INcitate knowledge

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1.- What research are you currently developing?

As our research group is computationally oriented, my research is theoretical in nature, spanning from mathematical and/or molecular modelling of protein structure and function, to structure-based drug design and pharmacological compound profiling. Primarily my work is concentrated on a family of membrane receptor proteins involved in human neuronal signalling: the metabotropic glutamate receptors (mGluRs) 1-8, which belong to the Class C GPCR family. In particular, I am focussed on understanding the way in which mGluR 4 and 5 function and how they are activated/deactivated, and the way in which their dysregulation contributes to human disease. It is already known that these two receptors are involved in pain transmission, schizophrenia, depression, and also likely modulatory in Parkinson's and Alzheimers. Therefore finding new and improved allosteric drugs specifically targeting these receptors will likely have multiple therapeutic benefits. In light of this, and in collaboration with synthetic chemists, our group has already contributed to the identification of a new range of allosteric compounds with novel and interesting chemical features, and we seek to improve these features further over the coming months.

In addition to Class C GPCRs that are involved in CNS function, I am also investigating Class A GPCRs, both generally in terms of overall activation/deactivation pathways, and specifically in terms of the CXCR1 receptor, which is responsible for binding chemokines in inflammatory pathways triggering neutrophil migration. Understanding the way these intermolecular interactions take place will potentially help the design of better anti-inflammatory drugs. I am also interested in investigating the role of oligomerization “cross-talk” between Class A and Class C GPCRs in the brain and subsequent effects on the progression of various neuronal diseases.

2.- How is the day-to-day inside your laboratory?

I can typically be found at my desk using several computers at the same time! As I'm involved in many projects simultaneously, I typically run several different modelling and bioinformatic algorithms every day, which requires a lot of planning and careful assessment of results. I also run computationally-demanding molecular dynamic simulations, either locally on university machines or through the CESCA supercomputer, which means computer system maintenance takes up some of my

time too. I am usually working on a paper of some kind almost every day, either one of my own or one that is collaborative in nature, which requires a significant amount of multi-tasking! In addition to all this, we have regular group meetings to try to help solve each other's problems in the laboratory, and to try to synchronise our work so we can best use our computational resources and produce complementary, meaningful, and publishable results. Communication is particularly important for computational scientists because we collaborate a lot with experimentalists, and we have to understand each other requirements as best as we can!

3.- What therapeutic applications do you think can your research have?

Potentially our research on mGluR 4 and 5 can help to identify new, more specific treatments with reduced side-effects for a variety of neurological disorders, such as chronic pain, depression, schizophrenia, Alzheimer's, and Parkinson's. This potential comes from the structure-based drug design of novel allosteric compounds, as well as from a better understanding of how inter-receptor interactions across different families govern inherent GPCR function, e.g. the interaction between mGluRs and the Class A GPCR Dopamine-D2 receptor. Potentially, inhibiting these intermolecular interactions through protein-protein inhibitors may yield therapeutically exciting results one day. On a more wider note, by analysing common features between all GPCRs, and through identifying a common activation/deactivation mechanism, agonists or antagonists for a wide range of GPCRs (many of which have not been crystallized yet) may be discovered or optimized, creating new and exciting treatments for a wide range of cell signalling-mediated diseases.

4.- How you encourage future scientists to be part of neuroscience research?

More than just neuroscience, which is a highly specific area, I recommend all biologically-minded scientists, whether younger or older, to gain a good understanding of structural biology, as this knowledge governs more and more the way in which we understand life and the human body at a molecular level. Being able to understand biomolecules through 3-D visualization of static and dynamic protein or DNA/RNA structures is a distinct advantage compared to the way biochemistry and molecular biology was historically performed. Therefore, I would say to all aspiring scientists to be as multi-faceted as possible, to be able to perform experiments in the laboratory but also to be able to plan, analyse and visualize results with appropriate computational skills. Regarding neuroscience in particular, it is an area that I always wanted to investigate myself, but took some time to reach. I highly recommend and

emphasize the importance of neuroscience research wherever possible because it is an expanding and exciting field, which is becoming more high profile due to an increased awareness of Alzheimer's and Parkinson's, in particular. Therefore, as an aspiring scientist it is an excellent place to be situated in terms of a fulfilling career, as it is at the very cutting edge of biomedicine. Furthermore as neuroscience researchers, potentially we can have a direct and very positive effect on many people lives. I believe this is a worthy aspiration for any future scientist.