BIOGRAPHICAL SKETCH

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NAME: Jayaraj Rajagopal

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

POSITION TITLE: Professor, Harvard Medical School

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
Harvard University, Cambridge, MA	AB, *summa*	06/1990	Biochemistry
Harvard Medical School, Boston, MA	MD	06/1994	
Massachusetts General Hospital, Boston, MA	Intern	06/1995	Internal Medicine
Massachusetts General Hospital, Boston, MA	Resident	06/1997	Internal Medicine
Massachusetts General Hospital, Boston, MA	Clinical Fellow	03/1999	Pulmonology
Massachusetts General Hospital, Boston, MA	Chief Resident	12/1999	Internal Medicine

A. Personal Statement:

I have been trained as a pulmonologist and a developmental biologist. Our laboratory focuses on lung developmental biology, stem cell biology, and Regenerative Medicine. Experimentally, we have expertise in murine genetic modeling, murine and human stem cell biology, and injury/disease modeling. Recently, we have published a revised epithelial hierarchy of the murine and human airway using single cell sequencing and lineage tracing to identify new cell types and cell subtypes, including the ionocyte and subsets of tuft and goblet cells.

We focus on the role of developmental regulators in airway regeneration and allergic, inflammatory, fibrotic, and malignant disease. Areas of interest include cell differentiation, cellular plasticity, epithelia signaling, squamous metaplasia, mucous metaplasia, and the molecular regulation of stem cell differentiation mediated by Notch and Yap signaling. Thus our proposed work on COVID-19/SARS-CoV2 infection builds on this foundation. In the area of stem cell biology we have made a number of fundamental conceptual advances: (1) that mature airway cells are plastic and can dedifferentiate into stem cells after injury, (2) that seemingly homogenous primary airway, nasal, and other basal stem cells are comprised of several unique and functional subpopulations all of which can be expanded used dual SMAD inhibition, (3) that stem cells send forward signals to other cells in a tissue to orchestrate the regenerative process.

We have also developed protocols for the long term expansion of airway basal stem cells that will permit large scale screening and mechanistic investigations that require large quantities of human airway epithelial cells. The protocols we have developed and published will be used as the platform to COVID-19/SARS-CoV2 infection.

1. Tata PR, Mou H, Pardo-Saganta A, Zhao R, Prabhu M, Law BM, Vinarsky V, Cho JL, Breton S, Sahay A, Medoff BD, **Rajagopal J.** Dedifferentiation of committed luminal epithelial cells into

functional stem cells *in vivo*. Nature, 2013;503; 218-223 (highlighted in Nature News and Views, featured in Cell Leading Edge Select and a Cell Stem Cell preview, selected as an F1000 Prime article). PMID: 24196716.

2. Pardo-Saganta A, Law BM, Tata PR, Villoria J, Saez B, Mou H, Zhao R, **Rajagopal J.** Injury Induces Direct Lineage Segregation of Functionally Distinct Airway Basal Stem/Progenitor Cell Subpopulations. Cell Stem Cell. 2015 Feb 5; 16(2):184-197. Previewed in Cell Stem Cell, 107-109. PMID: 25658372.
3. Pardo-Saganta A, Tata PR, Law BM, Saez B, Chow RD, Prabhu M, Gridley T, **Rajagopal J**. Parent Stem Cells Can Serve as Niches for their Daughter Cells. Nature 2015 July 30; 523(7562): 597-601. PMID: 26147083. Reviewed in Cell (Stem Cells Show Parental Control) 2015 Jul 30; 162(3):476-7. PMID 26232219.
4. Montoro DT, Haber AL, Biton M, Vinarsky V, Lin B, Birket SE, Yuan F, Chen S, Leung HM, Villoria J, Rogel N, Burgin G, Tsankov AM, Waghray A, Slyper M, Waldman J, Nguyen L, Dionne D, Rozenblatt-Rosen O, Tata PR, Mou H, Shivaraju M, Bihler H, Mense M, Tearney GJ, Rowe SM, Engelhardt JF, Regev A, **Rajagopal** J. A revised airway epithelial hierarchy includes CFTR-expressing ionocytes. Nature. 2018 Aug 1.560 (7718): 319-324. Highlighted in Nature News and Views). PMID: 30069044.

