Faculty of Biological Sciences  
Astbury Centre for Structural Molecular Biology  
School of Molecular and Cellular Biology

Post-doctoral Research Fellow: Structural Mechanism of Amyloid Formation

Full time on a fixed term basis until 31 December 2018.

“The molecular mechanisms of structural conversion in amyloid disease”

Applications are invited for a Wellcome Trust-funded postdoctoral research assistant to join a dynamic interdisciplinary team focusing on using a combination of biophysical and biochemical methods to investigate the mechanisms of protein aggregation into amyloid fibrils in vitro. The project will focus on the aggregation of beta-2-microglobulin into amyloid fibrils which is associated with the disorder dialysis related amyloidosis. The person appointed will be a specialist in NMR spectroscopy applied to protein systems and will use a wide range of NMR and other biophysical methods to determine the structure and dynamics of intermediates in amyloid assembly and the molecular recognition events that govern assembly into amyloid fibrils. In addition, by mapping the interfaces involved in amyloid formation, you will develop protein aptamers able to inhibit amyloid formation and test their effects in vitro.

The project is funded jointly between the laboratories of Professors Sheena Radford, and Dr Eric Hewitt within the Astbury Centre for Structural Molecular Biology at the University of Leeds. You should have (or be close to completing) a PhD in biochemistry or a related area. Experience in NMR spectroscopy and/or characterisation of proteins using biophysical methods is required.

University Grade 7 (£32,004 - £38,183 p.a.) Due to funding limitations it is unlikely an appointment will be made above £32,004 p.a.

Informal enquiries to may be made to Prof Sheena E Radford, email s.e.radford@leeds.ac.uk
See also http://www.astbury.leeds.ac.uk and http://bmbsgi10.leeds.ac.uk.

Ref: FBSMB1085

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 School of Molecular and Cellular Biology
Reports to: Professor Sheena Radford

Main duties and responsibilities

Background to the post

This 2 year post is funded by the Wellcome Trust and builds on an on-going collaboration between the Radford and Hewitt laboratories at the University of Leeds.

The overall aim of the project is to use a combination of NMR and other biophysical methods to map the protein interfaces formed in the early stages of aggregation of the β2-microglobulin variant, βN6, and to use the information to design and evolve protein aptamers able to inhibit assembly.

Specifically, we aim to:

1. Map the interfaces formed early in the assembly of βN6 using NMR methods, protein engineering, kinetic assembly reactions and EM
2. Use the resulting information to design or evolve protein scaffolds (aptamers) able to inhibit assembly and to enhance their efficacy using protein evolution methods
3. Use the discoveries made to develop new strategies for inhibiting amyloid formation of other proteins, including wild-type β2m and its amyloidogenic variant D76N

The person appointed to this post will:

- Produce β2m as recombinant protein for use in your own studies including protein labelled with $^{15}\text{N}$ and/or $^{13}\text{C}$ or $^2\text{H}$ for different analyses using NMR
- Use NMR chemical shifts ($^1\text{H}$, $^{13}\text{C}$ and $^{15}\text{N}$), relaxation dispersion and other experiments to characterise the interfaces involved in amyloid formation of β2m and βN6 (see Eichner et al., Mol Cell (2011); Karamanos et al., Mol Cell (2014) and Karamanos et al., JACS (2016))
- Measure inter-molecular paramagnetic relaxation enhancements using variants of βN6 containing newly introduced Cys residues to determine the nature of the first protein-protein recognition events in β2m amyloid formation
- Trap stable β2m dimers en route to amyloid and determine their structural properties using NMR and their dynamics using NMR methods (e.g. hydrogen-deuterium exchange)
- Develop molecular dynamics/docking methods to reveal insights into protein assembly into amyloid fibrils and to derive experimental methods to test the outputs of these simulations
- Collaborate closely with all members of the research team and integrate your own results with those of others
- Prepare written summaries of your work and meet with the full team to discuss these reports on a monthly basis
- Attend group meetings and to present your work to others
- Generate and pursue independent and original research ideas in relation to the project
- Design and conduct a programme of investigation together with the principal investigators
- Evaluate the methods and techniques used and interpret the results obtained in order to relate such evaluations appropriately to the project
- Communicate and present research results through publication or at meetings/conferences
- Understand the broader issues relating to the management of research
- Contribute to the supervision of less experienced researchers as appropriate
- Liaise with research colleagues and support staff in relation to the project
- Take part in knowledge transfer activities where appropriate
- Maintain your own continuing professional development and act as a mentor to less experienced colleagues, as appropriate
- Maintain a safe work environment, including ensuring compliance with legislation and the undertaking of risk assessments
- Undertake any other duties commensurate with the post and grade as directed by the Director of the School or nominee

**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/](http://www.leeds.ac.uk/comms/strategy/).

The University of Leeds’ commitment to women in science has been recognised with a national accolade. The University has received the Athena SWAN Bronze Award and the Faculty of Biological Science holds the Athena SWAN Bronze Award in recognition of our success in recruiting, retaining and developing/promoting women in Science, Technology, Engineering, Maths and Medicine (STEMM). We are proud of our commitment to equality and inclusiveness.

