A brief guide to the

4th CURED EGID Research Conference and Patient Education Program

at the

Cincinnati Center for Eosinophilic Disorders

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Dr. Marc and Joy Rothenberg

Welcome

Welcome to the 4th CURED EGID Research Conference and Patient Education Program. I would like to express my deep gratitude to the CURED Foundation for their partnership in this conference and so many other notable and meaningful endeavors that truly change the outcome, together, for individuals with eosinophilic gastrointestinal disorders and to thank all of the attendees, presenters and sponsors and dedicated organizers who have brought this wonderful community together again for these exciting few days of sharing and learning.

Great strides have been made this year due to the amazing collaboration in of clinical and research professionals and families, as embodied by continuing and diverse projects here at the Cincinnati Center for Eosinophilic Disorders and nationally and internationally with the Consortium of Eosinophilic Gastrointestinal Researchers (CEGIR). For example, the CEGIR observational study is designed to track the outcomes of patients with eosinophilic esophagitis (EoE), eosinophilic gastritis (EG) and eosinophilic colitis (EC) and has now enrolled over 600 patients across 10 leading sites in the USA. This study, called OMEGA for **O**utcome **M**easures for **E**osinophilic **G**astrointestinal Diseases across **A**ges, is providing researchers and clinicians a better idea of the correlation of symptoms to the tissue pathology, helping them to find clues about the disease in the tissue samples and to assess how this information can be used in the future to guide diagnosis and treatment plans. Exciting early data concerning this study are already emerging and will be presented at this meeting.

In closing, I have high hopes for a great conference of learning and sharing and more advances in the years to come.

Marc E. Rothenberg MD, PhD
Professor of Pediatrics
Bunning Chair of Allergy and Immunology
Director, Division of Allergy and Immunology
Director, Cincinnati Center for Eosinophilic Disorders
Cincinnati Children's Hospital Medical Center

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Courtesies

- WiFi "chmc-guest" password "childrens"
- Please silence all electronic devices in the auditoriums and lecture rooms
- The cafeteria of the main hospital is open 24 hours a day
- Transportation: Taxis pick up in location C of the main circle entrance
  Towne Taxi: 513-761-7700, Moe's Taxi Service: 513-332-2862, Uber and Lyft available

The health care providers participating in the conference are committed to the highest standards of safe and ethical care and so are not able to engage in individual consultations or to answer specific questions about the diagnosis or treatment of individual patients at this conference. Thank you for understanding.

About the 4th CURED EGID Research Conference and Patient Education Program

This event is held by the Campaign Urging Research for Eosinophilic Disease (CURED) Foundation in collaboration with the Cincinnati Center for Eosinophilic Disorders and the Consortium of Eosinophilic Gastrointestinal Disease Researchers (CEGIR), which is part of the National Institutes of Health (NIH). The program features renowned international experts on eosinophilic gastrointestinal disorders (EGID) speaking over three days, the first two days being focused on EGID research and the third day on patient and family education. Over 40 abstracts have been accepted for poster presentations with many late breaking discoveries being presented as oral presentations. The agenda is downloadable online at www.regonline.com/cured2017 .

This is the fourth such meeting, and is being attended by nearly 200 individuals from 15 states in the USA, 7 countries and 6 continents. This meeting is expected to be even more successful than past meetings, as eosinophilic disorders have garnered increased understanding and attention, and the program has been extended from two to three days.

Conference Objectives

- Discuss the latest research advances in EGID and their application to patient care
- Present updates on the diagnostic criteria for EGID
- Discuss the psychosocial factors faced by families and patients and how to apply this knowledge to improve disease management
- Discuss therapeutic options and resources for patients who have EGID
- Discuss pathways for drug development

Eosinophilic Gastrointestinal Disorders

Eosinophils are a normal cellular component of the blood and also of certain tissues. When the body wants to attack a substance, such as an allergy-triggering food or airborne allergen, eosinophils respond by moving into the area and releasing a variety of toxins. However, when the body produces too many eosinophils, they can cause chronic inflammation resulting in tissue damage. EGIDs occur when eosinophils are found in above-normal amounts in various parts of the gastrointestinal tract. EGID are chronic disorders, affecting at least 1:1000 people. Current treatment options consist of steroids, humanized antibodies, and/or dietary therapy. Recent research suggests that EGID development occurs through a combination of environmental and genetic factors. Despite off-label usage of approved medicines and active drug development, there are currently no approved drugs for EGID, making this conference timely.

About CURED

The story of the Campaign Urging Research for Eosinophilic Disease (CURED) Foundation in the words of their founders:

> *In January 2003, our daughter, Jori, was diagnosed with Eosinophilic Disease. It took a long time to make that diagnosis. Her red blood levels showed that she was malnourished. She had a lot of stomach aches and nausea. The doctors believed she had Celiac disease. She eventually had an endoscope and when they scoped her they found her stomach filled with inflammation, polyps and severe bleeding.*
>
> *We had no idea where to turn to. So little was, and still is, known about the illness that we spent hundreds of hours researching where to go and what to do. We have found some solace through support groups and our journey has brought some wonderful people into our lives.*
>
> *The one thing we could not grasp was that there is no cure for Eosinophilic disease. And there is little treatment. This has been the hardest part of all – feeling helpless and watching our daughter suffer.*
>
> *And so began our journey of starting a foundation. With energy and determination that we did not know we had, we elicited the help of family and friends. Within a year, CURED was founded. As its name suggests, Campaign Urging Research for Eosinophilic Disease we are committed to finding a CURE for Eosinophilic disease.*
>
> *We are still amazed at the wonderful response we have gotten. We began CURED at our kitchen table in a northwest suburb of Chicago. We now operate fundraisers across the country. And we are still growing thanks to so many people who have shown how much they truly care.*
>
> *Thank you for your support.*
>
> *Ellyn & Fred Kodroff*
>
> *At CURED we pride ourselves on being available to all those suffering from this illness. Whether you are looking to share ideas, stories or just talk contact Ellyn Kodroff at Ellyn@curedfoundation.org*

A few words from Marc E. Rothenberg, MD, PhD, Director of the Cincinnati Center for Eosinophilic Disorders (CCED) and Principal Investigator of the Consortium of Eosinophilic Gastrointestinal Disease Researchers (CEGIR):

> *CURED has been an essential partner for the eosinophil disease community, deeply impacting our understanding and treatment of eosinophilic gastrointestinal disorders and other related conditions.*

Conference Overview

Thursday, October 19

Research Sessions *8:00 AM – 5:00 PM, Research Auditorium (Location R)*
Research-focused presentations and a keynote lecture by Dr. Anne Pariser, deputy director at the Office of Rare Diseases Research, National Center for Advancing Translational Sciences, National Institutes of Health. *No child care will be available

Poster Reception *6:00 PM - 8:30 PM, Sabin Auditorium*
*No child care available

Friday, October 20

Research Sessions *8:00 AM – 5:15 PM, Sabin Auditorium*
Research-focused sessions and keynote lectures by Dr. Ariel Munitz, Department of Microbiology and Clinical Immunology at the Sackler School of Medicine, Tel-Aviv University; Dr. Bruce Bochner, Allergist/ Immunologist at Northwestern Feinberg School of Medicine; and Dr. Joe Selby, executive director of Patient-Centered Outcomes Research-Institute (PCORI). *Child care will be available for pre-registered children

Research Lab Tour *5:15 PM - 6:00 PM, Rothenberg Lab*
Research areas are restricted. Attendees will need to gather at the registration desk in the Sabin Auditorium Atrium between 5:15-5:30 PM and be escorted by Cincinnati Children's staff. *No child care will be available; children are welcome to attend the tour

Saturday, October 21

Patient Education Sessions
Family-focused sessions covering EGIDS diagnosis and therapy, Feeding Problems, Coping with EGID, Pain in EGID/IBD and Nutrition-based presentations for patients and families. *Child care will be available for pre-registered children

Special Event: Family Fun Night! *7:30 PM – 9:30 PM, Kingsgate Marriot*
This is a family-oriented event for all conference attendees. It is a wonderful opportunity to raise funds vital to medical research and meet and greet other families and friends in the EGID community.

Sunday, October 22

Special Event: Closing Breakfast Lecture *9:00 AM – 11:00 AM, Kingsgate Marriot*
Join other families for a closing breakfast on Sunday morning with a special lecture from Dr. Marc Rothenberg, Director, Cincinnati Center for Eosinophilic Disorders.

Conference Agenda

Thursday, October 19, 2017 ***All Topics and Speakers are Tentative***
Research Session I, Research Auditorium

8:00 AM	**Opening Remarks**	*Marc E. Rothenberg, MD, PhD; Cincinnati Children's*
	Welcome	*Ellyn Kodroff, Founder, CURED*

General Features chaired by Noam Zevit, MD; Schneider Children's Medical Center

8:20 AM	**EoE Pearls: 10 Things That I Want You To Know**	*Philip E. Putnam, MD, FAAP; Cincinnati Children's*
8:40 AM	**Guidelines for Diagnosing EoE and Other EGID**	*Margaret H. Collins, MD; Cincinnati Children's*
9:00 AM	**European Experience in EoE**	*Stephen Attwood, MD; University of Durham, UK*
9:20 AM	**EGID Beyond the Esophagus**	*Nirmala Gonsalves, MD; Northwestern University Feinberg School of Medicine*
9:40 AM	**Living with EGID as a Parent**	*Ann Sebastian, Cincinnati, OH*

9:50 AM – 10:10 AM Break

Clinical Features of EGID chaired by Thomas J. Fischer, MD, Cincinnati Children's

10:10 AM	**Clinical Presentation of EoE**	*Amal H. Assa'ad, MD; Cincinnati Children's*
10:30 AM	**Approach to Esophageal Strictures**	*Jonathan Kushner, MD; University Of Cincinnati Medical Center*
10:50 AM	**PPI Responsive Esophageal Eosinophilia**	*Stuart Spechler, MD; Baylor University Medical Center at Dallas*
11:10 AM	**EoE Related Syndromes and Presentations**	*Mirna Chehade, MD; Mount Sinai Hospital*
11:30 AM	**Remodeling, Stiffening and Epithelial Mesenchymal Transformation in the Esophagus**	*Amanda Muir, MD; Children's Hospital of Philadelphia*
11:50 PM	**Late Breaking Award Discovery: Sub-laryngeal Esophageal Tissue Does Not Resemble Mid and Distal Tissue in Patients with Active Eosinophilic Esophagitis**	*Yash Choksi, MD; Vanderbilt University Medical Center*

12:00 PM – 1:00 PM Lunch Research Library and Auditorium

Introduction by Marc E. Rothenberg, MD, PhD; Cincinnati Children's

1:00 PM **Keynote Speaker: Rare Disease Clinical Research Consortium Network**
Anne Pariser, MD, Deputy Director
Office of Rare Diseases Research, National Center for Advancing Translational Sciences (NCATS), National Institutes of Health

Immunology of EoE chaired by Marjorie Walker, MD; University of New Castle, Austrailia

1:25 PM	**EoE and Autoimmunity**	*Kathryn Peterson, MD; University Of Utah School of Medicine*
1:45 PM	**Dissecting the Adaptive Immune System in EoE**	*Antonella Cianferoni, MD, PhD; Children's Hospital of Philadelphia*
2:05 PM	**Dissecting EoE Cell by Cell: Single Cell Analysis**	*Ting Wen, MD, PhD; Cincinnati Children's*
2:25 PM	**Uncovering the Cause of EoE through Big Data/Computational Analysis**	*Bruce J. Aronow, PhD; Cincinnati Children's*
2:45 PM	**Regulation of Eosinophilia by Innate Immunocytes**	*Yui-Hsi Wang, PhD; Sanofi*
3:05 PM	**Effector Functions of Eosinophils**	*Lisa Spencer, PhD; Harvard Medical School*

3:25 PM – 3:50 PM Break

Next Generation Ideas in EGID chaired by Kenneth Kaufman, PhD, Cincinnati Children's

3:50 PM	**Late Breaking Award Discovery: Transcriptional and Epigenetic Signature of IL-13 Response in Esophageal Epithelial Cells**	*Mark Rochman,PhD; Cincinnati Children's*
4:00 PM	**Late Breaking Award Discovery: Raman Microspectroscopy Reveals Distinct Biochemistry of Esophageal Biopsies Obtained from Children with Eosinophilic Esophagitis**	*Girish Hiremath, MD, MPH; Children's Hospital at Vanderilt*
4:10 PM	**Research Through the Internet: Validation of CEGIR Online Registry**	*J. Pablo Abonia, MD; Cincinnati Children's*
4:25 PM	**The Role of Neuroendocrine Cells in the Pathogenesis of EoE**	*Anil Mishra, PhD; Tulane University*
4:45 PM	**Role of Mast Cells in EoE**	*Joshua Wechsler, MD; Lurie Children's Hospital of Chicago*
5:00 PM	**Late Breaking Award Discovery: Deletion of SPINK7 by CRISPR/Cas9 Elicits Pro-inflammatory and Impaired Epithelial Barrier Responses in Esophageal Epithelial Cells**	*Ayushi Jain, BS,MBA; Cincinnati Children's*

Meeting Adjourned

Join us!
Dinner and Poster Reception, Sabin Auditorium 6:00 PM-8:30 PM
(Poster viewing starts at 6:00 PM, Dinner at 6:30 PM, Entertainment at 7:30 PM)

Friday, October 20, 2017
Research Session II, Sabin Auditorium

Introduction by Michael Fisher, CEO; Cincinnati Children's

8:00 AM	**Keynote Speaker: Checkpoints for Regulating and Treating Eosinophilic Disorders including Asthma** *Ariel Munitz, PhD; Department of Microbiology and Clinical Immunology, Tel-Aviv University*

EoE Pathogenesis chaired by Edda Fiebiger, PhD; Boston Children's Hospital

8:25 AM	**Tissue Remodeling in EoE**	*Seema Aceves, MD, PhD; University of San Diego*
8:45 AM	**EGID Microbiome**	*Sophie Fillon, PhD; Children's Hospital Colorado*
9:05 AM	**Overview of EGID Pathophysiology**	*Marc E. Rothenberg, MD, PhD; Cincinnati Children's*
9:30 AM	**Late Breaking Award Discovery: Barrier Impairment in EoE** *Nurit Azouz, PhD; Cincinnati Children's*	
9:45 AM	**Living with EGID as a Family** *Kara Root, Bella Vista, Arkansas*	

9:30 am: Adult Patient Breakout Session
with Dr. Bruce Bochner, MD;*Northwestern University Feinberg School of Medicine*
In Room D2.28 (9:30am-10:05am)

10:05 AM – 10:20 AM Break

EoE Inheritance and Genetic Testing chaired by Eileen King, PhD; Cincinnati Children's Hospital

10:20 AM	**Trends in Epidemiology and Sex (for EGID)**	*Evan S. Dellon, MD, MPH; University of North Carolina School of Medicine*
10:40 AM	**Early Life Risk Factors of EGID**	*Elizabeth Jensen, PhD; Wake Forest School of Medicine*
11:00 AM	**Genetic Risk Factors of EGID**	*Leah C. Kottyan, PhD; Cincinnati Children's*
11: 20 AM	**Gene-Environment Interactions in EGID**	*Lisa J. Martin, PhD; Cincinnati Children's*

Introduction by Glenn Furuta, MD; Children's Hospital Colorado

11:40 PM	**Keynote Speaker: Eosinophil Directed Therapeutic Breakthroughs** *Bruce Bochner, MD; Northwestern University Feinberg School of Medicine*

12:05 PM - 1: 10 PM Lunch and Poster Session, Sabin Atrium & Auditorium

Introduction by Margaret K. Hostetter, MD; Director; Cincinnati Children's Research Foundation

1:10 PM	**Keynote Speaker: Interfacing with Washington**	*Joe V. Selby, MD, MPH; Executive Director, PCORI*

Therapy chaired by Nicholas Talley, MD; University of New Castle, Austrailia

1:35 PM	**Emerging Therapies for EGID**	*Ikuo Hirano, MD; Northwestern University Feinberg School of Medicine*
1:55 PM	**EGID-related Adverse Events of Oral Immunotherapy**	*Yitzhak Katz, MD; Tel Aviv University*
2:15 PM	**Risks and Benefits of Swallowed Glucocorticoids**	*David Katzka, MD; Mayo Clinic*
2:35 PM	**Risks and Benefits of Dietary Therapy**	*Jonathan Spergel, MD,PhD; Children's Hospital of Philadelphia*
2:55 PM	**Late Breaking Award Discover: Dupilumab Efficacy and Safety in Adult Patients With Active Eosinophilic Esophagitis: A Randomized Double-Blind Placebo-Controlled Phase 2 Trail**	*TBA*
3:05 PM	**Late Breaking Award Discovery: Adult eosinophilic esophagitis patients' satisfaction with different disease-specific treatment modalities**	*Ekaterina Safroneeva, PhD; University of Bern, Switzerland*

3:15 PM – 3:30 PM Break

Fighting EGID and Winning chaired by Bruce Aronow, PhD; Cincinnati Children's

3:30 PM	**Moving EoE through the NIH**	*Mike Minnicozzi, PhD; NIH-NIAID*
3:50PM	**Newer and Promising Ways to Assess Disease**	*Sandeep K Gupta, MD; Children's Hospital of Illinois*
4:10 PM	**Late Breaking Award Discovery: Food Elimination Diets are Effective for Long-term Treatment of Adults with EoE**	*Craig C. Reed MD; University of North Carolina School of Medicine*

Clinical Research Studies chaired by Edaire Cheng, MD; University of Texas Southwestern

4:20 PM	**CEGIR Longitudinal Study - OMEGA**	*Glenn T. Furuta, MD; Children's Hospital Colorado*
4:30 PM	**SOFEED Trial (Six vs One Food EoE Diet) Trial**	*Vincent A. Mukkada, MD; Cincinnati Children's*
4:40 PM	**1 Food vs 4 Food Elimination Diet PCORI Trial in EoE**	*Kara L. Kliewer, PhD, RD; Cincinnati Children's*
4:50 PM	**Closing Remarks: Translating Research to Patient Care- Better Treatments and Cure**	*Marc E. Rothenberg, MD, PhD; Cincinnati Children's*
5:00pm	**Rothenberg Lab Tour** – *meet lab tour guides in atrium*	

Saturday, October 21, 2017
Family Session, Sabin Auditorium

8:00 AM	**Welcome**	
8:10 AM	**Eosinophils 101: Why do we have these cells?**	*Bruce Bochner, MD; Northwestern University Feinberg School of Medicine*
8:30 AM	**Types of EoE Overview**	*Seema Aceves, MD, PhD; University of San Diego*
9:10 AM	**Biopsies and Diagnosis of EGID**	*Margaret H. Collins, MD; Cincinnati Children's*
9:50 AM	**Overview of EGID: Diagnosis & Therapy**	*Philip E. Putnam, MD; Cincinnati Children's*
10:20 AM – 10:35 AM Break		
10:35 PM	**Eosinophilic Gastroenteritis and Colitis**	*Robert D. Pesek, MD; University of Arkansas for Medical Sciences*
10:55AM	**Patient Perspective: Living with an EGID** *TBA*	***11:00 am Room D2.22 Alternate Session for Adults with EGID: EGID in Adults*** *Evan S. Dellon, MD, MPH; University of North Carolina*
11:15 AM	**Food & EoE Young Adults Vs. Children** *Bethany Doerfler, MS, RDN; Northwestern Memorial Hospital and Raquel Durban, MS, RD; Division Director Food Allergy Institute at Asthma & Allergy Specialists, PA*	***11:25 am Room D 2.22 Alternate Session for Adults with EGID: EGID in Adults*** *Ikuo Hirano, MD; Northwestern University Feinberg School of Medicine*
11:45 AM	**Feeding Problems in EGIDs – More than just "Food Gets Stuck in my Throat"** *Vincent A. Mukkada, MD; Cincinnati Children's*	***11:50 am Room D 2.22 Alternate Session for Adults with EGID: Diet Selection in Adults*** *Bethany Doerfler, MS, RDN; Northwestern Memorial Hospital and Raquel Durban, MS, RD; Division Director Food Allergy Institute at Asthma & Allergy Specialists, PA*
12:15 PM – 1:15 PM Lunch Sabin Atrium & Auditorium		
1:15 PM	**Individual Education Plans and 504's** *John Price, Attorney at Law, Ohio Disability Rights Law and Policy Center, Inc.*	***1:15 pm Room D 2.22 Alternate Session for Adults with EGID:*** *Personal Chef: Tammy Stafford*
2:00 PM	**Practical Nutritional Aspects of EGID**	*Bethany Doerfler, MS, RDN; Northwestern Memorial Hospital Raquel Durban, MS, RD; Division Director Food Allergy Institute at Asthma & Allergy Specialists, PA*
2:20 PM	**Coping with EGID**	*Nicole E. Zahka, PhD; Cincinnati Children's*
3:00 PM	**Pain in EoE/IBD: Like an Ogre, It's an Onion**	*Kenneth Goldschneider, MD, FAAP; Cincinnati Children's*
3:20 PM – 3:35 PM Break		
3:35 PM	**Measuring Patient Outcomes and Quality of Life**	*Lisa J. Martin, PhD; Cincinnati Children's*
3:55 PM	**How to Build a Stronger Community to Support Research and Each Other: A Foundation Perspective**	*Mrs. Ellyn Kodroff, CURED and Mrs. Shay Kyle, CURED*

