

MEDA PHARMACEUTICALS, INC. and  
 CIPLA LTD.  
  
 Plaintiffs,  
  
 v.  
  
 APOTEX, INC. and APOTEX CORP.  
  
 Defendants.

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 ) Civil Action No. 1:14-cv-01453-LPS  
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Argentum Pharmaceuticals LLC v. Cipla Ltd.  
CIP2011  
IPR2017-00807

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1. I, Robert P. Schleimer, have been retained by Defendants Apotex, Inc., and Apotex Corp. as an expert to analyze certain claims of U.S. Patent Nos. 8,163,723 (“the ’723 patent”); 8,168,620 (“the ’620 patent”); and 9,259,428 (“the ’428 patent”), in connection with this lawsuit.

2. I have developed certain opinions about those patents and their asserted claims, which I set forth in this report. I expect to testify about them at trial if asked to do so. To form my opinions, I relied on documents and other materials cited in this report, my education, and my years of experience, teaching, and performing research in this field.

3. I reserve the right to amend or supplement my opinions in light of evidence presented by or on behalf of the plaintiffs, or in connection with additional information that may later be made available to me. At trial, I may use demonstrative exhibits if useful for explaining and understanding the opinions in this report, and I may testify about background scientific concepts related to pharmacology to explain as necessary the context of the claims.

4. I am being compensated for my time on this matter at a rate of \$400/hour for consulting and \$600/hour for testimony. Those are my standard consulting rates. My compensation is in no way dependent on the outcome of this case.

5. I have not given testimony or written an expert report in connection with litigation in the last five years.

## **I. PROFESSIONAL BACKGROUND**

6. I am the Roy and Elaine Patterson Professor of Medicine and the Chief, Division of Medicine-Allergy-Immunology, at the Feinberg School of Medicine, Northwestern University.

7. I received my B.A. from the University of California at San Diego and my Ph.D. from the University of California at Davis. My Ph.D. is in Pharmacology-Toxicology and I have

received training as an Immuno-pharmacologist. My postdoctoral fellowship was at the Johns Hopkins University School of Medicine where I studied mechanisms of allergic diseases using both *in vitro* and *in vivo* approaches. The *in vivo* challenge models of human disease included nasal challenge of human subjects with allergen to assess allergic rhinitis mechanisms, bronchial challenges of human subjects with allergen to assess asthma mechanisms, and studies of the skin and sinuses. Between 1982 and 2004 I was on the faculty at Johns Hopkins, and since 2004 I have been on the faculty at Northwestern. During my time at Johns Hopkins and subsequently at Northwestern, allergic rhinitis has been one of the major allergic diseases I have studied.

8. I have published widely on the use of steroids and antihistamines. A Pubmed search of my publications reveals 61 papers for the search term “steroid” and 64 papers for the search term “histamine.” These are listed in my *curriculum vitae*, attached hereto as Exhibit A (current as of December 2015). I am recognized as an international expert in the study of the mechanisms of anti-inflammatory steroid actions in allergic disease.

9. I have taught Pharmacology and/or Allergy-Immunology at Northwestern Feinberg School of Medicine, Johns Hopkins School of Medicine, California State University at Chico, and the University of California at Davis. I have trained dozens of scientific investigators holding either the Ph.D. or M.D. degree, and many of my former trainees are now recognized as international experts in the mechanisms of allergic disease.

10. I also have significant experience outside of the academic setting. For instance, I have served as a full time member on three standing National Institutes of Health grant review committees—Lung Biology and Pathology (LBPA), Lung Cell and Molecular Immunology (LCMI), and the Specialized Center of Clinically Oriented Research (SCCOR). I have also served as a member and served as the Chairman for two NIH study sections (Lung Cell and

Molecular Immunology (LCMI) and Severe Asthma Research Program (SARP)). I have served on numerous other National Institutes of Health committees, including Strategic Planning, Asthma Outcomes, Immunological Aspects, Outstanding New Environmental Scientist (ONES) review, the NIAID Biomarkers committee, Scientific Counselors, and others. These study sections reviewed dozens of multimillion dollar grants in the area of molecular and cellular mechanisms of allergic disease and the effects of drugs on these diseases. I have been on numerous committees at Northwestern University and at Johns Hopkins during my tenure at each institution.

11. I serve or have served on editorial boards for many major biomedical journals. This includes service as an Associate Editor on the Journal of Allergy and Clinical Immunology, the worldwide leading journal in the field of allergy. This journal publishes the best research in the field relevant to the actions of antihistamines and glucocorticoids (a class of steroids) in allergic disease.

12. I am presently serving as an advisor or advisory board member for several pharmaceutical companies (AstraZeneca, Genentech, GlaxoSmithKline, Intersect ENT, Merck, Regeneron, Sanofi). I am also a founder of a startup company, Allakos. Allakos is developing drugs to treat severe allergic diseases.

13. My additional qualifications, including a complete list of papers I have published and book chapters I have co-authored, can be found on my *curriculum vitae*. Also included in my CV is my record of NIH funding (continuous funding for the past 33 years), a record of international and domestic invited lectures, honors and awards that I have received (including named lectures), a list of invited visits with pharmaceutical companies over the years (from which my advisory service can be inferred), and patents issued in my name.

14. In light of all of this experience, I consider myself to be an expert at least in the areas of allergic rhinitis, its pathophysiology, and its treatment with antihistamines and steroids through any route of administration.

15. In addition to my knowledge, education, and experience in the fields of allergy, immunology, and pharmacology, I have reviewed certain materials in forming the opinions I express in this report and I have attached a full list of those materials as Exhibit B.

## **II. LEGAL STANDARDS**

16. Counsel for Apotex has asked me to offer my opinions on whether or not I think the asserted claims of the patents-in-suit and particular aspects of them are inventive or obvious; whether or not certain of the asserted claims have satisfied the written description requirement of the patent law; and whether or not certain of the asserted claims have satisfied the enablement requirement of the patent law.

17. In order to form my opinions on these questions in the context of this litigation, counsel has explained to me certain legal standards. I include below my understanding of these relevant legal standards, as these make up the framework in which I did my analysis.

### **A. Obviousness**

18. I have been informed a patent claim is invalid as obvious if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time that the invention was made to a person of ordinary skill in the art (a “POSA”). For my analysis of obviousness, I have considered and applied the following factors: (a) the scope and content of the prior art; (b) the differences between the prior art and the asserted claims; and (c) the level of ordinary skill in the field of the invention. I also understand that courts may review certain other objective indicators tending to show that patent claims are non-obvious or obvious. I have identified some of my opinions on

such indicators in this report. I reserve the right to supplement those opinions based on evidence, arguments, or opinions presented by or on behalf of Meda or Cipla.

19. I also have been informed and understand that a claimed invention may be obvious if at the time of the alleged invention there was a reason that would have prompted a POSA in the field of the invention to combine known elements in a way the claimed invention does, taking into account such factors as: (1) whether the claimed invention was merely the predictable result of using prior art elements according to their known functions; (2) whether the claimed invention provides an obvious solution to a known problem in the relevant field; (3) whether the prior art teaches or suggests the desirability of combining elements claimed in the invention; (4) whether the prior art teaches away from combining elements in the claimed invention; (5) whether it would have been obvious to try the combinations of elements, such as when there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions; and (6) whether the change from the prior art resulted more from design incentives or other market forces.

20. I also have been informed that a claimed invention may be obvious to try where at the time of the invention there was a known problem or need in the art, there was a finite number of identified, predictable potential solutions to that need or problem, and a POSA could have pursued those solutions with a reasonable expectation of success. If this leads to the claimed invention, it is not because of innovation but because of ordinary skill and common sense.

21. I further understand that the prior art must provide to the POSA a reasonable expectation of successfully making and using the alleged invention.

22. I further understand that in determining whether the claimed invention was obvious, one must not use hindsight, and must instead consider only what was known at the time



of the invention.

**B. Written Description and Enablement**

23. I have also been informed and understand that a patent claim is invalid for lack of written description if the patent specification fails to provide an adequate written description of the full scope of the claimed invention. I understand that the written description requirement is satisfied if a POSA reading the patent application as originally filed, would recognize that the patent application described the full scope of the invention as claimed. The written description is adequate if it shows that the inventors were in possession of the full scope of the claimed invention at the time the application for the patent was filed. It is not necessary that each and every aspect of the claim be explicitly discussed in the specification, so long as the patent application when and as originally filed still reflects that the named inventors possessed the full scope of the claimed invention.

24. Likewise, I have been informed and understand that a patent claim is invalid for lack of enablement if the specification of the patent as of its earliest claimed filing date does not enable a POSA to make and use the claimed invention without undue experimentation. I understand that whether practicing a claim requires undue experimentation requires weighing a number of factual considerations. They include: (1) the quantity of experimentation necessary; (2) the amount of direction or guidance presented; (3) the presence or absence of working examples; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims.

**C. Person of Ordinary Skill in the Art**

25. I evaluated the questions of obviousness and the written description and

enablement requirements from the perspective of a POSA. I was informed that to determine the level of ordinary skill in the subject matter of the asserted patents, I should consider: (1) the levels of education and experience of the inventor(s) and other persons actively working in the field; (2) the types of problems encountered in the field; (3) prior art solutions to those problems; (4) rapidity with which innovations are made; and (5) the sophistication of the technology. The subject matter of the asserted patents is generally directed to pharmaceutical compositions comprising an intranasal steroid and intranasal antihistamine, and methods of using such compositions, for the treatment of allergic rhinitis and other conditions.

26. I understand that for the obviousness analysis I was to conduct my analysis from the perspective of a POSA as of the date of the alleged invention of the asserted claims. For my analysis of written description and enablement, I understand that the evaluation is conducted from the perspective of a POSA as of the earliest claimed filing date of the asserted patents. I have been asked to assume that the date of invention is June 2002, and the earliest claimed patent application filing date is June 13, 2003. My opinions are the same regardless of which date is correct for the analysis.

27. Based on those factors, it is my opinion that a POSA in the field of the asserted patents would have an M.D., Ph.D. or Pharm.D. in the field of allergy/immunology and/or pharmacology (or the equivalent), and at least three additional years of experience in the treatment, or research for treatments, of allergic rhinitis, including with nasally administered steroids and antihistamines. I have also reviewed the report of Dr. Maureen Donovan, and she defines the qualifications of a person of ordinary skill in the field of pharmaceutical formulations as follows:

In my opinion, the relevant “art” to which the patents are directed is pharmaceutical formulations of topical agents, specifically nasal suspensions

and/or solutions. A person of ordinary skill in this field has at least a bachelor's degree in chemistry, biology, chemical engineering or pharmaceutical sciences with significant experience, 3-5 years in formulation development of nasal dosage forms and the ability to operate independently on formulation activities. A person of skill in the art would also have familiarity with pharmaceutical excipients and their uses.

A person of ordinary skill in the art may also have a Master's degree in chemistry, biology, chemical engineering, or pharmaceutical sciences with 1-3 years in formulation development of nasal agents as well as the ability to operate independently on formulation activities. Such a person may also have a Ph.D. in chemistry, chemical engineering, or pharmaceutical sciences with at least one year of experience in formulation development of sterile dosage forms. These persons would also have familiarity with pharmaceutical excipients and their uses.

28. I agree with the above definition. I also agree with her opinion that a person of ordinary skill in the field of research for and treatment of allergic rhinitis would collaborate with a person of ordinary skill in pharmaceutical formulations.

### **III. SUMMARY OF OPINIONS**

29. I have analyzed the patents-in-suit and their file histories, and offer the following opinions concerning the asserted claims, which I understand are Claims 8, 11, 14, 25 and 28 of the '723 patent; Claims 4, 29, and 42-44 of the '620 patent; and Claims 10, 11, 13, 15, 16, 18-20, 22-24, 26, and 28-30 of the '428 patent.

30. **First**, each of the asserted claims covers, among other things, pharmaceutical compositions containing, or methods of using, a combination of azelastine hydrochloride (HCl) and fluticasone propionate for the treatment of allergic rhinitis via a single nasal spray. It is my opinion that these aspects of each of the asserted claims would have been obvious to a POSA.

31. It was well known at the time of the alleged invention that there was a dual etiology underlying allergic rhinitis. An early-phase allergic response characterized by sneezing, itching, and rhinorrhea (*i.e.*, runny nose) was due largely to activity of histamine at histamine (H<sub>1</sub>) receptor sites. A late-phase response characterized by congestion and nasal blockage was

the result of an inflammatory reaction. It was also well known at the time of the alleged invention that antihistamines such as azelastine antagonize the H<sub>1</sub>-receptor site and treat primarily the early-phase response, and that intranasal steroids such as fluticasone primarily treat late-phase inflammation.

32. Because of these different mechanisms and methods of action, a POSA would have had a motivation to combine antihistamine and steroid therapies for additive clinical effects. Therapies combining antihistamines and steroids were well known in the prior art to be effective for the treatment of allergic rhinitis. The prior art disclosed both the dual intranasal use of an antihistamine product and a steroid product, and even disclosed the simultaneous intranasal administration of azelastine and fluticasone specifically in a single pharmaceutical composition, for the treatment of allergic rhinitis. There was thus a motivation to combine and a reasonable expectation that combining azelastine and fluticasone into a single nasal spray for the treatment of allergic rhinitis would have led to a treatment at least as successful as azelastine or fluticasone alone, and likely with additive clinical effects.

33. Prior art combination therapies using azelastine and fluticasone were also known to overcome certain shortcomings of their individual use. For instance, steroids like fluticasone were known to have a delayed onset of action relative to antihistamines, sometimes requiring several days of use before effective symptom relief would be achieved. The prior art taught that administering the drugs together would help increase compliance rates with the steroid, because the antihistamine would give some initial relief to patients during the pre-onset phase of the steroid treatment. Doctors in fact already practiced this teaching by prescribing both Astelin<sup>®</sup> (intranasal azelastine hydrochloride) and Flonase<sup>®</sup> (intranasal fluticasone propionate) to individual patients.

34. **Second**, Claim 8 of the '723 patent encompasses a method for the prophylaxis or treatment in a mammal of allergic rhinitis, comprising intranasal administration of a therapeutically effective amount of a pharmaceutical composition comprising azelastine HCl and fluticasone propionate. That subject matter would have been obvious to a POSA for the same reasons I discussed above, and in further detail below.

35. **Third**, asserted claims 29 of the '620 patent, and 10, 11, 13, 15, 16, 18-20, 22-24, 26 and 28-30 of the '428 patent, cover specific amounts or ranges of amounts of azelastine HCl and fluticasone propionate to be used as part of the claimed composition or method of treatment. It is my opinion that those specific amounts and/or ranges of amounts would have been obvious to a POSA for use in a combination product like that encompassed by all of the claims. Among the strongest reasons supporting that opinion is that those exact amounts, or amounts squarely within the claimed ranges, had been used and were commercially available in individual azelastine and fluticasone treatments in the prior art. Claim 14 of the '723 patent covers specific ranges of amounts of azelastine HCl and of fluticasone propionate or fluticasone valerate, and is obvious for the same reasons.

36. **Fourth**, in addition to the subject matter I just described, many of the asserted claims contain limitations about excipient ingredients, amounts of those ingredients, and other properties of the combination azelastine/fluticasone product(s) covered by the claims. My opinion is that it would have been obvious to a POSA to try to make and use the combination product that, as stated above, I opine would have been obvious to a POSA. That is evidenced, in part, by the fact that both azelastine HCl and fluticasone propionate had been formulated into FDA-approved, commercialized nasal spray products by the time of the alleged invention. I do not mean to suggest that FDA approval and commercialization would have been necessary to

make these concepts obvious, but it is certainly relevant.

37. I also understand that Apotex has retained Dr. Maureen Donovan to offer opinions concerning the ways a POSA would have formulated a combination azelastine/fluticasone nasal spray at the time of the alleged invention. I have read her report and agree with her conclusions.

38. *Fifth*, it is my opinion that the plaintiffs' evidence of unexpectedly superior results, in the form of the clinical studies reported in Joachim Maus's declaration to the patent examiner, does not actually show unexpected or superior results compared to the closest prior art. The superiority of the combination product compared to either azelastine alone or fluticasone alone would not have been surprising or unexpected to a POSA for the same reasons the asserted claims are obvious: because antihistamines and steroids were known to have different mechanisms of action, additive results would not have been surprising when combining the two into a single therapy. Moreover, the results of the studies were not actually superior to the closest prior art—the simultaneous or sequential administration of an antihistamine and a steroid, and the simultaneous or sequential use of Astelin<sup>®</sup> (azelastine hydrochloride) and Flonase<sup>®</sup> (fluticasone propionate) in particular. Studies comparing a co-administration of azelastine hydrochloride and fluticasone propionate in separate sprays showed a magnitude of superiority over the administration of either alone that was similar to the superiority of the combination product in the clinical trials reported in Dr. Maus's declaration. Thus, there is no evidence that the effectiveness of the combination is superior to the effectiveness of simultaneous use of both drugs given separately.

#### IV. ANALYSIS

39. To formulate my opinions on whether or not the subject matter of the asserted claims would or would not have been obvious to a POSA, I first put myself in the mindset of a

POSA prior to June 2002 to assess the scope of the art at that time in the field of treatments of allergic rhinitis.

**A. The etiology of allergic rhinitis: early-phase and late-phase reactions.**

40. Allergic rhinitis (“AR”), commonly called “Hay Fever,” is caused when a person becomes sensitized to ordinarily innocuous allergens in the air such as pollen grains, animal dander, or material from insects such as house dust mites or cockroaches.

41. Exposure of a sensitized person to these allergens quickly causes their histamine-containing mast cells and basophils to release histamine and other pharmacologically active mediators that cause blood vessels to swell and leak, cause smooth muscle in the nose and throat to constrict, and stimulate nerves that cause sneezing, wheezing, and coughing. This is referred to as the early-phase AR response. As one author explains: “Prolonged exposure to indoor allergens results in production of IgE antibodies that bind to mucosal mast cells and circulating basophils. Thus sensitised, the patient develops acute nasal and ocular symptoms following further exposure. This response, which can occur within minutes of exposure and is termed the early-phase allergic response, is caused primarily by the release of mast cell mediators. These include histamine, tryptase, prostaglandin D<sub>2</sub> and the cysteinyl leukotrienes (LT) C<sub>4</sub>, D<sub>4</sub> and E<sub>4</sub>.” Galant & Wilkinson (2001), at 455. It was thus known well before the alleged date of invention that histamine was one cause of the early-phase AR response.

42. As I noted above, however, there is also a late-phase AR response. “A late-phase response that occurs 4 to 8 hours after allergen exposure in 50% of patients is thought to be due to cytokine release by mast cells and thymic-derived helper T cells called T<sub>H</sub>2 cells. The late-phase response is characterized by profound infiltration and activation of migrating and resident cells. This inflammatory response is thought to be responsible for the persistent, chronic signs and symptoms of AR, particularly nasal obstruction and increased sensitivity of the nasal mucosa

to allergens and irritants.” Galant & Wilkinson (2001), at 455. It was thus known well before the alleged date of invention that the late-phase AR response was primarily inflammatory in nature.

43. Other sources also reflect the established knowledge that AR generally comes in two phases. Drouin (1995), for example, explains: “The nasal response to allergen challenge can be divided into an early reaction (occurring within minutes of allergen exposure) and a late-phase reaction (occurring 4 to 10 hours after allergen challenge in about half of patients).” Drouin (1995), at 341.

**B. Prior art treatment of allergic rhinitis.**

**1. Antihistamines were known to treat primarily the early-phase response.**

44. Antihistamines are a class of drugs that, as the name suggests, block the activity of histamine in the body. As noted above, histamine has long been known to play a role in the early-phase response of AR. It causes, among other things, dilation of blood vessels (vasodilation), which can lead to runny nose, watery eyes and, ultimately, congestion. It can also stimulate mucus-secreting glands, which also contributes to these symptoms. Histamine in AR can also stimulate receptors in the nose that cause sneezing and coughing.

45. It was also known long before the alleged date of invention that antihistamines are useful in stopping or reducing these reactions. The usefulness of antihistamines in treating AR was first discovered in the first half of the twentieth century. Feinberg & Friedlaender (1945).

46. The first generation of antihistamines was shown to inhibit the early phase of AR, but have little or no effect on the late phase. Grönneberg et al. (1981). However, a second generation of antihistamines was shown before the alleged date of invention to inhibit the responses of not only mast cells, but also other inflammatory cells at high concentrations,



thereby providing some (not complete) relief for the late-phase response of AR and adding to their efficacy.

