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**Review Article**

# Targeting Fcγ receptors: potential therapeutic approaches in inflammation, autoimmune disease and cancer

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**CONTENTS**



**Abstract**

A healthy immune system responds only to foreign antigens to protect the body from an uncontrolled immune response against its own cells and tissues. Immunoglobulin G (IgG) receptors, or FcγRs, are critical players in maintaining a balanced immune response, which is achieved by the co-existence of activating and inhibitory receptor pairs in the same cell. The importance of FcγR signaling in the pathogenesis of autoimmune diseases and cancer has provided the basis for new therapeutic strategies based on selective modulation of FcγRs for the treatment of these disorders.

## Introduction

The immune system has the ability to distinguish self- and non-self-antigens in order to ensure an adequate immune response against foreign pathogens, thus protecting the body's own components. This ability, known as immunological tolerance, is acquired by clonal deletion or inactivation of developing lymphocytes reactive to self-antigens, but it is not the only mechanism in place to prevent the generation of self-destructive reactions. A balance between activation and inhibitory signaling regulates the threshold for activation of immune effector cell responses. Thus, deletion of the inhibitory pathways could lead to hyperreactivity, eventually resulting in autoimmune disease. In this context, receptors for the constant fraction (Fc) of IgG, or FcγRs, have been demonstrated to be essential in maintaining this equilibrium. The discovery of their role in autoimmune and inflammatory diseases has made them attractive targets for therapeutic modulation of the immune response, either by attenuating excessive responses in autoimmune diseases or by enhancing immune responses against tumor cells.

## Biology and function of FcγRs

FcγRs present in immune cells (Table I) can bind antigen-IgG antibody complexes (or immune complexes: ICs) through the antibody's Fc region and trigger a variety of immune responses, including macrophage phagocytosis, antibody-dependent cellular cytotoxicity (ADCC) by natural killer (NK) cells or inhibition of B-cell activation, hence linking antibody-mediated responses with cellular immunity. But how can FcγRs preserve a balanced immune response? FcγRs contain associated intracellular regions called ITAM or ITIM for immunoreceptor tyrosine-based activation or inhibitory motifs, which determine their activating or inhibitory nature. Both activating and inhibitory FcγRs are usually co-expressed on the cell surface and function in combination. Immune complexes can simultaneously co-engage both activating and inhibitory FcγRs (Fig. 1), prompting a cellular response that will vary depending on the ratio between both components of the receptor pair. External factors such as cytokines regulate the proportion of inhibitory and activating FcγRs. In this sense, Th2 cytokines (IL-4, IL-10, TGF-β) will upregulate the expression of inhibitory FcγRs, hence raising the threshold for immune effector cell activation. On the other hand, proinflammatory mediators, such as lipopolysaccharide (LPS) or Th1 cytokines (interferon gamma: IFNγ), upregulate activating FcγRs or decrease their inhibitory analogues (1).

Four different classes of FcγRs have been identified: FcγRI (CD64), FcγRII (CD32), FcγRIII (CD16) and FcγRIV (Table I). FcγRI and FcγRIV possess only an ITAM motif, whereas one activating (a) and one inhibitory (b) subtype exist for FcγRII and FcγRIII, respectively. Also, FcγRII and FcγRIII display low binding affinity for the Fc region of IgG monomers, since they physiologically bind only immune complexes. In contrast, FcγRI and FcγRIV have high and

*Table I: Classification of FcγRs.*

| Receptor | CD antigen | Type of receptor | Cellular expression | Binding |
|---|---|---|---|---|
| FcγRIa | CD64 | Activating | Macrophages, monocytes, neutrophils, eosinophils, DC | High affinity |
| FcγRIIa | CD32A | Activating | Macrophages, neutrophils, eosinophils, platelets, DC, LC | Low affinity |
| FcγRIIb | CD32B | Inhibitory | B-cells, macrophages, neutrophils, eosinophils, mast cells, DC, LC | Low affinity |
| FcγRIIIa | CD16A | Activating | NK cells, eosinophils, macrophages, monocytes, neutrophils, mast cells, DC | Low affinity |
| FcγRIIIb | CD16B | Inhibitory | Neutrophils, eosinophils | Low affinity |
| FcγRIV | | Activating | Neutrophils, monocytes, macrophages, DC | Intermediate affinity |

DC: dendritic cells; LC: Langerhans cells.

