

Project Title:	Peroxisome Proliferator-Activated Receptor-gamma: a novel therapeutic target for asthma?
Project Ref:	08-246-02
Cost:	£92,094
Lead Applicant & Institution:	Professor Alan Knox Centre for Respiratory Medicine University of Nottingham
Start Date:	1 January 2010
Plain English Summary:	<p>Asthma is one of the commonest chronic diseases to affect people in more developed countries. It is an important cause of illness in children as well as adults and can lead to absence from school and work, frequent hospital visits and continues to cause a significant number of deaths. The annual cost to the NHS of providing care for people with asthma has been estimated to be around £1 billion. Although many people with asthma are treated effectively, a sizeable proportion of people struggle with poorly controlled asthma, which greatly affects their quality of life and leads to substantial use of NHS resources. New effective ways of treating asthma are needed.</p> <p>Studies in the laboratory that we and others have carried out using cells grown from the airways of people with asthma have shown that drugs that stimulate a certain receptor (called peroxisome proliferator-activated receptor-gamma or PPAR-gamma) have anti-inflammatory effects and could, therefore, be useful in the treatment of asthma. The proposed project will determine whether the effects seen in the laboratory can also be seen in people with asthma. This will involve us carrying out a small clinical trial in which 100 people with asthma are given either pioglitazone (a drug that stimulates the PPAR-gamma receptor) or a placebo (dummy treatment that looks like the pioglitazone treatment but doesn't contain active drug) for 12 weeks. We will then measure markers of asthma control (for example lung function) and effects on markers of inflammation in sputum samples in the group of patients who were given pioglitazone and the group who were given the dummy treatment and compare these measures between the groups using statistical tests. This will help us to determine whether drugs that stimulate these receptors could become a completely new approach for the treatment of asthma.</p> <p>The project will be carried out by a team of researchers with a strong track record of successfully designing and completing clinical studies in patients with asthma and other respiratory diseases. It will be conducted in state of the art research facilities at the University of Nottingham and will benefit from the recent award of a Biomedical Research Unit in Respiratory diseases, a £6.1 million investment by the National Institute for Health</p>

	<p>Research. Specifically, the project will be supported by a dedicated research nurse and doctor, other members of the clinical trials research team and will also benefit from established clinical trials resources and state of the art research facilities.</p>
<p>Abstract:</p>	<p>This study will translate molecular pathophysiology studies from our group identifying peroxisome proliferator-activated receptor (PPAR) -gamma as a potential drug target in asthma. The key question is whether stimulation of PPAR-gamma receptors produce measurable biological airway and clinical responses in patients with asthma that would justify exploring PPAR-gamma stimulation as a novel therapeutic modality</p> <p><u>Design:</u> Randomized, double blind, placebo controlled two parallel group clinical trial</p> <p><u>Setting:</u> Nottingham University Hospitals NHS Trust.</p> <p><u>Target population:</u> People aged 18-75 of either sex with a clinical diagnosis of asthma, FEV1 60 % predicted or higher and an increase in FEV1 of greater than 12 % following inhaled salbutamol 400mcg or PEF variability > 12 % during run-in taking 0 to 800 mcg inhaled beclometasone dipropionate or equivalent and as required short acting beta agonist. The exclusion criteria will be inability to produce a sputum sample on induction, current smoking, > 10 pack years smoking history, treatment with leukotriene antagonists, liver or cardiovascular disease, oral steroid treatment or exacerbation within 6 weeks, females who are pregnant, lactating or not using adequate contraception, any contra-indication to pioglitazone and lactose intolerance.</p> <p><u>Interventions being evaluated:</u> Active intervention: 30 mg pioglitazone daily for 4 weeks, increasing to 45 mg pioglitazone daily for 8 weeks. Placebo intervention: placebo matching 30 mg pioglitazone daily for 4 weeks followed by placebo matching 45 mg pioglitazone daily for 8 weeks. Participants will be randomised to one or other intervention using a web-based randomisation system and allocation concealed by blinding of participants and investigators.</p> <p><u>Measurement of clinical outcomes and duration of follow-up:</u></p> <p><u>Primary outcome:</u> FEV1 at 12 weeks.</p> <p><u>Secondary outcomes:</u> daily asthma symptoms, mean morning and evening PEF, Juniper Asthma Control Questionnaire and Asthma Quality of Life Questionnaire scores, exhaled nitric oxide level, bronchial hyper-responsiveness, induced sputum cell counts & analysis detailed below, BMI, glucose & adverse effects. Follow up will take place at 0, 4, 8, 12, & 16 weeks for data collection.</p> <p><u>Additional Laboratory Outcomes:</u> Our previous studies have suggested that the mechanism of action of PPAR-gamma agonists in vitro involves effects on gene transcription. Gene transcription is a complex process involving binding of transcription factors to their recognition sequences on gene promoters. Access to these recognition sequences requires DNA to unravel and this process is controlled by covalent modification of core histone molecules around which DNA is wrapped. The most important covalent modification is acetylation of histone H4 which is regulated by two competing groups of enzymes, histone acetyl transferases (HATs) and histone deacetylases (HDACs). HATs increase transcription whereas HDACs reduce it. In our studies of eotaxin we found that acetylation of histone H4 was reduced by PPAR agonists but we have not determined whether this is due to a reduced HAT</p>

