Project Details	
Project Code	MRC23IIAREx Beall
Title	Pharmacological targeting of AMP-activated protein kinase for immune cell regulation in Type 1 Diabetes
Research Theme	Infection, Immunity, Antimicrobial Resistance and Repair
Summary	The ambition of this project is to discover new approaches to dampen the immune-mediated attack on the pancreatic beta cell seen in type-1 diabetes. Using immune cells from healthy and diabetic pre-clinical research models, this project will employ pharmacological approaches to measure production of inflammatory and cytotoxic molecules as well as assessment of how novel drugs affect immunometabolism, an emerging area of research involved in many diseases.
Description	In Type 1 Diabetes (T1D), the immune system targets and kills pancreatic beta cells. The coordinated action of a number of different immune cells play a role in beta cell death including macrophages and T cells, which release factors that ultimately lead to beta cell death. One emerging therapeutic target is an enzyme called AMP-activated protein kinase (AMPK). The enzyme is activated by energy stress and once active, the kinase limits energy consumption by switching off energy consuming processes such as protein synthesis and fatty acid synthesis and stimulates energy-producing pathways such as fatty acid oxidation or by enhancing glucose uptake into the cell. Importantly pharmacological activation of AMPK increases glucose uptake into skeletal muscle, by enhancing glucose transporter 4 (GLUT4) translocation to the plasma membrane. This has led to significant interest in developing AMPK activators for treatment of Type 2 diabetes, with a number of drug companies recently reporting glucose-lowering benefits of AMPK activators in models of diabetes and in people with type 2 diabetes. New data: We have new unpublished data demonstrating for the first time that pharmacological activation of AMPK in bone marrow-derived macrophages suppresses the release of a key pro-inflammatory cytokine called macrophage migration inhibitory factor (MIF). Importantly, MIF knockout animals are protected from developing auto-immune diabetes, which taken together with our new data suggest that perhaps AMPK activation, which already looks like an attractive target for treating type 2 diabetes, may also be useful for preventing or delaying the onset of type 1 diabetes. Student ownership: In this project, the candidate will have the opportunity to interrogate how pharmacological AMPK activation alters MIF release from macrophages and/or other cells such as dendritic cells, T cells or even within the pancreatic beta cells themselves. They will then have the opportunity to direct the project towards their interest by examining the role of AMPK activation, MIF signalling in other immune cells relevant to project. This could involve examining of cellular metabolism using extracellular flux analysis or examining cellular signalling cascades using Western blotting, gene expression and ELISAs. The student could also perform live cell calcium imaging analyses as well as fixed cell and tissue analysis using confocal and wide-field microscopy or high throughput multiplex image analyses. There is scope for performing co-cultures of different types of immune cells and the possibility to progress to an in vivo study, should the data support this. In addition, the candidate will be supported to obtain a

	Home Office personal licence and receive training and encouraged to shadow in vivo studies in other groups should they wish to. Key research questions: Is MIF release altered in bone-derived macrophages isolated from pre-diabetic and diabetic NOD mice, and can altering AMPK activity influence MIF release? Does macrophage-specific manipulation of AMPK alter T cell activation? Techniques available to learn: primary cell/tissue isolation aseptic cell culture, Western blotting, ELISA, live cell calcium imaging, fixed cell/tissue imaging using confocal and wide-field microscopy, extracellular flux analyses, in vivo metabolic measures.
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