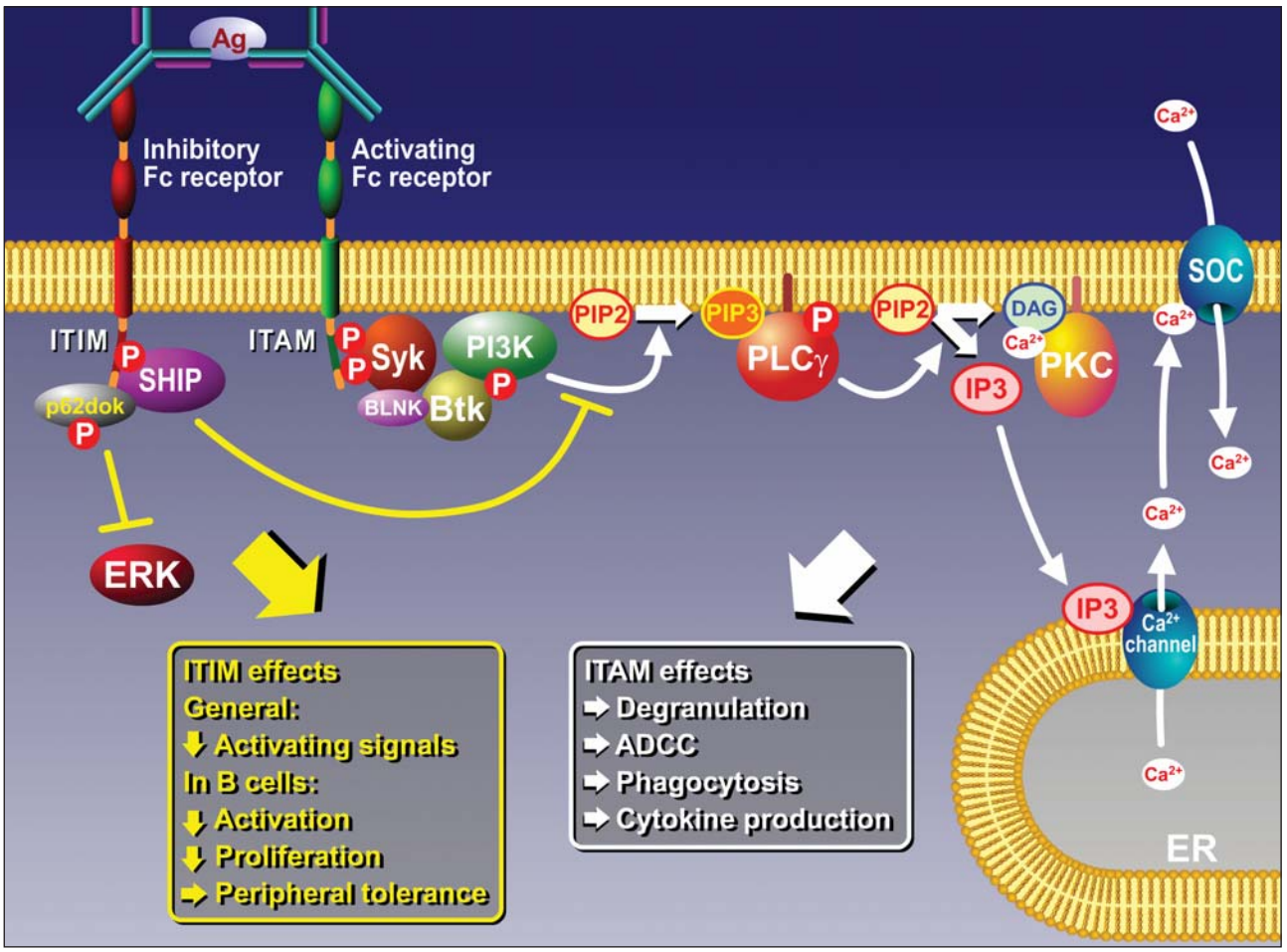


Fig. 1. The presence of immunoreceptor tyrosine-based activation (or inhibitory) motifs (ITAM or ITIM) will determine the activating or inhibitory nature of FcγRs. Immune cells usually co-express both activating and inhibitory FcγRs on the cell surface, and the existing ratio between both components of the receptor pair will determine the cellular response. A balance between activation and inhibitory signaling regulates the threshold for activation of immune effector cell responses.

intermediate binding affinity, respectively. The activating/inhibitory (a/b) receptor pairs are generally co-expressed in all immune system cell types, with the exception of B-lymphocytes and NK cells, which only express the inhibitory FcγRIIb and the activating FcγRIIIa, respectively. This restricted pattern of expression determines cellular responses of B- and NK cells. In this sense, ADCC is mediated by the activating FcγRIIIa in NK cells upon interaction with the antibodies opsonizing the pathogen cell surface. In general, activating signals are transmitted though the ITAM motif (Fig. 1), which after ligand binding undergoes tyrosine phosphorylation, initiat-

ing a signaling cascade that involves Syk protein recruitment to the ITAM motif and activation of phosphatidylinositol 3-kinase (PI3K), which leads to production of phosphatidylinositol 3,4,5-trisphosphate ($PIP_3$). Posterior recruitment and activation of phospholipase C (PLC) will generate diacylglycerol (DAG) and inositol trisphosphate ($IP_3$), favoring activation of protein kinase C (PKC) and causing sustained intracellular calcium mobilization (2).

In addition to ADCC, cytokine production, degranulation and phagocytosis are other responses triggered by activating FcγRs (2). Inhibitory FcγRs, in particular the FcγRIIb subtype, play a central role as negative modulators of innate and adaptive immune responses by limiting activating signals mediated by ITAM-containing receptors. In