**University of Leicester**

**MRC AIM Studentship Project 2025-6 entry.**

|  |  |
| --- | --- |
| **First Supervisor** | Dr James Hodgkinson |
| **School/Department** | School of Chemistry and Leicester Institute of Structural and Chemical Biology |
| **Email** | [jthodgkinson@leicester.ac.uk](mailto:jthodgkinson@leicester.ac.uk) |

|  |  |
| --- | --- |
| **Second Supervisor** | Dr Emma Hesketh |
| **School/Department** | Leicester Institute of Structural and Chemical Biology |
| **Email** | [emma.hesketh@leicester.ac.uk](mailto:emma.hesketh@leicester.ac.uk) |

|  |  |
| --- | --- |
| **Additional Supervisor** | Prof John Schwabe |

**iCASE partners, Sygnature Discovery (Peak Proteins):**

Alex Brown

Duncan Smith

Valerie Pye

**Section 2 – *Project Information***

|  |  |
| --- | --- |
| **Project Title** | iCase: Using CryoEM to trap and visualise PROTAC drugs in action against cancer targets |
| **Project Summary** | |
| This PhD project is an exciting opportunity to explore the innovative drug strategy PROTACs by Cryo-Electron microscopy, a cutting-edge structural biology technique.  This project involves a close partnership and collaboration with a world-leading drug discovery CRO where the student will learn protein expression/purification amongst industry experts, producing the therapeutic target proteins SOS1 and LSD1.  At Leicester you will learn the chemistry of making PROTACS – novel bi-functional drugs that promise to ‘drug the undruggable’ by marking target proteins for degradation rather than inhibition. To determine the structure-activity relationship of these PROTACS, you will use state of the art cryo-electron microscopy at the regional facility based at Leicester.  SOS1 and LSD1 are both important cancer therapeutic targets with substantial prospect for future drug development:  SOS1 is cytoplasmic guanine nucleotide exchange factor that plays a critical and essential role in the KRAS signalling pathway. Inhibitors of SOS1 have shown considerable potential for targeting RAS-driven tumours.  LSD1 is a histone demethylase enzyme that plays a critical role in the endothelial to mesenchymal transition that is a key step in allowing tumours to metastasize. Inhibition of LSD1 has been shown to be a promising treatment for melanoma in mouse models. | |
| **References** | |
| *Comprehensive Transcriptomic Analysis of Novel Class I HDAC Proteolysis Targeting Chimeras (PROTACs),* I.M. Baker, J.P. Smalley, K.A. Sabat, J.T. Hodgkinson, S.M. Cowley, *Biochemistry*, **2023**, *62*, 645.  *Optimization of Class I Histone Deacetylase PROTACs Reveals that HDAC1/2 Degradation is Critical to Induce Apoptosis and Cell Arrest in Cancer Cells,*J.P. Smalley, I.M. Baker, W.A. Pytel, L.Y. Lin, K.J. Bowmann, J.W.R. Schwabe, S.M. Cowley, J.T. Hodgkinson, *J. Med. Chem.***2022**, *65*, 5642-5659.  *A ‘Click’ Chemistry Approach to Novel Entinostat (MS-275) based Class I Histone Deacetylase Proteolysis Targeting Chimeras*, J. M. Cross, M. E. Coulson, J. P. Smalley, W. A. Pytel, O. Ismail, J. S. Trory, S. M. Cowley, J. T. Hodgkinson, *RSC Med. Chem*., **2022**, 13, 1634.  *HDAC Degrader*, S. M. Cowley, J. T. Hodgkinson, J. W. R. Schwabe, J. P. Smalley, G. E. Adams, C. J. Millard, *WO application 2021148811 (A1)* , published 29.07.**2021**  *PROTAC-mediated degradation of class I histone deacetylase enzymes in corepressor complexes,* J. P. Smalley, G. E. Adams, C. J. Millard, Y. Song, J. K. S. Norris,  J. W. R. Schwabe, S. M. Cowley, J. T. Hodgkinson, *Chem. Commun.*,**2020**, *56*, 4476-4479.  Functional and structural coupling between LSD1 and HDAC1 in the CoREST complex. Song Y., Dagil l., Fairall L., Robertson N., Wu M., Ragan T.J., Savva G.C., Morone N., Kunze M.B.A., Jamieson A.G., Cole P.A., Hansen D.F., Schwabe J.W.R. (2020) **Cell Reports** 30, 2699.  Targeting the CoREST complex with dual histone deacetylase and demethylase inhibitors Kalin, J.H., Wu, M., Gomez, A.V., Song, Y., Das, J., Hayward, D., Adejola, N., Wu, M., Panova, I., Chung, H.J., Kim, E., Roberts, H.J., Roberts, J.M., Prusevich, P., Jeliazkov, J.R., Roy Burman, S.S., Fairall, L., Milano, C., Eroglu, A., Proby, C.M., Dinkova-Kostova, A.T., Hancock, W.W., Gray, J.J., Bradner, J.E., Valente, S., Mai, A., Anders, N.M., Rudek, M.A., Hu, Y., Ryu, B., \*Schwabe, J.W.R., \*Mattevi, A., \*Alani, R.M., \*Cole, P.A., (2018). **Nature Communications**, (2018) 9(1), 53. <http://doi.org/10.1038/s41467-017-02242-4>. **\*Co-corresponding authors** | |