47. The prior art succinctly summarizes what would have been well known to a POSA about the role of histamine and antihistamines in AR before 2002. As Galant & Wilkinson reported, “First- and second-generation antihistamines are very effective in the treatment of AR because they alleviate both nasal and ocular symptoms. Antihistamines antagonise histamine directly, but reversibly, at the H<sub>1</sub> receptor, thereby blocking the physiological effects of histamine on blood vessels, mucous-secreting glands, and sensory nerve endings in the nose. In addition, several antihistamines, including the second-generation agents fexofenadine hydrochloride and loratadine, also appear to block release of histamine and other inflammatory mediators from mast cells and basophils *in vivo*. The second-generation antihistamine cetirizine inhibits LTC<sub>4</sub> and D<sub>4</sub> production in nasal secretions and inhibits recruitment of eosinophils in the cutaneous late-phase model.” Galant & Wilkinson (2001), at 456. Drouin (1995) similarly taught that “H<sub>1</sub>-receptor antagonists relieve the ocular symptoms that accompany SAR [seasonal allergic rhinitis] and help prevent and relieve sneezing, nasal itching, and rhinorrhea[.]” Drouin (1995), at 341-42.

**i. Azelastine HCl**

48. One second-generation antihistamine that was well known in the prior art was azelastine HCl, which, as with other such antihistamines, was shown well in advance of the priority date to inhibit the responses of both mast cells and other inflammatory cells at high concentrations, thereby providing some relief for the late-phase response of AR and increasing efficacy. *See* Fields et al. (1984); Fischer & Schmutzler (1981); Katayama et al. (1987); Church & Gradidge (1980); Lytinas et al. (2002); Kusters et al. at (2002); Hide et al. (1997); Honda et al. (1982); Togias et al. (1989); Ciprandi et al. (1996); Wang et al. (1997); Mosges & Klimek

(1998); Jacobi et al. (1999). As Galant & Wilkinson explained in 2001, “Another second-generation agent, azelastine hydrochloride, in addition to high affinity for the H<sub>1</sub> receptor administered as a nasal spray, is inhibitory to several cells and chemical mediators of the inflammatory response.” Galant & Wilkinson (2001), at 456.

49. Lieberman (2001) and Berger (1999) both summarize the literature on azelastine. Lieberman (2001) explained that in addition to its antihistaminic mechanism, azelastine had “several putative mechanisms including a diminution in the production of neurokinin, the prevention of mast cell degranulation, a reduction in eosinophil accumulation associated with a decrease in expression of adhesion molecules, and a decrease in the synthesis of inflammatory cytokines and nitric oxide *via* an effect on transcription mediated through NF-KB. The latter observation signifies that azelastine has significant effects on transcription.” Lieberman (2001), at 202; *see also* Berger (1999), at 535 (“In addition to H<sub>1</sub>-receptor antagonism, azelastine also affects cells and chemical mediators of the inflammatory response as shown in in vitro studies and in animal models of allergic inflammation. In clinical trials in patients with seasonal allergic rhinitis, azelastine reduced levels of leukotrienes and kinins following nasal allergen challenge and downregulated intercellular adhesion molecule-1 (ICAM-1) expression while reducing eosinophil and neutrophil infiltration in both the early- and late-phase of the allergic response.”); *see also id.* at 536 (“Many patients with nasal congestion also experienced improvement in this symptom, an effect not typically associated with oral antihistamines.”); *see also id.* at 539-40 (“The ability of azelastine to affect inflammatory cells and inflammatory mediators in addition to histamine suggested that azelastine nasal spray could be effective treatment for both the histamine-related early-phase symptoms as well as the late-phase effects of seasonal allergic rhinitis....Studies in animal models of allergy demonstrated that azelastine significantly inhibited

leukotriene-mediated lung anaphylaxis. In vitro studies showed that azelastine inhibited phospholipase A2, leukotriene C4 synthase, and 5-lipoxygenase all of which are enzymes required for the synthesis of leukotrienes from arachidonic acid. Additionally, azelastine has been identified as a 5-lipoxygenase activating protein (FLAP) inhibitor. 5-Lipoxygenase activating protein couples with 5-lipoxygenase to initiate the oxidation of arachidonic acid that is liberated from membrane phospholipid by phospholipase A2. In addition, azelastine caused dose-dependent inhibition of superoxide free radical production in human neutrophils and eosinophils. These in vitro and in vivo effects on chemical mediators of inflammation have been substantiated in controlled clinical trials.”).

50. Azelastine was also an FDA-approved, commercially available nasal spray in the U.S. before the alleged date of invention. As Galant & Wilkinson (2001) said, it was a nasal spray that was reported to be effective in treating allergic rhinitis. Galant & Wilkinson (2001), at 457-58. As Lieberman also reported, “Recently, azelastine was granted approval by the Food and Drug and Administration (FDA) for the treatment of this disorder [AR]. In clinical trials it has been shown to reduce components of the symptom complex including postnasal drainage, sneezing, rhinorrhea, and congestion.” Lieberman (2001), at 201. It was approved not only in the U.S. as a product called Astelin<sup>®</sup>.

51. Berger (1999) also reported that “Azelastine hydrochloride is an H<sub>1</sub>-receptor antagonist with anti-inflammatory properties that is available in the US as Astelin Nasal Spray for the treatment of seasonal allergic rhinitis....In United States clinical trials, azelastine nasal spray, at a dosage of 2 sprays per nostril bid (1.1 mg/day), was effective in the management of a complex of symptoms associated with seasonal allergic rhinitis, including rhinorrhea, sneezing, nasal pruritus, post-nasal drip, and itchy and watery eyes.” Berger (1999), at 535-36; *see also*

Galant & Wilkinson (2001), at 457-58 (“Azelastine nasal spray (0.14 mg/metered dose per nostril twice daily) was reported to be effective and well tolerated in children aged 5 to 12 years with PAR [perennial allergic rhinitis] by Herman et al. using a placebo-controlled, double-blind protocol. In addition to relief of the usual symptoms of AR, nasal obstruction was also reduced.”). Additionally, the Hettche reference, U.S. Patent No. 5,164,194 (Astelin<sup>®</sup>’s patent) taught a nasal formulation in which “0.03 to 3 mg of azelastine base should be released per individual actuation.” Hettche, at col. 2, ll. 20-23.

52. The characteristics I note above that were known to a POSA in the prior art made azelastine HCl a very attractive antihistamine for use in the treatment of AR. It was approved by the FDA and readily available in the U.S., which means it had been proven both safe and effective in the treatment of AR. It was known as a second-generation antihistamine, which meant that in addition to treating the early-phase AR response it had some effect on the late-phase response. It was also available as a nasal spray, which of course meant that it works as a nasal spray. While that route of administration is not required to treat AR, a POSA would have understood well before 2002 that it has significant benefits, as topical application of the active ingredient at the site of action can produce higher levels of that drug at the desired site, improving both speed of benefit and safety in one maneuver. Howarth (2000); ARIA (2001) at S229. For patients suffering from AR, that increased speed of relief and was desirable. Finally, *in vitro* studies indicated that azelastine was particularly potent compared to other topically active antihistamines. Fields et al. (1984).

53. I have reviewed a product insert for Astelin<sup>®</sup> that was publicly available before 2002. The product initially earned U.S. FDA approval in 1996 for the treatment of seasonal AR. The label contains the following statements about the ingredients in the product and/or their

amounts:

**Astelin® Nasal Spray contains 0.1% azelastine hydrochloride in an aqueous solution at pH  $6.8 \pm 0.3$ . It also contains benzalkonium chloride (125 mcg/mL), edetate disodium, hydroxypropyl methyl cellulose, citric acid, dibasic sodium phosphate, sodium chloride, and purified water.**

**After priming, each metered spray delivers a 0.137 mL mean volume containing 137 mcg of azelastine hydrochloride (equivalent to 125 mcg of azelastine base). Each bottle can deliver 100 metered sprays.**

Astelin® Label at 1.

## **2. Steroids were known to treat the late-phase response.**

54. As of the date of the invention, antihistamines were not the only drugs commonly used to treat AR. Anti-inflammatory steroids, also referred to as glucocorticosteroids, glucocorticoids, or corticosteroids, were another class of drug used for that indication.

55. Topical formulations of these steroids have several properties that make them excellent drugs used locally, including low systemic absorption, rapid metabolism after absorption, high affinity for the glucocorticoid receptor that makes them very potent, and lipophilicity that retains them at the site of administration. Schleimer (1998). As Galant & Wilkinson (2001) noted about the intranasal administration of steroids, steroids “are highly effective and have been approved for use in children with both SAR and PAR. They relieve a range of signs and symptoms that include nasal congestion, rhinorrhea, itching and sneezing, but are less effective for ocular symptoms.” Galant & Wilkinson (2001), at 458-59.

56. Much was known as of the date of the alleged invention about the general effects of steroids that made them effective against AR. Galant & Wilkinson (2001) noted that “the major pathway involves binding of the steroid molecule to a cytoplasmic receptor that is then transported to the nucleus where it binds to the DNA at the glucocorticoid response element.

This results in inhibition of a variety of pro-inflammatory cytokines that decrease the inflammatory response.” Galant & Wilkinson (2001), at 459.

57. Steroids were also regarded as most effective against the late-phase, inflammatory response of AR. “Systemic corticosteroids reduce symptoms and mediator release in the late and rechallenge phases of the process but have little effect on the early phase.” Drouin (1995), at 341; *see also* Lieberman (2001), at 201 (“It is assumed that the anti-inflammatory activities of topical corticosteroids account for their beneficial effect in this condition. Fluticasone nasal spray, applied unilaterally, has been shown to decrease the number of CD3 + cells, the amount of major basic protein, and the number of tryptase-positive cells in subjects with nonallergic rhinitis.”).

58. Some studies suggested that steroids also had effects on the early-phase AR response. *E.g.*, Drouin (1995), at 341. However, in work that was first done by my laboratory, it was shown that glucocorticoid steroids do not inhibit the release of mediators from human mast cells *in vitro*. These mediators are responsible for the early-phase reaction. That is also the case for mast cells residing in the tissue. In other words, the acute (or early) phase response to mast cell mediators still largely takes place in the presence of steroid treatment. Schulman et al. (1982); Schleimer et al. (1983); Dunskey et al. (1977); Slott & Zweiman (1974); Slott & Zweiman (1975); Pipkorn et al. (1987).

**i. Steroids were known to have delayed onsets of action compared to antihistamines.**

59. One drawback of steroids for patients was their relatively slow onset of action compared to antihistamines.

60. The prior art discussed this characteristic. “Although intranasal steroids are considered effective drugs for managing allergic rhinitis, symptomatic response to intranasal

steroids may not be evident for several days after therapy is initiated, and some patients may require a therapeutic trial of 2 to 3 weeks to determine whether the treatment is satisfactory.” Spector (1999), at S387; *see also* Nielsen et al. (2001), at 1567 (“It has been generally considered that INCS [intranasal corticosteroids] have a slow onset of action. However, they usually act within 12 to 24 hours.”).

61. That was in contrast to the action of antihistamines. Berger (1999) noted that “[o]nset and duration of action assessments showed that azelastine nasal spray improved baseline symptom scores within 1 to 3 hours, while other studies suggested that improvements may be evidenced in less than 30 minutes in some patients.” Berger (1999), at 536; *see also* ARIA (2001) at S229-30 (“Intranasal azelastine is more rapidly effective than beclomethasone dipropionate but in the long term, its effects are less potent.”).

62. The slower response time led to a lack in patient compliance because patients who did not see immediate results from steroid treatments sometimes stopped steroid treatment altogether, before they were expected to appreciate any therapeutic effectiveness. Any maneuver that could improve adherence, such as mixing a fast-acting drug having one mechanism with a slow-acting drug having another, would have been thought to improve outcomes. In the asthma field, for example, combinations of inhaled steroids with fast- and long-acting bronchodilators were known to be highly effective, benefiting from the behavior-reinforcing effect of the immediate bronchodilation caused by the bronchodilator along with the superior anti-inflammatory effects of the inhaled steroid. The tremendous success of this combination of topical drugs would be well known to a POSA in 2002, as these combinations of drugs were well on their way to being the most popular asthma medications in history. Hancox et al. (1999); Markham & Jarvis (2000); Barnes (2001); Stoloff et al. (2002).

**ii. Fluticasone propionate was a nasally administered steroid approved for the treatment of AR.**

63. At the time of the alleged invention, a steroid called fluticasone propionate had been approved for use by regulatory authorities in at least the United States. Flonase<sup>®</sup> was a drug product that had fluticasone propionate as its active ingredient and was indicated for the treatment of allergic rhinitis. It was first approved in 1998. Its label says the following about its ingredients:

FLONASE Nasal Spray 50 mcg is an aqueous suspension of microfine fluticasone propionate for topical administration to the nasal mucosa by means of a metering, atomizing spray pump. FLONASE Nasal Spray also contains microcrystalline cellulose and carboxymethylcellulose sodium, dextrose, 0.02% w/w benzalkonium chloride, polysorbate 80, and 0.25% w/w phenylethyl alcohol, and has a pH between 5 and 7.

It is necessary to prime the pump before first use or after a period of non-use (1 week or more). After initial priming (six actuations), each actuation delivers 50 mcg of fluticasone propionate in 100 mg of formulation through the nasal adapter. Each bottle of FLONASE Nasal Spray provides 120 metered sprays. After 120 metered sprays, the amount of fluticasone propionate delivered per actuation may not be consistent and the unit should be discarded.

Flonase<sup>®</sup> Label, at 1, *ll.* 17-26.

64. The Flonase<sup>®</sup> label teachings are consistent with the knowledge I described above. It describes the drug as “a synthetic...corticosteroid with anti-inflammatory activity.” *Id.* at *ll.* 28-29. It further states, “The precise mechanism through which fluticasone propionate affects allergic rhinitis symptoms is not known[, c]orticosteroids have been shown to have a wide range of effects on multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, and cytokines) involved in inflammation. In seven trials in adults, FLONASE nasal spray has decreased nasal mucosal eosinophils in 66% (35% for placebo) of patients and basophils in 39% (28% for placebo) of patients.” *Id.* at 2, *ll.* 37-42.

65. The labeling similarly mentioned the slower onset of action compared to antihistamines: “FLONASE Nasal Spray, like other corticosteroids, is an agent that does not



have an immediate effect on allergic symptoms. A decrease in nasal symptoms has been noted in some patients 12 hours after initial treatment with FLONASE Nasal Spray. Maximum benefit may not be reached for several days.” *Id.* at ll. 44-47.

66. Topical steroids vary in their potency, but doses used in commercially available preparations adjust for differences in potency making the major intranasal and inhaled steroid preparations of similar efficacy. Martin et al. (2002); Stellato et al. (1999). Fluticasone propionate is one of the more potent topical steroids, and potency is an important issue when considering drug combinations, as the weight of the dose required is lower for a more potent drug than it is for an equally effective drug that is less potent.

**C. Combination antihistamine/steroid therapies were well known in the prior art.**

67. Azelastine HCl and fluticasone propionate had been approved in the U.S. for treatment of AR long before the alleged invention date. The combination of the two for treatment of AR was also known to a POSA prior to the invention date.

**1. The medical literature recommended combining antihistamine and steroids.**

68. There are several reasons why prior to 2002 the field of allergy moved to combination antihistamine/steroid therapies generally.

69. *First*, as discussed above, the two types of drugs were each thought to act primarily on a different phase of AR—antihistamines being generally more effective at treating the early-phase response, and steroids being generally more effective at treating the late-phase response. It was thus known to a POSA at the time of the alleged invention that combining antihistamines with steroids would create an additive therapeutic efficacy (as compared to each drug separately) that treated both main phases of the AR response more effectively than either drug alone.

70. The prior art identified this potential benefit. Drouin (1995) noted that “[c]linically, patients respond differently following treatment of allergic rhinitis with antihistamines or intranasal steroids. Antihistamines relieve pruritus, sneezing, rhinorrhea, and ocular symptoms but do not control nasal stuffiness. Intranasal steroids can attenuate all nasal symptoms but are most effective against stuffiness and rhinorrhea. Thus, treatment that combines an antihistamine and a steroid nasal spray may maximize clinical efficacy.” Drouin (1995), at 347; *see also id.* at 341 (“Current pharmacologic management of rhinitis provides less than complete relief of symptoms and may be associated with variable degrees of adverse effects. Because many of the drugs currently available affect different components of the allergic response, combinations of drugs with complementary effects can maximize therapeutic efficacy.”)

71. Galant & Wilkinson (2001) noted that “[i]f AR symptoms are not completely controlled [in children receiving intranasal corticosteroids] or eye symptoms are prominent, a second-generation antihistamine may be added to the regimen.” Galant & Wilkinson (2001), 461-62.

72. Berger (1999) stated that “[p]atients whose symptoms do not respond adequately [to an antihistamine or steroid alone] are often prescribed a combination of both an antihistamine and an intranasal corticosteroid.” Berger (1999), at 535; *see also id.* at 536. Berger (1999) additionally concluded, “Azelastine nasal spray represents a useful addition to the available therapies for the treatment of seasonal allergic rhinitis. Azelastine nasal spray can be used either in place of oral antihistamines or in combination with intranasal corticosteroids....” *Id.* at 540.

73. The 2001 Guidelines published by ARIA (“Allergic Rhinitis and its Impact on Asthma”) explained that intranasal azelastine was more rapidly effective than intranasal steroids,

but that its long-term anti-inflammatory effects were less potent—suggesting a motivation to combine azelastine with a steroid. ARIA (2001) at S229-30 (“Intranasal azelastine is more rapidly effective than beclomethasone dipropionate but in the long term, its effects are less potent. It was observed in some studies that azelastine was effective on nasal obstruction but, apparently, to a lesser extent than intranasal glucocorticosteroids. Intranasal fluticasone was found to be significantly more effective than levocabastine [another topical antihistamine] in the treatment of seasonal allergic rhinitis.”).

74. Lieberman (2001) stated, “In summary, the mainstay of the treatment of chronic nonallergic rhinitis is the application of topical nasal steroids and/or azelastine,” thereby calling out azelastine as an antihistamine that would have been preferred by a POSA. Lieberman (2001), at 202. The ARIA (2001) guidelines summarized: “Topical H1-antihistamines have a rapid onset of action (less than 15 minutes) at low drug dosage, but they act only on the treated organ. Topical H1-antihistamines usually require bi-daily (BID) administrations to maintain a satisfactory clinical effect. Their use may therefore be recommended for mild organ-limited disease, as an ‘on demand’ medication *in conjunction with a continuous one*.” ARIA (2001) at S230 (emphasis added).

75. The ARIA guidelines thus recommended a “stepwise approach” for the treatment of moderate/severe persistent allergic rhinitis. ARIA (2001) at S251. It “advised to use intranasal glucocorticosteroids as a first-line treatment.” *Id.* “If the patient does not improve,” however, “add: H1-antihistamines if the major symptoms are sneezing, itching, or rhinorrhea.” *Id.*

76. The combination of these two categories of drugs was backed by research. Nielsen et al. (2001), at 1572, reported that a clinical study by Brooks et al. showed superior

efficacy for an oral antihistamine and intranasal steroid combination over either the antihistamine or the steroid alone. Several studies showed similar results, as reported by Drouin (1995): “Backhouse and colleagues found that terfenadine [an antihistamine] reduced SAR symptoms but that terfenadine plus flunisolide [a steroid] nasal spray relieved symptoms more effectively than did terfenadine alone. Wihl et al. showed that astemizole [an antihistamine] improved rhinitis symptoms but that astemizole plus BDP [a steroid] nasal spray was more effective.... Juniper et al showed that [i]ndividuals taking astemizole alone or with BDP had fewer ocular symptoms and used fewer eye drops than those taking BDP alone; eye symptoms were best controlled when patients took both medications. This study demonstrates that the addition of an antihistamine to topical intranasal steroid therapy improved the control of most SAR symptoms. Loratadine plus intranasal BDP improved the symptoms of moderately severe SAR to a greater degree than did BDP plus placebo.” Drouin (1995), at 347. I am prepared to and able to discuss each of the references discussed above in more detail if asked to do so at trial.

77. Finally, I am not aware of any studies showing that the combination of a steroid and an antihistamine, by any route of administration, decreased the therapeutic effect of either drug alone. A POSA would thus have no reason not to try a combination of the two drugs. The worst outcome would be the same efficacy as the prior art formulations.

