FINDING THE RIGHT TARGET

STEVE REES, Vice-President of Discovery Biology, **AstraZeneca**

Steve Rees is Vice-President of the Reagents and Assay Development Department at AstraZenea with global responsibility for reagent generation, assay development and functional genomics. Prior to this Steve led the Screening Sciences and Sample Management at AstraZeneca with accountability for Compound Management, the human tissue BioBank, Hit Discovery and Lead Optimisation biology support to preclinical discovery projects. Prior to joining AstraZeneca, Steve worked at GlaxoSmithKline for 24 years in various roles. Steve has led multiple international collaborations, has authored >65 scientific papers and has spoken at many international symposia. He is currently Chairman of the European laboratory Research and Innovation Group, and a member of the Scientific Advisory Board for Medical Research Council Technology, the Centre for Membrane Protein Receptor Research at the Universities of Birmingham and Nottingham and Axol Bioscience Ltd.

Steve Rees, Vice-President of Discovery Biology at AstraZeneca, describes some of the exciting innovations he has led in the field and discusses the technologies that are enabling target based drug discovery research. Steve also considers the opportunities and challenges in drug discovery.

Finding the 'right target' has led AstraZeneca to collaborate with Cancer Research UK and launch the Functional Genomics Centre, a centre of excellence for genetic screening, cancer modelling and big data processing aimed at accelerating the discovery of new cancer medicines. Functional genomics aims to understand the complex relationship between genetic changes happening within DNA and how these translate to cellular changes in disease. Knowing the functional genomic drivers of disease enables scientists to more accurately select the right drug targets and increases the probability of success in the clinic.

In our interview with Steve, we gain insights into the results, impact and the outlook of target based discovery strategies, and the functional Genomics innovation that enable the future successes of drug discovery programmes.

What is your role at AstraZeneca, and could you briefly describe AstraZeneca's collaboration with Cancer Research UK?

In my role at AstraZeneca I lead the Discovery Biology department. We are accountable for the creation of biochemical and cellular reagents to support the discovery pipeline, the identification and validation of new drug targets, and the development of new therapeutic modalities. We are hugely excited about the potential of Functional Genomics to identify both new drug targets and resistance and sensitisation mechanisms to our medicines. Internally we have created the capability to screen arrayed and pooled libraries of CRISPR reagents to delete or activate every gene in the genome to identify genes that affect the biology of the cellular system under study. In partnership with Cancer Research UK we are creating the CRUK AstraZeneca Functional Genomics Centre at the Milner Institute in Cambridge. Together this centre will have the capacity to run 150 pooled CRISPR Functional Genomics screens a year to help us better understand, and develop new medicines, for Cancer. By working with CRUK we can create a centre with world leading capabilities to enable both academic and industrial science. I am hugely excited by the discoveries that will from this centre, which formally opens in November 2019.

Could you briefly outline the latest results of the collaboration and the advantages of target-based drug discovery?

This collaboration will identify new drug targets. Through identifying targets by screening CRISPR libraries in disease relevant cancer cellular models we expect to increase our success in developing cancer medicines going forward.

Do CRISPR and functional genomic tools boost the success rates in target discovery?

Since the discovery of CRISPR in 2012 it has been rapidly adopted across the field to create complex cellular and animal models of disease, in CRISPR based Functional Genomics screens and as a therapeutic agent in its own right. While it is too early to conclude that the adoption of CRISPR has increased the success rates in target discovery, there are many examples in our own drug discovery programs where we have used these techniques to both validate, and equally important, devalidate targets in disease. Going forward we expect to see a significant proportion of our discovery portfolio enabled through the use of CRISPR

What are the opportunities and challenges in drug discovery?

The opportunities and challenges in drug discovery remain the same; the requirement to identify a novel target with confidence that perturbation of that target will be effective in disease, the ability to develop a therapeutic agent with activity at that target, and the ability to stratify the patient population to ensure that the medicine is tested in the right patient. The technologies available to us today, whether advances in cell biology, genomics, proteomics, transcriptomics and functional genomics to discover new targets; the developments in new therapeutic modalities including PROTACs and messenger RNA to develop ways to drug targets that previously were considered intractable; and the ability to develop biomarkers and companion diagnostics to stratify patients and monitor the effectiveness of our medicines, give us a unique opportunity to develop transformative medicines. These laboratory methods are supported by the massive advances in the application of Machine Learning and Artificial Intelligence to enable us to better manage and generate knowledge from our data. Together this gives huge opportunity to discover medicines to treat both rare and common diseases.

What is your aim in attending the congress?

To learn about advances in science and to network with colleagues from across the field.