BIOGRAPHICAL SKETCH

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NAME: **Yost, H. Joseph**

eRA COMMONS USER NAME: JOSEPHYOST

POSITION TITLE: Vice Chairman for Basic Science Research, Department of Pediatrics; Richard L. Stimson Presidential Endowed Chair; Professor of Neurobiology & Anatomy, University of Utah School of Medicine

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	YEAR	FIELD OF STUDY
Creighton University, Omaha, NE	BS	1981	Honors Program & Biology
The University of Chicago, Chicago, IL	PhD	1987	Genetics
University of California, Berkeley, CA	Postdoc	1988-1991	Developmental Biology

A. Personal Statement

Genetics and Genomics Research: We are working at the intersection between model organism genetics and the discovery of novel disease-causing mutations in human genomes. My long-term research goal is to understand the gene regulatory networks and developmental mechanisms that assign different cell identities in functionally appropriate positions in the vertebrate embryo, and to utilize this knowledge for the advancement of human medicine. This includes building bioinformatics tools that are disease agnostic and species agnostic, that we have applied to human genomes as well as model organism genomes. My lab is recognized as a founder and leader in the field of vertebrate left-right (LR) development, discovering genetic pathways and mechanisms that convert bilateral symmetry to left-right asymmetry, including essential functional and/or structural asymmetries in the heart, brain and digestive system. Disruptions of LR asymmetry result in a large percentage of complex congenital heart defects affecting approximately thirty-five thousand births per year in the US. We have generated zebrafish genetic models of human congenital heart disease (CHD), ciliopathies, Roberts syndrome, Li-Fraumeni syndrome, colon cancer and rare/orphan diseases in pediatrics.

As the PI of the NIH Cardiovascular Development Consortium (CvDC) we are utilizing zebrafish to generate and analyze large genome-wide databases to discover gene regulatory networks that control normal heart development, to determine the etiologies of CHD. As a co-leader of the NIH Pediatric Cardiac Genomics Consortium (PCGC) we are utilizing human genomics and unique bioinformatics tools to identify new complex disease models for CHD, and to set the stage for understanding clinical outcomes and long-term neurological impacts in children with CHD. The project described here on Neural Crest derived cardiomyocytes (NC-Cms) is a spin-off of our work in the roles of various gene regulatory networks and cell lineages in heart development.

Team Building and Leadership: My deep commitment and success in training and mentoring the next generation of biomedical scientists is reflected in the following four activities: (1) I serve as **Vice Chairman in Pediatrics,** giving me the unique opportunity to promote research that is relevant to children's health, and to bridge between basic and clinical sciences throughout the university. Pediatrics is one of the largest departments at the University of Utah, with 310 faculty encompassing a broad range of research activities. The mission of our Research Enterprise office is to build research, training and outreach programs that are relevant to children's health. We foster a team approach to research development, implementation, and management. Our infrastructure provides faculty mentoring and career development, grant writing workshops, grant proposal preparation, grants budgeting and reporting, human subjects IRBs and animal welfare IACUC protocol development, clinical trials and network expertise, data development and analysis, and biostatistical support. Our goal is to build one of the top ten Pediatrics research departments in the country. I have extensive experience in a variety of genetics model organisms, including yeast, *Drosophila*, *Xenopus,* mice*,* zebrafish and cell culture, and bring this broad perspective to our team-building programs. (2) We are enhancing the pipeline for the next generation of biomedical scientists with unique education outreach programs at all levels, including a **Mentored Program in Pediatric Research** for medical students, a **Native American Summer Research Internship** program and **Genomics Summer Research for Minorities** program for undergraduates, an **Academic Associates** program for undergraduates, and the innovative **BioEyes outreach programs** for 4th-12th grade students in local schools with underrepresented populations. (3) I serve as the PI on a long-standing NIH **T32 Training program** in Developmental Biology. (4) I am the training director on our AHA Strategically Focused Research Network project. (5) My **Research Lab** has successfully trained 30 undergraduates, 15 Ph.D. or M.D./Ph.D. students, and 30 postdoctoral fellows or Pediatrics junior faculty. My former trainees are working around the country as leaders of their own research teams as tenured or tenure-track faculty, or pursuing successful careers in medicine, biotechnology, public policy or law.

