A systems approach to predict the influence of antibody host genetics upon IgG-FcγR complex formation post HIV vaccination

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Background:
Antibody Fc-effector functions have been correlated with protection in the RV144 HIV vaccine trial and delayed disease progression. Fc-functions are activated by IgG antibodies engaging with Fc receptors (FcRs) to form activating complexes on innate immune cells. Genetic variation in both IgGs and FcRs have the capacity to alter IgG-FcR complex formation *via* changes in binding affinity and concentration. A growing challenge lies in dissecting the importance of multiple host genetic variations, especially in the context of vaccine trials that are rarely conducted in homogenous genetic populations. However, experimental evaluation of all possible host genetic changes in HIV-IgG-FcR interactions is costly, time intensive, and results are difficult to deconvolute into relative contributions from multiple parallel system alterations.

Methods:
Here we developed a systems approach using ordinary differential equation models to predict IgG-FcγRIIIa complex formation based upon HIV-specific IgG1, IgG2, IgG3

& IgG4 concentrations, antibody affinity to HIV and host genetics. Parallel *in silico* and *in vitro* experimental assays were conducted to compare and validate the accuracy of the model's ability to predict IgG-FcγRIIIa complex formation using RV144 HIV vaccine plasma samples. Upon validation of the model, the influence of different IgG1 allotypes and FcγRIIIa polymorphisms were predicted post RV144 vaccination and upon variable different boosting strategies.

Results:
Model results correlated well with experimentally measured IgG-FcγRIIIa complex formation (Spearman R= 0.92, p<0.0001) from RV144 Vaccine plasma samples. The model was able to illustrate how different vaccine boosting strategies could be applied to maximize IgG-FcγRIIIa complex formation dependent upon different genetic backgrounds. Individuals with the G1m1,17 and G1m1,3 allotypes were predicted to be more responsive to vaccine adjuvant strategies that increase FcγRIIIa affinity (e.g. glycosylation modifications), compared to the G1m-1,3 allotype which was predicted to be more responsive to vaccine regimens that increase IgG1 antibody titers (concentration).

Conclusion:
Overall, we present a rapid, cost-effective tool for evaluating genetic differences underlying FcR activation, and for the rational improvement of Fc-mediated functions post-HIV vaccination, which is relevant for ongoing efforts to improve vaccine efficacy

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