B-lymphocytes, co-engagement of ICs with the B-cell receptor (BCR) and the inhibitory FcγRIIb triggers an ITIM-dependent signaling cascade involving recruitment of the inositol phosphatase SHIP (SH2-containing inositol polyphosphate 5-phosphatase) to the ITIM motif, which will promote $PIP_3$ hydrolysis, thus preventing calcium signaling and subsequent B-cell activation (Fig. 1).

Inhibition of B-cell proliferation is also ITIM-dependent via activation of the adaptor protein Dok and subsequent inactivation of mitogen-activated protein (MAP) kinases. Independent of its ITIM motif, FcγRIIb is also able to trigger B-cell apoptosis. Upon engagement of nonspecific ICs, FcγRIIb molecules aggregate in the membrane, triggering a proapoptotic signal, which has been proposed as a system to maintain peripheral tolerance by eliminating self-reactive B-cells that may have escaped central tolerance checkpoints in the bone marrow (3).

Besides its role in regulating B-cell activation, the FcγRIIb also appears to be critical in dendritic cells (DCs). The primary role of DCs is to process and present antigens as peptides bound to major histocompatibility complex (MHC), to both T- and B-lymphocytes. Boruchov *et al.* (4), using a novel and highly specific antibody for FcγRIIb, demonstrated that DCs co-express activating FcγRIIa and inhibitory FcγRIIb receptor pairs, the expression of which can be modulated by different stimuli, as commented earlier. Thus, proinflammatory IFNγ upregulated the expression of activating FcγRIIa in immature DCs, while soluble IgG (which has antiinflammatory properties) decreased FcγRIIa density on the cell membrane. Furthermore, this work presented the first evidence that the FcγRIIb is involved in peripheral T-cell tolerance, since co-engagement of both FcγRIIa and FcγRIIb limited FcγRIIa-mediated DC maturation. Immature DCs regulate peripheral T-cell tolerance by self-reactive T-cell elimination and by stimulating the formation of $CD4^+$ $CD25^+$ regulatory T-cells (Tregs) (5).