B. Positions and Honors

Positions and Employment

1999-2009	Instructor in Medicine, Harvard Medical School, Boston, MA
1999-2009	Assistant in Medicine, Massachusetts General Hospital, Boston, MA
2000-2004	Physician Postdoctoral Fellow, Harvard University, Dept. of Cellular and Molecular Biology, Howard Hughes Medical Institute, Cambridge, MA
2005-2009	Physician Postdoctoral Research Associate, Harvard University, Dept. of Cellular and Molecular Biology, Howard Hughes Medical Institute, Cambridge, MA
2009-present	Assistant Biologist, Center for Regenerative Medicine, MGH
2010-present	Assistant Physician, Massachusetts General Hospital, Boston, MA
2010-2015	Assistant Professor, Harvard Medical School
2010-present	Member, Biological Sciences Graduate Program, Harvard Medical School
2015-present	Associate Professor, Harvard Medical School
2018-present	Professor of Medicine, Harvard Medical School

Awards and Honors

1986-1990	John Harvard Scholarship for academic achievement of high distinction, Harvard College
1990	Henderson Prize for the Outstanding Student in Biochemical Sciences, Harvard College
1990	Hoopes Prize for Outstanding Senior Thesis, Harvard University
1990	Phi Beta Kappa, Harvard College
1990	Letters of Commendation for Excellence, Metabolism and Physiology, Harvard Medical School
2011	Wyeth Award, American Society of Transplant Surgeons
2013	Krane Award for Physician Scientists, Massachusetts General Hospital
2013	Martin Prize for Best Basic Science Paper, Massachusetts General Hospital
2014	Maroni Research Scholar Award, Massachusetts General Hospital
2014	Robertson Investigator Award, New York Stem Cell Foundation
2014	MGH Research Scholar Award, Massachusetts General Hospital
2016	Howard Hughes Faculty Scholars Award, Howard Hughes Medical Institute
2016	Outstanding Young Investigator Award, International Society for Stem Cell Research (ISSCR)

C. Contributions to Science

1. Creation of airway epithelium from patient-specific iPS cells and human primary stem cells:
There is a dearth of actual human lung tissue for study in the laboratory. We were the first group to have converted induced-pluripotent stem cells into human airway epithelium. Furthermore our iPS cells were derived using skin fibroblasts obtained from Cystic Fibrosis patients. We have also developed systems for the culture of airway basal cells that are suitable for both large scale therapeutic screening and mechanistic investigations that will require large quantities of human airway epithelial cells.

    a. Mou H, Zhao R, Sherwood R, Ahfeldt T, Lapey A, Sicilian L, Izvolsky K, Musunuru K, Cowan C, **Rajagopal J**. Generation of multipotent lung and airway progenitors from mouse ESCs and patient-specific Cystic Fibrosis iPSCs. Cell Stem Cell. 2012; 10:385-387. PMCID: PMC3474327.
    b. Mou H, Vinarsky V, Purushothama Rao T, Brazauskas K, Choi SH, Crooke AK, Zhang B, Solomon GM, Turner B, Bihler H, Harrington J, Lapey A, Channick C, Keyes C, Freund A, Artandi S, Mense M, Rowe S, Engelhardt JF, Hsu YC, **Rajagopal J**. Dual SMAD inhibition allows the long term expansion of diverse epithelial stem cells. Cell Stem Cell. 2016 Aug 4; 19(2): 217-31. PMID: 27320041.

2. Identification of new cell types and subtypes in the murine and human lung including the pulmonary ionocyte.

    5. Montoro DT, Haber AL, Biton M, Vinarsky V, Lin B, Birket SE, Yuan F, Chen S, Leung HM, Villoria J, Rogel N, Burgin G, Tsankov AM, Waghray A, Slyper M, Waldman J, Nguyen L, Dionne D, Rozenblatt-Rosen O, Tata PR, Mou H, Shivaraju M, Bihler H, Mense M, Tearney GJ, Rowe SM, Engelhardt JF, Regev A, **Rajagopal** J. A revised airway epithelial hierarchy includes CFTR-expressing ionocytes. Nature. 2018 Aug 1.560 (7718): 319-324. Highlighted in Nature News and Views). PMID: 30069044.

3. New technology development for analyzing and modulating airway epithelial cells:
When we started our work there were 2 fundamental limitations that prevented the modern study of airway regeneration. The first was the lack of an ability to image *in vivo* the regeneration process and the second was an inability to modulate genes specifically in the airway. We have overcome the first obstacle by developing a unique confocal probe that can enable real time imaging of airway epithelial regeneration. Secondly, we have developed a methodology to use inhalation gene activation to allow lung specific gene alteration. Finally, we have developed a feeder free culture system for mouse and human basal cells.
    a. Kim JK, Vinarsky V, Wain JC, Zhao R, Jung K, Choi J, Lam A, Pardo-Saganta A, Breton S, **Rajagopal J**, Yun SH. In vivo imaging of tracheal epithelial cells in mice during airway regeneration. Am J Respir Cell Mol Biol. 2012; 47:864-868. PMCID: PMC3547097.
    b. Tata PR, Pardo-Saganta A, Prabhu M, Vinarsky V, Law BM, Fontaine BA, Tager AM, **Rajagopal J.** Airway specific inducible transgene expression using aerosolized doxycycline. Am J Respir Cell Mol Biol. 2013 Am J Respir Cell Mol Biol. 2013; Dec: 49(6): 1048-1056. PMID: 23848320.

