BIOGRAPHICAL SKETCH

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NAME: Jeffrey D. Axelrod, M.D., Ph.D.

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

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
Brown University, Providence, RI	Sc.B.	06/1981	Biochemistry
Washington Univ. School of Medicine, St. Louis, MO	M.D., Ph.D.	06/1991	Medicine/Molecular Biology
Brigham and Women's Hospital, Boston, MA	Resident	7/1994	Clinical Pathology
Brigham and Women's Hospital, Boston, MA	Research Fellow	2/1998	Pathology
Harvard medical School, Boston, MA	Postdoctoral Fellow	2/1998	Genetics/Developmental and Cell Biology

A. Personal Statement

During development, epithelial cells in many tissues acquire a polarity orthogonal to their apical-basal axis. This polarity, referred to as planar cell polarity (PCP), or tissue polarity, is essential for normal physiological function. Early studies of PCP focused on insect epithelia, and indeed, most of our mechanistic understanding of PCP derives from the ongoing use of Drosophila as a model system. However, a range of medically important developmental defects and physiological processes are under control of PCP mechanisms that appear to conserve much or all of the mechanism uncovered in flies, driving considerable interest in studying PCP both in Drosophila and in vertebrate model systems. Genetic and molecular analyses in Drosophila have identified components of the PCP signaling mechanism, and have suggested that they may be divided into three modules. A "core" module polarizes individual cells, and coordinates polarization between neighboring cells, thereby propagating polarity locally from cell to cell. A "global" module orients the direction of polarization with the tissue axes, and a series of "tissue specific effector" modules execute tissue specific morphological polarization programs. The major focus of my lab has been the elucidation of a molecular and cell biological understanding of the mechanisms underlying PCP. We use Drosophila as a model system to take advantage of powerful genetic methods, and mice to perform comparative studies, as well as to investigate vertebrate-specific features of PCP signaling. My lab has a strong record of consistent contributions to the understanding of PCP, and a strong record of mentoring trainees, who have gone on to successfully obtain appropriate positions at the next stage of their career development.

B. Positions and Honors

Positions and Employment

1991-1994 Resident in Clinical Pathology, Brigham and Women's Hospital
1994-1995 Chief Resident in Clinical Pathology, Brigham and Women's Hospital
1994-1998 Research Fellow in Pathology, Brigham and Women's Hospital
1993-1998 Post-doctoral fellow, Department of Genetics, Harvard Medical School, Dr. Norbert Perrimon, sponsor
1998-2005 Assistant Professor of Pathology (tenure line), Stanford University School of Medicine
2005-2013 Associate Professor of Pathology (with tenure), Stanford University School of Medicine

2013-present Professor of Pathology (with tenure), Stanford University School of Medicine

Honors and Awards

1980 Phi Beta Kappa, Elected in Junior Year
1981 Sigma Xi
1981 Sc.B. Magna Cum Laude with Honors in Biochemistry
1982 NIH National Research Service Award, Medical Scientist
1991 Alpha Omega Alpha
1993-1996 NIH Clinical Investigator Award
1994 Academy of Clinical Laboratory Physicians and Scientists Paul E. Strandjord Young Investigator Award
1998 Howard Hughes Medical Institute Junior Faculty Scholars Award
1999 Connie and Bob Lurie Scholar of the Cancer Research Fund of the Damon Runyon-Walter Winchell Foundation
2004 American Society for Clinical Investigation – Election to Membership
2011 Association of American Physicians – Election to Membership
2014 American Association of University Pathologists (The Pluto Society) – Election to Membership
2014 NIH MERIT Award

Other Experience and Professional Memberships

Stanford University School of Medicine:

1998-present Faculty organizer, Current Concepts Conference (CME accredited)
1998-present Medical Scientist Training Program Committee
1998-2002 Medical Scholars Committee
2000-present Various faculty search committees, Department of Pathology
2000-present Cancer Biology Program Steering Committee
2002-2003 Chair, Medical Scholars Committee
2002-2017 Pathology Resident Selection Steering Committee
2003-2007 Cancer Biology Program, Admissions coordinator
2003-2006 Senator-at-large, Stanford University School of Medicine Faculty Senate
2003-present Advisory Committee for the Scholarly Concentration in the Molecular Basis of Medicine
2005-2011 Director of the Scholarly Concentration in the Molecular Basis of Medicine