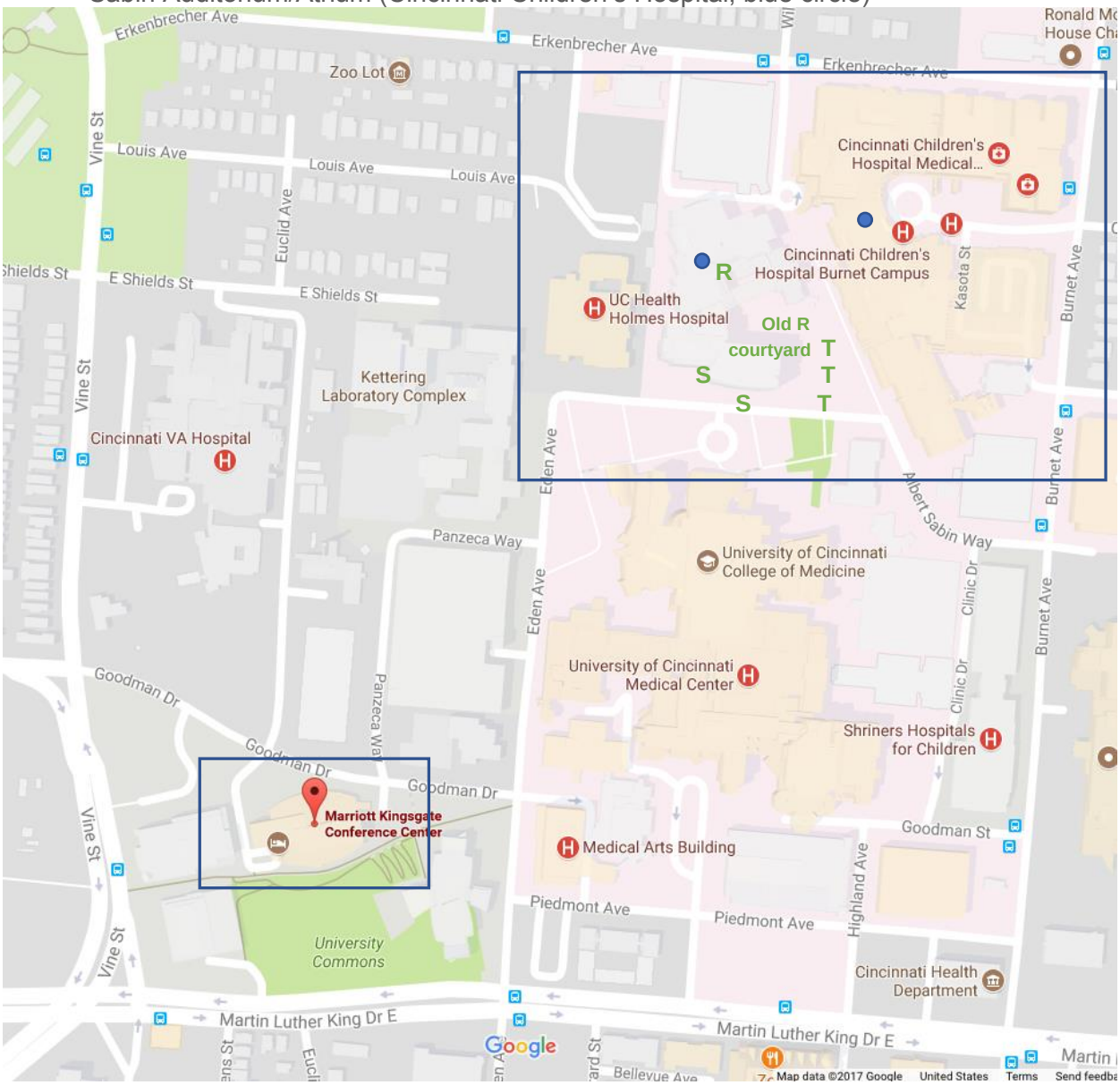
Special Event: Saturday, Oct. 21: Family Fun Night! Kingsgate Marriott 7:30-9:30 PM

This is a family oriented event for all conference attendees. It is a wonderful opportunity to raise funds vital to medical research, and meet and greet families.

Maps and Directions

Area Map

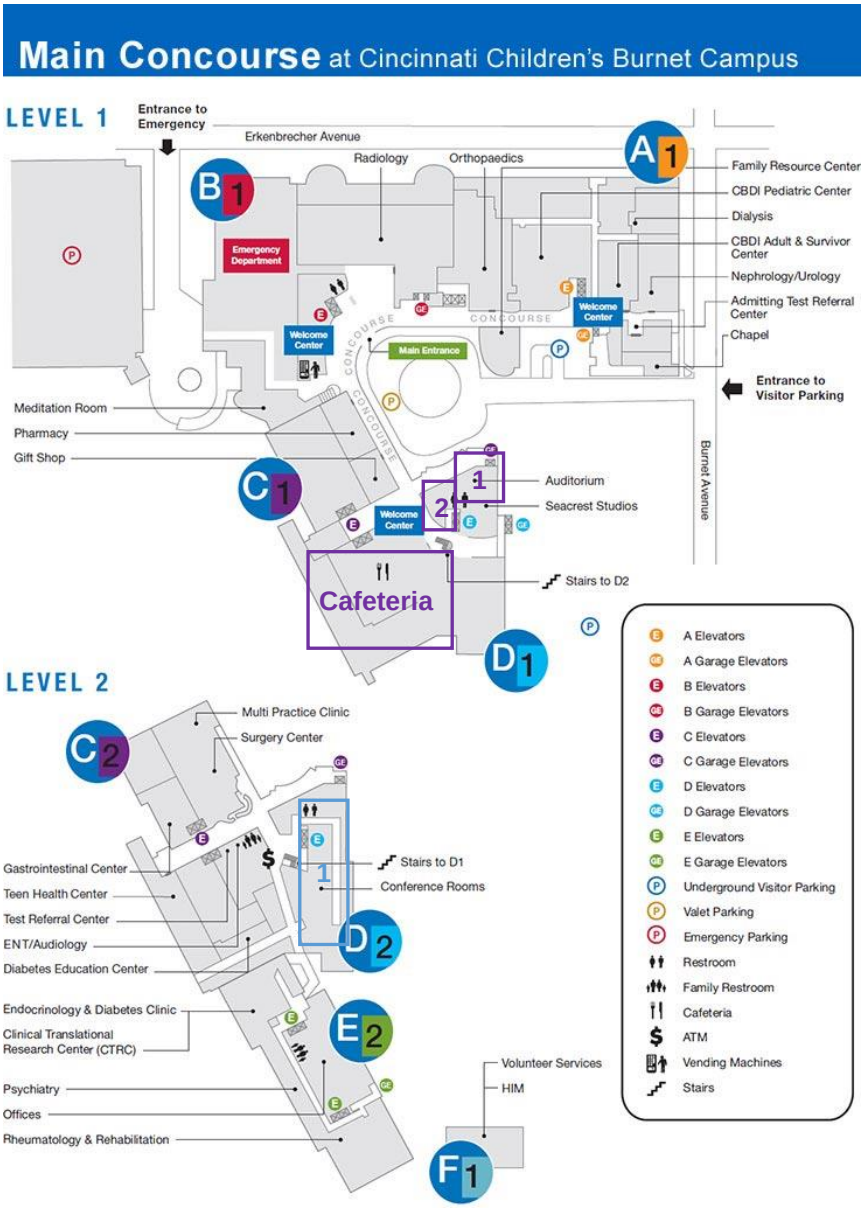
- Kingsgate Marriot Conference Center (small rectangle)
  151 Goodman Drive, Cincinnati, Ohio 45219 USA; Phone: 513-487-3800
- Cincinnati Children's Main Campus (large rectangle)
- Research Auditorium (Location "old" R, blue circle)
- Sabin Auditorium/Atrium (Cincinnati Children's Hospital, blue circle)



Cincinnati Children's Main Campus Map

3333 Burnet Avenue, Cincinnati, OH 45229-3039; Phone: 513-636-4200

- Child Care Location (Main Hospital, D2.23-26, D2.40, blue box 1)
- Break Out Rooms (Main Hospital, D2.22, D2.28, D2.44, blue box 1)
- Sabin Auditorium (purple box 1)
- Sabin Auditorium Atrium (purple box 2)



Special Events

Saturday, October 21

Special Event: Family Fun Night! *7:30 PM – 9:30 PM, Kingsgate Marriot*

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Sunday, October 22

Special Event: Closing Breakfast Lecture *9:00 AM – 11:00 AM, Kingsgate Marriot*

Join other families for a closing breakfast on Sunday morning with a special lecture from Dr. Marc Rothenberg, Director, Cincinnati Center for Eosinophilic Disorders.

Related Articles in *JACI*

A special thank you to the *Journal of Allergy and Clinical Immunology* for providing free access to the following articles about eosinophils and eosinophilic conditions from October through November.

To access these articles, please visit
http://www.jacionline.org/content/collection_cured

Prenatal, intrapartum, and postnatal factors are associated with pediatric eosinophilic esophagitis
Jensen ET, Kuhl JT, Martin LJ, Rothenberg ME, Dellon ES.
J Allergy Clin Immunol. 2017 Jun 7. [Epub ahead of print]

Calpain-14 and its association with eosinophilic esophagitis
Litosh VA, Rochman M, Rymer JK, Porollo A, Kottyan LC, Rothenberg ME.
J Allergy Clin Immunol. 2017 Jun;139(6):1762-1771.e7.
PubMed Central ID: PMC5461191.

TGF-β1-induced PAI-1 contributes to a profibrotic network in patients with eosinophilic esophagitis
Rawson R, Yang T, Newbury RO, Aquino M, Doshi A, Bell B, Broide DH, Dohil R, Kurten R, Aceves SS.
J Allergy Clin Immunol. 2016 Sep;138(3):791-800.e4.
PubMed Central PMCID: PMC5014565.

Transcriptome analysis of proton pump inhibitor-responsive esophageal eosinophilia reveals proton pump inhibitor-reversible allergic inflammation
Wen T, Dellon ES, Moawad FJ, Furuta GT, Aceves SS, Rothenberg ME.
J Allergy Clin Immunol. 2015 Jan;135(1):187-97.
PubMed Central ID: PMC4289084.

Eosinophilic esophagitis: updated consensus recommendations for children and adults
Liacouras CA, Furuta GT, Hirano I, Atkins D, Attwood SE, Bonis PA, Burks AW, Chehade M, Collins MH, Dellon ES, Dohil R, Falk GW, Gonsalves N, Gupta SK, Katzka DA, Lucendo AJ, Markowitz JE, Noel RJ, Odze RD, Putnam PE, Richter JE, Romero Y, Ruchelli E, Sampson HA, Schoepfer A, Shaheen NJ, Sicherer SH, Spechler S, Spergel JM, Straumann A, Wershil BK, Rothenberg ME, Aceves SS.
J Allergy Clin Immunol. 2011 Jul;128(1):3-20.e6

Keynote Speakers

Anne R. Pariser, MD

Deputy Director
Office of Rare Diseases Research,
National Center for Advancing Translational Sciences,
National Institutes of Health, USA

Keynote Lecture: "Rare Disease Clinical Research Consortium Network"

The Rare Diseases Clinical Research Network (RDCRN) was established in 2003 to facilitate rare disease research through the establishment of centers of excellence for rare diseases, including eosinophilic gastrointestinal disorders. The RDCRN consortia conduct rare diseases clinical research, train new investigators, and demonstrate diagnostic and treatment methods for rare diseases. The RDCRN's 15-year history and next steps will be reviewed.

More about Anne R. Pariser, MD

Anne R. Pariser, MD is the deputy director of the Office of Rare Diseases Research at the National Center for Advancing Translational Sciences (NCATS), National Institutes of Health (NIH). Her work includes guiding and overseeing NCATS' Rare Diseases Clinical Research Network (RDCRN), Genetic and Rare Diseases Information Center, and the NIH/NCATS Toolkit for Patient-focused Therapy Development. Before joining NCATS, Dr. Pariser worked for 16 years at the US Food and Drug Administration Center for Drug Evaluation and Research, where she founded the Rare Diseases Program in the FDA CDER's Office of New Drugs in 2010. Dr. Pariser earned her MD from Georgetown University in Washington, DC and is board certified in Internal Medicine. Her research interests include regulatory and translational science development for rare diseases.

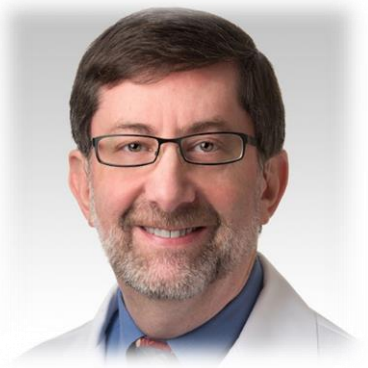
Ariel Munitz, PhD
Associate Professor
Department of Clinical Microbiology and Immunology,
The Sackler School of Medicine,
Tel-Aviv University, Israel

Keynote Lecture: “Checkpoints for Regulating and Treating Eosinophilic Disorders including Asthma”

Eosinophil differentiation, migration and activation are tightly regulated by a balance of activation and inhibitory signals. In this presentation, the role of immunoreceptor tyrosine-based inhibition motif (ITIM)–bearing receptors, such as paired immunoglobulin-like receptor B (PIR-B) and CD300f, in regulating eosinophil migration and activation in the gastrointestinal tract will be described. Specifically, the potential to target such receptors on eosinophils as a new therapeutic strategy will be discussed.

More about Ariel Munitz, PhD

Ariel Munitz, PhD is an Associate Professor in the Department of Clinical Microbiology and Immunology at the Sackler School of Medicine of Tel-Aviv University. He is the head of the MSc Program for Biomedical Research at the Sackler School of Medicine and the Chair of the Ela Kodets Institute for Research in Infectious Diseases. Before joining Tel-Aviv University, he spent three years investigating various aspects of mucosal immunology in the Division of Allergy and Immunology at Cincinnati Children’s. Dr. Munitz has a dedicated interest in the role of inflammation in various diseases affecting mucosal organs, including the lung and gastrointestinal tract. His research focuses on the role of eosinophils in health and disease, with a specific interest in the function of cell surface receptors with the capacity to “shut down” the activation of immune cells and thereby dampen inflammatory processes involving eosinophils. Dr. Munitz and colleagues have shown that these receptors have critical roles in the immune system and are therefore potent pharmacologic targets in asthma, atopic dermatitis, lung fibrosis, colitis and colorectal cancer.



Bruce S. Bochner, MD
Samuel M. Feinberg Professor of Medicine
Division of Allergy and Immunology,
Northwestern University Feinberg School of Medicine, USA

Keynote Lecture: "Eosinophil Directed Therapeutic Breakthroughs"
This talk will describe and compare selective anti-eosinophil therapies that are currently approved, as well as those in various stages of development.

More about Bruce S. Bochner, MD
Bruce S. Bochner, MD is the Samuel M. Feinberg Professor of Medicine in the Division of Allergy-Immunology at the Northwestern University Feinberg School of Medicine. As a physician-scientist devoting >80% effort to NIH-funded research, his overarching research philosophy has been to delineate novel mechanisms of human allergic diseases, working whenever possible with primary human cells and tissues, and at the same time attempting to identify targets that might be amenable to the development of new therapies. His ongoing research work focuses on the function of inhibitory receptors on cells of the immune system. Most of his lab's NIH-funded efforts focus on exploiting and optimizing antibody and sugar-ligand targeting of Siglec-8 on eosinophils and mast cells while exploring natural tissue ligands for this molecule—work that has already identified an important airway source of such ligands. He also uses pharmacology to test disease-related hypotheses in humans. For example, he is testing whether certain drugs, approved for non-allergy related purposes, have the ability to favorably alter mast cell function as a way of preventing food allergy responses. He sees patients with allergic and immunologic conditions, has a particular interest in the diagnosis and treatment of eosinophilic disorders, and is board-certified in both Internal Medicine and Allergy and Immunology.

Joe V. Selby, MD, MPH

Executive Director
Patient-Centered Outcomes Research Institute

Keynote Lecture: "Interfacing with Washington"

This address will cover PCORI's research portfolio as a reflection of the vast need for pragmatic, comparative clinical research; a look at PCORnet as an approach to meeting the needs of payers, health systems, clinicians and patients for research evidence; and how one learns to do patient-centered comparative effectiveness research, including news of a new funding announcement for a training program in this area."

More about Joe V. Selby, MD, MPH

Joe V. Selby, MD, MPH became the first Executive Director of the Patient-Centered Outcome Research Institute (PCORI) in 2011. PCORI's mandate is to improve the quality and relevance of the evidence available in order to help patients, caregivers, employers, insurers and policy makers make informed healthcare decisions. A family physician, clinical epidemiologist, and health services researcher, Dr. Selby has more than 35 years of experience in patient care, research, and administration. He is responsible for identifying strategic issues and opportunities for PCORI and implementing and administering programs authorized by the PCORI Board of Governors. Dr. Selby joined PCORI from Kaiser Permanente, Northern California, where he worked for 27 years and was Director of the Division of Research for 13 years, overseeing a department of more than 50 investigators and 500 research staff members working on more than 250 ongoing studies. His publications cover a spectrum of topics, including effectiveness studies of colorectal cancer screening strategies; treatment effectiveness, population management, and disparities in diabetes mellitus; primary care delivery; and quality measurement.

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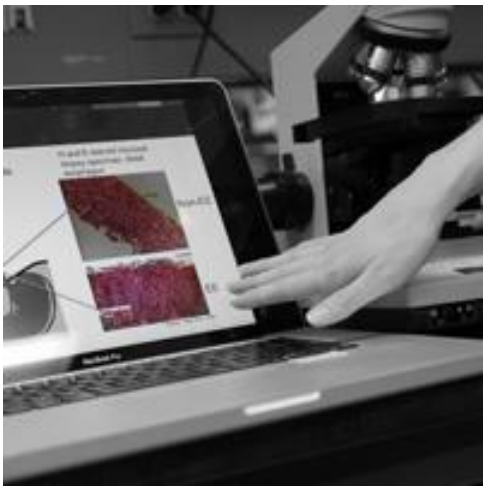

Abstracts

Awards Committee

A special thank you to the awards committee members for their service and all the poster presenters for sharing their valuable research.

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Awards

Awardees present their findings as late-breaking discoveries. The awardees are listed below alphabetically by the first author's last name.