B. Positions and Honors

Positions and Employment

1981	Undergraduate Research Program, Argonne National Laboratories
1981-1987	PhD, Committee on Genetics, The University of Chicago (Advisor: Dr. Susan L. Lindquist)
1988-1991	NIH Postdoctoral Research Fellow & American Cancer Society Senior Postdoctoral Fellow, Molecular & Cell Biology, University of California, Berkeley (Advisor: Dr. John C. Gerhart)
1991-1997	Assistant Professor, Department of Cell Biology and Neuroanatomy, University of Minnesota
1997	Associate Professor (tenure), Dept. Cell Biology and Neuroanatomy, University of Minnesota
1996-2002	American Heart Association Established Investigator
1997-2001	Associate Professor (tenure), Department of Oncological Sciences, University of Utah
1997-2001	Adjunct Associate Professor, Department of Pediatrics, University of Utah
1997-2007	Investigator, Huntsman Cancer Institute, University of Utah
2001-2006	Program Leader, NCI Cancer Center, University of Utah
2001-2007	Director, Center for Children, Huntsman Cancer Institute
2001-2007	Professor (tenure), Department of Oncological Sciences, University of Utah
2002-present	Adjunct Professor, Department of Pediatrics, University of Utah
2007-present	Professor (tenure), Department of Neurobiology & Anatomy, University of Utah
2013-present	Vice Chairman for Basic Science Research, Department of Pediatrics, University of Utah
2017-2018	interim Co-Director, University of Utah Molecular Medicine Program

Honors and Service

Awards and Honors: 2019 University of Utah Graduate Student and Postdoctoral Scholar Distinguished Mentor Award; 2017 Henry Gray Scientific Achievement Award, American Association of Anatomists; Fellow, American Association of Anatomists (elected 2017); Richard L. Stimson Presidential Endowed Chair, University of Utah School of Medicine (2015-present); "Heart of Gold" American Heart Association (2013); American Heart Association Established Investigator (1996-2001); University of Minnesota McKnight Land-Grant Professorship (1994-1996).

Organizer and Editorial Service: Associate Editor, *Developmental Dynamics* (2002-present, managing ~30 to 60 ms/yr); Organizer, Society for Developmental Biology, SW Regional, Salt Lake City (2013); Organizer, Weinstein Cardiovascular Development Conference (2002); Editorial Board, *Developmental Biology* (1997- present); Guest Editor, *Developmental Genetics* (1998).

National Advisory Committee Service: Coalition for Pediatric Medical Research (2014-present); Society for Developmental Biology Public Affairs Committee (2017-present); National Scientific Affairs Committee, American Association of Anatomists (2016-2019); FASEB Science Policy Committee (2014-2016); Chairman, National Public Affairs Committee, American Association of Anatomists (2012-2016); Utah Genome Project Scientific Advisory Board (2015-present); Board of Directors, Society for Developmental Biology (elected SW Regional Rep 2002-05; 2005-08); Weinstein Cardiovascular Development Steering Committee (2002-2011); External Advisory Board, Nevada IdeA Network for Biomedical Research Excellence (2004-2009); NIHLB Task Force on Cardiovascular Development (2001).

Review Panel Chairman: NIH Cardiovascular Development & Disease (interim, 2012-13); AHA National (2009-11); Cardiovascular and Respiratory Sciences Editorial Review Panel (2011); Special Emphasis Panel ZHD1 (2010); NIH SBIR Peer Review Panel (2009); NIH Special Emphasis Panel "Tools for Zebrafish Research" (2009); NIH Special Emphasis Panel "Zebrafish Genetic Screens" (2009); AHA National (2008); NIH Hematology Special Emphasis Panel (2004); AHA, Western Affiliate (1999-2002).

