L'appropriatezza nel Servizio Sanitario Nazionale
Condivisione di strategie tra Ospedale e Territorio
22-23 giugno 2015 Hotel Excelsior - Napoli

Relazione struttura - attività dei Biosimilari: implicazioni farmacodinamiche ed indicazioni d'uso

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1- DEFINIZIONE DI FARMACO BIOLOGICO E BIOSIMILARE

2- VALUTAZIONE DEI BIOSIMILARI ED ENTI REGOLATORI

3- STUDI DI COMPARABILITA' INFLIXIMAB BIOSIMILARE

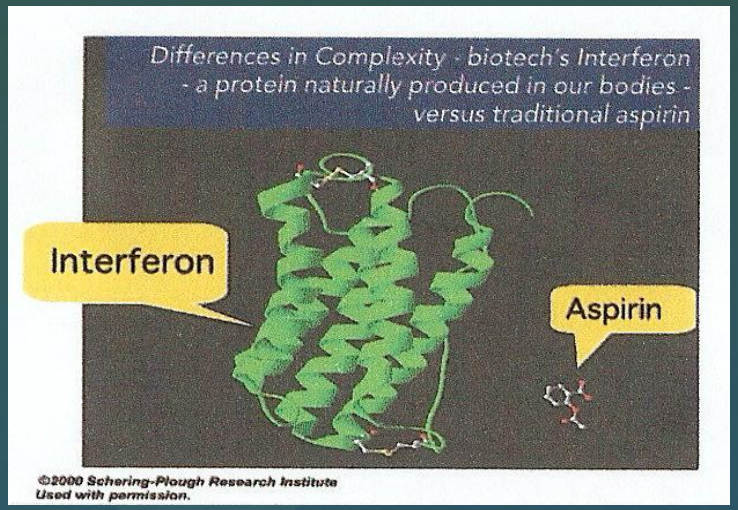
4- STUDIO IN CORSO Università di Bari

5- CONCLUSIONI

DEFINIZIONE

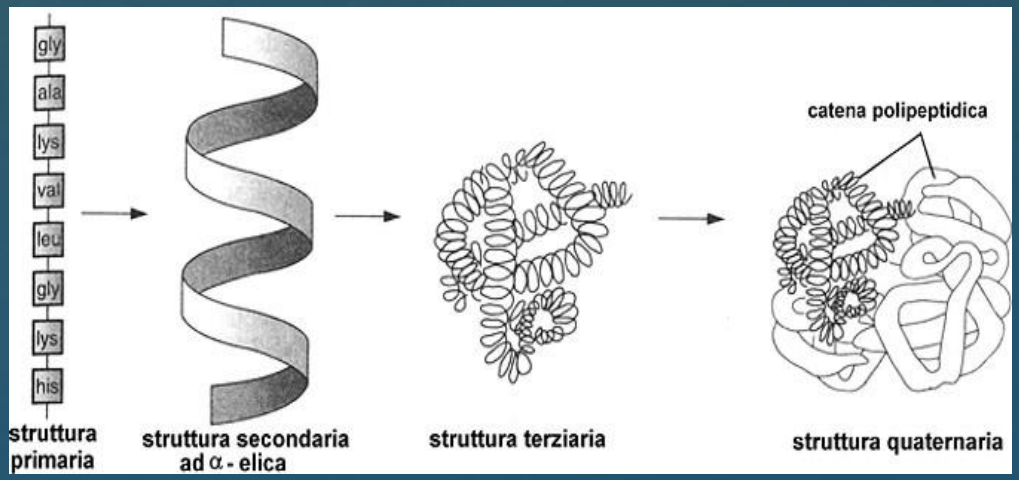
Farmaci biologici

Sono molecole di medio-alto peso molecolare di natura proteica e glicoproteica, polisaccaridica (ormoni ed enzimi, emoderivati, immunoglobuline, anticorpi monoclonali).



Farmaci biosimilari

Devono mostrare la stessa struttura primaria e secondaria degli originator .
Possono mostrare differenze nella struttura 3D per de amminazione, glicosilazione ed ossidazione.



Non sono quindi strutturalmente identici ai rispettivi prodotti di riferimento biologici per i quali è scaduto il brevetto.

Hanno la stessa via di somministrazione, la stessa forma farmaceutica, la stessa dose, le stesse indicazioni terapeutiche e modo di utilizzo del prodotto di riferimento.

Cloning and Protein Expression

Transfer into Host Cell

- ***Variabilità strutturale dei farmaci biologici e biosimilari*** *è intrinseca ai complessi processi produttivi che impiegano cellule viventi: la si può osservare anche tra lotti differenti di uno stesso originator*

- ***Ottimizzazione dei processi di produzione*** *allo scopo di minimizzare la variabilità biologia ed aumentare l'efficacia dei mAbs*

- ***Favorita la produzione di mAbs glicosilati*** *in Asn 297/300*

- ***Nella nuova generazione di mAbs e biobetter*** *è favorita la produzione di anticorpi monoclonali* ***umani o umanizzati privi di fucosile*** *in Asn 297/300*

media, method media, conditions elution standards

Figure 2 Biologics manufacturing process.
From Mellstedt H, Niederwieser D, Ludwig H. The challenge of biosimilars. Ann Oncol 2008;19:412–419; by permission of Oxford University Press.

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LA VALUTAZIONE DEL BIOSIMILARE RICHIEDE STUDI DI COMPARABILITA' *si applica in EU, USA, CANADA….*

- *Comparabilità chimico-fisica e biologica*

- *Comparabilità pre-clinica : Studi di farmacodinamica su linee cellulari*
  Studi di binding recettoriale
  Studi in vivo in animali di cinetica e distribuzione
  Studi di tossic. a singola dose per analisi di tolleranza,
  Studi a dose ripetuta

- *Comparabilità clinica : Studi di PD/PK di fase I*
  Studi di efficacia e sicurezza di fase III di non inferiorità
  In almeno una delle indicazioni dell'originator.

