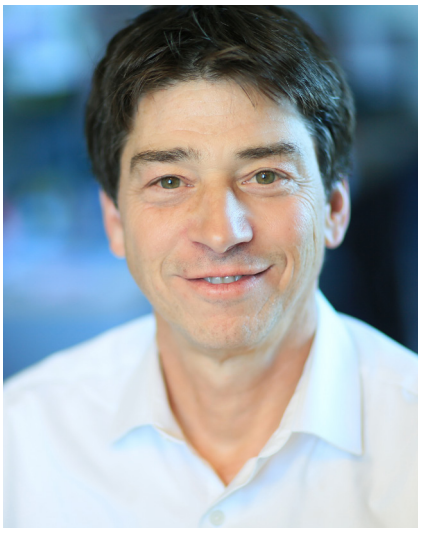
Research Effort by Cincinnati Children's Investigators Helps Enable

First New Class of Asthma Drugs in Over a Decade



Many years of research and testing by physicians and scientists all over the world, with key leadership from Cincinnati Children's Hospital Medical Center and its Division of Allergy and Immunology, contributed to the development of a new class of drugs to help treat severe eosinophilic asthma. On November 4, 2015, the U.S. Food and Drug Administration (FDA) approved the first such drug for use in adolescent (over age 12) and adult patients with high blood eosinophil levels. Subsequently, on March 23, 2016, the FDA approved the second such drug in this class for adults with the same indications. Asthma is one of the most common triggers for pediatric hospitalization, and this new drug class targeting eosinophils has been shown to decrease hospital visits and asthma exacerbations, and is expected to save lives.

GROUNDBREAKING RESEARCH

Marc Rothenberg, MD, PhD, director of the Cincinnati Children's Division of Allergy and Immunology and the Cincinnati Center for Eosinophilic Disorders, and his investigational team are considered pioneers in researching and treating eosinophilic conditions, and substantially contributed to characterizing the cellular and molecular pathway that led to this new class of asthma drugs.

In this pathway, the cytokine interleukin 5 (IL-5), a signaling protein primarily expressed by T cells in asthmatic airways, amplifies the allergic response by promoting cellular inflammation involving a specific pro-inflammatory white blood cell, the eosinophil. Rothenberg and his investigative team have provided repeated evidence that IL-5 directs eosinophil formation, as well as accumulation, survival and activation. The new drugs, mepolizumab (Nucala®) and reslizumab (CINQAIR®), are humanized monoclonal antibodies that neutralize IL-5, blocking eosinophil production and activation and reducing the IL-5-mediated immune response.

In addition to performing basic laboratory studies that established the molecular target for this therapy, Cincinnati Children's also helped conduct clinical trials testing the safety and efficacy of these drugs in patients.

The thirty-year story of the development of this new class of drugs for asthma (see timeline), largely through the efforts of Cincinnati Children's investigators led by Dr. Rothenberg, illustrates the value of Cincinnati Children's approach to and investment in research. Rothenberg's research team has included postdoctoral fellows and graduate and college students from around the world. These scientists, alongside technicians and Cincinnati Children's faculty colleagues including Simon Hogan, PhD, associate professor, and Amal Assa'ad, MD, professor, have all made important contributions to this work. This remarkable journey shows how commitment and persistence can keep a valuable idea alive—in this case, a path to better treatments for patients suffering from diverse eosinophilic disorders.

CONTACT US

To speak with a member of the program directly, please call.

Phone: **513-636-2233**

www.cincinnatichildrens.org/eosinophils

RESEARCH TIMELINE

1988 As a PhD candidate at Harvard, Rothenberg identifies a family of eosinophil-directed immune hormones (cytokines, including IL-5, previously described in mice) involved in regulating eosinophil development and cellular survival. Rothenberg is the first to identify the role of IL-5 in human disorders, demonstrating that an IL-5-mediated cytokine regulatory immune response is over-produced in hypereosinophilic syndromes (HES).

EARLY 1990s Simon Hogan, PhD, Associate Professor at Cincinnati Children's, while a PhD candidate at the Australian National University, provides evidence through antibody neutralization and gene deletion technologies that IL-5 blockade is beneficial in experimental asthma.

MID-1990s Compelling evidence of the likely utility of IL-5 blockade in the treatment of asthma leads pharmaceutical companies to develop humanized monoclonal antibodies to neutralize IL-5.

1999-2000 The study of 24 asthma patients treated with anti-IL-5 antibody shows no improvement; the asthma "eosinophil hypothesis" is questioned amid criticism that animal/mouse models may not relate to human disease.

2001 Believing the 24-patient study inconclusive, the Rothenberg Lab (and others) persist. The Cincinnati Center for Eosinophilic Disorders is formed, as well as patient advocacy groups such as the Campaign Urging Research for Eosinophilic Disease (CURED) and the American Partnership for Eosinophilic Disorders (APFED).

2002 Rothenberg receives an FDA grant to study the impact of anti-IL-5 humanized antibody therapy in select eosinophilic patients; Rothenberg and his colleagues show certain groups of patients benefit significantly. This result renews drug company interest.

2007-2008 Rothenberg and others show through more focused studies that IL-5-neutralizing antibodies are highly effective for treating severe asthma and hypereosinophilic syndrome (HES) in subgroups of patients, such as those with moderate-severe asthma and mildly elevated eosinophil counts.

2009-2012 A series of large-scale Phase III studies show that anti-IL-5 reagents are highly beneficial to severe asthma patients, particularly when relatively high levels of eosinophils are present in the sputum or blood.

2014 Rothenberg becomes the founder and director of the Consortium of Eosinophilic Gastrointestinal Disease Researchers (CEGIR) involving over ten national sites, supported by the NIH Rare Diseases Clinical Research Network with funds from three NIH institutes.

2015, 2016 The FDA approves the first of a new class of asthma drugs (mepolizumab and reslizumab).

THE FUTURE Rothenberg and his colleagues at Cincinnati Children's will continue researching this and other agents targeting multiple eosinophilic diseases, including asthma, eosinophilic esophagitis, eosinophilic gastrointestinal disorders (EGID) and HES.

Note: Dr. Rothenberg receives royalties for reslizumab (Teva Pharmaceuticals).

BRV163493