**BBSRC MIBTP Studentship Project**

**September 2023**

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| **Project Title** | Molecular Modelling of P2X receptor function |
| **Project Summary**  |
| Extracellular ATP is a key signalling molecule in many physiological processes including immune response and neurotransmission. It acts on P2X receptors (P2XR), a family of ligand-gated ion channels, which are activated upon binding of extracellular ATP. P2XR activation and channel opening allows the influx of small cations into the cell hereby mediating Ca2+ signalling. The human genome encodes seven P2XR homologs (P2XR1-P2XR7) that have distinct roles and show tissue specific expression raising their therapeutic potential. Structurally, P2XRs form homo-trimers and hetero-trimers involving different P2XR homologs. Subunit variation of trimeric complexes provides the machinery for the modulation of cell-type specific responses to extracellular ATP. Each subunit in a homo- or hetero P2XR trimer is characterised by a large extracellular ligand binding domain, two transmembrane helices, and N- and C-termini forming an intracellular cap domain. P2XRs work by cycling through at least three states that are to some extent structurally characterized: a closed apo state with no ATP bound, an open state formed upon binding of ATP, and a desensitized state where the ion channel is closed despite ATP still being bound. The key questions for P2X receptor function we intend to address in this project are how ATP triggers the opening of the channel, how the receptor transits through the different states upon binding and unbinding of ATP, and how steric and allosteric small molecule antagonists affect different states and receptor function. We will use computational techniques such as homology modelling and AlphaFold modelling to generate relevant structural models in different states and subunit combinations, ligand docking and molecular dynamics simulations to unravel the mechanistic details required for understanding how P2X receptors work at a molecular level and informing drug design, and in depth phylogenetic analysis to elucidate the evolutionary history of this enticing protein family. For recent work see references.Techniques that will be undertaken during the project:* protein structure prediction
* molecular dynamics simulations
* ligand docking
* phylogenetic analysis

BBSRC Strategic Research Priority: Understanding the Rules of Life – Immunology, Neuroscience and behaviour, Structural Biology |
| **References** |
| Bidula S, Nadzirin IB, Cominetti M, Hickey H, Cullum SA, Searcey M, **Schmid R**, Fountain SJ (2022). Mol Pharm. 101, 33-44.Stavrou A, Evans RJ, **Schmid R** (2020). Biochem Biophys Res Com. 523, 190-195.Dayel AB, Evans RJ, **R Schmid** R (2019) Mol. Pharm. 96, 355-363.**Schmid R**, RJ Evans RJ (2019) Ann. Rev. Physiol. 81, 43-62.Allsopp RC, Dayl S, **R Schmid R**, Evans RJ (2017) Sci. Rep. 7, 1-12 |