{-}21\,days}$=area under the serum concentration–time curve from 0-21 days; $C_{max}$=maximum serum concentration. $T_{max}$=time to $C_{max}$. *Geometric mean ratio 1·33 (90% CI 1·24–1·44). †Geometric mean ratio 0·67 (90% CI 0·63–0·71). ‡n=233 in subcutaneous trastuzumab group. §Geometric mean ratio 1·07 (90% CI 1·01–1·12).

***Table 2:*** **Trastuzumab pharmacokinetic parameters before surgery in the per-protocol pharmacokinetic population**




## TRASTUZUMAB 5 ml (120 mg/mL di mAb e 2000 U/mL rHuPH20)

Ismael G, Hegg R, Muehlbauer S et al. Subcutaneous versus intravenous administration of (neo)adjuvant trastuzumab in patients with HER2-positive, clinical stage I-III breast cancer (HannaH study): a phase 3, open-label, multicentre, randomised trial. Lancet Oncol. 2012 ; 13: 869-878.

# TRASTUZUMAB S.C.: EMA Approval

**Table 2** European Union indications for subcutaneous trastuzumab in HER2-positive breast cancer (HER2 overexpression or *HER2* gene amplification must be based on an accurate and validated assay)

| Early breast cancer | Metastatic breast cancer |
|---|---|
| Following surgery, neoadjuvant/adjuvant chemotherapy (and radiotherapy where applicable) | As monotherapy after ≥2 chemotherapy regimens for metastatic disease that included an anthracycline and taxane regimen; in hormonal receptor-positive patients, after failed hormonal therapy |
| In combination with paclitaxel or docetaxel following adjuvant doxorubicin and cyclophosphamide | In combination with paclitaxel in patients not suitable for an anthracycline who have not received chemotherapy for metastatic disease |
| In combination with adjuvant docetaxel and carboplatin | In combination with docetaxel in patients who have not received chemotherapy for metastatic disease |
| As neoadjuvant/adjuvant therapy in combination with neoadjuvant chemotherapy in locally advanced (including inflammatory) disease and for tumors >2 cm in diameter | In combination with an aromatase inhibitor in trastuzumab-naïve postmenopausal patients with hormone receptor-positive disease |

Sanford M. Subcutaneous trastuzumab: a review of its use in HER2-positive breast cancer. Target Oncol. 2014; 9: 85-94.

