International Headache Society

FELLOWSHIP REPORT FORM

Please complete this form giving details of your IHS Fellowship.

Personal details

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Fellowship

Dates of fellowship	1st of October 2015 – 30th of September 2016
Institution name	Erasmus Medical Centre, Rotterdam, The Netherlands
Mentor name	Dr. Antoinette MaassenVanDenBrink
Title of study	PUREMEDY

Research details

Short summary of initial plan (max 200 words)
The long term aim of **PUREMEDY** is to identify novel purinergic targets as a migraine remedy that will not affect the heart. Current treatments are all vasoconstrictors, contraindicated in people with cardiovascular disease. Therefore, we aimed to explore novel migraine remedy targets, and to focus on the purinergic receptors (receptors for nucleotides and nucleosides). To find possible purinergic targets for migraine remedy that does not affect the human heart, the first aim was to characterize the receptor profile of the coronary circulation. Thereafter, in vivo measurements on the contractility of the middle meningeal artery was planned to be performed. We planned to explore differences between ex vivo and the new in vivo measurements which could indicate involvement of other factors, e.g. mast cells, intervening trigeminal nerves or purinergic induction of CGRP release, with also focus on gender differences. Our final aim was to investigate whether ATP and purinergic receptors could be migraine triggers and pain modulators in the trigeminal ganglion, which is believed to be a strong participant in migraine pathophysiology.

Short summary of your actual research (max 200 words)

We have investigated potential purinergic anti-migraine targets. The focus has been on the P2Y13 and the P2Y14 receptor. Little is known on the P2Y14 receptor, so we did a full characterization in the human coronary circulation and bypass grafts where it, unlike for rodents, did not cause any contractions. In the meningeal artery, it produced dilation *per se*; we did not yet investigate its effect on CGRP release. The ligand for P2Y13, ADPβS, is known to be devoid of contractile properties in the human coronary circulation. In the human middle meningeal artery it caused a minor contraction. Using periarterial electrical nerve stimulation and closed skull videomicroscopy, ADPβS could inhibit CGRP release from the sensory neurons surrounding the rat middle meningeal artery. Adenosine, a nucleoside, causes vasodilation of the middle meningeal artery; however this has not been shown *in vivo*. We showed that caffeine inhibits the dilation and that A_{2A} and A_1 receptors are important in the vasodilatory response. As a side project, we also studied purinergic changes in vascular ageing. The main finding is that P2Y13 appears to be an interesting small molecule anti-migraine target, that will be devoid of coronary side effects, and therefore is a potential anti-migraine target.

Overview of activities on a monthly basis

1st quarter
Large myograph/dissection training
Characterization of the human coronary arteries from explanted hearts
Human middle meningeal artery characterization
2nd quarter
Intravital training and pilot
Adenosine intravital
Human middle meningeal characterization
Ageing in the coronary circulation
3rd quarter
Intravital P2Y13, P2X and olcegepant studies
Human bypass artery characterization, focus on P2Y14
Human middle meningeal characterization
Ageing in the coronary circulation
4th quarter
Writing of manuscripts (adenosine + P2Y14)
CGRP release from rat hemiskull pilot (to be continued in DK)
Human middle meningeal artery characterization

More detailed description: The initial experiments were focused on characterizing the coronary circulation, and we also started in the middle meningeal artery (which we usually got around 2-3 per month), using both larger organ baths and Mulvany mygraphs. The results from the coronary circulation combined with the human bypass arteries has resulted in a manuscript: **Effects of UDP-glucose in human coronary and coronary bypass arteries.** Furthermore, we characterized the effect of caffeine on the middle meningeal, together with some previous results this resulted in the manuscript: **Characterization of several adenosine A_{2A} receptor antagonists using an *in vivo* pharmacological model of migraine.** The combined experiments of the human middle meningeal artery and the intravital microscopy, lead to the finding that the P2Y13 ligand, ADPβS, caused a minor contraction in the human artery, but more interestingly could inhibit CGRP release. This work is in the progress of being written to a manuscript which will be named: **Targeting the purinergic P2Y13 receptor has potential antimigraine effects.** In addition, I had the pleasure of collaborating with Dr. Anton Roks, which gave me insight in the field of aging with particular focus on the vasculature. Here I did some studies on age-related changes in purinergic signalling in the coronary circulation, for which I also will be a co-author in the coming manuscript. We have so far published a letter (see below for reference), commenting on the second CGRP receptor in the trigeminal system, which might have implications for understanding the complex role of CGRP in migraine.

Haanes KA, Chan KY, MaassenVanDenBrink A. **Comment on "A second trigeminal CGRP receptor: function and expression of the AMY1 receptor".** Ann Clin Transl Neurol. 2016 Feb 26;3(4):307-8. doi: 10.1002/acn3.286 eCollection 2016.

Has the Fellowship met all your initial aims?
The fellowship met the two main aims; The scientific aim of finding a possible purinergic anti-migraine target and the career aim of creating a solid collaboration combined with methodological and theoretical knowledge-transfer. Not all the scientific aims where met fully. We could not do a full investigation of the purinergic receptors in the rat meningeal circulation, due to animal regulations changes at Erasmus, however, we performed the most important and crucial experiments. We did not have the possibility to study the ATP levels of the trigeminal ganglion, although that is now one of the foci for the future research. Finally, due to animal protocol regulations, experiments where only performed in male animals, although we initially planned to include female rats.
What, if any, problems did you encounter
Generally the stay was very fruitful and most practicalities went without any problems. However, the main obstacle to perform some of the experiment where changes in the animal experiment regulations at Erasmus MC, which caused a limitation on the experiments that could be performed. Nevertheless, this did not prevent a successful outcome of the fellowship, and we have several publications and our main aim was met.
How will the fellowship affect your future career?
All in all the fellowship had a great scientific outcome, with many upcoming publications, which is important in building a scientific career. In addition I developed a lot on a personal level, giving me motivation for my future research career. I had the pleasure of spending time with Prof. Carlos Villalon who was a visiting professor during the initial month of the fellowship, and we developed a joined project, which we will be followed up in the coming years. I was also involved in supervision of two new PhD students, which was very fruitful and will continue for 3 more years. Last but not least, it was rewarding to learn from Dr. Antoinette MaassenVanDenBrink, particularly on the importance of including the circulation and particularly the coronary circulation in the pursuit for new anti-migraine treatments. She has also further motivated me to continue research within both coronary and migraine research. I am now back in Denmark where I will co-supervise a PhD student focusing on migraine research and my own project will be more focused on coronary research. I believe that the IHS fellowship was an important part of my post doc giving valuable abroad experience.
What would you recommend to future IHS Fellowship applicants?
I highly recommend the IHS fellowship; it has given a great contribution to my career development. Also, since the fellowship is of rather limited time, at least for basic science 1 year is not that long; the fellowship needs to be focused. Like I did, go to a place where methods are running, this greatly increases the chance of success. Although a minor point, ensure that the experimental permission for animals, and your animal experimental license addressed before you arrive.
Please include five photos/images of your stay