	<p>or increased HDAC activity. To examine things further we will perform studies in cells obtained from induced sputum to analyse 1) HDAC and HAT activities by HDAC Fluorescent Activity Assay Kit (BIOMOL) and HAT Assay Kit (Upstate Biotechnology). We have shown from preliminary experiments that we can obtain enough cells from induced sputum for these assays. 2) PPAR-gamma activation (nuclear translocation) by western blotting. This will be conducted on a subset of samples from each group to confirm the effect of pioglitazone. We will also perform studies in supernatant obtained from induced sputum to analyse 1) the concentration of chemokines (eotaxin, MCP-1, IP-10) and growth factors (VEGF) by ELISA; 2) effector mediators (cyst-leukotriens, eosinophil cationic protein (ECP) and histamine) by radio-immuno assay. These analyses will be conducted with samples obtained from participants at baseline and week 12 (end of each treatment). The results will be normalised against total cell numbers to allow comparison.</p> <p><u>Sample Size:</u> Assuming the SD of differences in FEV1 over 12 weeks is 250 (Clin Exp Allergy 2003;33:1355-9) a study with 88 participants will allow us to detect a difference between treatments of 150 ml with 80 % power at 5 % two sided significance level. 100 subjects will be recruited to allow for drop-outs and some participants using inhaled steroids.</p> <p><u>Planned Analyses:</u> The analysis of the primary response variable (FEV1 at 12 weeks) will be performed using a General Linear Model incorporating terms for baseline value, treatment arm, stratum, and baseline characteristics which are thought a priori to strongly predict outcome. Secondary response variables will be treated similarly, after transformation to approximate Normality as required (as, for example with PD20, Percentage eosinophil count and exhaled NO concentrations). Mean morning and evening PEFR and the percentage of days and nights free of symptoms and relief inhaler use will be calculated for the 14 days prior to each visit and analysed as above. All analyses will be performed using Stata v10. No interim or sub-group analyses are planned for efficacy. Trial data will be monitored by DMEC for safety.</p> <p><u>Project Timetables And Recruitment Rate:</u> Already completed: All study related documentation produced and approved by Nottingham Research Ethics committee 2; quote for production of active and placebo IMP obtained. In progress: R&D review at Nottingham University Hospitals NHS Trust; MHRA review of CTA application. 0 to 52 weeks: 100 participants identified, screened, randomized and run through trial with a recruitment rate of approximately 2 per week (ie randomisation of 25, 50, 75 and 100 participants by 3, 6, 9 and 12 months respectively). 52 to 68 weeks: participants continue to run through study with the last participant completing by 68 weeks. 68 to 78 weeks: Double data entry, Data checks, Source document verification. 78 to 88 weeks: Analysis of data. 88 to 98 weeks: Presentation of findings at an international conference and preparation of paper for publication in a peer-reviewed journal. Our estimated recruitment rate is based on a recently completed clinical trial of 400 participants with asthma for which we had similar participant selection criteria to the proposed trial.</p>
<p>ISRCTN: (if applicable)</p>	<p>80109258</p>
<p>Project Protocol:</p>	<p>www.eme.ac.uk/projectfiles/0824602protocol.pdf</p>

Project website: (if applicable)	To follow
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