## Therapeutic potential of FcγR modulation

Deregulation of the immune response may lead to self-destructive autoimmune processes. Excessive autoantibody production, hyperactive lymphocytes and inflammatory reactions due to deposition of ICs in affected tissues are the hallmarks of autoimmune disease. Animal models deficient in inhibitory FcγRs may lose peripheral tolerance and develop spontaneous autoimmunity. In fact, FcγRIIb deficiency in mice has been linked to autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura (ITP), autoimmune glomerulonephritis, autoimmune lung disease, autoimmune arthritis and systemic lupus erythematosus (SLE). Conversely, a deficiency of activating FcγRs has been shown to confer resistance to autoimmune diseases (6).

These models have been very useful for studying the implication of FcγRs in different autoimmune and inflammatory disorders. Therapeutic manipulation of activating or inhibitory receptor expression has been proposed as a means of regulating the immune response in inflammatory and autoimmune diseases. In these scenarios, favoring inhibitory signaling, for instance, would attenuate or prevent the consequences of an exaggerated immune response towards self-components. On the other hand, enhancing the host immune response by increasing ADCC to eliminate cancer cells has shown therapeutic potential in experimental animal models.

### *FcγR modulation by intravenous IgG*

Therapeutic modulation of FcγRs is a strategy with proven success in experimental animal models of autoimmune disease, supporting the development of similar treatment approaches for human disease. A few years ago, the molecular mechanism for the well-known antiinflammatory effects of intravenous IgG (IVIG) was discovered in a murine model of ITP. In this study, FcγRIIb was found to be essential for the action of IVIG, since receptor blockade by genetic deletion or using a specific antibody abolished its protective effect on platelet count. This finding suggested a potential upregulation of FcγRIIb, confirmed in experiments where macrophage FcγRIIb expression was upregulated after IVIG treatment (7). Another study showed that exposure to IVIG causes immature DCs to downregulate the expression of activating FcγRIIa, thus preventing the triggering of a proinflammatory cascade (4).

### *FcγRs in rheumatoid arthritis*

The involvement of FcγRs in the pathogenesis of rheumatoid arthritis (RA) has been studied in animal models lacking the inhibitory FcγRIIb receptor. In rodent collagen-induced arthritis (CIA), an animal model for human RA, FcγRIIb-deficient mice developed an exaggerated IgG-mediated response to type II collagen that was associated with increased arthritis progression and a more severe symptomatology than wild-type controls. Furthermore, deletion of activating FcγRs (FcγRI or FcγRIII) protected mice from CIA (8, 9). In humans, elevated expression of both FcγRIIa and FcγRIIb was detected in synovial DCs of patients with active RA, but shifted towards the inhibitory subtype (10). Since augmented FcγRIIb expression was only found in patients with active disease, a counteractive mechanism to attenuate proin-

flammatory responses in RA was hypothesized. Other studies have reported an increase in the inhibitory FcγRIII in RA patients with active disease (8). In addition, the activating FcγRIIa has been at least partially involved in the increased production of proinflammatory TNF-α in synovial fluid monocytes (11). Thus, FcγRIIa blockade reduced IC-induced TNF-α production by more than 50%, and may therefore represent a potential therapeutic strategy to reduce inflammation due to ICs in RA.

