

Dr Robin Bon, Dr Martin McPhillie, Prof Andrew Wilson & Heiko Wurdak

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Developing small-molecule inhibitors of mitochondrial metabolism for the treatment of brain cancer

Across the world, 250,000 people are diagnosed with brain cancer (glioblastoma) every year, and survival rates are far worse than for other types of cancer (e.g., lung and breast) because it is difficult to remove every single brain cancer cell via surgery and chemotherapy. We have shown that a compound called KHS101 can 'force' brain cancer cells to 'shut down' their energy production and exhaust them to death, while not affecting the healthy brain cells. KHS101 itself is not sufficiently potent to be a drug but it should be developed further because it is selective to brain cancer cells and, crucially, can get across the blood-brain-barrier. We have found that KHS101 works by inhibiting a key mitochondrial protein needed for glioblastoma metabolism: heat shock protein member D1 (HSPD1), through a mechanism that is unique for HSPD1.^{1, 2}

During this PhD project, the student will improve the potency and stability of KHS101 using multi-parameter lead optimisation and structure-guided expertise within the supervisory team, building on their previous experience of synthesising bioactive small molecules. The student will carry out 'design, make, test' cycles using in-house in vitro assays, and work with brain cancer researchers in the School of Medicine to assess activities of compounds in patient-derived brain cells. The student will also develop chemical probes and assays to study the interaction of new compounds with HSPD1, for example through photoaffinity labelling and mass spectrometry.

The project will combine medicinal chemistry and chemical biology approaches to develop and test new KHS101 analogues for the treatment of glioblastoma. Candidates will have a background in synthetic chemistry, ideally in the synthesis of bioactive small molecules, with a strong desire to work in an interdisciplinary research environment. The student will gain experience in a wide range of transferable skills, including medicinal chemistry, mass spectrometry, in silico ligand design, in vitro assays and cancer biology.

References

1. D. P. Klebl, M. C. Feasey, E. L. Hesketh, N. A. Ranson, H. Wurdak, F. Sobott, R. S. Bon and S. P. Muench, *iScience*, 2021, **24**.
2. E. S. Polson, V. B. Kuchler, C. Abbosh, E. M. Ross, R. K. Mathew, H. A. Beard, B. da Silva, A. N. Holding, S. Ballereau, E. Chuntharpursat-Bon, J. Williams, H. B. S. Griffiths, H. Shao, A. Patel, A. J. Davies, A. Droop, P. Chumas, S. C. Short, M. Lorgier, J. E. Gestwicki, L. D. Roberts, R. S. Bon, S. J. Allison, S. Zhu, F. Markowitz and H. Wurdak, *Sci. Transl. Med.*, 2018, **10**, eaar2718.

Keywords Protein-protein interactions, chemical biology, biophysics, nuclear magnetic resonance, intrinsically disordered regions

How to apply Formal applications for research degree study should be made online through the University's website. See <https://www.leeds.ac.uk/research-applying/doc/applying-research-degrees>. Please state clearly in the Planned Course of Study section that you are applying for PhD Chemistry and in the research information section that the research degree you wish to be considered for is "Developing small-molecule inhibitors of mitochondrial metabolism for the treatment of brain cancer" as well as Professor Andy Wilson and Dr Robin Bon as your proposed supervisors. Applications must be submitted by April 15th 2022.

If English is not your first language, you must provide evidence that you meet the University's minimum English language requirements (below).

We actively encourage applicants from diverse career paths and backgrounds and from all sections of the community, regardless of age, disability, ethnicity, gender, gender expression, sexual orientation and transgender status. We also support applications from those returning from a career break or from other roles. We consider offering flexible study arrangements (including part-time), carer support funds for conferences, and peer support networks for parents and carers.

Entry requirements At least a 2:1 honours degree in a relevant subject, or equivalent. The interdisciplinary nature of this programme means that we welcome applications from students with backgrounds in any chemical, and/or physical/biological science. Please contact Dr Robin Bon (r.bon@leeds.ac.uk) or Prof Andy Wilson (a.j.wilson@leeds.ac.uk) for further details about this project.

English language requirements The minimum English language entry requirement for research postgraduate research study is an IELTS of 6.0 overall with at least 5.5 in each component (reading, writing, listening and speaking) or equivalent. The test must be dated within two years of the start date of the course in order to be valid.

Funding on offer A highly competitive University of Leeds/Dr Simon Waterworth Alumni Donor Studentship consisting of the award of fees with a maintenance grant of £16,062 for session 2022/23 for 3 years. Additional funding will be available for expenses and travel relating to the research project.

This opportunity is open to UK applicants only. All candidates will be placed into the University of Leeds/Dr Simon Waterworth Alumni Donor Studentship Competition and selection is based on academic merit.

Contact details For further information please contact Doctoral College Admissions by email: phd@engineering.leeds.ac.uk