University Alliance
Doctoral Training Alliance

DTA3/COFUND Programme Research Project Proforma

Page 1 – General Information

Project Code	HUAB01
Partner University	University of Huddersfield
Faculty/School/Department/Research Centres	Department of Biological and Geographical Sciences, School of Applied Sciences
First supervisor Please provide name and weblink	Dr Tarja Kinnunen https://pure.hud.ac.uk/en/persons/tarja-kinnunen
Second supervisor Please provide name and weblink	Dr Partick McHugh https://pure.hud.ac.uk/en/persons/patrick-mchugh
Third supervisor Please provide name and weblink	Professor Michael Ginger https://pure.hud.ac.uk/en/persons/michael-ginger
Fourth (external) supervisor	
External/industrial supervisor	TBC
Which of the supervisors listed above is an early-career-researcher	
Contact details for project for informal applicant queries Email address	T.Kinnunen@hud.ac.uk
DTA Programme: Please delete as necessary which DTA programme this project relates to:	DTA Applied Biosciences for Health
Project title	Identification of the molecular mechanisms of longevity in long-lived mutants of insulin and Klotho signalling

Co-funded by the Horizon 2020 programme of the European Union

This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 801604.

Page 2 – Project Description

Scientific Excellence (500 words)	Klotho/beta-Klotho (KLB) are transmembrane proteins that act as co-receptors for endocrine fibroblast growth factors (FGF19, -21 and -23) to activate their cognate FGF receptors (FGFRs). Klotho was originally identified as ageing-related gene when disruption of *Klotho* gene in mice led to phenotypes resembling ageing and shortened life-span[1]. We have previously shown that the function of Klotho/KLB in ageing is evolutionarily conserved in the nematode *C. elegans*[2], which has two Klotho/KLB orthologs. *C. elegans* also has evolutionarily conserved insulin signalling and the role of insulin signalling in longevity and the effects of glucose on shortening lifespan were first discovered in *C. elegans*[3]. These effects are mediated via the forkhead box O (FOXO) transcription factor DAF-16[3]. The long-lived *C. elegans* mutants in insulin signalling remain healthy and mobile after wild type worms look old, suggesting that the mutations not only prolong lifespan but also enhance healthspan of the aged. References: 1. Kuro-o *et al* (1997) *Nature*, 390; 45; 2. Polanska *et al* (2011) *J Biol Chem* 286; 5657; 3. Lee *et al* (2009) *Cell Metab*, 10; 379
Aim (400 words)	I. Aim and hypothesis The aim of this project is to understand at molecular level the cellular changes that are regulated by insulin signalling and Klotho in longevity. Specifically we will identify the FOXO/DAF-16 target genes up- or down regulated in long-lived *C. elegans* mutants. I. Methodology and innovations a) To identify the downstream targets of FOXO/DAF-16, our existing long-lived *C. elegans* mutant strains will be used (either alone or in various combinations) and quantitative PCR (qPCR) of candidate target genes and/or transcriptome analysis using microarrays will be carried out. The datasets will be referenced to wild type *C. elegans*.

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	b) To validate any identified hits in (*a*), genetic mutants (where available, or RNAi/targeted mutagenesis of the identified hits) will be used in combination with classical genetic methods (e.g. epistasis analysis) to assess how mutations in the identified hits alter longevity of the long-lived worms
Strategic Relevance (300 words)	Over the past decades, life expectancy in the UK has increased from 75.8 years to 81.6 years. This has led to challenges in healthcare and in understanding the factors affecting healthy ageing. Given the evolutionarily conserved molecular pathways of insulin and Klotho signalling, our results will provide insight into key molecules critically involved in prolonged healthy lifespan. Ultimately our discoveries may lead to identification of novel therapeutic targets.
Interdisciplinarity and fit with DTA3	This project will train the prospective student in whole-organism genetics, gene analysis (qPCR, transcriptomics, microarrays), and in understanding of the human health.
Industrial Relevance (300 words)	TBC
Economic and Societal Impact (300 words)	This project will provide further understanding of the molecular changes occurring at cellular level during the ageing process. Findings from the project will be timely disseminated to wider scientific audiences via conference presentations (e.g. BSCB/BSDB and BSRAmeetings) and publication in high impact journals (e.g. Ageing Cell, Plos Biology, Open Biology). Reagents such as *C. elegans* strains (via deposition to the Caenorhabditis Stock Centre) and DNA constructs made during the project will be made freely available to scientific community at minimum upon publication. Further understanding of the cellular ageing process at the molecular level will help in better designing of healthcare (including personalised healthcare) and developing novel therapeutic treatments of the ageing population. This will lead to economic benefits as ageing related health complaints may be prevented and problems arising from multi-disease treatments may be avoided. Better designed and more

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	individualised treatment will lead to less hospital admissions and lower medical costs. Societal impacts include better healthspan of the ageing population leading to longer independent living and overall better quality of life.

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Page 3 – Admission Requirements

Specific Admission Requirements Detail any subject specific degree qualifications or disciplines, relevant skills, experience	Applicants require an undergraduate degree (1st or Upper Second Class/equivalent) and preferably a Masters degree in molecular biology, genetics, cellular or developmental biology or in a related biology area. Practical experience in molecular biology, biochemistry or *C. elegans* manipulation would be welcome but not essential.
Minimum IELTS score	6.0 with no lower than 5.5 in any element

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