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# Human IgG subclass cross-species reactivity to mouse and cynomolgus monkey Fcγ receptors

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## Highlights

- Affinities of human, murine and cyno monkey FcγRs against human IgGs is presented.
- Cyno FcγRs had higher affinities to human IgGs compared to corresponding human FcγRs.
- Cyno FcγRI had nanomolar affinity to human IgG4 PAA while human FcγRI bound weakly.

## Abstract

In therapeutic antibody discovery and early development, mice and cynomolgus monkey are used as animal models to assess toxicity, efficacy and other properties of candidate molecules. As more candidate antibodies are based on human immunoglobulin (IgG) subclasses, many strategies are pursued to simulate the human system in the test animal. However, translation rate from a successful preclinical trial to an approved drug is extremely low. This may partly be due to differences in interaction of human IgG based candidate molecules to endogenous Fcγ receptors of model animals in comparison to those of human Fcγ receptors. In this study, we compare binding characteristics of human IgG subclasses commonly used in drug development (IgG1, IgG2, IgG4) and their respective Fc silent versions (IgG1σ, IgG2σ, IgG4 PAA) to human, mouse, and cynomolgus monkey Fcγ

receptors. To control interactions between Fab and Fc domains, the test IgGs all have the same variable region sequences. We found distinct variations of interaction of human IgG subclasses to model animal Fcγ receptors in comparison to their human counterparts. Particularly, cynomolgus monkey Fcγ receptors showed consistently tighter binding to human IgGs than human Fcγ receptors. Moreover, the presumably Fc silent human IgG4 PAA framework bound to cynomolgus monkey FcγRI with nanomolar affinity while only very weak binding was observed for the human FcγRI. Our results highlighted the need for a thorough *in vitro* affinity characterization of candidate IgGs against model animal Fcγ receptors and careful design of preclinical studies.

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Keywords

Immunoglobulin G (IgG); Fcγ receptors; Animal models; Cross-species reactivity; Fc-silent IgGs; Surface Plasmon Resonance (SPR)

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