Diagnostic and Therapeutic Targets for Asthma

Cincinnati Children's
Center for Technology Commercialization

TECHNICAL FIELD
Diagnostic and Therapeutic Targets: Asthma (2001-1120, 2002-1220A, 2004-0901)

BACKGROUND
Asthma is a chronic inflammatory disorder and, in genetically susceptible individuals, this inflammation leads to increased airway responsiveness to a variety of stimuli and recurrent airway obstruction. Approximately 5% of adults and 7-10% of children in the U.S. have asthma. Roughly 50% of cases develop before the age of 10 and another 33% before the age of 40. Asthma is the fourth leading cause of morbidity and the number one cause of childhood hospitalizations in the U.S. accounting for 1.6 million emergency room visits and 10 million office visits per year. In 1998, asthma accounted for $11.3 billion in health care costs in the U.S.

Because of the prevalence of asthma and the high cost of treating it, new diagnostic methods and therapeutic targets are particularly beneficial.

TECHNOLOGY
Using microarray analysis, the laboratory of Dr. Marc Rothenberg has identified a set of signature genes for use in the phenotypic evaluation and diagnosis of asthma. From this signature, they noted that genes related to arginine metabolism were prominent among asthma-induced gene transcripts. Additional studies determined that arginase inhibition may be an effective pharmacological target in airway inflammation.

Dr. Rothenberg's laboratory has also discovered a method to reduce an allergic response in asthma patients by regulating expression and/or function of resistin-like molecule beta (RELM-β), a member of a structurally related group of cytokines that have been associated with resistance to insulin and are thus associated with obesity. In turn, obesity is associated with a number of pulmonary abnormalities. The induction of RELM-β by respiratory allergens, such as ovalbumin and Aspergillus funigatus, and by Th2 cytokines IL-4 and IL-13, links the pathogenesis of insulin-resistant obesity and asthma.

Furthermore, in mice challenged with different allergens in different models of allergen-induced asthma, the level of mRNA for RELM-β was consistently elevated. Specifically, DNA microarray analysis revealed that expression of RELM-β in the lungs of mice increased 985-fold when challenged with ovalbumin and 600-fold when challenged with Aspergillus fumigatus antigen, compared to saline-challenged controls. Similar quantitative increases were seen in mRNA and positive correlations with increase in IL-4 and IL-13 were direct in both models.

The Cincinnati Children's Research Foundation is actively seeking a collaborator to help develop these technologies into diagnostic tests or to identify potential therapeutics that target asthma- or allergy-related disorders.

APPLICATIONS
1. **Diagnostic tests**
2. **Therapeutic targets**
3. **Research tools**

ADVANTAGES
- **Use of "signature genes" to diagnose asthma**
- **Identifies multiple unique targets for pharmacological intervention**
- **Identifies a link between obesity and pulmonary abnormalities**

INVESTIGATOR
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STATUS
Patent applications pending.

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THE INVENTOR

Marc E. Rothenberg, MD, PhD
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BACKGROUND

MD, PhD: Harvard Medical School, Cambridge,MA, 1990.
Residency: Pediatrics, Children's Hospital, Boston, MA, 1991-1992.
Fellowship: Immunology / Allergy, Children's Hospital, Boston, MA, 1992-1994;
Hematology / Oncology, Children's Hospital and Dana Farber Cancer Institute, Boston, MA, 1992-1995.
Certification: National Board of Medical Examiners, 1991;
Board of Registration in Medicine, MA, 1992;
American Board of Pediatrics, 1995, 2001;
Ohio State Medical Board, 1997;
American Board of Allergy and Immunology, 1997;
American Board of Pediatrics recertification, 2000.

Dr. Rothenberg investigates the mechanisms of allergic responses especially in mucosal tissues with a primary focus on the gastrointestinal tract. The goal of the research is to develop the best treatment strategy for allergic disorders (especially eosinophilic gastrointestinal disorders (EGIDs) based on mechanism-driven research.

He uses multiple approaches involving analysis of the cellular and molecular processes in vitro and in vivo, often utilizing genetically engineered mice. In addition, several novel models of antigen-driven allergic gastrointestinal disorders have been developed and these provide the experimental framework for identifying mechanisms of disease.

Furthermore, translational research involving several aspects of patient-based research including innovative drug intervention clinical trials, genome wide expression profiling of intestinal tissue, and genetic analysis using candidate gene approaches are underway. For example, early results with humanized anti-IL-5 therapy in patients with EGIDS have revealed a promising role for this new biological modifier, prompting an ongoing placebo-controlled clinical trial.