OMB No. 0925-0001/0002 (Rev. 08/12 Approved Through 8/31/2015)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: S. Paul Oh

eRA COMMONS USER NAME (credential, e.g., agency login): SUKPOH

POSITION TITLE: Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Korea University, Seoul, Korea	B.S.	02/1985	Chemistry
Harvard University, Cambridge, MA	Ph.D.	06/1993	Cell & Dev. Biology
Massachusetts General Hospital	Post Doctoral	06/1993~10/1997	Cardiovascular Research

A. Personal Statement

My laboratory has been dedicated for studying two genetic vascular diseases caused by the deficiency of TGF-β family receptors; hereditary hemorrhagic telangiectasia (HHT, a vascular disease with dilated lumen and thin arterial vessel walls) and pulmonary arterial hypertension (PAH, a vascular disease with narrowed or occluded lumen and thickened arterial vessel walls). During graduate and postdoctoral training periods, I had received intense trainings for every aspect of the gene targeting technology, and generated numerous mutant strains. Since I moved to University of Florida as an Assistant Professor in 1997, I have been studying the role of TGF-β family receptors in vascular development and pathogenesis of HHT and PAH. HHT is caused by heterozygous mutations in endoglin (*ENG*), activin receptor-like kinase 1 (*ALK1*), or *SMAD4* genes. However, precise pathogenetic mechanisms underlying HHT remain elusive; and thus, treatment options for this malady are limited. *The ultimate goal of my laboratory is to develop novel therapeutic reagents for treating HHT patients.* To reach this goal we set out the following five stepwise goals: 1) development of mouse models that reproduce clinical features of vascular lesions found in HHT patients; 2) elucidation of pathogenetic mechanisms that underlie the vascular malformations using the animal model; 3) discovery of potential therapeutic targets that can prevent or reverse the pathology based on the mechanism; 4) preclinical validation of effects of the potential therapies using the animal models; 5) clinical trials of validated therapies. I have been serving as an advisory member of HHT International, a session chair and organizing committee of HHT international conferences, and an invited speaker for HHT patient conferences representing the basic science of HHT.

- Shovlin C and Oh SP (2010) Hereditary Hemorrhagic Telangiectasia. In *Humana Series-MolecularBasis of Lung Disease-Insights from Rare Disorders (Chapter 7)*, F. McCormack, editor, Humana Press
- Tual Chalot S, Oh SP, and Arthur HM* (2015) Mouse Models of HHT: Recent Advances and Future Challenges. Frontiers in Genetics. 6:1-12. PMID: 25741358
- Arthur H, Geisthoff U, Gossage JR, Hughes CC, Lacombe P, Meek ME, Oh SP, Roman BL, Trerotola SO, Velthuis S, Wooderchak-Donahue W. (2015) Executive summary of the 11th HHT international scientific conference. Angiogenesis. 18:511-24. PMID: 26391603.

B. Positions and Honors

Positions and Employment

1997 - Present Assistant Professor, Associate Professor (with Tenure; 2003), Professor (2012), Department of Physiology and Functional Genomics, University of Florida, Gainesville, FL

2008 – 2013 (adjunct) Professor, World Class University Program, Gachon University Medicine & Science, S. Korea

2013 – Present (adjunct) Professor, Lee Gil Ya Cancer Diabetes Institute, Gachon University Medicine & Science, S. Korea

Other Experience and Professional Memberships

1999 - Present Member, Center for Mammalian Genetics, University of Florida, Gainesville, FL
2004 - Present Member, Shands Cancer Center, University of Florida, Gainesville, FL
2000 - 2008 Member, AHA National Peer Review Committee
2003 - 2005 Associate Director, Transgenic Core Facility, UFSCC, Gainesville, FL
2004 - Present Ad Hoc Member, NIH study section (BDCN-2, ZRG-1, Dev2, BINP, and ZHL1)
2006 - Present Global Research and Medical Advisory Board of HHT Foundation International

Honors and Awards

1984 The Best Student in College of Natural Science, Korea University
1995 -1997 Individual National Research Service Award (NRSA), NICHD
1999 Larry Gentry Memorial Award for 3rd international conference for TGF-β NIH, Bethesda.
1999 - 2003 Scientist Development Grant, AHA (National Center)
2001 Keynote speaker, IVth International Hereditary Hemorrhagic Telangiectasia Conference, April 20-26, Tenerife, Spain
2005, 2008 Exemplary Teacher, College of Medicine, University of Florida
2009 1st Allison Raaen Memorial Lecture for Brain AVM research, UCSF
2012 PhD Thesis Mentor's Award, College of Medicine, University of Florida
2014 Keynote speaker, The 20th Workshop of the International Society for the Study of Vascular Anomalies, April 1-4, 2014, Melbourne, AU

