Job Description

DEPARTMENT OF PHYSIOLOGY, ANATOMY & GENETICS

Job title	Postdoctoral Research Scientists – **TWO posts** *"Surviving metabolism: acid handling and signalling"*
Division	Medical Sciences
Department	Physiology, Anatomy & Genetics
Location	Sherrington Building, South Parks Road, Oxford OX1 3PT
Grade and salary	Grade 7: £31,076 to £38,183
Hours	Full time
Contract type	Fixed-term for up to 60 months, ending 31st May 2022. The two posts will run in parallel.
Reporting to	1) Assoc Prof Pawel Swietach 2) Dr Alzbeta Hulikova 3) Professor Sir Walter Bodmer
Vacancy reference	AV17005 (HRIS vacancy number 127672)

Research topic	The molecular biology of acid handling and signalling in cancer
Principal Investigator	Assoc Prof Pawel Swietach
Project team	The two successful candidates will join a DPAG-based team that has excellent collaborative links with Oxford's department of Oncology and access to state-of-the-art research facilities across the university. The five year programme is divided into four work-packages and it is expected that each post-holder will take primary responsibility for two of these. Our research group includes experienced post-doctoral researchers and project students, coming from diverse scientific background, including cell biology, physiology, pathophysiology and biophysics.

Project web site	https://www.dpag.ox.ac.uk/research/swietach-group
Funding partner	This ambitious project is funded by Consolidator Grant from the European Research Council (Horizon 2020 European Union funding for research & innovation)
Recent publications	Connexin-43 channels are a pathway for discharging lactate from glycolytic pancreatic ductal adenocarcinoma cells. Dovmark TH, Saccomano M, Hulikova A, Alves F, Swietach P. *Oncogene* (in press). Stromal uptake and transmission of acid is a pathway for venting cancer cell-generated acid. Hulikova A, Black N, Hsia LT, Wilding J, Bodmer WF, Swietach P. *Proc Natl Acad Sci U S A.* 2016; 113(36):E5344-53. Disrupting Hypoxia-Induced Bicarbonate Transport Acidifies Tumor Cells and Suppresses Tumor Growth. McIntyre A, Hulikova A, Ledaki I, Snell C, Singleton D, Steers G, Seden P, Jones D, Bridges E, Wigfield S, Li JL, Russell A, Swietach P, Harris AL. *Cancer Res.* 2016; 76(13):3744-55. Nuclear proton dynamics and interactions with calcium signaling. Hulikova A, Swietach P. *J Mol Cell Cardiol.* 2016 Jul; 96:26-37 Rapid CO_2 permeation across biological membranes: implications for CO_2 venting from tissue. Hulikova A, Swietach P. *FASEB J.* 2014; 28(7):2762-74 Antitumor efficacy of a monoclonal antibody that inhibits the activity of cancer-associated carbonic anhydrase XII. Gondi G, Mysliwietz J, Hulikova A, Jen JP, Swietach P, Kremmer E, Zeidler R. *Cancer Res.* 2013; 73(21):6494-503. Coupled Ca^{2+}/H^{+} transport by cytoplasmic buffers regulates local Ca^{2+} and H^{+} ion signaling. Swietach P, Youm JB, Saegusa N, Leem CH, Spitzer KW, Vaughan-Jones RD. *Proc Natl Acad Sci U S A.* 2013; 110(22):E2064-73 Regulation of intracellular pH in cancer cell lines under normoxia and hypoxia. Hulikova A, Harris AL, Vaughan-Jones RD, Swietach P. *J Cell Physiol.* 2013; 228(4):743-52. Carbonic anhydrase IX promotes tumor growth and necrosis in vivo and inhibition enhances anti-VEGF therapy. McIntyre A, Patiar S, Wigfield S, Li JL, Ledaki I, Turley H, Leek R, Snell C, Gatter K, Sly WS, Vaughan-Jones RD, Swietach P, Harris AL. *Clin Cancer Res.* 2012; 18(11):3100-11. Tumor-associated carbonic anhydrase 9 spatially coordinates intracellular pH in three-dimensional multicellular growths. Swietach P, Wigfield S, Cobden P, Supuran CT, Harris AL, Vaughan-Jones RD. *J Biol Chem.* 2008; 283(29):20473-83.