Polyclonal B-cell activation is also associated with the production of autoantibodies in RA. In particular, 60-80% of RA patients are positive for rheumatoid factor (RF), a type of autoantibody (IgA or IgM) against the Fc portion of IgG that may contribute to some of the clinical manifestations of RA. RF autoantibodies are not exclusive of RA patients and can be present in the serum of patients with other autoimmune or inflammatory disorders. RF production in B-cells occurs upon BCR uptake of immune complexes and can be inhibited by the interaction between the IgG fraction in ICs and the inhibitory FcγRIIb. Since BCR activation can be prevented by co-engagement of BCR and FcγRIIb through ITIM signaling, FcγRIIb appears to be essential for the modulation of RF development (12). In fact, abundant RF production was found in FcγRIIb-deficient mice, therefore validating this hypothesis. However, no genetic dysfunction of FcγRIIb has been associated with the development of RF in human RA. In any case, modulation of FcγRIIb activity could be an interesting approach to decrease RF, hence ameliorating the pathology of RA.

An interesting study by Petkova *et al.* demonstrated the pathogenic potential of human IgG autoantibodies. Injection of plasma from an RA patient to FcγRIIb-deficient mice caused the development of inflammatory arthritis in these animals, as evidenced by joint inflammation and arthritic lesions. In contrast, the presence of the inhibitory FcγRIIb protected control mice from arthritis onset. Plasma from RA patients showed hypergammaglobulinemia with different types of associated autoantibodies. Further analysis attributed the arthritogenic capacity to the IgG fraction of human plasma, since the IgG-negative fraction was unable to induce arthritis in FcγRIIb mice. Besides corroborating the pathogenic role of humoral autoimmunity, this study also provided an excellent animal RA model to test novel therapies (13).

Polymorphisms in human FcγR genes have been associated with RA. A study in a large cohort of RA patients encountered an increased frequency of the FcγRIIIa 158V allele compared with controls (14). This variant of the FcγRIIIa has also been associated with RA in individuals positive for anti-glucose-6-phosphate isomerase arthritogenic antibodies (15). In a recent study, researchers at Seoul National University reported that engagement of FcγRIII on NK lymphocytes by IgG deposited in joint tissues is essential to induce NK cell activation and promote antibody-induced arthritis (16). Specific NK cell FcγRIII blockade therefore represents a novel strategy for the treatment of RA.

*FcγRs in systemic lupus erythematosus (SLE)*

SLE is a common autoimmune disorder characterized by elevated levels of autoantibodies against nuclear antigens, which are considered to be responsible for the disease pathogenesis. Deposition of autoantibody nuclear antigen ICs in different tissues may locally activate innate immunity, resulting in multisystem organ damage. SLE has been attributed to several causes, including genetic and environmental factors. Sex and race may also play a role, since a higher prevalence of SLE in women of childbearing age and African American descent has been described (17). In murine models of lupus, FcγRIIb deficiency leads to systemic autoimmunity, with the production of pathogenic IgG anti-DNA antibodies and the development of autoimmune glomerulonephritis (18, 19). Further investigations revealed that FcγRIIb appears to regulate the development of autoimmune responses by restricting the production of IgG anti-DNA antibodies by plasma cells, thus contributing to the maintenance of peripheral tolerance (20).

Interestingly, upregulation of FcγRIIb on B-cells of susceptible mice has been demonstrated to prevent disease manifestations. In this study, transduction of FcγRIIb via a viral vector into lupus-prone mice resulted in reduced IC deposition and histological lupus signs in lungs and kidneys, hence improving renal function and increasing overall survival (21).

