Leslie Fund Studentship

Musculoskeletal Research

2017/2018

Contents

Leslie Fund

This area is interpreted in the widest manner and can include basic to translational research, for example: musculoskeletal development, musculoskeletal disease (from inflammatory conditions to osteoarthritis and pain syndromes, dystrophies etc), physiology, physiotherapy, and regenerative medicine.

The successful candidate will follow the 0+4 pathway of the DTP, they will start immediately on their PhD project and will not participate in rotation projects. They will participate in all other training and cohort activities of the DTP.

When choosing a project from this catalogue in the funding section of the online application form (and it the 'Project Title' section) please enter **LESLIE_FUND**

Deadline for application: Sunday 7th May 2017

Shortlisted candidates will be contacted in early June and invited to an interview on June 15th.

Interviews: 15 June 2017

The 2017/18 studentships will commence in September 2017.

For further Information or queries relating to the application process please contact

mrc-dtp@kcl.ac.uk

Projects listed in this catalogue are subject to amendments, candidates invited to interview will have the opportunity to discuss projects in further detail.

1.5 Pathophysiology of New Genetic Muscle Diseases

Co-Supervisor 1A: Dr. Julien Ochala
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Co-Supervisor 1B: Dr. Heinz Jungbluth
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Project Description:

Genetic muscle diseases are often life threatening due to severe weakness. The understanding of this group of disorders has advanced in recent years through the identification of new causative gene mutations such as TNPO3. The aim of the present project is to underpin the hitherto pathophysiological mechanisms by which these TNPO3 mutations lead to muscle weakness. As TNPO3 encodes transportin-3, a nuclear membrane protein, we hypothesise that the deficiency in transportin-3 in patients, alters nuclear movement, positioning and protein synthesis, preventing the full growth of muscle fibres. To prove this, the present project will be divided into three sub-objectives:

Sub-objective 1 (year 1): Characterising how a transportin-3 deficiency modifies nuclear movement in myoblasts.
Sub-objective 2 (years 2): Determining how the absence of transportin-3 affects nuclear positioning in muscle fibres.
Sub-objective 3 (years 3 and 4): Identifying how nuclear mispositioning affects nuclear cooperation, protein and transcription and muscle growth.

At the end of this project, the student should be able to:

- Master biophysical techniques and advanced microscopy,
- Apply his newly developed skills to normal and diseased cells/molecules,
- Generate and analyse large sets of data,
- Synthetize the findings by writing scientific papers.

One representative publication from each co-supervisor:

Cullup T, Kho AL, Dionisi-Vici C, Brandmeier B, Smith F, Urry Z, Simpson MA, Yau S, Bertini E, McClelland V, Al-Owain M, Koelker S, Koerner C, Hoffmann GF, Wijburg FA, ten Hoedt AE, Rogers RC, Manchester D, Miyata R, Hayashi M, Said E, Soler D, Kroisel PM, Windpassinger C, Filloux FM, Al-Kaabi S, Hertecant J, Del Campo M, Buk S, Bodi I, Goebel HH, Sewry CA, Abbs S, Mohammed S, Josifova D, Gautel M, Jungbluth H. (2013) Recessive mutations in EPG5 cause Vici syndrome, a multisystem disorder with defective autophagy. Nat Genet. 45: 83-87.

Ochala J, Gokhin DS, Penisson-Besnier I, Quijano-Roy S, Monnier N, Lunardi J, Romero NB, Fowler VM. (2012) *Congenital myopathy-causing tropomyosin mutations induce thin filament dysfunction via distinct physiological mechanisms.* Hum Mol Genet. 21: 4473-4485.

2.5 Interrogation of a novel subset of B cells that is increased in frequency in systemic lupus erythematosus.

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Co-Supervisor 1B: Susan John
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Project Description:
Systemic lupus erythematosus (SLE) is a chronic inflammatory autoimmune disease that frequently affects the musculoskeletal system including small and large joints. We have identified B cells with the hallmarks of T cell independence; having reduced CD40 and HLA class II expressionthat differs in frequency between tissues and blood, and is increased in frequency in the blood of patients with SLE compared to healthy controls. The aim of this project is to investigate this subset in health and SLE to identify how it differs functionally from other B cell subsets and how it may contribute to autoimmune inflammatory disease.

