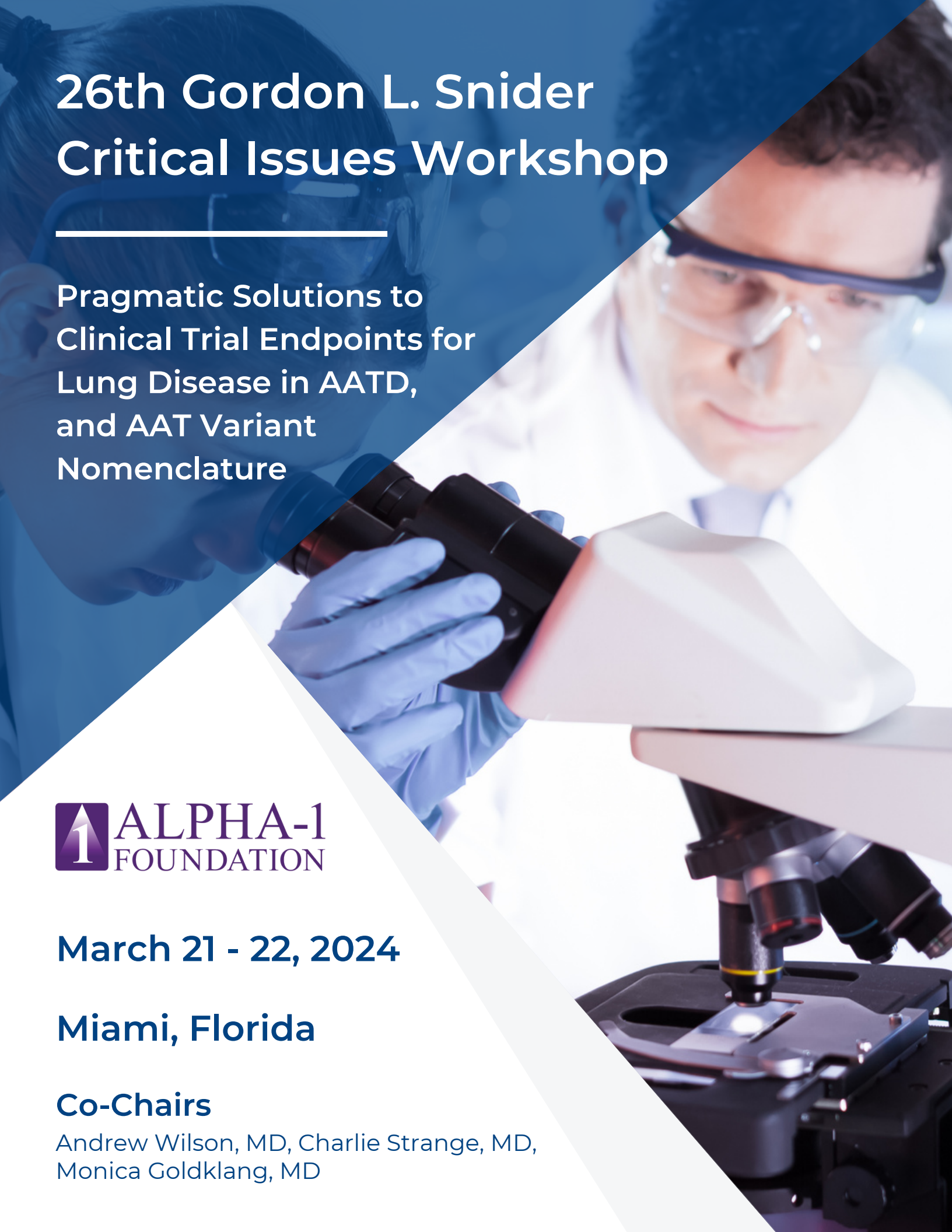
26th Gordon L. Snider Critical Issues Workshop

Pragmatic Solutions to Clinical Trial Endpoints for Lung Disease in AATD, and AAT Variant Nomenclature



