Response to Krieger *et al.* re: “TSHR/IGF-1R Cross-Talk, Not IGF-1R Stimulating Antibodies, Mediates Graves’ Ophthalmopathy Pathogenesis” (*Thyroid* 2017;27:746–747)

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Dear Editor:

We are responding to the letter from Krieger *et al.* (1) in which they comment on our earlier article (2). In that review, we believe that we presented a balanced and comprehensive overview of the controversies surrounding how insulin-like growth factor 1 receptor (IGF-IR) might be involved in the pathogenesis of thyroid-associated ophthalmopathy (TAO). We find several misleading statements in their letter.

First, Krieger *et al.* fail to consider the literature concerning IGF-IR in TAO by omitting reference to important studies. For example, Graves’ disease-associated immunoglobulins (GD-IgGs) from patients with TAO could enhance actions of thyrotropin (TSH) and could displace IGF-I binding. We have described an activating autoantibody that appears to target IGF-IR in GD. The Gershengorn group has challenged the existence of these IGF-IR-targeting antibodies. Although purported to provide support for their contention, figure 1 in their letter (1) offers no evidence about whether antibodies generated in GD bind to IGF-IR. Those data only confirm that M22, a monoclonal TSI, does not recognize IGF-IR.

Second, the authors state that we argue against thyrotropin receptor (TSHR)/IGF-IR crosstalk in TAO and incorrectly describe our views on interactions between these proteins. This assertion is untrue. In fact, Tsui *et al.* (3) in the Smith lab identified both physical and functional interactions between the two receptors. That report for the first time recognized the dependence of TSHR signaling on intact IGF-IR activity. In our recent paper, we reviewed both sides of the argument that a receptor/receptor interaction exists (2). We continue to endorse the concept that IGF-IR is required for TSHR signaling.

Third, Krieger *et al.* feel that we incorrectly interpreted the absence of detectable IGF-IR auto-phosphorylation in response to M22 and GD-IgG, despite the inhibition by OSI-906 of ligand-dependent hyaluronan accumulation. OSI-906 has been shown to inhibit ligand-dependent IGF-IR auto-phosphorylation. We therefore would propose that their

phosphorylation assay is inadequately sensitive for detecting a kinase signal. They instead propose that OSI-906 inhibits by inducing an IGF-IR conformational change, independent of phosphorylation. Their assertion is speculative and unsupported by evidence. While IGF-IR inhibition can be associated with conformational changes in a kinase-independent manner (biased signaling), no such activities have thus far been attributed to OSI-906.

Krieger *et al.* correctly point out that we did not comment that OSI-906 and one anti-IGF-IR blocking antibody (1H7) inhibited the induction by M22 of hyaluronan secretion while another (AF305) did not. They contend that the absent inhibition with AF305 supports their assertion that stimulatory anti-IGF-IR do not interact with that receptor. In contrast, we interpret their findings as suggesting that AF305 recognizes epitopes not directly involved in GD-IgG binding and IGF-IR activation.

A notable absence in their letter is any attempt to reconcile evidence supporting the presence of activating anti-IGF-IR antibodies in GD (4) and rheumatoid arthritis (5) with their own views. TSIs are not usually found in patients with rheumatoid arthritis. Further, Krieger *et al.* fail to discuss the consistent generation of anti-IGF-IR antibodies in mice immunized with TSHR.

We value balanced dialogue between parties with differing views in this controversial matter. We believe this matter is of considerable importance, underscored by the recent finding that the inhibitory anti-IGF-IR monoclonal antibody, teprotumumab, is safe and highly effective in TAO (6).

References

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Rebuttal to Smith and Janssen (*Thyroid* 2017;27:746–747. DOI: 10.1089/thy.2017.0281)

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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-1R 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