In the first year, B cell subset responses in vitro to factors such as cross-linking the B cell receptor, CD40 ligation and innate stimuli such as CpG will be studied. Changes in cell division and phenotype associated with differentiation will be studied by flow cytometry. Complex tissue culture and flow cytometry would be learned in this phase.

During the second year the signalling pathways induced by culture conditions will be investigated by western blotting following in vitro stimulation via different routes described above.

In the third year the genotypic profiles of this novel B cell subset in health and SLE will be determined by microarray analysis to determine functional pathways active in the novel B cell subset compared to others that are better understood.

The final year will be spent on further validation of data as required that will involve quantitative PCR and flow cytometry before completing the PhD thesis.

One representative publication from each co-supervisor:
Vossenkämper A, Blair PA, Safinia N, Fraser LD, Das L, Sanders TJ, Stagg AJ, Sanderson JD, Taylor K, Chang F, Choong LM, D'Cruz DP, Macdonald TT, Lombardi G, Spencer J. A role for gut-associated lymphoid tissue in shaping the human B cell repertoire. J Exp Med. 2013 Aug 26;210(9):1665-74.

Afzali B, Mitchell PJ, Edozie FC, Povoleri GA, Dowson SE, Demandt L, Walter G, Canavan JB, Scotta C, Menon B, Chana PS, Khamri W, Kordasti SY, Heck S, Grimbacher B, Tree T, Cope AP, Taams LS, Lechler RI, John S, Lombardi G. CD161 expression characterizes a subpopulation of human regulatory T cells that produces IL-17 in a STAT3-dependent manner. Eur J Immunol. 2013 Aug;43(8):2043-54. doi: 10.1002/eji.201243296

3.5 Molecular basis of arthritic pain: roles of HCN ion channels and AT2 receptors

Co-Supervisor 1A: Prof Peter McNaughton
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Co-Supervisor 1B: Prof Marzia Malcangio
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Project Description:

The overall aim of the project is to extend our understanding of the roles of the HCN2 ion channel and the angiotensin II – AT2 receptor pathway in arthritic pain. The HCN2 ion channel is a pacemaker channel which promotes action potential firing in pain-sensitive (nociceptive) nerve fibres. We have shown that HCN2 play2 an important role in both inflammatory and neuropathic pain, and the work will extend this to a study of the role of HCN2 in the pain of rheumatoid arthritis and osteoarthritis.

Preliminary evidence from our group also shows that the peptide angiotensin II is a potent pro-inflammatory agent which acts via HCN2 ion channels, and together with other recent evidence that the AT2 receptor for angiotensin II in an important analgesic target, this work suggests that the angiotensin II-AT2-HCN2 pathway will be important in arthritic pain. The aim of the work is therefore to delineate the scientific basis for novel drug targets that will be important in treating arthritis.

Skills: animal models of pain, electrophysiology (patch clamp), pharmacology, cell and molecular biology

Objectives
Year 1: Determine the role of HCN2 ion channels in mouse models of arthritis
Year 2: Determine the role of angiotensin II and AT2 receptors in arthritis
Year 3: Investigate signalling pathways which mediate coupling between AT2 receptors and HCN2 ion channels.

One representative publication from each co-supervisor:
P. McNaughton:
Tsantoulas, C., Mooney, E.R. & McNaughton, P.A. (2016). HCN ion channels: basic science opens up possibilities for therapeutic intervention in neuropathic pain. Biochem J. 473, 2717-36.

M. Malcangio:
Nieto, F. R. et al. Neuron-immune mechanisms contribute to pain in early stages of arthritis. J Neuroinflammation 13, 96, doi:10.1186/s12974-016-0556-0 (2016).

