VUMC Spring 2014 Update

Pulmonary Arterial Hypertension Research Progress on our research currently funded by National Institutes of Health Grants

Safety and Mechanism of ACE2 to Treat PAH

In this Project, we are working on the theory that PAH can be treated by fixing cell-cell junctions in blood vessels with a drug called recombinant ACE2. Definition: Cell-cell junctions- all of our organs and body structures are made from cells. Normally, these cells (think of a balloon filled with water) line up right next to each other so that the cell membranes touch each other. Materials can flow from one cell to the next. In PAH patients it is believed that the cells in the linings of the small arteries are not able to line up together as they should.

Mutations in BMPR2, the most common cause of familial PAH, cause problems in the system that moves proteins around inside and between each cell. ACE2 may correct this problem, we are working on establishing the background information needed to be able to safely move into human trials.

Endothelial Dysfunction in PAH (Endothelial cells form the lining of blood vessels.) The goal of this project is to identify blood-based and other methods to detect PAH in patients and among subjects who are healthy but at risk of developing PAH. In the past year we have made tremendous progress in terms of participant enrollment, including now over 60 subjects enrolled. In addition to blood, subjects are evaluated using a modified blood pressure and blood flow measure to determine if changes in fingertip blood flow are present in PAH patients. Study enrollment

Spotlight: Dr. James West

Dr. James West's laboratory investigates the consequences of BMPR2 mutation using a variety of genetically engineered mouse models, and cell culture derived from both human pulmonary hypertension patients and mouse models, with a focus on downstream molecular consequences of BMPR2 mutation.

Spring 2014

- Safety and Mechanism of ACE2 to Treat PAH
- Endothelial Dysfunction in PAH
- Genetic Variations in Pulmonary Arterial Hypertension (PAH)
- *Spotlight:* Dr. James West Dr. Eric Austin & Dr. Rizwan Hamid

Fall 2014

- Introduction to Educational Series
- Metformin Study
- Vaso Responders vs. Non Responders
- *Spotlight:* Dr. Anna Hemnes Dr. Evan Brittain

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continues to move forward and we appreciate your participation. With your support we continue to enroll subjects and collect samples for our studies. Thank you all for your participation and enthusiasm. Both DeWayne Ames and Shannon Cordell actively enroll subjects in the clinics and in the General Clinical Research Center of Vanderbilt in this project.

as direct investigations of de-identified human samples generously donated by our research participants. As with all of our studies, our genetics work involves a number of collaborations in North America and Europe, as well. Over the past year, we have made progress on a large number of fronts, including better understanding of why our mouse and cell-based models are good

Spotlight: Drs. Eric Austin & Rizwan Hamid

The long-term objectives of genetic studies are to better understand the factors that play a role in the pathogenesis of PAH and to use that information to improve disease diagnosis and therapy.

Genetic Variations in Pulmonary Arterial Hypertension (PAH)

This broad project includes multiple studies which examine changes in genes and gene expression which may cause or aggravate PAH. The various studies include mouse and cell-based studies, as well as direct investigations of de-identified human samples generously donated by our research participants. As with all of our studies, our genetics work involves a number of collaborations in North America and Europe, as well. Over the past year, we have made progress on a large number of fronts, including better understanding of why our mouse and cell-based models are good representations of human PAH, new discoveries of genes which cause PAH, as well as some promising information as to why some subjects respond to medications differently than others.

Check out our new website:
https://medschool.vanderbilt.edu/pah/

If you have questions, concerns, or comments about this research; please contact Lisa Wheeler, Study Coordinator: 800-288-0378 or lisa.wheeler@vanderbilt.edu.

We will be attending the PHA's International Conference in June 2014. Please come see us in the research room!

Recent Publication Highlights

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Role of BMPR2 alternative splicing in heritable pulmonary arterial hypertension penetrance. Circulation. 2012 Oct 9;126(15):1907-16. Cogan, J.

Metabolomic analysis of bone morphogenetic protein receptor type 2 mutations in human pulmonary endothelium reveals widespread metabolic reprogramming. Pulm Circ. 2012 Apr-Jun;2(2):201-13. Fessel JP.

Right ventricular plasticity and functional imaging. Pulm Circ. 2012 Jul;2(3):309-26. Brittain, EL.

Genome-wide association analysis identifies a susceptibility locus for pulmonary arterial hypertension. Nat Genet. 2013 May;45(5):518-21. doi: 10.1038/ng.2581. Epub 2013 Mar 17. Germain, M. Austin, ED.

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