University of Hertfordshire UH

Early Career and returning to Research Staff Research Grants Competition for 2016/17

Application Form Preamble

All applications will be considered on their research merits and assessed by a panel of senior research-active staff. The membership of the panel will be agreed by the Pro Vice-Chancellor Research Management Group who will ratify its recommendations.

The following criteria will be applied:

- the quality and significance of the proposed research, and/or external funding application, and its relevance beyond the University
- the appropriateness, effectiveness and feasibility of the proposed research methods, including a clear completion strategy
- the impact potential of the project and plans to support this
- the creation of a discrete and measurable research outcome(s) (i.e. published journal article(s), research monograph, substantial funding application, exhibition, etc.)

Applicants should pay particular attention to the following:

- ensure that they keep within the word limit
- budgets should be taken seriously and properly defined.

Award winners must submit an end of project report on the approved Research Office template by 1 September 2017.

As with other funders, support from the University should be acknowledged in any major outputs arising from the grant.

Finally, please note that all funding allocated through this scheme must be spent by 31 July 2017.

If you have any queries regarding the process, please contact Dr Catherine Manthorpe, email: c.manthorpe@herts.ac.uk

University of Hertfordshire UH

Early Career and returning to Research Staff Research Grants Competition for 2016/17

APPLICATION FORM

1. Name of applicant **Internal Address**

Title:	Doctor	Department of Pharmacy, Pharmacology and Postgraduate Medicine College lane Campus New Science Building, Room 2J030 AL10 9AB Hatfield, Herts Tel no: 01707289330 07563574264 Email: e.hoffman@herts.ac.uk
First name:	Ewelina	
Surname:	Hoffman	

2. Present appointment

Present appointment and School

Post-Doctoral Research Fellow

3. Details of grant requested

Title of project (not more than 15 words)	Sum requested to the nearest £
Investigating the impact of macrophage polarization on foamy macrophage response *in vitro.*	**£ 4000**

4. Which Research Theme does your project fall under (you may select more than one as appropriate)

Food	
Global Economy	
Health and Wellbeing	**X**
Heritage, Communities and Cultures	
Information and Security	
Space	

5. Project summary (Maximum 50 words.)

Many inhaled medicines in development currently fail in pre-clinical studies due to immune responses observed. The aim of this project is to characterize responses of alveolar macrophages to different stimuli to identify if these are adverse or adaptive.

[Words Count 38]

6. Co-applicant(s) if relevant
Title, First name(s), Surname (underlined)

1. Dr Victoria Hutter

2.

7. Commitment to the project
Please give details below of the anticipated average number of hours per week that will be devoted to the project.

	Average Hours Per Week
Principal applicant	16
Co-applicant (1)	0.5-1
Co-applicant (2)	

8. Scheme of research

Please describe in no more than 500 words the scheme of research or process of application development for which you are seeking an award, using the following sub-headings as appropriate: research question(s) or problem; aims & objectives; research context; research methods and project management. (It is recognised that not all projects in all subject areas will easily divide under these headings.)

Research problem
Many new inhaled medicines fail during development due to the induction of a "foamy" alveolar macrophage response in pre-clinical studies. There is limited understanding if a highly vacuolated macrophage phenotype response to an inhaled stimulus is adverse or adaptive. Macrophages dynamically alter their phenotype and function depending on their underlying microenvironment resulting in abnormal shifts in their polarization state between classically (M1) and alternatively (M2) activated. It is currently unknown if foamy macrophage responses are triggered by macrophage polarization. Understanding this process may play a pivotal role in understanding foamy phenotype induction during drug exposure studies. Developing improved in vitro assays to better predict airway responses will reduce the cost and time associated with developing inhaled medicines which fail in in vivo studies.

Aim
To identify the relation between polarization state and cellular response of alveolar macrophages challenged by foamy-macrophage inducers.