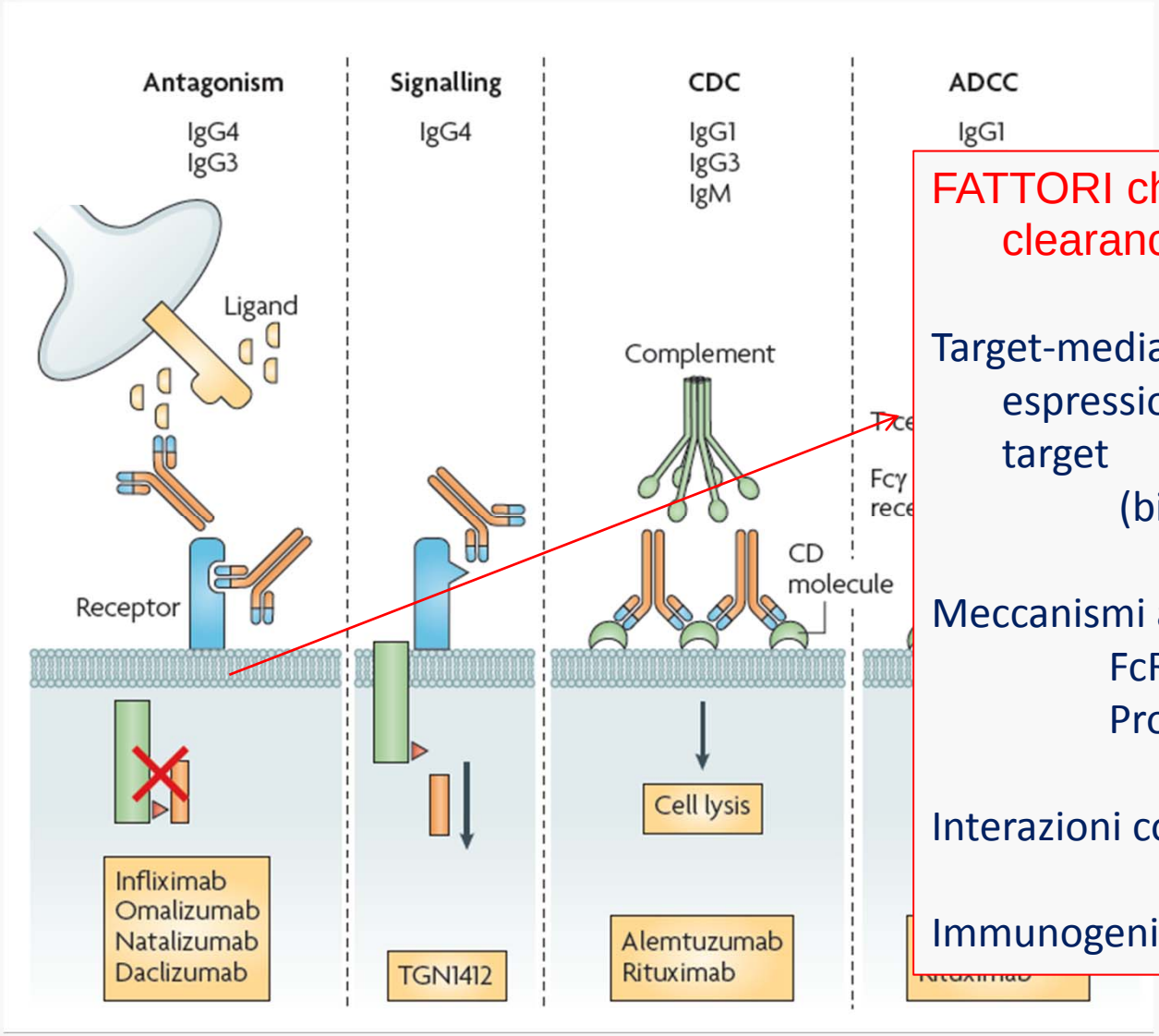
# FARMACOCINETICA mAbs

**Table II.** Reported elimination half-life ($t_{½}$) and population pharmacokinetic (PopPK) parameters for monoclonal antibodies (mAbs)[a]

| Generic name | $t_{½}$ | PopPK model | $k_a$ ($d^{-1}$) | CL (L/d) | $V_{max}$ (mg/d)/ Km (mg/L) | $V_d$ (L) | Q (L/d) | $V_2$ (L) | Covariates |
|---|---|---|---|---|---|---|---|---|---|
| Abciximab | 30 min | | | | | | | | |
| Adalimumab | 14 d | | | 0.288 | | 4.7–6.0[b] | | | (AA + AGE + DOSE + RF + CRP) ~ CL |
| Alemtuzumab | 6 d | 2-comp, NLE | | | 24.48/0.338 | 11.3 | 25.2 | 41.5 | (WBC) ~ $V_{max}$ |
| Basiliximab | 7.2 d | 2-comp, LE | | 0.881 | | 3.6 | | 4.4 | (WT, AGE) ~ CL |
| Bevazicumab | 20 d | 2-comp, LE | | 0.207 | | 2.66 | 0.593 | 2.76 | (WT, SEX, ALB, AP, SGOT, CHEM) ~ CL; (SEX, WT, ALB) ~ $V_d$ |
| Canakinumab | 26 d | | | 0.174[c] | | 6.01[c] | | | |
| Catumaxomab | 2.5 d | | | | | | | | |
| Certolizumab pegol | 14 d | | | 0.408 | | 6.4[b] | | | AA + ADM + WT + IMM |
| Cetuximab | 70–100 h | 2-comp, NLE | | | 105.1/74 | 2.83 | 2.472 | 2.43 | |
| Daclizumab | 20 d | | | | | | | | (WT, AGE, SEX, PU, RACE) ~ CL |
| Eculizumab | 11.3 d | 1-comp, LE | | 0.528 | | 7.7 | | | |
| Efalizumab | 5.5–10.5 d | 1-comp; LE, LA | 0.191 | 1.29 | | 9.13 | | | (WT, OBS, PASI, LYM, AGE, DOSE) ~ CL |
| Gemtuzumab ozogamicin | 1.9 d | | | | | | | | |
| Golimumab | 12.5 d | 1-comp; LE, LA | 0.908 | 0.68[c] | | 12.5 | | | MTX |

Keizer RJ, Huitema AD, Schellens JH, Beijnen JH. Clinical pharmacokinetics of therapeutic monoclonal antibodies. Clin Pharmacokinet. 2010; 49: 493-507.

# MECCANISMO di AZIONE di mAbs




FATTORI che regolano la clearance di mAbs

Target-mediati
- espressione e localizzazione del target
  - (binding/internalizzazione)