Panel Membership: NIH DEV-1 (2018); NIH Cardiovascular Differentiation and Development (2012-2016); NIH Special Emphasis Panel "Tools for Zebrafish Research" (2012); NIH Special Emphasis Panel "Zebrafish Genetic Screens" (2012); NSF Animal Developmental Mechanisms (2011); Cellular and Molecular Biology of the Kidney (2009); ZRG1 BDA-A Special Emphasis Panel (2009); CVRS-B Challenge Grants Panel (2009); *charter member*, NIH DEV-1 (2002-2007); NSF Developmental Biology Panel (1996-2000; 2001-2005); NIH Cardiovascular Differentiation and Development (2005); NIH Special Emphasis P01 Panel (2004); NIH RFA Diamond-Blackfan Panel (2004); NIH/NIHLB PPG (2000); NIH Cell Biology and Physiology -1 Study Section (1998); American Heart Association, National (1996-2000); AHA, MN Affiliate (1995-1997); NIH/NIHLB RFA (1995).

CONTRIBUTIONS TO SCIENCE

1. **Left-Right (LR) Patterning and Cardiovascular Disease in Vertebrates:** My lab was one of the earliest to investigate the embryological and cellular mechanisms that govern global LR patterning in vertebrates, starting with a seminal paper in *Nature* in 1992 that established a critical role for cell-extracellular signals. This began the hunt for the molecular sources for asymmetry in vertebrate embryos. Using a combination of embryological techniques in *Xenopus* and genetics in zebrafish, we were the first to show the importance of two transient structures in the embryo for the establishment and maintenance of LR asymmetry, that continue to be intensely investigated by many labs. The embryonic midline (notochord and floorplate) separates the two sides of the embryo and prevents asymmetric signals from crossing this barrier. Kupffer's vesicle was described in the 1860's by the famous anatomist Karl Wilhelm von Kupffer, but its function was unknown until our lab demonstrated that it has motile cilia that beat in unison to produce an asymmetric flow of extracellular fluid from right to left. We named this structure, which has analogues in mice, amphibians and other vertebrates, the "ciliated organ of asymmetry" and it is responsible LR patterning in the brain, heart and gut. We found the first asymmetrically expressed gene in a vertebrate brain, and we continue to make inroads into the complex LR patterning pathways.

   a. **Yost HJ**. Regulation of vertebrate left-right asymmetries by extracellular matrix. *Nature.* 1992 May 14;357(6374):158-161.
   b. Hyatt BA, Lohr JL, **Yost HJ**. Initiation of vertebrate left-right axis formation by maternal Vg1. *Nature.* 1996 Nov 7;384(6604):62-65.
   c. Essner JJ, Vogan KJ, Wagner MK, Tabin CJ, **Yost HJ**, Brueckner M. Conserved function for embryonic nodal cilia. *Nature.* 2002 Jul 4;418(6893):37-38.
   d. Bisgrove BW, Su YC, **Yost HJ**. Maternal Gdf3 is an obligatory cofactor in nodal signaling for embryonic axis formation in zebrafish. *eLife*. 2017 Nov 15;6. pii: e28534. doi: 10.7554/eLife.28534.

2. **Cardiac Neural Crest in zebrafish.** Cardiac neural crest in chick and mice were thought to contribute to the development of the cardiac outflow tract, which then divides and reorganizes LR asymmetrically into the systemic and pulmonary circulation of air-breathing animals. As we first described, the primitive outflow tract in zebrafish is not reorganized in water-living vertebrates, so, from an evolutionary perspective, it was reasonable to hypothesize that cardiac neural crest would not be present in zebrafish. In contrast, we discovered that zebrafish have cardiac neural crest, and importantly, some neural crest fate mapped to ventricular cardiomyocytes. Several prominent labs have substantiated these findings with a variety of fate-mapping techniques. However, as explained in this proposal, the ability to exclusively ablate Neural Crest derived Cardiomyocytes (NC-Cms) and test their functions has been elusive until our recent development of transgenic tools. This proposal builds on our discoveries that NC-Cms and Notch ligand *jag2b* have critical functions in cardiac development and in adult-onset cardiomyopathy, recently published in Nature Communications.

