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## MRC/AZ compound collaboration

### Case studies

#### Hope for millions of people suffering from chronic cough

Lead researcher: Dr Jacky Smith, University of Manchester

AZ compound: [AZD3355](#) (GABABR1 receptor agonist)

Project type: small clinical trial

Scientists from the University of Manchester will conduct a small clinical trial of a new treatment for chronic cough, using an AstraZeneca compound developed to treat acid reflux (heartburn).

Cough is the single most common reason that people seek medical care. It is thought that up to 23 per cent of the population suffer from chronic coughing (lasting longer than eight weeks), which can have a huge impact on their quality of life. Yet remarkably little is understood about the mechanism behind the human cough reflex.

Previous work by Dr Smith's team has shown that in around half of people with chronic cough, the cough reflex is triggered by another condition known as gastro-oesophageal reflux, where the stomach contents escape back up into the food pipe causing a burning sensation.

Most people with oesophageal reflux suffer from heartburn and are treated with acid suppressants, but these fail to dampen the cough reflex in people with chronic cough suggesting acid is not the problem.

This project will study a new drug, known as a GABA-B receptor agonist, which was developed to reduce the gastro-oesophageal reflux. In previous clinical trials, this medicine was not found to be helpful in patients with heartburn who were already taking acid-blocking treatments, but may improve cough which has been triggered by the reflux.

Scientists will test the medication in both healthy volunteers and in chronic cough patients, who will be monitored using a small device worn round the waist which records coughing sounds over a 24-hour period. If these studies show this GABA-B receptor agonist improves chronic cough, the researchers will aim to carry out larger clinical trials.

Dr Smith said: "My team and I are very excited to be involved in this innovative collaboration between the MRC and Astra-Zeneca. The treatment of chronic cough is extremely challenging, and effective, well-tolerated treatments are a significant unmet need. This project will improve our understanding of mechanisms in chronic cough and assess a potential new treatment."

For more information, or to speak to Dr Smith, contact Hannah Isom in the MRC Press Office on 0207 395 2274 (07818 428 297 out of hours) or email [press.office@headoffice.mrc.ac.uk](mailto:press.office@headoffice.mrc.ac.uk)

## **Lung disease drug could be re-purposed to treat Muscular Dystrophies**

Lead researcher: Professor Dominic Wells, Royal Veterinary College, University of London.

AZ compound: [AZD1236](#) (Matrix metallopeptidase 9/12 [MMP9/MMP12] inhibitor).  
Project type: pre-clinical study in mouse models.

For the rare genetic diseases that fall under the umbrella term muscular dystrophy (MD), there are currently no approved drugs that prevent the progressive muscle wastage that eventually leads to severe disability and premature death.

There are more than 30 types of MD, of varying severity. Each is caused by a mutation in the patient's genes, which causes their muscles to become fragile and break down over time.

Even when the destroyed muscle tissue tries to repair itself, the process doesn't work properly and leads to the formation of non-functional scar tissue. If this affects the muscles that control the heart or breathing, the condition becomes life-threatening.

Researchers at the Royal Veterinary College, University of London believe they may be able to interrupt this gradual deterioration by blocking one of the enzymes involved in the formation of scar tissue.

They will use a drug, developed by AstraZeneca to treat a type of lung disease known as chronic obstructive pulmonary disease, in mouse models of two types of MD (Duchenne and Limb Girdle MD), to see if they can slow progression of the disease.

If successful, the study will provide the evidence they need to plan human trials of the drug, with the ultimate aim of giving all MD patients a better quality, longer life.

For more information, or to speak to Professor Wells, contact Hannah Isom in the MRC Press Office on 0207 395 2274 (07818 428 297 out of hours) or email [press.office@headoffice.mrc.ac.uk](mailto:press.office@headoffice.mrc.ac.uk)

## **A new approach to treating Alzheimer's by improving brain blood flow**

Lead researcher: Professor Seth Love, University of Bristol  
AZ compound: [zibotentan](#) (Endothelin A Receptor Antagonist)  
Project type: pre-clinical proof-of-concept

Researchers led by Professor Seth Love at the University of Bristol will investigate whether a compound originally evaluated by AstraZeneca for the treatment of prostate cancer could delay, or even reverse, the progression of Alzheimer's disease by improving blood flow through the brain.

Alzheimer's is the most common form of dementia. It is thought to affect around half a million people in the UK and its occurrence in the population is on the rise. It occurs when protein plaques and tangles develop in the brain, damaging the nerve cells. No-one knows exactly what causes the disease, in which there is build up of a protein called amyloid beta (Abeta) in the brain.

Prof Love and his colleagues have been investigating why blood flow through the brain is reduced in people with Alzheimer's. The more severe this reduction, the worse their symptoms and the more rapidly the disease progresses. In recent studies the group has found that the Abeta causes cells in the brain to overproduce enzymes that act on blood vessels in the brain and cause them to narrow.

By blocking the action of these enzymes, the scientists hope they can restore blood flow to the brain and improve cognitive function (or at least slow the decline). This is a completely new approach to treating Alzheimer's as most people are currently treated with drugs that increase levels of chemical messengers known as neurotransmitters in the brain.

This Bristol-based collaborative study will test the AstraZeneca compound (zibotentan), and another drug (losartan) developed to treat high blood pressure, to assess whether they are capable of blocking the effects of Abeta on brain blood flow. If successful, the researchers hope to secure funds to carry out a randomised controlled trial in patients with Alzheimer's disease to see whether zibotentan can halt or slow the dementia and improve their quality of life.

Professor Love said: "We were delighted to have the chance to collaborate with AstraZeneca on such an exciting project. We now have a great opportunity to test a fundamentally new approach to Alzheimer's treatment that if successful could be rapidly translated into the clinic."

For more information, or to speak to Professor Love, contact Hannah Isom in the MRC Press Office on 0207 395 2274 (07818 428 297 out of hours) or email [press.office@headoffice.mrc.ac.uk](mailto:press.office@headoffice.mrc.ac.uk)