- *Studi di farmacovigilanza in fase di post autorizzazione*

- *Possono essere prescritti dalle agenzie regolatorie studi clinici in fase post-autorizzativa*

LE AGENZIE REGOLATORIE POSSONO PER ESTRAPOLAZIONE DARE AL BIOSIMILARE LE ALTRE INDICAZIONI DELL'ORIGINATOR

senza dimostrarne l'efficacia clinica e sicurezza in studi sperimentali in fase pre-autorizzativa

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I GENERATION BIOSIMILAR approved by EMA 2006-2010

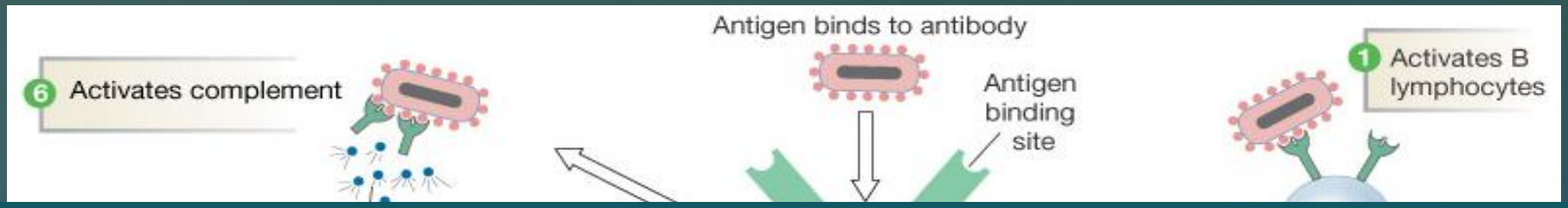
Non-proprietary name	Reference product trade name	Biosimilar product trade name	Biosimilar sponsor company	Year of biosimilar product approval
Somatropin	Genotropin®	Omnitrope®	Sandoz GmbH	2006
Somatropin	Humatrope®	Valtropin®	BioPartners GmbH	2006
Filgrastim	Neupogen®	Ratiograstim®	ratiopharm GmbH	2008
Filgrastim	Neupogen®	Filgrastim ratiopharm®	ratiopharm GmbH	2008
Filgrastim	Neupogen®	Filgrastim Hexal®	Hexal AG	2009
Filgrastim	Neupogen®	Filgrastim Zarzio®	Sandoz GmbH	2009
Filgrastim	Neupogen®	Nivestim®	Hospira Enterprises B.V.	2010

PROPERTIES : *Low structural complexity (medium molecular weight = 30-70 kDa)*

Narrow spectrum of biological activity

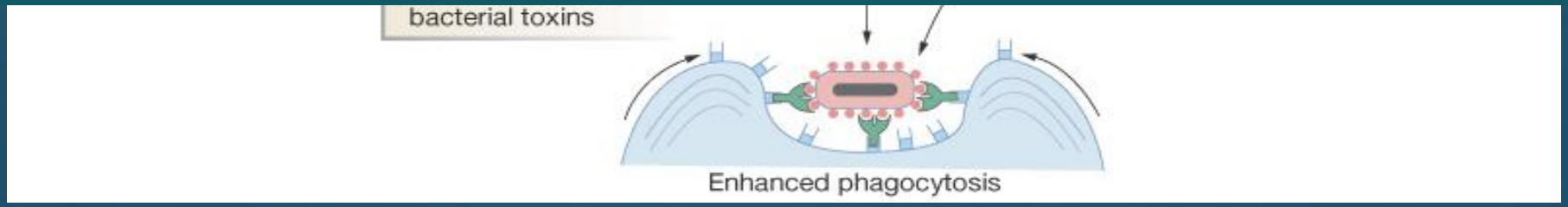
II GENERATIONS BIOSIMILAR ANTIBODIES POISED TO PENETRATE MARKET

Draft regulations will pave the way for copycat antibodies and other large molecules.
Ledford H, Nature news 468, 18-19 (2010)



PROPERTIES: *Elevated structural complexity (high molecular weight = 150 kDa)*

Large spectrum of biological activity



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Comparability with the Reference Medicinal Product

CASE STUDY: CP-13 biosimilar vs RMP originator Infliximab

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

27 June 2013
EMA/CHMP/589422/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Inflectra

International non-proprietary name: Infliximab

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

27 June 2013
EMA/CHMP/589317/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Remsima

International non-proprietary name: Infliximab

Procedure No. EMEA/H/C/002576/0000

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Comparability with the Reference Medicinal Product

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Primary and higher order structures

The primary structure of CT-P13 and the RMP was confirmed to be identical by amino acid analysis, sequencing using peptide mapping (in combination with MS/MS), N-terminal sequencing and C-terminal sequencing, except for differences in the levels of C-terminal lysine. In relation to the C-terminal lysine

- *Struttura primaria amminocidica = identica (ad ec. alti livelli di varianti senza lisina nel carbossi terminale della catena pesante del biosimilare K0 vs originator K1)*
- *Livelli di varianti mAbs ossidate lievemente maggiori nel biosimilare vs originator in seguito a stress test*
- *Livelli di proteina totale lievemente maggiori nel biosimilare vs originator*
- *Differenze nella composizione glicosidica in Asn 300 tra biosimilare e originator*

is more susceptible to oxidation. The forced degradation study demonstrated that a substantial increase

Protein content

Slightly higher protein content was measured in CT-P13 compared to Remicade using the validated UV method. Protein concentration data from further CT-P13 and Remicade batches were submitted to show

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Biological activity

No differences between the bioactivity of CT-P13 and Remicade were detected in the *in vitro* TNFα neutralisation assay, the apoptosis assay (using tmTNFα Jurkat cells), the cell-based TNFα binding

- *Non si osservano differenze nel binding del FAB Infliximab e TNFalpha vs FAB biosimilare e TNFalpha*
- *Non si osservano differenze tra biosimilare vs originator nei meccanismi di attivazione del complemento CDC*

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The Applicant has provided more information on the observed binding difference between infliximab in Inflectra and Remicade towards FcγRIIIa and discussed the possible reason behind this difference. The Applicant confirmed that V-type FcγRIIIa polymorphic variant was employed in the initial assays

