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Lessons From Anti-TSH-Receptor Autoantibodies: Challenges And Pitfalls In Diagnostics

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Objective: Autoantibodies to the thyrotropin hormone receptor (TSH-R) directly mediate Graves' disease (GD) and orbital manifestations of Graves' orbitopathy (GO). To explore their heterogeneous function, TSH-R autoantibody binding in immunoassays (TRAb) versus their functional activity; stimulators of cAMP in bioassay (TSIs or TSAbs) or inhibitors of the thyrotropic hormone (TSH) binding to TSH-R, detected by decreased cAMP in bioassay (TBAbs), is assessed.

Methods: TRAb measurements by automated electrochemical luminescence immunoassays (ECLIA) and stimulating and blocking activity on Chinese hamster ovary cell (CHO) Mc4 bioassays (Thyretain ®, Quidel). The activity of patient immunoglobulins on ECLIA; M22 Mab competition (cobas elecsys, Roche) or TSH-R bridge assay (Immulite,Siemens) versus Mc4 TSI bioassay were correlated with GO clinical activity by meta-analysis of complete Pubmed-published data sets (n=5).

Results: The automated ECLIA show less sensitivity than cell-based bioassay for detection of TRAbs (Fig 1A and 1B) and do not distinguish between stimulator MAbs; M22 and KSAb (Fig 1A and 1B) versus the blocker MAb K1-70 (Fig 1C). In contrast, Mc4 TSAb bioassay of K1-70 detected null stimulatory activity (Fig 1C), in contrast to strong cAMP inhibition in Mc4 TBAb blocker reporter bioassay (Fig 1D). Diagnostic performances of Mc4 TSAb bioassay and automated TRAb ECLIA in untreated GD show high sensitivities 97% (95-100) and specificities 98% (96-100%). Meta-analysis of GD and/or GO undergoing treatment reveal lower percent positive on Mc4 TSI Bioassay (56%, range 13-87%) than ECLIA TRAb immunoassays (98.5%, range 98-99%; OR=2.76, p=0.09). The Forest plot total random effects of correlation coefficients of autoantibody activity with GO clinical activity were greater on Mc4 bioassay (r=0.4, I2 =92% (95% CI 89-95), p<0.0.001) versus TRAb immunoassay (r=0.2, I2 =39% (95% CI 0-70%), p=0.0.8).

Conclusion: Diagnostic distinction of TSAbs and TBAbs is of paramount clinical importance. Cell-based bioassays are the only method to distinguish between TSAbs and TBAbs. To avoid the pitfall of incorrect reporting on automated TRAb binding assays, TSI or TSAb is strongly recommended for results of bioassays; whereas the results of automated ECLIA should be reported as TRAbs (of undetermined functional significance).

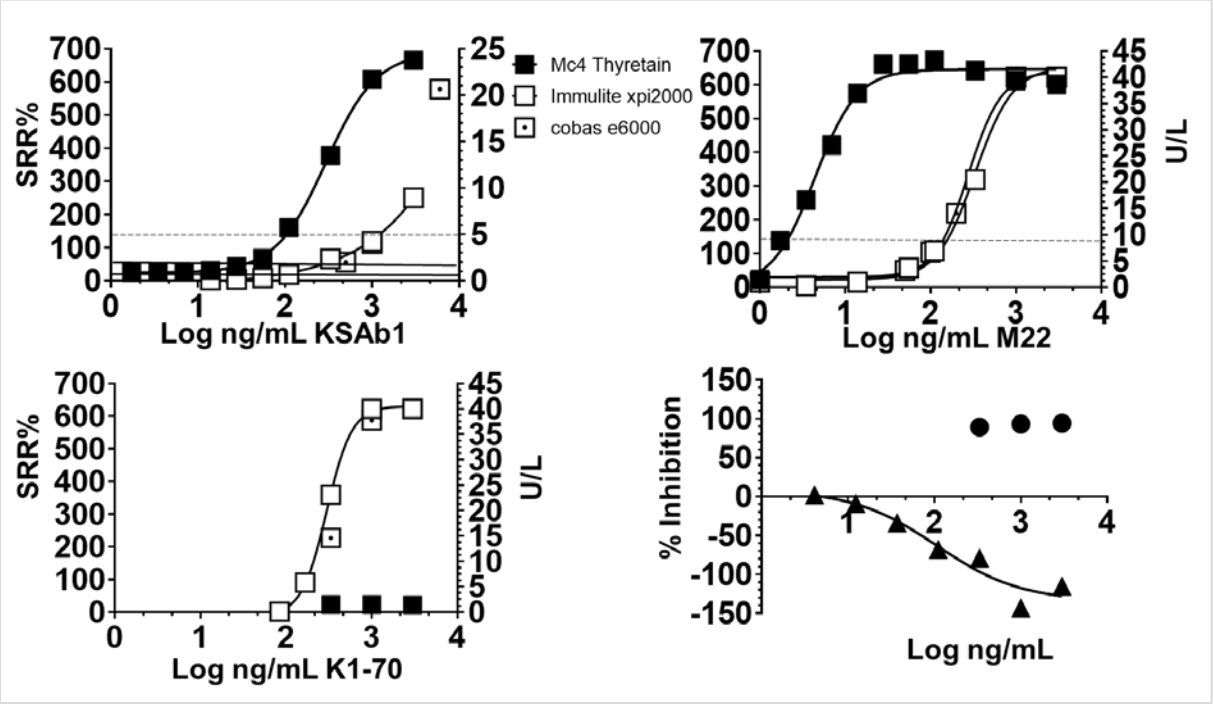

Figure 1. *Analytical sensitivity of the TSH-R bioassays versus binding immunoassays. Titration of the concentrations of anti-TSH-R monoclonal autoantibodies A) mouse stimulatory KSAb1 (22,40) B) human stimulatory M22 (RSR Ltd Cardiff UK, Cat Nr M22/FD/0.0*

Reference: Frontiers in Bioscience, Landmark, 23, 2028-2043, 2018.