78. **Second**, combining a steroid with a faster-acting antihistamine gave patients a sense of immediate benefit from the antihistamine, while ensuring the continued use of the combination while the steroid effects were developing. That combination led to greater overall efficacy in treating AR than either drug alone. ARIA (2001) at S229-30 (discussed above).

79. Counsel has provided me with the deposition testimony of Dr. Accetta. I have reviewed his testimony, which confirms that doctors actually practiced this prior art by

prescribing both intranasal azelastine (Astelin<sup>®</sup>) and an intranasal steroid, often fluticasone (Flonase<sup>®</sup>). *See, e.g.,* Accetta Tr., at 22:16-23:5; 55:16-56:13.

**i. Prior art at the time would not have discouraged a POSA from seeking a combination therapy with an expectation of success.**

80. I am aware that some prior art studies suggested that patients taking both an *oral* antihistamine and an intranasal steroid did not show significant improvement over those patients taking intranasal steroids alone. *E.g.,* Juniper et al. (1989); Ratner et al. (1998); Simpson et al. (1994). These studies do not change my opinion, because they would not have discouraged a POSA from seeking a combination therapy with an expectation of success, however, for the following three reasons.

81. ***First***, these studies all compared patients who adhered to the steroid therapy with those who took both oral antihistamines and an intranasal steroid. As explained above, however, a POSA would have known that patients outside of clinical trials often failed to adhere to intranasal steroid treatment because of its slow onset of action. A POSA therefore would have continued to expect that a combination therapy would provide superior results for patients because it was more likely that patients would adhere to treatment with the addition of a fast-acting antihistamine.

82. ***Second***, several studies, as explained above, did show additive benefits for patients taking both an oral antihistamine and an intranasal steroid over those patients taking only intranasal steroids, and the medical literature continued to recommend that such a combination be practiced. Drouin (1995); Berger (1999); Spector (1999); Lieberman (2001); Galant & Wilkinson (2001); ARIA (2001); Nielsen et al. (2001) (citing Brooks et al.).

83. ***Third***, a POSA would also still have been motivated to combine an *intranasal* antihistamine with an intranasal steroid, knowing that localized application permitted higher

concentrations with better, faster, and safer effects. *See, e.g.*, Nielsen et al. (2001), at 1565 (azelastine has “a faster onset of action than oral antihistamines and act[s] within 15 to 30 minutes.”).

**2. Antihistamines and steroids were taught to be administered together as a single product.**

84. Additionally, a POSA knew that one could make and use a single pharmaceutical composition having both an effective amount of a steroid and an effective amount of an antihistamine. A POSA also knew that using azelastine HCl and fluticasone propionate was an attractive option.

85. The Cramer reference (European Patent Application No. EP 780 127 A1) taught in the prior art that a POSA could create “pharmaceutical compositions for nasal administration comprising: a) a safe and effective amount of a glucocorticoid selected from the group consisting of beclomethasone, flunisolide, triamcinolone, fluticasone, mometasone, budesonide, pharmaceutically acceptable salts thereof and mixtures thereof; b) a safe and effective amount of a leukotriene inhibiting antihistamine selected from the group consisting of cetirizine, loratadine, azelastine, pharmaceutically acceptable salts thereof, optically active racemates thereof and mixtures thereof; and c.) an intranasal carrier.” Cramer, at 2 *ll.* 36-44.

86. The Segal reference similarly taught pharmaceutical formulations that provide “topically applicable nasal compositions comprising a therapeutically effective amount of a topical antiinflammatory agent and a therapeutically effective amount of at least one agent suitable for topical nasal administration and selected from the group consisting of a vasoconstrictor, a neuramidinase inhibitor, an anticholinergic agent, a leukotriene inhibitor, an antihistamine, an antiallergic agent, an anesthetic, and a mucolytic agent.” Segal, at 2 *ll.* 10-15. “The topical antiinflammatory agents in the compositions of the present invention are

corticosteroids known in the art to suppress inflammation. In a preferred embodiment, the topical antiinflammatory agent is beclomethasone dipropionate, budesonide, dexamethasone, mometasone furoate, fluticasone propionate or triamcinolone acetonide.” *Id.* at 11, 22-26. “Suitable antihistamines are diphenhydramine, chlorpheniramine, cetirizine, terfenadine, fenofexadine, astemizole, norastemizole, azelastine, and azatidine.” *Id.* at 3, 11, 19-20.

87. A POSA knew before the date of the alleged invention that these dual-therapy, single-product compositions would provide even more benefits than sequential administration of a steroid and an antihistamine.

88. **First**, providing a combination of a known antihistamine and a known steroid in a single administration ensured that the dosing and administration of each drug was optimal. For example, it was known that excessive administration of liquids into the nasal cavities might be less effective due to drainage, and this might happen with sequential administration. *See, e.g.*, Harris et al. (1986). Thus, a POSA would have been motivated to combine active ingredients in a single formulation to ensure maximal absorption.

89. **Second**, providing two drugs combined is more convenient than taking both drugs separately (and prescription of both antihistamine and topical steroid in separate formulations was wide spread at the time).

90. **Third**, there were potential cost savings involved with using a single product rather than two products sequentially.

**3. A POSA would have known azelastine HCl and fluticasone propionate were appropriate choices for combined administration.**

91. A POSA considering what antihistamine to use in a combination product would have considered azelastine HCl to be an obvious choice. It was a second-generation antihistamine that was already approved and available for nasal administration. That means a

POSA knew it was safe, effective, and could be administered directly in the nose. *E.g.*, Nielsen et al. (2001), at 1565; *see also* Lieberman (2001), at 201 (“Only two classes of medication have received Federal Drug Administration approval for use in chronic rhinitis. Included are first-generation oral antihistamines, topical corticosteroids and the topical second-generation antihistamine azelastine.”). Of the two available antihistamines for intranasal use—azelastine and levocabastine—azelastine was demonstrated prior to June 2002 to be more safe and effective than levocabastine. Falser et al. (2001).

92. A POSA considering what steroid to use in a combination product would have considered fluticasone propionate to be an obvious choice. It was already approved and available for nasal administration. That means a POSA knew it was safe, effective, and could be administered directly in the nose. *E.g.*, Nielsen et al. (2001), at 1565; *see also* Lieberman (2001), at 201 (“The topical corticosteroid preparations that have been approved for use are beclomethasone, fluticasone, and budesonide.”). The FDA-approved fluticasone propionate product, Flonase<sup>®</sup>, was extremely popular with doctors and patients.

93. Consistent with this opinion, both the Cramer and Segal references discussed above identified both azelastine and fluticasone as useful drugs for combination therapy.

94. It is with this background in mind that I analyzed the following general question: What would a POSA have done prior to June 2002 in order to create a better treatment for allergic rhinitis than what was already available on the market?

95. In my opinion, it would have been obvious to a POSA at that time to have been motivated and to try to make and administer a drug product that contained both an effective amount of a steroid and an antihistamine. It would have been particularly obvious in doing so to select azelastine HCl and fluticasone propionate—two drugs that were known to have different



and complementary effects on AR patients, and which had already been approved and marketed in the U.S. and elsewhere.

96. There were several good reasons and motivations for making this combination drug product, as discussed above, including the limitations that each product by itself had in treating patients with AR.

97. The POSA would have seen making this combination drug product as merely the combination of known prior art elements according to known uses so that they would perform their known functions. The result was also predictable—a drug product that is effective for treating AR. It would not have been surprising to a POSA at all that combining these two drugs would provide an effective treatment for AR, especially considering that it was already practiced in the art at that time. The POSA would have had a reasonable expectation of success when combining the two drugs into one formulation.

98. Moreover, it would not have been unexpected that a combination of azelastine HCl and fluticasone propionate in one pharmaceutical formulation would have been a more effective treatment of AR than any single composition previously available to consumers. The prior art taught and suggested the desirability of that combination, and by no means taught away from it. As I mentioned, there was no available research suggesting that combining a steroid and an antihistamine would have a worse effect than administering either drug alone. At the very least, it would have been obvious to try this combination from a finite number of options that were available to a POSA in an effort to make a better and more convenient AR treatment, with a reasonable chance of success.

## **V. THE ASSERTED PATENTS**

99. In the next part of my analysis, I considered the file history, specification, and claims of the asserted patents to determine if there were any differences between the prior art and

the scope of the asserted claims. If there were differences, I analyzed whether any new elements of the asserted claims nevertheless would have been obvious to a POSA.

**A. Specification**

100. I am familiar with the entire specification of the asserted patents. It discusses that it was “known to use antihistamines in nasal sprays and eye drops to treat allergy-related conditions.” ’723 patent at 1:29-30. The specification further discloses azelastine as a known antihistamine, and teaches its use “as a nasal spray against seasonal or perennial allergic rhinitis.” *Id.* at 1:30-34. Moreover, the specification discloses that it was “known to treat [A.R.] conditions using a corticosteroid, which will suppress nasal and ocular inflammatory conditions.” *Id.* at 35-37. And the specification also discloses fluticasone as a “corticosteroid known for nasal use.” *Id.* at 1:37-38. The specification further discloses examples of combinations of these “known” active ingredients. The specification contains no *in vivo* or *in vitro* experimental data about the claimed combination product. There is no clinical data concerning its administration to any patients.

**B. Asserted Claims**

101. I understand that plaintiffs assert Claims 8, 11, 14, 25, and 28 of the ’723 patent; Claims 4, 29, and 42-44 of the ’620 patent; and Claims 10, 11, 13, 15, 16, 18-20, 22-24, 26, and 28-30 of the ’428 patent.

**1. The ’723 Patent (8, 11, 14, 25 and 28).**

102. The ’723 patent issued on April 24, 2012. Below are the asserted claims (in bold), along with any claims on which they depend:

1. A method for the prophylaxis or treatment in a mammal of a condition for which administration of one or more antihistamines and/or one or more steroids is indicated, comprising intranasal administration to said mammal of a therapeutically effective amount of a pharmaceutical composition comprising (a)

azelastine, or a pharmaceutically acceptable salt thereof; and (b) a pharmaceutically acceptable ester of fluticasone.

**8. The method of claim 1, wherein said condition is allergic rhinitis.**

10. The method of 1, wherein said pharmaceutical composition comprises a pharmaceutically acceptable ester of fluticasone in an amount from about 50 micrograms/ml to about 5 mg/ml of the composition.

**11. The method of claim 10, wherein the pharmaceutical composition has a particle size of less than 10  $\mu$ m.**

12. The method of claim 1, wherein said pharmaceutical composition is an aqueous suspension comprising from about 0.0005% to about 2% (weight/weight) of azelastine or a pharmaceutically acceptable salt of azelastine, and from about 0.0357% to about 1.5% (weight/weight) of pharmaceutically acceptable ester of fluticasone.

**14. The method of Claim 12, wherein said pharmaceutical composition is an aqueous suspension comprising 0.1% or 0.15% (weight/weight) of azelastine HCl and from about 0.0357% to about 1.5% (weight/weight) of fluticasone propionate or fluticasone valerate.**

17. The method of claim 1, wherein said pharmaceutical composition further comprises at least one isotonic agent selected from the group consisting of sodium chloride, saccharose, glucose, glycerine, sorbitol, 1,2-propylene glycol, and combinations thereof.

**25. The method of claim 17, wherein said isotonic agent comprises glycerine.**

**28. The method of claim 1, wherein the pharmaceutical composition further comprises edetate disodium, glycerine, a thickening agent comprising microcrystalline cellulose and sodium carboxy methyl cellulose, polysorbate 80, benzalkonium chloride, phenyl ethyl alcohol, and purified water.**

**2. The '620 Patent (4, 29, 42-44).**

103. The '620 patent issued on May 1, 2012. Below are the asserted claims (in bold), along with any claims on which they depend:

1. A pharmaceutical formulation comprising: azelastine, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable ester of fluticasone, wherein said pharmaceutical formulation is in a dosage form suitable for nasal administration.

**4. The pharmaceutical formulation of claim 1, wherein said formulation has a particle size of less than 10  $\mu\text{m}$ .**

5. The pharmaceutical formulation of claim 1, wherein said formulation is an aqueous suspension comprising from 0.0005% (weight/weight) to 2% (weight/weight) of said azelastine, or said pharmaceutically acceptable salt thereof, and from 0.0357% (weight/weight) to 1.5% (weight/weight) of said pharmaceutically acceptable ester of fluticasone.

6. The pharmaceutical formulation according to claim 5, comprising from 0.001% (weight/weight) to 1% (weight/weight) of said azelastine, or said pharmaceutically acceptable salt thereof, and from 0.0357% (weight/weight) to 1.5% (weight/weight) of said pharmaceutically acceptable ester of fluticasone.

24. A pharmaceutical formulation comprising azelastine hydrochloride; and, fluticasone propionate, wherein said formulation is in the dosage form of as a nasal spray, and wherein said formulation is used in the treatment of conditions for which administration of one or more anti-histamine and/or one or more steroid is indicated.

26. The pharmaceutical formulation of claim 6, comprising 0.1% (weight/weight) of azelastine hydrochloride, and from 0.0357% to 1.5% (weight/weight) of fluticasone propionate.

**29. The pharmaceutical formulation of claim 26, wherein said dosage form suitable for nasal administration comprises a nasal spray.**

25. A nasal spray formulation comprising (i) azelastine, or a pharmaceutically acceptable salt thereof, (ii) a pharmaceutically acceptable ester of fluticasone, and (iii) a pharmaceutically acceptable carrier or excipient therefor.

**42. The pharmaceutical formulation of claim 1, further comprising edetate disodium, glycerine, a thickening agent comprising microcrystalline cellulose and sodium carboxy methyl cellulose, polysorbate 80, benzalkonium chloride, phenyl ethyl alcohol, and purified water.**

**43. The pharmaceutical formulation of claim 24, further comprising edetate disodium, glycerine, a thickening agent comprising microcrystalline cellulose and sodium carboxy methyl cellulose, polysorbate 80, benzalkonium chloride, phenyl ethyl alcohol, and purified water.**

**44. The pharmaceutical formulation of claim 25, further comprising edetate disodium, glycerine, a thickening agent comprising microcrystalline cellulose and sodium carboxy methyl cellulose, polysorbate 80, benzalkonium chloride, phenyl ethyl alcohol, and purified water.**

**3. The '428 Patent (10, 11, 13, 15, 16, 18-20, 22-24, 26, 28-30)**

104. The '428 patent issued on February 16, 2016. Below are the asserted claims (in bold), along with any claims on which they depend:

1. A method for the treatment of seasonal allergic rhinitis, comprising administration of a therapeutically effective amount of nasal spray formulation comprising: from 0.001% (weight/weight) to 1% (weight/weight) of azelastine hydrochloride; from 0.0357% (weight/weight) to 1.5% (weight/weight) of fluticasone propionate; one or more preservatives; one or more thickening agents; one or more surfactants; and one or more isotonicization agents.

9. The method of claim 1, wherein the formulation comprises edetate disodium, benzalkonium chloride, microcrystalline cellulose, carboxymethyl cellulose sodium, polysorbate 80, glycerine, and phenyl ethyl alcohol.

**10. The method of claim 9, wherein the formulation comprises: from 0.002% (weight/weight) to 0.05% (weight/weight) of edetate disodium; from 0.002% (weight/weight) to 0.05% (weight/weight) of benzalkonium chloride; from 0.65% (weight/weight) to 3% (weight/weight) of a combination of microcrystalline cellulose and carboxymethyl cellulose sodium; and from 2.3% (weight/weight) to 2.6% (weight/weight) of glycerine.**

**11. The method of claim 1, wherein the formulation comprises: 0.1% (weight/weight) azelastine hydrochloride; from 0.0357% (weight/weight) to 1.5% (weight/weight) of fluticasone propionate; from 0.002% (weight/weight) to 0.05% (weight/weight) of edetate disodium; from 0.002% (weight/weight) to 0.02% (weight/weight) of benzalkonium chloride; from 0.65% (weight/weight) to 3% (weight/weight) of**

a combination of microcrystalline and carboxymethyl cellulose sodium; polysorbate 80; 2.3% (weight/weight) of glycerine; and 0.25% (weight/weight) of phenyl ethyl alcohol.

**13. The method of claim 1, wherein the formulation is contained in a nasal spray product; and wherein from 0.03 mg to 3 mg of azelastine hydrochloride and from 0.05 mg to 0.15 mg of fluticasone propionate is released per individual actuation of the nasal spray product.**

**14. A method for minimizing symptoms of seasonal allergic rhinitis, comprising administration of a therapeutically effective amount of a nasal spray formulation comprising: from 0.001% (weight/weight) to 1% (weight/weight) of azelastine hydrochloride; from 0.0357% (weight/weight) to 1.5% (weight/weight) of fluticasone propionate; one or more preservatives; one or more thickening agents; one or more surfactants; and one or more isotonization agents.**

**15. The method of claim 14, wherein the formulation has a pH of 4.5 to about 6.5.**

**16. The method of claim 14, wherein the formulation is an aqueous suspension.**

**18. The method of claim 14, wherein the one or more thickening agents comprise microcrystalline cellulose and carboxymethyl cellulose sodium.**

**19. The method of claim 14, wherein the one or more surfactants comprise polysorbate 80.**

**20. The method of claim 14, wherein the one or more isotonization agents comprise from 2.3% (weight/weight) to 2.6% (weight/weight) of glycerine.**

**22. The method of claim 14, wherein the formulation comprises edetate disodium, benzalkonium chloride, microcrystalline cellulose, carboxymethyl cellulose sodium, polysorbate 80, glycerine, and phenyl ethyl alcohol.**

**23. The method of claim 22, wherein the formulation comprises: from 0.002% (weight/weight) to 0.05% (weight/weight) of edetate disodium; from 0.002% (weight/weight) to 0.05% (weight/weight) of benzalkonium chloride; from 0.65% (weight/weight) to 3% (weight/weight) of**

a combination of microcrystalline cellulose and carboxymethyl cellulose sodium; and from 2.3% (weight/weight) to 2.6% (weight/weight) of glycerine.

24. The method of claim 14, wherein the formulation comprises: 0.1% (weight/weight) azelastine hydrochloride; from 0.0357 (weight/weight) to 1.5% (weight/weight) of fluticasone propionate; from 0.002% (weight/weight) to 0.05% (weight/weight) of edetate disodium; from 0.002% (weight/weight) to 0.02% (weight/weight) of benzalkonium chloride; from 0.65% (weight/weight) to 3% (weight/weight) of a combination of microcrystalline and carboxymethyl cellulose sodium; polysorbate 80; 2.3% (weight/weight) of glycerine; and 0.25% (weight/weight) of phenyl ethyl alcohol.

26. The method of claim 14, wherein the formulation is contained in a nasal spray product; and wherein from 0.03 mg to 3 mg of azelastine hydrochloride and from 0.05 mg to 0.15 mg of fluticasone propionate is released per individual actuation of the nasal spray product.

28. A method for the treatment of seasonal allergic rhinitis, comprising administration of a therapeutically effective amount of nasal spray formulation comprising: from 0.001% (weight/weight) to 1% (weight/weight) of azelastine hydrochloride; from about 50 µg/mL to about 5 mg/mL of fluticasone propionate; from 0.002% (weight/weight) to 0.05% (weight/weight) of benzalkonium chloride; from 0.002% (weight/weight) to 0.05% (weight/weight) of edetate disodium; glycerine; polysorbate; and a thickening agent; wherein the formulation has a pH of 4.5 to about 6.5; and wherein the formulation is an aqueous suspension.

29. The method of claim 28, wherein the formulation is contained in a nasal spray product; and wherein from 0.03 mg to 3 mg of azelastine hydrochloride and from 0.05 mg to 0.15 mg of fluticasone propionate is released per individual actuation of the nasal spray product.

30. The method of claim 28, wherein the thickening agent comprises microcrystalline cellulose and carboxymethyl cellulose sodium.

## **VI. THE ASSERTED CLAIMS ARE OBVIOUS IN VIEW OF THE PRIOR ART.**

105. Based on my review of the asserted patents, their related prosecution histories,

and the other materials discussed and referenced above, it is my opinion that a POSA would have found that any differences between the prior art I discussed above and these asserted claims to be obvious over the prior art before 2002.

106. Each of the asserted claims covers, among other things, pharmaceutical compositions containing, or methods of using, a combination of azelastine hydrochloride (HCl) and fluticasone propionate for the treatment of allergic rhinitis via a single nasal spray. It is my opinion that these aspects of each of the asserted claims would have been obvious to a POSA.