-Sono riportate differenze tra biosimilare ed originator ***a favore dell'originator nella affinità di legame con i recettori cellulari Fc*** *(FcgammaIII A/B) che mediano la risposta infiammatoria delle cellule natural killer*

-Sono riportate differenze tra biosimilare ed originator ***nella attività biologica citotossica anticorpo mediata (ADCC) a favore dell'originator***

patients of all genotypes, with reduced binding for CT-P13 (in V/V genotype and V/F genotype) compared with Remicade, but no difference in overall mean binding using NK cells from patients of F/F genotype. Binding of CT-P13 and Remicade to NK cells was also performed in the presence of diluted Crohn's disease patient serum, to mimic the *in vivo* environment. This showed an overall reduction in total binding, but the level of residual binding was comparable, showing an abrogation of the difference in binding previously seen with CT-P13 and Remicade (in the absence of serum) for V/V and V/F genotypes. It is suggested that this reduction in overall binding and abrogation of any observed

ASSESMENT REPORT INFLECTRA

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2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

Overall, the quality of Inflectra is considered to be in line with the quality of other approved monoclonal

ply

Si conclude che la qualità del biosimilare è comparabile a quella dell'originator ed è in linea con quella di altri mAbs

La commissione evidenzia la bassa attività biologica ADCC del biosimilare vs originator ritenendo che comunque possa non avere impatto clinico

COMPARATIVE NON CLINICAL DATA

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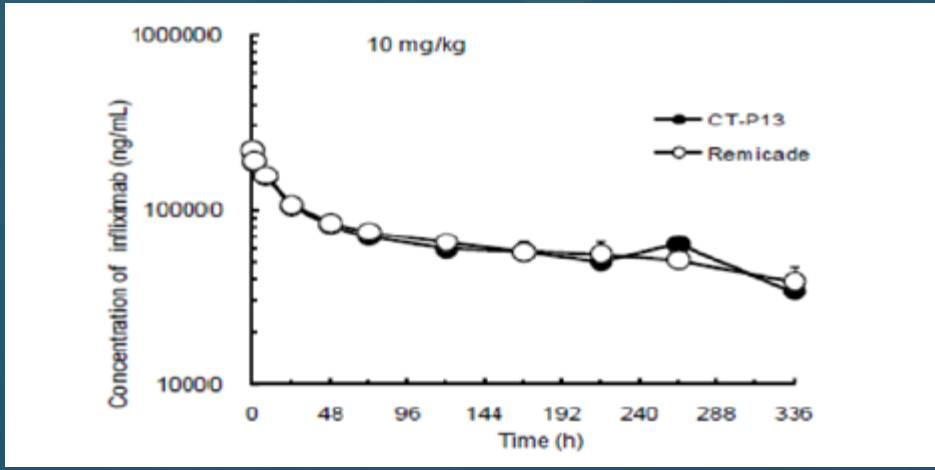
The *in vivo* comparative 2 week toxicity studies in rats and immunohistochemistry study of cross-reactivity in human tissues were performed in compliance with GLP requirements.

Non sono state osservate differenze statisticamente significative negli studi di farmacocinetica sui roditori tra biosimilare e originator e negli studi di tossicità nel cane

detect and quantify CT-P13, Remicade and antibody formation performed for GLP studies.



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CLINICAL REGISTRATIVE STUDIES

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The clinical data demonstrating similarity between Inflectra and Remicade consisted of two main clinical trials: a pivotal pharmacokinetic study in patients with ankylosing spondylitis (AS) (Study CT-P13 1.1) and a pivotal efficacy and safety study in patients with active rheumatoid arthritis (RA) (Study CT-P13 3.1). The pharmacokinetic trial in AS patients showed, at the dose of 5 mg/kg, comparable profiles between Inflectra and Remicade at steady state (after 5 doses) with the 90% confidence intervals of the

Non sono state osservate differenze statisticamente significative tra biosimilare vs originator nei due studi registrativi di fase I e III di non inferiorità nella spondilite anchilosante e nella artrite reumatoide

confidence interval for the difference in the ACR20 response rate at Week 30 was contained within the

predefined equivalence margin (± 15%) in both the all-randomised (95% CI: -0.06, 0.10) and Per Protocol populations (95% CI: -0.04, 0.12). At week 30, the results of the secondary endpoints (in particular ACR50 and ACR70, decreases in DAS28, SDAI and CDAI, increases in SF-36) were all consistent with the results of the primary endpoint. These data were further supported by comparable response rates at Week 54. Additional supportive efficacy data were provided in another indication by the PK study CT-P13 1.1 conducted in AS patients. The efficacy results were comparable between treatment arms up to Week 54.

CLINICAL REGISTRATIVE STUDIES

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products up to 54 weeks and the impact of antibodies on efficacy and safety was comparable. A numerical imbalance in serious adverse events was observed in the study CT-P13 3.1 with a higher number of serious infections, including active tuberculosis. However, the numbers were low and the CHMP, based on a thorough review of all available evidence, was of the opinion that the observed difference was most likely a chance finding. It was also noted that there is no plausible explanation from a mechanistic point of view for a difference in host defence. Serious infections, including tuberculosis will be closely monitored on a longer term and in larger cohorts of patients as part of the post-marketing setting through several registries conducted in different patient populations as described in the risk management plan, such as

The CHMP concluded that the benefit/risk balance of Inflectra as a biosimilar product to Remicade is positive. Several post-authorisation studies and registries, as detailed in the risk management plan, will provide further long-term efficacy data, including in the treatment of inflammatory bowel diseases, and further characterise the long-term safety profile of Inflectra.