Research on the genetic causes of SLE has led to the discovery of human polymorphisms in the gene encoding both FcγRIIa and FcγRIIb receptors. For instance, the FcγRIIa 131R genotype has been described as a susceptibility factor for SLE in Caucasians, African Americans and Koreans, whereas the FcγRIIb I232T variant contributes to SLE susceptibility in Japanese, Thai and Chinese (8). A recent report associated the increased susceptibility to lupus in Asians with the fact that the I232T polymorphism affects the localization of the FcγRIIb by decreasing its affinity for membrane lipid rafts, which are critical sites for BCR interaction and signaling, suggesting that this may impair inhibitory FcγRIIb function (22). Increased susceptibility in Caucasians has also been associated with a polymorphism in the FcγRIIb promoter leading to decreased transcription of the FcγRIIb gene (23).

*FcγRs in cancer*

In the last few years, the development of selective monoclonal antibodies (MAbs) against specific antigens present in malignant cells has represented a remarkable advance in cancer therapy. It has been proposed that binding of FcγRs to effector cells contributes to the therapeutic activity of antitumor MAbs (24). In that study, the presence of activating FcγRs was required to mediate the antitumor activity *in vivo* of rituximab and trastuzumab. Also, tumor growth inhibition by MAbs was greater in FcγRIIb-deficient mice, which showed enhanced ADCC, indicating that inhibitory signals participate in the modula-

tion of this response. These results suggested the importance of designing antitumor antibodies that preferentially bind activating over inhibitory FcγRs. The cellular mechanisms of FcγR-mediated antitumor activity depend on the cell type and it has been suggested that different cells might cooperate to induce tumor cell killing (25).

Several studies have demonstrated the therapeutic potential of DCs in cancer. As commented earlier, DC maturation is crucial for effective T-cell stimulation and to prevent the development of peripheral tolerance, which appears to be regulated by inhibitory FcγRs. Thus, suppressing the inhibitory signal would allow DC maturation and stimulate T-cell-mediated tumor immunity. Kalergis *et al.* (26) tested this approach by injecting DCs derived from FcγRIIb-deficient mice, previously matured in the presence of ovalbumin ICs, into naïve mice that were subsequently challenged with a melanoma cell line expressing ovalbumin. Immunization with FγRIIb-deficient DCs significantly reduced tumor growth and prevented tumor appearance by a mechanism involving DC-mediated expansion of ovalbumin-specific $CD8^+$ cells. Therefore, tumor immunity can be achieved by selective engagement of activating FcγRs by ICs, thus triggering a strong T-cell response against the tumor. Similarly, the activating FcγRIa has been shown to mediate the antitumor efficacy of TA-99, an MAb specific for the gp75 tumor antigen, since tumor-bearing FcγRIa knockout mice remained unaffected by TA-99, whereas tumor scores in wild-type mice were markedly reduced (27). Also, the efficacy of daclizumab was found to be dependent on activating FcγRs, as evidenced by the lack of antitumor effect in a murine model of adult T-cell leukemia (28).

## Current developments

Research on FcRs has intensified, with special emphasis on new molecules targeting Fc receptors, as evidenced by the increasing number of patents issued over the past few years (see Table II). Collaborative research at Medarex, the University Medical Center Utrecht and Thomas Jefferson University led to the discovery of MDE-8, an MAb targeting FcγRIIa, which was effective in a murine model of antibody-induced hemolytic anemia, resembling human autoimmune hemolytic anemia, an acquired disorder characterized by autoantibodies directed against erythrocytes. MDE-8 administered 1 h before anemia induction (by i.p. injection of the murine $IgG_1$ anti-mouse erythrocyte antibody 105.2H) maintained erythrocyte levels comparable to those found in control mice (29). MDE-8 has been claimed in the patent literature (30). Another patent issued by Medarex highlighted the activity of HuMAb 611, which downregulated the surface expression of the activating FcγRIa in U-937 cells (31).

MacroGenics is also focusing on FcR technology and recently reported a novel MAb (MAb 2B6), which demonstrated high affinity for the human FcγRIIb *in vitro*, lacking reactivity against the activating FcγRIIa. Chimerized and humanized forms of MAb 2B6 demonstrated antitumor activity *in vivo,* decreasing tumor growth and increasing survival in mice bearing B-lymphoma xenografts (32). MAb 2B6 has also been described in the patent literature (33, 34). GMA-161 is another humanized MAb targeting the FcγRIIIa originally developed at MacroGenics and currently in phase I clinical trials at Genzyme and MacroGenics for the treatment of ITP (35).