4.5 Linking Genotype to Phenotype in Psoriatic Arthritis: determining the role of disease-associated genes in Tc17 cell function and development

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Co-Supervisor 2: Dr Francesca Capon
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Project Description:

Psoriatic arthritis (PsA) is an inflammatory disease of the joints, with frequent skin involvement. The disease is typically associated with HLA class I, suggesting a role for CD8+ T cells. We previously demonstrated that the inflamed joints of patients with PsA contain higher frequencies of CD8+ T cells expressing the pro-inflammatory cytokine IL-17. These IL-17+ CD8+ T cells (Tc17 cells) correlate with clinical parameters of disease activity. Tc17 cells are also found in the skin of patients with psoriasis. In addition to particular HLA class I associations, a number of other genetic variants have been associated with PsA and psoriasis. Interestingly, some of these genetic variants relate to the IL-17 pathway (e.g. *IL23R*, *TRAF3IP2*). Together, this leads us to hypothesize that (i) the presence of Tc17 cells in the inflamed joint is driven by particular HLA class I associations, and (ii) IL-17 production by CD8+ T cells can be influenced by particular non-HLA genetic variants.

Overarching objectives:

Year 1: determine HLA genotypes and other genetic variants in existing samples from patients with PsA, and link this information to Tc17 frequency.

Year 2/3: assess gene/protein expression of PsA-associated genetic variants that are associated with the IL-17 pathway in relevant immune cells.

Year 3/4: determine the functional effects of these genetic variants on the expression of IL-17 by CD8+ (and CD4+) T cells, and Tc17 development and function.

Skills training: mononuclear cell isolation, cell culture, intracellular cytokine staining, multi-colour flow cytometry, ELISA, Western blotting, DNA/RNA extraction, qPCR, genotyping, overexpression/knockdown, bioinformatics.

One representative publication from each co-supervisor:

Menon B, Gullick NJ, Walter GJ, Rajasekhar M, Garrood T, Evans HG, **Taams LS***, **Kirkham BW*** (*joint senior authors). Interleukin-17+CD8+ T Cells Are Enriched in the Joints of Patients With Psoriatic Arthritis and Correlate With Disease Activity and Joint Damage Progression. Arthritis Rheumatol. 66 (5): 1272–1281 (2014)

Mahil SK, Twelves S, Farkas K, Setta-Kaffetzi N, Burden AD, Gach JE, Irvine AD, Képíró L, Mockenhaupt M, Oon HH, Pinner J, Ranki A, Seyger MM, Soler-Palacin P, Storan ER, Tan ES, Valeyrie-Allanore L, Young HS, Trembath RC, Choon SE, Szell M, Bata-Csorgo Z, Smith CH, Di Meglio P, Barker JN, **Capon F**. *AP1S3* mutations cause skin autoinflammation by disrupting keratinocyte autophagy and up-regulating IL-36 production. *J Invest Dermatol* Epub ahead of print 4th July 2016; doi: 10.1016/j.jid.2016.06.618

5.5 Molecular mechanisms underlying the contractile dysfunction in ageing-related muscle weakness

Co-Supervisor 1A: Dr. Yin-Biao Sun (basic scientist)
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Project Description:

Ageing-related muscle weakness represents a major, and growing, healthcare burden, which leads to declines in physical function, independency and quality of life. The molecular mechanisms underlying such phenomena remain unclear but potentially include a dysfunction of the molecular motor, myosin, that can only partly explain the decline in the force-generating capacity. In the present project, we aim to precisely characterise such myosin dysfunction. Understanding the mechanisms underpinning such contractile dysfunction is essential in the development of effective 'preventative' or 'therapeutic' interventions.

We are going to apply two of the state-of-the-art techniques, the Fluorescence for In Situ Structure (FISS) and the Small-angle X-ray scattering, to study both structural and functional effect of aging on myosin in human skeletal muscle cells. We will use muscle biopsy specimens that we have already obtained from healthy young adults, and three groups of older individuals aged over 75 years who represent the health and activity span.

Performing FISS and X-ray experiment requires a unique combination of expertise, ranging from molecular biology, protein biochemistry, muscle physiology to biophysics of data interpretation. Depends on the student's background and previous experience, he/she will have opportunities to be trained in all these skills.

Years 1 and 2 (with Dr. Sun): trainings in basic skills required for the experiment and performing FISS to complete the control experiments using myosin probes.