DIFFERENZE TRA BIOSIMILARI E INFLIXIMAB ORIGINATOR NEGLI STUDI

Differenze chimico-fisiche nella norma per i farmaci biologici nel 2013

CONTROVERSIA:

Differenze di attività biologica (ADCC) a favore di Infliximab Originator *ritenute non clinicamente rilevanti da EMA ed FDA per le indicazioni in cui sono stati sperimentati i biosimilari come l'artite reumatoide e la spondilite anchilosante nel 2013*

Nel 2014 l'Agenzia Canadese *per la Salute* **www.hc-sc.gc.ca ha ritenuto rilevanti le differenze di attività biologica ADCC osservate tra Infliximab originator e Biosimilari** *per quelle indicazioni per le quali i Biosimilari hanno comunque avuto l'estensione d'uso in assenza di sperimentazione come le patologie autoimmuni Chron' s e la colite ulcerosa*
(Brian G. Feagan et al. The challenge of indication extrapolation for infliximab biosimilars. ***Biologicals 42 (2014) 177e183)***

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Summary Basis of Decision (SBD) for Inflectra
Date SBD Issued: 2014/03/04
Health Canada
www.hc-sc.gc.ca

The sponsor requested authorization for all of the indications and uses currently authorized to Remicade. Remicade is currently authorized for indications and uses in rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, Crohn's disease, and ulcerative colitis. The indications on rheumatoid arthritis and ankylosing spondylitis were acceptable on the basis of the comparability Phase I and III studies. The extension of indications to psoriatic arthritis and plaque psoriasis were granted on the basis of similarity and the absence of meaningful differences, between Inflectra and the reference product, in product quality, mechanism of action, disease pathophysiology, safety profile, dosage regimen and on clinical experience with the reference product. ……..; **however, extrapolation to indications and uses pertaining to Crohn's disease and ulcerative colitis could not be recommended due to differences between Inflectra and the reference product, that could have an impact on the clinical safety and efficacy of these products in these indications.** As a result, the benefit/risk assessments for Inflectra in rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis were considered to be positive, while the benefit/risk assessment of Inflectra in patients with Crohn's disease or ulcerative colitis could not be completed. The sponsor used a range of orthogonal methodologies to compare the primary and higher order structure, as well as the charged variants and glycan structures of Inflectra and Remicade. In addition, biological assays were used to compare the biological activity of Inflectra and Remicade *in vitro*. Inflectra was demonstrated to be comparable to Remicade in a battery of assays evaluating primary and higher order structure and biological activity with respect to TNF binding and neutralization. **However, there was an observed quantitative and qualitative difference in the glycosylation pattern. Specifically, Inflectra contains a lower level of afucosylated species as compared to Remicade. The degree of afucosylation is known to have a potential impact on Fcγ receptor binding. With respect to biological activity, no differences were observed in the TNFα binding/ neutralization activity of Inflectra and Remicade. ……..The data has shown that there is a difference in the NK cell-mediated Antibody-Dependent Cell-mediated Cytotoxicity (ADCC) activity between Inflectra and Remicade**, but that the difference in activity seems to disappear in the presence of other leukocytes. The sponsor stated that the NK cell assays are less physiologically relevant and that it is likely that *in vivo* there would be no difference. However, the nature of these cell-based assays and the manipulations required to perform standardized assays of this sort make it difficult to conclusively exclude the potential for a difference in ADCC activity, though the binding differences suggest that only NK cell-mediated ADCC would be affected.

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STUDIO IN CORSO

OBIETTIVO

INVESTIGARE SUI MECCANISMI RESPONSABILI della BASSA/ASSENTE ATTIVITA' CITOTOSSICA anticorpo mediata ADCC del biosimilare rispetto a quella dell'originator

1)Sono meccanismi basati su fattori secondari che influenzano indirettamente l'ADCC ?

o

2) Sono meccanismi basati su fattori primari come le interazioni ligando-recettore ?

Abbiamo avviato uno STUDIO IN SILICO sulle possibili interazioni dei frammenti Fc di Infliximab biosimilare vs originator con i recettori Fc cellulari e possibile ruolo della fucosilazione su queste interazioni

Influence of glycosylation/fucosylation of anti-TNF alpha antibodies on the biological activity of the IgG mAb

