

## Developing “discovery toolkits” for thiamine diphosphate-dependent enzymes as herbicide targets

### Supervisory team:

**Main supervisor:** Prof Nicholas Harmer (University of Exeter)

**Second supervisor:** Prof Jennifer Littlechild (University of Exeter)

**Non-academic (CASE) supervisor:** Dr Christian Noble (Syngenta)

**Host institution:** University of Exeter (Streatham/St Luke's)

**CASE partner:** Syngenta

### Project description:

In this project, you will make the first steps in a discovery campaign aimed at identifying novel herbicides. The project will teach you skills in protein preparation, enzymology, protein structure determination, microbiology, molecular biology, and molecular modelling. You will learn protein science and enzymology methods broadly applicable to drug discovery. For protein structure determination, the project will provide opportunities to work with experts in X-ray crystallography and single particle cryo-electron microscopy, with the possibility of using micro-electron diffraction if suitable samples are obtained. You will also have the opportunity to carry out small scale compound screens against suitable targets.

The aim of the project will be to develop a “discovery toolkit” for one or more enzymes found in model weeds. These enzymes are expected to be essential for weed growth and are not found in humans. In the project, you will prepare these enzymes and determine their kinetic properties to identify likely ideal binding sites for inhibitors. You will determine the structures of the proteins in complex with their substrates or products. Finally, you will build assays that could be used for testing potential inhibitors of the enzymes *in vitro* or *in vivo*, and test these with small inhibitor libraries. This collection of data and methods will allow the project partner to screen larger compound libraries in the future.

The project will offer a challenging and interdisciplinary PhD in cutting edge research areas. All these methods are well established in the supervisor’s groups. There will be opportunities to also learn associated methods that the laboratories specialise in as the project develops. The project will also offer considerable opportunities to interact with the partner Syngenta, and other collaborators in our wider network. Syngenta will host the industrial placement at its Jealott’s Hill site, which is Syngenta’s largest R&D site globally and includes multiple different disciplines from high-throughput screening to lead-optimisation, formulation and development. The placement will most likely be in the third year of the PhD.

This project will be based in the recently established Living Systems Institute in Exeter, which houses a diverse group of leading interdisciplinary researchers, and in the Henry Wellcome Building for Biocatalysis. You will join a vibrant group of young researchers with interests across a range of diseases.