Nurit P. Azouz, PhD
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Loss of esophageal epithelial SPINK7 unleashes uncontrolled proteolytic activity, impaired epithelial Barrier, defective differentiation and pro-inflammatory cytokine production (page 29)

Yash Choksi, MD
Vanderbilt University Medical Center, Nashville, TN
Sub-laryngeal esophageal tissue does not resemble mid and distal tissue in patients with active eosinophilic esophagitis (page 41)

Ikuo Hirano[1], Evan S. Dellon[2]
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Dupilumab Efficacy and Safety in Adult Patients With Active Eosinophilic Esophagitis: A Randomized Double-Blind Placebo-Controlled Phase 2 Trial (page 50)

Girish Hiremath, MD, MPH
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Raman Microspectroscopy Reveals Distinct Biochemistry of Esophageal biopsies Obtained from Children with Eosinophilic Esophagitis (page 38)

Ayushi Jain, BS, MBA
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Deletion of SPINK7 by CRISPR/Cas9 elicits pro-inflammatory and impaired epithelial barrier responses in esophageal epithelial cells (page 46)

Craig C. Reed, MD
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Food Elimination Diets are Effective for Long-term Treatment of Adults with Eosinophilic Esophagitis (page 31)

Mark Rochman, PhD
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Transcriptional and epigenetic signature of IL-13 response in esophageal epithelial cells (page 33)

Ekaterina Safroneeva, PhD
Institute of Social and Preventive Medicine, University of Bern, Switzerland
Adult eosinophilic esophagitis patients' satisfaction with different disease-specific treatment modalities (page 26)

Abstracts

Mitochondrial dysfunction in Eosinophilic Esophagitis; a tale from Whole-exome sequencing

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Background: Eosinophilic esophagitis (EoE) is T helper type 2 (Th2) mediated chronic allergic disorder of the esophagus which histologically presents ≥15 eosinophils per high power field (eos/hpf). Genome-wide association studies (GWAS) have revealed association of the common genetic variants at chromosomes 2p23 and 5q22 with EoE and recent genetic studies have identified calpain14 (*CAPN14*) as a gene that contributes to the risk of EoE. However, there have been limited advancements in identifying causal rare variants in EoE, particularly those that alter protein function. Herein, we utilized whole-exome sequencing (WES) to identify rare mutations predicted to damage protein function. Interestingly, WES revealed enrichment in rare damaging variants in dehydrogenase E1 and transketolase domain containing 1 (DHTKD1), a nuclear gene affecting mitochondrial function.
Methods: Whole-exome sequencing was performed on 61 patients with EoE and 63 unaffected family members using Illunima TruSeq library preparation followed by Illunina Hiseq200 sequencing. Using minor allele frequency (MAF) of <0.01 in the European ancestry population from 1,000 Genome Project as a cutoff, rare variants were filtered which were further subjected to a MAF threshold of <0.05 to define rare compound heterozygous variants. Sanger sequencing was used to validate *DHTKD1* variants. Whole genome profiling was done using RNA-sequencing. Lentiviral based shRNA system was utilized for gene silencing in esophageal epithelial (EPC2) cells which were grown using Air Liquid Interface (ALI) 3-D model. Mitochondrial functions were assessed using Seahorse XF Cell Mito Stress Test Kit.
Results: WES identified 10,725 rare putatively damaging variants in EoE patients including a novel nonsense (2500 C>T, p. Arg834*) and a predicted splicing mutation (1897 G>A) in *DHTKD1*. Rare variant burden analysis revealed an overabundance of putative, potentially damaging DHTKD1 mutations in EoE (p=0.01). Interestingly, functional studies showed that Arg834* mutation causes non-sense mediated decay (NMD) of C>T harboring *DHTKD1* transcript. Additionally, shRNA mediated silencing of *DHTKD1* in EPC2 cells showed there were considerable changes in mitochondrial function. *DHTKD1* knockdown led to remarkable reduction of ATP production together with decrease of basal and maximal respiration rates compared to controls. Esophageal fibroblasts from patients harboring *DHTKD1* mutation also showed significant reduction of ATP production and basal and maximal respiration rates. In addition to mitochondrial dysfunction, *DHTKD1* knockdown also led to increase viperin, a mitochondrial gene which is upregulated in EoE.
Conclusions: Using WES to we were able to identify a novel genetic and functional association of rare *DHTKD1* variants and mitochondrial dysfunction in EoE. Our study expands on the recent findings involving mitochondrial dysfunction in Th2 driven allergic diseases like asthma and provides opportunities for using mitochondria as novel target for therapeutic approaches in EoE.

Investigation of Complete Clinical Tolerance in a Pediatric Eosinophilic Esophagitis Population

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Background: Although food allergens have been demonstrated to play a pathologic role in eosinophilic esophagitis (EoE), the natural history of acquisition of clinical tolerance to food antigens in EoE patients is unclear. We have observed some EoE patients successfully reintroduce an open diet after therapeutic elimination diet, however, we hypothesize that this is rare given that for the majority of patients EoE symptoms are lifelong.
Methods: We sought to determine the frequency at which pediatric patients with EoE achieve complete clinical tolerance to all foods previously removed from the diet by conducting a retrospective chart review of a cohort of EoE patients one month through 18 years of age. Charts were reviewed if patients met clinical consensus criteria for EoE including report of esophageal symptoms and esophageal mucosal biopsy with more than 15 eosinophils per high powered field after treatment with proton pump inhibitor. 1812 patient charts were eligible for review. Criteria for inclusion in the study cohort included: normalization of esophageal biopsy with removal of food(s) from the diet, followed by patient successfully reintroduced all removed foods into the diet with normal biopsy and no recurrence of symptoms and no subsequent abnormal biopsies.
Results: 9 patients were identified who achieved complete clinical tolerance to all foods previously removed from the diet. This represents 0.5% of our overall EoE cohort. 44% of patients were female and only two patients used swallowed steroids for any length of time. Most common presenting symptoms were dysphagia (44%) and regurgitation/vomiting (44%). 78% of patients removed multiple foods from the diet, with milk being the most common trigger identified. All patients had at least one quiescent biopsy following food reintroduction. mean age of EoE diagnosis was 5.9±3.9 years and the mean age patients reached clinical tolerance to all foods was 11.0±3.9 years.
Conclusions: Although it is mechanistically unclear why this small group of patients experienced a period of clinical tolerance in their course of EoE, this study provides further insight into the natural history of EoE. Although quite uncommon, a subset of patients can have prolonged periods of clinical tolerance.

Adult eosinophilic esophagitis patients' satisfaction with different disease-specific treatment modalities

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Background: Treatment options for EoE patients include drugs (proton-pump inhibitors [PPI], swallowed topical corticosteroids [STC]), food elimination diets, and esophageal dilation. Knowledge about patients' view regarding the different therapeutic options is very limited. We aimed to assess adult EoE patients' satisfaction with different EoE-specific treatment modalities used in the past 12 months.
Methods: We first created a questionnaire that included items that queried general demographic characteristics (7), EoE-specific patient history and presence of atopic disease (8), past and present EoE-specific therapy (9), concomitant medication use (7), considerations for therapy choice (2), and satisfaction with various therapies recalled over a period of 12 months (assessed using the validated "Treatment Satisfaction Questionnaire for Medication" [TSQM], 52). The TSQM consists of 14 items falling into 4 scales: effectiveness (3), side effects (5), convenience (3), and overall satisfaction (3). The score for each scale ranges from 0 (dissatisfied) to 100 (satisfied). Three psychologist-guided focus groups with EoE patients were conducted to inform the content and the structure of the questionnaire and ensure that patient understand the items, instructions, and response options. The questionnaire was sent to 148 patients in Switzerland.
Results: Patient response rate was 74% (108/147). Mean patient age was 46.3 years (SD = 15.9), 85/108 patients (79%) were male, and mean disease duration was 6.8 years (SD = 5.1). In the last 12 months, 25%, 84%, 19%, and 13% were treated with PPI, STC, food elimination diet, and esophageal dilation, respectively (37.0% patients received more than one treatment; 7.4% of patients did not receive any treatment). Patients identified the following considerations as important for the therapy choice: the

treatment effect on the symptoms (89%), the treatment effect on esophageal inflammation (76%), possible side effects (69%), ease of therapy use (58%), physician's recommendation (50%), and compatibility of therapy with lifestyle (46%). When asked about the single most important criterion for the choice of therapy, 49%, 34%, and 12% of patients chose the effect of treatment on symptoms AND esophageal inflammation, the effect of the treatment on the symptoms, and the effect of treatment on esophageal inflammation, respectively, as deciding factor. The TSQM scales scores as well as average TSQM values for patients on PPI, STC, and diet are shown in Table 1.

Conclusions: Adult EoE patients consider both effect of medication on symptoms and esophageal inflammation as important criteria, when choosing EoE therapy. EoE patients appear to be satisfied with PPI, STC, and dietary therapy.

Provided Figures, Tables, References:

Table 1. Median TSQM scores and IQR. *For a side-effect scale, a score of 100 is given to patients, who do not experience side effects.

TSQM scales	PPI (n = 27); median treatment duration 6 years [3 - 9]	STC (n = 84; median treatment duration 5 years [2 - 6]	Diet (n=21; median treatment duration 2 years [1 – 4.5]
Effectiveness	66.7 [38.9-77.8]	83.3 [66.7 – 94.4]	77.8 [50 – 88.9]
Side-effects*	100 [100 – 100]	100 [100 – 100]	100 [100 – 100]
Convenience	88.9 [77.8 – 100]	83.3 [66.7 – 100]	50 [33.3 – 66.7]
Overall satisfaction	71.4 [50 -85.7]	78.6 [64.3 – 92.9]	78.6 [57.1 – 92.9]
Average score	79.8 [69.4 – 85.5]	84.4 [72.8 – 92.3]	76.6 [59.8 – 81.9]

Feasibility and clinical implications of esophageal microbiome transplantation

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Eosinophilic esophagitis (EoE) is a food-antigen driven, immune-mediated disease that is characterized by chronic inflammation and esophageal dysfunction. Recent research revealed that human esophagus is colonized with bacteria and it was proposed that esophageal dysbiosis is associated with EoE. In keeping with this premise, we and others have demonstrated that antibiotic use in infancy and caesarean delivery, which disrupt early-life bacterial colonization, are risk factors for EoE. It is unknown, however, how microbiota contributes to EoE and whether it is possible to relieve clinical manifestations of EoE via manipulation of the esophageal microbiota. We found that the esophagus of specific pathogen free (SPF) mice is colonized with bacteria. Herein, we assess the feasibility of esophageal microbiome manipulation using a murine model of fecal microbiota transplantation (FMT). Homogenized fecal and cecal contents from SPF donor were transplanted to germ-free (GF) recipient mice via oral gavage. Two weeks post FMT, esophageal DNA was isolated for microbiota analysis via 16S rRNA sequencing. We found that SPF murine esophageal microbiota composition is similar to the normal human esophageal microbiota as both are dominated by Firmicutes, mainly Lactobacilli and Streptococci. Principal coordinate analysis of esophageal microbial communities showed that recipient esophageal microbiota samples cluster close to that of donors. Only a minimal differences between donor and recipient microbiota composition (*P* value = 0.18) were revealed by an ADONIS test, demonstrating the fidelity of microbiota transplantation. To summarize, the esophagus is physically located in a primary position that is amenable to microbiota manipulation and our study demonstrates feasibility of esophageal microbiome manipulation via FMT in GF recipients. Further studies are needed to determine whether the FMT-based approach developed in this study could be used for treatment of esophageal dysbiosis.

Esophageal IgG4 Levels Are Elevated in Pediatric Eosinophilic Esophagitis and Correlate with Esophageal Histopathology Including Levels of Eosinophils

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Background: Recent data suggest an association between elevated levels of IgG4 and adult eosinophilic esophagitis (EoE). Herein, we hypothesize that tissue IgG4 levels are elevated in pediatric patients with EoE and tissue IgG4 levels correlate with tissue histopathology.
Methods: A case-control study was performed with pediatric patients with EoE (≥15 eosinophils/HPF) and non-EoE control subjects. Biopsies obtained for diagnosis were fixed in formalin and scored using the EoE histology scoring system (EoEHSS). Protein isolation/quantitation from additional esophageal biopsies was performed, and samples were diluted to equivalent total protein concentrations (100 µg/mL). IgA, IgM, IgG1, IgG2, IgG3, and IgG4 were measured using the Luminex 100 system and IgE was quantified by ELISA. All data were normalized (mg immunoglobulin/g total protein). IgE levels were expressed as IU/mL. Means were compared using Mann-Whitney U test.
Results: Small but significant increases of all IgG subclasses, as well as IgA and IgM, were seen in subjects with EoE relative to controls. The highest fold change between groups was seen in IgG4 (8.16 mg/mL vs. 0.57 mg/mL; p=0.0001). A four-fold increase in the percent of IgG4 relative to total IgG was observed in EoE biopsies compared to controls (17.92 ± 5.62% vs. 4.44 ± 2.90%; p<0.002). Tissue IgG4 level correlated with peak eosinophil count (p=0.0014) as well as mean histologic grade (p=0.0063) and stage (p=0.0401) scores. There was no significant difference in the tissue IgE level between the study groups.
Conclusions: Esophageal IgG4 levels are elevated in pediatric eosinophilic esophagitis and correlate with esophageal histopathology including peak eosinophil levels. These data substantiate the involvement of IgG4 in pediatric EoE.

Dynamic Chromatin Binding Regulates IL-33 Extracellular Release During Necrosis

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Interleukin 33 (IL-33) is a member of the IL-1 cytokine family with key roles in allergic diseases, including asthma, atopic dermatitis, and eosinophilic esophagitis. Under normal conditions, IL-33 is retained within the nucleus of the cell, bound to the nucleosome acidic patch. Upon necrosis, IL-33 is released and activates immune cells through its receptor, ST2. While most studies focus on the extracellular function of IL-33, the physical properties and functional significance of IL-33–chromatin binding remain largely understudied. Herein, we examined the molecular characteristics of IL-33–chromatin binding and tested the hypothesis that it regulates IL-33 extracellular release in esophageal epithelial cells. Wild-type IL-33 (IL-33^{WT}) was localized to the nucleus and was enriched in heterochromatic regions. In contrast, truncated IL-33 (IL-$33^{112\text{-}270}$), which lacks the chromatin binding domain, exhibited nuclear and cytoplasmic localization. Fluorescence recovery after photo-bleaching revealed that IL-33^{WT} has a 10-fold slower mobility ($p < 0.0001$) within the nucleus than that of the classic nuclear cytokine IL-1a. IL-$33^{112\text{-}270}$ was freely mobile similarly to the GFP control. These results indicate that IL-33 demonstrates slow, dynamic chromatin binding. After induction of cellular necrosis, IL-33^{WT} exhibited decreased extracellular release compared to IL-$33^{112\text{-}270}$. Time-lapse microscopy revealed intracellular retention of H2B and IL-33^{WT}, but not IL-1a or IL-$33^{112\text{-}270}$, after induction of necrosis. Under these conditions, IL-33^{WT} had a slow, linear release over time that was not observed for H2B. From our findings, we propose that IL-33–chromatin binding counter-regulates IL-33 extracellular release during necrosis to curtail downstream effects.

Loss of esophageal epithelial SPINK7 unleashes uncontrolled proteolytic activity, impaired epithelial Barrier, defective differentiation and pro-inflammatory cytokine production

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Background: Epithelial barrier impairment has been implicated in the development of allergic disease. However, the molecular mechanisms by which impaired epithelial barrier function induces Th2-type immune responses remain largely unknown. In this study, we examined the role of the serine peptidase inhibitor kazal type *(SPINK)7* on epithelial barrier function and mucosal Th2-associated immune responses in the esophagus, with a focus on eosinophilic esophagitis (EoE).
Methods: Primary human esophageal epithelial cells stably transduced with either control or *SPINK7*-directed shRNAs were cultured at the air-liquid interface (ALI) to induce squamous cell differentiation. The integrity of the barrier was examined by functional assays complemented with histological and ultrastructural analyses as well as quantitation and localization of junctional proteins by immunofluorescence microscopy. The impact of *SPINK7* on epithelial protease activity and global transcription was assessed. Furthermore, cytokine and chemokine secretion were analyzed following *SPINK7* silencing. *In vitro* assays using recombinant proteins were conducted to identify direct targets of SPINK7. Protease activity of human esophageal tissue was measured, and receptor expression of esophageal tissue-derived eosinophils was quantified. Using a genetic approach, we assessed whether genetic variants in the *SPINK7* gene were associated with EoE susceptibility.
Results: Loss of *SPINK7* expression caused a defect in epithelial cell differentiation, reduced expression of barrier proteins including filaggrin, impaired epithelial barrier function, and unleashed the production of a set of pro-inflammatory mediators including thymic stromal lymphopoietin (TSLP), IL-8, GM-CSF and CCL2. Mechanistically, SPINK7 inhibited urokinase plasminogen activator (uPA) and kallikrein (KLK)5 and translational studies revealed increased uPA activity in the esophagus of EoE patients and dynamic modulation of the uPA receptor by esophageal eosinophils. Genetic studies revealed a strong epistasis between genetic variants in *PLAU* (gene product, uPA) with the atopy risk variant in *TSLP* gene.
Conclusions: We propose that *SPINK7* deficiency and uncontrolled protease activity serve a causative role in compromising the esophageal barrier. We suggest that SPINK7 represents a novel checkpoint in regulating innate immunity, and its deficiency, as occurs in EoE, induces pro-inflammatory and pro-allergic responses characterized by excessive cytokine production and epithelial barrier impairment, likely via a KLK- and uPA-dependent mechanism. Additionally, EoE disease susceptibility is influenced by genetic interactions between variants in this pathway (*SPINK7* and *PLAU*) and cardinal atopy pathways (*ST2* and *TSLP*).

Treatment with Compounded Oral Viscous Budesonide is Effective and Provides a Durable Response in Patients with Eosinophilic Esophagitis

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Background and Aims: Because no FDA approved medications or esophageal-specific preparations exist for eosinophilic esophagitis (EoE), patients use off-label drugs and create their own formulations. It is possible that a compounded budesonide suspension is preferable, but this has not been extensively studied in EoE. We assessed the efficacy of a standardized compounded budesonide suspension in the primary and secondary treatment of EoE.

Methods: We conducted a retrospective cohort study utilizing the University of North Carolina EoE Clinicopathologic Database to identify all patients with EoE who were treated with compounded budesonide at our center. This was prescribed during routine clinical care and dispensed by a specialty compounding pharmacy, where budesonide was mixed with a methocel gel at a contentration of 1 mg/8 mL. Data were extracted from electronic medical records including: demographics, symptoms, previous treatments, endoscopic findings, and outcomes (symptomatic global response [yes/no], endoscopic response [% with individual findings], and histologic response [absolute eosinophil count; % with <15 eos/hpf]) after the initial and last compounded budesonide treatment in our system. Descriptive statistics characterized the cohort. Bivariate analysis was performed with McNemar's test and paired Wilcoxon Rank-Sum test.

Results: A total of 48 patients treated with compounded budesonide were included (mean age 33.6; 69% male; 96% white) (Table 1). Mean length of follow-up was 16.3 months (range: 2.4 - 51.6). The most common symptom prior to therapy was dysphagia (92%). There were 32 (67%) patients who previously received corticosteroids and/or a food elimination diet, which was discontinued for primary non-response or loss of response in 18 (56%). At the end of follow-up, there was a significant decrease in symptoms of dysphagia (89% vs. 39%, p < 0.001) and heartburn (33% vs. 6%, p=0.004) and a global symptom response in 79% (Figure 1A). Statistically significant improvements were documented for endoscopic features (Figure 1B): rings (84% vs. 55%, p = 0.001), furrows (86% vs. 50%, p < 0.001), white plaques (61% vs. 30%, p = 0.002), and decreased vascularity (70% vs. 46%, p = 0.005). The median of the peak eosinophil counts decreased from 58 eos/hpf to 14 (p<0.001) with 52% achieving a response of <15 eos/hpf (Figure 1C). In the 18 patients with prior steroid or food elimination diet non-response, 86% had symptomatic and 44% had histologic responses.

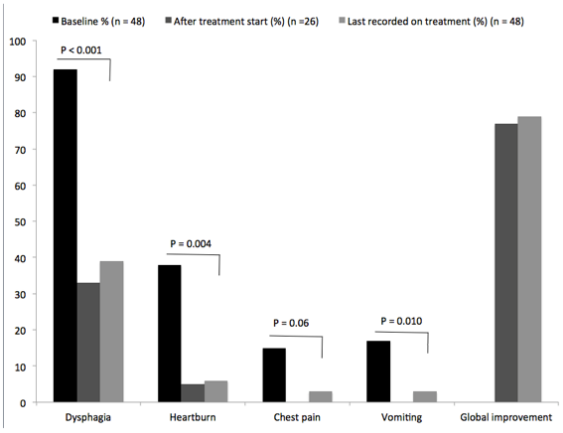
Conclusions: Compounded budesonide suspension produced a durable symptomatic, endoscopic, and histologic response in a cohort followed for more than a year. Many patients who were previously refractory to first-line therapy, including tCS, responded to compounded budesonide. This formulation can be used clinically until there are approved drugs with esophageal formulations for EoE.

