THE UNIVERSITY OF MANCHESTER

PARTICULARS OF APPOINTMENT

FACULTY OF SCIENCE & ENGINEERING

SCHOOL OF NATURAL SCIENCES

DEPARTMENT OF CHEMISTRY

RESEARCH ASSOCIATE IN CHEMICAL BIOLOGY

VACANCY REF: SAE-025559

Salary:	Grade 6 £36,024 to £44,263 per annum, depending on experience
Hours:	Full time
Duration:	Fixed term from 1 July 2024 until 30 June 2026
Location:	Oxford Road, Manchester

Enquiries about the vacancy, shortlisting and interviews:
Name: Professor Jason Micklefield & Dr Sarah Shepherd
Email: jason.micklefield@manchester.ac.uk and cc: sarah.shepherd@manchester.ac.uk

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Background

The Research Associate will be based in the Manchester Institute of Biotechnology (MIB) working on developing biosynthetic pathways or chemoenzymatic routes to pharmaceutical targets (e.g. antibiotics and other important bioactive compounds).

You will have a background in either synthetic organic chemistry and biological chemistry or possess expertise/knowledge in the enzymology/biochemistry and microbial biology areas. Knowledge that extends across these areas is useful, but not essential - we are open to candidates from both chemistry and biology backgrounds.

Research and selected publications from the Micklefield lab: Our labs provide a world-leading interdisciplinary research environment, with state-of-the-art facilities, which are ideal for developing new knowledge, diverse skills, and establishing a future career in academia or industry. Our friendly and talented team currently comprises over 20 researchers from Biology and/or Chemistry backgrounds. We have extensive experience in natural product biosynthesis, pathway engineering and biocatalysis.[1-6] For example our lab developed novel methods for engineering complex nonribosomal peptide synthetase (NRPS) enzymes that deliver new lipopeptide antibiotics.[1,7] We have discovered and characterised hybrid assembly lines including

NRPS and polyketide synthase (PKS) enzymes producing the structurally unique antibiotic K16[3] and epoxyketones (TMC-86A) that inspired development of new antitumour agents.[8] Our team also discovered and determined structures of novel ATP-dependent ligase enzymes, from PKS-NRPS pathways, which were engineered to produce agrochemicals and pharmaceuticals including drugs in clinical trials for COVID-19.[2] New synthetic biology approaches were also used to create a *de novo* pathway to thaxtomin phytotoxin derivatives, with improved herbicidal properties for crop protection.[9]

In addition to biosynthesis, our team is widely recognised for its research in enzyme engineering and biocatalysis. For example, we employed structure-guided mutagenesis and directed evolution to improve activity, expand the substrate scope and switch the regioselectivities of halogenase enzymes.[10,11] We showed how engineered halogenases can be integrated with Pd-catalysed cross-coupling chemistry, in one-pot reactions, to affect the direct regioselective arylation, alkenylation, cyanation and further functionalisation of C-H positions in diverse scaffolds.[4,6] Our lab also characterised various methyltransferases (MT), demonstrating how these can be used in the regioselective alkyl-diversification of tetrahydroisoquinolines, rapamycin immunosuppressive agents and other bioactive natural and non-natural products.[12-16] The lab succeeded in engineering orthogonal MT creating alternative bioalkylation pathways[13] and developed methods for selective derivatisation of tyrosine residues in peptides/proteins using MT and SAM analogues for labelling etc.[16] In addition, our team have characterised, engineered and developed many other important enzymes for synthetic applications.[17-19]

