Autoimmunity Reviews xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

Fc-gamma receptors: Attractive targets for autoimmune drug discovery searching for intelligent therapeutic designs

Carlos J. Bosques, Anthony M. Manning *

Momenta Pharmaceuticals, 675 West Kendall Street, Cambridge, MA 02142, USA

ARTICLE INFO

Article history:
Received 14 July 2016
Accepted 17 July 2016
Available online xxxx

Keywords:
Fc-gamma receptors
Autoimmune disease
Immune complex
Therapeutics

ABSTRACT

Autoantibody immune complexes (ICs) mediate pathogenesis in multiple autoimmune diseases via direct interference with target function, complement fixation, and interaction with Fc-gamma receptors (FcγRs). Through high avidity interactions, ICs are able to crosslink low affinity FcγRs expressed on a wide variety of effector cells, leading to secretion of pro-inflammatory mediators and inducing cytotoxicity, ultimately resulting in tissue injury. Given their relevance in numerous autoimmune diseases, FcγRs have been considered as attractive therapeutic targets for the last three decades. However, a limited number of investigational drug candidates have been developed targeting FcγRs and only a few approved therapeutics have been associated with impacting FcγRs. This review provides a historical overview of the different therapeutic approaches used to target FcγRs for the treatment of autoimmune and inflammatory diseases.

Contents

1. Introduction

Fc-gamma receptors (FcγRs) are a conserved family of cell-surface glycoproteins that recognize the Fc domain of IgG molecules and are expressed by multiple cells and tissues, including most immune cells [1–3]. Through interaction with the Fc domain of IgGs, FcγRs link the adaptive humoral immune response to the effector functions of the cells in the innate immune system, including macrophages, dendritic cells, neutrophils, natural killer cells, and mast cells [4]. The expression of FcγRs varies by cell type and depends on the activation state of the immune cells as well as individual genetic variations in the genes encoding these receptors [2,4].

* Corresponding author.
E-mail address: tmanning@momentapharma.com (A.M. Manning).

http://dx.doi.org/10.1016/j.autrev.2016.07.035
1568-9972/

Please cite this article as: Bosques CJ, Manning AM, Fc-gamma receptors: Attractive targets for autoimmune drug discovery searching for intelligent therapeutic designs, Autoimmun Rev (2016), http://dx.doi.org/10.1016/j.autrev.2016.07.035

In humans, there are six FcγRs, which differ in function, affinity, and distribution across different cell types. Signaling by FcγRs requires cross-linking of receptors, such as caused by binding to immune complexes. All but one of the FcγRs activate immune responses, typically through direct or indirect association with immunoreceptor tyrosine-based activation motif (ITAM) signaling domains [4,5]. In contrast, a single receptor, FcγRIIb inactivates immune responses through an immunoreceptor tyrosine-based inhibitory motif (ITIM) signaling domain [6]. FcγRI has high affinity (nanomolar Kd) towards the Fc portion of immunoglobulins, but the rest of the FcγRs have affinities in the micromolar range and are therefore considered low affinity receptors. Due to this low affinity, these receptors bind strongly to IgG immune complexes (ICs) containing multiple Fc domains [7]. This provides cells with the ability to distinguish between monomeric IgG and immune complexes, and thereby sense when antibody production requires further activation or down-regulation.

ICs mediate inflammatory mechanisms through their engagement of Fcγ receptors expressed in a variety of immune cells. For example, this IC–FcγR interaction can lead to cellular phagocytosis, neutrophil degranulation, cytokine release from myeloid cells, platelet activation, and antigen cross presentation, which may lead to T- and B-cell activation [4]. FcγRs bind the IgG-Fc domain within the N-terminal region of the CH2 domain, near the antibody hinge region, and the interaction depends on the IgG isotype and IgG-Fc glycosylation, providing further points of regulation and specificity in the immune response [4,8,9].

Despite promising research, progress towards the development of therapeutics targeting the FcγR family for autoimmune and inflammatory diseases has been slow, reflecting the complexity of the FcγR biology and competing development interest in soluble mediators and T cell targets. Interest in FcγRs resurfaced in light of proposals that the efficacy of intravenous immunoglobulin (IVIg) is mediated in part through FcRs [1,10]. Transgenic and humanized animal models have now been developed than can partially offset the challenge of generating proof of mechanism, dose estimation, and toxicology signals [11,12]. Consequently, a number of candidate therapeutics have been brought into early development, including agents that enhance regulatory signaling through the inhibitory FcγR, that inhibit the impact of signaling through stimulatory FcγR, or that block effector functions. In this review, we provide an overview of the evolution of drugs and drug candidates targeting FcγRs for the treatment of autoimmune and inflammatory diseases. To simplify the review, we divide the discussion of the therapeutic agents into five categories: IVIg and IgG-Fc fragments, inhibitors of activating FcγRs, modulators of inhibitory FcγRIIb, multivalent IgG-Fcs, and small-molecule inhibitors.

2. Intravenous immunoglobulins and Fc-fragments

IVIg is a complex, heterogeneous mixture of predominantly human polyclonal immunoglobulin G (IgG) originally developed as a replacement therapy for the treatment of agammaglobulinemia. However, following a serendipitous observation by Imbach in 1980 that IVIg increased platelet counts in idiopathic thrombocytopenic purpura (ITP) patients, IVIg has become the treatment option for several autoimmune and inflammatory diseases [13,14]. The mechanism of action of IVIg remains a topic of significant debate, and multiple mechanisms have been proposed to explain the efficacy of IVIg in autoimmune diseases. Both Fab- and Fc-mediated pathways have been proposed, and each may play a role in some disease states. In particular, Fc-mediated mechanisms have generated significant interest over the last three decades.

Some of the proposed IVIg Fc-mediated mechanisms may involve the antagonism of cellular activation through direct inhibition of activating Fcγ receptors (FcγR) and indirect antagonism through upregulation of the inhibitory FcγRIIb [10]. Significant evidence has been reported to support each proposed modulatory pathway, and because IVIg was not intentionally designed to target a specific anti-inflammatory mechanism, it is plausible that multiple mechanisms may be involved under different conditions. Nonetheless, the numerous reports documenting the anti-inflammatory effects of IVIg and its components in animal models and humans provide significant rationale for designing targeted, more efficacious drugs. For example, given the potential Fc-mediated anti-inflammatory activity of IVIg, IgG-Fc fragments have been extensively studied and have demonstrated good efficacy in animal models of rheumatoid arthritis (RA) [15,16], ITP [17], and immune complex-driven nephritis [18]. More importantly, they have also shown to be efficacious in patients with ITP [19] or Kawasaki disease [20]. Although these clinical observations have not yet translated into licensed therapeutic products, they have sparked significant interest in designing IgG-Fc-derived drug candidates or molecules able to intervene in IgG-Fc–FcγR interactions. Examples of these are discussed below.

3. Therapeutic candidates targeting activating FcγRs

Inhibition of FcγR-mediated cellular activation has long been proposed as an attractive approach to inhibit pro-inflammatory mechanisms and cellular/tissue damage in autoimmune diseases. However, designing optimal therapeutic antagonists has proved challenging due to the complexity of the FcγR system. For example, multiple FcγRs may be involved in concomitant and redundant pro-inflammatory signaling pathways. This redundancy makes it challenging to target one specific FcγR with selective monoclonal antibodies to inhibit broad pro-inflammatory processes. High sequence homology among different FcγRs, including activating and inhibitory receptors such as FcγRIIa, FcγRIIc, and FcγRIIb, has also complicated the development of specific anti-FcγRs antibodies. Furthermore, broad interactions between immune complexes and different FcγRs are drivers of pro- and anti-inflammatory events. However, the specific structural determinants controlling these interactions are poorly understood, thus making it challenging to design broad antagonists of IC-driven FcγRs activation.

Fc-gamma receptors are expressed in humans, including FcγRI, FcγRIIa, FcγRIIc, and FcγRIIIa [1]. Targeting the activating FcγRIIIa with an antibody was the first example of a promising therapeutic approach for an autoimmune disease, and over the years, several specific antibodies targeting the activating FcγRs have been developed and subjected to preclinical and clinical testing (Table 1).

