OMB No. 0925-0001 and 0925-0002 (Rev. 03/2020 Approved Through 02/28/2023)

BIOGRAPHICAL SKETCH

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, 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	Embryology & Development

A. PERSONAL STATEMENT

Mentoring and Leadership: My overall commitment to mentoring the next generation of biomedical scientists, with a focus on trainees who come from underrepresented (UR) groups, is reflected in eight activities: (1) I serve as **Vice Chairman for Basic Science Research in Pediatrics**, giving me the unique opportunity to mentor faculty and promote research that is relevant to children's health, and to bridge between basic and clinical sciences throughout the university. (2) With a focus on UR trainees, I am the PI on our **R25 Genomics Summer Research for Minorities (GSRM)** (R25HG009886) program for undergraduates and serve as a mentor in the **Native American Summer Research Internship (NARI)** program. (3) I brought the innovative **BioEyes** outreach program to Utah, which brings zebrafish experiments to 4th-12th grade students in local schools with UR populations. (4) I am contact MPI on a **T32 IMSD Program** (1T32GM139805) that provides four slots per year for new graduate students from UR groups, and mentors them throughout their graduate careers. (5) I serve as the PI on a long-standing NIH **T32 Developmental Biology Training Program (**T32 HD007491) that provides fellowships, mentoring and career development activities for seven predoctoral and two postdoctoral fellows per year, selected from several departments. (6) I served as **Training Director for our AHA SFRN** (Strategically Focused Research Network, 17SFRN33630041), training four research cross-disciplinary postdoctoral fellows in bioinformatics, population sciences and cardiology. (7) As a certified **CIMER Trained Facilitator** to Implement Research Mentor Training, I run CIMER (Center for the Improvement of Mentored Experiences in Research) workshops for faculty in various training programs. (8) My **Research Lab** has successfully trained 38 undergraduates, 17 Ph.D. or M.D./Ph.D. students, and 31 postdoctoral fellows or Pediatrics junior faculty. My former lab trainees are leaders of their own research teams as tenured or tenure-track faculty, or pursuing successful careers in medicine, biotechnology, public policy or law.

Cardiovascular 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, including congenital heart disease (CHD). 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. Our long-term work includes building, deploying and sharing bioinformatics tools that are disease agnostic and species agnostic, that we have applied to human genomes as well as model organism genomes. As PI of Utah's center in the **NIH Cardiovascular Development Consortium (CvDC) (**UM1HL098160) we utilized 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. I was contract PI for the previous **CvDC's DataHub,** and I am PI of the new **Cardiovascular Development Data Resource Center (CDDRC)** (U01HL153007), which will provide a cloud-based platform for big data analysis for the community. I have extensive experience in a variety of life sciences research approaches and model organisms, including yeast, *Drosophila*, *Xenopus*, mice, zebrafish, human cell culture and human genetics, and I bring this broad perspective to lead training, mentoring and career development opportunities for the trainees and mentors.

Current and recently completed <u>Training & Mentoring Projects</u> that I would like to highlight are:

R25HG009886 Yost (PI/PD) 09/20/2018-06/30/2023
Genomics Summer Research for Minorities: A Pathway to Promote Diversity in Science Research

The overall goals of this program are to provide undergraduate students from historically underrepresented groups opportunities to perform summer research programs in genomics.

T32 HD007491 (NIH / NICHD) Yost (PI/PD) 09/29/1995-04/30/2023
Developmental Biology Training Program.
This is a long-standing training program (>25years) built on the strengths of the developmental biology community at the University of Utah, currently training seven predoctoral and two postdoctoral fellows at a time. No salary support is provided for Dr. Yost by this training grant.

AHA 17SFRN33630041 Tristani-Firouzi/Yandell/Silver/Fagerlin/Yost (MPI) 07/01/2017-06/30/2022
Leveraging Big Data Science to Link Genomics, Epigenetics and Family to Improve Health of Children with CHD.
The overarching goals of the Utah SFRN Center are to improve quality of care and outcomes for children with congenital heart disease by (1) enhancing our understanding of disease etiology; (2) laying the foundation for prevention or prediction of CHD and outcomes; and (3) improving health care delivery using a family-centered outcomes approach and shared decision making. Role: Training Director

1T32GM139805 (NIH / NIGMS) Yost (contact)/Kwan MPI 02/01/2022- 01/31/2027
Initiative for Maximizing Student Development at the University of Utah (IMSD@U2)
The mission of the IMSD@U2 program is to build a diverse and inclusive biomedical workforce. We will train and launch the careers of graduate students from historically underrepresented (UR) groups. Our program provides a dynamic recruiting and onboarding experience to support a successful start to graduate school, personalized and cohort mentoring throughout their graduate career, peer outreach efforts and community building, leadership development, and mentoring faculty to better meet the needs of the UR community.