Meccanismi aspecifici
- FcRn binding
- Proteolisi

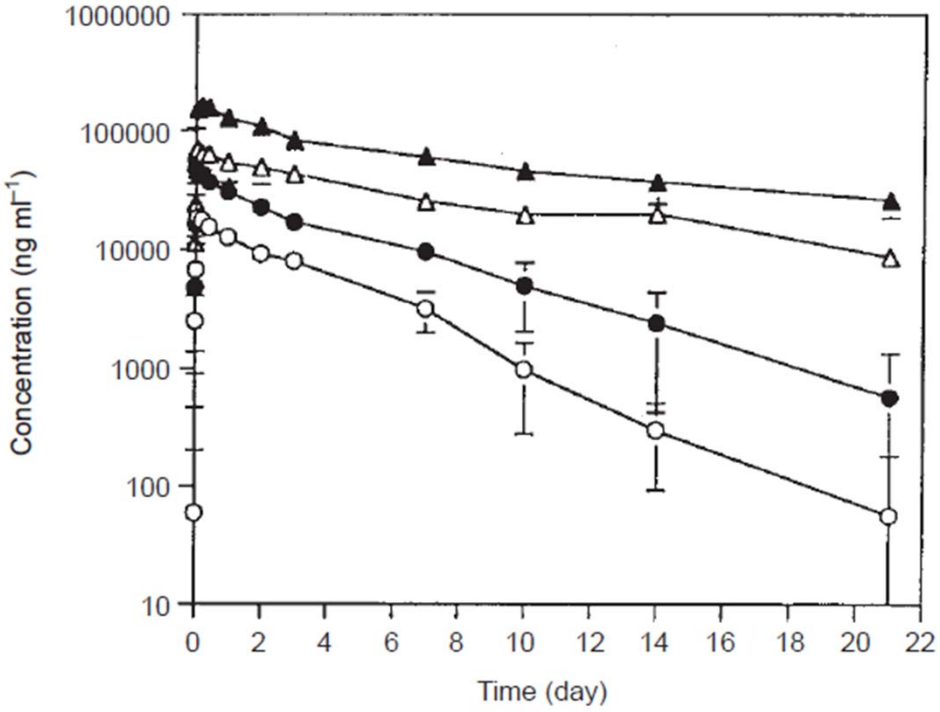
Interazioni con altri farmaci

Immunogenicità

Hansel TT, Kropshofer H, Singer T, Mitchell JA, George AJ. The safety and side effects of monoclonal antibodies. Net Rev Drug Discov 2010; 9: 325-338.

