MEK inhibitors as therapeutic agents and diagnostic tools for hemoglobinopathies, including thalassemia

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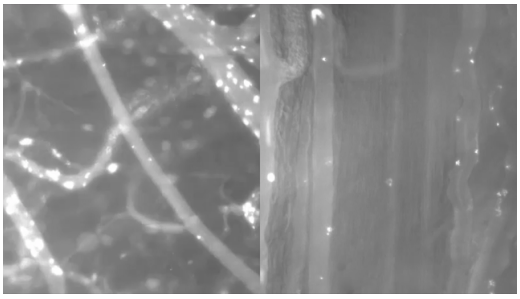

Value Proposition

Patients with sickle cell disease experience acute vaso-occlusive “crises”, which lead to significant pain, multiple organ damage, and eventually organ failure. Such crises are caused largely by their abnormal sickle red blood cells, which play an active role in vascular obstruction. The exact mechanisms by which sickle red cells stimulate blockade of small vessels are not known. Therefore, there are currently no clear therapeutic targets and no target-dierected therapies to prevent or treat vaso-occlusive crises.

Technology

Dr. Zennadi showed that in addition to targeting ERK1/2, two additional targets of this pathway in sickle red cells can be abnormally activated and could act upstream of ERK1/2 to mediate abnormal adhesion of sickle red cells to the endothelium and vaso-occlusion, suggesting that all these kinases could present novel potential therapeutic targets to prevent or treat painful vaso-occlusive crises associated with organ damage in patients with sickle cell disease. Animal studies and ultimately clinical trials will help us determine whether inhibiting these kinases will effectively prevent vaso-occlusion in patients with sickle cell disease.

Advantages

- A novel animal model that incorporates the use of normal or sickle red blood cells of human origin into the animal and a reliable visual readout of sickle red cell adhesion and vaso-occlusion for screening of all three targets
- Preliminary SAR surrounding the first of three targets
- A world class translational research apparatus within Duke University for Sickle Cell Disease
- Data to suggest dosing of MEK inhibitors at a fraction of the dose prescribed for the present marketed indication for these agents

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Links

- From the lab of Dr. Rahima Zennadi

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Publications

- MEK Inhibitors, Novel Anti-Adhesive Molecules, Reduce Sickle Red Blood Cell Adhesion In Vitro and In Vivo, and Vasoocclusion In Vivo (PLOS One, 2014)
- MEK Inhibitors, Novel Anti-Adhesive Molecules, Reverse Sickle Red Blood Cell Adhesion and Vaso-Occlusion in Vivo (Blood, 2014)
- Erythrocyte plasma membrane–bound ERK1/2 activation promotes ICAM-4–mediated sickle red cell adhesion to endothelium (Blood, 2012)
- Proteomic analysis of ERK1/2-mediated human sickle red blood cell membrane protein phosphorylation (Clinical Proteomics, 2012)

Patents

Patent Number: 9,592,236
Title: METHODS OF TREATING HEMOGLOBINOPATHIES
Country: United States of America

Patent Number: 10,195,204
Title: METHODS OF TREATING HEMOGLOBINOPATHIES
Country: United States of America