Provided Figures, Tables, References:

Table 1. Patient demographics (N = 48)

Age at diagnosis (mean ± SD)	33.6 ± 16.1
Symptom length before diagnosis (mean years ± SD)	10.8 ± 9.3
Length of follow-up (mean pt months ± SD; range)	16.3 ± 12.0; 2.4-51.6
Initial compounded budesonide dose (mean dose mg ± SD; range)	2.5 ± 1.1; 1 - 6
Final compounded budesonide dose	2.0 ± 1.1; 0.5 - 4

Figure 1A



(mean dose ± SD; range)	
% Concurrent food elimination diet	17
% Male	69
% White	96
% Private insurance	82
% Atopic disease diagnosis	56
% Food allergy	33

Figure 1B

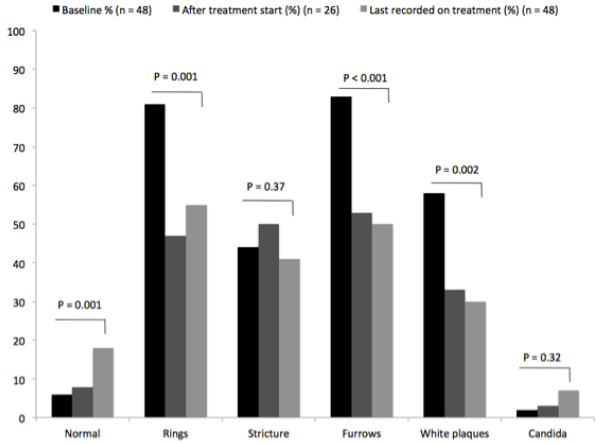
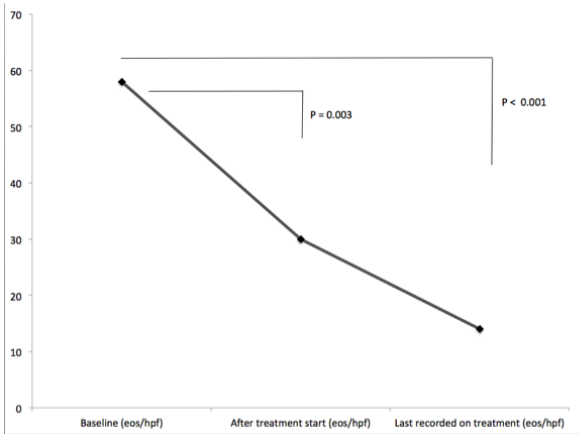


Figure 1C



Food Elimination Diets are Effective for Long-term Treatment of Adults with Eosinophilic Esophagitis

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Background: Dietary elimination of potential food allergens is recommended by guidelines as a first-line and long-term treatment of eosinophilic esophagitis (EoE). However, limited data exist on the long-term efficacy of this approach in adults. We assessed the long-term outcomes of food elimination diets (FED) for treatment of adults with EoE.

Methods: We conducted a retrospective cohort study utilizing the University of North Carolina EoE Clinicopathologic Database to identify all adult patients with EoE treated with a food elimination diet without concomitant corticosteroids as part of routine clinical care. Data were extracted from electronic medical records including: patient demographics, symptoms, previous treatments, endoscopic findings, and outcomes (symptomatic global response [yes/no], endoscopic response [EREFS score], and histologic response [absolute eosinophil count]) prior to and after a food elimination diet trial. Follow-up data were collected for patients with a histologic response (<15 eos/hpf) to a FED during and after food reintroduction. Descriptive statistics were used to characterize the cohort. Bivariate analysis was performed with McNemar's test for dichotomous variables and paired t-test for continuous variables.

Results: A total of 52 patients treated with a FED were included (mean age when FED started: 38.5 years; 60% female; 92% white) (Table 1). Partial to good adherence to a FED was documented in 94%. Most patients received a 6FED (35%) or targeted diet (62%) (Figure 1). The most common symptom prior to therapy was dysphagia (90%). Most patients (81%) were previously treated with corticosteroids, which

were discontinued for primary non-response or secondary loss of response in 15 (32%) and patient preference in the remainder. There were 21 (40%) patients with an initial histologic response to a FED. Mean length of follow-up for responders was 24.9 months (range: 4.2 - 74.4). Responders reported less dysphagia after instituting a FED (95% baseline vs. 11%; p = 0.001) and at the end of the follow-up period (95% baseline vs. 33%; p =0.008)(Figure 2A). Significant and durable endoscopic improvements were recorded at the same time points: (EREFS score: 3.2 vs. 0.7; p = 0.001) and (EREFS score: 3.2 vs. 1.7; p = 0.06) (Figure 2B). Histologic findings improved after the most restrictive diet in responders (49.8 vs. 4.1 eos/hpf; p = 0.001) and eosinophil counts remained suppressed in the 10 initial responders maintaining compliance at the end of follow-up (44.4 vs. 5.2 eos/hpf; p =0.02) (Figure 3).

Conclusions: Among EoE patients responding to a FED, maintenance dietary therapy produced good long-term symptomatic, endoscopic, and histologic disease control. These long-term data confirm that a FED is an effective maintenance treatment option in select adults with EoE.

Provided Figures, Tables, References:

Table 1. Baseline characteristics and clinical findings (N = 52)

Age when FED started (Mean years ± SD)	38.5 ± 12.0
Length of follow-up (Mean pt months ± SD; range)	24.9 ± 19.8; 4.2 - 74.4
% Partial to good FED adherence	94
% Female	60
% White	92
% Atopic disease diagnosis	73
% Patch, prick, or RAST testing	63
% Patients with formal allergen testing prior to a targeted elimination diet	78
% Food allergy by formal testing	79
Baseline symptoms (%)	
Dysphagia	90
Heartburn	33
Chest pain	17
Abdominal pain	16
Baseline endoscopic findings (%)	
Rings	66
Furrows	70
Decreased vascularity	30
White plaques	34
Stricture	26
Total EREFS (Mean ± SD)	4.1 ± 2.1
Baseline histology findings (Mean eos/hpf ± SD)	60.3 ± 59.2

Figure 1

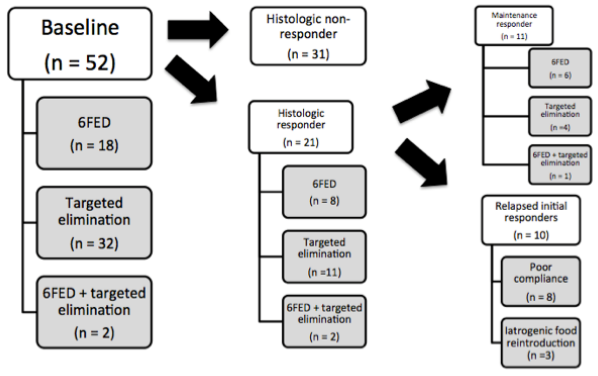
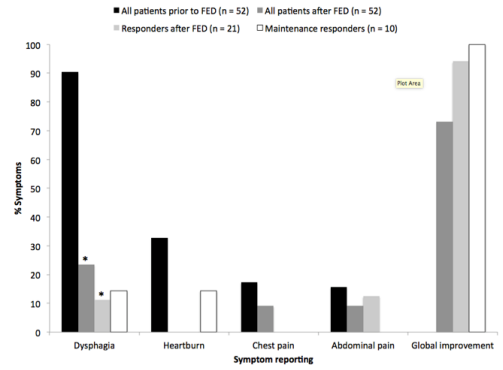
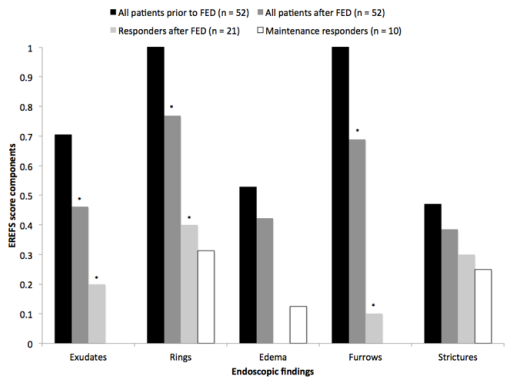


Figure 2(A)



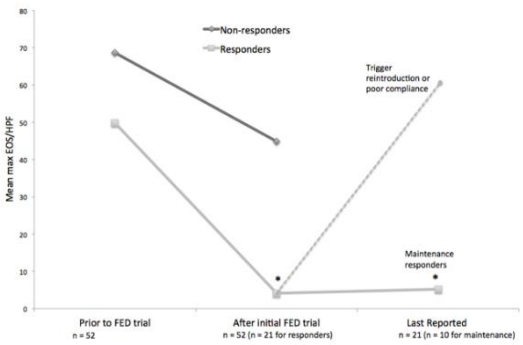
* Denotes p < 0.05 compared to baseline prior to FED initiation

Figure 2(B)



* Denotes p < 0.05 compared to baseline prior to FED initiation

Figure 3



* Denotes p < 0.05 compared to baseline prior to FED

Eosinophilic Esophagitis risk variant at 2p23 dampens IL-13-induced calpain-14 promoter activity in a STAT6-dependent manner

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Rationale: Eosinophilic esophagitis (EoE) is a chronic, food-driven, esophageal, inflammatory allergic disease. We have recently found that, in addition to genetic risk loci for allergic sensitization, EoE susceptibility is linked to a tissue-specific genetic factor(s) at 2p23, encoding the *CAPN14* gene. In our initial studies, we showed that *CAPN14* is dynamically up-regulated as a function of EoE disease activity and after exposure of epithelial cells to IL-13, a critical regulator of esophageal inflammation in EoE. Patients with EoE and the 2p23 risk haplotype express decreased esophageal *CAPN14*.
Methods: We performed a replication and fine-mapping study of the 2p23 locus in an additional cohort of subjects with and without EoE. Luciferase reporter assays were used to further define the IL-13 and genotype-dependent parts of the *CAPN14* promoter. An analysis of transcription and protein expression under various conditions of esophageal epithelial cell culture was used to identify the differentiation necessary for optimal expression of CAPN14.
Results: We identified the critical promoter elements of *CAPN14* using promoter deletion constructs. Chromatin immunoprecipitation confirmed STAT6 binding at the putative sites in the promoter of CAPN14. Each of the three STAT6 elements were required for the 10-fold increase in IL-13 induced promoter activity and for the 50% reduction in genotype-dependent expression. Optimal CAPN14 expression occurred with increased calcium and IL-13 stimulation and with air-liquid interface culture conditions.
Conclusions: Our work establishes a candidate molecular mechanism for EoE disease etiology in which the risk variant at 2p23 dampens IL-13-induced calpain-14 promoter activity in a STAT6-dependent manner in differentiated esophageal epithelial cells.

Transcriptional and epigenetic signature of IL-13 response in esophageal epithelial cells

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Eosinophilic Esophagitis (EoE) is a chronic inflammatory disease of the esophagus mediated by allergic response to food and characterized by an epithelial-driven transcriptional program, known as EoE transcriptome. Blocking of IL-13 in EoE patients by the anti-IL-13 antibody treatment normalizes the disease transcriptome and improves symptoms, demonstrating a critical role of IL-13 signaling in EoE pathogenesis and signifying a need for deeper understanding of the molecular mechanisms of the IL-13—mediated esophageal epithelial responses. We molecularly dissected IL-13—driven epithelial responses in EoE by generating the genome-wide transcriptional and epigenetic landscape following IL-13 stimulation of the esophageal epithelial cells EPC2 as a model system. RNA-sequencing analysis identified 434 genes whose transcription was significantly affected by IL-13 following 6 h of stimulation (p_{adj}<0.05, 1.5 fold). Approximately 40% of these genes overlapped with the EoE transcriptome. ChIP-sequencing analysis of the activating histone epigenetic marks (acetylation and methylation) revealed much broader response to IL-13 stimulation with thousands of epigenetic changes occurring throughout the genome within 6 h of stimulation. We further identified direct transcriptional targets of IL-13 by ChIP-sequencing analysis of the transcription factor that mediates IL-13 signaling, signal transducer and activator of transcription protein 6 (STAT6). We detected ~ 6700 peaks of STAT6 in the genome following short (up to 45 min) IL-13 stimulation which primarily localized around transcriptional start sites of the genes. STAT6 peaks overlapped with 158 genes transcriptionally altered by IL-13 in EPC2 cells and the majority of these genes were also epigenetically upregulated by IL-13. Notably, ~18% of the genes in the EoE transcriptome (292 genes) had STAT6 binding sites and 75% of these genes were upregulated in EoE. Functional enrichment analysis of the STAT6-associated genes from the EoE transcriptome revealed that the most significant pathways were programmed cell death and regulation of kinase signaling. In summary, we have generated a unique integrated genome-wide transcriptional and epigenetic signature of IL-13—driven esophageal epithelial response. We demonstrated that IL-13 elicits strong transcriptional response in esophageal epithelium which mimics in part EoE transcriptome. Moreover, IL-13 causes profound and rapid epigenetic alterations throughout the genome of esophageal epithelial cells which correlate with transcriptional response and often overlap with STAT6 binding sites. We identify program cell death and kinase activity pathways as early direct transcriptional and epigenetic targets of IL-13 in EoE pathogenesis thereby providing insight into molecular mechanisms of EoE.

Eosinophilic Esophagitis Presenting as Severe Stricturing Disease

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Background: Severe esophageal stricture is a rare presenting symptom of eosinophilic esophagitis and can present a medical and therapeutic challenge. Here, we present the case of an adolescent male with severe stricturing disease at presentation of Eosinophilic esophagitis (EoE).
Case: A 14 year old African American male presented to the hospital with dysphagia. He had an acute intolerance of liquids. An esophagram showed a tortuous and narrowed esophagus. There was complete esophageal obstruction below the level of T4 (Fig 1); a CT chest was normal. The gastroenterology and surgery services performed a joint endoscopy, however the endoscope was able to be advanced only 20 cm from the mouth. A watermelon seed was obstructing the esophagus (Fig 2,3).
Esophageal biopsies confirmed EoE. He was started on steroids and elemental feeds via gastrostomy tube. Upon discharge he was following the 6 food elimination diet and taking topical swallowed corticosteroids and a proton pump inhibitor. Esophagram 1 month after diagnosis was markedly improved but showed a long stricture. Endoscopic reevaluation is planned for 8 weeks after initial presentation.
Discussion: There are several ways in which EoE can present [1], however stricturing disease is rare in the pediatric population and is suggestive of delayed diagnosis. When a stricture is present, it represents on average a 6 years of disease [2]; our patient had been symptomatic for 7 years. Atypical symptoms in African Americans [3] may also contribute to delay in diagnosis. As children with EoE age, there is

decrease in the esophageal distensibility, increasing the likelihood of stricture [4]. Treatment for EoE strictures frequently require dilation, which our patient will likely require in the future.

Provided Figures, Tables, References:

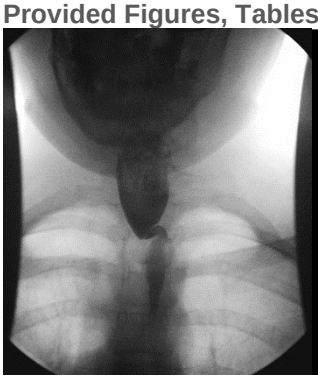
Figure 1: Esophagram

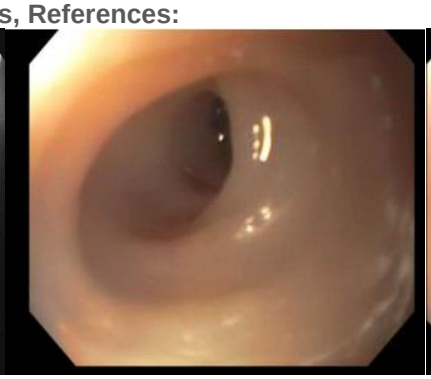
Figure 2: Proximal esophagus

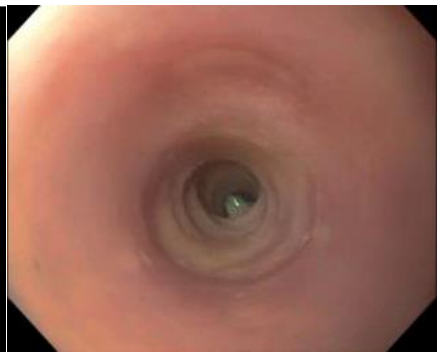
Figure 3: Ringed esophagus with watermelon seed

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Practice Differences in the Diagnosis and Management of Eosinophilic Esophagitis among Adult and Pediatric Gastroenterologists

Authors and Affiliations: Eyal Zifman[1], Hagar Banai[2], Raanan Shamir[3,4], Tamar Ringel-Kulka[5], and Noam Zevit[3,4]. [1]Pediatric Gastroenterology Clinic, Meir Medical Center, Kfar-Saba; [2]Department of Gastroenterology, Rabin Medical Center, Petach Tikva; [3]Institute of Gastroenterology, Schneider Children's Medical Center of Israel, Petach-Tikva; [4]Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel; [5]Department of Maternal and Child Health, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA.

Background: Eosinophilic esophagitis (EoE) guidelines call for similar practices in adults and children. We compared the diagnostic and management practices of gastroenterologists treating adult (AG) and pediatric (PG) patients suspected of having, or diagnosed with, EoE.
Methods: A multiple choice questionnaire was given to AG and PG during a scientific conference held in February 2016. Questions explored physician demographics, diagnosis and tissue sampling practices and management.
Results: Completed questionnaires were returned by 85/180 AG and 30/40 PG. Compared to PG, AG took esophageal biopsies significantly less frequently in several scenarios: endoscopy without esophageal symptoms or macroscopic findings (10% vs. 57%; p<0.001), dysphagia without macroscopic findings (83% vs. 100%; p=0.019), and gastroesophageal reflux symptoms with distal esophageal erythema (44% vs. 100%; p<0.001). Significantly fewer AG reported taking gastric and duodenal biopsies when EoE was suspected than did PG (29% vs. 90%; p<0.001). Both groups reported that they perform proton pump inhibitor tests routinely (77% vs. 83%; p=0.47). However, AG more often follow patients clinically (30% vs. 0%; p<0.001) rather than endoscopically. AG were also far less inclined to implement elimination diets as compared to PG (23% vs. 68%; p<0.001).
Conclusions: Significant disparities exist between gastroenterologists treating adult and pediatric EoE patients – spanning most of the diagnostic and management choices evaluated. These findings may impact rates of diagnosis, appropriate treatment, monitoring, and long term outcomes. Furthermore,

future studies should assess the reasons for these differences and develop educational/support programs to improve EoE patients' transition to adult care and consequently improve their health outcome.

Modulation of CD8+ cells infiltration and activity in eosinophilic esophagitis by six-food elimination diet

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Background: Eosinophilic esophagitis (EoE) is characterized by a dense intraepithelial inflammatory infiltrate of eosinophils, mast cells, and CD4 and CD8 lymphocytes. Histological and clinical remission after dietary exclusion supports immune-allergic mechanisms as the driving force in EoE. However, the role of CD8+ cells and CD8-specific cytotoxic molecules, as key contributors to EoE phatophysiology, has not been explored.
Methods: Naïve EoE patients (n=10; age: 33±10 years-old) who responded clinically and histologically to a six-food elimination diet (SFED: milk, cereals, egg, fish, legumes, nuts) and healthy-esophagus controls (C, n=10; age: 53±20 years-old) were included. Esophageal biopsies were collected in all subjects before and after therapy, and at baseline in controls. Clinical symptoms were assessed and analysed before and after SFED, and food triggers were identified. The number of eosinophils and CD8+ cells per high power field (hpf) were quantified after haematoxylin-eosin and immunofluorescense staining, respectively. Expression of eotaxin-3 and cytotoxic CD8-related molecules was assessed by qPCR.
Results: Main symptoms reported were dysphagia (70%), and food impaction (70%). The most frequent triggering foods were cereals (70%) and milk (60%). Compared to controls, eosinophils (EoE: 56.8±29.9/hpf vs. C:0±0/hpf) and CD8+ cells (EoE: 19.6±11.3 vs. C: 6.27±4.63) were higher in EoE patients ($P<0.05$). SFED significantly reduced cell counts (eosinophils: 3±4.22; CD8: 7.76±6.80; $P<0.05$) in parallel with clinical improvement.
Granzyme A, granzyme B, granulysin and eotaxin-3 gene expression were higher in EoE than in C (1.6 to 26-fold-change; $P<0.05$) and decreased to C values after SFED treatment.
The number of eosinophils positively correlated with CD8 counts (r_s =0.79) and perforin-1 gene expression (r_s =0,83, P=0.02). Moreover, eotaxin-3 gene expression correlated with dysphagia symptoms (r_s=0.73) and granzyme B gene expression (r_s =0.75; P=0.02).
Conclusion: Reduction in CD8 lymphocytes number and proteases expression, in association with clinical improvement after SFED, suggest that CD8-mediated cytotoxic mechanisms are involved in eosinophil recruitment and epithelial damage in active EoE.