ALPHA-1 FOUNDATION

March 21 - 22, 2024

Miami, Florida

Co-Chairs

Andrew Wilson, MD, Charlie Strange, MD, Monica Goldklang, MD

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Meeting Overview

Welcome to the 26th Gordon L. Snider Critical Issues (GLS) Workshop entitled, “Pragmatic Solutions to Clinical Trial Endpoints for Lung Disease in AATD” and “AAT Variant Nomenclature.” The goal of GLS topical workshops, is to provide new information that speeds the journey to a cure for Alpha-1 Antitrypsin Deficiency (Alpha-1). The twin goals of this workshop are 1) to optimize a single phase 3 clinical trial outcome measure from the scientific community that would be advanced to regulators to balance feasibility and science and allow new therapies for AATD to advance; and 2) to contemplate a simplified, rational approach to classifying and naming variants in the AAT gene, SERPINA1.

Alpha-1 lung disease is a rare disease that progresses slowly. Traditional outcome measures for COPD are able to draw upon 15 million individuals in the US and more internationally to fill clinical trials and study lung function, exacerbation number, and patient reported outcomes. Therapies are then applied to large numbers of affected individuals. In contrast, only 10,000-15,000 individuals are identified with Alpha-1 lung disease. Large databases suggest that more than half of these individuals have severe or very severe lung disease and are not currently eligible for most clinical trials. The small number of remaining eligible participants are not sufficient to enroll planned trials in the pipeline, particularly if phase 3 trial studies require 2-3 years of CT lung density data to demonstrate efficacy.

As an alternative, pragmatic trial design would allow the best biomarker of Alpha-1, the alpha-1 antitrypsin level, to serve as an outcome measure. This workshop will revisit the 1987 decision to allow a trough level of 11 micromolar to serve as a pragmatic biomarker. The limitations of this biomarker are well known in the Alpha-1 community leaving 2 potential options. One would be to abandon the Alpha-1 level as a biomarker. A second option and the goal of this workshop is to better define the technical details that would make an Alpha-1 blood level at a threshold above 11 micromolar acceptable to the scientific and regulatory communities. This GLS workshop will explore functional activity, targeted proteases, dosing, acute phase reactivity, and next steps to advance a pragmatic outcome measure for Alpha-1 lung disease.

Outside of a few common and well-known variants, naming of the >200 variants identified in the SERPINA1 gene that encodes AAT is complex, with many named for the birthplace of the first patient in whom they were identified. This approach has not helped to classify variants with similar biological effects in a way that might simplify communication or facilitate therapeutic discovery. With these goals in mind, this meeting will discuss and envision potential alternative approaches to current nomenclature.

The Foundation thanks the workshop’s co-chairs, Dr. Andrew Wilson, Dr. Charlie Strange, and Dr. Monica Goldklang, for their input into the conference program and for inviting and securing the participation of a group of experts. We would also like to thank the staff of the Alpha-1 Foundation for their hard work in putting this workshop together.

We look forward to making this a meaningful and memorable event!

Scott Santarella
President & Chief Executive Officer
Alpha-1 Foundation

Andrew Wilson, MD
Scientific Director
Alpha-1 Foundation

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Pragmatic Solutions to Clinical Trial Endpoints for Lung Disease in AATD, and AAT Variant Nomenclature

March 21 - 22, 2024

DAY 1 – March 21, 2024

Welcome and Introduction

03:00 pm - 03:10 pm	Scott Santarella (Alpha-1 Foundation), Andrew Wilson, MD (Boston University),

Session 1: SERPINA1 Variant Nomenclature: A Way Forward?