3.1. Anti-FcγRI

A humanized version of the murine H22 monoclonal antibody, MDX-33 (Medarex), binds to and downregulates FcγRI on human peripheral monocytes [21]. In a phase 1 study in healthy volunteers ($N = 17$), MDX-33 produced marked immunomodulation, with down-regulation of monocyte CD64 for >6 days after dosing [22]. The primary toxicities were chills, fever, headache, and muscle ache [22]. In a phase 2 study in patients with stable chronic ITP, a single dose of MDX-33 transiently elevated platelet counts [23]. Adverse events (AEs) were generally mild and similar to those reported in phase 1 testing. Although these data were generally positive, MDX-33 did not show sufficient promise, and development was discontinued [24].

The murine monoclonal antibody H197, which binds to two epitopes of FCγRI, was evaluated in a patient with refractory ITP. Clinical improvement and down-modulation of monocyte expression of FCγRI was observed but no alteration in platelet counts occurred [25]. No further studies are reported.

3.2. Anti-FcγRIIa

A potential role for monoclonal antibodies directed against FcγRIIa in autoimmune disorders has also been investigated [26]. An in vitro study using engineered Fc variant antibodies demonstrated enhanced macrophage phagocytosis of tumor cells [26]. Although to date, no such antibodies have entered clinical trials. TTI-314 (Trillium

Please cite this article as: Bosques CJ, Manning AM, Fc-gamma receptors: Attractive targets for autoimmune drug discovery searching for intelligent therapeutic designs, Autoimmun Rev (2016), http://dx.doi.org/10.1016/j.autrev.2016.07.035

Table 1
Therapeutics and therapeutic concepts targeting FcγRs for the treatment of autoimmune and inflammatory diseases.

Class	Therapeutic candidate	Product	Stage of development	Summary: benefits/limitations
Intravenous immunoglobulins and Fc-fragments	• Intravenous immunoglobulin	• IVIg (multiple commercial products available)	• 1980: pilot study in ITP (N = 6) [13,14] • 1981: pilot study in ITP (N = 13) [14] • 1980s–90s: multiple reports and clinical trials in autoimmune diseases [105] • 1984: IVIg approved by the FDA • 2016: 9 products currently approved by the FDA for various indications, including ITP, Kawasaki syndrome, and neuropathy [106]	• Platelet count increased in ITP • No severe adverse reactions • Non-specific
Targeting activating FcγRs	• Anti-FcγRI	• MDX-33 (humanized H22 monoclonal antibody)	• 1997: phase 1 in HV (N = 17) [22] • 2000: phase 2 in ITP (N = 30) [23] • 2003: reported to be discontinued [24]	• Evidence of immunomodulation • Transient increases in platelet counts • AEs included chills, fever, headache, muscle ache
		• H197 (murine monoclonal antibody)	• 2003: case study in ITP (N = 1) [25] • No further reports	• Evidence of immunomodulation • No alteration in platelet counts • AE of monocytopenia
	• Anti-FcγRIIa	• TTI-314	• 2013: discontinued during preclinical development [27]	• No published data
	• Anti-FcγRIIIa	• 3G8 (monoclonal murine antibody)	• 1986: case report in ITP (N = 1) [28] • 1988: pilot study in ITP (N = 7) [29] • 1993: case report in ITP (N = 1) [31] • 2009: pilot study in ITP (N = 11) [30]	• Generally short-term increased platelet counts • Repeated dosing resulted in attenuated response • Patients developed HAMAs • 2 patients died from ARDS • AEs included chills, fever, nausea and vomiting
		• GMA161 (humanized and chemically modified version of 3G8)	• 2006: pilot/phase 1 in ITP (N = 4; terminated early due to low enrollment) [30,33,34] • 2011: reported to be discontinued [35]	• Short-lived increased platelets • Transient WBC decreases • AEs included chills, fever, and vomiting
		• scFv–HSA fusion protein	• 2016: preclinical data only [36]	• Shows promise in murine ITP model • Potential for reduced toxicity
		• Afucosylated antibodies	• 2014: preclinical data only [37]	• Unclear
Targeting inhibitory FcRIIb	• Soluble FcγRIIb	• SM101/BAX 1810	• 2012: phase 1b/2a in ITP (N = 36) [40] • 2014: phase 2a in SLE (N = 51) [42] • 2016: phase 2 in IgA nephropathy (withdrawn) [44] • Development ongoing	• Ameliorated symptoms in 75% of ITP patients and 40% of SLE patients • AEs included infusion site reactions and WBC decrease • No anti-drug antibodies reported
	• Anti -FcγRIIb	• hu2B6/MGA 321	• 2007: preclinical data only [51] • 2016: reported to be discontinued [52]	• Unclear
		• SM201, SM211, SM301	• 2016: preclinical data only [43]	• Unclear
		• BI-1206	• 2015: preclinical data only [47]	• May be able to overcome resistance in B-cell malignancies • Effect in autoimmune diseases is unexplored
	• Forced co-localization of BCR and FcγRIIb	• XmAb5871	• 2015: phase 1b/2a in RA (N = 57) [55] • Development ongoing	• Reduced disease activity levels in 33% of RA patients • AEs included nausea, vomiting, diarrhea • Serious infusion-related reaction and venous thrombosis
		• XmAb7195	• 2016: phase 1 in HV (N = 72) [58]	• Appears to be in development for subjects with allergies
		• MGD010	• 2016: phase 1 in HV (N = 48) [60]	• Potential for efficacy in SLE • Favorable safety profile in non-human primates
Recombinant multimeric IgG-Fc	• Stradomer	• GL-2045	• 2015: preclinical data only [72] • Development ongoing	• May be able to increase treatment efficacy • Not yet tested in humans
	• SIF	• M230	• 2016: preclinical data only [80] • Development ongoing	
	• Hexamer	• HexaGard	• 2016: awaiting commercialization [79]	
Small-molecule inhibitors	• Syk inhibitors	• R406	• 2006: phase 1 in HV (N = 35) [83]	• Oral administration • Efficacy in animal models of RA • AEs include postural dizziness
		• R788/fostamatinib	• 2006: phase 1 in HV (N = 100) [84] • 2008–2015: phase 2 in RA (4 studies, N = 1144) [86–89] • 2009: phase 2 in ITP (N = 16) [82] • 2010: phase 2 in NHL and CLL (N = 68) [85] • 2014: phase 3 in RA (2 studies, N = 1241) [90,91] • 2014: development in RA terminated • 2015: orphan drug designation for ITP [92] • 2016: phase 3 in ITP underway (3 studies) [93–95]	• Oral administration • Efficacious in ITP and lymphoma • Mixed results from RA • AEs include GI-related toxicities, fatigue, cytopenias, hypertension, and liver enzyme abnormalities • Up to 7% of RA patients experienced serious AES, and 3 patients died • Safety profile may have impacted on efficacy in RA • Phase 3 results in ITP available in 2016

(continued on next page)

Please cite this article as: Bosques CJ, Manning AM, Fc-gamma receptors: Attractive targets for autoimmune drug discovery searching for intelligent therapeutic designs, Autoimmun Rev (2016), http://dx.doi.org/10.1016/j.autrev.2016.07.035

Table 1 (*continued*)

Class	Therapeutic candidate	Product	Stage of development	Summary: benefits/limitations
		• R112	• 2005: phase 2 in allergic rhinitis (2 studies, N = 715) [96,97] • 2006: development discontinued	• Positive results in one study but failed to meet primary endpoint in a second • Clinically insignificant AEs
		• GS-9973/entospletinib	• 2016: phase 2 in hematologic malignancies [99]	• No published data available
		• GS-9876	• 2016: phase 1 in autoimmune disorders [99]	
		• PRT062070/cerdulatinib	• 2016: phase 1/2a in hematologic malignancies [101]	
		• PRT2761	• 2016: preclinical [102]	
		• SKI-O-703	• 2016: preclinical [103]	
	• Pyrazole derivatives	• 1-phenyl-pyrazole compound	• 2013: preclinical [104,107]	• Evidence of immunomodulation • Low to negligible toxicity in animal models • No clinical data to date

AE, adverse event; ARDS, acute respiratory distress syndrome; CLL, chronic lymphocytic leukemia; HAMA, human anti-mouse antibodies; HV, healthy volunteers; ITP, idiopathic/immune thrombocytopenic purpura; NHL, non-Hodgkin lymphoma; RA, rheumatoid arthritis; SIF, selective immunomodulatory of Fc receptors; SLE, systemic lupus erythematosus; WBC, white blood cell.

