

# Fab-arm exchange is a misnomer

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There is increasing research activity aimed at understanding the molecular mechanisms underlying the phenomenon of so-called Fab-arm exchange, which has important implications for immunotherapies involving the anti-inflammatory IgG4 antibodies, and might also be relevant to our understanding of the etiology of the newly-described IgG4-related disease.<sup>1</sup> I would like to point out that “Fab”-arm exchange is a misnomer and is misleading. It implies that only the Fab portion of the antibody is being exchanged; in fact, this dynamic process involves also the exchange of the Fc segment. The assumption underlying the coinage of Fab-arm exchange,<sup>2</sup> I presume, was that the Fc portion of the IgG4 antibodies is identical and therefore, functionally, only

the Fab is being exchanged. This assumption, however, ignores the presence of two isoallotypes<sup>3</sup> on IgG4—valine309/leucine309 and arginine409/lysine409. Thus, IgG4 molecules in a person heterozygous at these loci would have Fc of distinct genotypes. Interestingly, one of these Fc genotypes has been shown to have a functional impact on “Fab”-arm exchange: the arginine409 allele enables the Fab-arm exchange, while the lysine409 allele abrogates it.<sup>4</sup> Thus, in view of the fact that this phenomenon is restricted to the antibodies of IgG4 subclass and that genetically distinct Fab and Fc segments of the antibody are being exchanged, I suggest that Fab-arm exchange be changed to IgG4-arm exchange.

## References

1. Stone JH, Zen Y, Deshpande V. IgG4-related disease. *N Engl J Med* 2012; 366:539-51; PMID:22316447; <http://dx.doi.org/10.1056/NEJMra1104650>
2. van der Neut Kolfschoten M, Schuurman J, Losen M, Bleeker WK, Martínez-Martínez P, Vermeulen E, et al. Anti-inflammatory activity of human IgG4 antibodies by dynamic Fab arm exchange. *Science* 2007; 317:1554-7; PMID:17872445; <http://dx.doi.org/10.1126/science.1144603>
3. Brusco A, Saviozzi S, Cinque F, DeMarchi M, Boccazzi C, de Lange G, et al. Molecular characterization of immunoglobulin G4 gene isoallotypes. *Eur J Immunogenet* 1998; 25:349-55; PMID:9805657; <http://dx.doi.org/10.1046/j.1365-2370.1998.00113.x>
4. Labrijn AF, Rispiens T, Meesters J, Rose RJ, den Bleker TH, Loverix SJ, et al. Species-specific determinants in the IgG CH3 domain enable Fab-arm exchange by affecting the noncovalent CH3-CH3 interaction strength. *J Immunol* 2011; 187:3238-46; PMID:21841137; <http://dx.doi.org/10.4049/jimmunol.1003336>