**A. The use of an azelastine HCl and fluticasone propionate combination.**

107. As explained above, it was well known at the time of the alleged invention that there was an early-phase allergic response characterized by sneezing, itching, and rhinorrhea (*i.e.*, runny nose) and a late-phase response characterized by congestion and nasal blockage. It was also well known at the time of the alleged invention that antihistamines such as azelastine antagonize the H<sub>1</sub>-receptor site and treat primarily the early-phase response, and that intranasal steroids such as fluticasone treat primarily the late-phase inflammation. Because of these different methods of action, a POSA would have had a motivation to combine antihistamine and steroid therapies to obtain at least additive clinical effects.

108. Therapies combining antihistamines and steroids were also well known in the prior art to be effective for the treatment of allergic rhinitis. The prior art disclosed the dual intranasal use of an antihistamine product and a steroid product, and doctors in fact already practiced this teaching by prescribing both Astelin<sup>®</sup> (intranasal azelastine hydrochloride) and Flonase<sup>®</sup> (intranasal fluticasone propionate) to individual patients. The prior art even disclosed the simultaneous intranasal administration of azelastine and fluticasone specifically in a single pharmaceutical composition for the treatment of allergic rhinitis. There was thus a reasonable expectation that combining azelastine and fluticasone into a single nasal spray for the treatment



of allergic rhinitis was not only feasible but would also have led to treatment success.

109. Prior art combination therapies using azelastine and fluticasone were also known to overcome certain shortcomings of their individual use. For instance, steroids like fluticasone were known to have a delayed onset of action relative to antihistamines, sometimes requiring several days of use before effective symptom relief would be achieved. The prior art taught that administering the drugs together would help increase compliance rates with the steroid, because the antihistamine would give some initial relief to patients during the pre-onset phase of the steroid treatment.

110. Thus, all of the claims, to the extent they all cover the combination of azelastine HCl and fluticasone propionate, would have been obvious at least over any of the medical literature or guidelines recommending coadministration of an intranasal steroid and an antihistamine—such as Drouin (1995), Berger (1999), Spector (1999), Galant & Wilkinson (2001), Lieberman (2001), and ARIA (2001)—alone or combined with labels for Flonase<sup>®</sup> and Astelin<sup>®</sup> demonstrating that fluticasone propionate and azelastine hydrochloride were effective and workable in a nasal spray formulation.

111. Additionally, all of the claims, to the extent they cover the combination of azelastine HCl and fluticasone propionate, would have been obvious at least over any of the medical literature demonstrating a different mechanism of action for an antihistamine and a steroid—such as Schulman et al. (1982); Schleimer et al. (1983); Dunskey et al. (1977); Slott & Zweiman (1974); Slott & Zweiman (1975); and Pipkorn et al. (1987)—alone or combined with the Flonase<sup>®</sup> and Astelin<sup>®</sup> labels demonstrating that fluticasone propionate and azelastine hydrochloride were effective and workable in nasal spray formulations.

112. Additionally, all of the claims, to the extent they cover the combination of

azelastine HCl and fluticasone propionate, are obvious at least over Cramer and Segal—teaching a combination of a steroid and an antihistamine, and fluticasone and azelastine in particular. To the extent it would not have been obvious to choose fluticasone and azelastine from among the lists of available steroids and antihistamines in these references, the claims are still obvious over Cramer and Segal combined with the Flonase<sup>®</sup> and Astelin<sup>®</sup> labels, which demonstrated that fluticasone propionate and azelastine hydrochloride were effective and workable in a nasal spray formulation.

**B. The use of certain amounts of azelastine HCl and fluticasone propionate.**

113. To the extent that asserted claims 29 of the '620 patent, and asserted claims 10, 11, 13, 15, 16, 18-20, 22-24, 26 and 28-30 of the '428 patent, require specific amounts or ranges of amounts of azelastine HCl and fluticasone propionate to be used as part of the claimed composition or method of treatment, these would have been obvious in light of the numerous prior art disclosing effective therapeutic concentrations of both azelastine and fluticasone. Claim 14 of the '723 patent requires specific ranges of amounts of azelastine HCl and of fluticasone propionate or fluticasone valerate, and is obvious for the same reasons.

114. As for fluticasone, Flonase<sup>®</sup> Nasal Spray contains 50 µg, which is equivalent to 0.05 mg, of fluticasone propionate per metered spray of 100 mg of solution. Flonase<sup>®</sup> Label, at 10, *ll.* 348-50. This results in a weight/weight concentration of 0.05%. As explained in more detail in Dr. Donovan's expert report, that is within the claimed ranges of fluticasone propionate. 0.05 mg is within the claimed range of fluticasone propionate per actuation of 0.05 mg to 0.15 mg, and 0.05% weight/weight is squarely within the claimed weight/weight range of 0.0357% to 1.5%. Additionally, because the density of the solution is approximately 1 g/mL (the density of water), that means 0.05 mg of fluticasone per 100 mg solution is equivalent to 0.05 mg per 0.1 g of solution, which is approximately per 0.1 mL of solution; thus, the weight/volume

concentration is 0.5 mg/mL, or 500 µg/mL. This is squarely within the claimed weight/volume range of 50 µg/mL – 5000 µg/mL. It would be entirely obvious to a POSA who was going to use fluticasone propionate in a combination product to use this amount, which had been previously approved in the U.S. as safe and effective. Doing so would reduce the amount of testing required to prove safety and efficacy before various regulatory bodies.

115. As for azelastine HCl, Astelin<sup>®</sup> Nasal Spray contains 137 µg, equivalent to 0.137 mg, of azelastine HCl per metered spray of 0.137 mL of solution. This results in a weight/volume concentration of 0.1%. As explained in more detail in Dr. Donovan's report, a POSA would know that because the Astelin<sup>®</sup> formulation is an aqueous solution comprising primarily water, it has a density of approximately 1.0 g/mL; indeed, Astelin<sup>®</sup>'s patent (Hettche) describes the formulation as having a density of 10.05 kg/10 L (col. 6, *l.* 19), which is effectively 1.0 g/mL. This results in a 0.1% weight/weight concentration to the appropriate number of significant figures. That concentration is squarely within the claim ranges, or identical to the claim amounts, concerning a weight/weight ratio of azelastine HCl in the formulation: 0.001% to 1% w/w; 0.1% or 0.15% w/w; and 0.1% w/w.

116. Additionally, and as described above, Hettche also teaches a nasal formulation in which "0.03 to 3 mg of azelastine base should be released per individual actuation." *Id.* at col. 2, *ll.* 20-23. Each of these numbers is within the claimed ranges of azelastine HCl. Those ranges include actual weights, from 0.03 mg to 3 mg per actuation. The 0.137 mg per Astelin<sup>®</sup> actuation is clearly within that range, and it would have been obvious to use that amount in a combination formulation for the same reasons I gave above with respect to fluticasone propionate: using an FDA-approved amount per actuation was known to work, and would reduce the amount of testing required to prove safety and efficacy before various regulatory bodies.

117. Galant & Wilkinson (2001) also discloses the specific therapeutically effective amounts of both azelastine and fluticasone. It discloses antihistamine administration through use of an azelastine nasal spray (p. 458, Table IV) and states: “Azelastine nasal spray (0.14 mg/metered dose per nostril twice daily) was reported to be effective and well tolerated in children aged 5 to 12 years with PAR by Herman et al. using a placebo-controlled, double-blind study” (457-58). It then discloses that “approved” intranasal corticosteroids include fluticasone propionate with 50 µg (.050 mg) per spray. Galant & Wilkinson (2001) at 459, table V.

118. The Cramer reference also teaches therapeutically effective amounts for both active ingredients: “Typically, dosage units may be prepared to deliver from about 0.5 mcg [0.0005 mg] to about 100 mcg [0.10 mg] of the glucocorticoid agent and from about 5 mcg [0.005 mg] to about 1000 mcg [1.0 mg] of the antihistaminic agent per spray actuation.” Cramer, at 3, *l.* 58 – p. 4, *l.* 1.

119. Therefore, claims 29 of the '620 patent, asserted claims 10, 11, 13, 15, 16, 18-20, 22-24, 26 and 28-30 of the '428 patent, and claim 14 of the '723 patent, are obvious over Flonase<sup>®</sup>, Astelin<sup>®</sup>, and Hettche, alone or in combination with Galant & Wilkinson or Cramer.

120. Finally, claim 11 of the '723 patent and claim 4 of the '620 patent additionally require a particle size limitation of 10 µm. Claims 25 and 28 of the '723 patent, claims 42-44 of the '620 patent, and all of the asserted claims of the '428 patent also require some combination of pharmaceutical excipients. Lastly, claims 15 and 28 of the '428 patent require a specific pH. I am not aware based on my experience of any data that would suggest that the additional limitations in these claims, such as specific pH or particle size requirements, were unusual, novel, or inventive.

121. For reasons explained above. it is my opinion that claims 8 and 14 of the '723

patent and claim 29 of the '620 patent are obvious in their entirety. Claim 8 of the '723 patent is a method for using azelastine and fluticasone in a pharmaceutical composition for the treatment of allergic rhinitis, and has no further limitations. Claim 14 of the '723 further specifies particular concentration ranges of azelastine and fluticasone, and has no further limitations. Claim 29 of the '620 patent further specifies concentration ranges of azelastine and fluticasone and a form suitable for nasal administration, and has no further limitations. Every other asserted claim is obvious at least to the extent it requires a combination of azelastine and fluticasone, or specific concentrations or ranges thereof, in forms suitable for nasal administration.

122. I have also reviewed the report of Dr. Maureen Donovan. Her opinions are that it would have been obvious to a POSA how to combine azelastine and fluticasone in a single pharmaceutical composition, and that the claim limitations on particle size, pH, and excipient concentrations are obvious. I agree with her opinions that these would have been obvious, and therefore conclude that all of the asserted claims are obvious in their entirety.

## **VII. OTHER EVIDENCE CONFIRMS MY CONCLUSION THAT THE ASSERTED CLAIMS ARE OBVIOUS.**

123. My opinions above are based on my analysis of the prior art from the perspective of a POSA as of 2002. Certain non-prior art evidence is consistent with and confirms my opinions that the asserted claims are obvious as I discussed above. For instance, the specification of the '723 patent, discussed above, explains that the active ingredients azelastine and fluticasone were "known" to be useful in treating allergic rhinitis. What is more, however, the specifications of the patents-in-suit do not include *any* clinical data from *in vivo* or *in vitro* studies. That is consistent with my opinions about what was obvious because it reflects that a POSA did not need to see such studies or experimental data to know that a combination product would be effective. No studies were needed to expect that the combination would be efficacious

in the treatment of AR. Indeed, I reviewed the inventor's deposition, and she herself stated that no clinical trials were conducted prior to the date that the application for the patents was filed. *See* Malhotra Deposition Tr. at 18-20, 208-09. She stated that her and her co-inventor's selection of azelastine and fluticasone "was based on the knowledge of what we knew of steroids and antihistamines." *Id.* at 209:7-9.

124. Also consistent with my opinion, though not the basis for it, is the testimony of a Meda/MedPointe employee who testified regarding the development process at MedPointe and Cipla in the early to mid-2000s. He explained that "MedPointe had also selected those two compounds [azelastine and fluticasone propionate] as the best two compounds to utilize" for any combination product they would have developed, and that "it was obvious to us that those were the two best compounds to use for any product we did develop." Fuge Deposition Tr. at 113:15-17 & 22-24. This supports my opinion that these were the best drugs to choose, although others would likely also suffice especially among the steroids.

#### **VIII. THERE ARE NO UNEXPECTEDLY SUPERIOR RESULTS FROM COMBINING AZELASTINE AND FLUTICASONE IN A SINGLE NASAL SPRAY.**

125. It is my understanding that, during the prosecution of the patents-in-suit, Meda submitted a declaration by Dr. Joachim Maus describing two studies in which the efficacy of the product that Meda says is covered by its patents—Dymista<sup>®</sup>—was compared to the efficacy of azelastine monotherapy and fluticasone monotherapy. It is my understanding that Dr. Maus concluded from these studies that the improved efficacy of Dymista<sup>®</sup> was unexpectedly superior to the monotherapies. However, it is my opinion that these results are not superior to the closest prior art in terms of efficacy, as the closest prior art for which actual clinical data is available—the sequential administration of Astelin<sup>®</sup> and Flonase<sup>®</sup>—shows the same efficacy improvement over either monotherapy as does Dymista<sup>®</sup>. Moreover, even if the monotherapies are the closest

prior art, the results of the study discussed in the Maus declaration are not unexpected in light of the expectation of additive benefits when combining an intranasal antihistamine and an intranasal steroid that is discussed at length in this declaration. I understand that plaintiffs carry the burden of proving secondary considerations, and so I reserve the right to respond to any expert reports from the plaintiffs on unexpected results or other secondary considerations.

**A. The closest prior art to a single product combining azelastine and fluticasone for nasal administration is the simultaneous or sequential intranasal administration of azelastine and fluticasone.**

126. It is my understanding that, to show unexpectedly superior results, the invention must be compared to the nearest prior art. It is my opinion that the closest prior art from prior to 2002 for which clinical data is available was the sequential administration of both fluticasone and azelastine in separate sprays. As explained above, this was recommended by numerous sources and was actually practiced by doctors.

127. When compared to the closest prior art, the Maus declaration study does not actually demonstrate superior results. Ratner et al. (2008) studied the efficacy of an administration of azelastine and fluticasone nasal sprays 15 to 30 minutes apart, compared to azelastine spray plus placebo and to fluticasone spray plus placebo. Ratner et al. (2008) at 75-76 [MEDA\_APTX01608674-75]. The authors reported: “These absolute improvements represent greater than 40% relative improvement compared with either agent alone ( $P = .007$  vs azelastine and  $P = .02$  vs fluticasone)” in terms of TNSS (total nasal symptom score). *Id.* at 77. More specifically, according to my calculations, Ratner et al.’s data demonstrate just under 40% improvement relative to fluticasone alone and just under 53% improvement relative to azelastine alone.

128. According to the study reported in Dr. Maus’s Declaration—Hampel et al. (2010)—the relative improvement of Dymista<sup>®</sup>, the commercial embodiment of the patents-in-

suit, in terms of TNSS, was just over 39% when compared to fluticasone alone, and just above 73% when compared to azelastine. Hampel et al. (2010) at 170 [MEDA\_APTX02308988]. Therefore, Dymista<sup>®</sup>'s improvement over fluticasone was essentially equivalent to the prior art's improvement over fluticasone. As for azelastine, both Dymista<sup>®</sup> and the sequential administration of the monotherapies also both showed improvement.

129. Therefore, my opinion is that an unexpected improvement in efficacy of a combination product over the closest prior art—sequential administration of each active ingredient—has not been demonstrated.

**B. If the monotherapies are the closest prior art, then the results are not unexpected.**

130. If the proper analysis is comparing Dymista<sup>®</sup> to the monotherapies administered alone, then, for all the reasons discussed in my report, the superior efficacy of a combination product is still not unexpected. Quite the opposite: such a result would be expected in light of the differences in the respective active ingredient's mechanism of action, numerous prior studies showing improved efficacy for combination products, the medical literature and guidelines recommending combining an antihistamine and a steroid, and other references that taught combination products combining an intranasal steroid and an intranasal antihistamine. Indeed, Figure 2 of Hampel (2010) shows that the magnitude of effect of the combination was roughly equal to the magnitudes of the effects of the two monotherapies added together, thus demonstrating the expected additivity of a combination product (and providing no evidence of synergy).

**IX. ALTERNATIVE OPINIONS**

131. The above discussion sets out the bases for my opinions about the obviousness of the asserted claims. However, I understand that the Plaintiffs in this case contend that the claims



are not obvious, but instead involved inventive work and that the Dymista<sup>®</sup> product has unexpectedly superior results over the prior art.

132. I disagree with Plaintiffs' contention. But if they are correct, then my opinion based on the relevant standards as I understand them is that the asserted claims are neither adequately described nor enabled by the specifications of the patents-in-suit.

133. As I noted above, the specifications contain no experimental data showing that the combination nasal drug products covered by the claims actually have any effect whatsoever in humans, animals, or even any *in vitro* tests. In my opinion that is consistent with my views on obviousness—a POSA was well aware of the uses of azelastine HCl and fluticasone propionate before 2002, and would not have been surprised at all to know that combining the two drugs would have an additive effect or, at the very least, would not have lower efficacy than the sequential administration of each drug as a monotherapy. But if one assumes, as I understand Plaintiffs do, that a POSA would think the combination was surprisingly useful to a POSA at 2002, then one must also assume a POSA did not know of the uses of azelastine HCl or fluticasone propionate for intranasal administration, and similarly would not know or think without some level of experimental data that the combined drugs would have any effect on any disease when administered in a nasal spray.

134. This alternative opinion holds true with respect to those claims that are limited to the use of the combination drug for the treatment of AR. But it is particularly true with respect to treatments for other conditions. Those are claims 11, 14, 25 and 28 of the '723 patent, which cover uses of the combination product to treat “conditions,” which I understand the Court has said means “disease or illness.” In 2002, there were a large number of diseases or illnesses for which clinicians intranasally applied steroids alone. *See, e.g.*, Di Cyan, E., “Steroid Hormones

and Other Steroidal Synthetics,” CRC Handbook of Chemistry and Physics, 68<sup>th</sup> Ed., pp. C-682-98, 1987. There were also a large number of conditions that were treated with antihistamines alone. *See, e.g.*, Sherman, W.B., THE USES AND ABUSES OF ANTIHISTAMINE DRUGS, pp. 309-25 (1951). The patents’ specifications, however, only describe “preventing or minimising allergic reactions” and “allergic rhinitis” and “perennial allergic conjunctivitis.” ’723 patent at col. 1, *ll.* 20-34. And there are no examples in the patent that use the invention to treat any condition. In short, those claims cover the use of azelastine HCl and fluticasone propionate for the treatment of multiple conditions despite the fact that there are no clinical data or examples in the specification supporting them evidencing any therapeutic effect in any condition.

135. The above claims also require “intranasal administration to said mammal of a therapeutically effective amount.” ’723 cl. 1. A POSA would not know which type of mammal to administer the claimed combination because there is a complete lack of clinical data in the specification to show the claimed combination’s efficacy for any mammal. And while the patents do give ranges of certain ingredients, a POSA would still not know what amount to give a patient for any antihistamine and/or corticosteroid indicated condition because the patent fails to teach what other conditions may be treated with the claimed combination.

136. It is inconsistent to argue on the one hand that the claimed drug combination is inventive and leads to unexpected superior results, yet at the same time allege that the written description and enablement requirements are satisfied by a specification that adds no new experimental data to the field beyond what was disclosed in the prior art I discussed above.

137. Thus, assuming Plaintiffs contentions are correct, it is my view that the specifications as of 2003 (or 2002) did not disclose to a POSA that the named inventors were actually in possession of the full scope of their invention. The POSA under Plaintiffs view

would not have understood the inventors to have been in possession of any pharmaceutically effective treatment in the absence of, for example, some evidence actually showing that it worked in more detail than what was described and shown in the specification.

138. Similarly, assuming Plaintiffs contentions are correct, it is my view that the specifications as of 2003 (or 2002) did not enable a POSA to make and use the claimed combination product without undue experimentation. The POSA, under Plaintiffs view, would not have understood that the claimed combination products were effective because there is a complete absence of supporting data in the specification.

## **X. CONCLUSION**

139. In conclusion, it is my opinion that all the asserted claims of the patents-in-suit are obvious in their entirety, or, alternatively, are invalid for a lack of written description or enablement.

## **XI. DECLARATION**

I declare that all statements made herein on my own knowledge are true and that all statements made on information and belief are believed to be true.

Date: June 30, 2016

By:   
\_\_\_\_\_

Robert Schleimer, Ph.D.

