

B6-Cd14-hFCAR(CD89)/hIGHA1

Strain Name: C57BL/6JGpt-*Cd14*^{em1Cin(hFCAR-CD89)}/*IGHA1*^{em1Cin(hIGHA1)}/Gpt

Strain Type: KI

Strain Number: T057918

Background: C57BL/6JGpt

Description

FCAR / CD89 is a member of the immunoglobulin gene superfamily and encodes a receptor for the Fc region of IgA. The Fc α RI gene is located on chromosome 19, within the leukocyte receptor cluster that encodes killer inhibitory receptors (KIR) and leukocyte Ig-like receptors (LIR), while other Fc receptors map on chromosome 1. In many other species, such as rats and chimpanzees, a homologue of the human CD89 was found, but not in mice. The receptor is a transmembrane glycoprotein present on the surface of myeloid lineage cells such as neutrophils, monocytes, macrophages, and eosinophils, where it mediates immunologic responses to pathogens. All forms of IgA bind to CD89, albeit with different binding affinities. IgA-immune complexes, and monomeric IgA (mIgA) or dimeric Ig (dIgA), bind to Fc α RI with comparable association rates, whereas, compared to IgA-immune complexes, mIgA and dIgA dissociation is faster, which results in low affinity ($K_a \approx 10-6m$) interactions for the latter forms. It has been demonstrated that CD89-mediated signaling can initiate either pro-inflammatory responses or inhibitory signals as a mechanism to dampen excessive immune responses.

A pro-inflammatory response is signaled when IgA molecules in an immune complex bind to multiple CD89, resulting in the activation of Src family kinases and the phosphorylation of the FcR γ -chain ITAMs by Lyn. The ensuing signaling cascades lead to pro-inflammatory responses such as release of cytokines, phagocytosis, respiratory bursts, antibody-dependent cell-mediated cytotoxicity, production of reactive oxygen species, and antigen presentation^[1]. Therefore, the therapies that aim to increase specific IgA titers against mucosal pathogens may help to fight (mucosal) infection. It has been demonstrated that infusion of antigen-specific IgA in human CD89 transgenic mice, but not wild-type mice, results in an enhanced clearance of *Mycobacterium tuberculosis* or *Bordetella pertussis*^[2]. In addition, excessive inflammation caused by IgA immune complex may lead to autoimmune diseases, such as immunoglobulin A(IgA) nephropathy (IgAN). It has been proposed that in IgAN there is specific pIgA-induced shedding into the circulation of this isoform from myeloid cells, and that

released sCD89 – pIgA complexes amplify the molecular size of circulating IgA-immune complexes (IgA-ICs) and promote mesangial IgA deposition^[3]. Mice transgenic for human CD89 develop circulating sCD89 – pIgA complexes, mesangial IgA deposition, glomerular and interstitial macrophage infiltration, mesangial matrix expansion, hematuria, and mild proteinuria, which indicated that CD89 played a key role in the pathogenesis of IgAN^[4].

CD89 not only acts as an activating receptor, but also acts as an inhibiting receptor. When CD89 monovalently binds monomeric, non-antigen bound IgA, the form most common in serum, the resulting signals result in inactivation of other activating receptors such as Fc γ R and Fc ϵ RI. The binding of the monomeric serum IgA causes Lyn to only partly phosphorylate the FcR γ -chain ITAMs^[5]. The anti-inflammatory role of monomeric IgA-CD89 binding may have implications for treatment of allergic asthma, as shown by targeting CD89 in transgenic mice models with anti-CD89 Fab antibodies, which mimic the binding of monomeric IgA. This CD89 targeting led to decreased infiltration of airway tissue by inflammatory leukocytes.

GemPharmatech generated the B6-Cd14-hFCAR(CD89)/hIGHA1 through breeding B6-Cd14-hFCAR(CD89) mice(T055679) with B6-hIGHA1 mice(T056195). This strain express of human CD89 regulated by the murine CD14 promoter and in the meanwhile express of human IGHA1. This strain is an ideal model for studying infectious diseases and autoimmune diseases.