Objectives

- To develop a high-throughput screen to distinguish between M1/M2 macrophage phenotype

- To investigate changes in macrophage activation and lipid content followed foamy inducers challenge

- To characterize interspecies (rat vs human) differences in macrophage polarization and response

Research context
Alveolar macrophages have a high plasticity allowing them to adapt their phenotype in response to different environmental stimuli[1]. One such phenotypical change is the appearance of foamy macrophages, which describes a vacuolated cytoplasmic appearance[2,3]. The phenotype may occur in certain diseases, infections or through exposure to xenobiotics[3-5]. Pathways leading to generation of the foamy phenotype have not been fully elucidated. At UH, we have established human and rat *in vitro* systems and have developed quantitative high-throughput morphometric screening assessments for a panel of foamy macrophage inducer compounds for the pharmaceutical industry[4]. This project will extend the current state-of-the-art to probe the biology of foamy macrophage induction to develop more detailed *in vitro* assays to predict adverse responses *in vivo*. The resulting in vitro screening tool will permit earlier go/no go decisions in pre-clinical screening and reduce the number of costly pre-clinical animal studies required.

Research methods
Rat macrophage (NR8383) and human monocyte (U937) cell lines will be cultured using standardised cell culture techniques. Cells will be activated to M1 or M2 macrophages by incubation with cytokines (IFNγ, LPS, IL-4). Cells will be exposed to different stimuli: amiodarone, staurosporine and salbutamol for 24h and 48h.

In collaboration with GE Healthcare and GSK, we have developed high content screens to evaluate cell health and lipid content. The current high-content technology (flow cytometer available at UH and InCell Analyzer accessible at Stevenage Bioscience Catalyst) will be used to additionally assess expression of polarization markers.

Project management
The experimental work is planned for five months (February – July 2017) and will be conducted by a PhD research assistant and myself. The research assistant will have an expertise in *in vitro* cell culture and will be familiar with proposed techniques. Fortnightly meetings will take place with Dr Hutter to discuss scientific progress. The results will be liaised with GSK group to discuss the strategy for further studies.

[Words Count 493]

1. Forbes B. et al. *Advanced drug delivery reviews*. 2014;71:15-33.
2. Lewis DJ. et al. *Journal of applied toxicology : JAT*. 2014;34:319-331.
3. Russell DG. et al. *Nature immunology*. 2009;10:943-948.
4. Hoffman E. et al. *Pharma Res.* 2016 (submitted)
5. Shaykhiev R. et al. *Journal of immunology (Baltimore, Md. : 1950)*. 2009;183:2867-2883.

9. Statement of eligibility

Applicants are asked to explain in no more than 100 words how they meet the eligibility criteria for the award as described above, and if there is any information relating to their professional career which they may wish to be taken into account in assessing this application. For example, details of a career break, or the effect of working on a part-time contract, may be relevant.

I have completed my PhD programme in cancer cellular biology at the University of Lodz in 2014. Having obtained my qualification, I had an opportunity to translate my skills to inhaled medicines development during six months post-doctoral fellowship at King's College London. Since March 2015, I have been working at UH as post-doctoral researcher. Over last 20 months I have broadened my scientific horizons and expertise and gained a clear vision for myself as an academic researcher. As an early career researcher, I find this grant as a significant opportunity to enhance my career development to become independent researcher.

[Word Count 99]

10. Outputs.

In no more than 250 words, please describe the proposed output(s) from the research: your plans for publication or other public output(s).

Publications: The work will be disseminated to wider research communities through publication of the research in high impact pharmaceutical research, analytical and medical journals, e.g. *Journal of cellular biochemistry (IF=3.2), Pharmaceutical Research (IF=3.2)*.
Two papers has been planned to be submitted:
(i) Methodology paper describing a newly developed high content assay for macrophage polarization assessment.
(ii) A paper presenting result of the impact of macrophage polarization on foamy macrophage response

Conference presentation: The research will be promoted at national and international conferences. The preliminary macrophage activation data will be presented at "*Advances in Cell and Tissue Culture*" conference taking place in Manchester, May 2017 and the main results will be prepared for presentation at "*Respiratory Drug Delivery*" conference, April 2018.