Identification of eosinophil cationic protein binding peptide by Phage display and its diagnostic potential for Eosinophilic esophagitis

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Background: Eosinophilic esophagitis (EoE) is usually diagnosed by invasive endoscopic procedures for histopathological examination. Noninvasive biomarkers would be valuable for diagnosis and monitoring of EoE. Our aim was to identify novel biomarkers for EoE diagnosis.
Methods: We performed a comparative proteomics analysis using liquid chromatography-tandem mass spectrometry (LC-MS/MS) of esophageal biopsies from pediatric patients with eosinophilic esophagitis,

gastroesophageal reflux disease and healthy individuals. Then, Phage Display technology was used to select peptides against up-regulated proteins from patients with EoE. Twelve phage clones were selected after three biopanning rounds, and their reactivity was evaluated in a phage- ELISA assay using patient mucus samples. Furthermore, sequences of the peptides were determined by sequencing and the binding between peptide and protein target analyzed by in silico prediction tools.
Results: Mass spectrometry results showed that eosinophil cationic protein (ECP) was up-regulated in EoE patients. ECP is an eosinophil granule protein that is deposited on tissues in diseases. A high reactive ECP- binding peptide (E8) was able to distinguish mucus of eosinophilic esophagitis patients from gastroesophageal reflux disease and healthy individuals by ELISA, achieving sensitivity of 84.62, specificity of 82.72, a positive likelihood ratio of 4,896, and an area under the curve of 0.84.
Conclusions: This is the first study to demonstrate the detection of eosinophil cationic protein using peptides identified by phage display. These peptides could be a useful diagnostic tool for the detection of EoE patients.

An mRNA-based medical algorithm identifies an eosinophilic esophagitis subpopulation with esophageal IgE production

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Background: Diagnostic evaluation of eosinophilic esophagitis (EoE) remains difficult and, currently, no predictive markers for patient subpopulations are available in the clinic.
Objective: Establish an automated medical algorithm to assist in the evaluation of EoE.
Methods: Machine learning techniques were used to establish a diagnostic probability score for EoE (pEoE) based on esophageal mRNA transcript patterns from proximal and distal biopsies of patients with EoE, gastroesophageal reflux disease, and controls. Dimensionality reduction in the training set established weighted factors, which were confirmed by immunohistochemistry. Following weighted factor analysis, p(EoE) was determined by Random Forest classification. Accuracy was tested in an external test set and predictive power was assessed with equivocal patients. Esophageal IgE production was quantified with epsilon germ line (IGHE) transcripts and correlated with serum IgE and the tissue Th2-type mRNA profile to establish an IGHE-score for esophageal tissue allergy.
Results: In the primary analysis, a three-class statistical model was used to generate a p(EoE) score based on common inflammatory characteristics of EoE. A p(EoE) ≥25 successfully identified EoE (sensitivity 94.4%, specificity 92.9%, AUC 0.985) and improved diagnosis of equivocal cases after first biopsy by 84.6%. A secondary analysis loop in EoE patients defined an IGHE-score≥37.5 for a patient subpopulation with increased esophageal allergic inflammation.
Conclusion: The development of intelligent data analysis from a machine learning perspective provides exciting opportunities to improve diagnostic precision and improve patient care in EoE. The p(EoE) and the IGHE-scores are first steps towards the development of decision trees that can help to define EoE subpopulations and, consequently, will facilitate individualized therapy.

Alpha One Antitrypsin Deficiency in Eosinophilic Esophagitis

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Background: Alpha one antitrypsin (A1AT) deficiency is an autosomal co-dominant disorder in which there is defective production of the serine protease inhibitor A1AT, which results in decreased A1AT activity leading to chronic emphysema. A 17 year old male with A1AT deficiency type ZZ and early

childhood cholestasis was diagnosed with eosinophilic esophagitis (EOE) and fibrosis of the esophagus- thus rasing the question if there was an association between A1AT deficiency and EOE.
Methods: The Advanced Cohort Explorer (ACE) is a data repository maintained by the Unified Data Platform which contains patient demographics, diagnosis, laboratory, flowsheets , clinical and pathology notes from multiple clinical and hospital source systems within the Mayo Clinic Rochester. With institutional review board approval, patients with the concomitant diagnosis A1AT deficiency and EOE were identified using ACE.
Results: 5,783 unique patients were identified with the diagnosis of EOE. Of those patients, 7 were identified with the diagnosis of A1AT deficiency. Age at diagnosis of EOE in the A1AT deficiency patients ranged from 11 years to 61 years with 5 patients diagnosed with EOE above age 30.
Conclusions: The prevalence of A1AT deficiency in the general population has been reported as 0.02% to 0.06%. The prevalence of A1AT deficiency in our EOE cohort was 0.12%- up to six times greater than what has been reported in the general population. The majority of the A1AT deficiency patients were diagnosed in adulthood. Further epidemiologic studies to examine the association between A1AT deficiency and EOE are indicated and if confirmed- may lead to further understanding of the pathogenesis of EOE.

Intracellular compartmentalization of calpain-14 in esophageal epithelial cells

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Background: Eosinophilic esophagitis (EoE) is an emerging allergic inflammatory disease of the esophagus. The esophageal specific, intracellular protease calpain-14 (CAPN14) was shown to be associated with EoE both genetically and by increased expression in esophageal biopsies from EoE patients. Yet its function and contribution to disease remains to be elucidated. In this study, we investigated subcellular localization of CAPN14 in human esophageal epithelial cells.
Methods: Biochemical fractionation was performed on immortalized human esophageal epithelial cells (EPC2) stably overexpressing CAPN14 grown in submerged culture. Fractionation was also carried out on untransduced EPC2 cells treated with IL-13 that were grown at the air-liquid interface (ALI) or in submerged culture. CAPN14 subcellular distribution was further characterized by fluorescence microscopy of live cells engineered to overexpress CAPN14-GFP. RNA-seq was performed on EPC2 cells overexpressing CAPN14 grown at the ALI.
Results: Fractionation revealed ~70% of CAPN14 to be in the cytoplasm, with ~10% detectable in the membrane and ~20% in the nucleus in undifferentiated EPC2 cells grown in submerged culture. However, following differentiation into a stratified squamous epithelium, endogenous CAPN14 was mainly localized in the nucleus. CAPN14-GFP displayed localization in the cytoplasm, plasma membrane, and nucleus; whereas the control CAPN1-GFP was limited to the cytoplasm. Analysis of RNA-seq data showed alterations in gene transcription in EPC2 cells overexpressing CAPN14 grown at ALI with enrichment in pathways involved in cell death, calcium-binding proteins, JAK-STAT cascade, and Wnt signaling.
Conclusions: CAPN14 is localized to the cytoplasm, membrane, and nucleus in human esophageal epithelial cells. Following cellular differentiation, CAPN14 shows changes in subcellular distribution, most notable by its presence in the nucleus. CAPN14-GFP also shows nuclear localization and its distribution appears distinct from that of CAPN1-GFP. Dynamic CAPN14 localization and altered gene transcription by overexpression suggest a key cellular function, yet to be described.

Raman Microspectroscopy Reveals Distinct Biochemistry of Esophageal biopsies Obtained from Children with Eosinophilic Esophagitis

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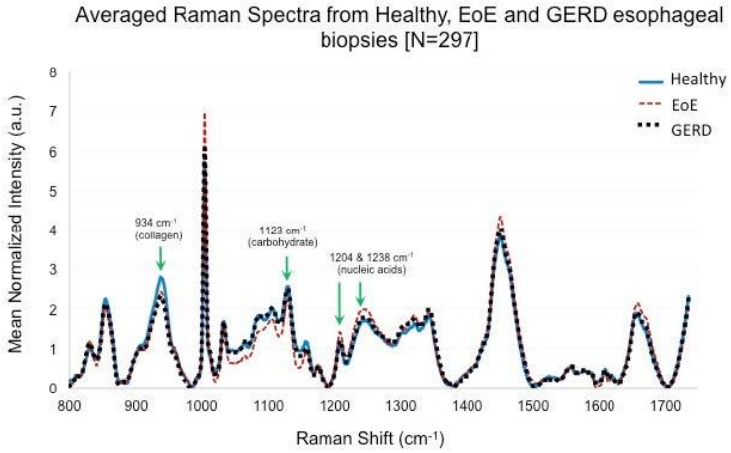
Background: Despite recent advances, there is a compelling need to develop approaches for objective diagnosis of eosinophilic esophagitis (EoE) and to characterize esophageal tissue in its entirety to elucidate the pathobiology. Raman spectroscopy is a versatile optical technique capable of accurately measuring subtle alterations in the nucleic acid, collagen, protein, and lipid content in the tissue, and distinguishing pathological states at the molecular level. The aims of this pilot study were to define the esophageal Raman spectra (RS) in EoE *ex vivo*, and to determine the accuracy of spectral features in differentiating EoE from gastroesophageal reflux disease (GERD) and healthy controls (HC).
Methods: Esophageal biopsies [EoE=3 (per current guidelines), GERD=3, and HC=5] were snap frozen at the time of collection. From each biopsy, three 20µm sections were obtained and atleast 24 spectra ranging from 796-1796 cm-1 wavenumbers at an excitation wavelength of 830nm were acquired using the inVia Raman microscope (Renishaw, UK). In parallel, a 5µm section was submitted for histopathologic analysis. The machine-learning algorithm was applied to identify RS unique to study groups. RS were correlated with the histologic features to determine the sensitivity, specificity and overall accuracy for identifying EoE.
Results: In all, 297 RS [EoE=79, GERD=88 and HC=130] were acquired and analyzed. The mean normalized intensity (MNI) when compared to HC was significantly lower for EoE and GERD at 934cm-1 indicating a lower collagen content and for EoE alone at 1123 cm-1 corresponding with lower polysaccharide/ carbohydrate fraction. The MNI was significantly higher for EoE at 1204 cm-1 and 1238 cm-1 illustrating an increased nucleic acid content compared to GERD and HC (Figure). The prominent Raman spectral features classified HC and disease group (EoE and GERD) with 81% sensitivity and 75% specificity (overall accuracy: 78%). Within the diseased group, the algorithm discriminated EoE from GERD with 94% sensitivity and 98% (overall accuracy: 96%)
Conclusions: Our initial findings indicate that the esophageal tissue in EoE has a distinct RS reflective of the tissue biochemistry, and Raman spectroscopy has the potential to accurately differentiate between EoE, GERD and HC. Raman spectroscopy based biochemical approach holds promise to open new avenues for the objective diagnosis of EoE and advancing our understanding of the EoE pathobiology.
Provided Figures, Tables, References:



Does Eosinophilic Esophagitis Affect Eating Behavior in School-aged Children? – Results from Interim Analysis

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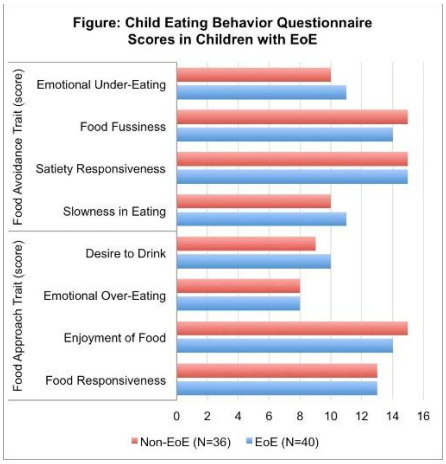
Background: Eosinophilic esophagitis (EoE) is known to affect the eating behavior of infants and toddlers. Its impact on the eating behavior of school-aged children is unclear. We present preliminary results of our ongoing case-control study aimed at examining the impact of EoE (cases) on the eating behavior of school-aged children compared to those without EoE (controls).
Methods: The intervention group comprised of 40 (53%) children with EoE and the control group was comprised of 36 (47%) children diagnosed with constipation and/or irritable bowel syndrome. We used the Child Eating Behavior Questionnaire, a validated instrument designed to assess parent-reported psychometric subscales of eating grouped into two eating traits. The 'food approach' trait indicates positive inclinations for eating and is comprised of: Food Responsiveness (FR), Enjoyment of Food (EF), Emotional Over-eating (EOE), Desire to Drink (DD) subscales. The 'food avoidant' trait is related to negative inclinations to food intake, and is comprised of: Slowness in Eating (SE), Satiety Responsiveness (SR), Food Fussiness (FF), and Emotional Under-eating (EUE) subscales. The responses in Likert-type scale with scores from 1 (complete absence) to 5 (highest intensity) were collected and analyzed. The children receiving tube feedings or parenteral nutrition, with feeding difficulties, esophageal surgery, neurodevelopmental, genetic, metabolic or behavioral disorders, and inflammatory bowel disease were excluded.
Results: The demographics of EoE and non-EoE controls were similar for ethnicity (White: 83%), gender (male: 85%), and age [median (IQR): 11 (7-14) years]. All eight psychometric subscale scores were comparable between the EoE and non-EoE controls. The 'food approach' trait score [44 (38-54) vs. 43 (39-51)] as well as the 'food avoidant' trait score [53 (47-35) vs. 53 (43-56)] were also similar between children with and without EoE (Figure). Results from multiple logistic regression revealed that ethnicity, gender and age did not influence this association.
Conclusions: Our preliminary results suggest that the impact of EoE on eating behavior in school-aged children is similar to that seen in non-EoE controls with gastrointestinal conditions. Since eating behavior develops during infancy and evolves throughout childhood, prospective studies with adequate sample size and healthy controls are warranted to elucidate the impact of EoE on childhood eating behavior.
Provided Figures, Tables, References:



Vitamin D Receptor Expression is Down Regulated in Peripheral Blood Eosinophils in Eosinophilic Esophagitis

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Background: Eosinophilic esophagitis (EoE), a chronic immune-mediated disease with no cure, is characterized by increased eosinophils in the esophagus. Eosinophil recruitment to the esophagus is abnormal, and their presence and activation *in situ* may mediate pathology associated with EoE, including fibrosis. While food allergens are often eliminated as part of the treatment regimen, the elimination of milk, a rich source of vitamin D, may have adverse effects on innate and adaptive immune responses. As such, we hypothesized that eosinophil TGFβ production can be regulated through the vitamin D receptor (VDR) on eosinophils in EoE.
Methods: All pediatric patients evaluated for EoE from Jan-July 2017 in the GI clinic of Le Bonheur Children's Hospital were eligible for participation in this ongoing prospective study. Serum, separated from blood collected from 23 patients, was used to quantify 25(OH) Vitamin D levels by ELISA. In accordance with the Pediatric Endocrine Society guidelines, we defined levels <30 ng/dL as deficient. Peripheral blood eosinophils purified by magnetic bead separation were used to extract RNA, and 50 ng of RNA was converted to cDNA. Gene expression of *VDR* and *TGFB1* was measured by qPCR using *HPRT1* as the housekeeping gene for normalization. Changes in gene expression were determined using the $2^{-\Delta\Delta Ct}$ method as a fold change over expression levels seen in control eosinophils. Purified eosinophils were also analyzed by flow cytometry for activation status.
Results: EoE patients were younger and more likely to be male than non-EoE patients (7.4±4, 100% male and 11.6±4, 44% male respectively). The majority of our patients (78%) were vitamin D deficient irrespective of EoE status, although EoE patients trended toward less serum vitamin D levels compared to non-EoE controls. Eosinophils from EoE patients had a significant downregulation of *VDR* expression ($p<0.007$) and upregulation of *TGFB1* expression ($p<0.03$) compared to cells from their non-EoE counterparts. Eosinophils from patients were $MHCI^{hi}$, $CD44^{int}$, and $CD69^{lo}$ suggesting low activation in the periphery.
Conclusions: Our preliminary studies suggest that eosinophils in EoE are transcriptionally pro-fibrogenic and ongoing studies are aimed at understanding the impact of vitamin D treatment on eosinophils in EoE.

Sub-laryngeal esophageal tissue does not resemble mid and distal tissue in patients with active eosinophilic esophagitis

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Background: While Eosinophilic Esophagitis (EoE) is classically described as an allergy-mediated disease, the pathogenesis is not completely understood and likely involves genetic, environmental, and immune factors. Our group has reported that characteristic endoscopic features of EoE are not present in the sub-laryngeal region proximal to 17 cm from the incisors. The purpose of this study was to confirm this observation, measure mucosal impedance (MI) of this area in controls and patients with active disease, and to quantify expression of candidate genes from sub-laryngeal tissue and compare it with distal tissue in patients with active EoE and controls.
Methods: 11 patients with active EoE and 10 controls had mucosal biopsies from sub-laryngeal, mid, and distal esophagus and the number of eosinophils from each site was counted. Controls were defined as patients undergoing endoscopy for dysphagia or GERD and did not have active EoE or history of EoE. MI was measured at 2 cm, 5 cm, and 10 cm from the GE junction as well as at the sub-laryngeal region in

5 of these patients as well as in 3 controls. qRTPCR and IHC was used to quantify desmoglein-1 (*DSG1*), filaggrin (*FLG*), and periostin (POSTN) in sub-laryngeal tissue and distal/middle tissue from both active EoE patients (n=3-7, 6/7 on PPI during time of EGD) and controls (n=3-5, 4/5 on PPI at time of EGD). Patients included in this analysis all had less than 15 eosinophils in sub-laryngeal tissue.
Results: In active EoE patients, the number of eosinophils in sub-laryngeal tissue is significantly less than in the mid (7.55 ± 14.80 vs 44.18 ± 43.89 vs, ****P*<0.0001) and distal tissue (7.55 ± 14.80, 43.73 ± 16.09, ****P*<0.001, Figure 1). MI values at the sub-laryngeal region between 5 patients with EoE and 3 controls were not significant (2985 ± 892.9 vs. 4211 ± 1924, *P*=0.40); however, the MI difference between the sub-laryngeal tissue and 5 cm from the GE junction in EoE patients was greater than controls and was nearly significant (1740 ± 922.4 vs 568 ± 468, *P*=0.071). As expected, *DSG1* and *FLG* expression was significantly lower in distal tissue of EoE patients by both qpcr (**P*<0.05, **P*<0.05 respectively) and IHC ((**P*<0.05, ***P*<0.01 respectively). *POSTN* expression was increased by qRTPCR (**P*<0.05) and IHC (**P*<0.05) in distal tissue. However, *POSTN* and *FLG* expression in sub-laryngeal tissue from EoE patients when compared with sub-laryngeal controls showed no difference by qRTPCR or IHC. *DSG1*, however, had decreased expression by qpcr in sub-laryngeal tissue of EoE patients versus control (**P*<0.05) but no difference by IHC.
Conclusion: The sub-laryngeal region of the esophagus differs from the mid and distal region of the esophagus in patients with active EoE in number of eosinophils, mucosal impedance, and expression of a subset of candidate genes. These differences may provide insights into the pathophysiology of the disease.