03:10 pm - 03:30 pm	**Rethinking Variant Nomenclature and Classification: The CF Experience** Johanna Rommens, PhD (The Hospital for Sick Children)
03:30 pm - 03:40 pm	Discussion
03:40 pm - 04:00 pm	**The Current Landscape of SERPINA1 Variants** Mark Brantly, MD (University of Florida)
04:00 pm - 04:10 pm	Discussion
04:10 pm - 04:30 pm	**Envisioning a New Approach to Naming and Classifying SERPINA1 Variants** Tomas Carroll, PhD (Royal College of Surgeons in Ireland)
04:30 pm - 04:40 pm	Discussion
04:40 pm - 05:10 pm	General Discussion
05:10 pm - 05:30 pm	Break

Session 2: Pragmatic Solutions to Clinical Trial Endpoints for Lung Disease in AATD

Introduction

05:30 pm - 05:40 pm	Andrew Wilson, MD (Boston University), Charlie Strange, MD (Medical University of South Carolina), Monica Goldklang, MD (Columbia University)
05:40 pm - 05:55 pm	**What is the Therapeutic Threshold and Why isn't it 11uM?** Mark Brantly, MD (University of Florida)
05:55 pm - 06:05 pm	Discussion
06:05 pm - 06:20 pm	**Pragmatic Proposal for Phase 3 Lung Studies** Charlie Strange, MD (Medical University of South Carolina)
06:20 pm - 06:30 pm	Discussion
06:30 pm - 06:45 pm	**Primer on Lung Proteases - Which Need to be Inhibited?** Jeanine D'Armiento, MD, PhD (Columbia University)
06:45 pm - 06:55 pm	Discussion

Wrap up - Day 1

06:55 pm - 07:00 pm	Scott Santarella (Alpha-1 Foundation)

DAY 2 – March 22, 2024

Welcome and Introduction

08:00 am - 08:05 am	Scott Santarella (Alpha-1 Foundation)

Session 2: Pragmatic Solutions to Clinical Trial Endpoints for Lung Disease in AATD

08:05 am - 08:20 am	**Practical Aspects of Protease Inhibition Assays** Carson Veldstra (Inhibrx)
08:20 am - 08:30 am	Discussion
08:30 am - 08:45 am	**Impact and Measurement of the Acute Phase Response** Monica Goldklang, MD (Columbia University)
08:45 am - 08:55 am	Discussion

08:55 am - 09:10 am	**Overview of Endpoint Biomarkers** Jeffrey Siegel, MD (Food and Drug Administration)
09:10 am - 09:15 am	Discussion
09:15 am - 09:25 am	**Endpoint Biomarkers for Gene Therapies** Prateek Shukla, MD (Food and Drug Administration)
09:25 am - 09:30 am	Discussion
09:30 am - 09:45 am	**Feel, Function and Survival: Searching for Meaningful Clinical Outcomes** Christine Wendt, MD (University of Minnesota)
09:45 am - 09:55 am	Discussion
09:55 am - 10:10 am	**CT Density as an Alternative Endpoint to Functional AAT Levels** Mark Forshag, MD, MHA (Medical Affairs and Clinical Development Consultant)
10:10 am - 10:15 am	Discussion
10:15 am - 10:30 am	Break
10:30 am - 10:45 am	**Inclusion and Exclusion Criteria for a Pragmatic Trial** Alice Turner, PhD (University of Birmingham)
10:45 am - 10:55 am	Discussion
10:55 am - 11:10 am	**Is There Any Other Way Forward for Phase 3 Trials?** Gerry McElvaney, MD (Royal College of Surgeons in Ireland)
11:10 am - 11:20 am	Discussion
11:20 am - 11:50 am	**Group Discussion: Return to the Pragmatic Proposal** Andrew Wilson, MD (Boston University), Charlie Strange, MD (Medical University of South Carolina), Monica Goldklang, MD (Columbia University)

Concluding Remarks

11:50 am - 11:55 am	Scott Santarella (Alpha-1 Foundation)