Years 3 and 4 (with Prof Harridge and Dr. Sun): specifically characterise the alterations in myosin function in aging muscle cells using both X-ray and FFSS techniques.

One representative publication from each co-supervisor:

Zhang X, Kampourakis T, Yan Z, Sevrieva I, Irving M, Sun Y-B (2017) Distinct contributions of the thin and thick filaments to length-dependent activation in heart muscle. *eLife* 6:e24081. doi:10.7554/eLife.24081

Alsharidah M, Agley C, George T, Lazarus N, Velloso C & Harridge SDR (2013) Primary human muscle precursor cells obtained from young and old donors produce similar proliferative, differentiation and senescent profiles in culture. *Aging Cell* 12(3):333-44.

6.5 Improving skeletal muscle function in the muscle wasting disease FSHD

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Co-Supervisor 1B: Professor Malcolm P.O. Logan
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Project Description:

Facioscapulohumeral muscular dystrophy (FSHD) is characterised by muscle weakness, where muscle wastes and connective tissue becomes deregulated, so scar tissue forms. FSHD is caused by ectopic expression of a transcription factor called DUX4. FSHD muscle cells are sensitive to oxidative stress, and treatment of FSHD patients with anti-oxidants vitamin E, vitamin C, zinc, and selenomethionine improves some muscle function measurements (clinicaltrials.gov:NCT01596803) (doi:10.1016/j.freeradbiomed.2014.09.014). Analysis of our FSHD gene expression (RNA-Seq) data has also implicated mediators of oxidative stress and mitochondrial generation, indicating activation of mitochondrial biogenesis as a therapeutic strategy. We have good preliminary data that several nutritional supplements target this pathway, improving muscle formation.

Hypothesis
Improving protection against oxidative stress and enhancing mitochondrial biogenesis will improve muscle function in FSHD.

Objectives
Year 1: Screen nutritional supplements that can affect mitochondrial biosynthesis/protect against oxidative stress on FSHD myoblasts/fibroblasts. Characterise connective tissue perturbation by analysing gene expression data from FSHD muscle biopsies.
Year 2: Test selected nutritional supplements on a range of FSHD patient cells lines.
Year 3: Measure effects of nutritional supplements on muscle and connective tissue expressing DUX4 both in vitro and in animal models.
Year 4: Investigate interaction of nutritional supplements with known/novel signalling pathways to identify mechanism.

Skills training
Molecular Biology (e.g. cloning), Cell Biology (mouse/human cell culture, retroviral-transduction, siRNA-mediated gene-knockdown), Animal Models, Gene Expression/Protein Analysis (RT-qPCR, Western blotting, immunolabeling), Imaging/Time-Lapse using state-of-the-art confocal/multiphoton microscopy and Bioinformatics.

Expertise
Zammit: muscle stem cell function in health and disease.
Logan: muscle associated connective tissue and its disease associations.

One representative publication from each co-supervisor:

Moyle L.A., Blanc E., Jaka O., Prueller J., Banerji C.R.S, Tedesco F.S., Harridge S.D.R., Knight, R.D. and Zammit P.S. (2016). Ret function in muscle stem cells points to tyrosine kinase inhibitor therapy for facioscapulohumeral muscular dystrophy. ***eLIFE* 5**:e11405. (doi: 10.7554/eLife.11405).

*Tbx4 and Tbx5 acting in connective tissue are required for limb muscle and tendon patterning.*Hasson, P; DeLaurier, A; Bennett, M; Grigorieva, E; Naiche, LA; Papaioannou, VE; Mohun, TJ and **Logan, MPO** (2010) Developmental Cell 18, 148-156

7.5 Epigenetic regulation of inflammatory and stem cell function during muscle regeneration

Co-Supervisor 1A: Robert Knight
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www.kcl.ac.uk/dentistry/research/divisions/craniofac/ResearchGroups/KnightLab/KnightLab.aspx

Co-Supervisor 1B: Fiona Wardle
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http://www.kcl.ac.uk/lsm/research/divisions/randall/research/sections/signalling/wardle/index.aspx

Project Description:

Muscle stem cells (muSCs) are critical for maintaining muscle strength. In disease, injury and ageing their function is compromised and this is associated with epigenetic changes. Inflammatory cells are recruited to damaged muscle and release TNF-alpha (TNF-a), which can activate muSCs. How epigenetic modifications alter the inflammatory cell responses to injury or the response of muSCs to TNF-a *in vivo* is unknown. This proposal therefore aims to use a zebrafish model of muscle regeneration in order to dissect how the Polycomb Repressor Complex 2 protein EZH2, controls the interaction between immune and muSCs during muscle repair.