   a. Hu N, **Yost HJ**, Clark EB. Cardiac morphology and blood pressure in the adult zebrafish. *Anat Rec*. 2001 Sep 1;264(1):1-12. PubMed PMID: 11505366. (featured on journal cover)
   b. Sato M, **Yost HJ**. Cardiac neural crest contributes to cardiomyogenesis in zebrafish. *Dev Biol.* 2003 May 1;257(1):127-39. PubMed PMID: 12710962.
   c. Sato M, Tsai HJ, **Yost HJ**. Semaphorin3D regulates invasion of cardiac neural crest cells into the primary heart field. *Dev Biol.* 2006 Oct 1;298(1):12-21. Epub 2006 Jun 2. PubMed PMID: 16860789.
   d. Abdul-Wajid S, Demarest B, **Yost HJ.** Loss of embryonic neural crest cardiomyocytes causes adult hypertrophic cardiomyopathy. *Nat Commun.* 2018 Nov 2;9(1):4603. doi: 10.1038/s41467-018-07054-8.

3. **Bioinformatics:** My team has created several novel and widely utilized bioinformatics tools for genome analyses in multiple organisms (available on our website). We developed High Resolution Melting Analysis (HRMA) to rapidly genotype mutants in zebrafish, and the Poly Peak Parser algorithm that parses direct sequencing results of heterozygous mutants (small insertions or deletions, such as those created by CRISPR targeted mutagenesis). These tools have been adopted by many other labs for mutation detection in a variety of organisms. By connecting human and zebrafish genetics, we have extensive experience mapping conserved non-coding regions and cardiac-specific differentially methylated regions. To date, our most important bioinformatics contribution is an algorithm called MMAPPR (Mutation Mapping Analysis Pipeline for Pooled RNA-seq) that allows discovery of new mutations in NGS datasets. Initially developed to discover mutations in zebrafish, MMAPPR is species agnostic and is used by over 150 research groups around the

world to identify mutations in *Ciona*, parasitic worms, maize, sorghum and other food crop genetics in India and China, and in wild populations of non-traditional organisms.

a. Parant JM, George SA, Pryor R, Wittwer CT, **Yost HJ**. A rapid and efficient method of genotyping zebrafish mutants. *Dev Dyn.* 2009 Dec;238(12):3168-3174. PMCID: PMC3888828
b. Hill JT, Demarest BL, Bisgrove BW, Gorsi B, Su YC, **Yost HJ**. MMAPPR: mutation mapping analysis pipeline for pooled RNA-seq. *Genome Res.* 2013 Apr;23(4):687-697. PMCID: PMC3613585
c. Maguire CT, Demarest BL, Hill JT, Palmer JD, Brothman AR, **Yost HJ**, Condic ML. Genome-wide analysis reveals the unique stem cell identity of human amniocytes. PLoS One. 2013;8(1):e53372. doi: 10.1371/journal.pone.0053372. Epub 2013 Jan 10. PubMed PMID: 23326421; PubMed Central PMCID: PMC3542377.
d. Hill JT, Demarest BL, Bisgrove BW, Su YC, Smith M, **Yost HJ**. Poly peak parser: Method and software for identification of unknown indels using sanger sequencing of polymerase chain reaction products. *Dev Dyn.* 2014 Dec;243(12):1632-1636.

