Please complete this form giving details of your IHS Fellowship.

**Personal details**

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**Fellowship**

<table>
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<tr>
<th>Dates of fellowship</th>
<th>January 20, 2017-February 7, 2018</th>
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<tr>
<td>Institution name</td>
<td>Neurovascular Research Laboratory, Harvard Medical School-Massachusetts General Hospital</td>
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Research details

## Short summary of initial plan (max 200 words)

Sulfotransferases (SULTs), are enzymes that detoxify drugs and chemicals which also play a role in the metabolism of neurotransmitters such as catecholamines (especially dopamine) which are known to alter cerebral excitability and susceptibility to cortical spreading depression (CSD), the most likely mechanism of aura and a headache trigger. Relevant to migraine pathogenesis, inhibition of SULTs, by certain food constituents may be responsible for triggering of migraine attack by such food items. Moreover, non-steroidal anti-inflammatory drugs (NSAIDs) also inhibit SULT1A enzymes. We hypothesize that SULT1A inhibition is a common mechanism by which food triggers and NSAIDs modulate migraine susceptibility, in a way that to explain food triggers of migraine attacks and medication overuse headache. We planned to dissect SULT1A modulation of CSD susceptibility in an in vivo experimental model using hesperidin, the main flavanone in orange and citrus fruits, as the common migraine food trigger, and mefenamic acid, a NSAID to simulate medication overuse headache. The study consisted of 2 experiments; in the first part, we planned to examine CSD threshold, speed, duration and amplitude after intraperitoneal (i.p.) administration of hesperidin or its vehicle. In the second part, following the administration of mefenamic acid or its vehicle (i.p.) chronically for 4 weeks, we planned to give a single dose of hesperidin or its vehicle (i.p.), in a 2x2 design and evaluate CSD susceptibility.

## Short summary of your actual research (max 200 words)

Objective: Our goal was to investigate SULT1A1 involvement in medication overuse (MO) and migraine triggers and to observe how cortical excitability is altered in MO after exposure to a trigger.

Methods: Hesperidin 100 mg/kg was used as SULT1A inhibitor found in orange juice, a migraine trigger and mefenamic acid (NSAID) 20 mg/kg, another SULT1A inhibitor, was used to induce MO. The study consisted of 3 experiments:

1. Hesperidin 100 mg/kg or its vehicle (DMSO) was administered (i.p.) and 30 min later, CSD susceptibility, speed, duration and amplitude were examined.
2. Mefenamic acid (20 mg/kg/d) or its vehicle (5% DMSO and sesame oil) was administered (i.p.) chronically for 4 weeks and on day 28, CSD susceptibility, speed, duration and amplitude were examined.
3. Mefenamic acid (20 mg/kg/d) was administered (i.p.) for 4-weeks and on day 28, hesperidin 100 mg/kg or its vehicle (DMSO) was given (i.p.). 30 min later, CSD susceptibility, speed, duration and amplitude were examined.

Results: Single dose hesperidin (100 mg/kg) exposure did not cause a statistically significant difference in CSD threshold and frequency/h when compared to its vehicle whereas chronic mefenamic acid exposure resulted in
lower CSD thresholds and higher CSD frequency/h in both hemispheres. When a single dose of hesperidin was given after 4-weeks of mefenamic acid treatment, lower CSD thresholds and higher CSD frequency/h in both hemispheres were observed compared to its vehicle. SULT1A1 enzyme activities are currently being analysed.

Conclusion: Single dose of hesperidin alone does not change CSD susceptibility, however when it is given after 4-week exposure to mefenamic acid, it results in increased CSD susceptibility. These two drugs have a synergistic effect in modulating CSD susceptibility. SULT1A inhibition may be the common mechanism by which food triggers and NSAIDs modulate migraine susceptibility.