Therapeutics) was in preclinical development for disorders including systemic lupus erythematosus (SLE), RA, and ITP, but the program was discontinued in 2013 [27].

3.3. Anti-FcγRIIIa

In small studies and a case report, the mouse monoclonal anti-FcγRIII antibody (3G8) demonstrated increases in platelet counts in patients with ITP [28–31]. The case report discussed a patient who was intravenously infused with two doses of 3G8 (25 mg and 42 mg). Doses were administered a week apart [28]. After receiving the first dose the number of platelets increased to 22,000 mm^3 in 6 h and continued to rise to a peak of 305,000 mm^3 until receiving the second dose [28]. In one of the small studies, patients (N = 7) were infused with an initial dose of 3G8 25 mg. In the first week, subsequent infusions were given to patients whose platelet counts did not respond to the initial infusion. Five patients had significant increases in platelet counts; 4 of these required just a single infusion [29]. In another study, 11 patients with low platelet counts after splenectomy were infused with 3G8 25 mg, with 55% (6/11) patients responding to treatment [30]. In another study, an HIV-positive patient with refractory ITP was infused with 3 doses (25 mg, 25 mg, and 50 mg) of 3G8 in 8 days [31]. The patient's platelet count initially lowered and then rebounded to a higher level with each injection, although the 50 mg dose demonstrated an increase of up to 60,000 mm^3 [31]. In each of these studies, the improvements were generally not sustained after infusion (i.e., platelet counts decreased in the weeks following treatment), and the antibody proved suboptimal for further clinical development due to significant immunogenicity. Several patients developed high titers of human anti-mouse antibodies, 2 patients with pre-existing lung conditions died shortly after infusion from acute respiratory distress syndrome, and fever, chills, and vomiting were commonly reported [28–31].

A second-generation humanized anti-FcγRIII antibody (GMA161, Genzyme/MacroGenics) was subsequently engineered, with the Fc portion devoid of carbohydrates, in an attempt to reduce binding to Fc receptors, minimize neutrophil and monocyte depletion, and limit cytokine release [32]. An open-label, single ascending-dose study in patients with ITP who had failed splenectomy and previous therapies was terminated early due to low enrollment [33]. Two of the first 4 patients who received GMA161 had short-lived increases in platelet counts and decreases in white blood cells [30,34]. As with 3G8, AEs included fever, chills, and vomiting [30,34]. A subsequently published non-clinical evaluation study for GMA16 in human transgenic mouse models containing both FcγRIII forms (FcγRIIIa and FcγRIIIb) suggested atypical hypersensitivity reactions mediated by platelet activating factor (PAF) [32], and development was discontinued [35].

More recently, novel approaches have emerged to leverage the therapeutic efficacy of anti-FcγRIII antibodies while circumventing their original limitations of suboptimal efficacy and high toxicity. Because modifications to the Fc region of GMA161 did not improve toxicity, some researchers focused on development of a monovalent Fab fragment for ITP therapy. One example is the anti-FcγRIIIa–Fab–albumin fusion protein, scFv–HSA, which retained the ability to inhibit the IgG–FcγRIIIa interaction in vitro [36]. A murine version of scFv–HSA has demonstrated efficacy in ITP mouse models, suggesting that AEs associated with previous anti-FcγRIII antibodies may be overcome by monovalent FcγR blockade [36].

Other research has focused on building antibodies with enhanced binding capabilities to FcγRIIIa, using glyco-engineering techniques to remove fucose moieties in the Fc region of the antibody [37]. This approach appears to induce higher rates of cellular toxicity in vitro [37] and has proven beneficial in the development of several anti-cancer therapeutics. It remains unclear whether such modifications will prove useful for the clinical treatment of autoimmune diseases.

4. Therapeutic candidates targeting inhibitory FcγRIIb

FcγRIIb is the primary inhibitory/regulatory Fc receptor in humans, and the primary FcγR expressed on B cells [1]. Activation of B cells by specific antigens through the B-cell receptor (BCR) leads to activation, proliferation, differentiation, specific antibody production, and initiation of a regulatory process that involves FcγRIIb expression [1]. When sufficient antibody is generated to engage most of the antigen in immune complexes (IC), IC co-localizes the BCR and FcγRIIb on antigen-specific B cells, leading to cell cycle arrest and regulation of inflammatory mediators, including IL-4, LPS, and BAFF [38]. Multiple lines of evidence indicate that dysfunction of FcγRIIb-dependent B-cell regulation contributes to failure of peripheral tolerance in systemic lupus (SLE), lupus nephritis (LN), chronic inflammatory demyelinating neuropathy (CIDP), and other autoimmune diseases, and that restoration of function may reduce production of autoantibodies and ameliorate disease [1,38,39]. Several novel approaches to therapeutic targeting of FcγRIIb are currently under investigation (Table 1).

4.1. Soluble FcγRIIb

A recombinant, soluble, human FcγRIIb (SM101; Baxalta [formerly SuppreMol]) is thought to compete with membrane-bound FcγR in the binding of ICs, resulting in down-modulation of the immune response [40]. SM101 has received orphan drug status for ITP in the US and Europe [41]. In ITP patients, treatment with SM101 resulted in sustained increases in platelet counts [40]. Treatment-related AEs included leukopenia/neutropenia and infusion site reaction and no anti-

Please cite this article as: Bosques CJ, Manning AM, Fc-gamma receptors: Attractive targets for autoimmune drug discovery searching for intelligent therapeutic designs, Autoimmun Rev (2016), http://dx.doi.org/10.1016/j.autrev.2016.07.035

drug antibodies were detected [40]. Promising results were also reported in a study of patients with SLE ± LN: 39% (n = 18) and 36% (n = 22) of patients responded to treatment with 6 and 12 mg/kg SM101, respectively, vs 18% (n = 11) of placebo-treated patients [42]. No safety signals attributable specifically to SM101 were reported [42]. SM101 remains in early clinical development [43], although a phase 2 trial in patients with immunoglobulin A nephropathy was recently withdrawn [44], and no other trials are ongoing.

4.2. Anti-FcγRIIb

SM201 (Baxalta [formerly SuppreMol]), a monoclonal antibody specific to FcγRIIb, which targets activated B cells but does not affect resting B cells, is in development. This would potentially allow down-modulation of autoreactive B cells in autoimmune diseases, while retaining a functional memory response [45]. SM201 is in preclinical development, as are several other anti-FcγRIIb antibodies (SM211 and SM301) [43,46].

In preclinical studies, the FcγRIIb-blocking antibody BI-1206 (BioInvent) was evaluated in chronic lymphocytic leukemia (CLL) and mantle cell lymphoma (MCL) hFcgRIIB-transgenic mice models [47]. The CLL model utilized primary human CLL cells that proliferated in clusters, whereas the MCL model involved immunodeficient mice engrafted with JeKo or primary MCL cells to model human conditions [47]. A tumor-suppressing effect that was able to overcome resistance to treatment with the CD20-specific antibody rituximab by preventing drug destruction was observed [47]. BI-1206 is scheduled to enter phase 1/2 clinical testing shortly to evaluate BI-1206 alone or in combination with rituximab for B-cell malignancy [48,49]. BI-1206 has not been evaluated in autoimmune disease.

hu2B6-3.5 (MacroGenics) is a humanized monoclonal antibody specific to FcγRIIb, capable of directing cytotoxicity against mononuclear cells in vitro and able to reduce tumor growth rates in mouse xenograft models of human B-cell lymphoma [50,51]. It was hypothesized that such antibodies could be used to aggregate FcγRIIb to generate a pro-apoptotic signal independent of the BCR; to date, no clinical data have been generated [52], and the company is developing dual affinity antibodies such as MGD010 (discussed later).

