Review

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Fc fusion as a platform technology: potential for modulating immunogenicity

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The platform technology of fragment crystallizable (Fc) fusion, in which the Fc region of an antibody is genetically linked to an active protein drug, is among the most successful of a new generation of bioengineering strategies. Immunogenicity is a critical safety concern in the development of any protein therapeutic. While the therapeutic goal of generating Fc-fusion proteins has been to extend half-life, there is a critical mass of literature from immunology indicating that appropriate design of the Fc component has the potential to engage the immune system for product-specific outcomes. In the context of Fc-fusion therapeutics, a review of progress in understanding Fc biology suggests the prospect of engineering products that have an extended half-life and are able to modulate the immune system.

Therapeutic Fc-fusion proteins

Biologically active proteins are playing an increasingly important role in the clinical management of some of the most challenging human diseases. Despite the vast diversity of proteins that can be exploited to modulate disease pathways, almost half of all protein therapeutics approved by the US FDA since 2009 have been monoclonal antibodies (mAbs) [1]. Given the range of protein–protein interactions, the specificity of natural ligand–receptor interactions, and the complexity of disease pathologies, it is often necessary to expand the repertoire beyond mAbs *per se*. In addition, many of the clinical benefits of protein therapeutics have come from replacement therapy for a defective protein [2], for which mAbs have limited utility.

The dominance of mAbs among protein therapeutics is largely due to their biological and pharmacological properties, many of which reside in the immunoglobulin (Ig) constant region Fc domain. The Fc domain of IgG salvages the protein from endosomal degradation by binding to the neonatal Fc receptor (FcR) (FcRn), facilitating recycling [3]. Proteins or peptides lacking a functional Fc may fail as drug products because they have a very short serum half-life due to fast renal clearance. Thus, so-called Fc-fusion technologies, in which the Ig Fc is fused genetically to a protein of interest, have emerged to confer antibody-like properties on proteins and peptides of therapeutic interest [4]. In addition to increasing serum half-life, Fc fusion has also resulted in an improvement in other properties such as stability and solubility. The use of this technology is advantageous for the manufacturing process because Fc fusion often results in increased expression and/or secretion and protein A affinity purification of Fc-fusion proteins simplifies the downstream purification of the protein drug. Consequently, Fc-fusion proteins have enjoyed considerable success in terms of the number of products approved, their application to diverse disease areas, and the value of global sales [5,6].

In the development and licensing of any therapeutic protein, immunogenicity is an important concern, as the development of neutralizing antidrug antibodies (nADAs) can affect both the safety and efficacy of the drug [7]. FDA guidance on immunogenicity (http://www.fda.gov/downloads/Drugs/./Guidances/UCM192750.pdf) states that primary sequence considerations are especially important in the evaluation of the immunogenicity of fusion proteins, because immune responses to neoantigens formed in the joining region may be elicited. Beside these considerations, which are common to all bioengineered protein therapeutics, Fc-based drugs demand additional considerations because interactions between the Fc domain and its receptors have immunological consequences. On the one hand, these interactions raise concerns about the long-term use of these products, which are often employed to treat chronic conditions. On the other hand, a suitably engineered Fc partner has the potential to improve the safety profile of biological agents or even play an active role in the treatment of disease.

Here we briefly review Fc interactions and discuss these in the context of Fc-based therapeutics. Such interactions have a potential impact on existing first-generation

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Fc-fusion proteins but can also be modulated to achieve desired therapeutic outcomes [8,9]. For example, a new generation of therapies might use Fc derived from different Ig classes for specific targeting. Fc from the IgA molecule targets the IgA FcR (FcαR) predominantly found in the mucosa, while Fc from the IgE molecule targets the IgE FcR (FcεR) to inhibit allergic responses [10–12]. We describe a novel group of fully recombinant Fc multimers designed to mimic the anti-inflammatory effects of intravenous Ig (IVIG), highlighting Stradomers™ as a case study [13,14]. Finally, we discuss the translational value of these emerging principles; for example, how they may be applied to engineer the Fc region of fusion proteins to design drugs with improved safety and efficacy profiles.

Interactions between Fc and FcRs

Nine Fc-fusion drugs have been approved by the FDA. All nine drugs contain the Fc domain of human IgG1 with the primary purpose of extending the serum half-life of the active moiety [6] (Figure 1). In addition to FcRn, the canonical IgG FcRs (FcγRs) also tightly control Fc-based immune responses (Box 1). While such Fc–FcR interactions are commonly defined by the ability of the receptor to transmit either activating or inhibitory signals, the range of biological activities mediated by these receptors is far more complex and includes: (i) transmission of activating and inhibitory signals; (ii) phagocytosis of multivalent antibody–antigen complexes, which can result in antigen receptor recycling or antigen presentation, degranulation, and secretion of inflammatory mediators by innate immune cells; (iii) activation or inhibition of cytokine secretion; (iv) selection of B cells with higher-affinity B cell receptors; (v) antibody-dependent cell cytotoxicity (ADCC) [15]; and (vi) association with other surface proteins (e.g., Dectin1) [16].

