University College London Collaboration Aims to Treat Alpha-1-Antitrypsin Deficiency

Alpha-1-antitrypsin deficiency is one of the most common inherited disorders in Caucasian populations. It is the only genetic factor that is widely accepted to predispose people to lung disease and can also cause a variety of liver disorders. In combination, these conditions have an estimated healthcare cost of nearly $50 billion a year in the US alone, and have a significant impact on the lives of the patients and their families.

Understanding what drives the development of alpha-1-antitrypsin deficiency has been a passion for Professor David Lomas, Dean of the Faculty of Medical Sciences at UCL (University College London), since he completed his medical degree and undertook a PhD working on the topic in the early 1980s. During these first years, he showed that the disease is caused by unwanted polymerization of alpha-1-antitrypsin in liver cells, where it is produced. This event is triggered by a mutation that is present in as many as 4% of the Caucasian population. The effect is that the protein cannot exit the liver and travel to the lungs to serve its protective function, leading to lung diseases such as chronic obstructive pulmonary disease (COPD).

A better appreciation of what causes alpha-1-antitrypsin polymerization, and therefore accumulation, provided important insights into how the process might be blocked, suggesting an avenue for treatment. At the same time, the polymerization of alpha-1-antitrypsin is used as a model for understanding a number of other diseases caused by members of the serine protease inhibitor (serpin) superfamily, the likes of which are associated with emphysema, thrombosis, angioedema, dementia and more.

Blocking polymerization

Over the course of a distinguished career, Professor Lomas has led academic research groups exploring the mechanism and importance of alpha-1-antitrypsin polymerization using a number of research tools. These range from investigating the purified protein with protein crystallography and biophysical methods through to in vitro studies using cell biology and in vivo experiments employing fruit fly models.

Having identified discrete areas of the alpha-1-antitrypsin protein involved in polymerization, Professor Lomas and his team collaborated with the Scripps Research Institute to use in silico screening in the hope of discovering small molecule inhibitors that might bind to the protein and inhibit polymerization. The initial compound was analyzed in more detail by Lomas' lab to see how it might perform in vitro and to optimize its properties to best inhibit alpha-1-antitrypsin polymerization. This compound was not a viable starting point for generating a medicine and therefore new chemical series were needed.

Professor David Lomas,
UCL (University College London)

Partnering to develop a treatment for alpha-1-antitrypsin deficiency

Having built a strong relationship with the GSK team over many years, starting in 1999 when he was co-lead Principal Investigator on the GSK International COPD Genetics Network and continuing through to his current position as chair of the GSK Respiratory Therapy Area Board, partnering with the company was a natural choice.

"It's not easy to optimize small molecule candidates for use as treatment compounds," said Lomas. "The best medicinal chemists tend to be in industry, and we felt that access to this knowledge was essential in our search for effective inhibitors of alpha-1-antitrypsin polymerization and treatments for associated liver and lung diseases."

He continued: "Realistically, although we have access to the right patients and samples as well as the disease area expertise to plan effective clinical trials, it is very challenging for academics to develop a drug all the way through from idea to marketed product on our own. Partnerships such as the one we have initiated with DPAc are perfect, as each partner brings something unique to the table, leveraging their specific skills for the good of the program. The aim of everyone involved is to find a cure. If we succeed then everyone wins, most importantly of all the patients."

To learn more about GSK's DPAc program, please visit dpac.gsk.com