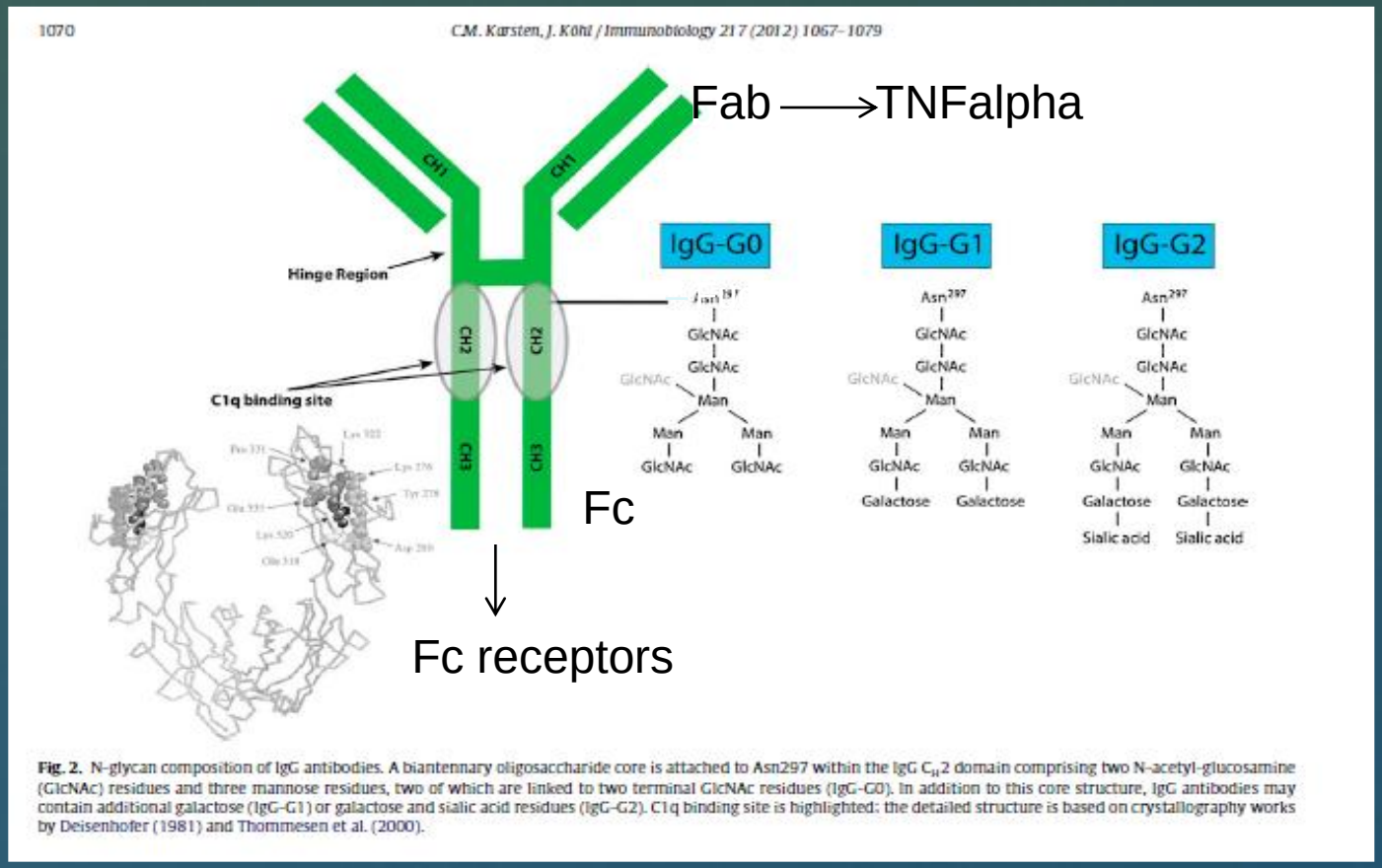
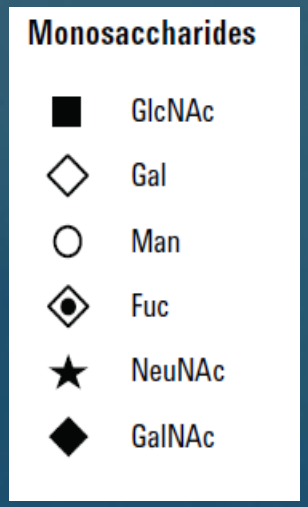
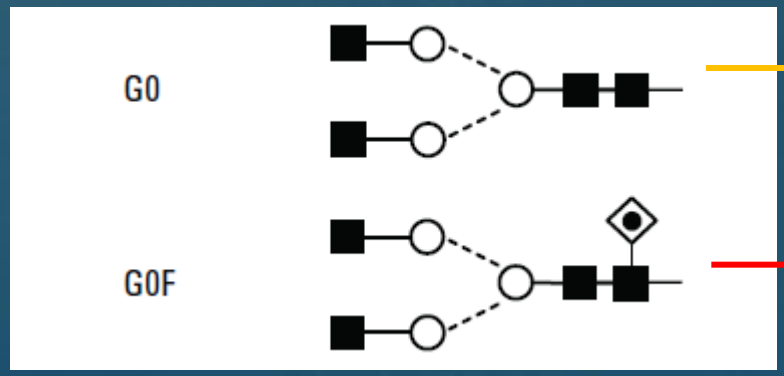


Fig. 2. N-glycan composition of IgG antibodies. A biantennary oligosaccharide core is attached to Asn297 within the IgG C_H2 domain comprising two N-acetyl-glucosamine (GlcNAc) residues and three mannose residues, two of which are linked to two terminal GlcNAc residues (IgG-G0). In addition to this core structure, IgG antibodies may contain additional galactose (IgG-G1) or galactose and sialic acid residues (IgG-G2). C1q binding site is highlighted: the detailed structure is based on crystallography works by Deisenhofer (1981) and Thommesen et al. (2000).





Originator : high binding affinity for FCgammaIII R

Biosimilars: Reduced binding and interaction to FCgammaIII R ?

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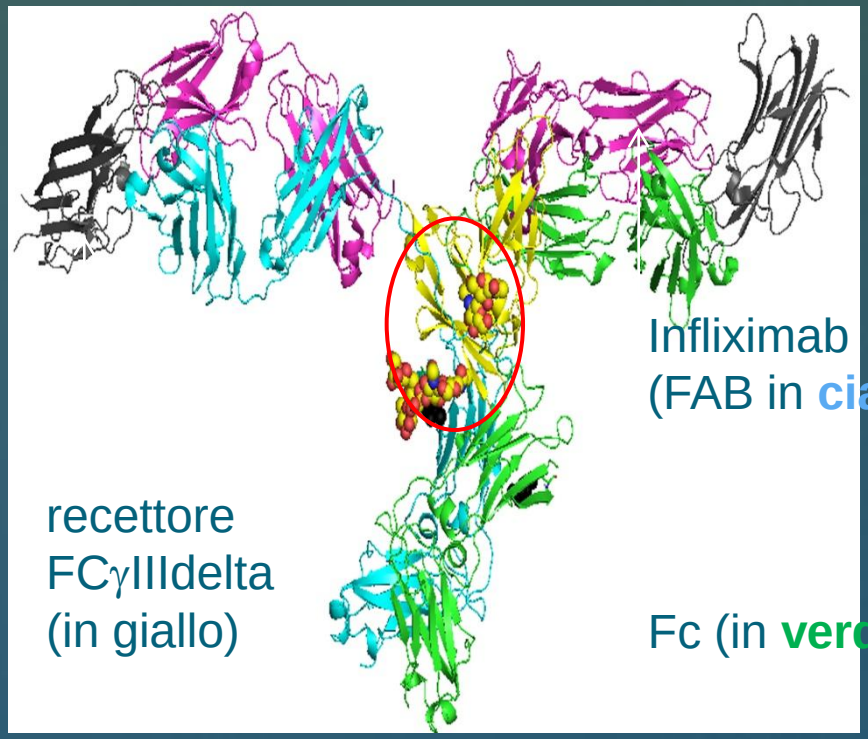
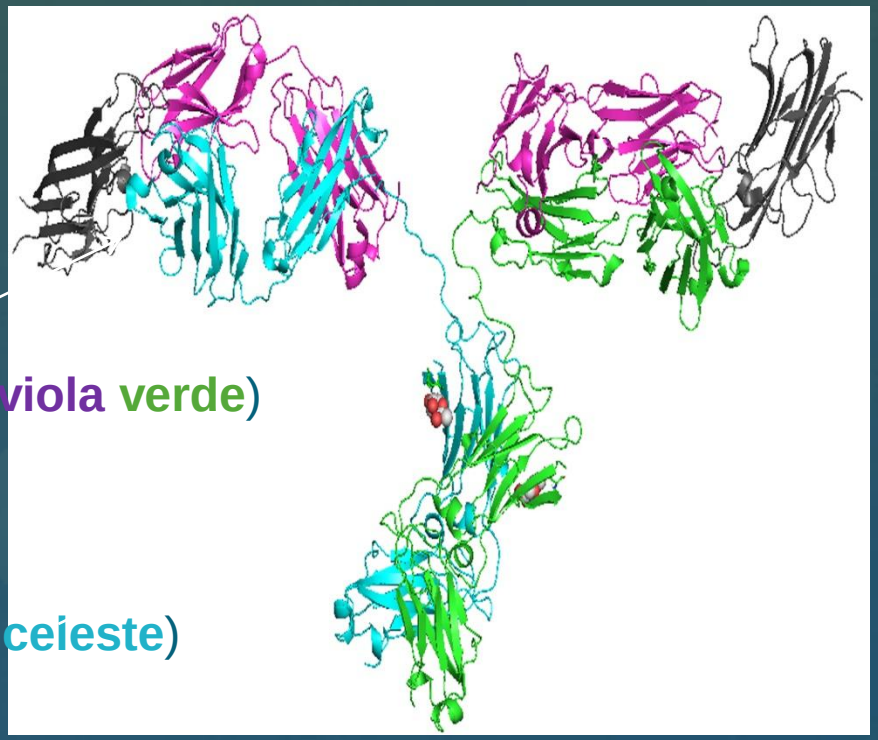
Pierri-Tricarico The FASEB J April 2015
www.fasebj.org/content/29/1.../941.9.short