In addition to such constitutive functions, Fc–FcR interactions can be 'fine-tuned' by the degree of Fc aggregation and the disease state of the host. Because most of these receptors are of low affinity, the size and strength of their interactions with antibodies or IgG-based fusion proteins is correlated with the degree of Fc multimerization [17]. Treatment with Fc-fusion drugs can induce aggregates

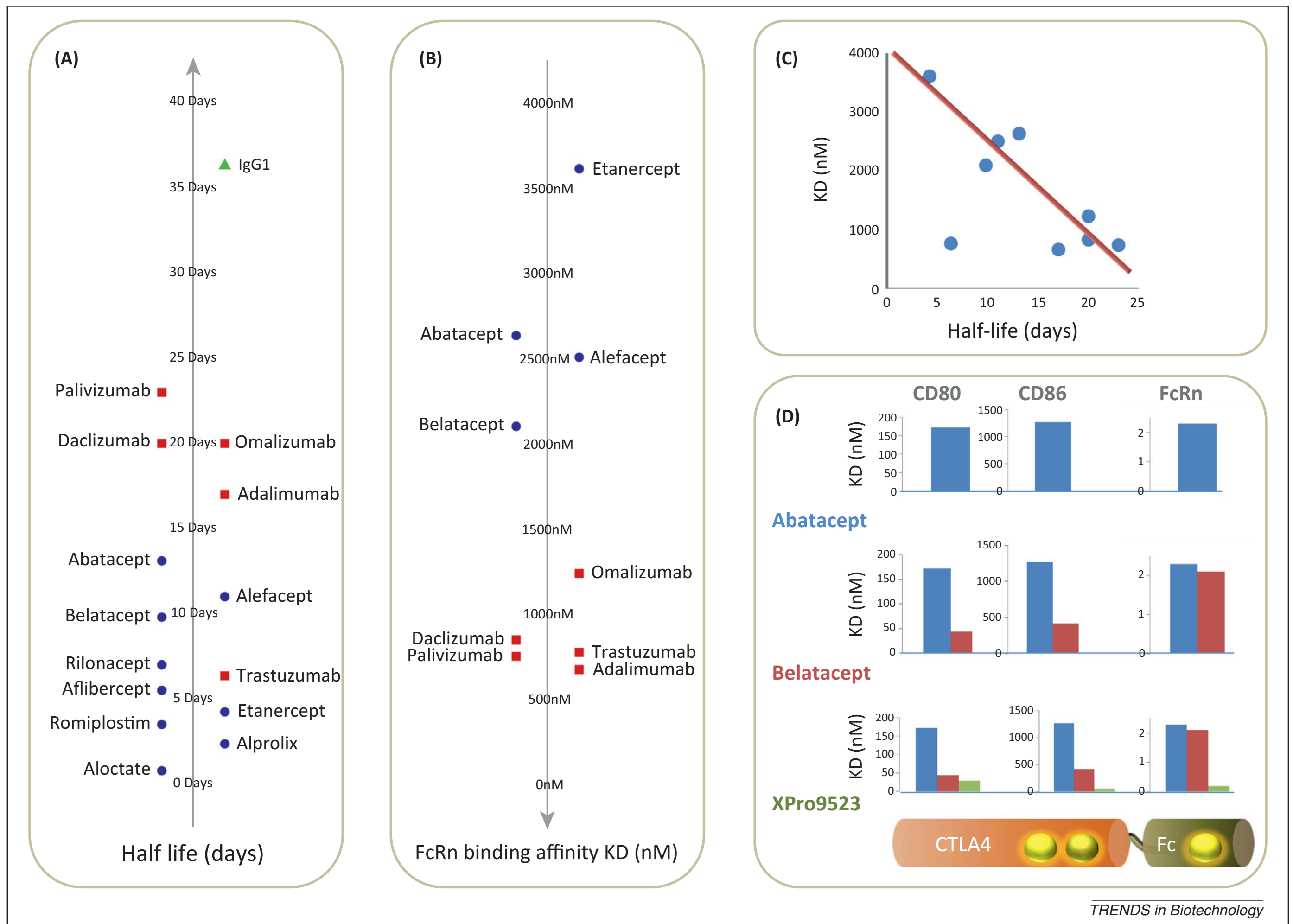

Figure 1. Properties of the fragment crystallizable (Fc) partner of fusion-protein drugs compared with therapeutic monoclonal antibodies (mAbs) and human IgG1. **(A)** Comparison of the half-life of Fc-fusion drugs (blue circles), therapeutic mAbs (red squares), and IgG1 (green triangle). **(B)** Neonatal Fc receptor (FcRn)-binding affinities (nM) of Fc-fusion drugs (blue circles) and therapeutic mAbs (red squares). **(C)** Correlation between half-life and FcRn-binding affinities of Fc-fusion drugs and therapeutic mAbs [36]. **(D)** Binding affinities for therapeutic targets (CD80, CD86) and FcRn are depicted for three generations of cytotoxic T lymphocyte-associated protein 4 (CTLA-4)–Fc-fusion drugs [72,73]. The active moiety CTLA-4 (orange cylinder) and Fc (green cylinder) were both engineered. Abatacept is the parent molecule and affinities are depicted as blue bars. The CTLA-4 domain was engineered in the second-generation belatacept, resulting in increased binding affinity for CD80 and CD86 but with no effect on affinity for FcRn (red bars). In the third-generation XPro9523, both the CTLA-4 and Fc domains were engineered, resulting in increased affinity for CD80, CD86, and FcRn (green bars).

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