Specific Aims are:
1. Determine the importance of EZH2 function for controlling inflammatory cell responses to muscle injury
2. Evaluate the importance of TNF signaling for regulating inflammatory cell and muSC responses during regeneration
3. Functionally test whether EZH2 regulates inflammatory cell and muSCs responses to TNF signaling.

Transgenic zebrafish will be used for gene over-expression and visualisation of cells during regeneration by confocal and multiphoton microscopy. TNF signaling and EZH2 function will be manipulated by genetic, pharmacological and over-expression techniques. To measure chromatin changes in muSCs and inflammatory cells in response to altered TNF or EZH2 function, RNA-SEQ and ChIP-SEQ will be performed on cells isolated by flow cytometry. Candidate genes regulated by EZH2 and TNF in muSCs and inflammatory cells will be identified using computational analyses of ChIP-SEQ and RNA-SEQ data. Selected candidate genes will then be tested for their role in controlling inflammatory cell and muSC responses to injury.

One representative publication from each co-supervisor:

Knappe, Stefanie; Zammit, Peter S.; **Knight, Robert D.** 'A population of Pax7- expressing muscle progenitor cells show differential responses to muscle injury dependent on developmental stage and injury extent'. Frontiers in aging neuroscience, Vol. 7, No. 161, 25.08.2015.

Nelson, A.C., Cutty, S.J., Niini, M., Stemple, D.L., Flicek, P., Corinne Houart, C., Bruce, A.E.E., **Wardle, F.C.** (2014). Global identification of Smad2 and Eomesodermin targets in zebrafish identifies a conserved transcriptional network in mesendoderm and a novel role for Eomesodermin in repression of ectodermal gene expression. *BMC* Biology, 12(1):81.

8.5 A novel approach to treating Fibromyalgia: Physiotherapy informed by Acceptance and Commitment Therapy (PACT)

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Co-Supervisor 1B: Professor Lance McCracken
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Project Description:

Background
Fibromyalgia (FM) affects 1-3 % of the population and causes much suffering and disability. Acceptance and Commitment Therapy (ACT) has shown promise (McCracken. 2017), but has yet to be tested in a treatment delivered by physiotherapists. Physiotherapy informed by ACT (PACT) has been developed and tested in persistent low back pain.

Design
This project will refine and test a bespoke ACT informed physiotherapy intervention to improve health outcomes in people with FM, based on the PACT model (Godfrey et al. 2016). The PhD will include a systematic review of literature on ACT for FM and semi-structured qualitative interviews exploring FM patient's experiences of pain and current management strategies. 40 people with FM referred to physiotherapy services across King's Health Partners will be recruited to a feasibility study. A mixed-methods evaluation of intervention acceptability (patients) and fidelity (physiotherapists) will be undertaken to investigate the acceptability of the PACT approach. If successful, a RCT testing PACT in FM will be designed.

Translational aspect
Results may improve quality of life in people with FM.

Description of the skills training available
a) Theory based intervention development and refinement
b) Qualitative skills: interviews with patients and focus groups with staff
c) Quantitative skills: feasibility methods and data analysis

Objectives for each year
a) Year 1: Conduct systematic review and semi-structured interviews
b) Year 2: Adapt PACT intervention and conduct feasibility study
c) Year 3: Conduct follow-up focus groups, analyse and write up all results
d) Year 4: PhD write up and protocol for RCT

One representative publication from each co-supervisor:

Godfrey E, Galea Holmes M, Wileman V, et al. Physiotherapy informed by Acceptance and Commitment Therapy (PACT): protocol for a randomised controlled trial of PACT versus usual physiotherapy care for adults with chronic low back pain. BMJ Open 2016; 6: e011548. doi:10.1136/bmjopen-2016-011548

Yu, L., Norton, S., Almarzooqi, S., McCracken, L. M. (2017). Preliminary investigation of pain acceptance and self-as-context in people with fibromyalgia. British Journal of Pain.

