

# PhD Opportunity

*In silico* modelling of endocannabinoid evolution

## Supervisory team

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## Director of Studies:

Dr Mathieu Di Miceli, Worcester Biomedical Research Group, School of Science and the Environment, University of Worcester. Dr Di Miceli has over 10 years of experience in neuroscience.

## Supervisors:

Dr Amy Cherry, (Protein biochemist) Worcester Biomedical Research Group, School of Science and the Environment, University of Worcester

Dr Mike Wheeler, (Expertise in Evolution and molecular biology.) Worcester Biomedical Research Group, School of Science and the Environment, University of Worcester

**Research Group:** [Worcester Biomedical Research Group \(WBRG\)](#)

## The PhD Opportunity

In the brain, the endocannabinoid (eCB) system maintains adequate neurotransmission ([Lu and Mackie 2016](#)). Indeed, the eCB system provides a negative feedback mechanism, preventing over-activation of synaptic transmission. This mechanism involves release of eCBs from the phospholipidic bilayer which, in turn, will activate specific receptors.

These receptors will then decrease neurotransmission. Such a system includes signalling molecules, such as 2-arachidonoyl glycerol (2-AG) and arachidonoyl ethanolamide (anandamide), as well as several receptors, such as the cannabinoid receptor 1 (CB<sub>1</sub>R), the orphan G-protein coupled receptor 55 (GPR<sub>55</sub>) and the transient receptor potential of vanilloid type-1 receptor (TRPV<sub>1</sub>).

The complex signalling ([Zou and Kumar 2018](#)) between effectors and receptors also involves enzymes responsible for the biosynthesis and metabolism of these molecules: Fatty Acid Amine Hydrolase (FAAH), *N*-acyl-phosphatidylethanolamine phospholipase D (NAPE-PLD) and phospholipase C beta-1 (PLC-β<sub>1</sub>).

In this project, we aim to further decipher the evolutionary origins of the eCB system, in light of what was previously observed ([Elphick 2012](#); [McPartland et al. 2006](#)). In addition, we also aim to decipher how the eCB system can be implicated in health and

disease. Indeed, several pathologies are currently under scrutiny for possible links with the eCB system (Cheung et al. 2019; Forte et al. 2020; Moreno et al. 2019), such as pain, epilepsy, neurodevelopmental disorders.

This project will involve: bioinformatics, *in silico* modelling and data mining. Examples of potential useful techniques can be found in the following articles: Arias-Gaguancela et al. 2023; Bian et al. 2019; Kono et al. 2013; Li et al. 2019; Wichmann and Althaus 2020; Wickert et al. 2018. Preliminary results have already been obtained in our department.

## References

- Arias-Gaguancela, O. et al. (2023) Two legume fatty acid amide hydrolase isoforms with distinct preferences for microbial- and plant-derived acylamides. *Scientific Reports*. [Online] 13 (1), Nature Publishing Group, 7486. Available from: doi:10.1038/s41598-023-34754-z.
- Bian, Y.-M. et al. (2019) Computational systems pharmacology analysis of cannabidiol: a combination of chemogenomics-knowledgebase network analysis and integrated in silico modeling and simulation. *Acta Pharmacologica Sinica*. [Online] 40 (3), 374–386. Available from: doi:10.1038/s41401-018-0071-1.
- Cheung, K.A.K. et al. (2019) The Interplay between the Endocannabinoid System, Epilepsy and Cannabinoids. *International Journal of Molecular Sciences*. [Online] 20 (23), 6079. Available from: doi:10.3390/ijms20236079.
- Elphick, M.R. (2012) The evolution and comparative neurobiology of endocannabinoid signalling. *Philosophical Transactions of the Royal Society B: Biological Sciences*. [Online] 367 (1607), 3201–3215. Available from: doi:10.1098/rstb.2011.0394.
- Forte, N. et al. (2020) Obesity Affects the Microbiota-Gut-Brain Axis and the Regulation Thereof by Endocannabinoids and Related Mediators. *International Journal of Molecular Sciences*. [Online] 21 (5), 1554. Available from: doi:10.3390/ijms21051554.
- Kono, M. et al. (2013) Synthesis, SAR study, and biological evaluation of a series of piperazine ureas as fatty acid amide hydrolase (FAAH) inhibitors. *Bioorganic & Medicinal Chemistry*. [Online] 21 (1), 28–41. Available from: doi:10.1016/j.bmc.2012.11.006.
- Li, X. et al. (2019) Crystal Structure of the Human Cannabinoid Receptor CB2. *Cell*. [Online] 176 (3), 459-467.e13. Available from: doi:10.1016/j.cell.2018.12.011.
- Lu, H.-C. & Mackie, K. (2016) An introduction to the endogenous cannabinoid system. *Biological psychiatry*. [Online] 79 (7), 516–525. Available from: doi:10.1016/j.biopsych.2015.07.028.
- McPartland, J.M. et al. (2006) Evolutionary origins of the endocannabinoid system. *Gene*. [Online] 370, 64–74. Available from: doi:10.1016/j.gene.2005.11.004.
- Moreno, E. et al. (2019) The Endocannabinoid System as a Target in Cancer Diseases: Are We There Yet? *Frontiers in Pharmacology*. [Online] 10, 339. Available from: doi:10.3389/fphar.2019.00339.

