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This proposal is representative of the projects currently on offer in our group. For more details of active research projects, please visit our webpage at: https://wilson.leeds.ac.uk/

Stabilizers of the interaction between 14-3-3 and hDM2/hDMX

Transient protein-protein interactions (PPIs) control all cellular processes relevant to health and disease. Selective modulation of individual PPIs would thus facilitate both a greater understanding of biological mechanisms and provide new opportunities for therapeutic intervention. p53 is a critical tumour suppressor involved in DNA repair, inhibition of cell proliferation and cell cycle regulation. P53 is negatively regulated through interaction with *h*DM2 and/or *h*DMX. These proteins regulate localization of p53, physically block its interaction with DNA and act in concert to effect p53 degradation through ubiquitination and subsequent proteolytic degradation.[1] In turn *h*DM2 and *h*DMX function is regulated through phosphorylation dependent interaction with the adaptor protein 14-3-3.[2] Given that *h*DM2 and *h*DMX are overexpressed in numerous cancers, the p53/hDM2(X) interaction has received considerable attention as a drug-discovery target.[3]

This PhD project will pursue an alternative approach to target the oncogenic p53 pathway by identification and optimization of stabilizers of hDM2/14-3-3 and hDMX/14-3-3. The project will exploit our toolkit of enabling drug discovery capabilities,[4-5] in house crystallographic and biophysical data on the nature of the *h*DM2/14-3-3 and *h*DMX/14-3-3[6] interactions together with hit matter identified from conventional screening and dynamic fragment ligation experiments.[7] A range of methods will be employed including: computational prediction, peptide and small-molecule synthesis, screening technologies, biophysics and structural-molecular biology. As a collaborative CASE studentship with AstraZeneca, a research placement in Gothenburg will form part of the studentship. This will allow the design, synthesis and testing of candidate PPI stabilizers to discover a selective and cell-permeable modulators.

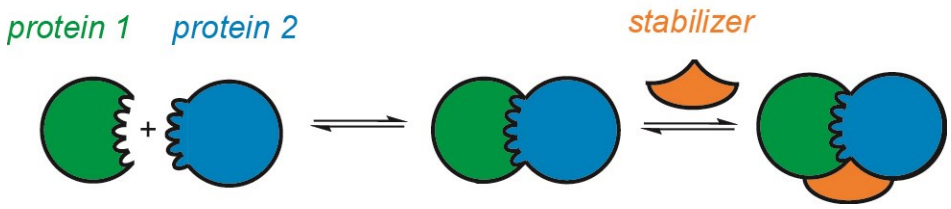

Figure 1. *Schematic depicting strategies for modulation of PPIs by stabilization.*

References

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Keywords structural molecular biology, medicinal chemistry, chemical biology

How to apply for this project; the successful applicant should ideally be able to take up the studentship at the earliest opportunity and candidates will be considered until the position is filled. An application for research degree study should be made online through the University's website see:

https://physicalsciences.leeds.ac.uk/info/9/research_degrees/20/how_to_apply

Please state clearly in the research information section that the research degree you wish to be considered for is *Stabilizers of the interaction between 14-3-3 and hDM2 and hDMX* as well as Prof Andy Wilson as your proposed supervisor.

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

Equality, diversity and inclusion is at the heart of all of our activities. We know that diversity strengthens our research community, leading to enhanced research creativity, productivity and quality, and societal and economic impact.

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 biological, chemical, and/or physical science, who are interested in using their skills in addressing biological questions. Please contact 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 Appointed candidates will be fully-funded for 3.5 years. The funding includes:

- Tax-free annual UKRI stipend (£15,609 for 2021/22 starts. Awards increase every year, typically with inflation).
- A CASE studentship stipend enhancement
- UK tuition fees (Around £4,500 per year)
- Research Training and Support Grant (RTSG)
- Centrally organised training and networking opportunities, including an annual student symposium

Contact details For further information please contact Doctoral College Admissions by email: maps.pgr.admissions@leeds.ac.uk.