Overview of activities on a monthly basis

February 2017: Completion of the Institutional Animal Care and Use Committee of the Massachusetts General Hospital training program

March 2017: Practice surgeries
- Femoral artery cannulation to monitor arterial blood pressure and pH, PCO$_2$ and PO$_2$ in arterial blood gas
- Tracheostomy for mechanical ventilation

April 2017: Practice Surgeries
- Craniotomy
- Microelectrode recording of cortical spreading depression

May 2017: Practice surgeries and microelectrode recordings

June 2017: CSD recordings and data collection for the first experiment of the study where I investigated the effect of single administration of hesperidin (i.p.) or its vehicle on CSD.

July 2017: First part of the experiment: Evaluation of CSD susceptibility 30 min after single dose administration of hesperidin (i.p.) or its vehicle

August 2017: First part of the experiment: Evaluation of CSD susceptibility after single dose of hesperidin (i.p.) or its vehicle

September 2017: Second part of the experiment: Evaluation of CSD susceptibility after 4 weeks administration of mefenamic acid (i.p.) or its vehicle

October 2017: Second part of the experiment: Evaluation of CSD susceptibility after 4 weeks administration of mefenamic acid (i.p.) or its vehicle

November 2017: Second part of the experiment: Evaluation of CSD susceptibility after 4 weeks administration of mefenamic acid (i.p.) or its vehicle

December 2017: Third part of the experiment: Evaluation of CSD susceptibility 30 min after a single dose of hesperidin or its vehicle was given to the animals that were chronically (4 weeks) treated with mefenamic acid (i.p.)

January 2018: Third part of the experiment: Evaluation of CSD susceptibility 30 min after a single dose of hesperidin or its vehicle was given to the animals that were chronically (4 weeks) treated with mefenamic acid (i.p.)
Has the Fellowship met all your initial aims?

This fellowship was a wonderful opportunity to conduct my research project in one of the best places which hosts a strong neuroscience research program. I had the chance to work with state-of-the-art electrophysiological tools to execute my project. This fellowship allowed me to gain new laboratory and basic research skills and expertise in “in vivo” electrophysiology and improve my scientific judgement. This year was a great step for my scientific career and personal development. The fellowship also provided me an opportunity to learn other cultures which I found really interesting. I started to learn Portuguese from my Brazilian friends. I worked in an environment that embraced different cultures with an open mind. Working with people all around the world during this fellowship broadened my vision. During this year, I also attended 18th Congress of the International Headache Society as an invited speaker for “Neurophysiology in Primary Headaches” session. It was a great platform for me to share my work on “Somatosensory Temporal Discrimination”. I think that this fellowship met all of my expectations and will help me meet my career goals. My mentor Dr. Ayata inspired and encouraged me to pursue a career in research. As a whole it was a great life experience. I can not thank the International Headache Society enough for such a tremendous opportunity.

What, if any, problems did you encounter

Even though I encountered some problems, my mentor Dr. Ayata helped me a great deal to overcome them with his comprehensive knowledge and foresight. One-to one meetings with my mentor to discuss about my data and progress and weekly lab meetings were of great help to overcome the challenges that you can not avoid when conducting a basic scientific research.

How will the fellowship affect your future career?

This fellowship was of a great benefit to my scientific career and personal education. I want to continue to work in multidimensional and translational headache research to better understand the pathophysiology of migraine and other headache disorders. In my opinion, integrating clinical care and basic science research has been extremely rewarding and I hope to continue this path. Certainly this experience will improve my future research projects. The knowledge and experience I gained over this year will aid me to pursue my academic career in the headache field and to contribute to the advancement of headache science in my country.

What would you recommend to future IHS Fellowship applicants?

The fellowship helps you to achieve your set goals and define your future goals and evaluate your own strengths and weaknesses. Working with researchers from all around the world, exchanging ideas, helping each other was invaluable. It was a once-in-a-lifetime experience. I strongly recommend them to apply
without hesitation. Since one year is a very limited period of time for basic research, I advise them to make plans in advance and work according to it and stay focused. It is also essential to choose the right institution which is well-equipped for your study.

Please include five photos/images of your stay

Some of my best memories from 2017