# Summer Student Research Program
# Project Description

**FACULTY SPONSOR'S NAME AND DEGREE:** *Melissa Rogers, Ph.D.*
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**PROJECT TITLE (200 Characters max):**

*The Impact of Bmp2 Regulation on Development and Pathological Soft Tissue Calcification*

## HYPOTHESIS:

*We hypothesize first that deletion of "ultra-conserved sequence (UCS)"in the Bone morphogenetic protein 2 (BMP2) mRNA will (1) disrupt embronic development & (2) induce BMP signaling and thus increase pathological soft tissue calcification. Our second hypothesis is that BMP signaling is elevated in conditions that stimulate calcifications such as aging and renal disease.*

## PROJECT DESCRIPTION **(Include design, methodology, data collection, techniques, data analysis to be employed and evaluation and interpretation methodology)**

*Bone morphogenetic protein 2 (BMP2) is an essential signal in neonatal development and adult physiology. Abnormal BMP2 levels cause birth defects, including lethal congenital malformations of the heart and other organs. Excessive BMP2 levels in the blood vasculature and coronary valves promote pathological calcification (e.g., atherosclerosis). A sequence within the regulatory part of the gene has been largely unchanged since fishes and mammals diverged, the "ultra-conserved sequence" (UCS). One role is to turn off BMP2 synthesis in clinically relevant cell types (e.g., proepicardium, epicardium, heart valves, and vascular cells). We have generated a transgenic mouse strain with a Bmp2 gene in which the UCS can be deleted. Analyses of the new Bmp2 allele determined that the UCS strongly influences embryogenesis and represses calcification in adult tissues. Our aim for this summer project is to test how UCS deletion influences BMP signaling, the level of soft tissue calcification, and tissue structure and function. A student also may investigate the impact of microRNAs that function via the UCS to repress Bmp2.*

**SPONSOR'S MOST RECENT PUBLICATIONS RELEVANT TO THIS RESEARCH:**

1. *Rogers, M. B., TA Shah, NN Shaikh. Turning Bone Morphogenetic Protein 2 (BMP2) On and Off in Mesenchymal Cells. Journal of Cellular Biochemistry 116(10):2127-38 (2015)*
*2. Fotinos, A, Fritz, DT, Lisica, S, Liu, Y, Rogers, M. B. Competing Repressive Factors Control Bone Morphogenetic Protein 2 (BMP2) in Mesenchymal Cells Journal of Cellular Biochemistry, 117:439–447 (2016)*
*3. Y Zhu, TA Shah, NN Shaikh, MA. Harris, SE Harris, MB Rogers. Characterization of New Bone Morphogenetic Protein (Bmp)-2 Regulatory Alleles. Submitted (2017)*

**IS THIS PROJECT SUPPORTED BY EXTRAMURAL FUNDS?**

**Yes** ☒ **or** **No** ☐

***(IF YES, PLEASE SUPPLY THE GRANTING AGENCY'S NAME)***

*"BMP2 Gene Regulation in Calcific Aortic Valve Disease"*
*Multiple Principal Investigators: Melissa B. Rogers, Ph.D. and Douglas Mortlock, Ph.D, Vanderbilt National Heart, Lung, and Blood Institute, 1R01HL114751; 07/01/2012 – 06/31/2017*
The goal is to understand the transcriptional and post-transcriptional mechanisms that control BMP2 in the developing and adult aortic valves.

*"Regulation of BMP2 in CKD Induced Calcification in the Klotho Aging Model"*
*Principal Investigator: Melissa B. Rogers, Ph.D.*
*National Institute on Aging, 1R56AG050762-01A1, 09/15/16 - 08/31/17*
The goal is to understand the post-transcriptional mechanisms that repress BMP2 in the aorta of normal aged mice and of mice with the Klotho-null premature aging phenotype.

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**THIS PROJECT IS:** ☐ **Clinical** ☒ **Laboratory** ☐ **Behavioral** ☐ **Other**

**THIS PROJECT IS CANCER-RELATED** ☒

**Please explain Cancer relevance**

*BMP2 levels are abnormally elevated in human lung tumors relative to non-malignant lung tissue. In vitro and in vivo experiments and patient studies indicate that elevated levels of BMP2 that BMP2 promotes lung tumor tumorigenesis and bone metastases. New preventative and therapeutic targets are needed for pathologies influenced by BMP2. The BMP2 regulatory mechanisms that are disrupted in our transgenic mice also are relevant to the regulation of BMP2 in cancers. Therefore findings revealed in cardiovascular tissues will identify specific hypotheses that will be tested in other tissues, such as normal and oncogenically transformed lung cells.*

**THIS PROJECT IS HEART, LUNG & BLOOD- RELATED** ☒

**Please explain Heart, Lung, Blood relevance**

*Congenital cardiovascular defects occur in a quarter of all infants who die from a birth defect. BMP2 is a critical signal whose concentration influences the carefully shaping of heart valves and the cardiac vasculature. The proposed study will greatly advance our understanding of how BMP2 regulates cell fate determination and tissue organization in the developing heart.*

*Vascular pathologies associated with atherosclerosis, coronary artery disease, post-angioplasty restenosis, diabetes, hypercholesterolemia, and chronic kidney disease are major causes of stroke, amputation, heart disease, and death. BMP2 is a critical protein whose concentration influences vascular cell behavior. This new allele will be used to illuminate the signaling processes that regulate the behavior of vascular cells and potentially reveal novel approaches to preventing and treating these devastating pathologies.*

**THIS PROJECT EMPLOYS RADIOISOTOPES** ☐

**THIS PROJECT INVOLVES THE USE OF ANIMALS** ☐
**PENDING** ☐ **APPROVED** ☒ **IACUC PROTOCOL #** 15069A1D0618

**THIS PROJECT INVOLVES THE USE OF HUMAN SUBJECTS** ☐
**PENDING** ☐ **APPROVED** ☐ **IRB PROTOCOL #**

**THIS PROJECT IS SUITABLE FOR:**

| | | | |
|---|---|---|---|
| UNDERGRADUATE STUDENTS | ☐ | ENTERING FRESHMAN | ☐ |
| SOPHMORES | ☐ | ALL STUDENTS | ☒ |

**THIS PROJECT IS WORK-STUDY:** **Yes** ☒ **or** **No** ☐

**THIS PROJECT WILL BE POSTED DURING ACADEMIC YEAR**

**FOR INTERESTED VOLUNTEERS?:** **Yes** ☒ **or** **No** ☐

**WHAT WILL THE STUDENT LEARN FROM THIS EXPERIENCE?**

*Molecular and cellular techniques. Animal breeding and embryology. Relevance of growth factors to pathologies.*