[1] Thong *et al Nature Commun* **2021**, *12*, 6872 (https://doi.org/10.1038/s41467-021-27139-1);
[2] Winn *et al, Nature* **2021**, *593*, 391-398 (https://doi.org/10.1038/s41586-021-03447-w);
[3] Law *et al, Nature Catalysis* **2018**, *1*, 977 (https://doi.org/10.1038/s41929-018-0178-2);
[4] Craven *et al, Nature Catalysis* **2021**, *4*, 385 (https://doi.org/10.1038/s41929-021-00603-3);
[5] Bering *et al, Nature Commun.* **2022,** *13,* 380 (https://doi.org/10.1038/s41467-022-28005-4);
[6] Latham *et al, Nature Commun* **2016**, 7, 11873 (http://dx.doi.org/10.1038/NCOMMS11873);
[7] Thirlway *et al Angew Chem Int Ed* **2012**, *51*, 7181 (http://dx.doi.org/10.1002/anie.201202043);
[8] Zabala *et al, J Am Chem Soc* **2016,** *138,* 4342 (http://dx.doi.org/10.1021/jacs.6b01619);
[9] Winn *et al, Angew Chem Int Ed* **2018**, *57*, 6830 (https://doi.org/10.1002/anie.201801525);
[10] Menon *et al Angew Chem Int Ed* **2017**, *56*, 11841 (http://dx.doi.org/10.1002/anie.201706342);
[11] Shepherd *et al Chem Sci* **2015** *6,* 3454 (http://dx.doi.org/10.1039/C5SC00913H);
[12] Bennett *et al Angew Chem Int Ed* **2018**, *57*, 10600 (http://dx.doi.org/10.1002/anie.201805060);
[13] Herbert *et al Angew Chem Int Ed* **2020**, *49*, 14950 (http://dx.doi.org/10.1002/anie.202004963);
[14] Law *et al Chem Sci* **2015**, *6,* 2885 (http://dx.doi.org/10.1039/C5SC00164A);
[15] Law *et al Angew Chem Int Ed* **2016** *55,* 2683 (http://dx.doi.org/10.1002/anie.201508287);
[16] Struck *et al J Am Chem Soc.* **2016** *138*, 3038 (http://dx.doi.org/10.1021/jacs.5b10928);
[17] Okrasa *et al Angew Chem Int Ed* **2009***, 48,* 7691 (http://dx.doi.org/10.1002/anie.200904112);
[18] Chesters *et al Angew Chem Int Ed* **2012**, *51*, 4344 (http://dx.doi.org/10.1002/anie.201200669);
[19] Francis *et al, ChemBioChem* **2017***, 18*, 382-386 (http://dx.doi.org/10.1002/cbic.201600471);

For more details of the diverse research interests of the Micklefield group & MIB see:
https://www.youtube.com/watch?v=EPUNhcfKtKU&t=13s
https://www.youtube.com/watch?v=qwvvTEa0ehk

http://www.micklefieldlab.chemistry.manchester.ac.uk
http://www.manchester.ac.uk/research/jason.micklefield/research
http://www.mib.manchester.ac.uk

Key Responsibilities, Accountabilities or Duties

The range of duties will include:

- Conduct individual and collaborative research projects according to the overall needs of the research program;
- Develop research objectives and proposals for your own or joint research, with the assistance of a mentor if required;
- Write up research work for publication;
- Continually update knowledge and understanding in field or specialism and translate this into research activity;
- Use initiative and creativity to identify areas for research, develop new research methods and extend the research portfolio;
- Use creativity to analyse and interpret research data and draw conclusions on the outcomes;
- Deal with routine communication using a range of media;
- Communicate complex information, orally, in writing and electronically, often of a specialist or highly technical nature;
- Help prepare proposals and applications to external bodies, e.g. for funding and contractual purposes;
- Liaise with colleagues and students, working on joint projects and areas of shared research interest, as required;
- Internally and externally build contacts and participate in networks for the exchange of information and to form relationships for future collaboration and identify potential sources of funding;
- Manage your own research and administrative activities, with guidance if required;
- Attend and contribute to relevant meetings;
- Use research resources, laboratories and workshops as appropriate;
- Plan and manage your own research activity in collaboration with others;
- Be aware of the risks in the work environment and their potential impact on their own work and that of others.

Person Specification

Essential Knowledge, Skills and Experience

- A PhD, or postdoctoral experience in one or more of the following areas - synthetic organic chemistry, biological chemistry, biochemistry/enzymology or molecular biology.
- A BSc, Masters or equivalent degree in Chemistry, Biochemistry, Biological Science, or related subjects with relevant practical laboratory experience;
- Excellent communication and interpersonal skills;
- Excellent time management and organisational skills;
- Ability to work independently and as part of a team;

- Ability to liaise confidently and effectively with a range of individuals;
- Flexible approach to dealing with research problems as they arise;
- Willingness to learn and develop;
- Ability to present in both written and oral publications;
- Ability to meet deadlines;
- Strong journal publication record;
- The ability to evaluate complex data;
- Ability to contribute to broader management and administrative processes;
- Ability to assess and organise resources;
- Understand equal opportunity issues as they may impact on areas of research content.

Desirable Knowledge, Skills and Experience

- Experience in synthetic chemistry
- Experience of the analytical techniques HPLC, LC-MS, MS, NMR etc.
- Biochemistry and enzymology skills for reconstitution of biosynthetic enzymes *in vitro*.
- Experience of enzyme assay development and analytical skills required for the *in vitro* characterisation of recombinant enzymes;
- General microbiology, molecular biology, gene cloning, mutagenesis, protein expression, protein purification skills;
- Experience in microbial fermentation and bacterial cultivation.
- Experience in natural product biosynthesis;
- Knowledge of engineering enzymes or biosynthetic pathways.
- A desire to expand your skill sets to cover some of the areas above.