International Headache Society

FELLOWSHIP REPORT FORM

Please complete this form giving details of your IHS Fellowship.

Personal details

Name	Inge Mulder
Nationality	Dutch

Fellowship

Dates of fellowship	Okt 2017 – Okt 2018
Institution name	Neurovascular Research Lab, Dept of Radiology, Mass General Hospital, Harvard Med School, USA
Mentor name	Cenk Ayata, MD PhD
Title of study	CGRP antagonism and the outcome after (transient) cerebral ischemia

Research details

Short summary of initial plan (max 200 words)
Migraine headache is thought to be caused by activation of the trigeminovascular system. Upon activation, calcitonin gene-related peptide (CGRP) is released. Blocking CGRP is a promising new therapeutic strategy for acute as well as chronic migraine. However, concerns exist about the safety of such a CGRP-blockade, as CGRP is believed to act as a cardio/cerebrovascular safeguard as a vasodilator. It is unknown whether mild or brief ischemic attacks (TIAs) that otherwise would not lead to infarcts or be small might evolve into larger lesions when CGRP is blocked. In this study, we aim to investigate the effect of chronic and acute blockade of CGRP on: (1) resting cerebral blood flow, (2) cerebral blood flow defect during focal cerebral arterial occlusion, and (3) focal ischemic tissue and neurological outcomes, in both wild type (WT) and familial hemiplegic migraine type 1 (FHM1) knock-in mice. We will employ cutting-edge full-field optical imaging tools, such as laser speckle flowmetry, to measure and two-dimensionally map cerebral blood flow in real time during middle cerebral artery occlusion.
Short summary of your actual research (max 200 words)
I've been able to investigate the effect of acute blockade of the CGRP-receptor on: (1) Resting cerebral blood flow, heart rate and blood pressure (2) Cerebral blood flow defect during focal cerebral arterial occlusion (3) Ischemic tissue and neurological outcomes in infarct and TIA brains, in both wild type (WT) and familial hemiplegic migraine type 1 (FHM1) knock-in mice, in young and old mice

(5) Two different dosages of Olcegepant and 3 different dosages of a second CGRP-receptor blocking agent Rimegepant were investigated.
To establish all these experiments, we've used 319 mice.

Overview of activities on a monthly basis

The first three months mainly consisted of getting familiar with the lab and all experimental equipment, training, setting up my experiments, performing surgeries and get reproducible outcomes (training and pilot experiments). The 3 months thereafter I started with the real experiments, first in a low-dose Olcegepant group, later we tried a higher dose to see the effect of the CGRP-receptor blocking agent on infarct and functional outcome. After this period, I performed the TIA-experiments and finished up the infarct experiments. In the last three months I finished all TIA-experimental groups, performed additional haemodynamic baseline experiments and I could even add some additional infarct and TIA experiments with a second CGRP-receptor inhibitor to get a more solid answer to our research question.

Has the Fellowship met all your initial aims?

No, unfortunately we were not able to do the proposed chronic experiments with the CGRP-receptor blocking agent. This was because we found out that the known mABs against CGRP (or it's receptor) are not available and/or are not working in mice or rats. Besides that, the biological half-life of the small molecules we've used is too short to do a reliable chronic treatment experiment. Because these aimed experiments were not possible, there was time to perform additional experiments, for example multiple age groups, males and females, different dosages and 2 different types of drug.

What, if any, problems did you encounter

The main problem we encountered was the point discussed in the previous answer; we found out that the chronic experiments were technically not possible.

How will the fellowship affect your future career?

Having done this fellowship at a renowned institution abroad will help greatly in my future scientific career. I've learned a lot during my stay about experimental animal work for migraine and stroke (gathering practical as well as theoretical knowledge). I think an experience like this will also teach you a lot about yourself, which is extremely valuable in life. Besides that, the IHS-grant and this fellowship will definitely lift my resume when applying for grants in the future, so I can keep doing what I love the most; performing reliable and valuable research.

What would you recommend to future IHS Fellowship applicants?

I would recommend to make sure you have experience with the main experimental techniques which you'll use in the lab where you will do the fellowship. I did that as well, and it saves a lot of time so you can spend more time on your actual research experiments.
Besides that, to be able to finish a big project, a 2-year fellowship would be preferable if possible.

Please include five photos/images of your stay


HARVARD MEDICAL SCHOOL


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Tuna


BOSTON
xfinity

Signature: _____ Date: *30-10-2018*

Mentor signature: Cenk Ayata Date: *30-10-2018*