Wichmann, L. & Althaus, M. (2020) Evolution of epithelial sodium channels: current concepts and hypotheses. *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology*. [Online] 319 (4), R387–R400. Available from: doi:10.1152/ajpregu.00144.2020.

Wickert, M. et al. (2018) The F238L Point Mutation in the Cannabinoid Type 1 Receptor Enhances Basal Endocytosis via Lipid Rafts. *Frontiers in Molecular Neuroscience*. [Online] 11. Available from: <https://www.frontiersin.org/articles/10.3389/fnmol.2018.00230> [Accessed: 22 June 2023].

Zou, S. & Kumar, U. (2018) Cannabinoid Receptors and the Endocannabinoid System: Signaling and Function in the Central Nervous System. *International Journal of Molecular Sciences*. [Online] 19 (3), 833. Available from: doi:10.3390/ijms19030833.

### Additional costs

There are no additional costs to this project, as this is an *in silico* only project. However, it is anticipated that the successful candidate invests in a high-specification computer, which will be essential to run CPU-intensive experiments.

### Application Process

To begin the application process please go to <https://www.worcester.ac.uk/courses/human-biology-mphilphd> and click on 'How to Apply' in the top menu. This PhD could be carried out on a part time or full time basis so please select the relevant application link. On the application form, please make it clear that you are applying for one of our advertised projects so we can direct it straight to the relevant people.

### The Interview

All successful applicants will be offered an interview with the proposed Supervisory Team. You will be contacted by a member of the Research School Team to find a suitable date. Interviews can be conducted in person or over Microsoft Teams.

### Funding your PhD

For information about Doctoral Loans please visit: <https://www.worc.ac.uk/study/fees-and-finance/doctoral-loans.aspx>

During your PhD you can access the Research Student Support Scheme to support dissemination costs associated with your research, up to £500 a year.

### Research at the University of Worcester

Research is central to the University's mission to make a difference in everything that we do. We are committed to delivering excellent research which extends the boundaries of human knowledge but which also improves people's lives by enabling better health outcomes, improving food security, developing environmentally sustainable solutions for crop production and socially sustainable solutions to our ageing population, enhancing public knowledge and understanding of the past and present.

The University hence focuses its research around five high-level challenges facing society, locally, nationally and globally:

- [Human Health and Wellbeing](#)
- [Sustainable Futures](#)
- [Digital Innovation](#)
- [Culture, Identity and Social Exclusion](#)
- [Professional Education](#)

The success of our research is reflected in our continuous improvement in external research assessment processes. In the most recent Research Excellence Framework, REF 2021, the University saw a near 50% increase in the scale of its research and 12% increase in quality, building on its performance in REF 2014 when it was the UK's most improved university in terms of Research Power, a combination of scale and quality.

### **Research Degrees at Worcester**

Our research students are central to our overall mission for research. They are working at the cutting edge of their disciplines and driving forward the quality of our research whilst enriching our research culture. We are looking to increase our research student numbers as a strategic imperative.

Our commitment to our students is reflected in the results of the Postgraduate Research Experience Survey 2023 in which we ranked 3<sup>rd</sup> for overall research student satisfaction nationally. Key to our success in this area is the Research School, a focal point for all our research students.

It provides:

- day-to-day support for our students, both administrative and practical, through our dedicated team
- a Research Student Study Space with both PCs and laptop docking station
- a comprehensive Researcher Development Programme for students and their supervisors
- a programme of student-led conferences and seminars

### **Research Group**

#### **Worcester Biomedical Research Group**

The Worcester Biomedical Research Group (WBRG) aims to promote multidisciplinary Biomedical Science research at the University of Worcester and fosters collaborations between staff (cross-institute), students and local health / industrial organisations.

Building sustainable societies through research into disease prevention, medical treatment and diagnostics, lies at the heart of the WBRG research ethos. We aim to achieve this goal through basic and translational Biomedical Research with particular focus on cancer, cardiovascular disease and neurodegeneration.

**Widening Participation:**

As part of its mission statement the University is committed to widening participation for its higher degrees. Although most candidates will have an undergraduate and/or a Masters degree, the University is happy to accept applications from candidates with relevant professional qualifications and work related experience.

**For further information** or an informal discussion on this project, please contact Dr Mathieu Di Micelli (Director of Studies) via email at [m.dimiceli@worc.ac.uk](mailto:m.dimiceli@worc.ac.uk)