Strategy

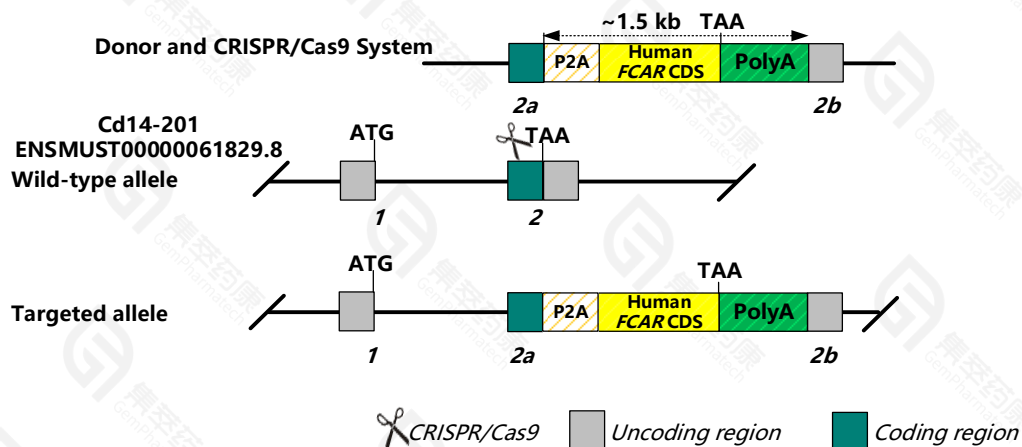


Fig 1. Schematic diagram of CD89 humanization strategy on B6-Cd14-hFCAR(CD89)/hIGHA1 mice.

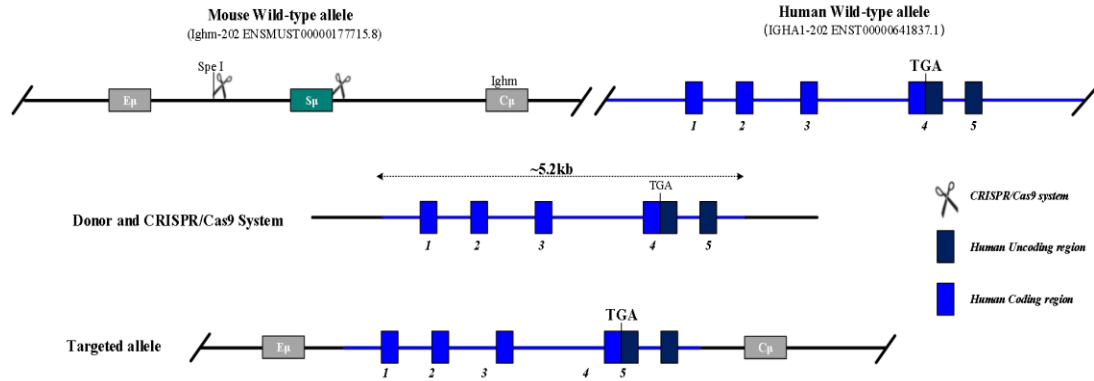


Fig 2. Schematic diagram of IGHA1 humanization strategy on B6-Cd14-hFCAR(CD89)/hIGHA1 mice.

Applications

1. Screening, preclinical efficacy evaluation and safety evaluation of anti-CD89 drugs and anti-IGHA1 drugs
2. Research on autoimmune diseases
3. Research on infectious diseases