Speaker Bios

Mark Brantly, MD

University of Florida

Dr. Mark Brantly is the Alpha 1 Foundation Professor of Medicine, Molecular Genetics and Microbiology in the Division of Pulmonary, Critical Care, and Sleep Medicine and Vice Chair of Research for the Department of Medicine at the University of Florida. Professor Brantly completed his undergraduate degree at Florida State University and received his MD at the NHLBI Pulmonary Branch. Dr. Brantly was a Parker B Francis Fellow from 1986-1990. He later joined the NICHD Genetics Branch as a section head and concluded his stay at NIH in the Pulmonary Division before joining the University of Florida Department of Medicine. In 2018, Dr. Brantly was honored with the John W. Walsh PAR Award for Excellence. Dr. Brantly is the former Scientific Director of the Alpha-1 Foundation and is currently a member of the Alpha-1 Foundation Board of Directors. Brantly has co/authored more than 200 publications, many of which are on the molecular basis of alpha-1-antitrypsin deficiency. Much of his lab's recent research has focused on the gain of toxicity associated with misfolding of Z alpha-1-antitrypsin in the liver and macrophages.

Tomás Carroll, PhD

Royal College of Surgeons in Ireland (RCSI) and Alpha-1 Foundation Ireland

Dr. Tomás Carroll is a senior lecturer in RCSI in Dublin, Ireland, and chief scientist with Alpha-1 Foundation Ireland. After studying at University College Galway (B.Sc. Biotechnology, M.Sc. Biomedical Science) he began a PhD in cystic fibrosis at RCSI working with Professor Gerry McElvaney. Following this, Tomás started working on Alpha-1 Antitrypsin Deficiency (AATD) in a position with Alpha-1 Foundation Ireland in 2004. The Foundation is dedicated to raising awareness, increasing diagnosis, promoting research, and improving the treatment of AATD in Ireland. Tomás has carried out research leading to over 50 publications spanning basic, clinical, and translational research. In addition, he coordinates the national targeted detection programme for AATD which has tested over 24,000 Irish people since it began in 2004. The programme provides free testing for AATD and has so far diagnosed over 6,000 Irish people with either severe or moderate AATD.

Jeanine D'Armiento, MD, PhD

Columbia University

Dr. Jeanine D'Armiento is a Professor of Medicine in Anesthesiology at Columbia University. Dr. D'Armiento is the Director of the Center for Molecular Pulmonary Disease in Anesthesiology and Physiology and Cellular Biophysics, and Director of the Center forLymphangiomyomatosis (LAM) and Rare Lung Disease. Dr. D'Armiento's research focuses on understanding the mechanisms of lung injury and repair. Her laboratory integrates both in vitro and in vivo approaches and is uniquely situated to characterize the molecular changes in the study of lung injury and disease to identify potential therapeutic targets. Dr. D'Armiento's clinical work focuses on Rare Diseases, and she is the Director of the Center for LAM and Rare Lung Diseases at

Columbia University, which serves one of the largest populations of women with Lymphangioleiomyomatosis (LAM) in addition to patients with Alpha-1 Antitrypsin Deficiency (AATD). Dr. D'Armiento serves as Chair of the Executive Committee of the Columbia University Senate. In addition, she is presently the Medical Liaison and past Chair of the Board of Directors of the Alpha-1 Foundation and serves as a Consultant to the Director of the Division of Rare Disease Research Innovations (DRDRI), NCATs.

Mark S. Forshag, MD, MHA

Medical Affairs and Clinical Development Consultant

Dr. Mark Forshag is a native of New Orleans and is a 1985 graduate of the Louisiana State University School of Medicine – New Orleans. He completed post-graduate clinical training in Internal Medicine, Pulmonary Diseases and Critical Care Medicine at the University of Alabama at Birmingham (UAB). He remained on faculty at UAB for two years before joining the Internal Medicine training program at Carolinas Medical Center (CMC) in Charlotte, North Carolina. While on faculty at CMA, he received a Master of Healthcare Administration from the University of North Carolina at Chapel Hill. Dr. Forshag made a mid-career transition to industry, joining Medical Affairs at Pfizer in support of the antibacterial and antifungal therapeutic areas. After six years, he joined Talecris and then Grifols, supporting both the Medical Affairs and Clinical Development functions focused on Alpha-1 Antitrypsin Deficiency (AATD). After a foray into severe asthma and COPD at GlaxoSmithKline, he returned to AATD at Vertex Pharmaceuticals, from which he retired in 2022. He now works part-time as a consultant to an industry focused on AATD and obstructive lung disease.