Sustained remission of Eosinophilic Esophagitis After Discontinuation of Dietary Elimination in Children

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Background: Eosinophilic Esophagitis (EoE) is a chronic disease characterized by both esophageal dysfunction and eosinophilic infiltration of the esophageal epithelium. Current treatments include elimination diets and topical steroids. Symptoms and/or eosinophilic infiltrates generally recur following withdrawal of treatment. Our aims were to describe a subset of children with EoE brought into remission with elimination diets, who remained in both clinical and histological remission (<15 Eos/hpf) despite complete reintroduction of all eliminated food allergens, and to assess for factors that could differentiate them from other EoE patients.
Methods: A retrospective chart review of pediatric patients diagnosed with EoE was performed. Patients treated with elimination diets who remained in both clinical and histological remission despite full antigenic reintroduction were identified, and records were re-evaluated for accuracy of data. We compared these patients to the entire EoE cohort, and to EoE patients treated solely with elimination diets.
Results: Of 410 pediatric EoE patients from 25 European centers, 15 (3.7% of the whole cohort, 10.6% of those treated only with diet) remained in sustained clinical and histological remission following complete allergen reintroduction. The median time from the final reintroduction to the most recent endoscopy in resolved EoE was 15 weeks (IQR 8-68). Neither male gender (73.3% vs 78.6%), age at diagnosis (8.4±4.7yrs vs 9.2±4.7yrs), performance of a PPI test (86.7% vs 70.4%), personal (69% vs 59%) or family history (53.8% vs 57.5%) of atopy could differentiate patients with resolving disease from EoE treated with diet (p>0.15 for all comparisons). Of presenting symptoms, only failure to thrive/poor weight gain was significantly more frequent in patients with resolved disease compared to the full EoE cohort (26.7% vs. 9.9%, p=0.037).
Conclusions: Sustained remission of EoE in children treated with elimination diets is feasible although uncommon. None of the examined parameters differentiate resolving vs. non-resolving EoE. Reintroduction of triggering foods may be considered periodically to assess the need for continuous allergen elimination in children with EoE.

A Prospective, Multicenter Study to Compare and Validate Endoscopic, Histologic, Molecular, and Patient-Reported Outcomes in Patients with Eosinophilic Gastro-intestinal Disease

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Objectives: Eosinophilic gastro-intestinal diseases (EGIDs) include Eosinophilic Esophagitis (EoE), Eosinophilic Gastritis (EG) and Eosinophilic Colitis (EC) are rare diseases in need of better understanding. The main aim of the trial is to determine clinical and pathological features of patients with EoE, EG, and EC in a cross-sectional and a longitudinal study. The data described below summarizes the demographics of the first 632 patients recruited into the study.
Methods: Recruitment started in January 2015. Patients were enrolled across the ten Consortium of Eosinophilic Gastrointestinal Disease Researchers (CEGIR) sites in the U.S. Clinical features of subjects were determined using the REGID (Registry for Eosinophilic GI Diseases) Intake Form. Data was analyzed using descriptive statistics.
Results: In total, *632* participants have been recruited into the study; 503 with EoE, 56 with EG and 13 with EC. Gender per EGID diagnosis indicated a male proportion of 67%, 56% and 50%, for EoE, EG and EC, respectively ($p<0.0001$ for EoE). Demographic information demonstrated an age range of 0-78 years (mean age 22 years), and race (91.0% white, 4.2% African American, 0.3% Native American, 2.4% Asian and 2.0% mixed races). Information on medical history was available on *420* cases. Of these, 370 reported a diagnosis of EoE only, 42 had EG only and 11 had isolated EC. Focusing on EoE, 24.1% (n=121) reported to be on dual therapy (diet and steroids), 20.3% (n=102) were on topical/oral steroids, 14.9 %(n=75) were on diet therapy and 40.8% (n=205) listed no treatment. For EG, 21.4% (n=12) reported to be on dual therapy (diet and steroids), 17.9% (n=10) were on steroid therapy, 10.7 %(n=6) were on diet therapy and 50.0% (n=50) listed no treatment. For EC, 7.7% (n=1) reported to be on dual therapy (n=2), 15.4% were on steroid therapy (n=2), 15.4% on diet therapy and (n=8) and 61.5% reported no therapy. Of those suffering from EoE, 14.4% (52/360) reported a history of impactions and 30.2% (107/354) had dilations in the past.
Conclusion: We have recruited 632 EGID participants. Diet, steroids and combination of both therapies were commonly employed. The enrichment of EoE amongst males is preliminarily not seen in EG and EC.

Eosinophilic pancreatitis is a rare or ignored diseases entity in human

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Background: Eosinophilic pancreatitis (EP) is reported in human; however, the etiology and the role of eosinophils in EP pathogenesis is a poorly understood and not excusably explored. Notably, pancreas is devoid of eosinophils in healthy individuals; however, eosinophils accumulation and degranulation in the tissue sections was still reported in human pancreatitis. Therefore, we tested the critical role of eosinophils in promoting pancreatitis pathogenesis including fibrosis.
Method: Cerulein-induced chronic pancreatitis in wild type and IL-5 gene deficient mice was performed. qPCR, ELISA, western blot, anti-MBP immunostaining, Chloroesterase and Massons' trichrome analysis were performed to examine transcript, protein levels of eosinophil active cytokines, chemokines, tissue accumulation of eosinophils, mast cells and collagen.
Results: Herein, we show that indeed eosinophils accumulate and degranulate in human chronic and malignant pancreatitis. Further, to establish eosinophils role in pancreatitis, we first time demonstrate eosinophils accumulation and degranulation association to acinar cells atrophy and collagen accumulation in the pancreas of cerulein-induced murine model of pancreatitis. Additionally, induced transcript and protein levels of pro-inflammatory and pro-fibrotic cytokines, chemokines like *IL-5, IL-18*,

eotaxin1 and eotaxin-2, *TGF-β1, collagen-1, collagen-3, fibronectin and α-SMA* were also observed in experimental pancreatitis in mice. Mechanistically, we report that endogenous IL-5 deficiency protects mice from the induction of pancreatic eosinophilia, mast cells, pro-inflammatory and pro-fibrotic cytokines as well as chemokines in cerulein-induced murine model of pancreatitis. Additionally, we report that GATA1 KO mice following cerulean treatment show reduced pancreatic fibrosis. The presented human and experimental data support our hypothesis that eosinophils accumulation and degranulation is critical in promoting pancreatitis pathogenesis including fibrosis.
Conclusion: Taken together, we provide the evidence that eosinophils has a critical role in promoting pancreatitis pathogenesis including fibrosis and EP is an independent entity that needs appropriate attention to understand the mechanism of the induction of pancreatic fibrosis including malignancy.

Body Ache and Fatigue are Common Complaints of Patients with Eosinophilic Gastrointestinal Diseases

Authors and Affiliations: J Pablo Abonia[1], JP Krischer[2], G Furuta[3], ME Rothenberg[1], and the CEGIR Contact Registry Committee (CCRC). Cincinnati Children's Hospital Medical Center, Cincinnati, OH[1]; University of South Florida, Tampa FL[2]; University of Colorado School of Medicine, Aurora, CO[3]

Background: The Consortium of Eosinophilic Gastrointestinal Disease Researchers (CEGIR) represents a nationwide collaborative effort including members from the clinical and research communities, and patient advocacy groups (PAGs). The overriding goal of CEGIR is to advance the clinical care for patients with eosinophilic gastrointestinal diseases (EGIDs) and to conduct research into these rare diseases. In response to this need, CEGIR has created an online contact registry (CR) under the auspices of the Rare Diseases Clinical Research Network (RDCRN). The goals of the CR are to promote the role of CEGIR by encouraging individuals with EGIDs to register to learn about CEGIR activities and its clinical studies to enhance enrollment opportunities and to provide descriptive information on quality of life end points.
Methods: Initiated in March, 2015, the CEGIR CR has enrolled 1,183 patients with varying types of EGID: 79% eosinophilic esophagitis, 4% gastritis, 3% each colitis and gastroenteritis. Supplemental demographic and disease-specific information was captured for 636 (54%) patients. Enrollees were also invited to complete a questionnaire in effort to capture disease information and quality of life outcomes.
Results: Key features noted in our survey included a high frequency of complaints of fatigue occurring daily in 32.1%, weekly in 21.6%, and monthly in 14.1% of respondents (n=588). Deep muscle / joint ache represents another common complaint for patients responding to the survey, occurring daily in 17.8%, weekly in 18.3%, and monthly in 13.4% of respondents (n=584). 13.8% of respondents reported having at least one family member in addition to the respondent diagnosed with an EGID.
Conclusions: The CEGIR Contact Registry Committee communicates with enrollees regarding ongoing CEGIR studies of interest and provides unique insights driven by the interaction of patients, their advocates, along with basic and clinical researchers. This report identifies areas of concern for patients with EGID that are not regularly addressed in the clinical literature and identifies problems to be validated in future research.

Modifying the genome of esophageal epithelial cells using CRISPR/Cas9 technology

Authors and Affiliations: Julie M. Caldwell[1], Adina Ballaban[1], Purnima Pathre[1], Nurit P. Azouz[1], Ayushi Jain[1], Marc E. Rothenberg[1]. [1]Division of Allergy and Immunology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH

Background: Multiple lines of evidence suggest that epithelial cells have a primary involvement in eosinophilic esophagitis (EoE). Therefore, analysis of the function and regulation of epithelial genes in relevant *in vitro* models of the esophageal epithelium is necessary to advance understanding of EoE pathogenesis. CRISPR/Cas9-mediated genome editing allows for the production of cells exhibiting knockout (KO) of specific genes, modification of regulatory sequences, or introduction of precise genomic changes. This technology thus represents a potential method to produce cells to study epithelial gene function and regulation.

Methods: Esophageal epithelial cell lines were subjected to CRISPR/Cas9-mediated gene editing to produce genetic KO cells. TE-7 or EPC2 cells were transiently transfected with constructs expressing Cas9 nuclease and guide RNAs complementary to sequences within the *CCL26*, *CAPN14*, or *SPINK7* open reading frames. Cells were subjected to puromycin selection, and surviving cells were expanded, dispersed, and plated to produce single-cell clones. Clones were expanded, and the genomic DNA and protein expression of the cells were assessed.
Results: Of TE-7 cell clones resulting after transfection with *CCL26* guide DNAs, 93% were edited on at least one allele. Of the edited clones, 70% had edits on both alleles that would result in a frameshift and thus a genetic KO. Clones identified as KO by genomic DNA sequencing were confirmed to be KO by measuring IL-13-mediated induction of CCL26 by ELISA. Of EPC2 cell clones resulting after transfection with *CCL26* guide DNAs, 14% were edited on at least one allele, and 7% resulted in a genetic KO. Two *CAPN14* KO EPC2 cell clones were produced and verified at the genomic DNA and protein levels. Additionally, *SPINK7* KO EPC2 cells were generated. Interestingly, *SPINK7* KO cells or their supernatants exhibited epithelial barrier defects and increased proteolytic activity, respectively, compared to control cells, similar to previous observations using EPC2 cells stably transduced with shRNA targeting *SPINK7*.
Conclusions: CRISPR/Cas9 technology can be utilized to produce genetic KO of non-essential genes in esophageal epithelial cell lines. These cells with stable genetic modifications can be used in long-term functional assays.

Identification of Eosinophilic Esophagitis Endotypes Using Cluster Analysis Based on Esophageal Transcripts

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Background: Patients with eosinophilic esophagitis (EoE) have varied clinical presentations, pathological findings, and responses to therapy. These observations suggest that EoE is clinically heterogeneous even though its underlying pathophysiology is related to an antigen-driven, Th2-associated allergic disorder. EoE gene expression has been evaluated for diagnosis of EoE. By contrast, its role in

understanding the diversity of disease expression at the molecular level is not well understood. We hypothesized that the heterogeneity in EoE could be captured by molecular profiles.
Methods: We evaluated 227 esophageal samples obtained from patients with EoE who were enrolled in a multicenter prospective observational study in the US. We analyzed the transcriptomic signature in esophageal biopsy samples using an EoE diagnostic panel (EDP) comprised of a set of 95 esophageal transcripts (Gastroenterology 2013). Cluster analysis was based solely on the EDP signature without using any clinical information. We analyzed associations among clusters and histological (n=126) and molecular (n=227) features. Histological features were assessed by peak eosinophil counts and the EoE histology scoring system (HSS). Molecular features were assessed by 95 EoE-related gene transcripts in EDP.
Results: Among 227 samples, 69.2% were male; median age at biopsy was 18.8 (Interquartile range 9.5 - 40.1). Cluster analysis based on EDP revealed the presence of four potential EoE clusters. Two clusters were associated with higher eosinophil counts/HSS scores (Cluster 3 and 4) and two clusters with lower eosinophil counts/HSS scores (Cluster 1 and 2). The group of higher eosinophil counts/HSS scores were divided into 2 clusters with Cluster 4 (n=21) showing the highest level of Th2 cytokines (TSLP, IL4, IL5RA, NTRK1) and steroid responding genes (FKBP5), and Cluster 3 (n=57) showing the lowest level of epithelial differentiation genes (FLG, SPINK7, CLDN10, UPK1A). The group of lower eosinophil counts/HSS scores was also divided into 2 clusters with Cluster 2 (n=81) showing the lowest level of inflammatory cytokines and enrichment of remission patients, and Cluster 1 (n=68) showing a mixed population between the group of higher eosinophil (Cluster 3 and 4) and Cluster 1, suggesting partial responder status.
Conclusions: Clustering analysis based on EDP identified four putative EoE clusters. Clusters with differential histological and molecular levels could represent underlying endotypes that have unique molecular signatures driving disease mechanisms. These findings have the potential to discriminate clinically relevant patient phenotypes but more data are needed.

Deletion of SPINK7 by CRISPR/Cas9 elicits pro-inflammatory and impaired epithelial barrier responses in esophageal epithelial cells

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Background: Eosinophilic esophagitis (EoE) is an inflammatory disorder characterized by impaired epithelial barrier and triggered by immune hypersensitivity to food antigens. Previous studies indicate that the serine peptidase inhibitor kazal type *(SPINK)7* is constitutively expressed during esophageal epithelial differentiation and is depleted in EoE. Herein, we aimed to test the consequences of CRISPR-Cas9-mediated knockout (KO) of SPINK7, focusing on the hypothesis that SPINK7 deficiency might recapitulate EoE features, at least in part.
Methods: The *SPINK7* locus was targeted for double-strand break introduction by transfecting human esophageal epithelial cells (EPC2) with a construct expressing Cas9 nuclease and gRNA complementary to sequence 3' of the start of the *SPINK7* open reading frame and immediately 5' of a protospacer adjacent motif (PAM). Control and SPINK7 KO cells were cultured at the air-liquid interface (ALI) or in high calcium-high confluency conditions to promote squamous cell differentiation. SPINK7 protein expression was analyzed by western blot, barrier integrity was examined by trans-epithelial electrical resistance measurements during differentiation, and mRNA expression of filaggrin was analyzed by quantitative PCR. Trypsin-like proteolytic activity and urokinase-plasminogen activator (uPA) activity were determined through functional assays. Additionally, pro-inflammatory cytokine release (i.e. thymic stromal lymphopoietin (TSLP) and interleukin (IL)-8) were assessed by enzyme-linked immunosorbent assays.
Results: CRISPR/Cas-9-mediated genetic editing produced genetic knockout of SPINK7 in human esophageal epithelial cells, verified by undetectable SPINK7 protein expression in knockout cells as compared to control cells. Functionally, SPINK7 KO cells produced lowered transepithelial resistance during differentiation and exhibited decreased expression of filaggrin, indicating impaired epithelial barrier

function in comparison to control cells. Loss of SPINK7 unleashed proteolytic activity observed by enhanced trypsin-like and uPA activities in SPINK7 KO compared to control cells. Further, a pro-inflammatory response was triggered with increased release of cytokines IL-8 and TSLP in SPINK7 KO as compared to control cells.
Conclusion: SPINK7 loss induces an EoE-like phenotype with impaired epithelial barrier integrity and unhindered proteolytic activity, as well as a pro-inflammatory cytokine response. Thus, SPINK7 deficiency during differentiation may weaken esophageal barrier function and initiate the inflammatory cascade of an allergic response. Verification of preliminary studies of SPINK7 loss with CRISPR-Cas9-edited cells validates the utility of the knockout model for further investigation of SPINK7 deficiency and potential drug screening.

Is the Endoscopic Reference Score (EREFS) a good tool to assess the diagnosis of Pediatric Eosinophilic Esophagitis?

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Background: The EREFS has been used for diagnosis assessment and predicting the activity and remission of the disease in EoE adult patients. However, there are a few studies in which the effectiveness of this endoscopic metric has been tested in children. The aim of this study was to characterize the EREFS features in a pediatric population undergoes to diagnostic endoscopy and assess the score utility for EoE diagnosis.
Methods: This was a pediatric endoscopic prospective cohort from January 2015 to August 2016. It has included patients without any previous diagnosis, who have presented general gastrointestinal symptoms and have been referred for diagnostic endoscopy at a reference public healthcare centre. At the first endoscopic procedure the original EREFS score was assessed, the biopsies from proximal and distal esophagus, stomach and duodenum were collected, and the demographic data was obtained. All enrolled patients were followed up at the pediatric gastroenterology outpatient clinic until completing the diagnoses of EoE, GERD or others, under the current guidelines recommendations. The descriptive analysis was done with mean and standard deviation for total (T-EREFS), inflammatory (I-EREFS), and fibrostenotic (F-EREFS) scores. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), were calculated and the ROC analysis was done for the scores.
Results: This prospective pediatric cohort enrolled 110 patients and analyzed data from 107. The T-EREFS were 3.31, 1.21 and 0.42 and I-EREFS were 3.06, 1.0 and 0.42 for EoE, GERD and controls patients, respectively. There was a significant statistic difference among the EoE, GERD, and controls in inflammatory e total scores. The sensitivity was 75% for T-EREFS and I-EREFS, and the specificity was higher than 85% for both. The T-EREFS had AUC of 0.94.
Conclusion: The inflammatory features are more frequently found than fibrostenotic features in the assessment of pediatric EoE diagnosis. The I-EREFS and T-EREFS have a good ability to predict EoE cases and separate from GERD patients. The F-EREFS is not expressive in pediatric EoE at the diagnosis.

Eosinophilic Esophagitis Reference Score Accurately Identifies Disease Activity and Treatment Effect in Children

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Background: The EoE Endoscopic Reference Score (EREFS) assesses severity of five endoscopic findings: edema, rings, exudates, furrows and strictures based on the validated description in adults. The relationship between endoscopic findings and histology as scored by the EREFS system in eosinophilic esophagitis (EoE) in children has not been previously explored. We aimed to determine the diagnostic utility of EREFS scoring and assess the relationship between endoscopic changes after treatment in children.
Methods: We performed a prospective study in children undergoing diagnostic or follow up post treatment endoscopy from December 2012 to December 2016. Incident cases of EoE were diagnosed based on 2011 consensus guidelines and treated with either elimination diet or topical steroids. EREFS scores and receiver operating characteristic were determined for 1) incident EoE cases (N= 77) vs controls (N= 115), 2) post-treatment active (N =101) vs inactive (N=128) EoE cases, and 3) paired pre- and post-treatment EoE cases (N=85). Component and composite EREFS scores were correlated with eosinophil counts.
Results: 192 diagnostic (mean age 10, 54% male, 92% Caucasian) and 229 post-treatment (mean age 10, 79% male, 90% Caucasian) endoscopies were evaluated in 421 children. The sensitivity/specificity of $\geq$ 1 visual abnormality at diagnosis were 89.6%/87.9% and 85.2%/50.8% post-treatment. The mean EREFS inflammatory score was 2.6 for incident EoE patients compared to 0.1 in controls ($p<0.001$). Post-treatment EREFS inflammatory score in responders decreased from a mean of 2.4 to 0.5 ($p<0.001$). The EREFS inflammatory score strongly correlated with peak eosinophilia ($p<0.001$). Baseline and post-treatment longitudinal data from 85 patients demonstrated a significant reduction in the composite EREFS inflammatory score from 2.4 to 0.7, ($p<0.001$) for treatment responders, with 92% of responders demonstrating score reduction.
Conclusions: The EREFS scoring system accurately identifies EoE in children at diagnosis. Treatment responders had significantly lower EREFS scores than non-responders. EREFS scoring system can be used as tool to identify children with EoE and monitor outcome following treatment in conjunction with histology.

