FELLOWSHIP REPORT FORM

Please complete this form giving details of your IHS Fellowship.

Personal details

<table>
<thead>
<tr>
<th>Name</th>
<th>Dr. Anisa Dehghani</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nationality</td>
<td>Iranian</td>
</tr>
<tr>
<td>Date of birth</td>
<td>16.5.1981</td>
</tr>
<tr>
<td>Full contact address</td>
<td>Rainout 18, 2202 PN, Noordwijk; Netherlands</td>
</tr>
<tr>
<td>Current working address</td>
<td>Einthovenweg 20, Building 2, room T3-54</td>
</tr>
<tr>
<td>Email address</td>
<td><a href="mailto:A.Dehghani_Mohammadi@lumc.nl">A.Dehghani_Mohammadi@lumc.nl</a></td>
</tr>
</tbody>
</table>

Fellowship

<table>
<thead>
<tr>
<th>Dates of fellowship</th>
<th>February 2019-February 2020</th>
</tr>
</thead>
<tbody>
<tr>
<td>Institution name</td>
<td>Leiden University Medical Centre, Department of Human Genetics, Migraine Group</td>
</tr>
<tr>
<td>Mentor name</td>
<td>Prof. Dr. Arn M.J.M. van den Maagdenberg</td>
</tr>
<tr>
<td>Title of study</td>
<td>Parenchymal neuroinflammation and pain behaviour upon optogenetically-induced cortical spreading depolarization in mice</td>
</tr>
</tbody>
</table>
Research details

Short summary of initial plan (max 200 words)

I focused on inducing CSD in a non-invasive manner with optogenetics to find the threshold for the induction of neuroinflammation and pain mimics in relation to the number of CSDs, without confounding factors of recent invasive surgery or the use of a restrainer. To further increase the translational value of the work we extended the research to mouse mutants that carry the S218L missense mutation in the α1A subunit of voltage-gated CavZ.1 channels that have been linked to FHM1, and can be considered a valuable mouse model to study certain aspects of migraine. Importantly, the mutant mice allowed me to investigate neuroinflammation and pain behavior in the context of a hyperexcitable brain with an increased susceptibility to CSD. I assessed the consequences of optogenetically-induced CSD on the extent of neuroinflammation in the context of HMGB1 release at different timing points, and simultaneously, the occurrence of pain-related behaviors, separately for female and male mice. To further enhance the clinical relevance of the study, I tested the effect of TAT-Panx-308, which is an interfering peptide that mimics the C-terminal epitope of Panx1 including the Y308 site and blocks activation of Panx1 channels, as a potential novel drug for the treatment of migraine.

Short summary of your actual research (max 200 words)

CSDs were non-invasively induced by optogenetic in freely moving mice. Neuroinflammatory marker HMGB1 in (sub)cortical brain areas, and neuronal activation marker pERK in trigeminal ganglia (TG) were studied by immunohistochemistry in WT and FHM1 mice with and without CSDs. Pain-related behaviors were analysed in all conditions. Effects of Panx1 channel inhibitor were examined by TAT-Panx-308. 

Results: Non-invasively triggered CSDs induced para-inflammatory responses in both FHM1 and WT mice combined with increased Mouse Grimace Scale (MGS) scores and Head Grooming (HG) but decreased Nest Building (NB) behaviors. In mutant mice, neuronal HMGB1 release was bilateral and prolonged (for 48 hours) following CSD in line with enhanced and prolonged higher scores of pain mimics and HG. Trigeminal ganglia were activated bilaterally after CSDs in both genotypes. CSD-related neuroinflammation and pain behavior were blocked by inhibitor of Panx1 channels.

I developed a novel method showing that non-invasively induced CSD triggers a para-inflammatory response that increases pain-related behaviour; both are stayed enhanced for a longer period in FHM1 mutant compared to WT. The contribution of Panx1 channel activation to this inflammatory response and pain outcome highlights its key role in aura para-inflammatory profile and migraine headache leading to a potential therapeutic route to cure migraine.

Overview of activities on a monthly basis

February 2019 : Get access to animal facility/having the licenses to start animal experiments/writing the work plan
March: Starting optogenetic surgeries and CSD experiments
April : Starting brain processing of the previous experiments and study HMGB1 release patterns
May: Opto-CSD experiments + pain-related behavioral analysis + HMGB1 imaging
June: Opto-CSD experiments + pain-related behavioral analysis + HMGB1 imaging
July: Opto-CSD experiments + pain-related behavioral analysis + HMGB1 imaging
August: Opto-CSD experiments + pain-related behavioral analysis + HMGB1 imaging
September: Opto-CSD experiments + pain-related behavioral analysis + HMGB1 quantification
October: Opto-CSD experiments + TAT-Panx1 application + behavioral analysis + HMGB1 quantification
November: Opto-CSD experiments + TAT-Panx1 application + behavioral analysis + HMGB1 quantification
December: Opto-CSD experiments + TAT-Panx1 application + behavioral analysis + HMGB1 quantification
January 2020: data analysis+ Writing the paper
Has the Fellowship met all your initial aims?

The initial plan I aimed to do also RNA sequencing but given the interesting results on HMGB1 release and pain mimics I instead increased the number of experimental groups to study the timing threshold for HMGB1 release and pain-related behavior in both genotypes and genders. Besides I added another dimension of pain-related behavior as Head Grooming and its different types such as oculotemporal strokes and laterality to investigate the importance of CSD effect on headache.

What, if any, problems did you encounter

I can say nothing except that due to very strict rules regarding animal rights in the Netherlands, in the beginning of my fellowship it took more than what I expected to get permission to have access to animal facilities and start the first animal experiment. Once the permits were in place the research really took off.

How will the fellowship affect your future career?

This fellowship allowed me to have the opportunity to work in the high-profile migraine research group in Leiden which can be an enormous boost for my career in neuroscience, and particularly in the migraine field. This will be an extremely important step for me in becoming a capable neuroscientist. By using the newest techniques related to optogenetic I could broaden my skills that I can take with me afterwards. The fellowship enabled me to investigate the pathophysiological mechanisms of migraine more efficiently, and independently and now finishing the project with high-impact publications will provide more certain opportunities and chances in my career for gaining funding for research. It also helped me to expand my network of scientists in different fields to have future joint researches together. Moreover, the fellowship made me able to participate in additional studies in the group because of my specific skills and this was an additional way to boost my career. Now, I can stay longer in Prof. van den Maagdenberg group because the results of the IHS grant will be used in a follow-up study.

What would you recommend to future IHS Fellowship applicants?

Write their proposal as precise as they can; use their imagination and all the possible techniques in the desired lab to invent new strategies and way of thinking about biology, neurophysiology and phenotype of all kinds of headache including Migraine. Try to find novel approaches in headache medication and combine it with state of the art technology, to make it possible deciphering still unknown mechanisms of migraine with aura and migraine without aura in respect to target the one with least undesirable side effect as a potential therapeutic approach.

Please include five photos/images of your stay

Signature: [Signature] Date: 20.2.2020

Mentor signature: [Signature] Date: 20-02-2020