At large:

1998-present Ad hoc reviewer for journals including (but not limited to): BioEssays, BMC Developmental Biology, Cell, Current Biology, Development, Developmental Biology, Developmental Dynamics, Developmental Cell, eLife, EMBO Journal, EMBO Reports, Genes and Development, Genetics, Human Mutation, Journal of Cell Biology, Journal of Cell Science, Journal of Neuroscience, Journal of Theoretical Biology, Mechanisms of Development, Molecular Biology of the Cell, Molecular and Cellular Biology, Nature, Nature Cell Biology, Nature Genetics, Nature Medicine, Nature Reviews, Proceedings of the National Academy of Sciences, Public Library of Science Biology, Public Library of Science Computational Biology, Public Library of Science Genetics, Science, Science Signaling, Trends in Cell Biology, Trends in Genetics
1999 International Wnt Meeting, co-organizer, Stanford University, July 17-19, 1999 Organizers Jeff Axelrod and Roel Nusse
2001-present Faculty of 1000, Faculty Contributor
2001 Ad-hoc reviewer: Canada Foundation for Innovation, Innovation Fund, Funds for Research Infrastructure
2002 Ad-hoc reviewer: The Wellcome Trust, Molecular and Cell Biology
2004 NIH/NIDCD Special Emphasis Panel/Initial Review Group ad hoc member
2005 Ad-hoc reviewer: International Research Fellowship Program
2005 Ad-hoc reviewer: March of Dimes Birth Defects Foundation
2005 Ad-hoc reviewer: The Wellcome Trust Project Grant
2005 NIH/NIDCD Special Emphasis Peer Review Panel
2006-2014 Editorial Board, Developmental Dynamics

2007-2010 Development Differentiation and Cancer Peer Review Committee of the American Cancer Society (Chair, 2009-2010)
2007 NIH/NICHD Developmental Biology Subcommittee Peer Review Panel, ad hoc member
2008 NSF Ad-hoc grant reviewer
2008 NIH ICI Special Emphasis Panel; ad hoc member
2009 NIH Special Emphasis Peer Review Panel; ad hoc member
2009 NIH Endocrinology, Metabolism, Nutrition and Reproductive Sciences Special Emphasis Review Panel; ad hoc member
2010 NIH DEV2 Grant Review Panel; ad hoc member
2011 NIH ICI Grant Review Panel; ad hoc member
2011 NIH Special Emphasis Panel: Biophysical and Biomechanical Aspects of Embryonic Development, Grant Review Panel Chair
2011 NIH DEV2 Grant Review Panel; ad hoc member
2012 NIH Special Emphasis Panel: Biophysical and Biomechanical Aspects of Embryonic Development, Grant Review Panel Chair
2012 United States-Israel Binational Science Foundation grant reviewer
2012-2017 NIH DEV2 Grant Review Panel; standing member (2016-17, Chair)
2012 US Army Peer Reviewed Medical Research Program, ad hoc reviewer
2014, 2018 Children's Tumor Foundation, ad hoc grant reviewer
2015 NIH Special Emphasis Panel: Polycystic Kidney Disease (PKD) Research and Translation Core Centers, Acting Chair
2017 National Science Foundation Grant reviewer
2018 American Cancer Society Council for Extramural Grants, ad hoc, standing member 2019-2023
2020 NIH Pilot Centers for Precision Disease Modeling (U54), Review Panel

C. Contribution to Science

1. My lab has devoted considerable effort to characterizing the core PCP signaling mechanism in Drosophila. Beginning with the discovery that many core proteins show unipolar asymmetric subcellular distributions, we have determined that these proteins establish asymmetry through a feedback mechanism in which proteins interact across intercellular boundaries. Our work has provided numerous insights into the molecular mechanisms by which these proteins function to generate subcellular molecular asymmetry.