*Table II: Selected patents reporting new therapeutic strategies targeting FcγRs (from Prous Science Integrity®).*

| Patent number | Organization | Patent description | Product |
|---|---|---|---|
| WO 2006039418 | Medarex | Human monoclonal antibodies to FcγRII (CD32A) for the treatment of autoimmune hemolytic anemia | MDE-8 |
| WO 2006002438 | Medarex | Human monoclonal antibodies to FcγRI (CD64) | HuMAb 611 |
| WO 1996040789 | Medarex | Therapeutic compounds comprised of anti-Fc receptor antibodies | |
| WO 2006104989 | Diversa/Medarex | Altered antibody Fc regions and uses thereof | |
| WO 2006105062 | Diversa | Altered antibody Fc regions and uses thereof | |
| WO 2006066078 | MacroGenics | FcγRIIb-specific antibodies and methods of use thereof | |
| WO 2005110474 | MacroGenics | Humanized FcγRIIb-specific antibodies and methods of use thereof | MAb h2B6 |
| WO 2005115452 | MacroGenics | FcγRIIb-specific antibodies and methods of use thereof | MAb h2B6 |
| WO 2004016750 | MacroGenics | FcγRIIb-specific antibodies and methods of use thereof | |
| WO 2004058747 | Trillium Therapeutics | Fc receptor-modulating compounds and compositions | |
| WO 2006028956 | Genentech | Anti-FcγRIIb antibody and uses thereof | 5A6/22E7 |
| EP 1674479 | Memorial Sloan-Kettering Cancer Center | Modulation of FcγRs for optimizing immunotherapy | |
| WO 2005052007 | Fraunhofer-Gesellschaft | Recombinant anti-CD64 immunotoxins | m22(scFv)2-ETA' |
| WO 2005051999 | Max-Planck-Gesellschaft zur Foerderung der Wissenschaften eV | Substance binding human IgG FcγRIIb | |
| WO 2003041737 | The University of Liverpool | Use of FcγRIIIb-inhibitory agents for the treatment of inflammatory conditions (*e.g.,* rheumatoid arthritis) | |
| WO 2006113665 | MacroGenics | Covalent diabodies and uses thereof | h2B6-h368 |

Trillium Therapeutics, in collaboration with its industrial partners and the Austin Research Institute in Australia, is developing both biological and small-molecule inhibitors of FcγRIIa that could be useful for the treatment of inflammatory and autoimmune disorders (http://www.trilliumtherapeutics.com).

Genentech's novel antibody 5A6/22E7 was also recently claimed in the patent literature (36). This compound, which targets the FcγRIIb and also an activating IgE Fc receptor (FcεRI), may be potentially useful for the treatment of disorders such as allergy, asthma and inflammation.

Other organizations currently investigating potential therapeutic FcγR-targeting molecules are summarized in Table II.

## Conclusions

Since their identification nearly 4 decades ago, substantial progress has been made in characterizing the *in vivo* functions of FcγRs. Animal models have been key in the elucidation of the pathogenic role of FcγRs in autoimmune and inflammatory diseases and have also provided clues to their manipulation in therapy. The nature of the interaction between either activating or inhibitory receptors and their corresponding IgG subtypes determines the magnitude of the immune response, and is also responsible for the efficacy of therapeutic MAbs in cancer therapy. The evidence gathered in preclinical studies should translate into the effective design of molecules targeting FcγRs for their further clinical development.

## Online links

Subscribers to Prous Science Integrity® can access the online animation (Antibody-Dependent Cellular Cytotoxicity) illustrating ADCC.

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