

Research Award: ADAM33 inhibitor and crystal structure project

Awarded to: Hans Michael Haitchi **Amount:** £23,100

Lay summary

AAIR Grant Award 2013/2016 “ADAM33 inhibitor and crystal structure project” – “Discovery of novel ADAM33 inhibitors as potential new treatment for asthma”, awarded to Associate Professor Dr Hans Michael Haitchi in support of postdoctoral research fellow Rajendra Gosain from the department of chemistry.

Asthma is a very common disease in the UK, which runs in families suggesting an underlying genetic contribution. The aim of our work is to understand how an asthma gene, known as ‘ADAM33’, contributes to the development of asthma. We have shown that the ‘faulty’ ADAM33 protein is not only increased in asthmatic lungs but plays an important role in driving the structural changes (remodelling) that occur in the airways of asthmatic patients. The aim of this project was to discover new chemical agents that can inhibit the ‘faulty’ ADAM33 protein and can be developed as a new asthma therapy.

Raj Gosain, a medicinal and structural chemist from the University of Southampton, was supported by this grant to discover new drugs that can block ADAM33. The ‘faulty’ ADAM33 protein is an enzyme with a unique protein structure that can cleave other proteins. We used a special computer program that allowed us to study new chemicals that would fit into this unique ADAM33 protein structure. For this we searched large databases of known chemical structures and found two lead drugs that we made and optimised in our chemical laboratory.

We then tested these drugs as blocker for the ‘faulty’ ADAM33 protein in petri dishes in our laboratory. Both were very potent. We also sent the drugs to a company in the USA to test them on other proteins that are similar to ADAM33. We showed that these two drugs are highly specific for blocking ADAM33.

Based on these newly discovered drugs we applied for further funding from the Medical Research Council and Wellcome Trust as part of specific new drug development schemes. Our aim has been to further develop and test these drugs in our ADAM33 mouse models. We got very positive feedback for our applications, but both funders wanted to see more experimental data.

We have also been in discussion with international pharmaceutical industry for starting collaborations around our work of ADAM33 and we will use our exciting preliminary data for further grant applications.

Presentations

R Gosain, ER Davies, I Tews, G Chen, P Gale, ST Holgate, JA Whitsett, DE Davies, HM Haitchi. Development of novel ADAM33 inhibitors as airway anti-remodelling treatment in asthma. UoS/UHS Translational Clinical Research Conference, Southampton, 13 Nov 2013.

External grants applied for

- Medical Research Council (MRC) Developmental Pathway Funding Scheme Grant: Novel and selective small molecules inhibitors of ADAM33 for prevention or treatment of airway remodelling in asthma. PI: HM Haitchi, Co-PI: DE Davies, I Tews, PA Gale, R Gosain, M Bradley, Industrial partner: Synairgen. Applied July 2013 with positive feedback and invitation to reapply. Revised application: Aug 2014, not successful.
- Wellcome Trust Seeding Drug Discovery Award: Novel and selective small molecule inhibitors of ADAM33-metalloprotease for prevention or treatment of airway remodelling in asthma. PI: HM Haitchi, Co-PI: DE Davies, I Tews, PA Gale, R Gosain, M Bradley, Industrial partner: Synairgen. Preliminary application: Nov 2014, not successful.
- MRC Confidence in Concept (CiC), University of Southampton: Development of ADAM33 inhibitors for treatment of airway remodelling in asthma. PI: HM Haitchi, Co-PI: DE Davies, I Tews. Applied June 2017, not successful.

Discussions with international pharmaceutical companies of further developments of our lead compounds as ADAM33 inhibitors.