B. POSITIONS AND HONORS

Positions and Employment

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

Honors and Service

Awards and Honors: 2023 Inaugural member, Society for Developmental Biology Academy; 2020 Gary C Schoenwolf Faculty Mentorship Award; 2019 University of Utah Graduate Student and Postdoctoral Scholar Distinguished Mentor Award; 2017 Henry Gray Scientific Achievement Award, American Association for Anatomy; Fellow, American Association for Anatomy (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 (1994-96).

Organizer and Editorial Service: Associate Editor, *Developmental Dynamics* (2002-present, managing ~30 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: FASEB Science Policy Committee (2014-16; 2019-21; 2021-24); FASEB Leadership Development Committee (2021-2024); FASEB Member Engagement Task Force (2021-

2022); Society for Developmental Biology Public Affairs Committee (2017-19; chair 2021-23); Coalition for Pediatric Medical Research (2014-present); HHS Human Fetal Tissue Research Ethics Advisory Board (2020); National Scientific Affairs Committee, American Association of Anatomists (2016-19); 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 (2002-11); External Advisory Board, Nevada IdeA Network for Biomedical Research Excellence (2004-09); 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: AHA panel (2023); NIH Director's Transformative Research Award Review (2021-2022); NIH Special Emphasis Panel ZRG1 VRS-C (2020); NIH DEV-1 (*ad hoc* 2018, 2020); NIH Cardiovascular Differentiation and Development (2005; 2012-16; *ad hoc* 2021, 2022); 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 Special Emphasis P01 Panel (2004); NIH RFA Diamond-Blackfan Panel (2004); NIH/NIHLB PPG (2000); NIH Cell Biology and Physiology Panel (1998); American Heart Association, National (1996-2000); AHA, MN Affiliate (1995-1997); NIH/NIHLB RFA (1995).

C. 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 Left-Right (LR) patterning in vertebrates, starting with a seminal paper in *Nature* in 1992 that established a critical role for cell-extracellular signals in heart and gut LR patterning. This began the hunt for the molecular sources of LR 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: (1) The embryonic midline (notochord and floorplate) separates the two sides of the embryo and prevents asymmetric signals from crossing this barrier. (2) 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" or "Left-Right Organizer." It is responsible for 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. 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 the gene regulatory networks that control cilia biology and that convert asymmetric fluid flow to gene function.
   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, 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.
   d. 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
   e. 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. PMCID: PMC5745076

2. **Modeling Human Diseases in Zebrafish:** We utilize a combination of human genetics/genomics and both forward genetics and reverse genetics approaches in zebrafish, to discover allelic variants, genes and gene regulatory networks that are implicated in human diseases, including human congenital heart disease (CHD), heterotaxy syndrome, ciliopathies, Kabuki Syndrome, Roberts syndrome, and Li-Fraumeni syndrome. For our focus on CHD, Dr. Yost is an MPI in the Pediatrics Cardiac Genomics Consortium (PCGC, NHLBI U01HL128711), which is translating human genomic discoveries into improved clinical care requires the ability to integrate genotypes with multiple variables, including gene pathways, maternal and patient comorbidities, ancestry, and gender to optimally empower outcomes prediction.
   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. Watkins WS, Hernandez EJ, Wesolowski S, Bisgrove BW, Sunderland RT, Lin E, Lemmon G, Demarest BL, Miller TA, Bernstein D, Brueckner M, Chung WK, Gelb BD, Goldmuntz E, Newburger JW, Seidman CE, Shen Y, **Yost HJ**, Yandell M, Tristani-Firouzi M. *De novo* and recessive forms of congenital heart disease have distinct genetic and phenotypic landscapes. *Nature Commun***.** 2019 Oct 17;10(1):4722. doi: 10.1038/s41467-019-12582-y.PMID: 31624253
   c. Serrano MA, Demarest BL, Tone-Pah-Hote T, Tristani-Firouzi M, **Yost HJ**. Inhibition of Notch signaling rescues cardiovascular development in Kabuki Syndrome. *PLoS Biol.* 2019 Sep 3;17(9):e3000087. PMCID: PMC6743796
   d. Parvez S, Herdman C, Beerens M, Chakraborti K, Harmer ZP, Yeh JJ, MacRae CA, **Yost HJ**, Peterson RT. MIC-Drop: A platform for large-scale in vivo CRISPR screens. *Science*. 2021 Sep 3;373(6559):1146-1151. Epub 20210819.

