Faculty of Mathematics and Physical Sciences
School of Chemistry

Marie Curie Early-Stage-Researcher in Targeted small-molecule Stabilisation of Protein-Protein Interactions (TASPPI)

Fixed term for 36 months

An Early Stage Researcher (ESR) position is available supported by an EU European Training Networks (ETN) called TASPPI (Targeted Small-Molecule Stabilisation of Protein-Protein Interactions, co-ordinator Professor C Ottmann, Tue Eindhoven, Netherlands). An Early Stage Researcher (ESR) position is a Marie Curie Fellowship for postgraduate research, and includes studies towards a doctoral degree (PhD). It is anticipated that the research performed will form all or part of your studies towards a postgraduate research degree (PhD) in chemical biology to be awarded by the University of Leeds. The Initial Training Network provides an excellent opportunity for scientific and personal development, with regular training courses in both scientific and general transferable skills at different locations throughout Europe. There is also the chance to meet and discuss research problems with leading scientists in the field.

It is anticipated that the research performed will form all or part of your studies towards a postgraduate research degree (PhD) in chemical biology. You will have an undergraduate degree (with a minimum 2.1 degree or above or equivalent) in Chemistry or a closely related discipline. You must be eligible to be appointed as an Early Stage Researcher in the UK.

As part of this programme, we are recruiting an ESR to join the Chemical Biology group at Leeds who will be supervised by Professor Andy Wilson. You will undertake interdisciplinary research as part of the programme and there will be multiple opportunities for personal development (including team-working), and secondments to our industrial and academic partners. Network-Wide Training Events in drug development will be organised by the TASPPI consortium. Indicative combinations of experimental and computational approaches to be used are as follows: peptide design and synthesis, biophysics and structural biology, small molecular synthesis, and evaluation of the cellular function of novel protein-protein interaction stabilizers.

You will develop a Personal Career Development Plan, designed with the supervisor at the beginning of the fellowship, covering training needs (including complementary skills) and scientific objectives. You will be expected to have at least one secondment to one of the non-UK partners.

For information on Marie Curie initial training networks, see: http://ec.europa.eu/research/mariecurieactions/
Applicants are asked to apply via the University of Leeds jobs website but should also supply the following:

- A personal statement of application referring to the project you are applying for that should also include:
  - The exact award date (day/month/year) of the degree that entitles you to embark on a PhD;
  - A list of countries you have lived, worked and studied in during the last 3 years (most recent first), including date from and to (day/month/year).
- A curriculum vitae including the details of 2 academic referees
- Degree transcripts and degree certificates
- Certificates of English language qualifications if you have them

A final decision on the appointment to this role will be taken by the TASPPI recruitment committee.

You will be offered a salary plus allowances in line with the Marie Skłodowska-Curie ITN requirements for Early Stage Researchers.

The ESR living allowance is fixed at €44,895.96 per annum plus allowances. This figure is before employers and employees' deduction for national insurance and taxes per year, which will be paid in Sterling using an appropriate conversion rate.

Informal enquiries may be made to Professor Andy Wilson, tel +44 (0)113 343 1409, email a.j.wilson@leeds.ac.uk

Closing Date: 3 June 2016

Ref: MAPCH1040

Click here for further information about working at the University of Leeds
www.leeds.ac.uk/info/20025/university_jobs
Job Description

Responsible to  Head of the School of Chemistry
Reports to  Professor Andrew J Wilson

Background to the Post

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. Whilst some success has been achieved with inhibitors of PPIs, stabilizers of PPIs are much less explored. Since current cancer therapy is often suboptimal, novel molecular approaches for the development of therapeutic agents are in high demand. Stabilisation of anti-tumour 14-3-3 protein-protein interactions represents such a novel approach. p53 is one of the most commonly mutated proteins in human cancers; it functions primarily as a transcription factor and regulates the activity of genes implicated in cell cycle arrest and apoptosis. It has been reported that binding of 14-3-3 proteins to the regulatory C-terminal domain (CTD) results in a stabilized p53 molecule with higher DNA binding and transcriptional activity and less susceptibility to hDM2-mediated degradation. Stabilization of the p53/14-3-3 interaction should result in overall higher activity of p53 in p53-impaired cancer cells. This would enhance the apoptotic response of cancer cells to DNA damage by ionizing radiation or drugs like cisplatin. The fellowship will build on the Wilson groups’ expertise in constrained peptides and proteomimetics as modulators of apoptotic proteins: it will involve design, synthesis and characterization of small molecules that directly stabilize the activating binding of 14-3-3 to p53. This will include small molecule/ fragment based screens, the design and synthesis of multivalent anionic ligands and constrained peptides, analysis of the interaction by biophysical methods like fluorescence anisotropy (FA) and isothermal titration calorimetry (ITC) together with cell based assays to probe for activation of the protein targets. In addition we will use x-ray structures of the target proteins to inform design of a range of ligands for these targets.