# CLEARANCE di mAbs: target di superficie

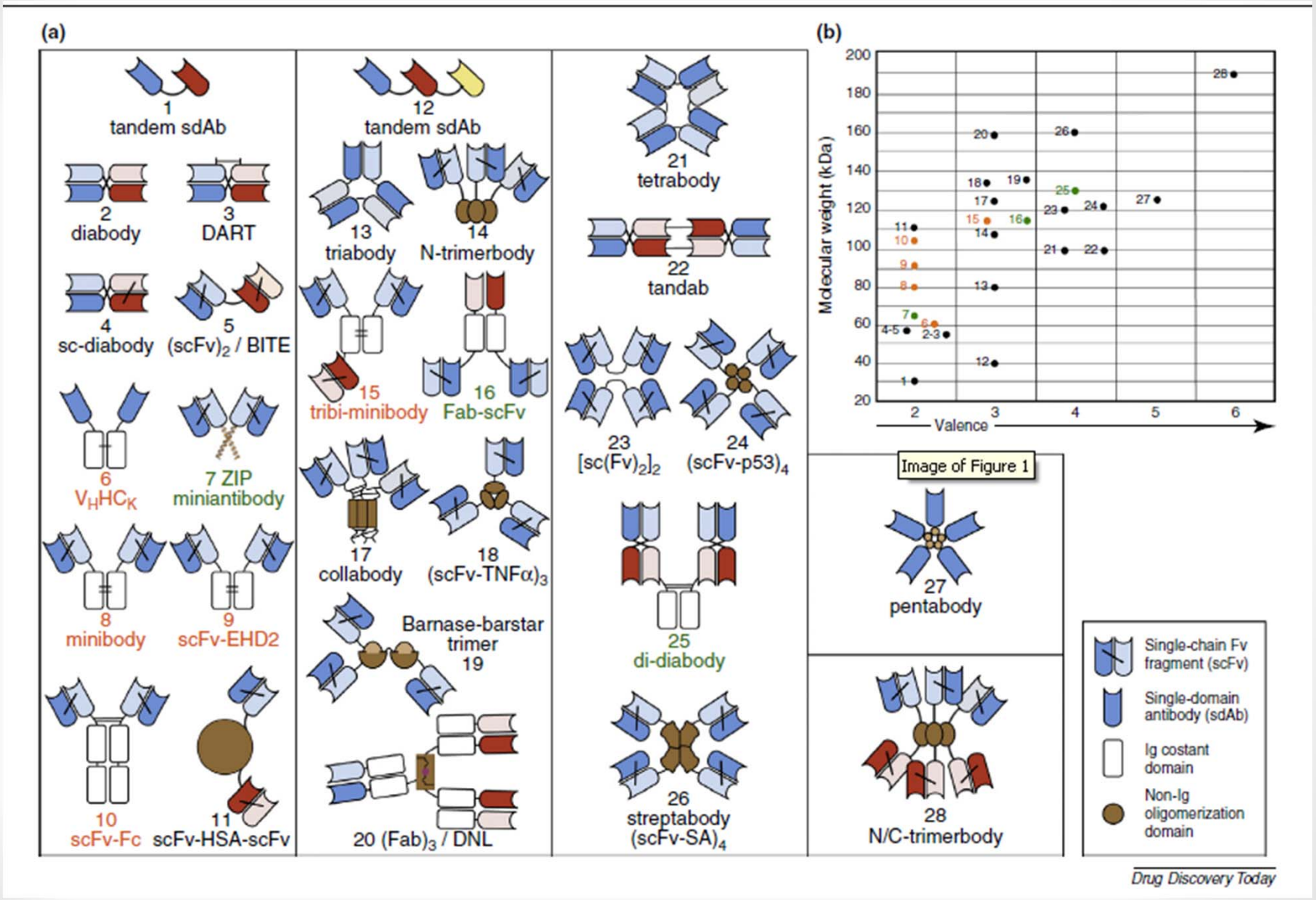

Humanized anti-HER2 monoclonal Ab: TRASTUZUMAB




Muller PY, Brennan FR. Safety assessment and dose selection for first-in-human clinical trials with immunomodulatory monoclonal antibodies. Clin Pharmacol Ther. 2009; 85: 247-258.

Tokuda Y, Watanabe T, Omuro Y et al. Dose escalation and pharmacokinetic study of a humanized anti-HER2 monoclonal antibody in patients with HER2/neu-overexpressing metastatic breast cancer. Br J Cancer. 1999; 81: 1419-1425.

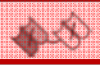
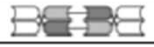
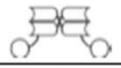
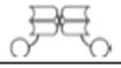
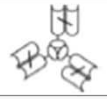
# mAbs di nuova generazione




Nuñez-Prado N, Compte M, Harwood S et al. The coming of age of engineered multivalent antibodies. Drug Discov Today. 2015 Mar 7. pii: S1359-6446(15)00098-7.

# mAbs di nuova generazione

Pharmacokinetics:
Following continuous intravenous infusion, blinatumomab pharmacokinetics were linear at dosages ranging from 5 to 90 µg/m2/day, with steady-state concentrations reached within a day. The mean blinatumomab elimination half-life was 2.1 h

| Comprehensive summary o | | | | | | |
|---|---|---|---|---|---|---|
| Name | Fo | | | | | |
| ALX-0061 | Bi | | | | | II |
| ALX-0081/ALX-0681 (caplacizumab) | Bi | | | | | II |
| ATN-103 (ozoralizumab) | Tr | | | | | II |
| ALX-0761 | Tr | | | | | I |
| ALX-0141 | Tr | | | | | I |
| ALX-0171 | Trivalent monospecific nanobody | | 42 | F protein of RSV | RSV infection | Phase I |
| AMG 103 (blinatumomab) | BiTE |  | 55 | CD19 × CD3 | ALL; NHL | Approved; Phase II |
| AMG 212 (BAY2010112) | BiTE |  | 55 | PSMA × CD3 | Prostate cancer | Phase I |
| AMG 110 (solitomab) | BiTE |  | 55 | EpCAM × CD3 | Epithelial cancers | Phase I |
| AMG 211 (MEDI-565) | BiTE |  | 55 | CEA x CD3 | Gastrointestinal cancers | Phase I |
| MGD006 | DART |  | 55 | CD123 × CD3 | AML | Phase I |
| MGD007 | DART |  | 55 | gpA33 × CD3 | Metastatic CRC | Phase I |
| MM-111 | Bispecific scFv-HSA fusion |  | 110 | HER2 × HER3 | Gastric cancer | Phase II |
| AFM13 | Tetravalent bispecific tandAb |  | 110 | CD30 x CD16 | HL | Phase I |
| AFM11 | Tetravalent bispecific tandAb |  | 110 | CD19 × CD3 | ALL; NHL | Phase I |
| F16-IL2 (teleukin) | Bivalent diabody immunocytokine |  | 80 | TNC-A1 | Breast cancer; lung cancer | Phase Ib/II |
| L19-IL2 (darleukin) | Bivalent diabody immunocytokine |  | 80 | FN-EDB | Melanoma; RCC; pancreatic cancer | Phase IIb |
| L19-TNF (fibromun) | Trivalent scFv immunocytokine |  | 140 | FN-EDB | Melanoma Sarcoma | Phase I/II |

Nuñez-Prado N, Compte M, Harwood S et al. The coming of age of engineered multivalent antibodies. Drug Discov Today. 2015 Mar 7. pii: S1359-6446(15)00098-7.