4. **Modeling human diseases in zebrafish.** We utilize both forward genetics and reverse genetics approaches in zebrafish, in combination with human genetics, to discover allelic variants, genes and gene regulatory pathways that are implicated in human diseases, including human congenital heart disease, heterotaxy syndrome, ciliopathies, Kabuki Syndrome, Roberts syndrome, and Li-Fraumeni syndrome.

a. Parant JM, George SA, Holden JA, **Yost HJ**. Genetic modeling of Li-Fraumeni syndrome in zebrafish. *Dis Model Mech.* 2010 Jan-Feb;3(1-2):45-56. PMCID: PMC2806900
b. Samson SC, Ferrer T, Jou CJ, Sachse FB, Shankaran SS, Shaw RM, Chi NC, Tristani-Firouzi M, **Yost HJ**. 3-OST-7 regulates BMP-dependent cardiac contraction. *PLoS Biol.* 2013 Dec;11(12):e1001727. PMCID: PMC3849020
c. Jin SC, Homsy J, Zaidi S, Lu Q, Morton S, DePalma SR, Zeng X, Qi H, Chang W, Sierant MC, Hung WC, Haider S, Zhang J, Knight J, Bjornson RD, Castaldi C, Tikhonoa IR, Bilguvar K, Mane SM, Sanders SJ, Mital S, Russell MW, Gaynor JW, Deanfield J, Giardini A, Porter GA Jr, Srivastava D, Lo CW, Shen Y, Watkins WS, Yandell M, **Yost HJ**, Tristani-Firouzi M, Newburger JW, Roberts AE, Kim R, Zhao H, Kaltman JR, Goldmuntz E, Chung WK, Seidman JG, Gelb BD, Seidman CE, Lifton RP, Brueckner M. Contribution of rare inherited and de novo variants in 2,871 congenital heart disease probands. *Nature Genet*. 2017 Oct 9. doi: 10.1038/ng.3970. PMID: 28991257
d. Serrano MA, Demarest BL, Tone-Pah-Hote T, Tristani-Firouzi M, **Yost HJ**. Inhibition of Notch signaling rescues cardiovascular development in Kabuki Syndrome. bioRxiv 489757; doi: https://doi.org/10.1101/489757

5. **Ciliopathies and Motile Cilia Biology:** The field of cilia biology has exploded in the last decade. Building on our discovery that specialized cilia control LR patterning in zebrafish, we extended our studies to understand the cell-cell signals and Gene Regulatory Networks that control the cellular morphogenesis (precursor cell specification, cell migration, epithelialization, lumen formation) of ciliated cells as well as the length, form and function of motile cilia. Our lab has been at the forefront of this field, publishing over 30 research studies that have received over 3100 citations. We invented techniques that allow visualization and quantification of asymmetric fluid flow and knockdown of gene function specifically in ciliated cell lineages, providing first definitive demonstration in any vertebrate for the cell autonomous role of ciliated cells in LR patterning. We are currently studying how asymmetric fluid flow regulates gene expression, discovering novel mechanisms by which major cell-cell signaling pathways (FGF, TGFβ and Wnt) intersect with cilia-dependent cellular pathways. Using genome-wide analyses, we are currently studying the gene regulatory networks that control cilia biology and that convert asymmetric fluid flow to gene function.

a. Essner JJ, Amack JD, Nyholm MK, Harris EB, **Yost HJ**. Kupffer's vesicle is a ciliated organ of asymmetry in the zebrafish embryo that initiates left-right development of the brain, heart and gut. *Development.* 2005 Mar;132(6):1247-1260.
b. Bisgrove BW, **Yost HJ**. The roles of cilia in developmental disorders and disease. *Development.* 2006 Nov;133(21):4131-4143.
c. Neugebauer JM, Amack JD, Peterson AG, Bisgrove BW, **Yost HJ**. FGF signalling during embryo development regulates cilia length in diverse epithelia. *Nature.* 2009 Apr 2;458(7238):651-654. PMCID: PMC2688717
d. Peterson AG, Wang X, **Yost HJ**. Dvr1 transfers left-right asymmetric signals from Kupffer's vesicle to lateral plate mesoderm in zebrafish. *Dev Biol.* 2013 Oct 1;382(1):198-208. PMCID: PMC3888838