Rappresentazione 3D interazione di Infliximab + TNFalfa + recettore FCγIII

Infliximab+TNFalfa+recettore



Infliximab+TNFalfa



Modello 3D in silico *che include la porzione FAB di Infliximab complessato con TNFalpha (coordinate cristallografiche 4G3Y.pdb), il frammento Fc di un anticorpo IGhG1 fucosilato (3SGJ) e il corrispondente non fucosilato (3SGK) complessato con il recettore FcγRIIIa.*

La sovrapposizione molecolare dei mAbs-TNF alfa fucosilato e non fucosilato complessati con il recettore FcγRIIIa ci ha permesso di quantificare e comparare il numero di interazioni e la qualità in termini di distanza interatomica nei due casi.

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Pierri-Tricarico The FASEB J April 2015
www.fasebj.org/content/29/1.../941.9.short

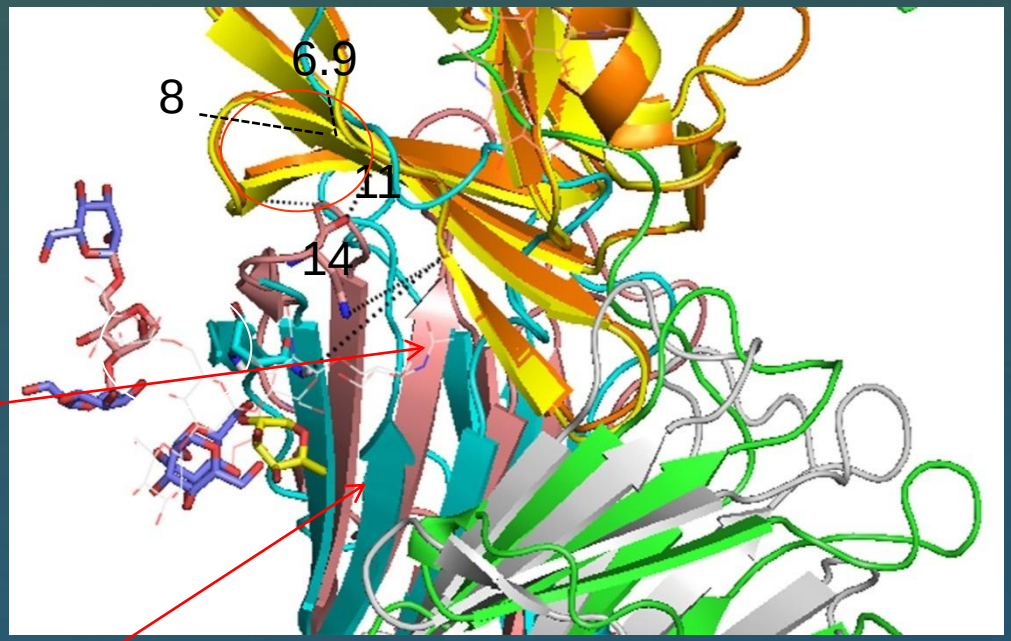
Sovrapposizione 3D di due cristalli di Infliximab-TNFalfa in presenza ed in assenza di fucosio

2 Å. risoluzione

Cristallo 3SGK umano

FCγIIIdelta/NAG(in giallo) - IGg1 mab (**in rosa-grigio**) in assenza di fucosio ma con mannosio (in **violetto-rosso**) .
Asn 297 (in **rosa-rosso**) su beta sheet del mab (**in rosa**).

<u>In assenza di fucosio nell' originator</u>
3 interazioni pari a 8, 6.97 ed 11 Å si possono misurare tra la Asn 297 (in viola-rosso) del mAb e il recettore (in giallo).



Cristallo 3SGJ umano

In presenza di **Fucosio** (**giallo-rosso**), l' Asn 297 (**celeste-rosso**) si orienta in basso distorcendo il beta sheet del mAb (**ciano-verde**) allontanando l'Asn 297 dal recettore FCγIIIdelta/NAG (**marrone**)

<u>In presenza di Fucosio nel biosimilare</u> **1 sola interazione** si può misurare con il recettore pari a 14 Å.