Supporting Data

1. hIGHA1 protein expression analysis

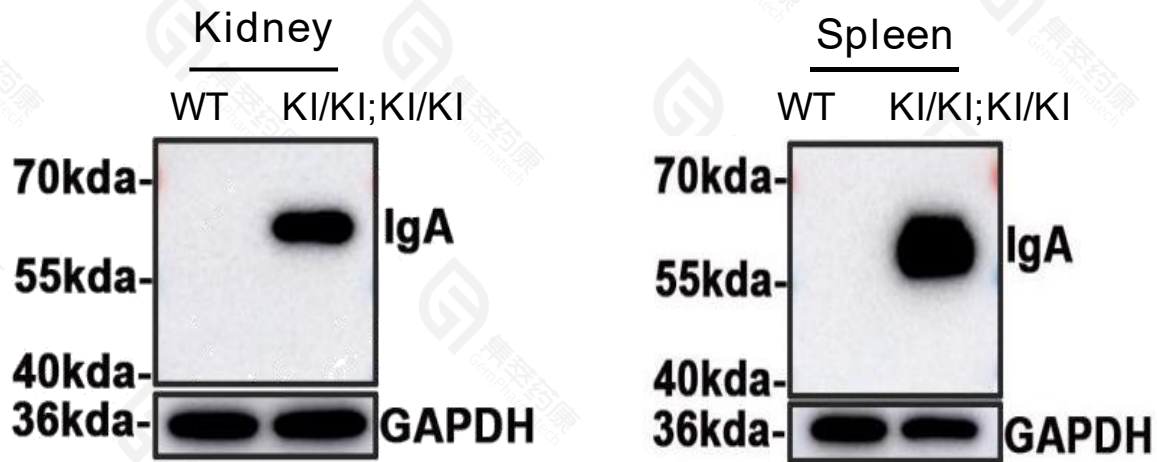


Fig.3 Detection of IGHA1 expression in B6-Cd14-hFCAR(CD89)/hIGHA1 mice(female, 34w).

The expression of human IGHA1 protein can be detected in spleen and kidney of B6-Cd14-hFCAR(CD89)/hIGHA1 but not B6 wild type mice through western blot

2. hCD89 protein expression analysis

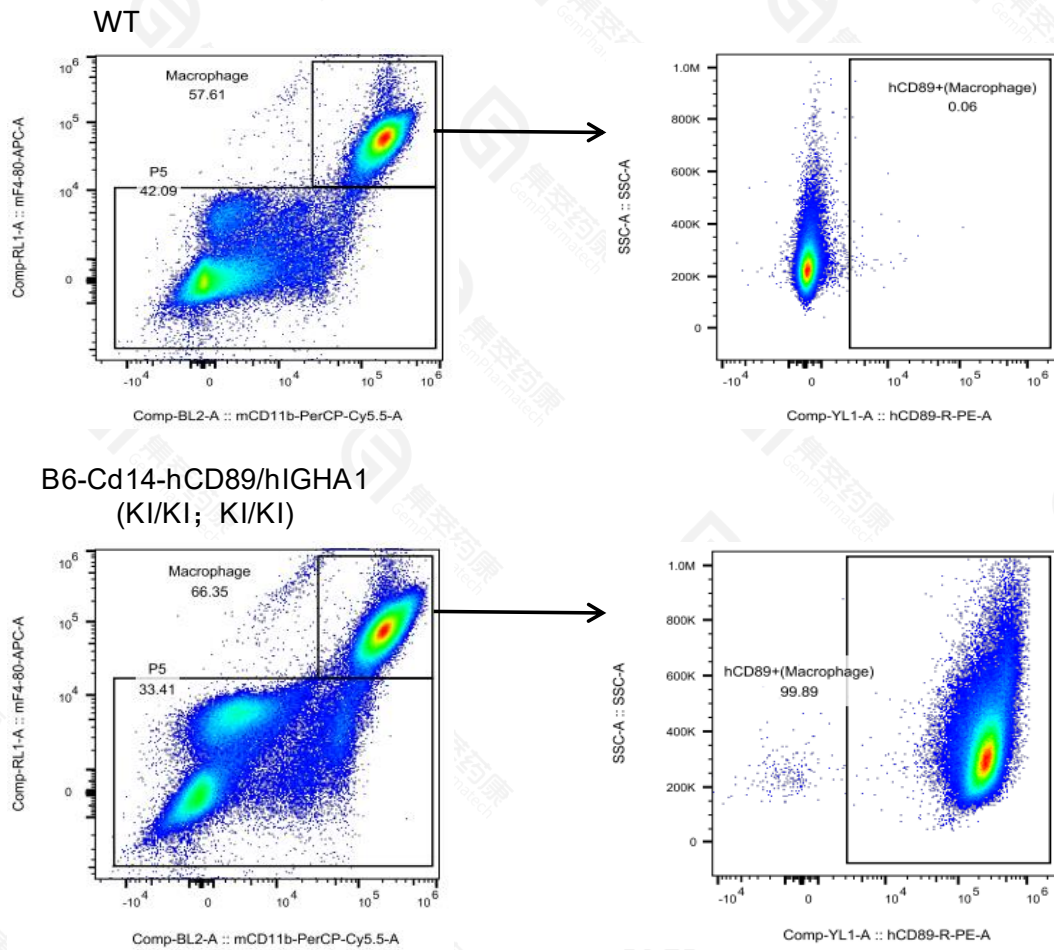
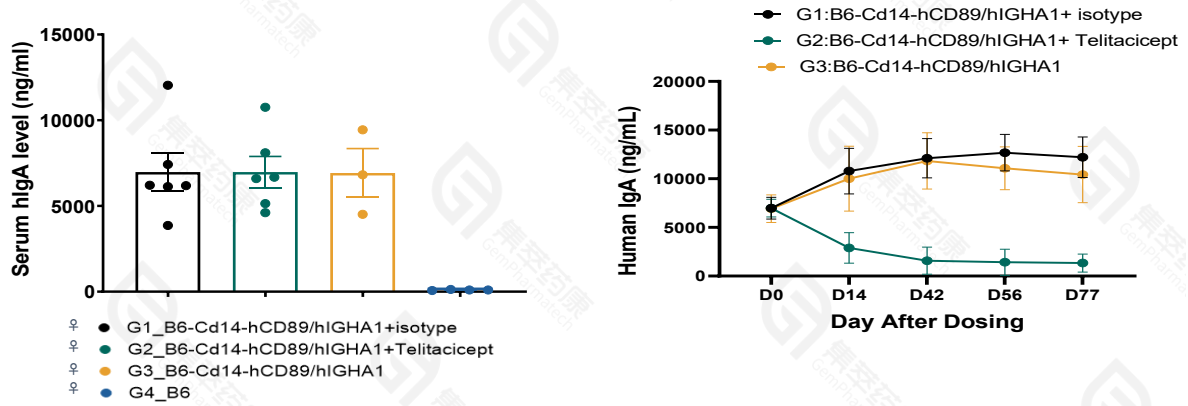


