**University of Leicester**

**Chemistry GTA Studentship Project 2022**

**Section 1 – *Supervisor Information***

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| **First Supervisor (Name and Title)** | Dr Richard Hopkinson |
| **School** | Chemistry |
| **Email**  | richard.hopkinson@leicester.ac.uk |

**Section 2 – *Project Information***

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| **Project Title** | Modulating cellular aldehydes using small molecule tools |
| **Project Highlights:** | 1. | Design and synthesise next-generation aldehyde-releasing small molecules (ARMs) that release aldehydes in cells in response to various stimuli. |
| 2. | Validate ARMs as aldehyde releasers using spectroscopic techniques and determine the kinetics and mechanisms of formaldehyde release. |
| 3. | Test the ARMs in human cell assays to determine their cytotoxicity, their ability to modify cellular aldehyde concentrations, and their functional effects. |
| **Project Overview**  |
| Many aldehydes are human metabolites and environmental pollutants. At high cellular concentrations, many aldehydes are toxic – however, the underlying mechanisms are often remarkably unknown. From a chemical perspective, aldehydes are highly reactive with biological molecules – this reactivity is likely responsible for at least some of their biological functions, although chemical evidence is lacking. In particular, some aldehydes are reported to cross-link biomolecules, which are almost certainly toxic in many cases. However, recent work also suggests that aldehyde have important ‘healthy’ functions. These observations are important because they imply different cellular aldehyde concentrations have different biological effects.For aldehyde biology to be analysed accurately, it is essential that we can quantifiably and controllably modify cellular aldehyde concentrations. To date, this has proved challenging. Therefore, for the field to progress, it is essential that we develop novel methods deliver aldehydes to cells. One promising strategy for HCHO delivery is via ‘**A**ldehyde-**R**eleasing **M**olecules (ARMs), which degrade into aldehydes when internalised within cells. The aim of this project is to design, synthesise and (bio)chemically validate next-generation ARMs, and then to determine their aldehyde-releasing capability and phenotypic effects in cells. Ultimately, these studies will develop the ARMs necessary for further biological work, including studies to identify aldehyde-biomolecule adducts, and will therefore be vital tools in the aldehyde biological research field. Ultimately, the work will also give insight into the therapeutic potential of aldehyde modulation in humans.  |
| **Methodology**  |
| Initially, next-generation ARMs will be designed using literature precedence and preliminary insight from our group. In particular, ARMS will be designed so that they promote aldehyde release in response to different stimuli in a spatiotemporal manner. They will also likely contain solubilising groups and/or groups that induce intracellular localisation. After their design, the compounds, as well as insensitive negative controls, will be synthesised, characterised, and purified ready for cellular studies. These studies will involve testing the ARMs’ susceptibility to their respective aldehyde-releasing stimuli, which will be monitored using a variety of spectroscopic techniques, e.g. MS, NMR, fluorescence. The kinetics of aldehyde release will also be monitored by the same methods. Finally, suitably sensitive ARMs will be analysed in cellular assays to determine their cytotoxicity, their ability to increase cellular aldehyde concentrations, and their effects on cell morphology. Later work may also include functional studies in aldehyde-relevant disease models. |
| **Further Reading:** | R. J. Hopkinson, P. S. Barlow, C. J. Schofield and T. D. W. Claridge, Org. Biomol. Chem., 2010, 8, 4915.S. Shishodia, D. Zhang, A. El-Sagheer, T. Brown, T. D. W. Claridge, C. J. Schofield, R. J. Hopkinson\*, Org. Biomol. Chem., 2018, 16, 4021.J. Kamps, R. J. Hopkinson\*, C. J. Schofield\*, T. D. W. Claridge\*, Commun. Chem., 2019, 2, 126.G. Burgos-Barragan, N. Wit, J. Meiser, F. A. Dingler, M. Pietzke, L. Mulderrig, L. B. Pontel, I. V. Rosado, T. F. Brewer, R. L. Cordell, P. S. Monks, C. J. Chang, A. Vazquez, K. J. Patel, Nature, 2017, 548, 612.A. Nudelman, E. Gnizi , Y. Katz, R. Azulai, M. Cohen-Ohana, R. Zhuk, S. R. Sampson, L. Langzam, E. Fibach, E. Prus, V. Pugach, A. Rephaeli, European Journal of Medicinal Chemistry, 2001, 36, 63. |