a. Axelrod JD (2001) Unipolar membrane association of Dishevelled mediates Frizzled planar cell polarity signaling. **Genes Dev** 15(10), 1182-1187.
b. Tree DR, Shulman JM, Rousset R, Scott MP, Gubb D, & Axelrod JD (2002) Prickle mediates feedback amplification to generate asymmetric planar cell polarity signaling. **Cell** 109(3), 371-381.
c. Chen WS, Antic D, Matis M, Logan CY, Povelones M, Anderson GA, Nusse R, & Axelrod JD (2008) Asymmetric homotypic interactions of the atypical cadherin flamingo mediate intercellular polarity signaling. **Cell** 133(6), 1093-1105. PMCID: 2446404.
d. Cho B, Pierre-Louis G, Sagner A, Eaton S, & Axelrod JD (2015) Clustering and negative feedback by endocytosis in planar cell polarity signaling is modulated by ubiquitinylation of Prickle. **PLoS Genet**, 11(5), e1005259.

2. With Mike Simon, we discovered and characterised a second PCP signaling module, the Fat/Dachsous/Four-jointed (global) signaling module. We found that the atypical cadherins Ft and Ds form heterodimers that interact across intercellular boundaries, and that graded expression of Ds and Fj bias the direction of heterodimer orientation, thereby linking directionality to the tissue axes. Based on genetic arguments, we proposed that the Ft/Ds/Fj module provides directional bias to the core module.

a. Yang CH, Axelrod JD, & Simon MA (2002) Regulation of Frizzled by Fat-like cadherins during planar polarity signaling in the *Drosophila* compound eye. **Cell** 108(5), 675-688.
b. Ma D, Yang CH, McNeill H, Simon MA, & Axelrod JD (2003) Fidelity in planar cell polarity signalling. **Nature** 421(6922), 543-547.
c. Cho B, Song S, & Axelrod JD (2020) Prickle isoforms determine handedness of helical morphogenesis. **eLife** 9. doi: 10.7554/eLife.51456

3. In collaboration with my colleague, Claire Tomlin, we have used mathematical modeling to relate our molecular models to patterns of polarity, a problem too complex for intuitive analysis. Through development

and application of this approach, we have addressed significant biological questions including verifying the feasibility of our feedback loop model to explain the range of complex patterns resulting from clonal loss or gain of function of each core component, as well as a number of other biologically significant questions.

a. Amonlirdviman K, Khare NA, Tree DR, Chen WS, Axelrod JD, & Tomlin CJ (2005) Mathematical modeling of planar cell polarity to understand domineering nonautonomy. **Science** 307(5708), 423-426.
b. Ma D, Amonlirdviman K, Raffard RL, Abate A, Tomlin CJ, & Axelrod JD (2008) Cell packing influences planar cell polarity signaling. **Proc Natl Acad Sci U S A** 105(48), 18800-18805. PMCID: 2585485
c. Raffard R, Amonlirdviman K, Axelrod JD, & Tomlin CJ (2008) An Adjoint-based Parameter Identifcation Algorithm applied to Planar Cell Polarity Signaling. **Joint special issue of IEEE Transactions on Circuits and Systems and IEEE Transactions on Automatic Control** pp. 109-121. http://ieeexplore.ieee.org/stamp/stamp.jsp?tp=&arnumber=4439823&isnumber=4439798.
d. Matis M, Russler-Germain DA, Hu Q, Tomlin CJ, & Axelrod JD (2014) Microtubules provide directional information for core PCP function. **eLife**, 2014;3:e02893 doi: 10.7554/eLife.02893

4. We have leveraged our understanding of PCP signaling in Drosophila to investigate vertebrate PCP, identifying considerable conservation, as well as vertebrate and tissue specific adaptations. These studies have examined planar polarized tissues in mouse and frogs including the inner ear, the embryonic node where left-right asymmetry is established, the kidney and the tracheal epithelium. The tracheal epithelium has been particularly rewarding as we can complement in vivo studies with a culture system in which tracheal epithelial cells planar polarize in vitro. This work has led us to some clinically relevant studies.