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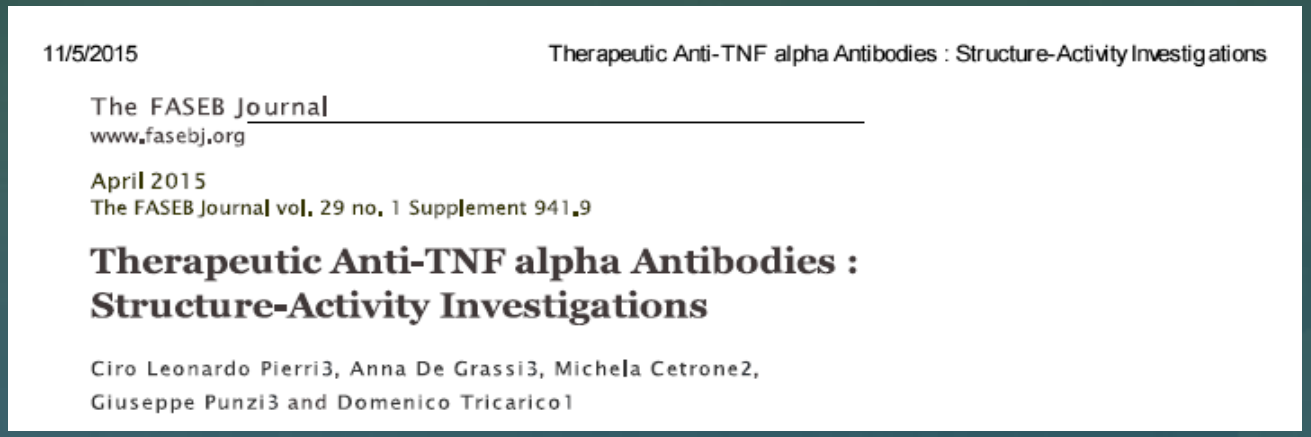

11/5/2015 Therapeutic Anti-TNF alpha Antibodies : Structure-Activity Investigations

The FASEB Journal
www.fasebj.org

April 2015
The FASEB Journal vol. 29 no. 1 Supplement 941.9

Therapeutic Anti-TNF alpha Antibodies : Structure-Activity Investigations

Ciro Leonardo Pierri3, Anna De Grassi3, Michela Cetrone2, Giuseppe Punzi3 and Domenico Tricarico1

Nel nostro studio in silico

il basso numero di interazioni misurato in presenza di fucosio spiega la riduzione dell'affinità della forma fucosilata biosimilare vs la forma non fucosilata dell' infliximab originator nei confronti del recettore Fc e la perdita di attività ADCC del biosimilare osservata negli studi non clinici pre-registrativi.

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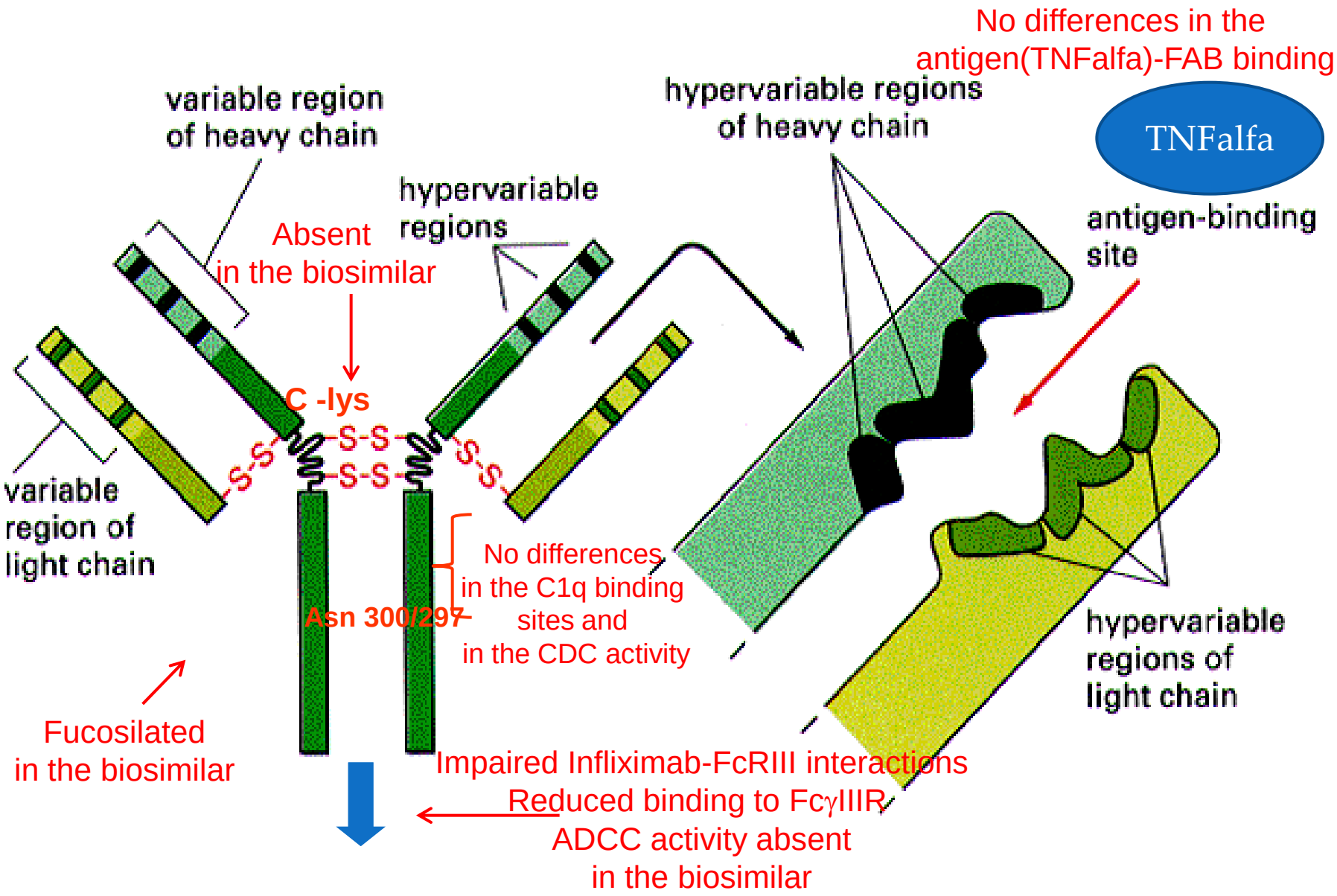
Non clinical differences between Infliximab Biosimilar vs Originator