9.5 How do muscles sense force in order to grow strong?

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Co-Supervisor 1B: Prof Mathias Gautel
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http://www.kcl.ac.uk/lsm/research/divisions/randall/research/sections/signalling/gautel/index.aspx

Project Description:

Muscles grow in response to high force exercise, but how the muscle senses force and how this then triggers growth is unknown. We recently developed a zebrafish larva model in which a single bought of force generation triggers 30% muscle growth in 24 hours and rapidly changes expression of a novel cohort of mechanosensitive genes. We now want to understand the molecular mechanism(s) driving growth. We know that both cell size and number increases during the growth, implicating regulation of muscle stem cell function, and that the TORC1 general growth pathway is required.

Project objectives will use our series of recently-created CRISPR/Cas9 genome edited mutants and fluorescent reporter transgenes to test hypotheses on:

a) the mechanism of TORC1 involvement (Year 1),
b) the role of titin, a muscle mechanotransducer located in the sarcomere (Year 2),
c) how the growth stimulus regulates muscle stem cells by analysis of the cell autonomy of gene action (Year 3),
d) how the muscle senses physical force (Year 4).

New genome editing will be used to screen other candidate mechanosensitive cohort genes for roles in muscle growth (Years 1-4).

Skills to be acquired. To analyse mutants the student will learn a series of approaches already used in the PI's laboratories: i) developmental genetics, ii) molecular biology, iii) 4D confocal microscopy, iv) stem cell biology, v) high-throughput RNAseq and other bioinformatic analysis.
By understanding force-dependent muscle growth, we aim to develop therapies for muscle diseases and to preserve muscle function in the elderly.

One representative publication from each co-supervisor:
*Pipalia, T.G., *Koth, J., Roy, S.D., Hammond, C.L.. Kawakami, K. and **S.M. Hughes** (2016) Cellular dynamics of regeneration reveals role of two distinct Pax7 stem cell populations in larval zebrafish

muscle repair. ***Disease Mod. Mech***. 9: 671-684. doi: 10.1242/dmm.022251 PMID: 27149989

Pernigo, S., Fukuzawa, A., Beedle, A.E., Holt, A., Round, A., Pandini, A., Garcia-Manyes, S., **Gautel, M.**, and Steiner, R.A., Binding of myomesin to obscurin-like-1 at the muscle M-band provides a strategy for isoform-specific mechanical protection. ***Structure***, 2017. **25**(1): 107-120. doi: 10.1016/j.str.2016.11.015**.** PMID: 27989621

10.5 A novel marine natural product that targets bone cells for the management of osteoporosis and metabolic bone disease.

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Co-Supervisor 1B: Professor Paul Long
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Name of Collaborating Clinician (if not one of the two co-supervisors) Dr Geeta Hampson
Research Division or CAG: GRIIDA
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Website: https://kclpure.kcl.ac.uk/portal/en/persons/geeta-hampson.html
Summary of role: Measurement of biochemical markers of bone turnover (Wnt inhibitors, RANKL, OPG) used clinically in the evaluation of the efficacy of anti-osteoporotic drugs and investigation of their mechanisms of action. Use of primary blood monocytes from patients for evaluation of bone cell activity *in vitro*.