4.3. Forced co-localization of BCR and FcγRIIb

One potential mechanism which could be exploited for therapeutic intervention in autoimmune diseases is the forced co-localization of BCR and FcγRIIb independent of cognate antigen. Researchers have produced a number of antibodies targeting B cells which have been engineered to bind selectively, and with high affinity, to FcγRIIb.

XmAb5871 (Xencor) contains an Fc domain with high affinity for FcγRIIb combined with a humanized Fv domain that recognizes human CD19 [38]. This antibody targets all CD19 B cells, blocking BCR-induced activation and suppressing the immune response in severe combined immunodeficiency mice [38]. Preclinical data also suggest a role in the treatment of RA [53,54] In RA patients, XmAb5871 10 mg/kg reduced disease activity levels; AEs included nausea, vomiting, infusion-related reactions, and venous thrombosis [55]. Development of this product for the treatment of moderate to severe RA and IgG4-related disease is ongoing [56].

XmAb7195 (Xencor) contains a mutated Fc domain with high affinity for FcγRIIb, combined with a humanized Fv domain that engages only IgE, effectively sequestering IgE. [57] This antibody is currently in phase 1 trials in healthy volunteers and patients with allergies [58].

MGD010 (MacroGenics) is a bi-specific molecule that co-ligates the inhibitory FcγRIIb and the BCR component CD79B on B cells. In ex vivo samples from patients with autoimmune disorders, MGD010 blocked B-cell activation, and in animal models, it was able to inhibit humoral immune response [59]. MGD010 entered clinical development in 2015, and a phase 1 study in healthy volunteers is ongoing [60,61].

5. Indirect modulation of FcγRIIb

Indirect modulation of the inhibitory FcγRIIb has emerged as one of the proposed anti-inflammatory mechanisms of action of IVIg [1,2,10]. Clinical studies have shown a relationship between the levels of Fc-sialylation in circulating antibodies and diseases severity as well as an increase in Fc-sialylation upon treatment with IVIg [62–64]. More importantly, in a series of studies in animal models of autoimmune diseases, it was demonstrated that Fc-sialylation serves as an anti-inflammatory modulator through indirect upregulation of FcγRIIb [65–67]. These findings led to the development of a tetra-Fc-sialylated IVIg therapeutic candidate which exhibited a significant enhancement of anti-inflammatory activity over IVIg across different animal models of autoimmune diseases [68]. This candidate is currently in preclinical development [69].

6. Recombinant *oligomeric* IgG-Fc

Commercial IVIg preparations contain a small fraction of higher order IgG structures (i.e., dimers and aggregates) which have been proposed to be important for IVIg anti-inflammatory activity [70]. These observations have stimulated the development of recombinant oligomeric Fc proteins as potential replacement to IVIg [71]. Stradomer (GL-2045) generated by Gliknik/Pfizer [72] is a drug candidate consisting of a mixture of heterogenous IgG-Fc oligomeric structures (which prevented the onset of ITP [73] and ameliorated symptoms in other autoimmune diseases including collagen-induced arthritis [73], experimental autoimmune neuritis [74], and autoimmune myasthenia gravis [75]. This drug candidate is in preclinical development, and in 2015, it received orphan drug status in the US for the treatment of chronic inflammatory demyelinating polyradiculoneuropathy [76]. Hexameric Fc proteins with altered effector functions were also generated by Richard Pleass as potential alternatives to IVIg [77,78] although these proteins have been shown to activate complement pathways [77]. These proteins have yet to advance to the clinic, although researchers claim that it should be more effective and less expensive to produce than IVIg [79].

More recently, we have introduced the concept of selectively antagonizing the activating FcγR system without activating pro-inflammatory pathways. Through novel insights on the modulation of the FcγR pathways, a trivalent-IgG-Fc recombinant product candidate,M230 was designed (manuscript in preparation). M230 selectively immune-modulates the FcγR system and has been shown to have 40-fold greater potency than IVIg in animal models of autoimmune diseases such as arthritis and immune thrombocytopenia. This drug candidate is currently in preclinical development [80].

7. Small-molecule inhibitors

As an alternative to engineered antibodies, there is also great interest in the development of orally administered, small-molecule agents targeting key protein kinases involved in downstream FcγR signaling and immune regulation (Table 1).

7.1. Syk inhibitors

One potential target for autoimmune therapy is spleen tyrosine kinase (Syk), a non-receptor tyrosine protein kinase critical for B-cell activation and FcγR signaling [81]. In ITP, autoantibodies to platelet glycoproteins crosslink FcγRs on macrophages, which results in the recruitment of Syk, and ultimately leads to the phagocytic engulfment of antibody-opsonized platelets. Because Syk has a central role in FcγR-mediated signal transduction and propagation of the inflammatory response, it is thought that blocking Syk enzymatic activity may reduce phagocytic macrophage activity and ameliorate platelet destruction [82]. Syk also likely plays key roles in RA, SLE, multiple sclerosis, and

Please cite this article as: Bosques CJ, Manning AM, Fc-gamma receptors: Attractive targets for autoimmune drug discovery searching for intelligent therapeutic designs, Autoimmun Rev (2016), http://dx.doi.org/10.1016/j.autrev.2016.07.035

allergies as demonstrated in FcγR-deficient mouse and animal models [81].

R406 (Rigel Pharmaceuticals) is an orally available, potent inhibitor of FcγR signaling which primarily targets Syk [83]. In mouse models of arthritis, R406 inhibited paw inflammation and reduced joint damage [83]. R406 was well-tolerated in the 27 healthy volunteers that received it (N = 35) and postural dizziness was the only reported AE [83]. The company is focusing further development on a prodrug of R406 (R788), which was engineered to improve bioavailability for potential oral administration [84].

Fostamatinib disodium (R788; Rigel Pharmaceuticals), like R406, was investigated in six phase 2 studies in ITP, lymphoma/leukemia, and RA. Each of these studies evaluated different treatment regimens in terms of dose and duration of treatment in order to assess fostamatinib efficacy. In patients (N = 16) with chronic, refractory ITP, fostamatinib induced sustained improvement in platelet count in 50% (8/16) of patients [82]. In heavily pre-treated and relapsed patients with non-Hodgkin lymphoma or CLL (N = 68), fostamatinib treatment resulted in overall response rates of 10% for patients with follicular lymphoma and 55% for patients with small lymphocytic leukemia/CLL [85]. Results from 4 RA studies were mixed. Two reported significantly greater (57–65%) American College of Rheumatology 20% (ACR20) responses with fostamatinib than with placebo ($p < 0.01$) [86,87]. However, in RA patients (N = 219) who had failed biologic therapy, no difference from placebo was observed [88], although a higher proportion of patients in the R788 group was receiving prednisone (42% vs 31%) and failed to respond to ≥3 biologic therapies (21% vs 12%) at baseline in this study [88]. In a study in patients with RA not currently receiving DMARDs (N = 279), fostamatinib was superior to placebo but statistically significantly inferior to adalimumab [89]. Common toxicities were gastrointestinal (diarrhea, nausea, vomiting), fatigue, cytopenias, hypertension, and alterations in liver enzymes [82,85–89].

Two phase 3 RA studies, OSKIRA-1 (N = 918) and OSKIRA-3 (N = 323), showed greater ACR20 responses but no difference in radiographic progression compared to placebo [90,91]. Significantly more patients treated with fostamatinib achieved ACR20 at week 24 compared with placebo: 49.0% for fostamatinib 100 mg twice daily for 52 weeks vs 34.2% for placebo (95% CI 8–22%, $p < 0.001$) and 44.4% for fostamatinib 100 mg twice daily for 4 weeks vs 34.2% for placebo (95% CI 3–18%, $p = 0.0006$) [90] in the OSKIRA-1 study and 36.2% for fostamatinib 100 mg twice daily for 24 weeks vs 21.1% for placebo ($p = 0.004$) in the OSKIRA-3 study [91] The safety profile was generally consistent with the phase 2 studies, although a large proportion of patients (up to 7%) reported serious AEs, and three deaths occurred [90,91]. Based on these results, development in RA was halted [90,91]. In 2015, Rigel received orphan drug designation from the FDA for fostamatinib in ITP [92]. Three phase 3 clinical studies are currently underway in patients with ITP [93–95], and results are expected later in 2016.