Fig 4. Detection of hCD89 expression in peritoneal macrophages of B6-Cd14-FCAR(CD89)/hIGHA1 mice.

Peritoneal macrophages were collected from B6 and homozygous B6-Cd14-FCAR(CD89)/hIGHA1 mice (KI/KI; KI/KI), and the expression of CD89 in peritoneal macrophages was detected. Compared with the wild-type mice, B6-Cd14-FCAR(CD89)/hIGHA1 mice could express humanized CD89 protein on the surface of peritoneal macrophages.

3. Phenotypic manifestations of B6-Cd14-hFCAR(CD89)/hIGHA1

A



B

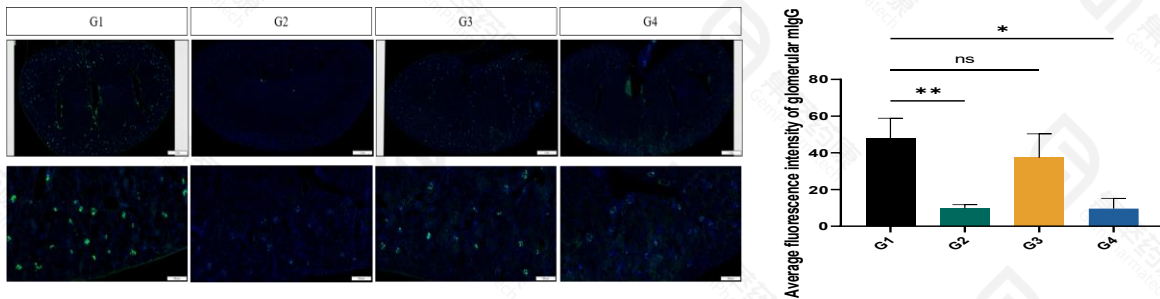


Fig 5. Efficacy data of B6-Cd14-hFCAR(CD89)/hIGHA1

A. 10-week-old female B6-Cd14-FCAR(CD89)/hIGHA1 mice (KI/KI; KI/KI) were randomly grouped based on serum hlgA levels. Telitacept administration significantly decreased serum hlgA levels.

B. At study endpoint, renal human IgA deposition was significantly increased in B6-Cd14-FCAR(CD89)/hIGHA1 female mice compared with B6 mice, while telitacept administration reduced IgA deposition.

References

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