# EXHIBIT A

**CURRENT APPOINTMENT**

2004 - Roy and Elaine Patterson Professor,  
Chief, Division of Allergy-Immunology;  
Professor of Medicine

OFFICE ADDRESS: Northwestern University Feinberg School of Medicine  
Department of Medicine/Division of Allergy-Immunology  
240 E. Huron, Rm M-318  
Chicago, IL 60611  
Phone #: (312) 503-0076  
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HOME ADDRESS: 100 E. Huron, #4501  
Chicago, IL 60611  
Phone #: (312) 335-1872

DATE OF BIRTH: April 8, 1952  
PLACE OF BIRTH: New York, New York

**EDUCATION**

1970 - 1974 Univ. of California, San Diego, John Muir College, B.A. with Honors in Biology  
1972 - 1973 University of Sussex, Brighton, England, Education Abroad Program  
1974 - 1979 University of California, Davis, Ph.D. program in Pharmacology and  
Toxicology; Degree awarded February 1980  
Thesis Chairman: Dr. Eliezer Benjamini; Chairman, Graduate Group in  
Immunology; Professor, Department of Medical Microbiology  
2007 Kellogg School of Business, Northwestern University,  
Executive Business Course (Diploma)

**RESEARCH EXPERIENCE**

1974 University of California at San Diego, Dept of Biology; Laboratory of Dr. Stanley Mills  
1974 - 1976 University of California at Davis, School of Medicine, Department of Pharmacology;  
Laboratory of Dr. Gary Henderson, and Department of Anesthesiology; Laboratory of  
Dr. John Eisele  
1974 - 1979 University of California at Davis, School of Medicine, Department of Medical  
Microbiology; Laboratory of Dr. Eliezer Benjamini  
1975 - 1976 University of California at Davis, School of Medicine, Department of  
Pharmacology, Teaching Assistant  
1978 - 1979 Sacramento Medical Center Blood Bank, Instructor  
1986 Tohoku University, Japan. Visiting Faculty  
1993 - 1994 Sabbatical, Dr. Santa Ono's Laboratory, Johns Hopkins University School of Medicine

## ACADEMIC APPOINTMENTS

1977	California State University at Chico, Spring Semester; Full-Time Faculty, Department of Biology
1979 - 1981	Johns Hopkins University School of Medicine, Department of Medicine/Clinical Immunology Division; Postdoctoral Fellow, Laboratory of Dr. Lawrence Lichtenstein
1981 - 1982	Johns Hopkins University School of Medicine, Department of Medicine/Clinical Immunology Division; Instructor in Medicine
1982 - 1987	Johns Hopkins University School of Medicine, Department of Medicine/Clinical Immunology Division; Assistant Professor of Medicine
1987 - 1992	Johns Hopkins University School of Medicine, Department of Medicine/Division of Clinical Immunology; Associate Professor of Medicine
1992 - 2004	Johns Hopkins University School of Medicine, Department of Medicine/Division of Clinical Immunology; Professor of Medicine
2004-	Northwestern University Feinberg School of Medicine, Department of Medicine, The Roy and Elaine Patterson Professor of Medicine
2009-	Northwestern Memorial Hospital, Department of Medicine, appointment to Doctorate Level
2010-	Northwestern University Feinberg School of Medicine, Department of Otolaryngology-Head and Neck Surgery; Professor of Otolaryngology

## HONORS AND AWARDS

1975 - 1976	Earle C. Anthony Fellow in Pharmacology and Toxicology
1976 - 1977	Earle C. Anthony Fellow in Pharmacology and Toxicology
1977 - 1978	University of California Regent's Fellow
1978 - 1979	Earle C. Anthony Fellow in Pharmacology and Toxicology
1987	American Academy of Allergy and Immunology - Annual Meeting. President's Award (best paper) - presented to Dr. Bruce S. Bochner (postdoctoral fellow). \$5000 awarded to the laboratory
1988	American Academy of Allergy and Immunology - Annual Meeting. President's Award (best paper) - presented to Dr. Ana M. Lamas (postdoctoral fellow). \$5000 awarded to the laboratory
1993	American College of Allergy and Immunology. Clemens Von Pirquet Award - presented to Dr. Michael Vicksman (postdoctoral fellow).
1993	Fogerty International Award - presented to Dr. Cristiana Stellato (postdoctoral fellow).
1994	The Allergy 2000 International Young Investigator Award, Schering Plough International (\$10,000) - presented to Dr. Motohiro Ebisawa (postdoctoral fellow).
1995	The Allergy 2000 International Young Investigator Award, Schering Plough International (\$3,000) - presented to Dr. Cristiana Stellato (postdoctoral fellow).
1995	The Sheldon C. Siegel Lectureship, AAAAI
1997	American Academy of Allergy, Asthma and Immunology - Annual Meeting Cytokine abstract award for Fellows-in-Training (best abstract) - presented to Dr. Cristiana Stellato (postdoctoral fellow).
1998	The Richard S. Farr Memorial Lectureship, AAAAI
2002	Recognition as one of the most highly cited researchers in the last two decades. Institute of Scientific Information
2005	Northwestern University Graduate Faculty member
2006	The Joseph A. Kwasman Memorial Lecture, University of Rochester
2008	The Jack Pepys Memorial Lecture, British Society of Allergy Clinical Immunology, 2008
2008	The Giles F. Filley Lecture, Aspen Lung Meeting
2008	Featured poster, AAAAI Annual Meeting
2008	American College of Allergy, Asthma & Immunology, Clemens Von Pirquet Award (best paper) – presented to Dr. Seong Cho (postdoctoral fellow) \$10,000 awarded to the laboratory

2011	The Elliot Middleton Memorial Lectureship, AAAAI Annual Meeting
2012	Johns Hopkins University Society of Scholars
2014	The Frederick E. Hargreave Memorial Lecture, McMaster Univ, Hamilton
2014	10 <sup>th</sup> Annual Respiratory Disease Young Investigators Forum, Washington DC, Award for Best Clinical Research Presentation by Dr. Whitney Stevens (postdoctoral fellow) in Schleimer Lab
2015	AAAAI Intersect-Section Fellow-in-Training Abstract Award – presented to Dr. Whitney Stevens (postdoctoral fellow) in Schleimer Lab
2015	The Tripartite Prize, Northwestern University (cash award)
2015	DOM Accomplished Scientist Speaker Lecture, National Jewish Health, Denver CO
2015	American College of Allergy, Asthma & Immunology, First Place Clemens Von Pirquet Award (outstanding abstract) – presented to Dr. Whitney Stevens (postdoctoral fellow)

## MEMBERSHIPS IN PROFESSIONAL SOCIETIES

Sigma Xi  
 American Association of Immunologists  
 New York Academy of Sciences  
 American Society of Hematology  
 American Association for the Advancement of Science  
 Fellow, American Academy of Allergy, Asthma and Immunology  
 Fellow, Illinois Society of Asthma, Allergy and Immunology  
 International Eosinophil Society

## EDITORIAL BOARDS

1983 - 1987	Associate Editor: Journal of Immunology
1990 – 2000	Editorial Board – Year Book of Pharmacology, CRC Press
1990 - 1996	Editorial Board - Journal of Allergy and Clinical Immunology
1992 - 1995	Associate Editor: Journal of Immunology
1993 - 1998	Senior Associate Editor: Journal of Allergy and Clinical Immunology
2000 - 2001	Editorial Board - Respiratory Research
2007 - 2011	Member, Editorial Board of Allergy
2007 -	American Journal of Respiratory Cell and Molecular Biology
2008 -	Associate Editor - Clinical and Experimental Allergy
2008 - Present	Member, Editorial Board of Proceedings of the American Thoracic Society
2008 -	Editorial Board - International Journal of Interferon, Cytokine and Mediator Research
2011 -	Editorial Board - Allergology International

## ACADEMIC ADVISORY BOARDS

2001 - 2006	Editor, Disease Markers
2001 - 2013	Scientific Outside Advisory Board for the Center for Childhood Asthma in Urban Environment, Johns Hopkins University
2006 - 2011	Duke University SCOR Advisory Board
2006 - 2010	Member, U. of Louisville Allergy & Immunology External Adv. Committee
2006 - 2008	University Wisconsin Asthma SCOR Advisory Board
2006 - 2008	Johns Hopkins University J32 Training Grant External Advisory Committee
2007 - 2008	National Jewish PPG Advisory Board



## ACTIVITIES AT JOHNS HOPKINS UNIVERSITY

1982 - 1990	Clinical Immunology Division Safety Officer
1984 - 1994	Clinical Immunology Division Journal Review, Co-Director
1986 - 2002	Johns Hopkins Immunology Council - Henry G. Kunkel Lecture Committee
1987 - 1989	Clinical Immunology Division Research Conferences, Director
1989 - 1991	Johns Hopkins Immunology Council Seminar Committee
1991	Department of Medicine Annual Retreat Committee
1991	Johns Hopkins Asthma and Allergy Center Annual Symposium, Director
1991	Clinical Immunology Division Recruitment Committee, Chairman
1992	Chairman-Elect, Johns Hopkins Immunology Council
1993 - 1994	Chairman, Johns Hopkins Immunology Council
1993 - 1995	Department of Medicine Advisory Committee
1995 - 2002	Counselor, Johns Hopkins Immunology Council
1997	Co-chairman, Molecular Medicine Retreat
1997	Graduate Student Advisor, Molecular Medicine Graduate Program
1998 - 2004	Advisory Board, Johns Hopkins Center for the Asthmatic Child in the Urban Environment.
1998	Advisory Board, Cell and Molecular Medicine
1998	Co-Chairman, Cell and Molecular Medicine
1998 - 1999	Organizing Committee, CMM Committees
1999	Chairman, Johns Hopkins University, Dept. of Medicine Development - An Exploration of Who We Are
1999	Member, Pulmonary Division Chief Search Committee
2006 - Present	Member, External Advisory Committee for the T-32 Training Program Renewal in Pulmonary and Critical Care Medicine at Johns Hopkins
2008 -	Member, External Advisory Board for the Center for Childhood Asthma in the Urban Environment, Johns Hopkins School of Public Health

## ACTIVITIES AT NORTHWESTERN

2004 - 2005	Hematology-Oncology Chief Search Committee
2005 -2010	Member, NUFSM Appointment, Promotion and Tenure Committee
2005 -	Member, NUFSM Pulmonary & Critical Care Medicine, Search Committee for Sleep Medicine Research
2006	Member, Microbiology-Immunology Chair Search Committee
2006	NMH Resident Research Symposium & Presentations (participating Judge for presentations)
2006 - 2008	Member, NU Dept of Microbiology-Immunology, Faculty Search Committee
2006 -	Member, External Advisory Board for the Program Project Grant in Acute Lung Injury, NUFSM Pulmonary & Critical Care Medicine
2006 - 2007	Member, NUFSM Deans Research Council
2007 - 2008	Member & Chair, NUFSM Faculty Task Force
2007 - 2009	Member, NU Patent Policy Committee
2007 - 2013	Member, NUFSM Senior Faculty Research Advisory Committee
2007 - 2010	Member, NUFSM One Northwestern Task Force – Promotion and Tenure Subgroup
2007 - 2009	Member, NUFSM Immunology Planning Committee
2008 - 2009	Member & Chair, NUFSM Nephrology Chief Search Committee
2008	Member & Reviewer, NMH Priority Programs Collaborative Development Initiative Committee
2008	Member, NUFSM Immunology/Infectious Disease/Transplantation Strategy Committee
2008 -	Member, FOCIS Advisory Board of the Center of Excellence in Clinical Immunology

2008	Member, Pathology Faculty Recruitment Committee
2009	Member, NUFMS Office of Research ICR Initiative Workgroup
2010	Member, NUFMS Rheumatology Basic Science Research Faculty Search Committee
2010 -	ENT Appointment, Promotions and Tenure Committee
2010 - 2012	Member, NUFMS Basic Sciences Task Force
2011	Member, NU Office of Research Life Sciences Advisory Board
2011 -	Member, NUFMS, Department of Medicine Research Council
2012 - 2013	Member, Pharmacology Department Chair Search Committee
2012 - 2014	Member, Skin Disease Research Program
2013 - 2014	Galter Library Director Search Committee

## ACTIVITIES ASSOCIATED WITH THE NATIONAL INSTITUTES OF HEALTH

### Committees

1992 - 1996	AdHoc Reviewer, Immunological Sciences and Allergy and Immunology Study Sections
September, 1995	National Advisory Council on Allergy and Infectious Diseases. Session on Asthma and Inflammation Bethesda, Maryland
1996 - 2001	Lung Biology and Pathology Study Section
March, 1996	NHLBI, Lung SCOR Parent Committee Study Section Bethesda, Maryland
1996	Cellular and Molecular Mechanisms of Asthma Study Section
June, 1997	NHLBI Special Emphasis Panel Chevy Chase, Maryland
September, 1999	NHLBI - Working Group on Novel Therapeutic Approaches for the Treatment and Prevention of Asthma, Bethesda, MD
February, 2003	Center for Scientific Review Special Emphasis Panel Bethesda, MD
April 9-10, 2003	NHLBI - Future Research Directions in Asthma Working Group “Mechanisms of Airway Inflammation/Injury/Repair Remodeling” “Vascular Basis of Mechanisms in Asthma” Division of Lung Diseases, Rockville, MD
March 30, 2004	NIH – Center for Scientific Review Special Emphasis Panel Washington, DC
November 2005	NIH – Center for Scientific Review Special Emphasis Panel Grants Review Meeting (teleconference meeting) Washington, DC
November 2005	NHLBI Strategic Plan DLD Executive Planning Committee
January 2006	Washington, DC
February 2006	NHLBI-Host Factors SCCOR Meeting, Baltimore, MD
March 2006	NIH/NIEHS Ad-Hoc Reviewer for the Laboratory of Signal Transduction and the Laboratory of Molecular Toxicology Meeting, Durham, NC
May 2006	Consortium for Food Allergy Research (External Reviewer)
June 2006	NIAID, NIH, DHHS Bethesda, MD NHLBI Strategic Plan DLD Theme 2: Interactive Approaches to Pathogenetic Research Mtg, Bethesda, MD
July 2006	NIH-Center for Scientific Review -LCMI Special Emphasis Panel Grants Review Mtg (teleconference mtg) Washington DC
October 2006	NHLBI Level 2- Strategic Plan Mtg

March 2007	Bethesda, MD NIH/NIEHS ONES Review Meeting
December 2007	Durham, NC NIH-Board of Scientific Counselors Review Meeting
October 2007-Present	Bethesda, MD NIH-Center for Scientific Review/LCMI Study Section Grants Review Mtg, Regular Member
September 2008	NHLBI Working Group on Basic & Clinical Immunological Aspects that Characterize Asthma, COPD and IPF Patients, Chair, Bethesda, MD
October 2008-Present	NIH-Center for Scientific Review/LCMI Study Section Grants Review Mtg, Chair, Study Section (two year term)
October 2008	NIH-Center for Scientific Review/LCMI Study Section Grants Review Mtg, Seattle, WA
January 2009	NIH-New Study Section Chair Orientation Mtg Hilton Chicago Ohare Hotel
February 2009	NIH-Center for Scientific Review/LCMI Study Section Grants Review Mtg, Baltimore, MD
May 2009-Present	NIAID/NIH-Asthma Outcomes Workshop, Biomarkers Subcommittee member, (teleconference mtgs)
June 2009	NIH-Center for Scientific Review/LCMI Study Section Grants Review Mtg, Baltimore, MD
October 2009	NIH-Center for Scientific Review/LCMI Study Section Grants Review Mtg, San Diego, CA
February 2010	NIH-Center for Scientific Review/LCMI Study Section Grants Review Mtg, Baltimore, MD
March 2010	NIH/NHLBI Asthma Outcomes Workshop Baltimore, MD
June 2010	NIH-Center for Scientific Review/LCMI Study Section Grants Review Mtg, Baltimore, MD
October 2010	NIH-Center for Scientific Review/LCMI Study Section Grants Review Mtg, San Francisco, CA
March 2011	NIH-Special Emphasis Panel/Scientific Review Group Mtg Baltimore, MD
June 2011	NIH-Center for Scientific Review/LCMI Study Section Grants Review Mtg, Baltimore, MD
October, 2014	Asthma Center Program Project Investigator's Meeting

### **Lectures at NIH Programs**

March, 1993	National Institutes of Health, Lecture Invited by: Dr. Goldstein Bethesda, MD
May, 1998	Occupational Asthma: In and Out of the Workplace NIOSH Conference Sponsored by the West Virginia University School of Medicine Office of Continuing Medical Education "Integration of inflammatory response components (cells, chemokines, mediators, adhesion molecules)". Morgantown, WV
April, 1999	NIH Conference "Biomarkers and Surrogate Endpoints:

March, 2001  
 Advancing Clinical Research and Applications”  
 “Markers of Inflammation for Asthma”  
 Bethesda, MD  
 Breathless in Bethesda: the Biology of Asthma  
 Organizer: Dr. Deborah Beebe  
 “Mechanisms of allergic pathogenesis”  
 Bethesda, MD

## **CURRENT SUPPORT**

### **NIH Grants**

5R37 HL068546

08/01/2010 - 07/31/2018

NIH/NHLBI; Schleimer (PI)

Glucocorticoid Action in Inflammatory Disease. To assess the mechanisms of glucocorticoid actions in allergic disease and experimental antigen challenges.

T32A1083216

08/15/2010 – 07/31/2020

NIH/NIAID; Schleimer (Program Director)

Northwestern University Allergy Immunology Research Program (NUAIR)

The overall aim of the NUAIR program is to train postdoctoral scientists in translational research, here defined as research of disease mechanisms that includes investigations in human subjects or human samples.

U19AI106683

08/05/2013 – 07/31/2018

NIH/NIAID; Schleimer (PI)

Chronic Rhinosinusitis Integrative Studies Program (CRISP)

The Chronic Rhinosinusitis Integrative Studies Program (CRISP) unifies and integrates three world-class research groups to understand the epidemiology, genetics and pathology of chronic rhinosinusitis. CRISP proposes highly interactive studies that leverage the population cohorts, expertise and resources of groups at Northwestern University, the University of Chicago and the Geisinger Health Systems in order to advance our understanding of chronic rhinosinusitis and point the way toward new therapeutic strategies.

