JOB TITLE	Postdoctoral Researcher in Molecular and cellular imaging of membrane interactions in pathogen attack and immune defence
FACULTY & SCHOOL/DEPARTMENT	Biological Sciences, Institute of Structural and Molecular Biology
REPORTS TO	Professor Helen Saibil
SUPERVISES	Not applicable
POST REFERENCE	11181
GRADE	Grade 7 **DATE** Nov 2013

Birkbeck is a world-class institution, a vibrant centre of academic engagement and excellence and the UK's leading provider of part-time, evening education for mature students. There are nearly 19,000 students studying short courses, certificates, diplomas, first degrees, postgraduate taught and postgraduate research degrees. Birkbeck provides Londoners with the unique opportunity to fit study around their busy lives. Founded in 1823 as the London Mechanics' Institute, Birkbeck was incorporated in the University of London in 1920.

PURPOSE OF THE JOB

To contribute to the development of research proposals and/or objectives, and to conduct and write up both individual and collective research projects for publication.

Project

Molecular and cellular imaging of membrane interactions in pathogen attack and immune defence

The battle for survival in pathogen attack and host defence is a major driver of evolution. Front line actions in the battles between cells involve breaking through target cell membranes. This is done either by delivering toxins that penetrate or destroy the cell membrane, or by hijacking normal entry pathways such as endocytosis and subsequent escape of intracellular pathogens such as *Toxoplasma gondii* by breaching the endosome or vacuole and plasma membranes. A major line of immune defence is the formation of pores for delivery of lethal granzyme proteases from cytotoxic lymphocytes into virally infected or cancerous cells, but the mechanism and pathway of this cell killing *in situ* are unclear. Likewise, the virulence factors by which pathogens disrupt cellular membranes are often known, but their *in vivo* actions have not previously been accessible to molecular structural analysis. It has recently become feasible to obtain 3D images of macromolecular machines in their native, cellular environment. In this work, we wish to use these new approaches to address the molecular mechanisms involved in these attacks on cellular membranes. This work not only opens up avenues for development of new therapeutic approaches for immune dysfunction and major infectious diseases, but also addresses a fundamental aspect of protein structure and stability – the dramatic conversion of pore forming

proteins from a soluble monomeric form to an oligomeric assembly that inserts into membranes to form a protein-lined aqueous channel. The superfamily of pore-forming proteins that are the subject of this research have been adopted both by eukaryotic hosts and their pathogens for breaking and penetrating membrane barriers. The superfamily includes the membrane attack complex/perforin (MACPF) proteins used by the immune system, as well as the cholesterol dependent cytolysins (CDCs), which act as bacterial toxins. Their *in vivo* actions are thought to range from surgical hole punching followed by rapid repair to large scale membrane destruction in the wake of pathogen exit.

The aim of the project is to determine the molecular mechanisms of membrane disruption by pore-forming proteins in their cellular context. The cellular site and nature of action of these proteins will be related to high-resolution information on their assembly mechanisms obtained from model membrane systems. This work will reveal how intracellular pathogens get through host membranes during different stages of their life cycle and how cytotoxic lymphocytes kill virally infected and cancerous cells. These goals will require the application of state-of-the-art methods in imaging and three-dimensional (3D) reconstruction, using a combination of cryo electron microscopy (cryo-EM), both single particle and tomography, correlative fluorescence/EM and cryo X-ray microscopy, along with molecular biological, crystallographic, biochemical and nanotechnology approaches. Our previous, low-resolution cryo EM structures of membrane pores have revealed the overall conformational changes, and we now have the microscopy methods, collaborations and systems in place to open up new frontiers in the study of these cellular machines.

The work involves research collaborations with Professors James Whisstock (Monash University, Melbourne), Joe Trapani and Ilia Voskoboinik (Peter Macallum Cancer Centre, Melbourne), Peter Andrew (University of Leicester), Vern Carruthers (University of Michigan) and Gillian Griffiths (Cambridge Institute for Medical Research). Interaction with these collaborators will involve some international travel.

The successful candidate will join a small team with Dr N Lukoyanova who is very experienced in the structural analysis of these pore forming proteins and also to cell tomography of the immune synapse. Depending on the interests of the successful candidate, the postdoctoral researcher will have the opportunity to learn and employ a range of EM methods from cell tomography to single particle analysis.