C. Contribution to Science (* corresponding author)

O **Expression and function of ALK1:**

While I was studying the role of TGFβ family receptors in development during my postdoctoral training period I happened to take the project of generating a knockout mouse strain for *Alk1* gene. I began characterizing the Alk1-null mice before Marchuk's group published the paper demonstrating that *ALK1* is a causative gene for HHT2. My postdoc mentor, Dr. En Li, allowed me to carry the *Alk1*-KO project when I began my independent career at the University of Florida in 1997. I showed that ALK1-deficiency results in mid-gestational embryonic lethality with severe dilation of blood vessels (Oh et al, PNAS, 2000). I also reported that TGF-β1 can bind to ALK1 as well as ALK5 in HUVECs, and suggested a balance model that the TGF-β1 signal can be transduced by two type I receptors in endothelial cells (ECs), and that such a balance may play an important role in the regulation of cellular properties, e.g. proliferation and migration of ECs, during angiogenesis. This hypothesis has been tested in cultured ECs by several groups, and evolved into more complex forms. It was also shown in biochemical studies that ALK5 is required for ALK1 signaling. My laboratory later developed a lacZ reporter line, and demonstrated that vascular ECs are the primary cell type expressing Alk1, and Alk1 is predominantly expressed arterial over venous ECs (Seki et al., Circ Res, 2003). With transgenic mice, my lab demonstrated that a 9.2 kb genomic fragment including intron 2 is sufficient for arterial endothelial-specific Alk1 expression (Seki et al., Circ Res, 2004). Our group also developed a lacZ knock-in reporter line in the *Alk5* locus. We showed that Alk5 is expressed predominantly in smooth muscle layer while Alk1 is expressed in ECs of the blood vessels during embryonic development. The differential expression pattern between Alk1 and Alk5 in blood vessels challenged the ALK1-ALK5 balance hypothesis, a premise of which is a simultaneous expression of both Alk1 and Alk5 in the same cell (Seki et al., Lab Invest, 2006).

1. Oh SP*, Seki T, Goss KA, Yi Y, Imamura T, Donahoe PK, ten Dijke P, Miyazono K, Kim S, and Li E. (2000) Activin Receptor-Like Kinase-1 (ALK-1) modulates TGF-β1 signaling in regulation of angiogenesis. **Proc. Nat. Acad. Sci. (USA)** 97, 2626-2631. PMID:10716993
2. Seki T, Yun J, and Oh SP* (2003) Arterial-specific activin receptor-like kinase 1 expression suggests a novel pathogenetic mechanism for Hereditary Hemorrhagic Telangiectasia. **Circ. Res.** 93, 682-689. PMID:12970115
3. Seki T, Hong K-H, Yun J, Kim S-J, and Oh SP* (2004) Isolation of a regulatory region of activin receptor-like kinase 1 gene sufficient for arterial endothelium-specific expression. **Circ. Res.** 94, e72-77. PMID:15059937

4. Seki T, Hong K-H, and Oh SP* (2006) Non-overlapping expression patterns of two transforming growth factor β type I receptors suggest distinct roles of each receptor in the vascular development. **Lab. Invest.** 86, 116-129. PMID:16344855