Background to the project

Metabolism generates vast quantities of acid (protons). Essentially all biological processes are pH-sensitive, therefore the regulation of acid/base chemistry is a fundamental homeostatic priority. However, controlled intracellular pH (pH_i) dynamics are, potentially, a versatile form of cell signalling with a broad remit of targets because protonation of proteins is an enzyme-independent post-translational modification. Indeed, many examples of orchestrated spatio-temporal changes in pH_i have been demonstrated to take place inside cells, yielding the concept of protons as *bona fide* signals.

We and others have now made a compelling case for studying acid handling and signalling in cancer. Acidity is an established chemical signature of the tumour microenvironment. It arises because cancer metabolism releases an exceptionally large acid-load into the extracellular space. Due to abnormal vascular function, this acid-load is not promptly washed away; instead, it produces the low extracellular pH (pH_e) measured reproducibly in solid tumours *in vivo*. Extracellular acidity is not merely a chemical consequence of metabolism, but a biological signal that feeds back on tumour biology somewhat analogously to hypoxia.

Carefully exercised acid handling is pivotal for cancer survival because it aims to maintain a favourable combination of pH_i and pH_e. Essentially all cells devolve a substantial fraction of their energetic and synthetic resources to keeping pH_i within a narrow range that is conducive for biological activity, although a degree of cell-to-cell variation in pH_i control is normally observed within a population of cells. Dysregulated acid-base balance has been shown to perturb or even kill cancer cells therefore each cell, based on its acid handling phenotype, can be ascribed a fitness to survive at a particular microenvironmental pH_e. An important pH_i-regulating process is acid-extrusion by membrane-bound proteins that export H^+ ions (e.g. Na^+/H^+ exchangers) or import base (e.g. Na^+-HCO_3^- cotransporters), but in the diffusion-limited tumour microenvironment, acid handling must also consider the diffusive transport of protons across the intra- and extracellular fluids and the role of non-cancer cells present in the tumour stroma, such as fibroblasts.

Proton signalling underlies the cellular responses to changes in acid/base chemistry. The majority of proton targets are intracellular and many examples of proton sensors have been reported, mostly on the basis of acute readouts. The longer-term effects of protons, such as on gene expression, are highly relevant to cancer cells living under acid-stress, but remain poorly characterised, despite evidence for proton-sensing transcription factors. Extracellular acidity has been proposed to exert a Darwinian selection pressure that favours a sub-population of cancer cells bearing a compatible acid handling and signalling phenotype. An analogy can be drawn to hypoxic-selection, although acid-selection has the added complexity of an intricately regulated pH_e/pH_i relationship. On the premise that more fit 'pH phenotypes' are more aggressive (e.g. are associated with cancer stem cells, CSC), acid-selection could play a major role in cancer progression. However, the definition of 'pH-fitness' and its relationship with stemness remain unclear.

To summarise: acidity is a potent, endogenous and broad-spectrum modulator of biological function that is regulated by a relatively small number of proteins. In principle, these characteristics should make acidity an ideal candidate for the therapeutic management of tumour growth. In reality, translating the sum of our understanding of acid handling and signalling into therapy is not trivial, and none of the major approved therapies are based explicitly on disrupting acid handling and/or signalling. Reasons for this paradox relate to inadequacies in our understanding of pH handling and signalling in cancer, exacerbated by the experimental challenges associated with pH studies.

The role

The successful candidates will report directly to Pawel Swietach. In addition, they will work under the supervision of Alzbeta Hulikova and Walter Bodmer. It is anticipated that the post-holders will be pro-active in liaising and working closely with colleagues in other groups in DPAG and in affiliated departments of Oxford. The successful candidates will be asked to actively support other postdocs, PhD students and research assistants in the team.

The project consists of four inter-related work-packages (WP1-4) which will be divided between the two successful candidates according to their experience, skills and potential. Recruitment for the two posts will take place in parallel, and we anticipate that each post-holder will take leadership in two of these work-packages, but also support the team as a whole. In the application cover letter, we ask candidates to rank and justify their preference (if any) for the work-packages.

WP1 addresses the question of how protons are carried in diffusion-limited tissue compartments of tumours. Our understanding of acid handling is based mainly on transport across membranes. However, proton transport across aqueous intra- and extracellular compartments is surprisingly slow and relies on assisted diffusion on mobile buffers. What are the molecules that facilitate proton diffusion in tumour cytoplasm? Are these proton-carriers essential for cancer pH homeostasis? How are these carrier molecules regulated?