U19AI106683

08/15/2015 – 7/31/2018

NIH/NIAID; Schleimer (PI)

CRISP Supplement: The Unified Barrier Hypothesis

Exciting new data suggest that Chronic Rhinosinusitis is characterized by defects in the epithelial barrier that are associated with changes in hormonal control systems. The work in this supplement will test this hypothesis using the sample set that is being generated with the CRISP program project grant

## OTHER CURRENT ACADEMIC ACTIVITIES

2006 - 2008	Member, U of Louisville Allergy & Immunology External Adv Committee
2008 - 2012	Member, AAAAI STAR Program Task Force
2008 - 2013	Member, AAAAI Annual Meeting Program Committee
2011 -	Member, Food Allergy Research and Education Advisory Board

## COURSES AT JOHNS HOPKINS UNIVERSITY

Occupational Medicine Residents Pulmonary Course, School of Hygiene and Public Health  
(Dr. Mel Tockman)

Graduate Immunology: The Immune Response, School of Hygiene and Public Health (Dr. Noel Rose)

Medical School Immunology Course, Johns Hopkins University Medical School (Dr. Hyun Shin)

Inflammation, Injury and Repair: Course Director - Dr. Arthur Dannenburg, School of Hygiene and Public Health

Johns Hopkins Asthma and Allergy Center "Frontiers" course (Dr. Peter Creticos)

Principles of Immunology, (offered at the School of Continuing Studies)

Graduate Immunology Course. School of Hygiene and Public Health (Dr. Alan Scott)

### Special lectures given at The Johns Hopkins University

2nd Annual Johns Hopkins Asthma Center Symposium (1991)

Conjoint Clinic (Guest of Dr. Paul Lietman)

Combined Research Conference, Johns Hopkins University, (Pulmonary/Medicine - 5 occasions)

Gerontology group - special Fellow's lecture (Guest of Dr. Jesse Roth)

Hematology (Guest of Dr. Peter Agre)

Johns Hopkins Immunology Council (3 occasions)

Clinical Immunology Research Conference (1 or 2 lectures/year)

Clinical Immunology Fellows Course (1 or 2 lectures/year)

Clinical Immunology Journal Club (1 each month)

Clinical Immunology Molecular Studies Journal Club (1 or 2 discussions/year)

Topics in Clinical Medicine (Guest of Dr. Hellmann)

Preceptorship Programs (5 or more lectures/year)

Gerontology Research Center, Research Seminar

Johns Hopkins Allergy Continuing Education Conference

Johns Hopkins Alumni College, 1 week lecture series at St. Mary's College (5 lectures)

Johns Hopkins Pediatric Allergy/Immunology Conference

Francis Scott Key Medical Center Grand Rounds

Dept of Pharmacology, "Chemokines and Allergic Diseases" (January, 1999)

### Invited Lectures/Meetings (Domestic)

February, 1992 Pfizer Pharmaceutical Company  
New Groton, Connecticut

February, 1992 Tanabe Pharmaceutical Company  
San Diego, California

March, 1992 Joint American - European Plenary Symposium at the American  
Academy of Allergy and Immunology National Meeting  
Orlando, Florida

April, 1992 Eosinophil Symposium - (Invited speaker) Federation of American  
Societies for Experimental Biology Annual Meeting  
Anaheim, California

May, 1992 Biomedical Res. Community of Baltimore. Clinical Research Societies  
Baltimore, Maryland

May, 1992	American Federation of Clinical Research - Special symposium Baltimore, Maryland
June, 1992	Virginia Allergy Society, 12th Annual Scientific Meeting Virginia Beach, Virginia
June, 1992	American Association of Immunologists Advanced Immunology Course Colorado Springs, Colorado
July, 1992	Aspen Allergy Conference Aspen, Colorado
October, 1992	ICI Delaware
October, 1992	Monsanto (Lecture) St. Louis, Missouri
January, 1993	SmithKline Beecham Philadelphia, Pennsylvania
March, 1993	National Institutes of Health (Lecture -Invited by Dr. Goldstein) Bethesda, Maryland
March, 1993	American Academy of Allergy and Immunology Chicago, Illinois
May, 1993	Khepri Pharmaceuticals, Inc. San Francisco, California
June, 1993	AAI Advanced Immunology Course Colorado Springs, Colorado
October, 1993	Hahnemann University Immunology Retreat Philadelphia, Pennsylvania
January, 1994	Frontiers Course in Research and Clinical Management Johns Hopkins Asthma and Allergy Center Baltimore, Maryland
March, 1994	American Academy of Allergy and Immunology Anaheim, California
April, 1994	Federation of American Societies for Experimental Biology, Annual Meeting, San Francisco, California
June, 1994	Glaxo, Visiting Professor McMaster University Hamilton, Ontario, Canada
July, 1994	Am. Association of Immunology Advanced Course and Joint U.S.-Japan Cooperative meeting Bozeman, Montana
January, 1995	Bowman Gray School of Medicine. Guest of Floyd Chilton, Ph.D. Winston-Salem, North Carolina
February, 1995	American Academy of Allergy and Immunology New York, New York
April, 1995	Federation of American Societies for Experimental Biology, Annual Meeting Atlanta, Georgia
May, 1995	Scleroderma meeting Washington, DC
May, 1995	SmithKline Beecham Philadelphia, Pennsylvania
May, 1995	American Thoracic Society International Conference Seattle, Washington
July, 1995	American Academy of Allergy and Immunology/American Thoracic Society Joint Conference. Asthma '95: Theory to Treatment Chicago, Illinois
September, 1995	National Advisory Council on Allergy and Infectious Diseases. Session on Asthma and Inflammation Bethesda, Maryland
October, 1995	NIH study section

December, 1995	Bethesda, Maryland American Academy of Asthma, Allergy and Immunology "Cytokines in Inflammation and Disease"
March, 1996	Bethesda, Maryland American Academy of Allergy, Asthma and Immunology, Annual Meeting Ad hoc committee to evaluate the annual meeting Speaker: "Epithelial derived mediators" Speaker: "Role of chemokines in allergic inflammation" Co-moderate: "Role of cytokines in regulation of allergic inflammation"
March, 1996	New Orleans, Louisiana Strategic Implications International Asthma: 1996 knowledge base on control and treatment
April, 1996	New Orleans, Louisiana Pfizer Inc. "Eosinophils, chemokines and airway inflammation"
April, 1996	Groton, Connecticut Scleroderma meeting
April, 1996	Chicago, Illinois Federation of American Societies for Experimental Biology, Annual Meeting "New approaches to the therapy of asthma - Cytokine and chemokine Modulators"
July, 1996	Washington, D.C. Glaxo Wellcome Preceptorship Johns Hopkins Asthma and Allergy Center "Pathogenesis of asthma: Cells/cytokines/mediators"
July, 1996	Baltimore, Maryland Meeting entitled "Allergic and non-allergic rhinitis - Clinical aspects" Sponsored by: Astra Draco (Drs. Durham, Mygind, and Naclerio) "Future therapies for allergic diseases of the airways"
September, 1996	Chicago, Illinois Bluegrass Society of Allergists Sponsored by: Astra Draco (Dr. Humilidad Anzures) "Mechanism of glucocorticoids in asthma"
October, 1996	Lexington, Kentucky Seventh Annual Scientific Symposium "The Genetics of Asthma and Atopic Disease"
October, 1996	Sponsored by: Asthma and Allergy Foundation of America Clinical Cutaneous Allergy and Immunology Sponsored by: American Academy of Allergy, Asthma and Immunology "Pharmacology in the Treatment of Skin Disease"
October, 1996	New York, New York 8th International Conference "Inflammation: Mechanisms and Therapeutics"
November, 1996	Sponsored by: SmithKline Beecham Pharmaceuticals Hershey, Pennsylvania Seminar "Inhaled Steroids for the Treatment of Asthma"
February, 1997	Sponsor: Searle (Walter Smith) Skokie, Illinois 19th Annual National Jewish Update on Allergy and Clinical Immunology "Mechanisms of steroid action in asthma"
February, 1997	"Mechanisms of allergic cell recruitment" Keystone, Colorado American Academy of Allergy, Asthma and Immunology, Annual

	Meeting
	"Role of Chemokines in Allergic Inflammation"
	Minisymposium entitled "Corticosteroids and Asthma"
	Symposium
	"Corticosteroids - Modes of Action in Asthma"
	Co-Chair
	"Adhesion Molecules and the Genesis of Allergic Inflammation"
	Co-Chair
	"Corticosteroids and Asthma"
	Minisymposium
March, 1997	The Theophylline Forum in Napa Valley, 97
	"The role of adhesion molecules in allergic inflammation and their suitability as targets of antiallergic therapy"
	Sponsored by: Mitsubishi chemical Corp and Nikken Chemicals Co., Ltd., Silverado Country Club and Resort, Napa Valley, California
March, 1997	Grand Rounds - St. Agnes Hospital
	Pediatric grand rounds - "Cytokines in Allergic Diseases"
	Organized by: Dr. Michael Burke
March, 1997	Millenium Pharmaceuticals
	"Cell recruitment, Epithelium and Glucocorticosteroids"
	Boston, Massachusetts
May, 1997	"Cellular responses in asthma and their modulation by glucocorticoids"
	Fourth Annual Allergy Fellows Symposium
	American Thoracic Society
	San Francisco, California
June, 1997	Cottle International Rhinology Centennial and XVIth ISIAN meeting
	"Mechanisms of allergic cell recruitment"
	Philadelphia, Pennsylvania
July, 1997	SmithKline Beecham
	"In vitro evaluation of glucocorticosteroid potencies"
	"Studies of chemokine biology"
	King of Prussia, PA
August, 1997	1997 Society for Leukocyte Biology National Meeting
	Hyatt Regency
	Baltimore, MD
October, 1997	Zeneca Pharmaceuticals
	Asthma Symposium
	"Mechanisms of eosinophilia in asthma"
	Wilmington, DE
October, 1997	Health Dimensions
	Allergy/Immunology and Neuroimmunology Fellows Symposium
	"Chemokines and their receptors in allergic inflammation"
	Phoenix, AZ
October, 1997	Pfizer Pharmaceuticals
	Providence, RI
October, 1997	The Allergy, Asthma and Immunology Society of
	Greater New York Annual Teaching Day
	"Nouvelle therapies of asthma"
	New York, NY
January, 1998	Medical Association
	Pharmacology of ICS
	Limo, OH
February, 1998	Mechanism of Glucocorticoid in Asthma
	Sponsored by Glaxo Wellcome
	Raleigh, NC
March, 1998	American Academy of Asthma, Allergy and Immunology, Annual Meeting



	<p>“Studies on the role of chemokines in allergic disease”</p> <p>Postgraduate Plenary Program</p> <p>"Pharmacology of inhaled glucocorticoids"</p> <p>RSLAAIS Symposium</p> <p>"Mechanisms of glucocorticoid actions"</p> <p>Other presentations:</p> <p>"Comparative studies of eosinophil active C-C chemokines"</p> <p>"The epithelium as a target for anti-inflammatory therapy"</p>
March, 1998	<p>Washington, DC</p> <p>1998 National Immunology Meeting</p> <p>Innovative Strategies for Immune Modulation of Host Responses</p> <p>"The role of chemokines in allergic diseases"</p>
April, 1998	<p>Bodega Bay, CA</p> <p>Cytokines and Chemokines in Pulmonary Disease</p> <p>Sponsored by the Inflammation Research Association and the Pulmonary Research Group at the New York Academy of Sciences</p> <p>"Overview of chemokines in the lung"</p>
April, 1998	<p>New York, NY</p> <p>Fifth Annual Allergy Fellows Symposium</p> <p>Sponsored by GlaxoWellcome</p> <p>"Mechanisms of glucocorticosteroid regulation of inflammation"</p>
June, 1998	<p>Chicago, IL</p> <p>Second Annual Yale University Asthma SCOR Symposium</p> <p>Sponsored by Pulmonary and Critical Care Medicine (Jack Elias, M.D.)</p> <p>“Regulation of Airway Responses by Endogenous GC”</p>
November, 1998	<p>New Haven Lawn Club</p> <p>New Haven, CT</p> <p>9th International Conference - Inflammatory Processes: Molecular</p> <p>“Mechanisms and Therapeutic Opportunities”</p> <p>Sponsored by IRA</p> <p>“The Role of Chemokines in Allergic Diseases of the Airways”</p>
January, 1999	<p>Hershey, PA</p> <p>The Wistar Institute</p> <p>“Chemokines and Allergic Diseases”</p> <p>Host: Hildegund Ertl, M.D.</p>
February, 1999	<p>Philadelphia, PA</p> <p>American Academy of Asthma, Allergy and Immunology, Annual Meeting</p> <p>“Asthma therapy: Present and future”</p> <p>“Comparative anti-inflammatory effects of currently available therapies”</p>
April, 1999	<p>Orlando, FL</p> <p>Federation of American Societies for Experimental Biology, Annual Meeting</p>
June, 1999	<p>Washington, DC</p> <p>1999 New Jersey Thoracic Society - Pulmonary Research Group</p> <p>“Molecular and Cellular Mechanisms of Glucocorticoid Action”</p> <p>Sponsored by: ATS and NJTS Pulmonary Research Group</p>
July, 1999	<p>New Brunswick, NJ</p> <p>Aspen Allergy Meeting</p> <p>“Chemokines and Allergic Diseases”</p>
September, 1999	<p>Aspen, CO</p> <p>Schering Plough</p>
September, 1999	<p>New Jersey</p> <p>Leukocyte Pharmaceutical Company</p>
October, 1999	<p>Boston, MA</p> <p>Philadelphia Allergy Society</p>

October, 1999	<p>“Mechanisms of Action of Topical Steroids”  Philadelphia, PA  University of Pennsylvania, Allergy Division  Chemokines and Allergic Disease</p>
December, 1999	<p>Philadelphia, PA  Cytokines in Asthma meeting  “Newly recognized glucocorticoids”  Sponsored by: Immunex  Coral Gables, FL</p>
January, 2000	<p>I&amp;R Seminar Series  “Chemokines and allergic diseases”  Sponsored by: Merck  New Jersey</p>
January, 2000	<p>Systemic aspects of allergic inflammatory disease  Sponsored by: Schering-Plough  “HPA axis and allergic inflammation”  Orlando, FL</p>
March, 2000	<p>American Academy of Asthma, Allergy and Immunology, Annual Meeting  “Molecular mechanisms and cellular targets”  “A new paradigm: Is there more to asthma than inflammation”  San Diego, CA</p>
March, 2000	<p>Neurocrine Biosciences, Inc.  CCR-3 Antagonist Project  San Diego, CA</p>
April, 2000	<p>Pfizer  Groton, CT</p>
June, 2000	<p>Schering-Plough and Bestmed  Desloratadine National Curriculum Council  New York, NY</p>
July, 2000	<p>GlaxoWellcome, Inc  Respiratory Speakers Alliance: Advancements in Asthma Controller Therapy  Carlsbad, CA</p>
July, 2000	<p>Asthma Ambassadors Communication Workshop  Sponsored by: GlaxoWellcome  Baltimore, MD</p>
September, 2000	<p>2000 National Respiratory Consultants meeting  Sponsored by: Merck and Co., Inc.  Aventura, FL</p>
September, 2000	<p>Respiratory Speakers Alliance: Advancements in Asthma Controller Therapy. Sponsored by: GlaxoWellcome  Amelia Island, FL</p>
November, 2000	<p>American College of Allergy, Asthma and Immunology  Sponsored by: Synergy Communications  “Molecular mechanisms and cellular targets”  Seattle, WA</p>
November, 2000	<p>Respiratory Leadership Forum  Sponsored by: Schering-Plough Respiratory  “Mechanisms of action and safety aspects”  Kenilworth, NJ</p>
November, 2000	<p>Asthma: An Update on Medical Management  Sponsored by: Health Science Ctr for Continuing Medical Education  “Use of steroids in asthma”.  New York, NY</p>
December, 2000	<p>Center for Childhood Asthma in the Urban Environment  “Airways epithelial cells and allergic inflammation”</p>

	School of Hygiene and Public Health Baltimore, MD
December, 2000	University of Alabama at Birmingham Department of Physiology and Biophysics “Airway epithelium, chemokines and asthma” Birmingham, AL
January, 2001	Schering-Plough Research Institute Kenilworth, NJ
February, 2001	Xolair: FDA Pulmonary-Allergy Drugs Advisory Committee Meeting Sponsored by: Genentech and Novartis San Francisco, CA
March, 2001	Advair Academic Advisory Board Sponsored by: GlaxoSmithKline Research Triangle Park, NC
March, 2001	Federation of American Societies for Experimental Biology, Annual Meeting. “Mechanisms of action of GC in inflammatory disease” Orlando, FL
June, 2001	American Society for Pharmacology and Experimental Therapeutics “Mechanisms of action of GC in inflammatory disease” Orlando, FL
July, 2001	World Asthma Meeting “Newly recognized glucocorticoid targets” Chicago, IL
July, 2001	Pfizer Visiting Professor University of Texas Medical Branch at Galveston “Mechanisms of allergic inflammation” Grand Rounds University of Texas Medical Branch at Galveston “Inhaled steroids and asthma” Galveston, Texas
August, 2001	Respiratory Speakers Summits Sponsored by: GlaxoSmithKline Hot Springs, VA and Vancouver, Canada
September, 2001	Respiratory Speakers Summit Sponsored by: GlaxoSmithKline Newport Beach, CA
October, 2001	Visiting Pulmonary Scholar Program Duke University West Campus Sponsored by: CIIT Centers for Health Research; Duke University (Div of Pulmonary and Critical Care Medicine); National Inst. of Environmental Health Sciences; NC State Univ. Veterinary School, Sepracor, Inc.; U.S. Environmental Protection Agency; and the Univ. of NC at Chapel Hill. “Regulation of allergic inflammation of the airways by cytokines and glucocorticoids” Durham, NC
October, 2001	Respiratory Speakers Summit Sponsored by: GlaxoSmithKline “Asthma pathophysiology and the scientific rationale for the use of inhaled corticosteroids with long-acting beta2 agonists in the management of asthma” Hot Springs, VA
October, 2001	Scientific Outside Advisory Board Meeting For the Center for Childhood Asthma in the Urban Environment. Invited by: Peyton Eggleston Baltimore, MD
November, 2001	Asthma Conference – Pulmonary and Critical Care Medicine, and

	<p>Allergy and Immunology  Washington University School of Medicine  Invited by: Mario Castro, M.D.  “Regulation of allergic airway inflammation”  Pulmonary Grand Rounds  “Inhaled steroids in asthma”  St. Louis, MO</p>
January, 2002	<p>Beta-agonists: New Insights into Biology  Content development meeting  Sponsored by: GlaxoSmithKline  Dallas, TX</p>
February, 2002	<p>GlaxoSmithKline COPD Speakers Alliance  Sponsored by: GlaxoSmithKline  “Scientific and clinical rationale”  Dana Point, CA</p>
March, 2002	<p>American Academy of Asthma, Allergy and Immunology, Annual Meeting Seminar: “New insights into GC actions”  Poster session: Cytokines and chemokines.  Postgraduate Plenary symposium: “The eosinophil controversy in allergy”  Dinner lecture at the Waldorf Astoria: “Interactions between glucocorticoids and long acting beta agonists”  New York, NY</p>
April, 2002	<p>Congress on Beta-Agonists: New Insights into Biology  Sponsored by: GlaxoSmithKline  Plenary session: “Interactions with other signaling mechanisms”  Mandarin Oriental Miami  Miami, FL</p>
April, 2002	<p>Federation of American Societies for Experimental Biology, Annual Meeting Chair: “Asthma mechanisms”  New Orleans, LA</p>
June, 2002	<p>AAI Introductory Course in Immunology  Tufts University  “Allergy and mast cell activation”  Medford, MA</p>
June, 2002	<p>GlaxoSmithKline Allergy Speakers Summit (PEDS)  The 2002 Allergy Speakers Summit  Sponsored by: GlaxoSmithKline  “Asthma pathophysiology and the scientific rationale for the use of inhaled corticosteroids (ICS) and long-acting <math>\beta_2</math>-agonists (LABA)”  San Francisco, CA</p>
July, 2002	<p>Asthma Academic Specialist Advisory Board  Sponsored by: GlaxoSmithKline  Denver, CO</p>
November, 2002	<p>Wyman Park Medical Society Meeting  “Pharmacology of glucocorticoids and beta agonists in asthma”  Wyman Park Medical Center</p>
November, 2002	<p>COPD Consultancy Meeting  Sponsored by: AstraZeneca  San Francisco, CA</p>
December, 2002	<p>Ciclesonide Preclinical Advisory Board Meeting  Sponsored by: Aventis  New York</p>
December, 2002	<p>Center for Childhood Asthma in the Urban Environment  Scientific outside advisory board meeting  Invited by: Peyton Eggleston  Baltimore, MD</p>
January, 2003	<p>Inhaled Corticosteroids in the Treatment of COPD Planning Meeting</p>

	Sponsored by: Healthmatters Communications, LLC New York
February, 2003	Management of Severe Refractory Asthma: The Role of Anti-TNF $\alpha$ Sponsored by: Centocor Miami, FL
February, 2003	Core Asthma Group Advisory Board Sponsored by: Aventis Las Vegas, NV
March, 2003	American Academy of Asthma, Allergy and Immunology National Institute of Allergy and Infectious Diseases (NIAID) Focus Group Meeting NIH/NIAID Symposium: Roles of epithelium in innate immunity, adaptive immunity and inflammation. Oral abstract session: Airway epithelial cells express multiple members of the B7 family. Dinner symposium: Chair: Evolving concepts in the treatment of asthma: Key insights into current and future therapies. Dinner symposium: IC Pharmacology: The complexities and the reality. Sponsored by: Aventis Oral abstract session: Detection and quantitation of C16 and C18 fatty acid acyl conjugates of triamcinolone acetonide (TAA) in airway epithelial cells using gas chromatography-mass spectrometry. Denver, CO
April, 2003	Elkton Physicians Group “Mechanisms of Asthma and Therapeutics” Elkton, MD
May, 2003	American Association of Immunologists Denver, CO
May, 2003	Upper Chesapeake Health” “Pharmacology of Inhaled Corticosteroids” BelAir, MD
May, 2003	Scientific Concepts Thought Leader Market Research Meeting Sponsored by: Merck Washington, DC
July, 2003	Congress on Inhaled Corticosteroids in the Treatment of Asthma and COPD, Sponsored by: Healthmatters Communications New York, NY
August, 2003	COPD Basic Science national Advisory Board Sponsored by: Healthcare Solutions Chicago, IL
July 2004	Daclizumab Asthma Advisory Board Mtg Newport Beach, CA
July 2004	Science of COPD: Opportunities for Combination Therapy Mtg Sponsored by GlaxoSmithKline Chicago, IL
July 2004	Aventis Pharmaceuticals Core Asthma Group Advisory Board Mtg New York, NY
September 2004	Bi-Annual NIAID Asthma and Allergic Diseases Research Centers Mtg, Bethesda, MD
September 2004	The Science of COPD: Opportunities for Combination Therapy Mtg, Sponsored by GlaxoSmithKline Miami, FL
September 2004	Northwestern University Department of Medicine Research Seminar Series: “Cellular and Molecular Mechanisms of Allergic Inflammation in Human Airways” Chicago, IL