Rigel also began development of another Syk inhibitor, R112, for the treatment of allergies. Initially, R112 was reported as effective in rapid reduction of symptoms of allergic rhinitis [96], but a second phase 2 study failed to show a statistically significant difference from placebo [97]. Development was subsequently halted.

GS-9973 (entospletinib; Gilead), an inhibitor of Syk with high selectivity against a panel of 359 kinases tested in the KINOMEScan® platform (DiscoverX Corporation, Fremont, CA) [98], is in phase 2 development for hematologic malignancies [99]. A second Syk inhibitor from Gilead, GS-9878, is in phase 1 development for autoimmune disorders; no data are available to date [99].

Cerdulatinib (Portola Pharmaceuticals), a dual inhibitor of Syk and Janus kinase (Jak) family kinases, was reported to suppress inflammation and autoantibody generation in a rat model of arthritis [100]. Clinical development has been in B-cell leukemia and lymphoma, although proof-of-concept studies in autoimmune disease are also planned [100,101].

PRT2761 (Portola Pharmaceuticals) is a potent and selective inhibitor of Syk, which may be efficacious in treating allergies. No preclinical or clinical data have been reported thus far [102].

Another selective Syk inhibitor, SKI-O-703 (Genosco), will begin phase 1 development for autoimmune diseases including ITP, RA, and SLE [103]. No further information on this molecule has been made available.

7.2. Pyrazole derivatives

Pyrazole derivatives have been shown to effectively inhibit FcγR-mediated phagocytosis. Research is ongoing to produce derivatives with increased solubility and potency for further development in a clinical environment [104].

Take-home messages

- Significant unmet needs still exists in the management of autoimmune diseases.
- Given their central role in modulating the inflammatory state of a wide variety of immune cells and tissues, FcγRs remain attractive therapeutic targets for numerous autoimmune diseases.
- Although no therapeutics specifically targeting FcγRs are currently approved for the treatment of autoimmune diseases, continued progress in the characterization of the molecular and cellular basis of the FcγR biology is promoting the development of new and promising therapeutic designs.

References

[1] Nimmerjahn F, Ravetch JV. Fcgamma receptors as regulators of immune responses. Nat Rev Immunol 2008;8:34–47.
[2] Nimmerjahn F, Ravetch JV. FcgammaRs in health and disease. Curr Top Microbiol Immunol 2011;350:105–25. http://dx.doi.org/10.1007/82_2010_86.
[3] Daeron M, Nimmerjahn F. High amounts of specific antibodies are produced upon antigen stimulation during adaptive immune responses. Preface. Curr Top Microbiol Immunol 2014;382:v–xi.
[4] Hogarth PM, Pietersz GA. Fc receptor-targeted therapies for the treatment of inflammation, cancer and beyond. Nat Rev Drug Discov 2012;11:311–31. http://dx.doi.org/10.1038/nrd2909 [nrd2909 [pii]].
[5] Unkeless JC, Shen Z, Lin CW, DeBeus E. Function of human Fc gamma RIIA and Fc gamma RIIIB. Semin Immunol 1995;7:37–44.
[6] Lehmann B, Schwab I, Bohm S, Lux A, Biburger M, Nimmerjahn F. FcgammaRIIB: a modulator of cell activation and humoral tolerance. Expert Rev Clin Immunol 2012;8:243–54. http://dx.doi.org/10.1586/eci.12.5.
[7] Caaveiro JM, Kiyoshi M, Tsumoto K. Structural analysis of Fc/FcgammaR complexes: a blueprint for antibody design. Immunol Rev 2015;268:201–21. http://dx.doi.org/10.1111/imr.12365.
[8] Pincetic A, Bournazos S, DiLillo DJ, Maamary J, Wang TT, Dahan R, et al. Type I and type II Fc receptors regulate innate and adaptive immunity. Nat Immunol 2014;15:707–16. http://dx.doi.org/10.1038/ni.2939 [ni.2939 [pii]].
[9] Anthony RM, Nimmerjahn F. The role of differential IgG glycosylation in the interaction of antibodies with FcgammaRs in vivo. Curr Opin Organ Transplant 2011;16:7–14. http://dx.doi.org/10.1097/MOT.0b013e328342538f.
[10] Schwab I, Nimmerjahn F. Intravenous immunoglobulin therapy: how does IgG modulate the immune system? Nat Rev Immunol 2013;13:176–89.
[11] Smith P, DiLillo DJ, Bournazos S, Li F, Ravetch JV. Mouse model recapitulating human Fcgamma receptor structural and functional diversity. Proc Natl Acad Sci U S A 2012;109:6181–6. http://dx.doi.org/10.1073/pnas.1203954109 [1203954109 [pii]].
[12] Lux A, Nimmerjahn F. Of mice and men: the need for humanized mouse models to study human IgG activity in vivo. J Clin Immunol 2013;33(Suppl. 1):S4–8. http://dx.doi.org/10.1007/s10875–012–9782-0.
[13] Imbach P, Barandun S, Baumgartner C, Hirt A, Hofer F, Wagner HP. High-dose intravenous gammaglobulin therapy of refractory, in particular idiopathic thrombocytopenia in childhood. Helv Paediatr Acta 1981;36:81–6.
[14] Imbach P. Treatment of immune thrombocytopenia with intravenous immunoglobulin and insights for other diseases. A historical review. Swiss Med Wkly 2012;142:w13593.
[15] Anthony RM, Nimmerjahn F, Ashline DJ, Reinhold VN, Paulson JC, Ravetch JV. Recapitulation of IVIG anti-inflammatory activity with a recombinant IgG Fc. Science 2008;320:373–6.
[16] Campbell IK, Miescher S, Branch DR, Mott PJ, Lazarus AH, Han D, et al. Therapeutic effect of IVIG on inflammatory arthritis in mice is dependent on the Fc portion and independent of sialylation or basophils. J Immunol 2014;192:5031–8.
[17] Samuelsson A, Towers TL, Ravetch JV. Anti-inflammatory activity of IVIG mediated through the inhibitory Fc receptor. Science 2001;291:484–6.

Please cite this article as: Bosques CJ, Manning AM, Fc-gamma receptors: Attractive targets for autoimmune drug discovery searching for intelligent therapeutic designs, Autoimmun Rev (2016), http://dx.doi.org/10.1016/j.autrev.2016.07.035