Alternative Splicing Analysis of Eosinosphilic Esophagitis using high-depth RNA-seq

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Background: Allergic inflammation of the esophagus (eosinophilic esophagitis or EoE) in response to food antigens afflicts an estimated 139,000 American adults and 44,000 children, and can result in persistent pain, nutritional deficiency, food impaction, and esophageal tearing. Molecular characterization of inflammatory pathways and identification of disease markers will hopefully lead to better diagnosis, therapeutics, and targeted therapy to improve management of this chronic relapsing-remitting condition. Molecular screening based on gene expression alone may miss functional variation in isoforms resulting from alternative splicing of pre-mRNA to generate mRNA.
Methods: A pipeline was developed to fetch archived sequencing data and process raw RNA-seq unaligned read data in parallel on CCHMC's supercomputer cluster. Alternative splicing was assessed using high-depth RNA-seq (> 100 million reads) on esophageal biopsies from 10 patients with active eosinophilic esophagitis, 1 with chronic esophagitis, and 9 controls with normal histology, and data were analyzed with AltAnalyze.
Results: Cell lineage profiling identified irregular enrichment patterns in 2 of the normal controls, possibly indicating irregular cellularity in the samples and potential variability in the biopsy procedure. Hierarchical clustering revealed two expression clusters in our EoE samples. EoE Cluster 1 showed a distinct expression profile compared to controls, with characteristic signs of immune infiltration, cell proliferation, and loss of esophageal epithelial barrier function. EoE Cluster 2 displayed an expression profile resembling controls, including low markers of inflammation and immune infiltration, suggesting sampling variability in the biopsy procedure. A biopsy from a patient with chronic esophageal inflammation showed an expression profile that largely resembled active EoE but also shared characteristics with normal

controls. EoE Cluster 1 showed transcript and splicing differences in Ensembl genes compared to controls, including alternative N- (86 genes) and C-termini (110), alternative coding (35), and truncated products (26) or products likely to be degraded (35).
Conclusions: A subset of EoE shows a distinct expression profile compared to controls, with characteristic signs of immune infiltration, cell proliferation, and loss of esophageal epithelial barrier function. Post-transcriptional regulation may have a role in regulating gene activity that is currently being investigated.

Persistent post-treatment endoscopic abnormalities and symptoms despite histologic remission are associated with increased mast cell density and activation

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Background: Remission in Eosinophilic Esophagitis (EoE) is defined by a post-treatment endoscopy with less than 15 eosinophils per high powered field (eos/hpf). Despite histologic improvement, endoscopic abnormalities and symptoms can persist. Mast cells are elevated in active EoE and thought to have a role in pathogenesis via smooth muscle contractility and fibroblast activation. We evaluated the role of intra-epithelial mast cells in EoE patients with histologic remission. The aim was to determine if mast cell density and degranulation is increased in children with EoE in histologic remission with persistent endoscopic abnormalities and/or symptoms.
Methods: We performed a secondary analysis of prospective data collected in children undergoing post-treatment endoscopy at Lurie Children's Hospital of Chicago from 2011 to 2015. Data was analyzed from EoE patients with histologic remission along with non-EoE controls. Archived slides were obtained from the mid and distal esophagus and immunohistochemistry for tryptase was performed. Mast cell density (MC/hpf) and degranulated MC/hpf were quantified in all epithelial regions. Demographics were collected at enrollment; symptom surveys and endoscopic findings were recorded. Clinical remission was defined as absence of symptoms or endoscopic abnormalities.
Results: 92 EoE patients (mean age 10 yr, 71% male, 92% Caucasian) and 24 controls (mean age 11 yr, 50% male, 88% Caucasian) were evaluated. Mast cells were significantly elevated in EoE patients compared to controls (16.6 vs 5.2, $p<0.001$). Mast cell density was increased in patients with edema ($p=0.0025$), furrows ($p=0.002$), and rings ($p=0.012$) but not exudate. Furrowing was independently associated with elevated mast cell density and basal zone expansion in regression modeling ($p= 0.035$, $p=0.041$). Patients in clinical remission (n=15), with no endoscopic abnormalities or symptoms, had lower mast cell density and degranulation compared to non-clinical remission (10.7 vs 18.1, $p=0.01$) but no difference from control (10.7 vs 5.4). There was no difference in eosinophilia, treatment, or atopy between clinical remission and non-clinical remission. Patients with abdominal pain, early satiety, odynophagia, and reflux had increased mast cell density compared to those in clinical remission.
Conclusions: Mast cell density and degranulation is increased in children with EoE in histologic remission compared to controls. Patients with histologic remission but ongoing endoscopic abnormalities or symptoms had increased mast cell density and degranulation when compared to patients in clinical remission. These findings are independent of eosinophilia, type/duration of treatment and atopy. This suggests an independent role for mast cells in EoE as a potential outcome metric associated with a poor clinical response, and a potential role for mast cell targeted therapy.

Dupilumab Efficacy and Safety in Adult Patients With Active Eosinophilic Esophagitis: A Randomized Double-Blind Placebo-Controlled Phase 2 Trial

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Background: Patients (pts) with eosinophilic esophagitis (EoE) have high rates of comorbid type 2-mediated diseases (e.g. food allergy, atopic dermatitis [AD], asthma). Due to limited response to standard of care and lack of approved medications for EoE, there is a need for new treatment options for this chronic disease. Dupilumab, a fully human anti-interleukin (IL)-4Rα monoclonal antibody, inhibits signaling of IL-4 and IL-13, key drivers of type 2-mediated inflammation, and is approved in the USA for the treatment of adults with moderate-to-severe AD. This study assessed the efficacy and safety of dupilumab in adults with active moderate-to-severe EoE.
Methods: This was a randomized, double-blind, parallel, placebo (PBO)-controlled phase 2 study (NCT02379052). Adults with active EoE (histologically confirmed with dysphagia symptoms) were randomized (1:1) to receive weekly subcutaneous dupilumab 300 mg (loading dose 600 mg on Day 1) or PBO, for 12 weeks. The primary endpoint was change in Straumann Dysphagia Instrument (SDI) score from baseline (BL) to Week 10. Secondary endpoints included percent change in weekly Eosinophilic Esophagitis Activity Index (EEsAI) score from BL to Week 10, percent change in overall peak esophageal intraepithelial eosinophil count (eos/hpf), change in a modified EoE Endoscopic Reference Score (EoE-EREFS) from BL to Week 12, and safety. Exploratory endpoints included change in EoE Histological Scoring System (EoE-HSS) and esophageal distensibility from BL to Week 12.
Results: 47 pts (dupilumab n=23) received ≥1 dose of study drug. BL demographics and characteristics were balanced between treatment groups, except for mean total IgE (dupilumab 217.8 kU/L; PBO 468.2 kU/L). Dupilumab improved SDI score (−3 vs −1.3; *P*=0.0304) and numerically reduced EEsAI score (−34.6% vs −11.3%; *P*=0.085) vs PBO at Week 10 (**Table 1**). At Week 12, dupilumab reduced peak eosinophil count (eos/hpf) from BL by −94.1 (−91.8%) vs −7.4 (+15.1%) with PBO (*P*<0.0001), and decreased EoE-EREFS by −1.9 vs −0.3 with PBO (*P*=0.0006). Total EoE-HSS grade and stage scores and distensibility plateau were improved at Week 12 (all *P*<0.001 vs PBO). The most common treatment-emergent adverse events were injection-site erythema (dupilumab 34.8%; PBO 8.3%) and nasopharyngitis (dupilumab 17.4%; PBO 4.2%).
Conclusions: Dupilumab significantly improved dysphagia as well as histological and endoscopic measures of disease, and was generally well tolerated in adults with EoE.

Provided Figures, Tables, References:

Table 1.

	PBO (n=24)	Dupilumab 300 mg qw (n=23)	LS mean difference vs PBO (95% CI)
SDI score			
BL score, mean (SD)	6.4 (1.0)	6.4 (1.0)	
Week 10	n=14	n=17	

LS mean change from BL (SE)	−1.3 (0.6)	−3.0 (0.5)	−1.7 (−3.2, −0.2)*
EEsAI score			
BL score, mean (SD)	62.2 (16.5)	62.0 (18.4)	
Week 10	n=13	n=17	
LS mean % change from BL (SE)	–11.3 (9.9)	–34.6 (9.1)	–23.2 (–49.7, 3.2)#
Peak esophageal intraepithelial eosinophil count (eos/hpf)			
BL score, mean (SD)	101.1 (57.1)	102.1 (53.5)	
Week 12	n=22	n=22	
LS mean change from BL (SE)	−7.4 (9.6)	−94.1 (9.5)	−86.7 (−113.3, −60.2)**
LS mean % change from BL (SE)	15.1 (12.5)	−91.8 (12.3)	−106.9 (−141.4, −72.5)**
Pts with response <6 eos/hpf, n (%)	0.0	14 (60.9)	
Pts with response <15 eos/hpf, n (%)	0.0	18 (78.3)	
EoE-EREFS score			
BL score, mean (SD)	4.3 (1.5)	3.9 (1.9)	
Week 12	n=22	n=23	
LS mean change from BL (SE)	−0.3 (0.3)	−1.9 (0.3)	−1.6 (−2.5, −0.7)**
EoE-HSS score (excluding lamina propria)			
BL score – grade, mean (SD)	27.6 (8.4)	28.5 (7.9)	
Total – grade (severity) score			
Week 12	n=20	n=21	
All LS mean % change from BL (SE)	3.9 (6.6)	−64.2 (6.4)	−68.1 (−85.8, −50.3)**
Distal LS mean % change from BL (SE)	2.7 (5.3)	−57.0 (5.3)	−59.7 (−74.3, −45.1)**
Mid LS mean % change from BL (SE)	−8.1 (7.0)	−70.8 (6.8)	−62.7 (−81.7, −43.7)**
Proximal LS mean % change from BL (SE)	66.1 (27.4)	−50.2 (24.5)	−116.3 (−188.0, −44.5)**
BL score – stage, mean (SD)	27.4 (6.5)	27.9 (6.1)	
Total – stage (extent) score			
Week 12	n=20	n=21	
All LS mean % change from BL (SE)	−3.5 (5.0)	−58.1 (4.7)	−54.6 (−68.1, −41.0)**
Distal LS mean % change from BL (SE)	5.1 (6.3)	−50.6 (6.3)	−55.6 (−73.2, −38.1)**
Mid LS mean % change from BL (SE)	−18.4 (5.7)	−62.0 (5.5)	−43.5 (−59.1, −28.0)**
Proximal LS mean % change from BL (SE)	43.1 (21.6)	−46.9 (19.2)	−90.0 (−146.5, −33.5)**
Distensibility plateau, mm			
BL, mean (SD)	17.60 (2.9)	18.66 (3.8)	
Week 12	n=12	n=12	
LS mean % change from BL (SE)	−6.2 (2.7)	11.8 (2.7)	18.0 (10.9, 25.2)**

#*P*=0.085, **P*<0.05, ***P*<0.001 vs PBO. SDI is a 2-item measure of dysphagia; total score range 0−9 (higher scores indicate worse symptoms). EEsAI is a 5-item measure of dysphagia; total score range 0−100 (higher scores indicate worse symptoms). The EoE Histology Scoring System (EoE-HSS) measures eosinophil density, basal zone hyperplasia, eosinophil abscesses, eosinophil surface layering, surface epithelial alteration, dyskeratotic epithelial cells, and dilated intercellular spaces. Esophageal distensibility plateau was measured using the Functional Lumen Imaging Probe, a probe using impedence planimetry. The continuous efficacy endpoints were analyzed in the full analysis set (FAS) using multiple imputation (MI), followed by an analysis of covariance (ANCOVA) model, with treatment group as fixed effect, and baseline SDI and the relevant baseline value as covariates.
CI, confidence interval; LS, least-squares; qw, every week; SD, standard deviation; SE, standard error.

Intestinal IL-15 overexpression has an important role in food allergen induced Eosinophilic Gastro Intestinal Disease (EGID)

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Background: IL-15 associated overexpression in gastrointestinal disorders including eosinophilic esophagitis (EoE) and celiac disease are reported. However, the mechanistic role of IL-15 in promoting gastrointestinal disorders is largely unknown. The purpose of the current study is to test the hypothesis that IL-15 may have a critical role in promoting food intolerance and eosinophilic gastrointestinal disease (EGID).
Method: Intestinal IL-15 overexpressed mice were generated by using intestinal fatty acid binding promoter (iFABP). iFABP is specifically present in the jejunum; therefore, IL-15 is overexpressed only in

the small intestine (jejunum). Further, to test the role of IL-15 in food allergen-induced intestinal inflammation, Accordingly, wild type and iIL-15 transgenic mice were sensitized with intra-peritoneal injection of 200 mcg OVA with 1mg Alum on day 0 and day 7. The sensitized mice were challenged on day 14 intra-gastrically with OVA (100 mcg) 9 times on alternate days. The body temperature and weight loss were recorded after each challenge, and inflammatory cells accumulation, particularly eosinophil, goblet cells hyperplasia in the jejunum was assessed by immunohistochemistry, using anti-MBP antibody. **Results**: Therefore, we generated enterocyte overexpressed IL-15 transgenic mice using intestine specific Fabpi-promoter. The Fabpi-IL-15 (iIL-15) transgenic mice show ~ 10 fold increase of IL-15 levels in the jejunum with marked increases in the number of jejunum eosinophils; however, no induction of eosinophils in the blood or any other gastrointestinal segments was observed. Eosinophilia in the villus of jejunum was substantially higher in iIL-15 mice indicating a strong correlation with IL-15 intestinal expression. Highly induced goblet cells hyperplasia was also observed in the jejunum of iIL-15 mice. Furthermore, we observed that intestinal IL-15 transgenic mice have induced levels of IL-18 transcripts and protein levels and IL-15 transcript significantly correlates with the induced transcript levels of IL-18. Therefore, to understand the role of IL-18 in iIL-15 mice, we generated and examined endogenous IL-18-deficient-Fabpi-IL-15 transgenic mice. The analysis of IL-18$^{-/-}$iIL-15 mice indicated IL-18 and IL-15 association has an important role in promoting IL-15-induced eosinophilic gastrointestinal disorders (EGID). Since, intestinal IL-15 overexpression is observed in celiac disease; therefore we further examined OVA intolerance in iIL-15 mice. The. OVA sensitized and challenged iIL-15 mice showed loss of body weight and diarrhea along with induced jejunum eosinophilia compared to wild type mice. **Conclusion:** Taken together, our findings demonstrate that intestinal IL-15 overexpression induces compartmentalized eosinophils induction and food intolerance in mice.

Delayed diagnosis of eosinophilic esophagitis in a teenager presenting with failure to thrive – Case Report

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Background: Eosinophilic esophagitis (EoE) is an under recognized chronic condition in which symptoms of gastro esophageal reflux occur with eosinophilia in esophagus biopsy. This disorder affects both children and adults and is associated with atopic disorders. In advanced disease, severe complications such as esophageal stenosis and malnutrition could appear. Treatment is based on dietary elimination, corticosteroids and endoscopic dilatation. We report a case of delayed EoE diagnosis in a teenager presenting with failure to thrive and esophageal stenosis.
Case summary: This is a 14yo male with short stature and no puberty development complaining of dysphagia and choking for the last two years. His Pediatrician, who referred him to a psychologist, first attributed these symptoms to behavior problems. As patient evolved with worsening of the symptoms, his family decided to consult a Pediatric Gastroenterologist. Clinical characteristics including personal and family history for allergy, blood and skin tests were described. Esophagogastroduodenoscopy (EGD) showed longitudinal striae, proximal third thickening of the esophagus, and stenosis preventing the passage of the device of 9.8mm in diameter. Biopsies showed >20 eosinophils/hpm/field. Dietary therapy and omeprazole were initiated for treating EoE. Symptoms persisted and EGD and biopsies showed no response to treatment. Swallowing fluticasone was added but no improvement in EGD was noticed 4 months later. Considering the refractoriness of the treatment, he was referred for progressive endoscopic dilatations, with no complications. Patient progresses with improvement of symptoms, nutritional recuperation and is still in clinical follow-up.
Comments: EoE's natural history is largely unknown. There is paucity of clinical and epidemiologic data regarding EoE in children. Although its prevalence is increasing, the number of patients diagnosed in Brazil remains unknown. Data about its epidemiology will be presented. As its diagnosis is usually late

when complications are present, Pediatricians must be alert to the warning signs. EoE requires expensive, repeated, and invasive EGDs and biopsies for diagnosis and treatment, resulting in substantial physical, psychological, and financial impact. Additional enrollment and future studies would provide further validation and refinement of the diagnosis.

Eosinophilic Esophagitis Caused by Oral Immunotherapy to Peanuts: Two Case Reports

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Background: Eosinophilic esophagitis (EoE) is a known complication of oral immunotherapy (OIT). Here we report two cases of biopsy confirmed EoE in patients undergoing peanut OIT. HA and CJ are 9 and 6 year-old males, respectively with clinical and laboratory histories consistent with peanut IgE-mediated food allergy. HA has a h/o allergic rhinitis and asthma and complained of belly ache, nausea, and occasional episodes of vomiting soon after starting peanut OIT. CJ was non-atopic and had similar complaints which did not begin until he started a dose of 2 peanuts (~500mg peanut protein). Both noticed some symptom improvement after adding daily probiotic, ranitidine, and taking the peanut dose with food but eventually developed daily refractory nausea despite reducing the peanut dose necessitating referral to GI for EGD and biopsy. HA experienced grade 1 anaphylaxis with 1 and 7 peanut doses treated with epinephrine whereas CJ had no episodes of anaphylaxis during OIT.
Methods: Absolute eosinophil counts (AEC) pre-OIT and during OIT was used as a surrogate marker for inflammation and possible development of EoE. Proximal and distal esophagus biopsies were obtained while the patients were still receiving OIT. An eosinophil count >15 per high powered field was considered diagnostic of EoE.
Results: HA did not have a pre-OIT AEC however during OIT AEC was 0.50 K/mcL (range 0.00-0.50 K/mcL). For CJ pre-OIT AEC was 0.28 K/mcL; during OIT the AEC increased to 1.11 K/mcL at the time of biopsy. For HA, EGD revealed gross and microscopic features consistent with an EoE diagnosis (biopsy > 50 eos/hpf) confirmed by transcriptome analysis using EoGenius™. For CJ, EGD also revealed gross and microscopic feature of EoE; proximal and distal esophageal biopsies revealed ≥50 eosinophils/hpf. EoGenius™ was not performed in this patient. Clinical symptoms have resolved in both children after discontinuing OIT, biopsies have not been repeated.
Conclusions: Although peanut OIT appears to be safe and effective, EoE is a potential complication that requires monitoring during and after treatment. The current literature reports ~2.7% overall prevalence of new onset EoE with OIT (Lucendo et.al. 2014) which mirrors the experience in our practice. Monitoring peripheral eosinophils during OIT as a marker for suspected EoE requires further investigation.

Eosinophils support adipocyte maturation and promote glucose tolerance in obesity

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Although eosinophils have been considered destructive cells that mediate Th2 inflammation, they have also been shown to be involved in a number of regulatory responses in a variety of physiological processes.Whole-genome RNA sequencing of the small intestinal tract, where eosinophils primarily reside in steady state,suggested the presence of impaired lipid metabolism ineosinophil-deficient ΔdblGATA mice.Furthermore, we found that the perigonadal adipose tissue of high-fat diet (HFD)-fed wild-type (WT) mice showed increased expression of mRNAs of CC chemokine receptor 3 and eotaxin-1 and increased eosinophil frequency. The ΔdblGATA mice on a HFD showed reduced weight gain and

body fat and developedglucose intolerance. Based on these results, we hypothesized that the inability toappropriately expand adipose tissue may be an underlying reason for insulin resistance in ΔdblGATA mice. Perigonadal adipose tissue of HFD-fed ΔdblGATA mice showed impaired enlargement of adipocytes and decreased expression of adipogenic genes. The perigonadal adipose tissue of ΔdblGATA mice also showed increased infiltration of macrophages, $CD4^+$ T-cells, and B-cells, and higher levels of lactate, a marker for hypoxia. Increased mRNA levels of interferon (IFN)-γ and decreased mRNA expression of interleukin (IL)-4 and IL-13 were observedin the perigonadal adipose tissues of HFD-fed ΔdblGATA mice. When treated with IFN-γ,3T3L1 cells showed a significant decrease in lipid deposition, while IL-4 treatment promoted lipid accumulation in these cells. Excessive lipid accumulation in non-adipose tissues is associated with insulin resistance, and the HFD-fed ΔdblGATA mice showed increasedlipid storage in the liverthan the WT mice. Based on these findings, we propose that obesity might promote eosinophil infiltration into adipose tissues and that fat-infiltrated eosinophils might contribute to the maintenance of a homeostatic microenvironment that supports adipocyte maturation and improves the metabolic profile.