The postdoc will focus on cell tomography of *Toxoplasma* egress, to capture events in membrane disruption by the perforin-like protein, using the approaches of high pressure freezing, freeze substitution, cryo sectioning of vitrified cells, along with correlative fluorescence/EM. The role of this postdoc will also include some single particle studies of pathogen MACPF proteins, and may also involve participation in our first efforts to record tomograms of intact, vitrified cells by cryo X-ray microscopy.

A short description and references to our previous work in this area can be found at http://people.cryst.bbk.ac.uk/~ubcg16z/pore/pore.html

RESEARCH ENVIRONMENT AND FACILITIES

The Institute of Structural and Molecular Biology (ISMB)

The ISMB (http://www.ismb.lon.ac.uk) is a centre of excellence, which jointly consists of the Department of Biological Sciences at Birkbeck, the Research Department of Structural & Molecular Biology at UCL, and the Chemical Biology section of the

Department of Chemistry at UCL. The Institute provides a scientific environment conducive to world-class research in the field of biomolecular science. The ISMB (Director: Professor Gabriel Waksman FRS) is organised along 5 research programmes: Structural Biology (Head: Professor Helen Saibil FRS), Chemical Biology (Head: Professor Helen Hailes), Biophysics and Proteomics (Head: Professor Steve Perkins), Bioinformatics (Head: Professor David Jones), and Biochemistry and Molecular Biology (Head: Dr Katherine Bowers). Major research facilities at the ISMB include laboratories for X-ray crystallography, cryo-electron microscopy, NMR spectroscopy, biophysical methods, cell biology, optical microscopy, bioinformatics and ion mobility mass spectrometry. The ISMB organises multidisciplinary activities that are aimed at increasing collaborative, interdisciplinary research within speciality areas and between these areas and the vast body of biomedical research taking place at UCL, NIMR, and Birkbeck. ISMB activities include symposia, retreats, seminar series, and students/postdocs presentations. The ISMB also runs Wellcome Trust, MRC and BBSRC funded PhD programmes.

The Department of Biological Sciences at Birkbeck College
This department was created in 2009 from the merger of the School of Crystallography and the School of Biological and Chemical Sciences (http://www.bbk.ac.uk/biology/). It is a multidisciplinary department composed of 38 academic staff (including 6 joint with UCL), 17 HEFCE support staff and around 40 research fellows and research assistants. It houses the ISMB Biophysics Centre, the ISMB Cryo-EM facility, and the ISMB X-ray Crystallography facility.

The Birkbeck electron microscopy laboratory, based in the Crystallography part of the Department of Biological Sciences, is equipped for state of the art cryo-electron microscopy, electron tomography, high pressure freezing, cryo sectioning, freeze-substitution and correlative fluorescence/electron microscopy, along with all the necessary hardware and software for image processing and 3-dimensional reconstruction, including the latest generation of direct electron detectors (people.cryst.bbk.ac.uk~ubcg16z/empage.html).

Main Duties of the Jobholder

Research and Scholarship

- To develop research objectives and proposals for own or joint research, with the assistance of a mentor if required.
- To conduct individual and collaborative research projects and write up research for publication
- To update knowledge and understanding in field or specialism.
- To translate knowledge of advances in the subject area into research activity.
- To ensure that research content and the methods used are in accordance with equal opportunities.

Teaching & Learning

- To contribute to the assessment of student knowledge and supervision of their projects.
- To assist in the development of student research skills.

Communication

- To deal with routine communication using a range of media.
- To communicate complex information, and material of a specialist or highly technical nature orally, in writing, and electronically.
- To prepare proposals and applications to external bodies, for example, for funding and contractual purposes.

Working Relationships and Contacts

People Management and Teamwork

- To manage own research and administrative activities, with guidance if required.
- To work with colleagues on joint projects, as required
- To collaborate with academic colleagues on areas of shared research interest.
- To attend and contribute to relevant meetings.

Liaison and Networking

- To liaise with colleagues and students.
- To build internal contacts, and participate in internal networks for the exchange of information and to form relationships for future collaboration.
- To join external networks to share information and identify potential sources of funds.