Complete List of Published Work: http://www.ncbi.nlm.nih.gov/sites/myncbi/1FoQh-V7G3CQM/bibliography/44577036/public/?sort=date&direction=ascending

D. Current Training/Mentoring Grant Support

1 R25 HG009886 (National Human Genome Research Institute) Yost (PI) 09/01/2018-06/30/2023
Genomics Summer Research for Minorities: A Pathway to Promote Diversity in Science Research. This program provides underrepresented minority undergraduate participants (12 per year) with quality research opportunities in genomics fields, including training in bioinformatics and analysis of genomic datasets. We provide participants with professional development skills and a pathway to successfully navigate graduate school. Our long-term support services will ensure future success of all participants, increasing the pipeline of minority students into bioscience and genomics research careers.

T32 HD007491 (National Institute of Child Health & Development) Yost (PI) 09/29/1995-04/30/2022
Developmental Biology Training Program. This is a long-standing training program built on the strengths of the developmental biology community at the University of Utah, training seven predoctoral and two postdoctoral fellows at a time.

17SFRN33630041 (American Heart Association) Tristani/Yandell/Silver/Fagerlin/Yost 07/01/2017-06/30/2021
AHA SFRN: Leveraging Big Data Science to Link Genomics, Epigenetics and the Family to Improve the Health of Children with CHD. The team uses machine-learning data mining algorithms to approach congenital heart disease as a family disease, to look at causes, as well as the impact of maternal-fetal environment on health and improve decision-making between parents and physicians. Dr. Yost is the Training Director/Pi for this program.

Current Research Support

UM1 HL098160 (NIH/National Institute Heart, Lung, Blood) Yost (PI) 09/30/2009-08/31/2020
Genome-wide Analysis of Cardiac Development in Zebrafish. Our multidisciplinary Utah Cardiovascular Development Consortium center (Utah CvDC) is a collaborative group of zebrafish developmental geneticists, cardiac physiologists, experts in epigenomics, proteomics, genome-wide gene network profiling, bioengineering and bioinformatics at the University of Utah, in the NIH Bench-to-Bassinet (B2B) Consortia.

U01 HL098188 (NIH / NHLBI) Yost (subcontract PI) 06/01/2011-12/31/2020
CvDC Genomic Data Sharing Hub. This is a national data-sharing genomics hub for the CvDC consortium, including server hardware and web-based bioinformatics software at U. Utah. We are developing a unique bioinformatics algorithm called BioMiner, which allows comparative analyses of genomes, epigenomes and genome-wide expression datasets among multiple model organisms and humans.

UM1 HL128711 (NIH / NHLBI) Tristani-Firouzi/Yandell/Yost (MPI) 07/01/2015-06/31/2020
Bridging the Gap between Genomics and Clinical Outcomes in Congenital Heart Disease. We congenital heart disease (CHD) by leveraging novel bioinformatics tools (Phevor, VAAST2, pVAAST, etc) created at the University of Utah that enable integrated computation on personal genome/exome sequences, patient phenotype descriptions and pedigrees, patient-specific expression data, and model organism genome-wide analyses, all in a robust statistical framework. This project does not provide any support for research in Yost lab.

U01 HL131698 (NIH / NHLBI) Tristani-Firouzi/Yandell (MPI)/Yost (CoI) 04/01/2016-03/31/2020
Integrating Genomic and Clinical Approaches to Sudden Death in the Young (SDY). The goal of the Utah Center is to use innovative concepts and collaborative methodologies to define the genomic basis for autopsy-negative sudden death in SDY; functionally characterize candidate disease-causing variants; and facilitate evaluation of relatives of SDY victims. This project does not provide any support for research in Yost lab.

Completed Research Support (selected from thirty years of continuous NIH funding)

5R01 HL066292 (NIH / NHLBI) Yost (PI) 12/01/2000-05/31/2011
Genetic Regulation of Left-Right Organ Asymmetry. This project discovered genes and cell signaling mechanisms, including the roles of motile cilia, that control left right patterning during early development.