Q1: Please provide project supervisors contact details. These may be used by potential applicants wishing to discuss the project with you.

Supervisor 1 name: Professor Peter Jones
Supervisor 1 telephone: 02078 486273
Supervisor 1 email: peter.jones@kcl.ac.uk
Supervisor 1 organisation: King's College London
Number of PhD students/completions: >25

Supervisor 2 name: Dr Pratik Choudhary
Supervisor 2 telephone: 02078 485639
Supervisor 2 email: Pratik.choudhary@kcl.ac.uk
Supervisor 2 organisation: King's College London, King's College Hospital

Q2: Any additional supervisors, contact details and organisation

Dr Aileen King
Telephone: 02078 486402
Email: Aileen.king@kcl.ac.uk
Organisation: King's College London
Role in project: Dr King is an expert on animal models of diabetes and islet transplantation, and has been developing the use of constant glucose monitoring in mouse models.

Q3: Title of Research Project

Improving the outcomes of human islet transplantation as a therapy for Type 1 diabetes

Q4: Name of BRC Cluster the project sits under

Cluster 1 - Advanced Therapeutics and Experimental Medicine

Q5: Which BRC Themes does your project align with? Tick all that apply

Transplantation, Regenerative Medicine And Cellular Therapy
Q6: **Abstract of Research Project (max 500 words)**

Allogeneic islet transplantation is a novel treatment for people with Type 1 Diabetes (T1D). However, using current protocols, it is estimated that up to 50% of the islets are lost or malfunction in the first few days after transplantation. We have recently demonstrated improvements in islet function and transplantation outcomes in rodent models using Mesenchymal Stromal Cells (MSCs), and identified several mechanisms for these beneficial effects, including MSC-derived extracellular matrix and soluble secreted factors. Our current studies are directed towards refining a cocktail of MSC-derived molecules which, by pre-treating islets prior to transplantation, will improve islet survival and function in the all-important immediate post-transplantation period without the necessity for co-transplanting MSCs with the islet graft, thus avoiding issues of co-delivery of islets and MSCs to the intraportal site. We have now identified and characterised a number of MSC-derived biotherapeutic molecules which improve islet survival and/or function, both singly and in combination, including Annexin-A1 (ANXA1), CXCL-12, and Wnt5A.(1) We have already demonstrated qualitative similarities between human and mouse MSC secretomes using unbiased qRT-PCR gene screening methods (2) and demonstrated that selected molecules such as ANXA1 have similar beneficial effects on human and mouse islets. This project will translate these experimental observations in rodent models into clinically relevant human islet models; we will demonstrate improved efficiency of human islet grafts in a mouse model of diabetes; and conduct a proof – of –concept - first in human trial.

Initial experiments will optimise the cocktail of MSC derived factors using human islets and adipose MSCs. We will then assess the ability of the cocktail-treated human islets to regulate blood glucose in immune-compromised, diabetic SCID mice. Variability between human islet preparations in terms of insulin content and secretion means that commonly applied minimal mass experimental models for assessing islet function in vivo are not suitable for assessing human islet function. We will therefore use state of the art implantable continuous glucose sensors and radio-telemetry which is far more sensitive in revealing the impact of these factors on graft function than conventional minimal mass transplant models2. This innovative approach places the KCL group well ahead of our competitors in the ability to assess graft function in vivo.

During the pre-clinical phase, we will obtain MHRA approval to perform five first-in-man islet transplants using islets co-cultured with the MSC cocktail. This will be a safety trial, evaluating islet and patient safety looking at tolerability of the MSC co-factors (eg ANXA1, Wnt-5A are already approved for human use in other indications). We will measure insulin secretion pre-culture, at 24 – hours post culture and then assess islet graft function as per usual NHS protocols using mixed meal tests to measure stimulated C-peptide at 1, 3, 6, 9 and 12 months. We have tacit approval from the UKITC, a consortium of all the islet transplant centres in the UK for being able to offer this study to their patients. This preliminary safety trial will provide pilot data for a larger randomised trial that will be powered to show improved graft performance.

Q7: **Please provide up to three key references relevant to proposed work**


Q8: Outline the Departmental/Divisional research training and in-house research support in relation to this project

This PhD project will be performed within the environment of a large research group with excellent facilities for training and development. The Diabetes Research Group has an outstanding track record of mentoring postgraduate research students and we are justifiably proud of our 100% track record of completion within four years of registration. Among our current grant-maintained staff we currently have four independent Research Fellows, six other postdoctoral researchers and ten postgraduate research (PhD) students. This critical mass of young researchers encourages them to interact with, and learn from, each other as well as from the older, more experienced PIs in the Group, and to form friendships and collaborations that will continue long after they have left King’s College London. A number of formal mechanisms also exist to ensure appropriate training, progression and career development for our postgraduate students, which are co-ordinated and delivered by the Graduate School, as detailed at this URL http://www.kcl.ac.uk/study/graduate-school/researcher-development/index.aspx

Q9: Summarise the translational and experimental medicine component of the research, as well as the relevance of the project to the BRC Research Cluster(s)

One major strength of this project is the long-standing collaboration between basic scientists (PJ, AK) and clinical scientists (PC) which will ensure that the basic experimental observations are translated into improved clinical islet transplantation protocols. The supervisory team has internationally acknowledged expertise in the molecular/cell biology of islets and MSCs (PJ); in animal models of diabetes and islet transplantation (AK); and in human islet isolation and clinical transplantation (PC), placing us in a unique position in the UK to deliver this project and to capitalise on the outcomes. Our access to the KCL Human Islet Transplantation Programme and to the UKITC, a consortium of all the islet transplant centres in the UK, (via PC) will give us a direct translational route for data generated during the pre-clinical phase of the project. During the pre-clinical phase, we will obtain MHRA approval to perform five first-in-man islet transplants using islets co-cultured with the MSC cocktail. We have tacit approval from the UKITC for being able to offer this study to their patients. This preliminary safety trial will provide pilot data for a larger randomised trial that will be powered to show improved graft performance. This project is of obvious relevance to the Experimental Medicine Cluster, and the Transplantation and Cell Therapy Themes.

Q10: Please provide a KCL budget code relevant to the project Respondent skipped this question

Q11: Supervisor 1 details: Number of current PhD Student you are first supervisor for in each year 1-4

Year 4, one
Year 3, one

Q12: Supervisor 1: Students you have been supervisor for who have completed since October 2002 (Number completed and number who have completed within 4 years)

Thirteen as first supervisor; 12 graduated within 4 years, one currently submitted within 4 years awaiting examination.

Q13: Supervisor 2 details: Number of current PhD Student you are first supervisor for in each year 1-4

Year 3, one

Q14: Supervisor 2: Students you have been supervisor for who have completed since October 2002 (Number completed and number who have completed within 4 years)

Three, all completed within 4 years
Q15: Please provide project supervisors contact details - which can be used by potential applicants wishing to discuss the projects

Peter Jones peter.jones@kcl.ac.uk
http://www.kcl.ac.uk/lsm/research/divisions/dns/about/people/Profiles/peterjones.aspx

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