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RE: A Molecular Perspective on Th2-Promoting Cytokine Receptors in Allergic Disease

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To the Editor

We would like to thank Dr. Dreyfus for his comment on our review of Th2-promoting cytokine receptors.^{1, 2} The objective of our article was to highlight how the molecular features of various forms of these receptors, and their associated components, impacts their function in allergic disease. In particular, we discussed how Th2-promoting cytokines are integral to complex networks owing to their overlapping functions and multiple actions. Such networks undoubtedly conspire to undermine the efficacy of therapeutics designed to target specific molecules. In relation to this point, the concept of using combined therapies in order to attain optimal clinical benefit was mentioned. We agree that extending this notion to include strategies which suppress the expression of genes encoding cytokines and their receptors, or else downstream signaling molecules, might provide an additional weapon in the armory against allergic inflammation.

It is important to consider whether experimental evidence supports the ability for gene silencing approaches to effectively suppress Th2-driven allergic inflammation. The papers cited by Dr. Dreyfus describe administration of short interfering RNA (siRNA) to silence IL-13 or STAT6 *in vivo* using mouse models of OVA-induced airway inflammation.^{3, 4} In both models, mice were sensitized intraperitoneally, and then challenged repeatedly with aerosolized or intranasal allergen. Results showed that administration of siRNA prior to each challenge through either intravenous or intranasal routes, ameliorated allergen-induced airway dysfunction or inflammation. However, neither molecule alone inhibited both airway reactivity and infiltrating cells. Moreover, the inhibitory effects observed were incomplete. Indeed, a notable finding in mice treated with IL-13 siRNA was the lack of a reduction in IL-13 levels in bronchoalveolar lavage fluid, despite attenuation of airway hyperresponsiveness.³ Collectively, these observations underscore not only the pleiotropic and overlapping actions of Th2 cytokines, but also the need for combined therapies directed against multiple targets.

Beyond attaining gene silencing, challenges to developing effective siRNA-based therapies include the design of sequences to avoid “off-target” effects, and optimization of delivery

routes that are practical in the clinical setting.⁵ Chemical modification of the siRNA backbone, along with the use of nanoparticles and conjugate delivery systems may help to direct siRNA molecules to target tissues and prevent their degradation. Nonetheless, tailoring of siRNA therapies will be necessary to optimize safe and effective delivery to sites of allergic inflammation in humans. RNA interference strategies are currently being tested in clinical trials for the treatment of diverse diseases including viral infections and cancers.⁵ Given the potential broad applications for gene silencing therapies, it will be interesting to see where they may fit into the future therapeutic landscape for allergic disease.

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