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Rebuttal to Smith and Janssen

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Susanne Neumann and Marvin C. Gershengorn

Dear Editor:

We respond to the letter by Smith and Janssen (1) that states our conclusion was premature because they claim there is evidence for IGF-1R stimulating antibodies. However, in no report they referenced was a direct interaction with IGF-1R by a stimulatory antibody shown (see below). Moreover, they did not refute our major finding that the monoclonal thyrotropin receptor stimulating antibody (TSAb) M22 binds to thyrotropin receptor (TSHR), not to IGF-1R, yet involves IGF-1R in signaling (2). We showed previously that stimulation by thyrotropin (TSH) also involves IGF-1R in signaling (3,4). This is by definition TSHR/IGF-1R cross-talk—a concept that is endorsed by Smith and Janssen (5).

Our conclusion (2) that M22 (and TSH) activates TSHRs and IGF-1Rs, though it binds to TSHRs and not to IGF-1Rs, was not refuted by Smith and Janssen. We assume they think that M22 is not representative of all Graves' disease immunoglobulins (GD-Igs). We acknowledged this possibility (2) but suggested it is unlikely, since M22 and GD-Igs exhibit similar pharmacologic profiles.

We will comment on the criticisms made by Smith and Janssen.

We did not ''fail to consider the literature concerning IGF-1R in TAO [thyroid-associated ophthalmopathy]'' but provided our interpretation of those data. All of the reports referred to used GD-Igs containing TSAbs and other antibodies. When using GD-Igs containing multiple types of antibodies, one cannot conclude that the same antibody is mediating more than one effect. The reports that GD-Igs competed for IGF-1 binding could not demonstrate that these same antibodies were stimulatory. We agree that there are IGF-1R binding inhibitory antibodies in GD-Igs.

We did not ''incorrectly interpret the absence of detectable IGF-1R auto-phosphorylation.'' As stated (2), the assay used was highly sensitive, quantifying phosphorylated IGF-1R stimulated by extremely low IGF-1 doses.

We agree ''the recent finding that the inhibitory anti-IGF-IR monoclonal antibody teprotumumab'' is effective in treating Graves' ophthalmopathy (GO) is important. However, it should be noted that not all anti-IGF-1R antibodies inhibit GO-Ig activation of GO fibroblasts in culture (4). This difference is most likely because it is not inhibition caused by competition for GO-Ig binding, a potential characteristic of all these antibodies, but by inhibition of cross-talk. Moreover, it is important to consider that there are two components of GO-Ig stimulation: one that is IGF-1R-dependent (cross-talk), and another that is IGF-1R independent. We found that inhibition by an anti-IGF-1R antibody was partial, as it only inhibited the IGF-1R-dependent and not the IGF-1R-independent component of signaling (4). In this regard, we

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recently reported on the advantage of using antagonists directed at both TSHRs and IGF-1Rs in inhibiting activation of GO fibroblasts in culture (6).

As no single antibody that can bind and activate IGF-1R has been demonstrated, we conclude that the most likely cause of IGF-1R involvement in GD/GO-Ig signaling is via cross-talk initiated by binding to TSHR. In fact, to our knowledge, an antibody that binds and activates IGF-1Rs has not been shown definitively in any disease. Moreover, if one were to exist, it would likely cause diffuse cell hypertrophy/hyperplasia and tumor formation.

Thus, we concluded that the most likely cause of IGF-1R involvement in GD/GO pathogenesis is via TSHR/IGF-1R cross-talk initiated by TSAbs binding to TSHRs. At the very least, this idea presents a hypothesis that we have begun to test, whereas the supporters of the presence of IGF-1R stimulating antibodies have not reported direct support of their alternative hypothesis.

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