a. Vladar EK, Bayly RD, Sangoram AM, Scott MP, & Axelrod JD (2012) Microtubules enable the planar cell polarity of airway cilia. **Current Biology** 22(23), 2203-2212.
b. Vladar EK, Nayak JV, Milla CE, Axelrod JD (2016) Airway epithelial homeostasis and planar cell polarity signaling depend on multiciliated cell differentiation. **JCI Insight** 1(13):e88027. doi:10.1172/jci.insight.88027.
c. Kunimoto K, Bayly RD, Vladar EK, Vonderfecht T, Gallagher A-R, Axelrod JD (2017) Disruption of core planar cell polarity signaling regulates renal tubule morphogenesis but is not cystogenic. **Current Biology** 27(20), 3120-3131. https://doi.org/10.1016/j.cub.2017.09.011
d. Vladar EK, Stratton MB, Saal ML, Salazar-De Simone G, Wang X, Wolgemuth D, Stearns T, & Axelrod JD (2018) Cyclin-dependent kinase control of motile ciliogenesis. **eLife** 7. 10.7554/eLife.36375

5. We have studied the relationship between the Ft/Ds/Fj and core PCP signaling modules in Drosophila. Our early results suggested that the Ft/Ds/Fj module biases the directionality of core module polarization. However, this idea has proven very controversial. We have characterized a mechanism by which Ft/Ds/Fj orients apical microtubules upon which vesicles carrying core proteins move toward plus-ends, thereby biasing the direction of core polarization. Furthermore, isoforms of the Prickle-Spiny legs protein determine the direction of microtubule plus-ends with respect to Ft-Ds polarization, thereby introducing rectification that solves the problem that the core and Ft/Ds/Fj modules polarize in different directions with respect to each other in various tissues. Remarkably, this function of Prickle is more broadly deployed, acting in neurons, for example.

a. Matis M, Russler-Germain DA, Hu Q, Tomlin CJ, & Axelrod JD (2014) Microtubules provide directional information for core PCP function. **eLife**, e02893.
b. Olofsson J, Sharp KA, Matis M, Cho B, & Axelrod JD (2014) Prickle/spiny-legs isoforms control the polarity of the apical microtubule network in planar cell polarity. **Development** 141(14), 2866-2874.
c. Ehaideb SN, Iyengar A, Ueda A, Iacobucci GJ, Cranston C, Bassuk AG, Gubb D, Axelrod JD, Gunawardena S, Wu CF, & Manak JR (2014) prickle modulates microtubule polarity and axonal transport to ameliorate seizures in flies. **Proc Natl Acad Sci U S A** 111(30), 11187-11192.
d. Cho B, Song S, & Axelrod JD (2020) Prickle isoforms determine handedness of helical morphogenesis. **eLife** 9. doi: 10.7554/eLife.51456

Complete List of Published Work: https://www.ncbi.nlm.nih.gov/pubmed/?term=axelrod+jd

D. Research Support

Ongoing Research Support

1R35GM131914-01 (PI: Axelrod, Jeffrey D. - Project 135804) 09/16/2019-08/31/2024

National Institutes of Health

Planar Cell Polarity Mechanisms and Systems Architecture

Major Goals: *The major goal of this project is to characterize planar cell polarity signaling mechanisms and systems architecture across tissues.*

Completed in past 3 years

5R01GM098582-08 (PI: Axelrod, Jeffrey D. - Project 50878) 07/18/2011-03/31/2020

National Institutes of Health

PCP in Vertebrate Epithelial Tubes

Major Goals: *The major goals of this project are to leverage our understanding of PCP molecular mechanisms from the fly to pursue molecular mechanisms of core and global PCP module function in the mouse.*

5R01GM097081-80 (PI: Axelrod, Jeffrey D. - Project 49910) 01/04/2011-01/31/2020

National Institutes of Health

Comparative Analysis of PCP Signaling Architecture

Major Goals: *The major goal of this project is to identify whether conserved or differing PCP system architectures can produce apparently differing responses to mutations in several PCP responsive tissues.*

2R37GM059823-18 (PI: Axelrod, Jeffrey D. - Project 20742) 09/01/2000-03/31/2019

National Institutes of Health

Signaling Mechanisms Controlling Planar Cell Polarity

Major Goals: *The major goals of this project are to develop a mechanistic understanding of the core PCP signaling components and to determine how global asymmetry information is transduced to the core components in the fly wing.*

Overlap

none