- **Pathogenetic mechanisms of HHT and development of preclinical animal models for HHT:**
  To test the hypothesis that ALK5 is required for the ALK1 signaling in ECs, we deleted *Alk1*, *Alk5* or *Tgfbr2* in endothelial cells using a novel endothelial cre transgenic mouse line developed by my group. While *Alk1*-deletion resulted in late gestational embryonic lethality with vascular anomalies including AVMs, *Alk5*- or *Tgfbr2*-deletion by the same cre mice did not display any vascular defects. This data revealed that ALK1 signaling is independent from ALK5 or TGFBR2. It also suggested that TGF-β subfamily members may not be the relevant ligands of ALK1 for the pathogenesis of HHT (Park et al., Blood, 2008). In collaboration with Dr. Marchuk, we have shown that *Alk1*-heterozygous null mice develop HHT-like vascular lesions, supporting the genetic data that haploinsufficiency of ALK1 underlies HHT pathogenesis (Srinivasan et al., Hum. Mol. Gen, 2003). However, the severity, penetrance, and lesion locations are so variable; the *Alk1*-het mice are not a practical model for studying pathogenetic mechanism of HHT. We have developed a mouse model in which AVMs develop in predicted time and locations. We found that AVMs consistently develop in skin wound sites of adult mice when *Alk1*-deletion is induced. This was the first report demonstrating that AVM development requires secondary environmental factors in addition to genetic deletion of *Alk1*. We further developed a model utilizing the dorsal skinfold window chamber system with which we can observe the entire process of AVM development in real-time (Park et al., JCI, 2009). We showed that VEGF is sufficient to mimic the wound response, and VEGF neutralizing antibodies can inhibit the wound-induced AVM development in the *Alk1*-iKO model (Han et al., Angiogenesis, 2014). We reported that requirement of secondary factors such as wounding can be equally applied to *Eng* mouse models; and that endothelial cells are the primary cell type in which ALK1 or ENG functions for the establishment of proper arteriovenous networks.

1. Park SO., Lee, YJ, Seki T, Hong K-H, Fliess N, Jiang Z, Park A, Wu X, Kaartinen V, Roman B, and Oh SP*. (2008) ALK5- and TGFBR2-independent role of ALK1 in the pathogenesis of hereditary hemorrhagic telangiectasia type 2 (HHT2). **Blood** 111:633-642. **[Cover illustration]** PMID:17911384
2. Park SO, Wankhede M, Lee YJ, Choi E-J, Fliess N, Oh S-H, Walter G, Raizada MK, Sorg BS, and Oh SP*. (2009) Real-time imaging of *de novo* arteriovenous malformation in a mouse model of hereditary hemorrhagic telangiectasia. **J. Clin. Invest.** 119:3487-96. PMID:19805914
3. Han C, Choe SW, Kim YH, Acharya, AP, Keselowsky, BG, Sorg, BS, Lee YJ, and Oh SP*. (2014) VEGF neutralization can prevent and normalize arteriovenous malformations in an animal model for hereditary hemorrhagic telangiectasia 2. **Angiogenesis** 17:823-30. PMID:24957885
4. Garrido-Martin EM, Nguyen HL, Cunningham TA, Choe SW, Jiang Z, Arthur HM, Lee YJ, and Oh SP*. (2014) Common and distinctive pathogenetic features of arteriovenous malformations in HHT1 and HHT2 animal models. **ATVB** 34:2232-6. PMID:25082229

- **Angiogenesis and vascular development:**
  Using genetically engineered mouse strains (KO, cKO, reporter alleles) of TGFb family receptors and mediators, I investigated the role of TGFβ/BMP signaling on vascular development. We showed that arterial EC-specific expression pattern is conserved in umbilical and placental vessels, and Alk1 is essential for invasion of fetal vessels into the labyrinth layer and keeping separated umbilical arteries and veins (Hong et al., Lab Invest., 2007). Although TGFβ subfamily signals via TGFBR2 and ALK5 in ECs are not essential for vascular development at late gestational periods (Park et al., Blood, 2008), they play a crucial role for ECs invade into neuroepithelial layers to develop cerebral vascular network at midgestional period (Nguyen et al., Lab Invest, 2011). By generating and characterizing pulmonary endothelial cell lines in which the Alk1 gene deletion can be induced, we demonstrated that ALK1-deficient pECs more sensitively respond to angiogenic factor in terms of migration and invasion (Choi et al., PLoS One, 2013). We found that Tmem100, a transmembrane protein without known function, is a downstream target of ALK1 signaling. We lacZ reporter and conditional allele of Tmem100, we showed that Tmem100 is mainly expressed in arterial ECs similar to Alk1 (Moon et al., Genesis, 2010), but their contribution to HHT pathogenesis is limited (Moon et al., Cardiovasc Res., 2015).