The University offers generous terms and conditions of employment, a wide range of benefits, services, facilities and family friendly policies. Full details are available on the Human Resources web pages accessible at [www.leeds.ac.uk/hr/index.htm](http://www.leeds.ac.uk/hr/index.htm).
Person Specification

Understanding the structural nature of amyloid assembly is a rapidly advancing and highly competitive field. The research fellow employed on the project is required to be committed and organised with experience in the relevant areas.

Essential

- A PhD (or be close to completion) in Chemistry, Biochemistry, Biophysics or a related discipline
- Skilled experimentalist
- Previous experience of preparing and handling recombinant proteins
- Experience of molecular biology and the design and preparation of mutated proteins
- In depth theoretical and practical experience of NMR methods, applied to the study of protein structure/assembly and protein dynamics
- Previous experience of using other biophysical methods applied to understanding protein structure and dynamics, especially of self-assembling systems
- Experience of working in protein structural molecular biology including the detailed use of computational methods to understand and define molecular models based on different experimental measurements
- Good data management, analytical and computer skills
- Highly motivated, enthusiastic and hardworking
- Ability to absorb new ideas and to master new techniques rapidly and efficiently
- Good verbal and written communication skills
- A high standard of English and the ability to write high quality articles for publication
- Ability to design, execute and write up experimental work independently
- Good organisational and time management skills
- Ability to deal with and prioritise varied tasks to meet project deadlines
- Ability to work independently, but able work effectively as part of a team
- Commitment to own professional development

Desirable

- BSc in Chemistry, Biochemistry, Biophysics or a related subject
- Use of a range of software packages for visualisation and analysis of protein structures
- Experience of quantitative analysis of proteins (e.g., stability or binding constants or mathematical modelling of biochemical mechanisms)
- Experience of working with aggregating systems, especially involved in amyloid formation
- Skilled experimentalist with a ‘can-do’ attitude to work and problem solving
Additional Information

The University offers generous terms and conditions of employment, a wide range of benefits, services, facilities and family friendly policies. Full details are available on the Human Resources web pages accessible at www.leeds.ac.uk/hr

The Partnership

The Partnership has been developed by students and staff and describes the mutual expectations of us all as members of the University of Leeds community. More information about the Partnership is available at http://partnership.leeds.ac.uk

Criminal Record Checks

This post is covered by the Rehabilitation of Offenders Act 1974 and as such, applicants who have ‘unspent’ convictions, cautions, reprimands and warnings, including any pending criminal proceedings, must declare this in the ‘other personal details’ section of the application form and send details to the Recruitment Officer at disclosure@leeds.ac.uk.

Criminal record information will be held securely by the University and in accordance with the Data Protection Act and the University’s Data Protection policy, available at http://www.leeds.ac.uk/secretariat/data_protection_code_of_practice.html

Any offer of appointment will be in accordance with our policy, a copy of which is available at http://hr.leeds.ac.uk/criminal_records

Disabled Applicants

The post is located in the Faculty of Biological Sciences. 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 3431723.

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

Further information for applicants with disabilities, impairments or health conditions is available in the applicant guidance.
Further Information

Recent Relevant Publications

Recent publications from Radford/Hewitt group relevant to the post advertised include:

A full list of recent publications from the Radford, Homans and Hewitt laboratories can be found at [http://www.astbury.leeds.ac.uk](http://www.astbury.leeds.ac.uk). Recent publications relevant to the positions advertised include:


A full list of recent publications from the Principal Investigators can be found at http://www.astbury.leeds.ac.uk.