WP2 will investigate the mechanisms by which cancer cells exploit stromal cells to handle their acidic products. Tumours consist of many types of cell, including fibroblasts, with distinctly different pH-regulatory phenotypes to those in cancer cells. Despite the capacity for interplay, our understanding of pH regulation has focused on studying one of these cell types in isolation. What is the role of stromal cells in handling the acid generated by cancer cell metabolism? Does proton signalling in stromal cells influence cancer biology?

The aim of **WP3** is to establish how gene expression in cancer cells is physiologically responsive to proton signalling. Proteins are pH-sensitive because they contain residues, such as histidines, that can be protonated. Among the motifs enriched with His are DNA-binding domains of transcription factors. However, the pH-sensitivity of gene expression has not been investigated systematically in cancer. Do proton signals influence the gene expression landscape? Is the nucleus a compartment of distinct pH, and can it host private proton signals?

WP4 will study the mechanisms by which tumour extracellular acidity exerts a selection pressure. Due to inherent diversity in a population, the ability to survive at a particular pH_e varies from cell to cell. Thus, acidity can select a specific phenotype, but the molecular definition of 'pH fitness' is unclear. What are the molecular processes that provide survival benefit to cancer cells living under acid-stress? Are cell subpopulations gated by pH also distinct in other, cancer-related biological functions such as stemness and tumorigenesis *in vivo*?

Responsibilities

- To carry out the research programme directed by the supervisors. This includes, but is not limited to, developing and implementing research methods, adapting techniques for the purpose of the project, designing and performing experiments, and analysing and interpreting scientific data;
- To work closely with the associated post holder and to agree on a coordinated and synergistic research programme that best reflects experience, skills and potential of the two post holders;
- To undertake comprehensive and systematic literature reviews, prepare results for publication and write papers for publication in peer-reviewed journals;
- To contribute ideas for new research projects;
- To manage his/her own academic research and administrative activities and report results and plans to supervisors;
- To keep accurate and organised records of work conducted, protocols, archived samples and reagents;
- To assist with training collaborators and other group members on scientific protocols and experimental techniques;
- To ensure that all work in the laboratory is conducted safely and, in particular, that work is undertaken following the appropriate health and safety policies and procedures for the particular area, without compromise to his/her own safety or that of others who may be affected.
- Ad hoc teaching may be required.

Hazard-specific / Safety-critical duties

This job includes the following hazard-specific or safety-critical duties which will require successful pre-employment health screening through our Occupational Health Department before the successful candidate will be allowed to start work:

- "Handling human blood, blood products, tissues, hazard group 2/3 pathogens".
- "Regular manual handling".

Additional security pre-employment checks

These posts will require an enhanced level screening via the University Security Services due to the nature of the work involving research.

Selection criteria

Successful candidates must meet the following <u>essential criteria</u>. The applicant's cover letter should explain how these are met.

E1. Must hold (or be near completion of) a PhD in a relevant area of research such as cell biology, molecular biology, biochemistry, physiology, metabolism or genetics;

E2. Must have extensive experience in mammalian cell culture techniques;

E3. Must have excellent technical competence in molecular biology techniques (plasmid manipulation, cloning, mutagenesis, quantitative PCR) and immunotechnniques (western blot, immunofluorescence);

E4. Must have technical competence in microscopy;

E5. Must have experience in performing functional measurements, such as fluorescence ionic imaging, metabolite assays or high-throughput biological assays.

E6. Must have demonstrable IT skills in specialised software packages, such as image processing, mathematical or bioinformatics software.

E7. Must be strongly motivated with an enthusiastic approach to science and with excellent organisational and verbal skills;

E8. Must be able to work well independently and also as part of a team, and be prepared to work at a high level of productivity and meet timelines;

E9. Must be meticulous in practical work and in record-keeping;

E10. Must demonstrable ability to innovate, and ability to trouble-shoot technical problems;

E11. Must have good written and verbal English;

E12. Must have good interpersonal skills for effective interaction at all levels.

Successful candidates should meet at least several of the <u>desirable criteria</u> listed below. Whilst we do not expect candidates to meet all these criteria, candidates should meet the criteria that are most relevant to their preferred work-packages. The applicant's cover letter should explain how these criteria are met.

