Harnessing the proteinuria-reducing actions of Interferon beta to develop new treatments for kidney and cardiovascular disease.

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Environment
The Academic Renal Unit in Bristol is one of the premier renal research laboratories in the UK. We are internationally renowned for our work on kidney diseases resulting in proteinuria and on the glomerular pathophysiology which underlies them. We are a dynamic group of around 40 researchers, both clinicians and pure scientists, providing an excellent environment for an enjoyable, rewarding and productive research training. We expect our PhD student to publish their work in high impact journals. This project benefits from considerable preliminary data close to being ready for publication meaning that the student working on it can expect to generate papers relatively early in the course of their studies. The particular small protein GTPase we have identified and referred to below cannot be specified here for confidentiality reasons.

Background
We have shown previously that interferon beta (IFNβ) has powerful anti-proteinuric actions in three distinct rat models of glomerular disease,3 and more recently that IFNβ is similarly effective in other glomerular diseases (unpublished). In the absence of evidence of reduced inflammation in vivo, we hypothesised that IFNβ reduced proteinuria through direct effects on cells of the glomerular filtration barrier (GFB). We confirmed such effects on GFB cells to enhance their barrier integrity to macromolecules.3 More recently we have shown that IFNβ reduces permeability of glomerular endothelial cells (GEnC) and podocytes in vitro via a particular small protein GTPase.

Hypotheses
i) IFNβ, signalling through a particular small protein GTPase, enhances barrier properties of GEnC by actions on the glycocalyx and on podocytes by actions on the cytoskeleton and junctional adhesion molecules
ii) Expression of active small protein GTPase in GEnC or podocytes in vivo protects against proteinuria
iii) IFNβ reduces permeability in human glomeruli

Novel specific therapies for proteinuric renal disease are urgently required. Before the therapeutic promise of IFNβ (or analogues) can be realised, more detailed understanding of its actions is required. Our results will reveal key intermediaries which could be exploited more cost-effectively than by IFNβ itself and will form the basis for subsequent clinical trials.

Summary
Interferon beta (IFNβ) has powerful anti-proteinuric effects in animal models of glomerular disease. From in vitro studies in glomerular endothelial cells (GEnC) and podocytes, these effects appear to be through direct effects on glomerular cells acting through activation of a particular small protein GTPase. The overall aim of the project is to characterise the potential of IFNβ, and IFNβ-activated intracellular pathways, for application in anti-proteinuric therapies. The key goals of the project are i) to define the effector pathways in
GENC and podocytes which are activated downstream a particular small protein GTPase to modulate barrier properties, ii) confirm that a particular small protein GTPase activation is anti-proteinuric in glomerular disease in vivo and iii) to demonstrate that IFNβ also reverses permeability defects in human glomeruli. Detailed in vitro studies using unique conditionally immortalised human glomerular endothelial cells and podocytes will define IFNβ effects on endothelial glycocalyx and on morphology, signalling pathways and effector molecules downstream of a particular small protein GTPase (particularly the actin cytoskeleton and podocyte slit-diaphragm molecules) respectively. We will use a transgenic mouse model expressing the constitutively active small protein GTPase under control of the tetracycline-response operon promoter element in conjunction with podocyte and GENC-specific rtTA-expressing mice to generate mice in which the particular small protein GTPase can be inducibly and specifically activated in either podocytes or GENC. We will then directly test the anti-proteinuric effects of the particular small protein GTPase activation in diabetes. We will confirm that IFNβ modulates permeability via the particular small protein GTPase in human glomeruli. This study will provide essential data on which to base clinical trials of IFNβ in human glomerular disease and rational design of new drugs for proteinuric renal disease.

Experimental approaches
The project will include training in a wide range of laboratory techniques for example cell culture, western blotting, qPCR, processing of tissue samples, isolation of glomeruli cells including by FACS, immunofluorescence, confocal and electron microscopy, qPCR arrays, permeability assays, molecular biology to prepare constructs for viral delivery and models of diabetes amongst others.

References


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