**Location of the work**

You will be based in a well-resourced laboratory within the Astbury Centre for Structural Molecular Biology (ACSMB) within the School of Molecular and Cellular Biology at Leeds. Facilities in the applicants’ laboratories, together with those in ACSMB, provide a world-class research environment for studies of protein structure and dynamics. Prof. Radford’s research group comprises a dynamic and integrated team of post doctoral workers and PhD students (see http://bmbsgi10.leeds.ac.uk) with a broad range of background and skills, including physicists, biochemists, cell biologists and chemists. This team with broad skill set is also enhanced by close links with colleagues in the Schools of Chemistry and Physics. Our dynamic, active group meets regularly both formally and informally to exchange ideas, problem solve and for social occasions. In addition to the excellent research infrastructure described above, the laboratory also has full-time technical support. We have superb equipment infrastructure, of particular relevance to the advertised position, a recent University investment of £17M was used to create the Astbury Biostructure Laboratory that includes new cutting-edge NMR spectrometers ranging from 600MHz-950MHz, including cryo-probes. Dr Hewitt brings expertise in cell biology to the team. His laboratory is situated close to those of Radford and close links already exist between the groups, with Radford and Hewitt sharing a number of postdoctoral fellows and PhD students who focus on the effects of amyloid formation on cellular homeostasis. ACSMB, FBS and Chemistry all have regular seminar series with international speakers and ACSMB has an annual retreat to promote research excellence across its remit.

For more information about our laboratories please visit http://www.astbury.leeds.ac.uk

**Astbury Centre for Structural Molecular Biology**

The Astbury Centre for Structural Molecular Biology is a dynamic, multidisciplinary research centre involving 65 academic staff spanning physics, chemistry and the biological sciences at the University of Leeds. The Centre houses excellent research infrastructure for the purification and the biophysical and biochemical analysis of biomolecules. The equipment base includes dedicated high-field biomolecular NMR instruments (up to 950 MHz with cryoprobe currently, but shortly to be supplemented with two new-design cryoprobes, and an upgraded cryoprobe-equipped 600 MHz spectrometer with an automated robotic platform for high-throughput ligand
screening and titration studies). Facilities for X-ray crystallography and electron microscopy (including cryo-EM (200keV FEG), and two new 300 keV Titan Krios microscopes with direct electron detectors) and a range of facilities for the analysis of binding using DSC, ITC, CD, FTIR, fluorescence spectroscopy, AUC and SPR, and kinetic analysis using stopped flow methods. For single molecule fluorescence studies instruments capable of FCS, ALEX and TCCD are available. The MS Facility is located in a purpose-built suite in the heart of the ACSMB and has five ESI-MS instruments including: a new Synapt G2S with travelling wave IMS and an 8K quadrupole; two Synapt HDMS instruments with travelling wave IMS, one with a 32 K quadrupole for MS/MS of high m/z species, the other with nanoHPLC facilities; a customised LCT Premier with the highest m/z range currently available (m/z 60,000), collisional cooling for the analysis of non-covalently bound macromolecules. Our facilities are run by experienced core staff that are on hand to train new users and to offer advice on experimental design. For more information see http://www.astbury.leeds.ac.uk.

School of Molecular and Cellular Biology

The School comprises some 40 principal investigators, and exists in parallel with our sister Schools of Biology and Biomedical Sciences. The aim of the School is to provide a stimulating environment for the prosecution of world-class research. We have a strong emphasis on inter-disciplinary activity, with the aim of developing the boundaries between traditional disciplines. To this end, collaborations between members of SMCB and our sister Schools within FBS are strongly encouraged. Moreover, the Astbury Centre for Structural Molecular Biology is a cross-faculty centre that includes staff from FBS as well as the Faculty of Mathematics & Physical Sciences and the Faculty of Medicine & Health.

Biological Sciences

The Faculty of Biological Sciences is one of the leading groups of life-science researchers within the UK, offering superb facilities, providing a high quality research training environment and delivering an exceptional student education.

Our position amongst the UK elite for bioscience research was confirmed in the results of the recent Research Excellence Framework (REF) where we were ranked as 6th in the country for research impact. The assessment also identified that over 80% of biological science research at Leeds has a top quality rating of either "world leading" or "internationally excellent".

In addition to 110 academic staff, the Faculty has over 400 postdoctoral fellows and postgraduate students supported by a current active research grant portfolio of around £50m derived from a range of sources including charities, research councils, the European Union and industry.

With around 2000 undergraduate students and 150 taught postgraduate students, we are one of the largest life sciences faculties in the UK. Our programmes cover the breadth of the biological sciences with undergraduate programmes in the areas of biology, biochemistry, microbiology, sport and exercise sciences and medical sciences including physiology and neuroscience.
Significant investments in our infrastructure contribute to our dynamic and vibrant research environment, offering excellent opportunities for leading edge research focused around key areas, including neuroscience, sports and exercise science, membrane biology, and structural molecular biology.

The Faculty has 3 Schools:

- [School of Biomedical Sciences](#)
- [School of Molecular and Cellular Biology](#)
- [School of Biology](#)

Find out more about the Faculty [here](#).