[18] Gomez-Guerrero C, Duque N, Casado MT, Pastor C, Blanco J, Mampaso F, et al. Administration of IgG Fc fragments prevents glomerular injury in experimental immune complex nephritis. J Immunol 2000;164:2092–101.
[19] Debre M, Bonnet MC, Fridman WH, Carosella E, Philippe N, Reinert P, et al. Infusion of Fc gamma fragments for treatment of children with acute immune thrombocytopenic purpura. Lancet 1993;342:945–9.
[20] Hsu CH, Chen MR, Hwang FY, Kao HA, Hung HY, Hsu CH. Efficacy of plasmin-treated intravenous gamma-globulin for therapy of Kawasaki syndrome. Pediatr Infect Dis J 1993;12:509–12.
[21] Wallace PK, Keler T, Coleman K, Fisher J, Vitale L, Graziano RF, et al. Humanized mAb H22 binds the human high affinity Fc receptor for IgG (FcgammaRI), blocks phagocytosis, and modulates receptor expression. J Leukoc Biol 1997;62:469–79.
[22] Curnow RT. Clinical experience with CD64-directed immunotherapy. An overview. Cancer Immunol Immunother 1997;45:210–5.
[23] Terjanian T, Sher H, Vemuri R, Windsor K, Nicolay U, Vessey A, et al. A proof-of-concept phase 2 study of monoclonal antibody MDX-33 in adult subjects with chronic stable ITP. Blood 2000;96:1081.
[24] Adis Insight. MDX 33 alternative names: Mab h22. http://adisinsight.springer.com/drugs/800007380. [Updated September 12, 2003. Accessed April 8, 2016].
[25] Ericson SG, Coleman KD, Wardwell K, Baker S, Fanger MW, Guyre PM, et al. Monoclonal antibody 197 (anti-Fc gamma RI) infusion in a patient with immune thrombocytopenia purpura (ITP) results in down-modulation of Fc gamma RI on circulating monocytes. Br J Haematol 1996;92:718–24.
[26] Richards JO, Karki S, Lazar GA, Chen H, Dang W, Desjarlais JR. Optimization of antibody binding to FcgammaRIIa enhances macrophage phagocytosis of tumor cells. Mol Cancer Ther 2008;7:2517–27.
[27] Adis Insight. Research programme: autoimmune disorders therapy – Trillium Therapeutics. Alternative names: Anti-CD32a monoclonal antibody; TTI-314. http://adisinsight.springer.com/drugs/800019404. [Updated February 12, 2013. Accessed April 8, 2016].
[28] Clarkson SB, Bussel JB, Kimberly RP, Valinsky JE, Nachman RL, Unkeless JC. Treatment of refractory immune thrombocytopenic purpura with an anti-Fc gamma-receptor antibody. N Engl J Med 1986;314:1236–9.
[29] Bussel J, Kimberly R, Clarkson S, Nochman R, Valinsky J, Unkeless JC. Infusion of a monoclonal anti-FcR III in patients with refractory ITP. Neoadjuvant Chemother 1988;169:883–7.
[30] Nakar CT, Bussell JB. 3G8 and GMA161, anti FcγRIII inhibitory monoclonal antibodies in the treatment of chronic refractory ITP (summary of two pilot studies) [abstract]. Blood 2009;114 [Abstract 2404].
[31] Soubrane C, Tourani JM, Andrieu JM, Visonneau S, Beldjord K, Israel-Biet D, et al. Biologic response to anti-CD16 monoclonal antibody therapy in a human immunodeficiency virus-related immune thrombocytopenic purpura patient. Blood 1993;81:15–9.
[32] Flaherty MM, MacLachlan TK, Troutt M, Magee T, Tuaillon N, Johnson S, et al. Nonclinical evaluation of GMA161—an antihuman CD16 (FcgammaRIII) monoclonal antibody for treatment of autoimmune disorders in CD16 transgenic mice. Toxicol Sci 2012;125:299–309.
[33] Clinicaltrials.gov. Safety study of GMA161 in patients with idiopathic thrombocytopenic purpura (ITP). https://clinicaltrials.gov/show/NCT00244257ClinicalTrials. [Updated April 8, 2015. Accessed April 8, 2016].
[34] Bussel JB, Patel V, Dunbar C, Lemery S, Tibbs K, Watts M, et al. GMA161 treatment of refractory ITP: efficacy of Fcgamma-RIII blockade [abstract]. Blood 2006;108.
[35] Adis Insight. Anti-CD16 monoclonal antibody—Genzyme/MacroGenics. Alternative names: anti-CD16; CD16 Mab; GMA-161. http://adisinsight.springer.com/drugs/800020035. [Updated April 11, 2011. Accessed April 8, 2016].
[36] Yu X, Menard M, Prechl J, Bhakta V, Sheffield WP, Lazarus AH. Monovalent Fc receptor blockade by an anti-Fcgamma receptor/albumin fusion protein ameliorates murine ITP with abrogated toxicity. Blood 2016;127:132–8.
[37] Liu Z, Gunasekaran K, Wang W, Razinkov V, Sekirov L, Leng E, et al. Asymmetrical Fc engineering greatly enhances antibody-dependent cellular cytotoxicity (ADCC) effector function and stability of the modified antibodies. J Biol Chem 2014;289:3571–90.
[38] Horton HM, Chu SY, Ortiz EC, Pong E, Cemerski S, Leung IW, et al. Antibody-mediated coengagement of FcgammaRIIb and B cell receptor complex suppresses humoral immunity in systemic lupus erythematosus. J Immunol 2011;186:4223–33. http://dx.doi.org/10.4049/jimmunol.1003412 [jimmunol.1003412 [pii]].
[39] Smith KG, Clatworthy MR. FcgammaRIIB in autoimmunity and infection: evolutionary and therapeutic implications. Nat Rev Immunol 2010;10:328–43.
[40] Konstantinova TS, Ivanova VL, Hellman A, Kyrcz-Krzemien S, Tillmanns S, Sondermann P, et al. Interim results from a phase Ib/IIa clinical trial with the soluble Fc-gamma IIB receptor SM101 for the treatment of primary immune thrombocytopenia. Blood 2012;120 [abstract 3388].
[41] Adis Insight. SM 101. Alternative names: BAX 1810; FcγRIIb; human soluble Fc-gamma receptor IIb – Baxalta; SM-101. http://adisinsight.springer.com/drugs/800034348. [Updated February 22, 2016. Accessed April 8, 2016].
[42] Tillmanns S, Kolligs C, D'Cruz DP, Doria A, Hachulla E, Voll RE, et al. SM101, a novel recombinant, soluble, human FcgammaIIB receptor, in the treatment of systemic lupus erythematosus: results of a double-blind, placebo-controlled multicenter study. Poster abstract presented at: ACR/ARHP Annual Meeting; November 14–19, 2014; Boston, MA. Abstract S1238.
[43] Baxalta. Advancing the pipeline. http://www.baxalta.com/research-development/pharmaceutical-product-pipeline.page. [Updated March 7, 2016. Accessed April 8, 2016].
[44] ClinicalTrials.gov. Efficacy and safety of SM101 in the treatment of IgA nephropathy. https://clinicaltrials.gov/ct2/show/NCT02605525. [Updated February 2, 2016. Accessed April 8, 2016].
[45] Rieth N, Carle A, Muller MA, ter Meer D, Direnberger C, Pohl T, et al. Characterization of SM201, an anti-hFcgammaRIIB antibody not interfering with ligand binding that mediates immune complex dependent inhibition of B cells. Immunol Lett 2014;160:145–50.
[46] Adis Insight. Research programme: Fc receptor modulators - Baxalta. http://adisinsight.springer.com/drugs/800023695. [Updated October 15, 2015. Accessed May 25, 2016].
[47] Roghanian A, Teige I, Martensson L, Cox KL, Kovacek M, Ljungars A, et al. Antagonistic human FcgammaRIIB (CD32B) antibodies have anti-tumor activity and overcome resistance to antibody therapy in vivo. Cancer Cell 2015;27:473–88. http://dx.doi.org/10.1016/j.ccell.2015.03.005.
[48] BioInvent International. BI-1206 – Non Hodgkins lymphoma and cronic lymphatic leukemia. http://www.bioinvent.se/projects/projects/bi-1206/. [Accessed March 1, 2016].
[49] Cancer Research UK. Bioinvent's BI-1206 antibody to enter collaborative phase I/II trial funded and conducted by Cancer Research UK, Cancer Research Technology and Leukaemia & Lymphoma Research. http://www.cancerresearchuk.org/about-us/cancer-news/press-release/2015-01-20-bioinvents-bi-1206-antibody-to-enter-collaborative-phase-iii-trial-funded-and-conducted-by-cancer. [Accessed March 1, 2016].
[50] Rankin CT, Veri MC, Gorlatov S, Tuaillon N, Burke S, Huang L, et al. CD32B, the human inhibitory Fc-gamma receptor IIB, as a target for monoclonal antibody therapy of B-cell lymphoma. Blood 2006;108:2384–91.
[51] Veri MC, Gorlatov S, Li H, Burke S, Johnson S, Stavenhagen J, et al. Monoclonal antibodies capable of discriminating the human inhibitory Fcgamma-receptor IIB (CD32B) from the activating Fcgamma-receptor IIA (CD32A): biochemical, biological and functional characterization. Immunology 2007;121:392–404.
[52] Adis Insight. Research programme: anti-CD32B monoclonal antibodies – MacroGenics. http://adisinsight.springer.com/drugs/800021634. [Updated February 16, 2016. Accessed May 25, 2016].
[53] Chu SY, Yeter K, Kotha R, Pong E, Miranda Y, Phung S, et al. Suppression of rheumatoid arthritis B cells by XmAb5871, an anti-CD19 antibody that coengages B cell antigen receptor complex and Fcgamma receptor IIb inhibitory receptor. Arthritis Rheum 2014;66:1153–64. http://dx.doi.org/10.1002/art.38334.
[54] Szili D, Cserhalmi M, Banko Z, Nagy G, Szymkowski DE, Sarmay G. Suppression of innate and adaptive B cell activation pathways by antibody coengagement of FcgammaRIIb and CD19. MAbs 2014;6:991–9. http://dx.doi.org/10.4161/mabs.28841 [28841 [pii]].
[55] Zack D, Baumann MJ, Korkosz M, Sulyok G, Sramek P, Rojkovich B, et al. Results of a phase 1b/2a study of the safety, tolerability, pharmacokinetics and pharmacodynamics of XmAb®5871 in patients with rheumatoid arthritis (RA) [abstract]. Ann Rheum Dis 2016;74:2851.
[56] Xencor. XmAb®5871. http://www.xencor.com/pipeline/xmab%C2%AE5871/. [Accessed February 25, 2016].
[57] Chu SY, Horton HM, Pong E, Leung IW, Chen H, Nguyen DH, et al. Reduction of total IgE by targeted coengagement of IgE B-cell receptor and FcgammaRIIb with Fc-engineered antibody. J Allergy Clin Immunol 2012;129:1102–15. http://dx.doi.org/10.1016/j.jaci.2011.11.029 [S0091–6749(11)01834–3 [pii]].
[58] National Institutes of Health. Safety and tolerability of XmAb®7195 in adult healthy volunteers and adult subjects with a history of allergic rhinitis and/or allergic conjunctivitis and/or atopic dermatitis. https://www.clinicaltrials.gov/ct2/show/NCT02148744. [Accessed February 25, 2016].
[59] Chen W, Nordstrom J, Burke S, Shah K, Ciccarone V, Li H, et al. Development of human B-lymphocyte targeted bi-specific DART® molecules for the treatment of autoimmune disorders. J Immunol 2014;192 (1 Supplement).
[60] National Institutes of Health. Phase 1 study of MGD010 in healthy subjects. https://clinicaltrials.gov/ct2/show/NCT02376036. [Accessed February 25, 2016].
[61] Macrogenix. MGD010 (CD32B x CD79B). http://www.macrogenics.com/mgd010-cd32b-x-cd79b/. [Accessed February 25, 2016].
[62] Tackenberg B, Jelcic I, Baerenwaldt A, Oertel WH, Sommer N, Nimmerjahn F, et al. Impaired inhibitory Fcgamma receptor IIB expression on B cells in chronic inflammatory demyelinating polyneuropathy. Proc Natl Acad Sci U S A 2009;106:4788–92. http://dx.doi.org/10.1073/pnas.0807319106 [0807319106 [pii]].
[63] Quast I, Keller CW, Maurer MA, Giddens JP, Tackenberg B, Wang LX, et al. Sialylation of IgG Fc domain impairs complement-dependent cytotoxicity. J Clin Invest 2015;125:4160–70. http://dx.doi.org/10.1172/JCI82695 [82695 [pii]].
[64] Wong AH, Fukami Y, Sudo M, Kokubun N, Hamada S, Yuki N. Sialylated IgG-Fc: a novel biomarker of chronic inflammatory demyelinating polyneuropathy. J Neurol Neurosurg Psychiatry 2016;87:275–9. http://dx.doi.org/10.1136/jnnp-2014-309964 [jnnp-2014-309964 [pii]].
[65] Anthony RM, Wermeling F, Karlsson MC, Ravetch JV. Identification of a receptor required for the anti-inflammatory activity of IVIG. Proc Natl Acad Sci U S A 2008;105:19571–8. http://dx.doi.org/10.1073/pnas.0810163105 [0810163105 [pii]].
[66] Anthony RM, Kobayashi T, Wermeling F, Ravetch JV. Intravenous gammaglobulin suppresses inflammation through a novel T(H)2 pathway. Nature 2011;475:110–3. http://dx.doi.org/10.1038/nature10134 [nature10134 [pii]].
[67] Schwab I, Mihai S, Seeling M, Kasperkiewicz M, Ludwig RJ, Nimmerjahn F. Broad requirement for terminal sialic acid residues and FcgammaRIIB for the preventive and therapeutic activity of intravenous immunoglobulins in vivo. Eur J Immunol 2014;44:1444–53. http://dx.doi.org/10.1002/eji.201344230.
[68] Washburn N, Schwab I, Ortiz D, Bhatnagar N, Lansing JC, Medeiros A, et al. Controlled tetra-Fc sialylation of IVIg results in a drug candidate with consistent enhanced anti-inflammatory activity. Proc Natl Acad Sci U S A 2015;112:E1297–306. http://dx.doi.org/10.1073/pnas.1422481112 [1422481112 [pii]].
[69] Momenta Pharmaceuticals Incorporated. Novel autoimmune drugs. http://www.momentapharma.com/pipeline/novel-autoimmune-drugs.php. [Accessed May 19, 2016].

