

VUMC Spring 2015 Update

Pulmonary Arterial Hypertension Research: Progress on our research funded by National Institutes of Health and other Grants

Education on the Road Series 2014-2015

Our "Education on the Road" series is coming to an end. The final event is April 11, 2015 at Manchester-Coffee County Conference Center.

We have thoroughly enjoyed meeting with patients, caretakers and family members through this series and hope that you did too! Please sign up now for the last event to ensure your

place for lunch. We will have a videographer to document this event for our website and the PHA, so please let us know in advance if you do not want to be taped. **We look forward to seeing you there!**

For more information please contact Lisa Wheeler: 1-800-288-0378
lisa.wheeler@vanderbilt.edu or visit our website:
<https://medschool.vanderbilt.edu/pah/>



Spotlight: Dr. Josh Fessel

My studies focus on the most basic functions of cells - where their energy comes from, how they make new cells or new parts of cells, and how they regulate survival and death. Our investigations probe the mechanisms that cells use to control these processes normally, and how the control of these processes is disturbed in pulmonary arterial hypertension (and in other diseases such as cancer). By understanding where and how these processes stop being normal in PAH, we hope to identify new drug targets that will show positive effects in the cells most affected by disease and that will not have negative effects in cells that are behaving more normally.

Our most recent studies have focused on the function of mitochondria - the "powerhouses" of the cell. It is in mitochondria that the food we eat is converted to energy, and where we consume most of the oxygen our body uses (this is why we need to breathe to stay alive!). We and others in the PAH research community have found that there are multiple ways in which the mitochondria in PAH function differently from those in people without PAH. In particular, the mitochondria in PAH use different fuels, and the mitochondria tend to leak more "reactive oxygen species," which are by-products of metabolism that can cause damage to cells. By understanding the details of the processes that contribute to the development of PAH, we inch closer to figuring out ways to try to halt or reverse this disease.

Spring 2015

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- **How can oxygen be a double-edged sword in pulmonary hypertension?**
- **Newly Identified Stem Cells Regulate Microvessel Blood Flow in the Lung**
- **Spotlight:**
Dr. Josh Fessel
Dr. Sue Majka

Fall 2015

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- **Spotlight:**
Dr. John Newman
Dr. James Loyd

Update: Familial forms of Pulmonary Capillary Hemangiomatosis (PCH) and Pulmonary Veno-Occlusive Disease (PVOD) two rare forms of pulmonary arterial hypertension:

PVOD affects the tiniest veins surrounding the air sacs, causing the walls of these veins to thicken and the vessel opening to narrow. PCH is a disease of the lung capillaries, the smallest blood vessels linking the arteries to the veins



surrounding the air sacs. Both diseases are rare conditions that lead to the development of pulmonary hypertension (PH). PVOD and PCH can occur in families or as sporadic cases.

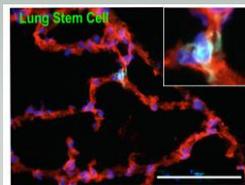
Two research groups, independently, found a genetic cause for these rare conditions. A well-established PH research group from France reported in Nature Genetics that the gene

EIF2AK4 (eukaryotic translation initiation factor 2 a kinase 4) is associated with PVOD in families showing a recessive form of transmission (2 copies of the gene must have the mutation for a person to have the disease, example cystic fibrosis). Another research group in the US (including researchers from Vanderbilt) found that EIF2AK4 appears to cause both familial and sporadic PCH in some, but not all, cases studied. The US

group now plans to look at PVOD families and sporadic subjects to see if the French finding holds true for US patients.

EIF2AK4 belongs to a family of proteins that control blood vessel growth when cells are under stress. We hope that this discovery will lead to new understanding of these two rare causes of pulmonary hypertension and, ultimately, to improved treatments.

*****Thanks for being a part of this meaningful research; we couldn't do it without you!!***



Spotlight: Dr. Susan Majka

The focus of the work in my laboratory is to understand how the normal and repair functions of lung stem cells (SC) are altered during the development and course of lung diseases including pulmonary hypertension, fibrosis and emphysema. In order to learn how these lung stem cells work we use mouse models. Additionally we use patient derived lung stem cells and induced pluripotent stem cells (stem cells made in the laboratory from easily obtained cells such as skin) as models to understand changes as a result of disease specific gene mutations.

Our laboratory has identified and characterized a unique cell population of lung stem cells. We have demonstrated that these cells are present in the area of the lung, associated with the smallest blood vessels that promote gas exchange in both mouse and human tissue. Recent studies in our lab have shown that normal function (of these lung stem cells) is to keep the smallest blood vessels in the lung working properly. When affected during the disease process these cells become abnormal, resulting in abnormal growth and causing loss of blood vessel function.

There is an increasing focus on the development of cell-based therapies to address these diseases. However, the lung is a difficult organ to utilize these types of therapies because of the many different cell types and functions. There is also a lack of understanding of how chronic disease processes affect stem cell differentiation (what stem cells become when mature). Therefore, prior to testing cell-based therapy, it is important to use research lab models of lung injury and chronic disease to determine how changes in the lung tissue during the development of disease affect the lung stem cell maturation process and function.

Recent Publication Highlights

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[EIF2AK4 mutations cause pulmonary veno-occlusive disease, a recessive form of pulmonary hypertension.](#) Eyries M, et al. Nat Genet. 2014 Jan;46(1):65-9. doi: 10.1038/ng.2844. Epub 2013 Dec 1. PMID: 24292273

[EIF2AK4 mutations in pulmonary capillary hemangiomatosis.](#) Best DH, et. al., Chest. 2014 Feb;145(2):231-6. doi: 10.1378/chest.13-2366. PMID: 24135949

[Peripheral blood signature of vasodilator-responsive pulmonary arterial hypertension.](#) Hemnes AR, et. al. Circulation. 2015 Jan 27;131(4):401-9. doi: 10.1161/CIRCULATIONAHA.114.013317. Epub 2014 Oct 31. PMID: 25361553

