EPD/23/08 - Applying Novel Computational Approaches and Machine Learning to Advance Therapeutic Discovery in ALS/MND

ALS/MND is an incurable rapidly progressive and invariably fatal neurodegenerative disease that results in paralysis, swallowing and breathing difficulties. 1 in 300 adults will get ALS and the majority of people die within 5 years. There is only one globally licensed treatment. It is called Riluzole and was licensed back in 1995. It prolongs life by only 1-3 months. There is thus an urgent unmet need for effective disease modifying therapies. Major advances in our understanding of the biology and genetics of ALS now make this a realistic prospect. My research is centered on using state-of-the-art computational approaches to exploit some of these breakthroughs in the area of RNA biology which is a key player in the causation of ALS.

The human genome is made up of DNA, which contains all the different instructions required to build and maintain cells, which make up the tissues and organs of the human body. For the instructions, or genes, to be read by the cell, a copy of the specific instruction manual required must first be made, or transcribed, into RNA. These RNA molecules then provide the instructions to produce the building blocks of a cell - proteins. Proteins require folding into certain 3D shapes, a little like assembling a flat-pack table. Different cell types in the body perform different functions and therefore require different RNA molecules and proteins to build different cell types. Transcriptomics is the technique used to measure the RNA molecules, in a cell. In disease, the ability of a cell to produce copies of the correct instructions goes wrong. This means that the cell no longer produces the correct mixture of proteins, that work together to carry out healthy cellular processes, such as cell growth, communication, and movement. In ALS, these processes go wrong and lead to an accumulation of incorrectly folded proteins in the motor nerves and their supporting cells. This results, over time, in death and loss of motor nerve cells which results in breathing problems and paralysis.

I will use a computational approach to find new therapeutics for ALS. First, I will identify how the pattern of RNA molecules in brain cells changes in ALS. To do this I will use transcriptomics to measure all the RNA molecules in healthy and diseased neurons. I will then compare the patterns to create a map of disease/ALS specific changes. I will then use an open access database that contains a wealth of data that shows the impact of many thousands of different medicines on the transcriptome (gene) signatures in cells. I will specifically search for those potential therapies that reverse the disease associated changes to look more like the profile in healthy nerve cells. We will then test this prediction in living nerve cells in the lab that have been generated from human stem cells. If this is successful, that would support taking the "therapy" into a formal clinical trial noting that my collaborators lead the largest ever clinical trial platform in ALS/MND called MND-SMART which is designed to allow new medicines to be introduced into the trial.