Main Duties and Responsibilities

- To perform original research, at a level suitable for a PhD, under the supervision of the project manager, in the general area of developing stabilizers of protein-protein interactions
- Pass progression requirements at various points during your studies (specifically at months 4, 11, 24 and 36) and meet all other School, Faculty and University requirements for PhD studies
- Meet with the supervisor on a regular agreed basis
- To participate in the activities of the “TASPPPI” Initial Training Network: attending training courses, collaborating with scientists from other sites in the network, exchanging scientific data, participating in visits to other sites
- To take responsibility for furthering your personal knowledge of the research area in which you will work
- To write up the results of your own research and contribute to research reports/publications. This will often be an iterative process, building on advice and guidance from others as appropriate
- To present findings of research e.g. prepare papers, make presentations with guidance and advice as appropriate
- Keep records of activities undertaken (including leaves of absence)

Career Expectations

The University of Leeds is committed to developing its staff. All staff participate in the Staff Review and Development scheme and we continue to work with individuals, supporting them to maximise their potential.
Progression to a higher grade is dependent on an individual taking on an increased level of responsibility. Vacancies that arise within the area or across the wider University are advertised on the HR website - http://jobs.leeds.ac.uk - to allow staff to apply for wider career development opportunities.

**University Values**

All staff are expected to operate in line with the university’s values and standards, which work as an integral part of our strategy and set out the principles of how we work together. More information about the university’s strategy and values is available at http://www.leeds.ac.uk/comms/strategy/
Person Specification

Essential

- An undergraduate degree (2:1 or above) in a relevant discipline, e.g. Chemistry
- You will satisfy the eligibility requirements set for an Early Stage Researcher funded by Marie Skłodowska-Curie and you must be eligible to be appointed as an Early Stage Researcher in the UK - this means:
  - At the time of recruitment, researchers must NOT already hold a doctorate degree and must be in the first 4 years of their research career (measured from the date of obtaining the degree which entitles you to embark on PhD studies)
  - At the time of recruitment, researchers must NOT have resided or carried out their main activity in the UK for more than 12 months in the 3 years immediately prior to their start date
- A strong interest in multidisciplinary science at the life sciences interface
- Excellent interpersonal and communication skills
- To meet the University's requirements in English as a foreign language if not a native speaker. Details can be found at: http://www.leeds.ac.uk/rsa/international/english_lang_requirements/english_language.html
- Willingness to register for a PhD
- Willingness to travel internationally
- Excellent communication skills, including written
- Ability to prioritise work and manage time effectively
- The ability to work with a wide range of professionals across a range of organisations
- Ability to work both independently using own initiative and as part of a team
- Flexibility and experience of working in a busy environment
- An enthusiastic, pro-active and co-operative approach

Desirable

- A track record of research dissemination activities
- Experience of public engagement activities
Additional Information

Details of the terms and conditions of employment for all staff at the University, including information on pensions and benefits, are available on the Human Resources web pages accessible via the links on the right hand side, or at http://www.leeds.ac.uk/hr/index.htm

Disclosure and Barring Service checks

A Disclosure and Barring Service (DBS) Check is not required for this position. However, applicants who have unspent convictions, cautions, reprimands and warnings, including any pending criminal proceedings must indicate this in the 'other personal details' section of the application form and send details to the Recruitment Officer at disclosure@leeds.ac.uk.

Disabled Applicants

The post is located in the School of Chemistry. Disabled applicants wishing to review access to the building are invited to contact the department direct. Additional information may be sought from the Recruitment Officer, email disclosure@leeds.ac.uk or tel +44 (0)113 343 1723.

Disabled applicants are not obliged to inform employers of their disability but will still be covered by the Disability Discrimination Act once their disability becomes known.

Further information for applicants with disabilities, impairments or health conditions is available in the applicant guidance.
Details of the School of Chemistry

The School of Chemistry has outstanding facilities for research in synthesis including refurbished laboratories, superb NMR equipment (including 600 MHz and three 500 MHz NMR machines and an LC-NMR facility), and X-ray crystallographic, mass spectrometry and microanalytical services. These facilities have been enormously enhanced and expanded by the award of >£7M (Chemistry share: £2.5M) under the JIF Scheme; further refurbished synthetic space houses new analytical HPLC, semi preparative LC-MS, preparative HPLC and robotic equipment. Infrastructure for the high-throughput synthesis, purification (including mass-directed HPLC) and analysis of bioactive small molecules is particularly relevant to this programme. The University science library has one of the best collections of journals and books to be found in any British university. The University subscribes to many journals (including ACS, RSC and Tetrahedron journals) and databases (SciFinder scholar and Beilstein on-line) which are accessible from offices adjoining the laboratories.

Details of The Astbury Centre for Structural Molecular Biology

The Astbury Centre brings together >300 researchers at Leeds at the interfaces between chemistry, biology and physics. The Centre provides a buoyant interdisciplinary environment for biomolecular science, for example through an annual research retreat, an annual lecture, a vigorous seminar programme and the biennial Astbury Conversation. The Astbury Centre’s infrastructure and technical support has been enormously expanded and enhanced through major initiatives including the £17M Astbury BioStructure Initiative. Relevant infrastructure includes surface plasmon resonance; isothermal titration calorimetry, fluorescence and circular dichroism spectroscopy and a mass spectrometry laboratory. From 2016 the centre will house 950MHz NMR and two Titan KRIOS 300 KeV electron microscopes supported by technical experts. The Mass Spectrometry Facility is dedicated to the analysis of biomolecules. There are five mass spectrometers including a new Synapt HDMS MS/MS instrument with nano-electrospray and in-built ion mobility capabilities, a Q-Tof equipped with nano-electrospray and capillary HPLC-MS/MS facilities for peptide sequencing; an LCT Premier with the highest m/z range available (m/z 60,000) for the analysis of non-covalently bound macromolecules, a Platform II electrospray instrument with on-line HPLC facilities, and a MALDI-Tof Protein chip Reader. Together these outstanding facilities and unparalleled collaborative opportunities for chemists, biologists and physicists provide the ideal environment in which to pursue multidisciplinary science.