Monica Goldklang, MD

Columbia University

Dr. Monica Goldklang is a pulmonary and critical care physician-scientist at Columbia University. She grew up in Michigan, completing undergraduate, medical school, and residency training at the University of Michigan. She then moved to Columbia University for a pulmonary and critical care fellowship and post-doctoral research training in the lab of Dr. Jeanine D'Armiento. In addition to caring for patients with rare lung diseases including Alpha-1 Antitrypsin Deficiency and Lymphan-gioleiomyomatosis, and working in the ICU, Dr. Goldklang has an active research portfolio. She has several clinical and translational studies in Alpha-1 Antitrypsin Deficiency, including an investigation into novel imaging biomarkers of lung disease as well as studies regarding long-term disease trajectory and serum biomarkers following acute exacerbations of COPD. Outside of work, she enjoys running and can be found most weekends with her husband, Mike, loudly cheering for sons Ben and Josh at hockey and baseball games.

Noel G. McElvaney, MD, BCh, BAO, FRCPI, FRCPC

Royal College of Surgeons in Ireland (RCSI)

Professor Gerry McElvaney is Chairman of the Department of Medicine and Professor of Medicine at the Royal College of Surgeons in Ireland, Dublin, Ireland. Prof. McElvaney received his medical education at University College Dublin and completed his postgraduate internal medicine training at the Mater Misericordiae Hospital, St. Laurence

Hospital, and Jervis Street Hospital in Dublin before pursuing a pulmonary Fellowship in Vancouver, Canada. Following that, Prof. McElvaney worked in the Pulmonary Branch, NHLBI, NIH, Bethesda, and Cornell University-Rockefeller University Hospital, New York. He returned to Ireland in 1996. Prof. McElvaney has a well-established track record in research in Alpha-1 Antitrypsin Deficiency and Cystic Fibrosis with substantial funding from National and International bodies. His work on inflammation and lung defenses has led to significant interactions with pharmaceutical companies interested in translational research. In 2003, Prof. McElvaney founded the Alpha One Foundation of Ireland and subsequently received funding from the Irish Department of Health and Children to set up an Alpha-1 research unit to further research into the condition. He also established the first National targeted detection program in Europe.

Johanna M. Rommens, PhD

The Hospital for Sick Children

Dr. Johanna Rommens has extensive experience in disease gene identification, genome analysis, and gene expression. Causal gene identification for genetic disease enables early diagnosis, but the realization of improved treatment strategies are frequently challenged by i) variation and range in encoded protein deficiencies due to different causal alleles, ii) limited understanding of the natural history of disease pathology and complications brought on by multi-organ involvement and, iii) additional variation in presentation due to genetic modifiers or environmental factors. Current research interests include two avenues. The first relates to understanding the ribosomal deficiencies and their consequences in affected organs in Shwachman-Diamond syndrome. The second involves the elucidation of underlying mechanisms of variability in the clinical presentation of cystic fibrosis due to modifier genes. Dr. Rommens is a member of the CFTR2 team (https://cftr2.org) that seeks to understand variations in the CFTR gene and to assign liability for variants that lead to cystic fibrosis. Collected data of the international initiative includes phenotypic information from >89,000 cases, from more than forty countries.

Scott Santarella

Alpha-1 Foundation

Mr. Scott Santarella is President and CEO of the Alpha-1 Foundation (A1F), leading strategic initiatives to find a cure for Alpha-1 Antitrypsin Deficiency (AATD) and improve the lives of people affected by AATD Worldwide. Prior to A1F Scott was CEO of Global Lyme Alliance (GLA) directing business strategy, operations, revenue-generation, educational programming and raising awareness to advance treatments for patients suffering from tick-borne illnesses. Prior to joining GLA, Scott was President and CEO of the Bonnie J. Addario Lung Cancer Foundation (ALCF), now the GO2 Foundation for Lung Cancer, where he led the expansion from regional lung cancer research/patient services organization to a globally recognized leader in the lung cancer community. Prior to ALCF he was President and CEO of the American Lung Association of New York (ALANY) and spent 10 years as the Executive Director and Chief Operating Officer of the Multiple Myeloma Research Foundation (MMRF). A 30-years senior executive with experience in strategic planning, creative messaging and marketing, industry partnership development, clinical research innovation, and raising public awareness for neglected, underfunded, and often stigmatized diseases, he received an Executive Leadership Certification from Harvard Business School and holds a Bachelor of Arts in Journalism from the University of Massachusetts, Amherst.

