Targeted Project / AY 2024 -2025

Artificial intelligence design of antibody modulators of GABA-A receptors

Project Code: TRG-CHEM-PS

Supervisor: Dr Pietro Sormanni (ps589@cam.ac.uk)

Department/Institute: Chemistry

Website: https://www-sormanni.ch.cam.ac.uk

Co-supervisor: Dr Paul Miller – expert in antibody modulation of ion channels and structural biology (cryo-EM) (Pharmacology)

Research area: Chemical biology, structural biology, artificial intelligence – with implications in pharmacology

BBSRC DTP main strategic theme: Transformative technologies

BBSRC DTP secondary strategic theme: Bioscience for an integrated understanding of health

Project outline:

We seek a motivated PhD candidate to lead a multidisciplinary project at the forefront of precision pharmacology in the biochemistry of the central nervous system. Gamma-aminobutyric acid type-A (GABA-A) receptors play key roles in inhibitory neurotransmission and are targets of several drugs. Different subtypes of GABA-A receptors contribute to distinct neurological processes such as cognition, anxiety, addiction, sedation, motor coordination, and nociception. However, current small molecule tools lack sufficient selectivity to unravel the distinct contributions of GABA-A subtypes. In contrast, antibodies offer improved specificity and open new avenues for biomedical research.

This PhD project is joint between the Sormanni lab (Chemistry) and the Miller lab (Pharmacology). It builds on the Miller lab's ground-breaking work in developing nanobody modulators against GABA-A receptors (1). Cryo-electron microscopy structures provided insights into the modulators' mechanisms of action and can serve as an excellent starting point for computational engineering approaches (2). The goal is to further develop and employ artificial intelligence (AI) antibody-design strategies available in the Sormanni lab (3, 4) on receptor-antibody structures to “jump” specificity between subtypes and create new pharmacological tools. In this way, novel dual-subtype selective modulators will be generated for the first time. Computational outputs will be tested, ratified, and studied using biophysical techniques, electrophysiology, and cryo-electron microscopy. By joining this project, the student will have the opportunity to contribute to the establishment of new antibody design strategies and the creation of novel pharmacological tools for neuroscience research.

(1) Kasaragod…Miller. Nature. 2022.

(2) Miller…Aricescu. Biorxiv. 2018

(3) Aguilar Rangel…Sormanni. Science Advances. 2022.

(4) Ramon…Sormanni. Biorxiv. 2023 (Nature Machine Intelligence under review)