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Fab-arm exchange
What's in a name?

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Immunology and structural biology are highly complex fields of study in which mechanisms and inter-relationships are often not easily understood. It is therefore quite common to use metaphors to make knowledge gained accessible to experts and non-experts alike. Thus we, for example, all know the antibody as a Y-shaped protein with two arms and a tail and we understand the specificity of antibody-antigen binding as a key-into-lock interaction. Are these metaphors strictly correct? No, of course not. Nevertheless, they are well-recognized and serve to provide some immediate and general understanding of key features.

When faced with the challenge of designing a simple descriptor or metaphor for the process leading to the exchange of human IgG4 "half-molecules," we discussed various options with experts in the field and came up with the term "Fab-arm exchange."[1] The phrase is simply meant to highlight the functional consequence of this mechanism, i.e., the exchange of antigen-binding parts between parental antibody molecules leading to novel binding combinations in the product.

Professor Pandey argues in his letter that Fab-arm exchange is a misnomer and should be changed to IgG4-arm exchange with the argument that allotypic differences are ignored.[2] Apart from the fact that, seen from Pandey's view, the phrase IgG4-arm exchange suffers from similar weaknesses as the original (and should be termed IgG4-arm-and-tail exchange instead), clearly we disagree. This is not only in view of the above, but also due to the observation that Fab-arm exchange occurs in many animals involving distinct non-IgG4 antibody subclasses.[3-5] In addition, we are obliged to point out that Pandey uses a weak example. Neither the V309/L309 nor the K409/R409 isoallotype[6] are likely to have a functional impact on the product. Thus, we have demonstrated in Labrijn et al.[3] that K409 abrogates Fab-arm exchange for human IgG4 molecules and the exchange between isoallotypes in individuals carrying both genes therefore cannot occur. The formation of V309-L309 IgG4 heterodimers, in our view, has limited relevance as there is no indication in the literature that the isoallotype at this position affects antibody function.

In fact, Pandey might have found a better argument outside of the field of IgG allotypes. Differences in Fc-associated carbohydrates, for example, may affect antibody effector function or half-life[7,8] and this therefore represents an example where the exchange of (half) Fc domains between antibody molecules might affect activity of the product. Nevertheless, we also believe that such exchange will not have significant functional consequences in a polyclonal response in vivo because of the dynamic recombination of these modifications with random antigen-binding specificities.

In summary, the reassortment of antigen-binding specificities is the major functional consequence of Fab-arm exchange and that's in the name.

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