Prateek Shukla, MD

Food and Drug Administration

Dr. Prateek Shukla completed his undergraduate degree in Biochemistry and Cell Biology before receiving his medical degree from University College Dublin, Ireland. He completed his first pediatric residency in Dublin, primarily at Children's University Hospital, Temple Street. Following return to the US, he completed his pediatric residency at MedStar Georgetown University Hospital. Dr. Shukla is a pediatric pulmonologist having completed a pediatric pulmonary fellowship at Children's National Medical Center in Washington, D.C. where he conducted bench research evaluating NFkB-responsive genes in cystic fibrosis lung epithelial cells. He joined the FDA in 2020 and is currently a physician medical officer in the Division of Clinical Evaluation General Medicine, Office of Therapeutic Products (OTP), Center for Biologics Evaluation and Research. His primary work is in the clinical review of cell and gene therapy products for rare diseases, reviewing Investigational New Drug (IND) and New Drug Applications (NDAs), as well as Biologic Licensing Applications (BLAs) with a multidisciplinary evaluation team.

Jeffrey Siegel, MD

Food and Drug Administration

Dr. Jeffrey Siegel is the director of the Office of Drug Evaluation Sciences (ODES) in the Office of New Drugs (OND), CDER, FDA. ODES oversees Clinical Outcome Assessments, Biomarker Qualification, Research and Bioinformatics in OND. Dr Siegel has over 20 years of experience in research, regulatory, and clinical drug development. Jeff received his B.A. from Columbia University and M.D. from Yale University. He trained in internal medicine at University Hospitals of Cleveland. Then he did a fellowship in Immunology and Signal Transduction at NIH. He served at FDA from 1996-2010 as a medical officer and then Medical Team Leader. In 2010, he left FDA for industry and worked at Genentech/Roche as global lead for Rheumatology and Rare Diseases and subsequently at Gilead Sciences as Translational Medicine lead in Clinical Research/Inflammation before rejoining FDA in February 2021.

Charlie Strange, MD

Medical University of South Carolina

Dr. Charlie Strange is a Professor of Pulmonary and Critical Care, Allergy, and Sleep Medicine at the Medical University of South Carolina in Charleston. Dr. Strange received his undergraduate degree at Davidson College in Davidson, North Carolina, and his medical degree at the Medical College of Virginia in Richmond. He completed subsequent training in Internal Medicine, Pulmonary Medicine, and Critical Care Medicine at the Medical University of South Carolina. Dr. Strange's research interests include novel clinical trials in chronic obstructive pulmonary disease and liver disease from alpha-1 antitrypsin deficiency, COPD imaging, and stem cell biology. Dr. Strange is the author or co-author of >300 publications in major medical journals. He is active as past chair of the Documents Committee of the American Thoracic Society and as Editor for the Expert Clinician Section in the Annals of the American Thoracic Society. He directed the Alpha-1 Foundation Research Registry from 2000-2019. In addition, he is presently the Medical Director of AlphaNet.

Alice Turner, MBChB, PhD

University of Birmingham

Dr. Alice Turner graduated from the University of Leicester and has done postgraduate training via the Universities of Dundee and Birmingham, and Ashridge-Hult business school, completing a PhD focussed on COPD and alpha 1 antitrypsin deficiency (AATD) and postgraduate qualifications in medical education, leadership, and quality improvement (QI). She is now a professor in respiratory medicine at the University of Birmingham and works as a consultant in respiratory medicine at Heartlands and Queen Elizabeth hospitals, where she is lead for COPD and AATD services, respectively. In addition, she is a member of the NIHR research prioritization committee and has past experience on a NICE health technology appraisal committee. She has published widely in COPD and AATD, and has ongoing research projects, mainly clinical trials, and observational clinical studies, in AATD and COPD funded by the NIHR and others.

