Fc-fusion proteins: therapeutic relevance and quality assessment

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INTRODUCTION

Fc-fusion proteins are bioengineered polypeptides that combine a biologically active protein with the crystallizable fragment (Fc) domain of an IgG to produce a molecule with unique properties and therapeutic potential (Linderholm and Chamow, 2014). Owing to its interaction with the salvage neonatal Fc-receptor, Fc domain substantially increases plasma half-life *in vivo* and reduces the clearance of Fc-fusion proteins, which prolongs their therapeutic activity (Czajkowsky et al., 2012). In addition, Fc fragment improves the solubility and stability of the fusion protein (Carter, 2011). Fc fusion proteins are very successful class of medicines with already 13 Fc-fusion proteins approved in the EU and in the USA (EMA, 2022; U.S. FDA, 2022). Currently four therapeutic Fc-fusion proteins including aflibercept, dulaglutide, etanercept and abatacept are among the 50 globally best-selling medicines (Buntz, 2022).

MATERIALS AND METHODS

In this work were used the data from biomedical and life sciences journals, information obtained from websites of drug regulatory agencies and other medical information sources

RESULTS AND DISCUSSION

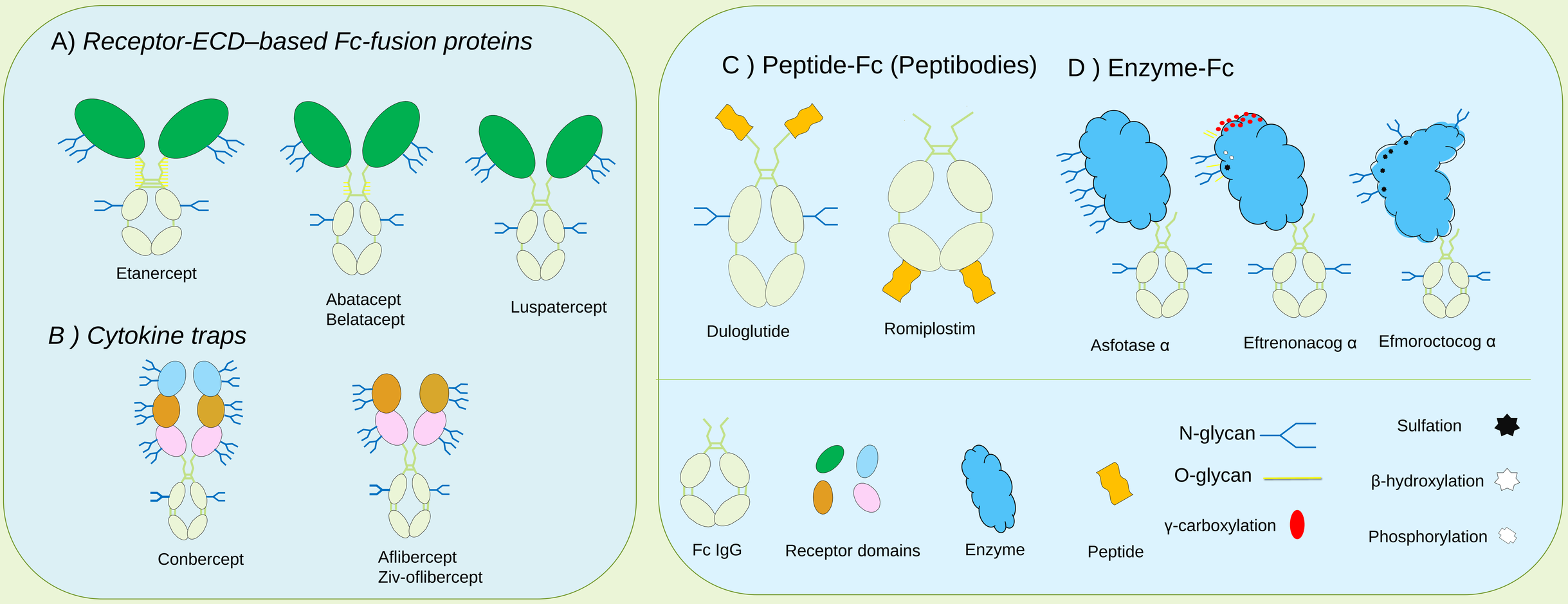

Figure 1. Construction of selected classes Fc-Fusion Proteins. Fusion partners and PTM are highlighted. According Duivelshof et al, 2021, slightly modified

Table 1. Approved Fc-fusion proteins.

Trade name (iNN)	Description	Indication of first FDA approval	FDA Approval	Company
Enbrel (etanercept)	TNFR fused to the Fc of human IgG1	Rheumatoid arthritis	1998	Amgen/Pfizer
Orencia (abatacept)	Mutated CTLA-4 fused to the Fc of human IgG1	Rheumatoid arthritis	2005	Bristol-Meyers Squib
Arcalyst (rilonacept)	IL-1R fused to the Fc of human IgG1	Cryopyrin-associated periodic syndromes	2008	Regeneron Pharmaceuticals
NPlate (romiplostim)	Thrombopoietin-binding peptide fused to the Fc of human IgG1	Thrombocytopenia in chronic immune thrombocytopenic purpura patients	2008	Amgen/Pfizer
Nulojix (belatacept)	CTLA-4 fused to the Fc of human IgG1	Organ rejection	2011	Bristol-Meyers Squibb
Eylea (aflibercept)	VEGFR1/VEGFR2 fused to the Fc of human IgG1	Age related macular degeneration	2011	Regeneron Pharmaceuticals
Zaltrap (ziv-aflibercept)	VEGFR1/VEGFR2 fused to the Fc of human IgG1	Age related macular degeneration	2012	Sanofi Aventis
Lumitin (conbercept)	VEGFR1/VEGFR2 fused to the Fc of human IgG1	Age related macular degeneration	2013 (CFDA)	Chengdu Kanghong Co. Ltd.
Elocta (efmoroctocog α)	recombinant Factor VIII fused to human IgG1 Fc	Hemophilia A	2014	Swedish Orphan Biovitrum AB
Alprolix (eftrenonacog α)	recombinant Factor VIII fused to human IgG1 Fc	Hemophilia B	2014	Bioverativ Therapeutics Inc.
Strensiq (asfosfatase α)	Catalytic domain TNSALP fused to the human IgG1 Fc	treatment of perinatal/infantile- and juvenile-onset hypophosphatasia	2015	Alexion Pharmaceuticals, Inc
Trulicity (dulaglutide)	GLP-1 fused to human IgG4 Fc	Type 2 diabetes mellitus	2015	Eli Lilly
Reblozyl (luspatercept)	Modified ECD of actRIIb fused to human IgG1 Fc	Anemia treatment in patients with beta thalassemia	2019	Bristol-Meyers Squib

CFDA = Chinese food and drug administration

CONCLUSION

The unique functional properties of the Fc-fusion proteins, such as half-life extension and great therapeutic potential, place these medicines in the front line of drug research and development. The diversity of the Fc-fusion proteins, along with the rapid grow of their biosimilars, impose the need for implementation of specific and highly sensitive chromatographic and electrophoretic techniques for the quality assessment of the CQAs of the Fc-fusion proteins (Nebija et al 2015).

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