1. Hong, K-H, Seki T., and Oh, S.P.* (2007) Activin receptor-like kinase 1 (ALK1) is essential for placental vascular development in mice. **Lab. Invest.** 87, 670-679. **[Cover illustration]**

2. Nguyen HL, Lee YJ, Shin JK, Lee EJ, Park SO, McCarty JH*, and Oh SP* (2011) TGF-β signaling in endothelial cells, but not in neuroepithelial cells, is essential for cerebral vascular development. **Lab. Invest.** 91:1554-63. **[Cover illustration]**
3. Choi E-J, Kim YH, Choe SW, Tak YG, Garrido-Martin EM, Chang M, Lee YJ, and Oh SP* (2013) Enhanced responses to angiogenic cues underlie the pathogenesis of hereditary hemorrhagic telangiectasia 2. **PLoS One** 10;8(5):e63138
4. Moon EH, Kim YS, Seo JY, Lee SB, Lee YJ*, and Oh SP* (2015) Limited contributions of TMEM100 as a downstream effector of ALK1 to the pathogenesis of hereditary hemorrhagic telangiectasia. **Cardiovasc Res.** 105:353-360.

- **Pulmonary hypertension:**
  Pulmonary arterial hypertension (PAH) is a rare but fatal lung disease. I became interested in PAH because a subset of HHT2 patients (ALK1 mutations) develop PAH. Genetic studies have shown that heterozygous mutations of the *BMPR2* (bone morphogenetic protein receptor type II) are associated with PAH. However, *Bmpr2*- or *Alk1*-heterozygous mice exhibited marginal or very week PAH phenotypes. To develop an animal models exhibiting more robust PAH phenotypes and to test if ECs are the primary cell type where BMPR2 responsible for homeostasis pulmonary vasculature, we employed selective EC-specific L1Cre mice, in which Cre recombinase is expressed in pulmonary ECs but not in endocardium. We showed that about a half of mice with homozygous deletion of Bmpr2 exhibited clear PAH phenotypes, indicating that EC is the primary cell type in which Bmpr2 mutations cause PAH (Hong, Circulation, 2009). Although BMPR2 is associated with PAH, involvement of BMPR2 signaling mediators was not known. With a similar approach, we demonstrated that SMAD1 is a pivotal mediator of BMPR2 for homeostasis of pulmonary vasculature. With data obtained from inducible *Bmpr2* pulmonary ECs, we proposed a balance of BMP and TGFβ for homeostasis of pulmonary vasculature (Han et al., Hypertension, 2013). Our expertise in PAH led us to collaborate with Dr. Raizada's group to demonstrate that angiotensin converting enzyme 2 (ACE2) is a potential therapeutic target for pulmonary hypertension (Yamazato Y et al, Hypertension, 2009; Ferreira et al., AJRCCM, 2009).

1. Hong K-H, Lee YJ, Park SO, Beppu H, Li E, Raizada M, Bloch KD, Oh SP*. (2008) Genetic ablation of the *Bmpr2* gene in pulmonary endothelium is sufficient to predispose to pulmonary arterial hypertension. **Circulation** 118: 722-730. PMID:18663089
2. Yamazato Y, Ferreira AJ, Hong KH, Sriramula S, Francis J, Yamazato M, Oh SP, Katovich MJ, and Raizada MK*. (2009) Prevention of pulmonary hypertension by angiotensin converting enzyme 2 gene transfer. **Hypertension** 54: 365-71.
3. Ferreira AJ, Shenoy V, Yamazato Y, Sriramula S, Francis J, Yuan L, Castellano RK, Ostrov DA, Oh SP, Katovich MJ, and Raizada MK*. (2009) Angiotensin converting enzyme 2 is a therapeutic target for the prevention of pulmonary hypertension. **Am. J. Resp. Crit. Care Med.** 179:1048-54.
4. Han C, Hong K-H, Kim YH, Kim M-J, Song C, Kim MJ, Kim S-J, Raizada M, and Oh SP*. (2013) SMAD1-deficiency in either endothelial or smooth muscle cells results in pulmonary hypertension. **Hypertension** 61:1044-52. [PMID: 23478097]

- **Mechanism of left-right asymmetry and vertebral patterning:**
  I was intensely interested in developmental biology from PhD training period. It is partly because of the Dr. Doug Melton's influence when I took his experimental embryology course at Harvard. The opportunity came when I characterized the phenotypes of KO mice for activin receptors (Acvr2a and Acvr2b) during postdoctoral training in Dr. En Li's lab. We are the first group reported about 'isomerism' on the LR axis (Oh and Li, Genes Dev., 1997). Later I took the project to UF and demonstrated that inversus viscerum (iv) mutations interact with activin receptors for controlling the LR asymmetry patterns, and that distribution of Nodal along the LR axis is a key mediator of the interaction (Oh and L1, Dev. Dyn, 2002). My lab also showed vertebral patterning is determined by a soluble factor (GDF11) via activin receptors (Oh et al., Genes Dev., 2002), by controlling the retinoic acid activities via Cyp26a at the presomitic mesoderm area (Lee at al., Dev. Biol, 2010). Due to the lack of funding support in this area of researches, I had to give up these projects.