Project Description:

The maintenance of the adult skeleton is largely controlled by cells that degrade bone called osteoclasts. Abnormal activation of osteoclasts leads to a host of diseases characterised by bone loss, including osteoporosis, arthritis and cancer metastases to bone. Targeting osteoclasts with specific inhibitors therefore remains a significant unmet need in musculoskeletal medicine, specifically for debilitating bone diseases that affect millions of people worldwide. We are working on a family of natural products called chondropsins from a Great Barrier Reef sponge. In particular, natural products from marine sponges show exceptional promise as potential pharmaceuticals. Our preliminary data show that chondropsins potently inhibit the ability of osteoclasts to resorb bone by targeting essential V-ATPase activity and autophagic pathways. Based on this, **the aim of this project is to use chondropsins as tools to manipulate bone cell activity both in vitro and in vivo, and provide mechanistic data that underpin development of novel antiresorptive drugs.** The project provides training for the student in multidisciplinary yet complementary skills of cell and molecular aspects of bone cell biology (Grigoriadis), natural product chemistry and pharmacology (Long), and analysis of compound efficacy from clinical osteoporotic samples (Hampson), to achieve the following project goals:

Years 1,2 – Identifying the mechanism of action of chondropsins *in vitro*, pharmacology, functional osteoclast assays, role of autophagy.

Years 2,3 – *In vivo* validation of chondropsin as an antiresorptive drug using mouse models of osteoporosis and osteoporotic patient-derived osteoclasts.

Year 4 – final data confirmation and writing up.

One representative publication from each co-supervisor:

Grigoriadis AE, Kennedy M, Bozec A, Brunton F, Stenbeck G, Park I-H, Wagner EF, Keller GM. 2010. Directed differentiation of hematopoietic precursors and functional osteoclasts from human ES and iPS cells. Blood, 115: 2769-2776.

Weston AJ, Dunlap WC, Beltran VH, Starcevic A, Hranueli D, Ward M, Long PF.
Proteomics links the redox state to calcium signaling during bleaching of the scleractinian coral *Acropora microphthalma* on exposure to high solar irradiance and thermal stress. Mol Cell Proteomics. 2015;14(3):585-95. doi: 10.1074/mcp.M114.043125.

11.5 Impact of critical care on peripheral muscle strength

Co-Supervisor 1A: Dr Gerrard Rafferty
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Co-Supervisor 1B: Professor Nicholas Hart
Research Division or CAG: Asthma Allergy & Lung Biology
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Project Description:
Skeletal muscle wasting and weakness occurs in up to 65% of ICU patients and is a major complication of critical illness. Intensive care unit-acquired weakness (ICU-AW) influences not only short term but also long-term clinical outcomes, contributing to 'post intensive care syndrome' a collection of common health disorders of which muscle weakness is a significant component. Muscle force generation is influenced by multiple factors and while the anatomical and physiological characteristics of muscle itself are significant determinants of strength, the central nervous system also plays an important role.

Research examining ICU-AW has focused primarily on peripheral neuromuscular function while much less is known regarding potentially important neurological changes within the central nervous system (CNS). Studies in healthy subjects employing short periods of limb immobilisation have described decrements in muscle strength greater than that expected from the degree of muscle atrophy observed. Such reductions in strength are, therefore, potentially due to reduced neural drive to the muscle from the CNS.

The proposed study examines the impact of critical illness on muscle strength and central nervous system and motor cortex function in patients following critical illness in relation to ICU-AW. Training in a broad range of human physiological technique to assess muscle strength and architecture and physical function will be provided including electrical and magnetic motor nerve stimulation and force assessment as well as transcranial magnetic stimulation. Year 1 training, study setup and commencement of data acquisition in controls. Year 2 - 3 patient data acquisition. Year 3-4 completion of data acquisition and PhD thesis preparation.

One representative publication from each co-supervisor:
Maddocks M, Jones M, Snell T, Connolly B, de Wolf-Linder S, Moxham J & **Rafferty GF**. (2014). Ankle dorsiflexor muscle size, composition and force with ageing and chronic obstructive pulmonary disease. *Experimental Physiology* **99,** 1078-1088.

Puthucheary ZA, Rawal J, McPhail M, Connolly B, Ratnayake G, Chan P, Hopkinson NS, Phadke R, Dew T, Sidhu PS, Velloso C, Seymour J, Agley CC, Selby A, Limb M, Edwards LM, Smith K, Rowlerson A, Rennie MJ, Moxham J, Harridge SD, **Hart N** & Montgomery HE. (2013). Acute skeletal muscle wasting in critical illness. *JAMA* **310,** 1591-1600.