Please cite this article as: Bosques CJ, Manning AM, Fc-gamma receptors: Attractive targets for autoimmune drug discovery searching for intelligent therapeutic designs, Autoimmun Rev (2016), http://dx.doi.org/10.1016/j.autrev.2016.07.035

[70] Teeling JL, Jansen-Hendriks T, Kuijpers TW, de Haas M, van de Winkel JG, Hack CE, et al. Therapeutic efficacy of intravenous immunoglobulin preparations depends on the immunoglobulin G dimers: studies in experimental immune thrombocytopenia. Blood 2001;98:1095–9.

[71] Zuercher AW, Spirig R, Baz MA, Kasermann F. IVIG in autoimmune disease – potential next generation biologics. Autoimmun Rev 2016. http://dx.doi.org/10.1016/j.autrev.2016.03.018 [S1568–9972(16)30075–1 [pii]].

[72] Gliknik. Gliknik pipeline products. http://www.gliknik.com/pipeline/. [Accessed May 25, 2016].

[73] Jain A, Olsen HS, Vyzasatya R, Burch E, Sakoda Y, Mérigeon EY, et al. Fully recombinant IgG2a Fc multimers (stradomers) effectively treat collagen-induced arthritis and prevent idiopathic thrombocytopenic purpura in mice. Arthritis Res Ther 2012;14:R192.

[74] Niknami M, Wang MX, Nguyen T, Pollard JD. Beneficial effect of a multimerized immunoglobulin Fc in an animal model of inflammatory neuropathy (experimental autoimmune neuritis). J Peripher Nerv Syst 2013;18:141–52. http://dx.doi.org/10.1111/jns5.12022.

[75] Thiruppathi M, Sheng JR, Li L, Prabhakar BS, Meriggioli MN. Recombinant IgG2a Fc (M045) multimers effectively suppress experimental autoimmune myasthenia gravis. J Autoimmun 2014;52:64–73. http://dx.doi.org/10.1016/j.jaut.2013.12.014 [S0896–8411(13)00161–3 [pii]].

[76] Adis Insight. Research programme: autoimmune disorder therapeutics – Gliknik GL-2045. http://adisinsight.springer.com/drugs/800035077. [Accessed March 1, 2016].

[77] Czajkowsky DM, Andersen JT, Fuchs A, Wilson TJ, Mekhaiel D, Colonna M, et al. Developing the IVIG biomimetic, hexa-Fc, for drug and vaccine applications. Sci Rep 2015;5:9526. http://dx.doi.org/10.1038/srep09526.:9526.

[78] Mekhaiel DN, Czajkowsky DM, Andersen JT, Shi J, El-Faham M, Doenhoff M, et al. Polymeric human Fc-fusion proteins with modified effector functions. Sci Rep 2011;1:124. http://dx.doi.org/10.1038/srep00124.

[79] Pleass R. LSTM seminar series – HexaGard: a biomimetic of intravenous immunoglobulin (IVIG) for the treatment of autoimmune disease. http://www.lstmed.ac.uk/news-events/news/lstm-seminar-series-hexagard-a-biomimetic-of-intravenous-immunoglobulin-ivig-for. [Accessed March 1, 2016].