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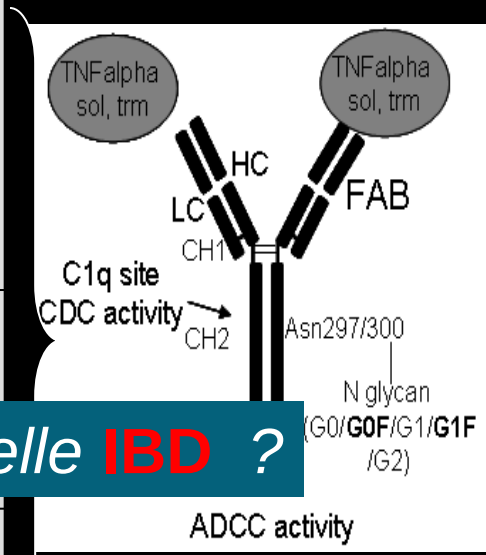
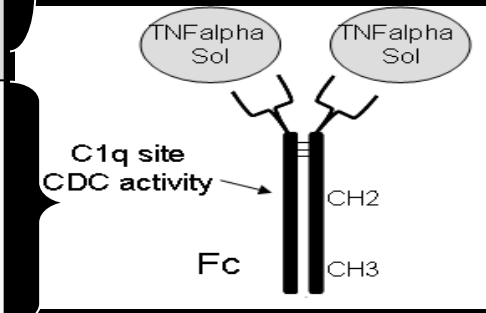
Modeling of chimeric mAbs for the treatment of the TNFalpha related immunological diseases

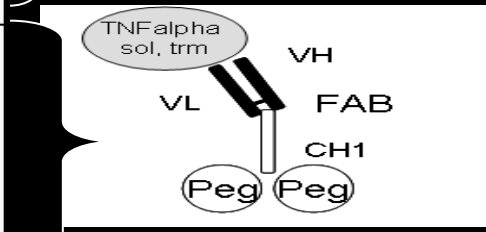
Ciro Pierri-Domenico Tricarico. submitted to Pharmacological Res & Perspective ASPET 2015

Infliximab (Remicade®) Bivalent chim. anti-TNF-alpha mAb **Remisima®-Inflectra® (Biosimilars)** Bivalent chim. anti-TNF-alpha mAb	1) Block of TNF-alpha (sol, trm)mono/trim. 2) Fc receptor interactions **2) Biosimilars : No Fc gamma III receptor interaction** 3) Apoptosis 4) CDC 5) ADCC **5) Biosimilars: No ADCC activity**	- rheumatoid arthritis - ankylosing spondylitis - psoriasis, psoriatic arthritis -Chron's D. and ulcerative colitis in adult and pediatric patients **Biosimilars : Chron's D. and ulcerative colitis in adult and pediatric patients following extension (under investigations)**
Adalimumab (Humira®) Bivalent human anti-TNF-alpha mAb	1) Block of TNF-alpha (sol, trm)mono/trim. 2) Fc receptor interactions 3) Apoptosis	- rheumatoid arthritis - ankylosing spondylitis - psoriatic arthritis, psoriasis
Golimumab (Simponi®) Bivalent human anti-TNF-alpha mAb	1) Block of TNF-alpha (sol, trm)mono/trim. 2) Fc receptor interactions 3) Reduced apoptosis 4) CDC 5) ADCC	- rheumatoid arthritis - psoriatic arthritis - ankylosing spondylitis - ulcerative colitis
Etanercept (Enbrel®) Monovalent mAb human fusion protein of TNF-alpha soluble receptor II	1) Block of TNF-alpha/beta trimeric (sol) 2) **Weak Fc receptor interactions** 3) Reduced apoptosis 4) CDC 5) **Reduced ADCC**	- rheumatoid arthritis - ankylosing spondylitis - psoriatic arthritis, psoriasis - arthritis idiophatic juv > 2AA - ----------
Certolizumab (Cimzia®) Monovalent mAb humanized anti-TNF-alpha mAb with **no Fc fragment**	1) Block of TNF-alpha (sol, trm) 2) No apoptosis 3) **No CDC** **4) No ADCC**	- rheumatoid arthritis - psoriatic arthritis - spondylitis - ---------- - ----------

Structural models







Efficacia e sicurezza dei biosimilari di Infliximab nelle **IBD** *?*

Ongoing studies to evaluate the efficacy/safety of the Biosimilar of Infliximab in IBD

Clinical Investigations Ongoing

ClinicalTrials.gov Identifier: NCT02066272 (SATIMOS)

ClinicalTrials.gov Identifier: NCT02148640 (Nor-Switch)

Clinical Trials.gov Identifier: NCT02096861 Demonstrate Non inferiority in Efficacy and to Assess Safety of CT-P13 in Patients With Active Crohn's Disease.

Structure-activity investigations of anti-TNF alpha mAbs in IBD ongoing

Linee guida

EMEA guideline on similar biological medicinal products CHMP/437/04 London, 30 October 2005

European Medicines Agency (2006) 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 (http://www.emea.europa.eu/pdfs/human/biosimilar /9452605en.pdf);
Guidance on similar medicinal products containing somatropin (http://www.emea.europa.eu/pdfs/human/biosimilar/9452805en.pdf),
Guidance on similar medicinal products containing recombinant human insulin (http://www.emea.europa.eu/pdfs/human/biosimilar/3277505en.pdf)
Guidance on similar medicinal products containing recombinant granulocyte-colony stimulating factor (G-CSF) (http://www.emea.europa.eu/pdfs/human/biosimilar/3132905en.pdf)

European Medicines Agency (2007) Guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins
(http://www.emea.europa.eu/pdfs/human/biosimilar/1432706enfin.pdf)

EMA adopts guideline on biosimilar monoclonal antibodies 11/02/2011

22 May 2014
EMA/CHMP/BWP/247713/2012
Committee for Medicinal Products for Human Use (CHMP)

GRAZIE PER L'ATTENZIONE

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