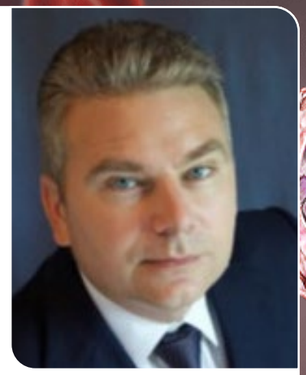
SPEAKER SPOTLIGHT:

Biomarker Development Within Inflammatory & Fibrotic Diseases

In the approach of the Autoimmunity and Immunology Congress, we spoke with Peter Schafer regarding his work at Bristol-Myers Squibb within Translational Development. Biomarkers are key for patient stratification within Autoimmune diseases to determine which patients may benefit from a given treatment. Here Peter discusses the current prognostic or predictive biomarkers used and being developed within the Lupus Field and his own CC-220 systemic lupus erythematosus clinical development programme. We further discuss this programme in addition to his current work with Prognostic Lung Fibrosis Consortium (PROLIFIC).



PETER H SCHAFER

Executive Director, Translational Medicine, Bristol-Myers Squibb

Peter Schafer is currently Executive Director of Translational Medicine at Bristol-Myers Squibb in Princeton, New Jersey. Peter has a Bachelor of Science in Biological Chemistry from the University of Chicago, and obtained a Ph.D. from the department of Biochemistry, Molecular Biology, and Cell Biology from Northwestern University. He completed a postdoctoral research fellowship at the R. W. Johnson Pharmaceutical Research Institute in Raritan, NJ. Peter joined Celgene Corporation in 1999, where he was part of the drug discovery and development team responsible for bringing the phosphodiesterase-4 inhibitor apremilast (Otezla) into the clinic, and its global regulatory approvals for psoriatic arthritis, psoriasis, and Behçet's disease. Peter has been co-leading the PROLIFIC prognostic lung fibrosis consortium since 2018. His current team is focussed on translational development of products for the treatment of immunological, cardiovascular, and fibrotic diseases.

What essential steps will overcome the translational gap between preclinical data and clinical outcomes in autoimmune diseases?

The essential steps which will overcome the translational gap between preclinical data and clinical outcomes in the therapeutic area of lupus are: 1) Understand the genetic drivers of autoimmunty in lupus, not only as targets in their own right, but as representative nodes of critical pathways of immune overactivation; 2) Formulate the therapeutic molecule with the necessary potency and selectivity to engage those targets in humans, and; 3) Apply the therapeutic required to the appropriate patient population, based upon their predominant clinical features or molecular endotype.

What are the important prognostic or predictive biomarkers used within the context of clinical trials?

The most important prognostic or predictive biomarkers in the field of lupus are: 1) High titers of autoantibodies (anti-nuclear, anti-double stranded DNA, anti-Smith, and anti-Ro antibodies) which have been shown to predict clinical response to belimumab; 2) A high level of expression of the type 1 interferon gene signature, which has been shown to be prognostic for development of serious clinical complications such as lupus nephritis, and; 3) Several others which are under investigation, including markers neutrophil activation and NETosis, monocyte/macrophage inflammation, and T cell exhaustion.

Please briefly describe your work in biomarker development for clinical development in inflammatory and fibrotic diseases

Our therapeutic focus areas include dermatology, rheumatology, gastroenterology, lung fibrosis, and liver fibrosis. As co-inventor of apremilast (Otezla®), now approved for psoriasis, psoriatic arthritis, and Behçet's Disease, we have utilized a deep understanding of its mechanism of action through the use of pharmacodynamic biomarkers such as TNF-alpha and interleukin-17 to guide its discovery, nonclinical and clinical development, regulatory approval, and life cycle management. We have co-discovered the mechanism of action of the IMiDs® compounds lenalidomide (Revlimid®) and pomalidomide (Pomalyst®) as targeting the cereblon substrates Ikaros and Aiolos, and translated their MoA to other therapeutic applications. Current areas of focus include late stage clinical translational development of iberdomide (CC-220), a Cereblon E3 ligase modulatory drug now in clinical development for lupus and other diseases, and the JNK inhibitor program in Idiopathic Pulmonary Fibrosis (IPF). Asset-independent translational research activities include meta-analysis of phase 2/3 clinical trial samples, curation of an Autoimmune Disease patient Biobank, and multiple disease-focused biomarker studies. This research has been published in >80 scientific publications and >80 patent applications.

Please explain your work in the CC-220 systemic lupus erythematosus clinical development programme.

Iberdomide (CC-220) is a Cereblon E3 Ligase modulating drug which causes the polyubiquitination and proteasonal degradation of Ikaros and Aiolos, which are key transcription factors that regulate immune cell hematopoiesis and homeostasis. Variants in the Ikaros and Aiolos genes have been linked to increased risk of systemic lupus erythematosus, and to specific clinical features, namely malar rash and nephritis. We have identified the minimum pharmacologically active dose of iberdomide through the use of target engagement and pharmacodynamic biomarkers in phase 1 healthy volunteer studies, and in a small phase 2a mechanistic study. Iberdomide is now in phase 2b clinical development for SLE and multiple myeloma. This work led to Celgene Corporation and inventors receiving the 2019 Thomas Alva Edison Patent Award in the Medical Technology category for "Methods for Determining Drug Efficacy using Cereblon-Associated Proteins" (U.S. Patent 9,857,359). This patent provides an understanding of how these agents work in tumor and immune cells, and describes Ikaros and Aiolos as cereblon substrates and some of their critical downstream functions for regulation of anti-tumor activity and in immune cells for immune-modulation.

Briefly outline the aims and work of the Prognostic Lung Fibrosis Consortium (PROLIFIC).

We have founded PROLIFIC (Prognostic Lung Fibrosis Consortium), an industry-wide consortium which was formed to develop well-qualified assays for important peripheral blood markers of pulmonary fibrosis, suitable for non-exclusive use as prognostic or predictive biomarkers within the context of clinical trials, and for potential commercial use. The consortium has selected a list of 12 biomarkers based on literature reports of utility for prognosis and/or pharmacodynamics, and for potential patient stratification and response prediction. The PROLIFIC collaborative research agreement has been signed by 8 organizations, including the Pulmonary Fibrosis Foundation and 7 pharmaceutical and biotech companies.

What would you like to gain from attending the congress?

We are interested in the cutting edge approaches to the application of biomarkers for the development of novel therapeutics in autoimmune, inflammatory, and fibrotic diseases. The scientific presentations and business networking provided by this Congress will facilitate our company's interactions with thought leaders and facilitate business opportunities, which are vital to maintaining not only a competitive edge, but also to provide a forum to foster pre-competitive collaborations.

Find out more about Peter and his involvement with the Immuno-Oncology Congress HERE