Dimensions

Problem Solving and Impact

- To use new research techniques and methods.
- To use own initiative and creativity to identify areas for research, develop new research methods, and extend the research portfolio.
- To use creativity to analyse and interpret research data and draw conclusions on the outcomes.
- To contribute to collaborative decision making with colleagues in areas of research.
- To understand equal opportunity issues as they may impact on areas of research content and methods.

Resource Management

- Plan and manage own research activity in collaboration with others.
- To use research resources, laboratories and workshops as appropriate.

Working Environment

- To balance, with help the competing pressures of research and administrative demands and deadlines.
- To carry out tasks that require the learning of certain skills.
- To engage in continuous professional development.
- To be aware of the risks in the work environment and their potential impact on their own work and that of others.

General Responsibilities

These are standard to all Birkbeck Job Descriptions

- To adhere to the College's Equal Opportunities policy in all activities, and to actively promote equality of opportunity wherever possible.
- To be responsible for your own health and safety and that of your colleagues, in accordance with the Health and Safety at Work Act (1974) and relevant EC directives.
- To work in accordance with the Data Protection Act and to ensure that all new systems are reported to your Data Protection Controller.
- To undertake such other duties as may be reasonably expected.
- To provide a healthy and comfortable working environment, smoking is prohibited throughout the College, except in specially designated areas.

FURTHER PARTICULARS & INFORMATION ON THE POST

Salary:	Grade 7 - £31,644 per annum plus the London Allowance of £3,006 per annum.
Probation:	The appointment is subject to a probationary period of six months.
Duration of post:	Fixed Term up to 40 months.
Hours:	Full-time, 35 hours per week
Annual leave entitlement:	25 days per year, plus an additional six days when the College is closed during the spring and winter breaks. This is in addition to the eight bank holidays.
Superannuation:	The post is superannuable under the USS scheme (Universities Superannuation Scheme).
Closing date:	17 January 2014
Interview date:	Early February 2014.
Start date:	As soon as possible

Informal enquiries can be made to:

Professor Helen Saibil, Crystallography, Birkbeck, Malet Street, London WC1E 7HX. (tel: 020 7631 6820, e-mail: h.saibil@mail.cryst.bbk.ac.uk. Web page: people.cryst.bbk.ac.uk/~ubcg16z).

PERSON SPECIFICATION

Job Title: Post-Doctoral Researcher (Level 2) **Post No:** 11181 **Faculty and Dept/School:** Biological Sciences/ Institute of Structural and Molecular Biology

Attributes	Essential	Desirable	Method of Assessment
Knowledge	• Possess sufficient breadth or depth of specialist knowledge of research approaches to work within a structural, molecular and cell biology research programme • A background in cell biology, structural biology, biochemistry or bioimaging	Knowledge of structural biology, protein biochemistry and specialist biochemical and biophysical methods. Knowledge in cell biology	*Application* *Presentation* *Interview*
Technical/Work-based Skills	• Skills in cell, molecular, and/or structural biology or biochemical methods • Effective oral and written communication skills, to write up complex research findings and to convey specialist/technical material. • Computer proficiency in standard office and presentation functions	Research skills in cell culture, electron tomography, image processing and 3-dimensional reconstruction, and in cell biology, immunology or parasitology.	*Application* *Presentation* *Interview*
General Skills/Attributes	• Initiative, commitment and creativity to ensure research is effective • Effective presentation skills. • Organisation and administration skills • Commitment to working with diversity. • Good networking and interpersonal skills • Ability to work independently but also to co-operate and interact with other group members and outside collaborators • Willingness to travel for meetings and workshops	Understanding of the processes of intracellular parasite infection. Specialist knowledge of key mammalian cellular processes. Understanding of diffraction and imaging methods, and 3-dimensional structure determination	*Application* *Presentation* *Interview*
Experience	• Experience using or developing research methods and techniques, particularly in structural or cellular biology • Previous experience of contributing to research	Experience in structural cell biology, biochemistry of membranes and membrane pore formation.	*Application* *Presentation* *Interview*
Qualifications	• PhD (or equivalent) in a relevant subject area, such as cell or structural biology, biochemistry or microbiology.		*Application*