D1. Research track record in the area of cancer biology, cancer physiology or cancer metabolism;

D2. An appreciation of pH homeostasis and signalling;

D3. Previous experience in viral production, transduction and optimization of viral uptake for overexpression and knockdown in mammalian cell cultures;

D4. Previous experience in using luciferase reporters to study the activity of transcription factors;

D5. Previous experience in culture and co-culture methods using bespoke scaffolds;

D6. Previous experience in sequencing, handling Big Data and using relevant bioinformatics tools;

D7. Previous experience in xenografting procedures and analysing tissue histology;

D8. A good publication record in peer-reviewed journals, as expected of their current career stage.

What to include in your application

- Your CV;
- Your publication list and a reprint of one article ranked as your best;
- A cover letter explaining how you meet the selection criteria and justifying the choice of work packages that you would wish to pursue.

About the University of Oxford

Welcome to the University of Oxford. We aim to lead the world in research and education for the benefit of society both in the UK and globally. Oxford's researchers engage with academic, commercial and cultural partners across the world to stimulate high-quality research and enable innovation through a broad range of social, policy and economic impacts.

We believe our strengths lie both in empowering individuals and teams to address fundamental questions of global significance, and in providing all of our staff with a welcoming and inclusive workplace that supports everyone to develop and do their best work. Recognising that diversity is a great strength, and vital for innovation and creativity, we aspire to build a truly diverse community which values and respects every individual's unique contribution.

While we have long traditions of scholarship, we are also forward-looking, creative and cutting-edge. Oxford is one of Europe's most entrepreneurial universities. Income from external research contracts in 2014/15 exceeded £522.9m and ranked first in the UK for university spin-outs, with more than 130 spin-off companies created to date. We are also recognised as leaders in support for social enterprise.

Join us and you will find a unique, democratic and international community, a great range of staff benefits and access to a vibrant array of cultural activities in the beautiful city of Oxford.

For more information please visit www.ox.ac.uk/about/organisation

Department of Physiology, Anatomy and Genetics

DPAG is the largest pre-clinical department within the Division of Medical Sciences. It has a world-class reputation in both its research and teaching. The Department was part of the University of Oxford's Biological Sciences submission to the Research Excellence Framework that was rated top for its world-leading research. Its mission is to build on its strong programmes of multi-disciplinary biomedical research, interfacing between the basic physical and life sciences and clinical/translational medicine, while creating an adaptable and forward-looking environment to provide outstanding training to the clinicians and biomedical scientists of the future.

The Department currently comprises approximately 450 people. Professor David Paterson is Head of the Department. There are approximately 60 academic and senior research staff, each with active research groups, and a further 170 academic-related research staff supported by external grants. Over 160 graduate students are registered for higher degrees in the Department. Both the teaching and research activities of the Department are supported by teams of technical, clerical and administrative staff

For more information please visit: http://www.dpag.ox.ac.uk

The Department of Physiology, Anatomy & Genetics holds a Silver Athena Swan award to recognise advancement of gender equality: representation, progression and success for all.

Medical Sciences Division

The Department is part of the University's Medical Sciences Division, which includes the pre-clinical departments (Physiology, Anatomy and Genetics, Pathology and Pharmacology) and all the clinical departments of the Medical School, plus the Department of Experimental Psychology. The Division is a major centre for clinical and non-clinical research in the UK, having achieved top scores in all the HEFCE research assessment exercises. The annual grant income from external sources for the Medical Sciences Division is over £80 million.

For more information please visit: http://www.ox.ac.uk/divisions/medical_sciences.html

How to apply

Before submitting an application, you may find it helpful to read the 'Tips on applying for a job at the University of Oxford' document, at www.ox.ac.uk/about/jobs/supportandtechnical/.

If you would like to apply, click on the **Apply Now** button on the 'Job Details' page and follow the on-screen instructions to register as a new user or log-in if you have applied previously. Please provide details of two referees and indicate whether we can contact them now.

You will also be asked to upload a CV and a supporting statement. The supporting statement should explain how you meet the selection criteria for the post using examples of your skills and experience. This may include experience gained in employment, education, or during career breaks (such as time out to care for dependants).

Your application will be judged solely on the basis of how you demonstrate that you meet the selection criteria stated in the job description.

Please upload all documents **as PDF files** with your name and the document type in the filename.

All applications must be received by **midday** on the closing date stated in the online advertisement.