3. **Bioinformatics:** My team has created several novel and widely utilized bioinformatics tools for genome analyses in multiple organisms. 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. These tools have been adopted by many other labs for mutation detection in a variety of organisms. 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 major goal of our current bioinformatics efforts is to build a cloud-based data sharing, processing and visualization platform, the **Cardiovascular Development Data Resource Center** (CDDRC, NHLBI U01HL153007, Yost contact MPI) and to develop new algorithms that can be executed on the platform by bringing in CDDRC Fellows and investigators throughout the country by innovative Challenge Prize competitions.
   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. 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. PMCID: PMC4525701

4. **Cardiac Neural Crest in Zebrafish:** We discovered that zebrafish have cardiac neural crest, and importantly, some neural crest cells invade the primary mesoderm of the heart tube and transform into functional ventricular cardiomyocytes. We developed a unique set of transgenic tools that allow exclusive lineage labeling and ablation of Neural Crest derived Cardiomyocytes (NC-Cms) at any stage of development, and found that NC-Cms and Notch ligand *jag2b* have critical functions in cardiac development. As an exciting example of fetal origins of adult disease, we found that ablation of NC-Cms during embryogenesis, or loss of NC-Cms-enriched components of the Notch signaling pathway, predisposes individuals to adult-onset cardiomyopathy and adult heart failure. The goal of this research program (NHLBI

R01HL146854) is to discover the roles of NC-CMs in adult cardiac disease and adult heart regeneration, using zebrafish genetics and transgenics as a model system.

a. Sato M, **Yost HJ**. Cardiac neural crest contributes to cardiomyogenesis in zebrafish. *Dev Biol.* 2003 May 1;257(1):127-39.
b. 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.
c. Abdul-Wajid S, Demarest B, **Yost HJ.** Loss of embryonic neural crest cardiomyocytes causes adult hypertrophic cardiomyopathy. *Nature Commun.* 2018 Nov 2;9(1):4603. PMCID: PMC6214924
d. Jurynec MJ, Bai X, Bisgrove BW, Jackson H, Nechiporuk A, Palu RAS, Grunwald HA, Su YC, Hoshijima K, **Yost HJ**, Zon LI, Grunwald DJ. The Paf1 complex and P-TEFb have reciprocal and antagonist roles in maintaining multipotent neural crest progenitors. *Development*. 2019 Dec 16;146(24) doi: 10.1242/dev.180133. PMID: 31784460

5. **Syndecans and Sugar Code hypothesis in development and disease.** Our studies in LR patterning led us to characterize the syndecan gene family of Heparan Sulfate Proteoglycan (HSPG) core proteins both in *Xenopus* and zebrafish. We then characterized the gene families that encode the biosynthetic pathways that make fine structural modifications on sugar chains attached to the HSPG core proteins. The working hypothesis is that rare and distinct marks on HSPG sugar chains at the surfaces of all cells serve as gatekeepers for all of the major cell-cell signaling pathways (Wnts, TGFb's, FGFs, etc) and for a multitude of cell-cell and cell-ECM interactions. Discovering how these codes are regulated and how they are utilized in biology might provide novel therapeutic targets for a wide range of human diseases.
   a. Kramer KL, Barnette JE, **Yost HJ**. PKCgamma regulates syndecan-2 inside-out signaling during xenopus left-right development. *Cell.* 2002 Dec 27;111(7):981-990.
   b. Cadwalader EL, Condic ML, **Yost HJ**. 2-O-sulfotransferase regulates Wnt signaling, cell adhesion and cell cycle during zebrafish epiboly. *Development.* 2012 Apr;139(7):1296-1305. PMCID: PMC3294434
   c. 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
   d. Poulain FE, **Yost HJ**. Heparan sulfate proteoglycans: a sugar code for vertebrate development? *Development.* 2015 Oct 15;142(20):3456-3467. PMCID: PMC4631762

Complete List of Published Work:
https://www.ncbi.nlm.nih.gov/myncbi/h.%20joseph.yost.1/bibliography/public/