1. Oh, S.P. and Li, E.* (1997) The signaling pathway mediated by the type IIB activin receptor controls axial patterning and lateral asymmetry in the mouse. **Gene Dev**. 11, 1812-1826
2. Oh, S.P.* and Li, E. (2002) Gene-dosage-sensitive genetic interactions between inversus viscerum (*iv*), *nodal*, and activin type IIB receptor (*ActRIIB*) genes in asymmetrical patterning of the visceral organs along the left-right axis. **Dev. Dynamics** 224, 279-290.

3. Oh SP*, Yeo C-Y, Lee YJ, Schrewe H, Whitman M, and Li, E. (2002) Activin type IIA and IIB receptors mediate Gdf11 in axial vertebral patterning. **Genes Dev.** 16, 2749-2754. PMC187472
4. Lee YJ, McPherron A, Choe S, Sakai Y, Chandraratna RA, Lee SJ, Oh SP*. (2010) Growth differentiation factor 11 signaling controls retinoic acid activity for axial vertebral development. **Dev Biol.** 347: 195-203.PMID: 20801112]

- **Complete list of publications available at:**
  http://www.ncbi.nlm.nih.gov/pubmed?term=(((Oh%20S%20OR%20Oh%20P)%20AND%20(Olsen%20B%20OR%20Kay%20E%20OR%20Li%20E))%20OR%20Oh%20SP)%20NOT%20Nam%20H

D. Research Support

- Ongoing Research Support

R01 HL128525 (PI: Oh) 7/06/2015 - 4/30/19
NIH/NHLBI
Role of Macrophages in HHT Pathogenesis and Therapy.
The major goal of this project is to investigate the roles of macrophages in the development of arteriovenous malformations in HHT mouse models by genetic and pharmacological approaches.
Role: PI

- Research Grant (PI: Oh) 2/15/15 - 02/14/16

Cure HHT Foundation Inc.
Role of Macrophages in the pathogenesis of HHT
This is a bridge funding from Cure HHT Foundation for us to continue our research for uncovering pathogenetic mechanisms of HHT and testing novel therapeutic drugs using HHT mouse models
Role: PI

- 1R01 HL105764 Jiang (PI) 4/1/2011 – 3/31/2016

NIH/NHLBI
The dichotomy of Alk1 and Alk5 signaling pathways in vascular response to injury:
The major goal of this project is to investigate the roles of TGF-β type I receptors ALK1 and ALK5 in the regulation of neointimal hyperplasia following vein graft.
Role: Co-I

- Research Grant Terada (PI) 8/15/2011 - 8/14/2016

Otsuka America Pharmateutical, Inc
Ant2 and Cancer
The major goal of this collaboration grant is to define the role of ANT2 in cancer formation and growth.
Role: Co-I

Completed Research Support (Completed in last three years)

- 3 R01 HL64024 Oh (PI) 3/15/2010 - 2/28/2015

NIH/NHLBI
Mechanism and Therapy for Arteriovenous Malformation:
The major goal of this project is to investigate the pathogenetic mechanisms underlying Hereditary Hemorrhagic Telangiectasia (HHT) and to utilize mouse models to test therapeutic potentials of several drug candidates for nose bleeding and GI hemorrhages.
Role: PI

- Postdoctoral Fellowship (PI: Garrido Martin, Sponsor: Oh) 07/01/2012 - 06/30/2014

American Heart Association
Unraveling cellular mechanisms responsible for arteriovenous malformation in hereditary hemorrhagic telangiectasia
Role: Sponsor

- Predoctoral Fellowship (PI: Kim, Sponsor: Oh) 07/01/2011 - 06/30/2013

American Heart Association
Preclinical assessment of angiopoietin2 inhibition as a potential therapy for hereditary hemorrhagic telangiectasia.
Role: Sponsor