4. Adult lung regeneration and new conceptual advances in stem cell biology focusing on cellular plasticity:
Our laboratory seeks to understand how cells, within a given tissue, act in concert. The airway epithelium is comprised of a very simple lineage of 3 distinct cell types that represent each of the major functional subtypes of cells that participate in regeneration: a stem cell, a progenitor cell, and a post-mitotic differentiated cell. Thus, the model captures the simplest degree of cellular complexity necessary for the general study of dynamic intercellular processes during homeostasis and regeneration after injury. Thus far, we have reported: (1) the first demonstration in any organ that a mature cell can revert into a stem cell *in vivo*, (2) the first demonstration in any organ that stem cells can themselves serve as niches for their own daughters, (3) the first demonstration in any organ that stem cells send signals forward to their daughters, and (4) that seemingly homogeneous airway stem cells are functionally unique.

    a. Tata PR, Mou H, Pardo-Saganta A, Zhao R, Prabhu M, Law BM, Vinarsky V, Cho JL, Breton S, Sahay A, Medoff BD, **Rajagopal J.** Dedifferentiation of committed luminal epithelial cells into functional stem cells *in vivo*. Nature, 2013;503; 218-223 (highlighted in Nature News and Views, featured in Cell Leading Edge Select and a Cell Stem Cell preview, selected as an F1000 Prime article). PMID: 24196716.

b. Pardo-Saganta A, Law BM, Tata PR, Villoria J, Saez B, Mou H, Zhao R, **Rajagopal J.** Injury Induces Direct Lineage Segregation of Functionally Distinct Airway Basal Stem/Progenitor Cell Subpopulations. Cell Stem Cell. 2015 Feb 5;16(2):184-197. Previewed in Cell Stem Cell, 107-109. PMID: 25658372.
c. Pardo-Saganta A, Tata PR, Law BM, Saez B, Chow RD, Prabhu M, Gridley T, **Rajagopal J**. Parent Stem Cells Can Serve as Niches for their Daughter Cells. Nature 2015 July 30;523(7562): 597-601. PMID: 26147083. Reviewed in Cell (Stem Cells Show Parental Control) 2015 Jul 30; 162(3):476-7. PMID 26232219.

5. Lung developmental biology and cell differentiation as related to murine and human metaplasia and cancer. I have developed longstanding expertise in lung developmental biology and organogenesis. We have deciphered the role of Notch and Wnt signaling in embryonic lung development and human airway epithelial cells. We have also shown that Notch regulates mucous metaplasia (one of the 2 cardinal pathologic responses of the airway epithelium) and that Wnt regulates airway progenitor cell expansion in the embryonic airway epithelium. Most recently, we have shown that the Hippo pathway regulator Yap is absolutely required for both stem cell maintenance and identity. Yap overexpression leads to squamous metaplasia, a precursor lesion in lung cancer. Additionally, we have begun to dissect the cells of origin of various pathologic entities in murine models of lung disease including cancer and have demonstrated that cellular plasticity and metaplastic tissue changes occur in murine and human mucinous adenocarcinoma. We hope to provide a developmental framework to understand how the reactivation and distortion of normal developmental processes results in human lung diseases characterized by metaplasia.

    a. Guseh JS, Bores SA, Stanger BZ, Zhou Q, Anderson WJ, Melton DA, **Rajagopal J**. Notch signaling promotes airway mucous metaplasia and inhibits alveolar development. Development. 2009; 136:161-71. PMCID: PMC2673763.
    b. Zhao R, Fallon TR, Saladi SV, Pardo-Saganta A, Villoria J, Mou H, Vinarsky V, Gonzalez-Celeiro M, Nunna N, Hariri LP, Camargo F, Ellisen LW, **Rajagopal J.** Yap Tunes Airway Epithelial Size and Architecture by regulating the Identity, Maintenance, and Self-renewal of Stem Cells. Developmental Cell. 2014 Jul 28; 30(2): 151-65 (Also reviewed in Developmental Cell). PMID: 25043474.
    c. Pardo-Saganta A, Law BM, Gonzalez-Celeiro M, Vinarsky V, **Rajagopal J**. Ciliated cells of pseudostratified airway epithelium do not become mucous cells after ovalbumin challenge. Am J Respir Cell Mol Biol. 2013; 48:364-73. PMCID: PMC3604083.
    d. Tata PR, Chow RD, Saladi SV, Tata A, Konkimalla A, Bara A, Montoro D, Hariri LP, Shih AR, Mino-Kenudson M, Mou H, Kimura S, Ellisen LW, **Rajagopal J**. Developmental History Provides a Roadmap for the Emergence of Tumor Plasticity. Dev Cell. 2018 Mar 26;44(6):679-693.e5. doi: 10.1016/j.devcel.2018.02.024.

Complete List of Published Work in My Bibliography:
http://www.ncbi.nlm.nih.gov/pubmed/?term=jayaraj+rajagopal