January 2005	Northwestern University Department of Pathology Lecture Series “Cellular and Molecular Mechanisms of Allergic Inflammation in Human Airways” Chicago, IL
March 2005	NIH-Center for Scientific Review-LCMI MC SEP Mtg Washington, DC
March 2005	American Academy of Allergy, Asthma & Immunology Mtg Workshop 2718: TLR and Allergic Inflammation “Interactions between innate immune responses and allergic inflammation” San Antonio, TX
March 2005	NIAID Focus Group Mtg San Antonio, TX
May 2005	University of Illinois Department of Pharmacology Research Seminars “Cellular and Molecular Mechanisms of Allergic Inflammation in Human Airways” Chicago, IL
May 2005	Rush University Medical Center Department of Immunology/Microbiology Research Seminar “Roles of Epithelium in Innate Immunity and Inflammatory Responses in the Airways” Chicago, IL
June 2005	Northwestern University Feinberg School of Medicine Grand Rounds “Regulation of Immunity and Inflammation in the Airways by Glucocorticoids” Chicago, IL
June 2005	19 <sup>th</sup> Annual Update: Johns Hopkins Frontiers in Research and Clinical Management of Asthma and Allergy mtg “T Cells: Both the Drivers and the Controllers” “The Emperor has New Clothes: New Considerations in Inhaled Corticosteroids” Baltimore, MD
June 2005	Altana Research Institute mtg Waltham, MA
July 2005	NCCAM: Mind and Body Conference Washington, DC
October 2005	Center for Comparative Respiratory Biology and Medicine Seminar “Regulation of Immunity and Inflammation in Airway Epithelium”, University of California at Davis Davis, CA
October 2005	Food Allergy Project Inaugural Symposium Chicago, IL
November 2005	BioMarck Scientific Advisory Board Meeting Durham, NC
January 2006	Scientific Outside Advisory Board Meeting for the Center for Childhood Asthma in Urban Environment Baltimore, MD
February 2006	Advances in 5-Lipoxygenase (5-L0) Science Meeting Las Vegas, NV sponsored by Critical Therapeutics

February 2006	University of Chicago Small Group Research Seminar Chicago, IL
February 2006	Core Asthma Group 2006 Advisory Board Meeting Sponsored by Sanofi-Aventis and ALTANA Pharm Phoenix, AZ
March 2006	American Academy of Allergy Asthma & Immunology Annual Meeting, STAR Program Symp #1121, Interactive Session, “Research Opportunities for PhDs in Allergy/Asthma Research” Miami Beach, FL
March 2006	AAAAI Annual Meeting, Dinner Symp #1901, “New Findings in Chronic Rhinosinusitis” Miami Beach, FL
March 2006	AAAAI Annual Meeting, Journal Club Seminar “High Impact Publications for Mechanisms of Asthma and Allergic Inflammation” Miami Beach, FL
March 2006	AAAAI Annual Meeting, Symp #3306, “Innate Immunity Modulation for the Treatment of Rhinitis, Sinusitis and Asthma” Miami Beach, FL
March 2006	AAAAI Annual Meeting, Cells & Mediators of Allergic Inflammation Committee Meeting Miami Beach, FL
March 2006	Scientific Specialist National Advisory Board Sponsored by GlaxoSmithKline Miami, FL
April 2006	4 <sup>th</sup> Annual Pittsburgh International Lung Conference “Regulation of Inflammation and Immunity in the Airways by Glucocorticoids” Pittsburgh, PA
June 2006	Michael Reese Hospital Medical Grand Rounds “Regulation of Immunity and Inflammation in the Airways by Glucocorticoids” Chicago, IL Chicago, IL
June 2006	Merck & Co National Respiratory Experts Forum Chicago, IL
July 2006	ICS/LABA Slide Development Working Group Mtg Sponsored by AstraZeneca Denver, CO
September 2006	Northwestern Univ Dept of Microbiology-Immunology Retreat Lake Geneva, WI
September 2006	Genentech Inc/Novartis Pharmaceuticals Corp: Xolair Disease Modification Advisory Board Meeting Chicago, IL
October 2006	Jos A Kwasman Mem Grand Rounds at the Univ of Rochester Rochester, NY
November 2006	The American College of Allergy, Asthma & Immunology Annual Scientific Meeting “Mechanisms of Corticosteroid Action in the Upper Airway” Philadelphia, PA

November 2006	35 <sup>th</sup> Annual Autumn Immunology Conference Chicago, IL
November 2006	NUFSM Dermatology Grand Rounds /Bench to Bedside “Inflammation, immunity and chronic rhinosinusitis” Chicago, IL
February 2007	American Academy of Allergy Asthma & Immunology Annual Meeting, STAR Program Symp 1181 presentation “Molecular Mechanisms of Allergic Inflammation” San Diego, CA
February 2007	AAAAI STAR Program Abstract Symp 1681, Moderator San Diego, CA
February 2007	AAAAI Annual Meeting oral abstract presentation 4607 “Mechanisms of Chronic Rhinosinusitis” San Diego, CA
April 2007	Xolair Disease Modification Advisory Board Meeting Chicago, IL
May 2007	Illinois Society of Allergy, Asthma & Immunology Annual Business Meeting and Food Allergy Prevention “Allergic Inflammation” Chicago, IL
July 2007	International Eosinophil Society Meeting Session moderator: Viral, Fungal, and Other Diseases Snowbird, UT
August 2007	Duke University SCCOR External Advisory Committee Meeting Durham, NC
October 2007	Core Asthma Group Advisory Board Meeting, sponsor, Aventis Phoenix, AZ
November 2007	Center for Childhood Asthma in the Urban Environment-Scientific Outside Advisory Board Meeting, Johns Hopkins Univ. Baltimore, MD
November 2007	36 <sup>th</sup> Annual Autumn Immunology Conference Chicago, IL
February 2008	Sepracor Allergy Advisory Board Meeting Boston, MA
March 2008	VentiRx Pharm Mtg “Toll-like Receptors in Allergic Rhinitis” Hilton Chicago Ohare Airport
March 2008	American Academy of Allergy Asthma & Immunology Annual Meeting, STAR Program Symp 1621, Moderator Philadelphia, PA
March 2008	AAAAI Annual Meeting, oral abstract session 3603, Moderator Philadelphia, PA
March 2008	AAAAI Annual Meeting, RSOD Featured Poster Session 585, “B cell-activating factor of the TNF family (BAFF) and a proliferation inducing ligand (APRIL) expression in chronic rhinosinusitis” Philadelphia, PA
March 2008	AAAAI Annual Meeting, Symposium 5306 presentation, “Immune Regulation”, Philadelphia, PA
March 2008	National Jewish Medical & Research Center, Visiting Professor Lecture, “Epithelial Regulation of Inflammation and Immunity” Denver, CO



April 2008	NUFSM invited panel discussion: Secrets of the Well-Funded Chicago, IL
April 2008	Experimental Biology/American Association of Immunologists Meeting, San Diego, CA
April 2008	NIEHS/Laboratory of Signal Transduction Seminar presentation "Regulation of Inflammation and Immunity by Epithelium" Research Triangle Park, NC
May 2008	University of Iowa Asthma Center Conference guest speaker presentation "Regulation and Inflammation and Immunity in the Airways by Epithelium", Iowa City, IA
May 2008	AAAAI Annual Meeting Program Committee mtg Hilton Chicago Ohare Airport
June 2008	Core Asthma Group Advisory Board Meeting, Aventis, Chicago, IL
June 2008	Thomas L. Petty Aspen Lung Conference Presented- Giles F. Filley Lecture "The Epithelium: Not Just an Innocent Bystander" at Given Istitute, Aspen, CO
June 2008	Feinberg School of Medicine- Immunology-Transplantation- Infectious Disease Mini-Retreat, Chicago, IL
September 2008	Boston City Wide Allergy-Immunology Rounds Presented "Regulation of inflammation and immunity in the Airways by epithelium", Boston, MA
November 2008	Duke University SCCOR External Advisory Committee Meeting Durham, NC
November 2008	37 <sup>th</sup> Annual Autumn Immunology Conference, Chicago, IL
December 2008	CNTO 3157 Advisory Board Mtg – Centocor Inc. Philadelphia, PA
February 2009	Recent Advances in the Pathophysiology of Allergic Disease mtg, sponsor: sanofi-aventis, Miami, FL
March 2009	AAAAI Annual Meeting, FIT Program Symp 1011 presentation, "Airway Mucosal Immunity" Washington, DC
March 2009	AAAAI Annual Meeting, STAR Program Symp 1021 presentation, "Mechanisms of Action of Glucocorticoids in the Airways"
March 2009	AAAAI Annual Meeting, STAR Program Symp 1521, Moderator
March 2009	AAAAI Annual Meeting, Workshop 2808 presentation, "Airway Epithelial and Chronic Rhinosinusitis"
March 2009	AAAAI Annual Meeting, Oral Abstract Session 4606, Moderator
April 2009	Rhinology World 2009 Meeting, guest lecturer for mini seminar "Mucosal Innate Immunity & CRS", Philadelphia, PA
May 2009	American Association of Immunologists Meeting, abstract presentation "Regulation and function of newly-recognized IL-1 family cytokines in human bronchial epithelial cells" Seattle, WA
May 2009	Center for Childhood Asthma in the Urban Environment-Scientific Outside Advisory Board Meeting, Johns Hopkins Univ. Baltimore, MD
July 2009	27 <sup>th</sup> Annual Aspen Allergy Conference at Given Institute, lecture presentation "Inflammation in chronic sinusitis", Aspen, CO
October 2009	Sixth Annual Respiratory Disease Young Investigators Forum,

	presentation- “Studies of chronic rhinosinusitis that illustrate the value of collaboration between PhD and MD scientist” Phoenix, AZ
November 2009	19 <sup>th</sup> Annual Johns Hopkins Asthma and Allergy Center Fall Symposium, presentation- “Inflammatory and immune responses in the upper airways and sinuses of humans”, Baltimore, MD
January 2010	Case Western Reserve University 2009-10 Seminar Series, presentation- “Studies of the human immune response in the upper airways”, Cleveland, OH
January 2010	Duke University SCCOR External Advisory Committee Meeting Durham, NC
January 2010	Childrens Hospital Medical Center Allergy Conference, presentation- “Inflammation and immune responses in the upper airways and sinuses of humans”, Cincinnati, OH
January 2010	MedImmune Inc Research Meeting, presentation- “Studies on the pathogenesis of chronic rhinosinusitis and identification of possible therapeutic targets”, Gaithersburg, MD
February 2010	AAAAI Annual Meeting, Discussion Leader, Seminar 2013 “Epithelial-derived cytokines in allergic airway inflammation”, New Orleans, LA
February 2010	AAAAI Annual Meeting, Symposium 3305 presentation, “Defects in epithelial barrier function in CRS”
February 2010	AAAAI Annual Meeting, Moderator, Symposium 4305
April 2010	Center for Childhood Asthma in the Urban Environment Advisory Board Meeting, Baltimore, MD
May 2010	American Association of Immunologists Meeting, abstract presentation “Local autoantibodies in chronic rhinosinusitis (CRS) with nasal polyps, Baltimore, MD
May 2010	Symposium on Infection and Immunity, University of Chicago Committee on Immunology, Chicago, IL
June 2010	AAAAI Annual Meeting Program Committee meeting, Hilton Chicago Ohare Airport
June 2010	2010 Lung Research Symposium, presentation- “Studies of inflammation and immunity in the upper airways of humans” Chicago, IL
August 2010	Grand Rounds at St. Joseph’s Hospital, lecture presentation “Studies on the pathogenesis of chronic rhinosinusitis” Chicago, IL
September 2010	GSK Respiratory CEDD Board Meeting, Philadelphia, PA
October 2010	Scientific Advisory Board Mtg, Chemocentryx Inc, Mountain View, CA
November 2010	Molecular & Cellular Biology Fall Seminar at Univ of Maryland- College Park, lecture presentation “Immune and inflammatory responses in the upper airways of humans” College Park, MD
November 2010	AAAAI Program Committee Abstract Review Meeting Washington, DC
November 2010	Pulmonary Research Conference-Ohio State University, lecture presentation “Studies of inflammation and immunity in the upper airways of humans”, Columbus, OH

December 2010	Pittsburgh International Lung Conference at University of Pittsburgh, lecture presentation “Studies on inflammation and immunity in the human upper airways”, Pittsburgh, PA
January 2011	WSAAI 49 <sup>th</sup> Annual Scientific Session, two lecture presentations “Of shrimp and mites: Roles of chitins in allergic disease”; “Epithelium, inflammation and immunity in the upper airways: Studies in chronic sinusitis”, Maui, Hawaii
February 2011	Human Genome Sciences Inc, invited external speaker “BAFF in asthma and chronic allergic rhinosinusitis”, Rockville, MD
February 2011	Guest speaker at Regeneron Pharmaceuticals Mtg, Tarrytown, NY
March 2011	AAAAI Annual Meeting, Moderator, 2701 Keynote Session “Polyvalen DNA: A new paradigm in molecular diagnostic and intracellular gene regulation”, San Francisco, CA
March 2011	AAAAI Annual Meeting, speaker, 3101 Plenary Session, presentation “Dysregulation of the immune barrier in chronic rhinosinusitis” (2011 Elliott Middleton Memorial Lectureship recognition)
April 2011	The 50 <sup>th</sup> Annual Swineford Allergy Conference at Univ of Virginia Guest speaker presentation “What is the “it is” in sinusitis?” Charlottesville, VA
April 2011	Mayo Clinic Internal Medicine Grand Rounds, presentation “Studies on the pathogenesis of chronic sinus disease”, Scottsdale, AZ
April 2011	Mayo Clinic Science of Medicine Research Seminary, presentation “Regulation of inflammation and immunity in the airways by glucocorticoids”, Scottsdale, AZ
May 2011	American Association of Immunologists (AAI) Meeting, San Francisco, CA
June 2011	AAAAI Annual Program Committee (AMPC) Mtg, Hilton Chicago Ohare Airport, IL
October 2011	Center for Childhood Asthma in the Urban Environment Advisory Board Meeting, Baltimore, MD
October 2011	The New York Asthma & Allergy Teaching Day, presentation “Studies on the Pathogenesis of Chronic Rhinosinusitis” Cornell Univ, New York, NY
November 2011	AAAAI Annual Program Committee (AMPC) Mtg, Hilton Chicago Ohare Airport, IL
March 2012	AAAAI Annual Meeting, 1011 FIT Symposium, presentation “Allergic and Non-Allergic Mechanisms Contributing to Upper Airway Inflammation”, Orlando, FL
March 2012	AAAAI Annual Meeting, 1604 NIAID Afternoon Course, presentation “Innate and Adaptive Immune Responses in Chronic Upper Airway Inflammation”, Orlando, FL
April 2012	Johns Hopkins Univ Asthma & Allergy Research Center, presentation “Studies of inflammation and immunity in chronic rhinosinusitis”, Baltimore, MD
May 2012	American Association of Immunologists (AAI) Meeting, Boston, MA
June 2012	Medical College of Wisconsin Allergy Grand Rounds presentation “Immune and Inflammation Responses in Chronic Rhinosinusitis”

June 2012	AAAAI Annual Program Committee (AMPC) Mtg, Hilton Chicago Ohare Airport, IL
July 2012	NU-IGP Course: Introduction to Translational Research, presentation to students, Chicago, IL
September 2012	Univ of Illinois Hospital and Health Sciences System Conference: Translational Approaches to Reducing Health Disparities in Lung Disease. Co-chair for Session V-Airway Diseases.
November 2012	Univ of California-Davis CCRBM Research Seminar, presentation “Studies on Inflammation and Immunity in the Upper Airway of Humans”, Davis, CA
November 2012	GSK Respiratory CEDD Board Meeting, Philadelphia, PA
January 2013	Second Allergy Drug Discovery & Development Conference, presentation “Mechanisms of pathogenesis in chronic sinus disease” San Diego, CA
February 2013	AAAAI Annual Meeting, speaker, 1205 AERD session “Pathophysiologic lessons: Studies from aspirin tolerant and Intolerant rhinosinusitis and nasal polyps”, San Antonio, TX
February 2013	AAAAI Annual Meeting, speaker, 1201 TIGERS session “CS”, San Antonio, TX
May 2013	GSK Respiratory CEDD Board Meeting, Philadelphia, PA
June 2013	MERCK Chronic Rhinosinusitis Scientific Input Engagement Meeting, presentation “Pathophysiology/Hot targets”, Newark Hilton, NJ
August 2013	Washington Univ Clinical Allergy for the Practicing Physician, presentations “Adaptive immunity, autoimmunity & AERD (Samter’s Triad)”, “Innate immunity and tissue remodeling in chronic rhinosinusitis”, St. Louis, MO
October 2013	GSK Respiratory CEDD Board Meeting, Philadelphia, PA
November 2013	8 <sup>th</sup> Annual Nemaclin Asthma Conference, presentation “Inflammation, immunity and remodeling in chronic rhinosinusitis” Farmington, PA
December 2013	GSK Respiratory CEDD Board Meeting, Philadelphia, PA
February 2014	Scientific Advisory Committee Review for the Cincinnati Childrens Hosp Med Ctr, Cincinnati, OH
February 2014	AAAAI Annual Meeting, speaker, Plenary Session 3101 Integrated Airways, “Host defense, inflammation and remodeling in the upper airway”, San Diego, CA
March 2014	Mayo Clinic Tackling Problematic Chronic Rhinosinusitis: A Conclave of Global Experts Conference, presentations “Remodeling in nasal polyp disease”, “B-cell targets”, Phoenix, AZ
May 2014	Geo Washington Univ Review of K12 Genomics Lung Scholars & research seminar presentation “Inflammation, immunity and remodeling in the upper airways of humans”, Washington, DC
July 2014	GSK Respiratory CEDD Board Meeting, Philadelphia, PA
September 2014	Greater Washington Asthma, Allergy & Immunology Society, presentation “New perspectives on the pathogenesis of chronic rhinosinusitis”, Bethesda, MD

October 2014	Asthma & Allergic Diseases Cooperative Research Centers Steering Committee (AADCRC) mtg, Bethesda MD (invited for PPG grant presentations)
February 2015	Sanofi Advisory Board Meeting, presentation “Overview of CRS Pathogenesis”, Newark, NJ
February 2015	AAAAI Annual Meeting, Session #1608 Aspirin-Exacerbated Respiratory Disease (AERD): Molecular Pathogenesis, presentation “Activation of the Innate and Adaptive Immune Systems in Nasal Polyposis”, Houston, TX
March 2015	Mayo Clinic Tackling Problematic Sinonasal Disease: Debates & Consensus, presentations “The 3D Global View CRS Pathophysiology”; “AERD: Investigations in Epidemiology and Pathogenesis”; “Future Targets in CRS Management”; “Bridging the Gaps Between the Lab and the Clinic: The Keys to Advancing in the CRS Research Field”, Phoenix, AZ
April 2015	National Jewish Health DOM Accomplished Scientist Speaker Program, presentation “Inflammation and remodeling in upper airways and sinuses of humans”, Denver, CO
May 2015	American Association of Immunologists (AAI) Immunology 2015 Meeting, New Orleans, LA
June 2015	American Rhinology Society 2015 FOCIS Mtg, presentation “The Big Picture”, San Diego, CA
May 2015	Mepolizumab Asthma Mock Advisory Committee Meeting, Research Triangle Park, NC
June 2015	AAAAI Annual Program Committee (AMPC) Mtg, Hyatt Regency Ohare Airport, Chicago, IL
July 2015	International Eosinophil Society 9 <sup>th</sup> Biennial Symposium, presentation, “State of the art: Role of eosinophils in chronic rhinosinusitis”, Chicago, IL
July 2015	Aspen Allergy Conference, presentation “Sinusitis Pathogenesis”, Aspen, CO
October 2015	ADRN External Scientific Advisory Committee Meeting, Rockville, MD
November 2015	Asthma and Allergic Diseases Cooperative Research Centers Steering Committee meeting, Rockville, MD
December 2015	University of Chicago Research Talk, presentation “Inflammation and remodeling in the human upper airways”, Chicago, IL
December 2015	Rush University Med Ctr Research Talk, Chicago, IL

#### **Invited Lectures/Meetings (International )**

May, 1992	19th Symposium of the Collegium Internationale Allergologicum. Capri, Italy
June, 1992	Eosinophils 92 Conference. Sponsored by UCB Pharma and Pfizer Labs. Limerick, Ireland