Carson Veldstra

Inhibrx

Mr. Carson Veldstra is the Director of Bioanalysis at Inhibrx, Inc. He earned a Bachelor of Science in Biochemistry from Westmont College in Santa Barbara CA.Starting his career with a role in GMP manufacturing of in-vitro diagnostics, he then moved on to regulated bioanalysis, where he's spent the last 14 years. Key areas of focus for him are novel assay development and validation, as well as GCLP-compliant sample analysis supporting early and late-stage clinical development. While working in this field Carson has supported primarily large molecule therapeutic candidates with indications in oncology, CNS, endocrinology, autoimmunity, and genetic disease at mid-stage and large biopharmaceutical companies. He holds the belief that high-quality assays and results ultimately lead to high-quality medical decisions and outcomes that patients deserve.

Christine Wendt, MD

University of Minnesota

Dr. Chris Wendt is a Professor of Medicine at the University of Minnesota and Section Chief of Pulmonary, Allergy, Critical Care, and Sleep (PACCS) at the Minneapolis VAMC. Her research has focused on both clinical and translational research in COPD and associated contributors including tobacco, HIV, air pollution, COPD as a causal pathway to lung cancer, and the role of the oral microbiome in COPD health. Her translational research uses a multi-omic approach including genomics, transcriptomics, proteomics, metabolomics, computational and systems biology. Discoveries include biomarkers and causal pathways in COPD leading to lung cancer and HIV-associated COPD. Dr. Wendt has a longstanding history of participating in NIH COPD trials, including the NIH COPD Clinical Research Network, COPDGene, and the VA Lung Precision Oncology Program. She and colleagues were amongst the first to characterize the lung microbiome in COPD and the role of the oral microbiome. A recently published study demonstrated that daily chlorhexidine improved patient-reported outcomes in COPD frequent exacerbators, demonstrating the role of the oral microbiome and health in COPD health.

Dr. Wendt's interest in air pollution and chronic lung disease dates to her participation as a delegate for the University of Minnesota and the Chinese Academy of Science to address the health effects of air pollution in China. This area of research has expanded to exploring the epidemiology of deployment-related air pollution exposure, including burn pit exposure; along with identifying biomarkers and phenotypes of exposure.

Andrew Wilson, MD

Boston University

Dr. Andrew Wilson is Professor of Medicine at the Boston University Chobanian & Avedisian School of Medicine. He is a Pulmonary and Critical Care physician-scientist with a focus on regenerative medicine and stem cell biology. The goal of his research is to advance understanding of and treatment for genetic causes of chronic obstructive pulmonary disease (COPD) and the lung and liver diseases associated with the Alpha-1 Antitrypsin Deficiency (AATD), largely through the platform of patient-derived stem cells. In association with his research efforts, he has compiled the world's largest repository of AATD patient-specific induced pluripotent stem cells (iPSCs) and has shared these cells widely with researchers around the world. In addition to laboratory-based science, he also participates in epidemiological studies to define the incidence of and risk factors for both liver and lung disease associated with AATD. He likewise serves as the Scientific Director of the Alpha-1 Foundation. Finally, he is the founding director of the Alpha-1 Center at Boston University and Boston Medical Center, one of the largest clinical centers for patients with AATD in the Northeast, where he cares for patients with AATD.

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The Alpha-1 Foundation acknowledges the following sponsors for their ongoing commitment to the advancement of research:

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The Alpha-1 Foundation is committed to finding a cure for Alpha-1 Antitrypsin Deficiency (Alpha-1) and to improving the lives of people affected by Alpha-1 worldwide.

The Foundation has invested over $97 million to support Alpha-1 research and programs in 129 institutions in North America, South America, Europe, the Middle East and Australia.

Alpha-1 Foundation
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