

Correspondence

Gene silencing and related oligonucleotide therapies for T_H2-promoting cytokines

To the Editor:

This letter is with regard to your excellent recent review of the pharmacology and mechanisms of T_H2-promoting cytokines.¹ The author's perspective is evidently focused on the protein-protein interactions and protein/peptide-based therapies, such as humanized mAbs and small molecules, in human clinical trials currently. However, in addressing "future directions," some mention should be made of the potential of gene-silencing therapies, such as antisense, small interfering RNA, and RNase P, in which the expression of receptors, cytokines, or both is interrupted at the mRNA level in addition to therapies directed at altering cytokine and receptor interactions.^{2,3} Elimination of cytokines or cytokine receptors by using gene silencing, although only tested in animal or *in vitro* systems, has the potential to block not only intercellular or paracrine cytokine signaling but also autocrine signaling, which might not be fully achieved by extracellular blockade of receptors after signaling. Decoy oligonucleotides and interference with downstream transcription factors activated by cytokines also have the potential to block cytokine signaling after receptor activation, also addressing the problem of autocrine signaling loops not blocked by partial inactivation of the cytokine receptors.⁴ Oligonucleotide-based therapies might have significant advantages in terms of cost and

topical administration because oligonucleotides, unlike immunoglobulins and peptides, are mostly effective for topical or local administration to respiratory or other epithelial tissues.² In the future, the authors would probably agree that some combination of antibody/peptide-based therapy and nucleotide-based gene silencing will be optimal for control of T_H2-promoting cytokines.

David H. Dreyfus, MD, PhD

From Keren Pharmaceutical, New Haven and Clinical Faculty, Yale SOM, New Haven, Conn. E-mail: dhdreyfusmd@gmail.com.

Disclosure of potential conflict of interest: D. H. Dreyfus has a patent with Yale SOM and has stock/stock options in Keren Pharmaceutical.

REFERENCES

1. Romeo MJ, Agrawal R, Pomés A, Woodfolk JA. A molecular perspective on T_H2-promoting cytokine receptors in patients with allergic disease. *J Allergy Clin Immunol* 2014;133:952-60.e1.
2. Dreyfus DH, Ghoda L. A review of recent patents concerning therapy of respiratory diseases using gene silencing by RNAi (RISC) and EGS (RNase P). *Recent Pat Inflamm Allergy Drug Discov* 2007;1:49-55.
3. Lively TN, Kossen K, Balhorn A, Koya T, Zinnen S, Takeda K, et al. Effect of chemically modified IL-13 short interfering RNA on development of airway hyperresponsiveness in mice. *J Allergy Clin Immunol* 2008;121:88-94.
4. Darcan-Nicolaisen Y, Meinicke H, Fels G, Hegend O, Haberland A, Kuhl A, et al. Small interfering RNA against transcription factor STAT6 inhibits allergic airway inflammation and hyperactivity in mice. *J Immunol* 2009;182:7501-8.

<http://dx.doi.org/10.1016/j.jaci.2014.06.008>