Co-occurrence of Eosinophilic Gastrointestinal Disorder Diagnoses and Inflammatory Bowel Disorders

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Eosinophilic gastrointestinal disorders (EGID) are chronic immune disorders that occur when eosinophils infiltrate the gastrointestinal tract resulting in tissue inflammation. EGID have been associated with other diseases such as IgE mediated food allergy, atopic dermatitis, and inflammatory bowel disease (IBD). Inflammatory bowel diseases cause chronic inflammation of the gastrointestinal tract, with Crohn's disease (CD) affecting any portion of the gastrointestinal tract and ulcerative colitis (UC) affecting the large intestine specifically. It has become evident that pediatric patients may be at increased risk of developing EGID in conjunction with CD and/or UC. We searched electronic medical records at Cincinnati Children's Hospital Medical Center (CCHMC) for the co-existence of EGID in patients with IBD. Of the 2508 patients who received an IBD diagnosis of CD, UC, or UC plus CD, 185 (7.4%) were diagnosed with EGID. Stratified, 1583 were diagnosed with CD, 556 with UC, and 369 were diagnosed with both UC and CD. Ninety-seven (6.1%) of the 1583 CD patients, 39 (7 %) of the 556 UC patients, and 49 (13.3%) of the 369 with both CD and UC had an EGID diagnosis. Compared with all patients within the electronic medical record, the odds ratio of developing EGID and CD and/or UC was 26.21245 with a 95% confidence interval (22.497,30.541). Our analysis has shown a marked increased risk of EGID combined with IBD with increased prevalence in patients with both UC and CD.

Child vs Parent Perceptions of Symptoms and Quality of Life in Eosinophilic Esophagitis

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Background: Discrepancies between child and parent assessment of symptoms and general well-being affect the clinical evaluation of pediatric patients' needs. Here, we compare child self-reports and parent proxy-reports of symptoms and health-related quality of life in eosinophilic esophagitis (EoE).
Methods: Patients (8 - 17 years old [mean 12.8 years]; 66% male) and parents completed the Pediatric EoE Symptom Score v2.0 and the Pediatric Quality of Life Inventory v4.0 Generic Core Scales (n = 44) before patients initiated treatment in a PCORI-sponsored EoE Diet Trial. Child and parent-proxy scores were analyzed using Wilcoxon rank sum test. Relationships between child and parent-proxy reports were measured using Spearman's rho correlations. Bland-Altman plots were used to assess agreement and bias between reports.
Results: Quality of life (QOL) scores were not different between parent and child groups. Bland-Altman plots revealed moderate inter-rater variation between individual parent and child QOL scores. Older children (13 – 17 years old) and parent reports of QOL were moderately correlated ($r = 0.62$, $p < 0.01$). Parent-proxy symptom scores tended to be higher than child scores (total score: 40.0 vs 31.9, $p = 0.07$; dysphagia score: 46.9 vs 35.9, $p = 0.09$; GERD score: 37.5 vs 25.0, $p = 0.05$). Bland-Altman plots showed moderate (occasionally large) differences between individual parent and child symptom scores with systematic bias apparent in parent vs child dysphagia and GERD symptom scores (bias = 8.6 and 7.5, $p < 0.05$, respectively). Clinically significant differences were present in a notable minority of parent vs child symptom scores. Child and parent-proxy symptom reports were correlated across dysphagia ($r = 0.61$, $p < 0.001$), GERD ($r = 0.51$, $p < 0.001$), pain ($r = 0.67$, $p < 0.001$) and nausea/vomiting ($r = 0.71$, $p < 0.001$) symptom domains.
Conclusions: Parent and child symptom and QOL reports were correlated and similar in the majority of this cohort of pediatric EoE patients with active disease. A non-trivial minority of children and parents scores, however, were discordant. Parent-proxy reports may serve as a substitute for child self-reports of symptoms and general well-being for many, but not all, children. Our findings highlight the importance of considering child reports of symptoms and general well-being as these reports add an extra dimension that may be important when evaluating the needs of pediatric patients. Larger studies are needed to identify the factors that influence agreement between child self-report and parent proxy-reports in EoE.

Unsedated In-Office Transnasal Endoscopy is Safe and Effective in Monitoring Disease Activity in Pediatric Eosinophilic Esophagitis

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Background: Eosinophilic esophagitis (EoE) is a chronic allergen-mediated disease characterized by esophageal dysfunction and dense esophageal eosinophilia. Clinical manifestations of EoE include dysphagia, food impaction, abdominal pain, and reflux-like symptoms. Traditionally, monitoring of disease activity is done by assessing the esophageal mucosa and by histopathological assessment of biopsies obtained during an esophagogastroduodenoscopy (EGD), which can be time consuming, expensive, and has risks associated with anesthesia. Recently, unsedated transnasal esophagoscopy (TNE) has been performed successfully in a small cohort of patients as an alternative to EGD for EoE surveillance. Unsedated TNE has advantages because it can be performed in an outpatient clinic room and requires no anesthesia or sedation. The aim of this study was to evaluate the completion rate, adverse events,

and quality/adequacy of pathology specimens obtained from TNE (2.8 mm or 4.0 mm bronchoscope) in pediatric patients with EoE.
Methods: A retrospective chart review of 120 subjects who underwent TNE between June 2014 and February 2017 was performed. Demographics were obtained. Informed consent was obtained prior to the procedure. Subjects were instructed to not eat or drink 2 hours prior to TNE. In a standard clinic room, subjects sat upright in a chair and were given 2-6 sprays of 4% aerosolized lidocaine to nares for topical anesthesia. Unsedated TNE was performed and biopsy specimens were obtained with either 2.8 mm or 4 mm flexible bronchoscopes. Visual findings of TNE, biopsy specimen analysis and adverse events of TNE were assessed.
Results: 178 TNEs were done on 120 subjects, aged 5-18 years. Visual findings were recorded and included visually normal (55%), linear furrowing (44%), exudate (8%), rings (2%) and edema (1%). 153 (88%) of TNEs were tolerated without adverse events. Of TNEs with adverse events, the most common were vomiting (4.5%), spit-up (3.4%), epistaxis (1.1%), nasal irritation (2.2%) and other events (1.8%). Biopsy specimens obtained from 178 TNEs were adequate and demonstrated basal cell hyperplasia (53%), rete peg elongation (52%), dilated interceullular spaces (53%), and lamina propria fibrosis (75%).
Conclusions: Unsedated TNE has advantages because it can be performed in an outpatient clinic room and requires no anesthesia or sedation. TNE was highly tolerated by a wide age range of children with minimal adverse events. All histopathological specimens were adequate for evaluation by pathology. Unsedated TNE is a safe and effective modality for monitoring disease activity in EoE. TNE has become an increasingly popular modality for the surveillance of EoE.

Outcomes of Oral Food Challenges In Patients With Eosinophilic Esophagitis

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Background: Oral food challenge (OFC) is a frequently employed procedure to determine if a patient who demonstrates sensitization by skin prick testing or specific IgE testing is allergic to a particular food. Eosinophilic Esophagitis (EoE) is an inflammatory condition involving dense eosinophilic infiltration of esophageal mucosa, resulting in dysphagia, feeding difficulty, and food intolerance. The relationship between EoE and food allergy is unclear. This study aims to s detect if there is a difference in outcomes of OFC between children with and without EoE.
Methods: We conducted a retrospective chart review of our registry of pediatric patients with food allergy and extracted the results of OFC performed in the outpatient clinic over a period of 24 months on pediatric patients. We identified the patients who had a diagnosis of EoE. We defined passing an OFC as ingesting a meal size portion of the food without developing any immediate allergic reactions during the challenge and one to two hours of observation.. Fisher's Exact Test was utilized to determine if there was a statistically significant difference in passing a food challenge between patients with EoE versus patients without EoE.
Results: OFC were performed in 641 patients, 16 of whom had a diagnosis of EoE. Of the 625 patients without EoE, 443 (70.9%) passed the OFC. Of the 16 patients with EoE, 10 (62.5%) passed the OFC. There was no statistically significant difference between the proportion of outcomes between patients with EoE and patients without EoE (p= 0.5781).
Conclusion: There is no statistically significant difference between outcomes of OFC in patients with EoE vs patients without EoE. These data suggest that diagnosis of EoE should not deter attempt at food challenge in a patient who is an otherwise good candidate for OFC.

Elucidation of the Molecular Mechanisms of Transcriptional Regulation of Serine Protease Inhibitor SPINK7

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Weirauch[2,3] Ph.D. and Marc E. Rothenberg[1] M.D., Ph.D.[1]Division of Allergy and Immunology, Cincinnati Children's Hospital Medical Center, Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, Ohio, USA. [2]Center for Autoimmune Genomics and Etiology, Cincinnati Children's Hospital Medical Center, Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, Ohio, USA. [3]Divisions of Biomedical Informatics and Developmental Biology, Cincinnati Children's Cincinnati, Ohio, USA.

Background: Serine peptidase inhibitor, Kazal-type 7 (SPINK7) is expressed in healthy esophageal epithelium; however, its expression is lost in eosinophilic esophagitis (EoE). Molecular mechanisms underlying tissue-selective expression of SPINK7 in EoE are unknown. We hypothesize the key *SPINK7* promoter exists within the immediate 4.5-kb region upstream to the putative transcription start site and promoter activity is upregulated in esophageal epithelial progenitor cells (EPC2) by calcium-induced cellular differentiation.
Methods: The 4.5-kb sequence was selected based on transcriptional and epigenetic data from ENCODE, CisBP and our institutional database. Constructs were created with luciferase-reporter vectors, and promoter activity was measured in relative light units (RLU) by luciferase assay after transient transfection of EPC2 in low-calcium (low-Ca) and high-calcium (high-Ca) conditions, which induces a differentiation-like state. Promoter activity was examined in several cell lines to determine tissue specificity.
Results: SPINK7-promoter activity was increased 135.6-fold in high-Ca ($p<0.0001$) and 41.8-fold in low-Ca conditions ($p <0.0001$) relative to empty vector. The magnitude of induction of promoter activity (after normalization to empty vector) was increased 3-fold in high-Ca relative to low-Ca conditions ($p< 0.0211$). The first 1-kb construct sufficiently induced promoter activity in the high-Ca condition ($p< 0.0004$). Relative expression of SPINK7-promoter activity varied from 1.9–35.6-fold compared to EPC2 in the high-Ca condition compared to other cell lines.
Conclusion: Herein, we demonstrated that the 4.5-kb region upstream to TSS of SPINK7 has promoter activity and the first 1-kb is sufficient to drive transcriptional activity of the gene. Regulation of promoter activity is dependent on epithelial cellular differentiation mediated by calcium.

About CCED Research

The Cincinnati Center for Eosinophilic Disorders provides leading treatment strategies to change the outcome for children and adults with these chronic inflammatory diseases. Our team includes international leaders who diagnose, treat and research eosinophilic disorders, working closely with patients and their families to help them experience the best quality of life possible.

At Cincinnati Children's Hospital Medical Center, we are passionate about finding a cure for eosinophilic disorders. Cincinnati Children's is leading the Consortium of Eosinophilic Gastrointestinal Disease Researchers (CEGIR), which is a collaboration of clinician-investigators, translational scientists, physicians, patients, families and patient advocacy groups with a common goal to conduct clinical research into eosinophilic disorders and to train investigators in how to conduct clinical research.

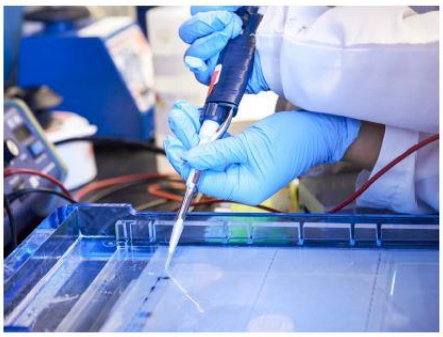
CEGIR is supported by the National Institutes of Health and is part of the Rare Diseases Clinical Research Network (RDCRN). Marc Rothenberg, MD, PhD, director of the Cincinnati Center for Eosinophilic Disorders, is principal investigator for this research, which also involves researchers from over ten hospitals, four universities and the National Institutes of Health.

GROUNDBREAKING RESEARCH

The recent clinical studies below reflect our commitment to improve the knowledge, research and outcomes for people living with eosinophilic disorders.

Establishing a better understanding of eosinophilic gastritis

Investigators at Cincinnati Children's conducted the first study to extensively characterize eosinophilic gastritis (EG). Published in *The Journal of Allergy and Clinical Immunology* (2014), the study found that EG is a systemic disorder that has high levels of eosinophils in the blood and gastrointestinal tract, involves a series of allergy-associated immune mechanisms, and has a gene expression pattern that is markedly distinct from that of the related disorder eosinophilic esophagitis (EoE). This study advances the understanding of EG through much-needed characterization of its fundamental molecular, histopathologic and clinical features.



Identifying a new genetic and molecular pathway that causes eosinophilic esophagitis

A team of researchers at Cincinnati Children's identified a molecular pathway specific to epithelial tissue in the esophagus that involves a gene called calpain 14 (CAPN14). The gene becomes dramatically upregulated in the disease process—something the researchers attribute to the immune cytokine interleukin 13 (IL-13), a well-known molecular activator of EoE. Our researchers demonstrated that CAPN14 effected a breakdown in the esophageal barrier. Because CAPN14 can be inhibited by drugs, the study opens up new therapeutic possibilities. The study was published in *Nature Genetics* (July 2014) and in *JCI Insights* (2016).

Humanized anti-interleukin 5 antibody therapy

Humanized anti-interleukin 5 (IL-5) antibodies are the first new class of asthma drugs approved by the FDA in 12 years. The anti-IL-5 treatments mepolizumab (marketed as Nucala®) and reslizumab (marketed as Cinqair®) are effective in treating the severe eosinophilic form of asthma in adolescent and adult patients. In collaboration with pharmaceutical companies and national experts, our divisional clinical research teams conducted multiple clinical trials testing the safety and efficacy of anti-IL-5 therapies for a range of eosinophilic disorders, including severe asthma, hypereosinophilic syndrome (HES) and EoE. Eosinophils, white blood cells that promote an excessive inflammatory response in allergies, are suppressed by this new class of drugs. These drugs target IL-5, an eosinophil growth, activation and survival factor. This is promising news not only for individuals with the eosinophilic form of asthma but also for individuals with other eosinophilic conditions.

Proton pump inhibitor-responsive esophageal eosinophilia

Proton pump inhibitor (PPI)—responsive esophageal eosinophilia (PPI-REE) presents with similar clinical features to EoE and is clinically, endoscopically and histologically indistinguishable from EoE. Whether PPI-REE reflects a gastroesophageal reflux disease (GERD) phenotype or shares an antigen-driven, T helper type 2-associated allergenic pathogenesis similar to EoE was previously unknown. This transcriptome study provides convincing evidence that PPI-REE is an EoE sub-entity with significant molecular overlap with EoE but that PPI therapy reverses nearly the entire allergic inflammatory transcriptome in PPI-REE. These expression data will inform about disease classification, molecular etiology and management strategies for patients with significant esophageal eosinophilia. The study was published in the *Journal of Allergy and Clinical Immunology* (2015).

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.

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).

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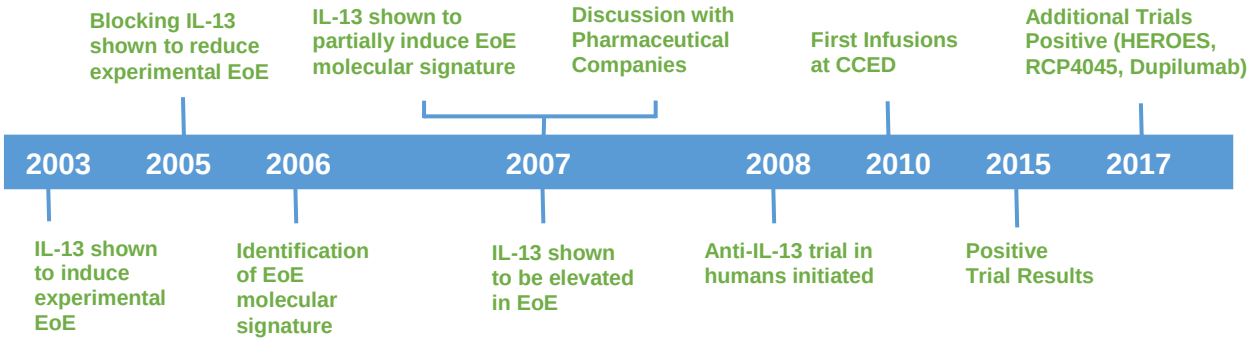
Blocking IL-13

Blocking Interleukin 13: An Example of the CCED Difference

Basic research leads to new discoveries essential for developing novel, viable therapeutics to treat human disease. For instance, a new therapeutic strategy for the treatment of EoE, blocking interleukin-13 (IL-13) signaling, is now in phase II clinical trials. The current anti-IL-13 antibody-based drugs being tested by biopharmaceutical companies, such as Novartis QAX576, Receptos RPC4046, and Sanofi/Regeneron Dupilumab, can be attributed to the research discoveries made at the Cincinnati Center for Eosinophilic Disorders (CCED) over the past decade.

CCED Research Discoveries that Provided the Rationale for Anti-IL-13

In 2003, Rothenberg *et al.* determined that administration of IL-13 could induce experimental EoE in mice, indicating its key role in this barely characterized disease. In 2005, Rothenberg *et al.* demonstrated that blocking IL-13 could reduce esophageal eosinophilia in mice, providing proof-of-principle of the utility of blocking IL-13 for treating inflammatory disease and esophageal eosinophilia. In 2006, Rothenberg *et al.* identified the EoE molecular signature and in 2007 showed that IL-13 could partially induce this EoE molecular signature, as well as establishing the increased levels and importance of IL-13 in human EoE. In 2010, Rothenberg *et al.* established that EoE in mice had similar pathological characteristics and gene expression changes to EoE in humans and identified the involvement of the IL-13 receptor in the disease process



Our subsequent partnership and discussion with pharmaceutical companies (e.g., Novartis, Receptos, and Sanofi/Regeneron) initiated the current anti-IL-13 and anti-IL-4Rα (part of the IL-13 receptor) clinical trials. All of these advancements in basic research and discovery were critical to the conception and development of blocking IL-13 as a therapeutic strategy for human EoE and would not have been possible without investment in fundamental research.

About CEGIR

CEGiR Consortium of Eosinophilic Gastrointestinal Disease Researchers

About

The Consortium of Eosinophilic Gastrointestinal Disease Researchers (CEGIR) is dedicated to improving the lives of individuals with eosinophilic gastrointestinal disorders through innovative research, clinical expertise and education via collaborations between scientists, health care providers, patients, and professional organizations. The disorders CEGIR focuses on are eosinophilic esophagitis (EoE), eosinophilic gastritis (EG) and eosinophilic colitis (EC). The team has a multidisciplinary approach and integrates expertise in pediatric and adult clinical specialties, including gastroenterology, allergy, immunology and pathology. Funded by the National Institutes of Health (NIH), CEGIR is part of the Rare Diseases Clinical Research Network (RDCRN).

Overall Goals

- Improve the lives of individuals with eosinophilic gastrointestinal disorders
- Facilitate research on eosinophilic esophagitis (EoE), eosinophilic gastritis (EG), and eosinophilic colitis (EC) through the development of a Consortium of Eosinophilic Gastrointestinal Disease Researchers (CEGIR)
- Establish a EGID Patient Contact Registry
- Develop and maintain a website with information for scientists, health care providers, patients, and professional organizations

Rare Clinical Diseases Research Network
Initiative of the National Center for Advancing Translational Sciences (NCATS)

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NIH National Institute of Diabetes and Digestive and Kidney Diseases

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§ Infants studied did not have CMA. Studies compared infants fed Enfamil Infant vs discontinued Enfamil without DHA and ARA with improvements shown to 18 months for brain and through 3 years for respiratory and skin-related immune outcomes, studied before the addition of probiotics.
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