August, 1992	8th International Congress on Immunology. New Trends in Immunological Activities in Glucocorticoids. Chairman, Special Satellite Budapest, Hungary
September, 1992	"Asthma IV" Conference Bermuda
January, 1993	The first international collegium on Advances in Asthma. Sponsored by Rhone-Poulenc Rorer International. Cancun, Mexico
February, 1994	National Children's Hospital Tokyo, Japan
February, 1994	Yamanouchi Pharmaceutical Tsukuba, Japan
February, 1994	Japan-Korea Allergy Society Meeting Utsunomiya, Japan
February, 1994	Tohoku University Sendai, Japan
March, 1994	Eosinophils and Basophils Chairpersons: Drs. Gleich and Lichtenstein Cabo San Lucas, Mexico
March, 1995	Allergy/Asthma Advisory Committee Sponsored by Rhone-Poulenc Rorer International Paris, France
June, 1995	Asthma - The Important Questions 3 Athens, Greece
September, 1995	1st Astra Draco Annual Research Seminar Sponsored by Astra Draco, Sweden Lund, Sweden
October, 1995	Glucocorticosteroid Resistance - Workshop Sponsored by Astra Draco, Sweden London, England
April, 1996	The Japanese Society of Allergology Spring Meeting of the 8th Japanese Congress of Allergology "Molecular biological approach on steroid treatment" Yokohama, Japan
May, 1996	Allergy and Asthma Advisory Committee Board Sponsored by Rhone-Poulence Rorer, Inc. Paris, France
June, 1996	International symposium on "Eosinophils in Allergic Inflammation and Parasitic and Infectious Diseases" "Eosinophils and glucocorticoids" Rio de Janeiro, Brazil
July, 1996	Workshop entitled "Efficacy and Safety of Inhaled Steroids" "Chemokines and other epithelial-derived leukocyte chemoattractants as targets of inhaled glucocorticoid actions" Sponsored by: Astra Draco, Sweden and Astra USA St. James, Antigua
December, 1996	Inspiraplex workshop on "Viruses and Glucocorticoids" "Steroids in asthma: What are the issues?" Sponsored by: Inspiraplex Network Vancouver, Canada
January, 1997	Workshop: "Methods for Comparing the Efficacy and Safety of Inhaled Glucocorticosteroids". "Potency of inhaled glucocorticoids" Brussels, Belgium
April, 1997	2nd Annual Astra Draco Annual Research Seminar Sponsored by: Astra Draco, Sweden Lund, Sweden

May, 1997	Asthma V meeting on "Asthma and Allergic Diseases - Physiology, Immunopharmacology and Treatment"
November, 1997	Naples, Italy McGill University / Meakins-Christie Laboratories "Mechanism of glucocorticoids in asthma" "Chemokines, epithelium and asthma"
February, 1998	Montreal, Canada Chemokines, Eosinophils, and Asthma - Network Centre of Excellence Workshop Sponsored by Merck Frosst, Canada Held at the Le Chateau Bromont Spa "C-C Chemokines - Comparative Studies"
February, 1998	Montreal, Canada "Management of Allergic Rhinitis with Topical Nasal Steroids: Symptomatic Release or Long-term Treatment" Sponsored by Schering-Plough "Mechanisms of Glucocorticoid Action in Allergic Disease"
February, 1998	Sienna, Italy The International Theophylline Symposium '98 Sponsored by The Mitsubishi Chemical Corporation and Nikken Chemicals Co., Ltd. "The role of chemokines and epithelial activation allergic inflammation"
March, 1998	Makuhari, Japan The Many Faces of Airway Inflammation Sponsored by Astra Draco, Sweden "Effects of Inhaled Steroids"
June, 1998	Whistler, Canada Perennial Rhinitis: How to Optimize Management Astra Satellite Symposium at EAACI '98 Sponsored by Astra Draco, Sweden "Future therapies for allergic diseases of the airways"
November, 1998	Birmingham, England Glaxo Asthma Forum Sponsored by Glaxo Wellcome, Nippon "Cellular and Molecular Mechanisms of Glucocorticoid Actions in Asthma"
November, 1998	Tokyo, Japan 3rd Astra Draco Research Seminar - Techniques and Knowledge for the 21st Century Sponsored by Astra, Sweden Lund, Sweden
December, 1998	Internet World Congress Novel Cellular and Molecular Mechanisms in Allergic Inflammation Chaired by: Judah A. Denburg, M.D., FRCP "Effects of Corticosteroids"
February, 1999	Cytokine and Chemokine Receptor Workshop Sponsored by Merck-Frosst Canada, Inc. "Chemokines in Allergic Inflammation"
March, 1999	Ste-Adele, Quebec Allergy 2000 - State of the Art "Management of Allergic Rhinitis in the New Millenium: "The role of cytokines in allergic disease. "Future therapies for allergic disease. "Mechanisms of action and use of topical nasal steroids for the management of allergic rhinitis" Sponsored by: The Royal College of Otolaryngology of Thailand and Schering-Plough, Thailand

March, 1999	Private Practice: Pediatricians Study Group “The role of cytokines in allergic diseases” Hong Kong
March, 1999	The Hong Kong Otorhinolaryngological Society “Potential use of cytokines and cytokine antagonists in allergic rhinitis” Hong Kong
March, 1999	Singapore Society of Otorhinolaryngology and Schering-Plough, Malaysia “Mechanisms of action and use of topical nasal steroids for the management of allergic rhinitis” Phuket, Thailand
May, 1999	International Seretide Launch meeting Sponsored by: Glaxo Wellcome Berlin, Germany
October, 1999	Eosinophil 1999 - An International Symposium on Eosinophil Biology in Health and Disease Sponsored by: AstraZeneca, Schering Plough, Pharmacia and Upjohn “Regulation of epithelial expression of eosinophil-active chemokines by cytokines and glucocorticoids” Lund, Sweden
March, 2000	IX International Respiratory Forum meeting Royal College of Surgeons Sponsored: GlaxoWellcome Research and Development Chairman and speaker “The scientific basis for a complementary approach to asthma treatment” London
May, 2000	7th Annual Allergy Fellows Symposium “The role of chemokines in allergic diseases” Toronto, Canada
May, 2000	23rd Collegium Internationale Allergologicum meeting Allergy in the 21st Century: New Answers to Old Questions Hakone, Japan
July, 2000	Schering-Plough Aerius Advisory Board Meeting Lisbon, Portugal
October, 2000	17th International Congress of Allergology and Clinical Immunology Sponsored by: Pharmacia Allergy Research Foundation “T cells and epithelial chemokines” Sydney, Australia
February, 2001	4 <sup>th</sup> Annual Meakins-Christie Workshop – The Pathogenesis of Asthma and COPD: Current and Future Aspects. Invited by: Qutayba Hamid, M.D. Montreal, Canada
March, 2001	Control through Synergy: Special Issues Advisory Board Sponsored by: GlaxoSmithKline London, England
April, 2001	Control through Synergy: Special Issues Advisory Board Sponsored by: GlaxoSmithKline Nice, France
May, 2001	The XXth Congress of the European Academy of Allergology and Clinical immunology Sponsored by: EAACI Berlin 2001 “Inflammatory cell trafficking: Adhesion molecules” Berlin, Germany
June, 2001	Preclinical Collaborators Workshop: “Long-acting $\beta$ 2-agonist/ corticosteroid interactions” Sponsored by: GlaxoSmithKline



August, 2001	Amsterdam, Netherlands Respiratory Speakers Summit Sponsored by: GlaxoSmithKline “Scientific Update” Vancouver, Canada
January, 2002	Rhinitis Advisory Board Meeting Sponsored by: AstraZeneca Westin Rio Mar Beach Resort Rio Grande, Puerto Rico
February, 2002	5 <sup>th</sup> Annual Meakins-Christie MUHC Research Institute Workshop Pathogenesis and Treatment of Asthma Sponsored by: Merck Frosst, 3M Canada, GSK, AstraZeneca. “Epithelium and allergic inflammation of the airways” Bromont, Quebec, Canada
February, 2002	Seretide Launches Sponsored by: SmithKline International “Combination therapy for bronchial asthma” El Salvador and Honduras
September, 2002	Western Medical Society Sponsored by: GlaxoSmithKline “Advances in asthma therapy” (CME accredited presentation) Kingston, Jamaica “Advances in asthma therapy” (CME accredited presentation) Mandaville, Jamaica “Advances in asthma therapy” (CME accredited presentation) Montego Bay, Jamaica
November, 2002	2002 CIA Symposium 24 <sup>th</sup> Symposium of the Collegium internationale Allergologicum Sponsored by: Aventis, ALK-Abello and Sepracor “On the central role for epithelium in immune and inflammatory responses in the airways” Bermuda
December, 2002	BSI/BSACI Joint Congress Society’s Annual Congress “Mechanisms of glucocorticoid actions in asthma: airway epithelium as an important target” Harrogate, North Yorkshire, London
December, 2002	Kyoto Hakka Symposium Latest Developments in Clinical and Basic Research on Mast Cells. “Basophils as important mediators of allergic disease” Tokyo, Japan
February, 2003	6 <sup>th</sup> Annual Meakins-Christie Workshop Invited by: Qutayba Hamid “Airway epithelium in immunity and inflammation: Montreal, Canada
May, 2003	Asthma and Allergic Diseases (Asthma VI) Invited by: Gianne Marone “Epithelial responses in airway inflammation and immunity” Ischia, Italy
June, 2003	GSK Senior Respiratory Consultants Meeting Sponsored by: GlaxoSmithKline, London
September, 2003	World Allergy Organization Congress – XVIII ICACI “Debate of the day – Is the eosinophil a player or interested bystander in asthma?” “Mechanisms of action in inhaled corticosteroids” Vancouver, Canada
February 2005	8 <sup>th</sup> Annual Meakins-Christie International Workshop

	Montreal, Canada
May 2005	4 <sup>th</sup> Biennial Congress of the International Eosinophil Society mtg “Integration of Inflammation and Innate Immunity in the Airways” Bern, Switzerland
July 2005	British Society for Allergy & Clinical Immunology Mtg (BSACI 2005) “Glucocorticoid Action in Allergic Diseases” Loughborough University, Leicestershire, UK
September 2005	14 <sup>th</sup> Airway Club Meeting in Sendai International Center, Abstract presentation “Glucocorticoids Suppress Inflammation but Spare Innate Immune Responses in Airway Epithelium” Sendai, Japan
October 2005	AllerGen NCE Inc. First Annual Research Conference Plenary Research Symposium: AllerGen: Innovation from Cell to Society Toronto, Ontario, Canada
February 2006	2006 Meakins-Christie International Workshop, lecture presentation- “Recent Advances in Asthma and COPD” Ste-Adele, Quebec, Canada
June 2006	Canadian Society for Immunology lecture presentation- “Innate Immunity and Allergic Disease” Halifax, Nova Scotia
February 2007	10 <sup>th</sup> Annual Meakins-Christie Workshop, lecture presentation- “The Role of Epithelium as an Integrator of Innate and adaptive Immune Responses”, St. Sauveur, Quebec, CANADA
May 2007	AllerGen International Scientific Excellence Advisory Committee Meeting, Toronto, Ontario, CANADA
June 2007	The 19 <sup>th</sup> Spring Meeting of the Japanese Society of Allergology Two lecture presentations: “Epithelium” and “Steroids” Yokohama, Japan
October 2007	Schering-Plough National Advisory Board Meeting Toronto, Ontario, CANADA
February 2008	11 <sup>th</sup> Annual Meakins-Christie Workshop, lecture presentation “Airway epithelium: At the interface between innate and adaptive immunity”, Manoir des Sables, Quebec, CANADA
July 2008	British Society for Allergy & Clinical Immunology Mtg (BSACI 2008), presented Jack Pepys Lecture “The roles of epithelium in the intergration of inflammatory and immune responses in the airways” Loughborough University, Leicestershire, UK
September 2008	COPD-The Important Questions VII COPD and asthma: Similarities and differences Presented “Cellular mechanisms in asthma”, Rome, Italy
November 2008	GSK Respiratory CEDD Board Meeting, London, UK
March 2009	GSK Respiratory CEDD Board Meeting, London, UK
June 2009	The 21 <sup>th</sup> Spring Meeting of the Japanese Society of Allergology Three lecture presentations: “Airway epithelium as a contact point of innate immunity and acquired immunity”, “Innate immunity and COPD” and “ICS treatment and innate immunity”, Gifu, Japan
June 2009	GSK Respiratory CEDD Board Meeting, London, UK
July 2009	6 <sup>th</sup> Biennial International Symposium of the International

September 2009	Eosinophil Society, lecture presentation “Molecular basis of corticosteroid action in eosinophilic disorders”, Bruges, Belgium
October 2009	GSK Respiratory CEDD Board Meeting, London, UK 59 <sup>th</sup> Annual Congress of Japanese Society of Allergology, lecture presentations “The role of epithelium in innate immunity and inflammation in chronic rhinosinusitis”, “Eosinophilic inflammatory responses in the upper airways and sinuses of humans”, Akita, Japan
November 2009	Severe Asthma Expert Panel Meeting, Windsor, UK
November 2009	GSK Respiratory CEDD Board Meeting, London, UK
February 2010	13 <sup>th</sup> Annual Meakins-Christie Workshop, presentation- “Studies of Inflammation and immunity in the upper airways of patients with chronic rhinosinusitis”, Montreal, Canada
February 2010	GSK Respiratory CEDD Board Meeting, London, UK
November 2010	GSK Respiratory CEDD Board Meeting, London, UK
March 2011	GSK Respiratory CEDD Board Meeting, London, UK
May 2011	GSK Respiratory CEDD Board Meeting, London, UK
May 2011	GSK Benlysta for Respiratory Diseases Advisory Board Meeting, London, UK
June 2011	International Eosinophil Society (IES) 7 <sup>th</sup> Biennial Symposium, presentation “Eosinophils and rhinosinusitis”, Quebec City, CANADA
September 2011	GSK Respiratory CEDD Board Meeting, London, UK
November 2011	GSK Respiratory CEDD Board Meeting, London, UK
February 2012	16 <sup>th</sup> Annual Meakins-Christie Workshop on Asthma and COPD, presentation “On the role of B lymphocytes in chronic sinus disease”, Montreal, Canada
April 2012	GSK Respiratory CEDD Board Meeting, London, UK
July 2012	GSK Respiratory CEDD Board Meeting, London, UK
September 2012	GSK Respiratory CEDD Board Meeting, London, UK
November 2012	Second International Allergy, Asthma & Clinical Immunology Conference, lecture presentation “The emerging pathogenesis of chronic rhinosinusitis” Jerusalem, Israel
March 2013	GSK Respiratory CEDD Board Meeting, London, UK
April 2013	Wuhan Nasal Endoscopic Technique & Rhinosinusitis Summit, presentation “Mechanisms of inflammation and Immunity in chronic rhinosinusitis” Wuhan, China
April 2013	TriSpecialty Allergy-Immunology, Otolaryngology & Thoracic Soc Meeting, presentations “Adaptive Immunity, Autoimmunity and CRS”, “Innate Immunity, Tissue Remodeling and CRS”, Vancouver BC
September 2013	52 <sup>nd</sup> Japanese Rhinologic Soc (JRS) Annual Congress, presentation “Inflammation, immunity and remodeling in chronic rhinosinusitis” Fukui City, Japan
October 2013	50 <sup>th</sup> Annual Meeting of the Japanese Soc of Pediatric Allergy & Clinical Immunology, presentations “Mechanisms of Allergy”, “Mechanisms of allergic disease: A celebration of 25 years of collaboration with Japan”, Yokohama, Japan
April 2014	GSK Respiratory CEDD Board Meeting, London, UK
Nov 2014	McMaster Univ Residents Research Day 2014, 3 lectures

	presented, Grand Rounds - 3 <sup>rd</sup> Frederick E. Hargreave Memorial Lecture: "Inflammation, Immunity and Remodeling in Chronic Rhinosinusitis", ENT lecture: "Inflammation, Immunity and Remodeling in Chronic Rhinosinusitis", Allergy Rounds: The Role of Epithelium in Chronic Rhinosinusitis", Hamilton Ontario, Canada
December 2014	GSK Respiratory CEDD Board Meeting, London, UK
February 2015	17 <sup>th</sup> Annual Meakins-Christie International Workshop on Asthma and COPD, Montreal, Canada

## PATENTS/INVENTIONS

Title: Polynucleotides encoding a sialoadhesin family member-2 (SAF-2).  
 Inventors: Bruce S. Bochner, Kristy K. Kikly, Connie L. Erickson-Miller, and Robert P. Schleimer.  
 JHU #: DM-3875  
 United States Patent #: 6,146,845  
 Date awarded: November 14, 2000

Title: Sialoadhesin factor-2 (SAF-2) antibodies.  
 Inventors: Bruce S. Bochner, Kristy K. Kikly, Connie L. Erickson-Miller, Julie A. Abrahamson, and Robert P. Schleimer  
 JHU #: DM-3906  
 Pending as of May, 2002

Title: Inhibition of cytokine generation.  
 Inventors: Robert Schleimer, John Schroeder, and William Kreutner  
 JHU #: DM-3586  
 Schering-Plough #: AL01143K  
 United States Patent #: 6,599,914 B2  
 Date awarded: July 29, 2003

Title: Sialoadhesin family member-2  
 Inventors: Kristine K. Kikly, Connie Lyn Erickson-Miller, Bruce Bochner and Robert Schleimer  
 United States Patent #: 7,214,772 B2  
 Date awarded: May 8, 2007

Title: Sialoadhesin factor-2 antibodies  
 Inventors: Julie A. Abrahamson, Connie L. Erickson-Miller, Kristine K. Kikly, Bruce Bochner, Robert Schleimer and T. Esra Nutku  
 United States Patent Application Publication #: US2008/0213212 A1  
 Date publ: Sept 4, 2008

Title: Sialoadhesin factor-2 antibodies

Inventors: Julie A. Abrahamson, Connie L. Erickson-Miller, Kristine K. Kikly, Bruce Bochner and Robert Schleimer

United States Patent #. 7,557,191 B2

Date awarded: July 7, 2009

Title: Sialoadhesin factor-2 antibodies

Inventors: Julie A. Abrahamson, Connie L. Erickson-Miller, Kristine K. Kikly, Bruce Bochner, Robert Schleimer and T. Esra Nutku

United States Patent Application Publication #. US2010/0056760 A1

Date publ: March 4, 2010

Title: Methods of use of sialoadhesin factor-2 antibodies

Inventors: Julie A. Abrahamson, Connie L. Erickson-Miller, Kristine K. Kikly, Bruce Bochner, Robert Schleimer and Esra Nutku

United States Patent #. 7,871,612 B2

Date awarded: Jan 18, 2011

Title: Peanut Allergy Treatment

Inventors: Daocheng Zhu, Robert P. Schleimer

United States Patent Application#: 13/933,312

Date awarded: Pending

## ACTIVE CONSULTING ACTIVITIES

Founder and Advisory Board Member, Allakos Inc.

Advisory Board Member, Aurasense Therapeutics

Advisory Board Member, Biomarck Therapeutics

Intersect ENT, Inc.

Merck

Sanofi Aventis

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2. Schleimer RP, Benjamini E, Eisele J, Henderson G. Pharmacokinetics of fentanyl as determined by radioimmunoassay. *Clin Pharmacol Exp Ther* 23(2):188-194, 1978.
3. Schleimer RP. Regulatory roles of histamine in the immune system. *Proc Western Pharmacol Soc* 21:145-151, 1978.
4. Schleimer RP, Leung C, Peterson W, Benjamini E. Immunochemical studies on the Enkephalins and Endorphins. *Proc Western Pharmacol Soc* 22:232-241, 1979.
5. Schleimer RP, Benjamini E. Specificity of mouse leukocyte binding to insolubilized histamine. *Proc Western Pharmacol Soc* 22:251-255, 1979.
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# EXHIBIT D

**Materials Considered for the Expert Report of Robert Schleimer, PH.D.**

<b>Description</b>	<b>Begin Bates</b>	<b>End Bates</b>
ARIA Guidelines (2001)	APOTEX_AZFL 0132361	APOTEX_AZFL 0132548
Advair Diskus Prescribing Information	APOTEX_AZFL 0059181	APOTEX_AZFL 0059242
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Declaration of Joachim Maus, MD for Application NO. 10/518,016	MED_DYM_00001334	MED_DYM_00001433

Description	Begin Bates	End Bates
(July 6, 2015)		
Deposition Transcript of Dennis Fuge (April 14, 2016)	N/A	N/A
Deposition Transcript of Donald Accetta (May 6, 2016)	N/A	N/A
Deposition Transcript of Geena Malhotra (April 25, 2016)	N/A	N/A
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