Grant application: Funding resources are very competitive and limited, which makes them very difficult to secure for young researchers. The preliminary data generated in this study will be crucial in further grant application. "*David Sainsbury Fellowship*" is an example of a scheme that supports young scientists with the transition to an independent career. The data acquired from this project will be a strong foundation in writing the David Sainsbury application in September 2017, which will be an opportunity to bring £ 200 000 UH Department of Pharmacy.
Finally, the preliminary results will be used to design further studies investigating foamy alveolar macrophage signaling pathways in cooperation with Dr Martin Bootman from Open University.

Industry-ready screening tool: The project will generate a more predictive drug safety tool with commercial potential.

[Word Count 249]

11. Pathways to Impact

Research Councils UK (RCUK) defines research impact as 'the demonstrable contribution that excellent research makes to society and the economy'. This section should address two questions: *who* will benefit from the research? And *how* will they benefit from the research? Applicants are asked to consider primarily those users and beneficiaries of the research who are outside the academic research community (individuals, specific organisations or groups/sectors). What will be done to ensure that these potential beneficiaries have the opportunity to engage with this research? Activities in support of impact may be included in costings. Max 250 words**.**

The project will benefit:

- **Patients** – Lung diseases are an increasing global health burden affecting hundreds of millions of people worldwide. The mechanistic studies of foamy macrophage biology will help to understand the foamy macrophage phenomenon and may offer potential insights to new targets or treatments. This in turn, will lead to therapies development and improvement of patients' health and quality of life.
- **Industry** - Despite considerable investment by pharmaceutical companies to develop new inhaled medicines, few new drugs have made it to the clinic in the past 30 years due to concerns of safety testing. The project is strong basis for collaboration with industry by development of novel screening tool. The high-content assay expanded by functional markers will improve predictive capacity of the screen. Over one third of inhaled medicines failed in pre-clinical studies due to lack of predictive *in vitro* tools. Applying such tool in an early drug development process will help to predict *in vivo* responses more accurately and eventually lead to reduction of number of in vivo experiments.
- **Scientists** – the work will be disseminated to the wider research communities through publications and conference presentations.

The project will be an opportunity for **other early career researcher** from our group (project/PhD students, post-docs) to be exposed to novel high-content screening techniques.

The project will provide a significant contribution to **my career development** by making my publication record stronger; expanding my leadership and individually thinking skills, which are crucial in continuation my research as a group leader.

[Word Count 250]

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12. Particulars of costs

Give a breakdown of the total costs requested*.*

Item of expenditure	**Cost**
Travel expenses: *please itemise each journey* *20 journeys to Stevenage Bioscience Catalys/ GSK x 10 GBP each*	**£ 200**
Subsistence whilst away from home: *please express costs in terms of x days at y pounds, bearing in mind University regulations relating to subsistence and travel.* *Not applicable*	
Short-term research, technical or secretarial assistance *@ £21.86 per hour (UH6 Bar 27including on costs).* Research assistant: 10 weeks x 9 hours/week x £21.86	**£ 1967.40**
Replacement teaching costs: *expressed as number of hours @ £53.76 per hour (Rate A UH7 point 32 including on costs). Please also specify the semester in which replacement teaching is requested.* Not applicable	
Consumable items Cell culture consumables (£832.60), antibodies (£800) and chemicals (£200)	**£ 1832.60**
Equipment/materials: *where applicable, please provide justification for such costs in the box below*	
Preparation of research for public output	
Impact Activities	
Other: *please specify and provide justification for such costs in the box below.*	
Total costs sought	**£ 4000**

University of Hertfordshire UH

13. Signatures and date

Signature of applicant		Date	

On behalf of the School

The School confirms that they support this application. Particular attention should be paid to items of expenditure listed under 11, as the School will be expected to facilitate this expenditure. N.B. replacement teaching can form a part of this.

Dean of School (or equivalent)

Title	Internal Address: e-mail: telephone:
First Name	
Surname	
Position	
Signature	Date

The completed application along with a **two page curriculum vitae** should be submitted in electronic form to Penny Matthews, Research Office Administrator, at: p.mathews@herts.ac.uk by no later than **Friday 16 December 2016.**