[80] Momenta Pharmaceuticals Incorporated. Novel autoimmune drugs. http://www.momentapharma.com/pipeline/novel-autoimmune-drugs.php. [Updated January 4, 2016. Accessed May 25, 2016].

[81] Wong BR, Grossbard EB, Payan DG, Masuda ES. Targeting Syk as a treatment for allergic and autoimmune disorders. Expert Opin Investig Drugs 2004;13:743–62. http://dx.doi.org/10.1517/13543784.13.7.743 [EID130702 [pii]].

[82] Podolanczuk A, Lazarus AH, Crow AR, Grossbard E, Bussel JB. Of mice and men: an open-label pilot study for treatment of immune thrombocytopenic purpura by an inhibitor of Syk. Blood 2009;113:3154–60. http://dx.doi.org/10.1182/blood-2008-07-166439 [blood-2008-07-166439 [pii]].

[83] Braselmann S, Taylor V, Zhao H, Wang S, Sylvain C, Baluom M, et al. R406, an orally available spleen tyrosine kinase inhibitor blocks fc receptor signaling and reduces immune complex-mediated inflammation. J Pharmacol Exp Ther 2006;319:998–1008. http://dx.doi.org/10.1124/jpet.106.109058 [jpet.106.109058 [pii]].

[84] McAdoo SP, Tam FW. Fostamatinib disodium. Drugs Future 2011;36:273.

[85] Friedberg JW, Sharman J, Sweetenham J, Johnston PB, Vose JM, Lacasce A, et al. Inhibition of Syk with fostamatinib disodium has significant clinical activity in non-Hodgkin lymphoma and chronic lymphocytic leukemia. Blood 2010;115:2578–85.

[86] Weinblatt ME, Kavanaugh A, Burgos-Vargas R, Dikranian AH, Medrano-Ramirez G, Morales-Torres JL, et al. Treatment of rheumatoid arthritis with a Syk kinase inhibitor: a twelve-week, randomized, placebo-controlled trial. Arthritis Rheum 2008;58:3309–18. http://dx.doi.org/10.1002/art.23992.

[87] Weinblatt ME, Kavanaugh A, Genovese MC, Musser TK, Grossbard EB, Magilavy DB. An oral spleen tyrosine kinase (Syk) inhibitor for rheumatoid arthritis. N Engl J Med 2010;363:1303–12. http://dx.doi.org/10.1056/NEJMoa1000500.

[88] Genovese MC, Kavanaugh A, Weinblatt ME, Peterfy C, DiCarlo J, White ML, et al. An oral Syk kinase inhibitor in the treatment of rheumatoid arthritis: a three-month randomized, placebo-controlled, phase II study in patients with active rheumatoid arthritis that did not respond to biologic agents. Arthritis Rheum 2011;63:337–45.

[89] Taylor PC, Genovese MC, Greenwood M, Ho M, Nasonov E, Oemar B, et al. OSKIRA-4: a phase IIb randomised, placebo-controlled study of the efficacy and safety of fostamatinib monotherapy. Ann Rheum Dis 2015;74:2123–9. http://dx.doi.org/10.1136/annrheumdis-2014-205361 [annrheumdis-2014-205361 [pii]].

[90] Weinblatt ME, Genovese MC, Ho M, Hollis S, Rosiak-Jedrychowicz K, Kavanaugh A, et al. Effects of fostamatinib, an oral spleen tyrosine kinase inhibitor, in rheumatoid arthritis patients with an inadequate response to methotrexate. Arthritis Rheum 2014;66:3255–64.

[91] Genovese MC, van der Heijde DM, Keystone EC, Spindler AJ, Benhamou C, Kavanaugh A, et al. A phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study of 2 dosing regimens of fostamatinib in patients with rheumatoid arthritis with an inadequate response to a tumor necrosis factor-alpha antagonist. J Rheumatol 2014;41:2120–8. http://dx.doi.org/10.3899/jrheum.140238 [jrheum.140238 [pii]].

[92] Rigel Pharmaceuticals Inc. Fostamatinib oral SYK inhibitor for ITP. http://www.rigel.com/index.php/fostamatinib-itp/. [Accessed March 1, 2016].

[93] US Food and Drug Administration. A efficacy and safety study of R935788 in the treatment of persistent/chronic immune thrombocytopenic purpura (ITP) (FIT). https://clinicaltrials.gov/ct2/show/NCT02076399. [Accessed March 1, 2016].

[94] Rigel Pharmaceuticals Inc. A efficacy and safety study of fostamatinib in the treatment of persistent/chronic immune thrombocytopenic purpura (ITP) (FIT). https://clinicaltrials.gov/ct2/show/NCT02076412. [Accessed March 1, 2016].

[95] US National Institutes of Health. Open label study of R788 in the treatment of persistent/chronic immune thrombocytopenic purpura (ITP). https://www.clinicaltrials.gov/ct2/show/record/NCT02077192. [Accessed March 1, 2016].

[96] Meltzer EO, Berkowitz RB, Grossbard EB. An intranasal Syk-kinase inhibitor (R112) improves the symptoms of seasonal allergic rhinitis in a park environment. J Allergy Clin Immunol 2005;115:791–6. http://dx.doi.org/10.1016/j.jaci.2005.01.040 [S0091674905001624 [pii]].

[97] FDA News. Rigel announces results from study of R112 for allergic rhinitis. http://www.fdanews.com/articles/82854-rigel-announces-results-from-study-of-r112-for-allergic-rhinitis. [Accessed May 25, 2016].

[98] Currie KS, Kropf JE, Lee T, Blomgren P, Xu J, Zhao Z, et al. Discovery of GS-9973, a selective and orally efficacious inhibitor of spleen tyrosine kinase. J Med Chem 2014;57:3856–73. http://dx.doi.org/10.1021/jm500228a.

[99] Gilead Sciences Ltd. Research pipeline – Gilead. http://www.gilead.com/research/pipeline. [Accessed March 1, 2016].

[100] Coffey G, Betz A, DeGuzman F, Pak Y, Inagaki M, Baker DC, et al. The novel kinase inhibitor PRT062070 (cerdulatinib) demonstrates efficacy in models of autoimmunity and B-cell cancer. J Pharmacol Exp Ther 2014;351:538–48. http://dx.doi.org/10.1124/jpet.114.218164 [jpet.114.218164 [pii]].

[101] Portola Pharmaceuticals Inc. Cerdulatinib: dual Syk-JAK inhibitor. https://www.portola.com/clinical-development/cerdulatinib-dual-syk-jak-inhibitor/. [Accessed March 1, 2016].

[102] Portola Pharmaceuticals. Clinical development. Syk-specific inhibitors. https://www.portola.com/clinical-development/prt2607-syk-specific-inhibitor/. [Accessed May 25, 2016].

[103] Genosco. Pipeline. http://www.genosco.com/pipeline.html. [Accessed March 1, 2016].

[104] Purohit MK, Scovell I, Neschadim A, Katsman Y, Branch DR, Kotra LP. Disulfide linked pyrazole derivatives inhibit phagocytosis of opsonized blood cells. Bioorg Med Chem Lett 2013;23:2324–7. http://dx.doi.org/10.1016/j.bmcl.2013.02.064 [S0960-894X(13)00240–0 [pii]].

[105] Orange JS, Hossny EM, Weiler CR, Ballow M, Berger M, Bonilla FA, et al. Use of intravenous immunoglobulin in human disease: a review of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology. J Allergy Clin Immunol 2006;117:S525–53.

[106] US Department of Health and Human Services. Immune globulin intravenous (IGIV) indications. http://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/ucm133691.htm. [Accessed March 1, 2016].

[107] Branch D, Purohit M, Scovell I, Neschadim A, Katsman Y, Kotra L. Small molecule inhibitors of phagocytosis for treatment of immune cytopenias [abstract]. Exp Hematol 2013;41:S66.

Please cite this article as: Bosques CJ, Manning AM, Fc-gamma receptors: Attractive targets for autoimmune drug discovery searching for intelligent therapeutic designs, Autoimmun Rev (2016), http://dx.doi.org/10.1016/j.autrev.2016.07.035