Interviews are likely to be held on March 31st, 2017

Information for priority candidates

A priority candidate is a University employee who is seeking redeployment because they have been advised that they are at risk of redundancy, or on grounds of ill-health/disability. Priority candidates are issued with a redeployment letter by their employing departments.

If you are a priority candidate, please ensure that you attach your redeployment letter to your application (or email it to the contact address on the advert if the application form used for the vacancy does not allow attachments)

Should you experience any difficulties using the online application system, please email recruitment.support@admin.ox.ac.uk. Further help and support is available from www.ox.ac.uk/about_the_university/jobs/support/. To return to the online application at any stage, please go to: www.recruit.ox.ac.uk.

Please note that you will be notified of the progress of your application by automatic emails from our e-recruitment system. **Please check your spam/junk mail** regularly to ensure that you receive all emails.

Important information for candidates

Pre-employment screening: Please note that the appointment of the successful candidate will be subject to standard pre-employment screening, as applicable to the post. This will include right-to-work, proof of identity and references. We advise all applicants to read the candidate notes on the University's pre-employment screening procedures, found at: www.ox.ac.uk/about/jobs/preemploymentscreening/.

The University's policy on retirement: The University operates an employer justified retirement age for all academic and academic-related posts (grade 6 and above), for which the retirement date is the 30 September immediately preceding the 68th birthday. The justification for this is explained at: www.admin.ox.ac.uk/personnel/end/retirement/revisedejra/revaim/. For **existing** employees any employment beyond the retirement age is subject to approval through the procedures: www.admin.ox.ac.uk/personnel/end/retirement/revisedejra/revproc/

Equality of Opportunity: Entry into employment with the University and progression within employment will be determined only by personal merit and the application of criteria which are related to the duties of each particular post and the relevant salary structure. In all cases, ability to perform the job will be the primary consideration. No applicant or member of staff shall be discriminated against because of age, disability, gender reassignment, marriage or civil partnership, pregnancy or maternity, race, religion or belief, sex, or sexual orientation.

Benefits of working at the University

Training and Development

A range of training and development opportunities are available at the University. Further details can be found at www.ox.ac.uk/staff/working_at_oxford/training_development/index.html.

For research staff only: Support for Research Staff

There is a particularly wide range of support for career development for research staff. Please visit: www.ox.ac.uk/research/support-researchers to find out more.

Pensions

The University offers generous occupational pension schemes for eligible staff members. Further details can be found at www.admin.ox.ac.uk/finance/epp/pensions/pensionspolicy/.

Information for international staff *(or those relocating from another part of the UK)*

A wealth of information is available on the University's International Staff website for staff who are relocating to Oxford from abroad, at www.admin.ox.ac.uk/personnel/staffinfo/international/.

The University of Oxford Newcomers' Club

The Newcomers' Club is aimed at helping partners of newly-arrived visiting scholars, graduate students and academic members of the University to settle in and to meet people in Oxford.

Transport schemes

The University offers a range of travel schemes and public transport travel discounts to staff. Full details are available at www.admin.ox.ac.uk/estates/ourservices/travel/.

University Club and University Sports Facilities

The University Club provides social, sporting and hospitality facilities. It incorporates a Club bar, a cafe and sporting facilities, including a gym. See www.club.ox.ac.uk for all further details.

University staff can use the University Sports Centre at discounted rates, and have the chance to join sports clubs. Please visit www.sport.ox.ac.uk/oxford-university-sports-facilities.

Childcare and Childcare Vouchers

The University offers quality childcare provision services at affordable prices to its employees. For full details about the services offered, please visit www.admin.ox.ac.uk/childcare/. **NB: Due to the high demand for the University's nursery places there is a long waiting list.**

The University also offers nursery fee payment schemes to eligible staff as an opportunity to save tax and national insurance on childcare costs. Please visit www.admin.ox.ac.uk/childcare.

Disabled staff

The University is committed to supporting members of staff with a disability or long-term health condition and has a dedicated Staff Disability Advisor. Please visit www.admin.ox.ac.uk/eop/disab/staff for further details.

BUPA - Eduhealth

Bupa Eduhealth Essentials private medical insurance offers special rates for University of Oxford staff and their families www.eduhealth.co.uk/mini-site/.

All other benefits

For other benefits, such as free entry to colleges, the Botanic Gardens and staff discounts offered by third party companies, please see www.admin.ox.ac.uk/personnel/staffinfo/benefits/.