

## Journal Scan:

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### **Discovery of 6 Amino-2-[(1S) 1-methylbutyl]oxy]-9-[5-(1-piperidinyl)pentyl]-7,9-dihydro 8H purin-8-one (GSK2245035), a highly Potent and Selective Intranasal Toll-Like receptor 7 agonist for the treatment of Asthma**

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Induction of IFN $\alpha$  in the upper airways via activation of TLR7 represents a novel immunomodulatory approach to the treatment of allergic asthma. Exploration of 8-oxoadenine derivatives bearing saturated oxygen or nitrogen heterocycles in the N-9 substituent has revealed a remarkable selective enhancement in IFN $\alpha$  inducing potency in the nitrogen series. Further potency enhancement was achieved with the novel (S)-pentyloxy substitution at C-2 leading to the selection of GSK2245035 (32) as an intranasal development candidate. In human cell cultures, compound 32 resulted in suppression of Th2 cytokine responses to allergens, while in vivo intranasal administration at very low doses led to local upregulation of TLR7-mediated cytokines (IP-10). Target engagement was confirmed in humans following single intranasal doses of 32 of  $\geq 20$  ng, and reproducible pharmacological response was demonstrated following repeat intranasal dosing at weekly intervals.

#### Comment

In the study authors employed variety of screening strategies to identify selective, safe and pharmacodynamically significant small molecule agonist (Compound 32) to TLR7 by inducing IFN $\alpha$  for treating asthma. The present findings focus on the significance of SAR studies by preferred chemical modifications and substitutions in optimizing, designing and developing a drug molecule.

*Keith Biggadike, Mahbub Ahmed, Doug I. Ball, Diane M. Coe, Deidre A. DalmasWilk, Chris D. Edwards, Bob H. Gibbon, Charlotte J. Hardy, Stephen A. Hermitage, Joanne O. Hessey, Aimee E. Hillegas, Stephen C. Hughes, Linos Lazarides, Xiao Q. Lewell, Amanda Lucas, David N. Mallett, Mark A. Price, Fiona M. Priest, Diana J. Quint, Poonam Shah, Anesh Sitaram, Stephen A. Smith, Richard Stocker, Naimisha A. Trivedi, Daphne C. Tsitoura, and Victoria Weller. J Med Chem, 2016, DOI: 10.1021/acs.jmedchem.5b01647.*

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### **A Potent D Protein Antagonist of VEGF A is nonimmunogenic, metabolically stable, and longer-Circulating in Vivo**

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Polypeptides composed entirely of D-amino acids and the achiral amino acid glycine (D-proteins) inherently have in vivo properties that are proposed to be near-optimal for a large molecule therapeutic agent. Specifically, D-proteins are resistant to degradation by proteases and are anticipated to be nonimmunogenic. Furthermore, D-proteins are manufactured chemically and can be engineered to have other desirable properties, such as improved stability, affinity, and pharmacokinetics. Thus, a well-designed D-protein therapeutic would likely have significant advantages over L-protein drugs. Toward the goal of developing D-protein therapeutics, we previously generated RFX001.D, a D-protein antagonist of natural vascular endothelial growth factor A (VEGF-A) that inhibited binding to its receptor. However, RFX001.D is unstable at physiological temperatures ( $T_m = 33$  °C). Here, we describe RFX037.D, a variant of RFX001.D with extreme thermal stability ( $T_m > 95$  °C), high



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affinity for VEGF-A ( $K_d = 6$  nM), and improved receptor blocking. Comparison of the two enantiomeric forms of RFX037 revealed that the D-protein is more stable in mouse, monkey, and human plasma and has a longer half-life in vivo in mice. Significantly, RFX037.D was nonimmunogenic in mice, whereas the L-enantiomer generated a strong immune response. These results confirm the potential utility of synthetic D-proteins as alternatives to therapeutic antibodies.

### **Comment**

In general protein therapeutics have advantages like large protein interaction surfaces, extreme specificity and affinity towards their targets than the small molecule therapeutics. Disadvantage of protein therapeutics is proteolytic degradation which leads to less stability, reduced in vivo half-life, and increased potency causing immunogenicity. In this study the authors proposed a D-protein (RFX001.D) as a therapeutic antagonist to treat angiogenesis. Stereochemistry of D-proteins overcomes the aforesaid disadvantages and D-proteins could make an important new class of pharmaceutical products.

*Maruti Uppalapati, Dong Jun Lee, Kalyaneswar Mandal, Hongyan Li, Les P. Miranda, Joshua Lowitz, John Kenney, Jarrett J. Adams, Dana Ault-Richei, Stephen B. H. Kent, and Sachdev S. Sidhu. ACS Chem. Biol. 2016, DOI: 10.1021/acscchembio.5b01006.*

### **Reviewers**

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