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; 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

Team Building, Program Development and Mentoring Leadership: My deep commitment and success in training and mentoring the next generation of biomedical scientists is reflected in multiple 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 over 300 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. Last fiscal year we were awarded over $57 Million in NIH grants and have climbed two places in the BRIMR ranking, moving toward our goal of building one of the top ten Pediatrics research departments in the country. (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 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 that provides fellowships for 7 predoctoral and 2 postdoctoral fellows per year, selected from several departments. This program builds on the strengths of the developmental biology community and provides trainees an outstanding environment and unique opportunities for career development. (4) My **Research Lab** has successfully trained 29 undergraduates, 15 Ph.D. or M.D./Ph.D. students, and 29 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.

Research: 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. We are working at the intersection between model organism genetics and the discovery of novel disease-causing mutations in humans. My lab is recognized as a founder and leader in the field of vertebrate left-right (LR) development, discovering 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), heterotaxy syndrome, ciliopathies, Roberts syndrome, Li-Fraumeni syndrome, colon cancer and rare/orphan diseases in pediatrics.

As the leader of the Utah 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 member of the 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. These collaborative genomic analysis projects serve as an additional foundation for mentoring and training postdoctoral fellows.

I have extensive experience in a variety of model organisms, including yeast, *Drosophila*, *Xenopus,* mice*,* zebrafish and cell culture, and bring this broad perspective to our team-building programs.

1. Martinez-Arias A, **Yost HJ**, Casadaban MJ. Role of an upstream regulatory element in leucine repression of the Saccharomyces cerevisiae leu2 gene. *Nature.* 1984 Feb 23-29;307(5953):740-742.
2. **Yost HJ**, Lindquist S. RNA splicing is interrupted by heat shock and is rescued by heat shock protein synthesis. *Cell.* 1986 Apr 25;45(2):185-193.
3. **Yost HJ**, Lindquist S. Translation of unspliced transcripts after heat shock. *Science.* 1988 Dec 16;242(4885):1544-1548.
4. **Yost HJ**. Inhibition of proteoglycan synthesis eliminates left-right asymmetry in Xenopus laevis cardiac looping. *Development.* 1990 Nov;110(3):865-874.

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
2011-present	Assistant Director, University of Utah Molecular Medicine Program
2013-present	Vice Chairman for Basic Science Research, Department of Pediatrics, University of Utah

Honors and Service

Awards and Honors: Fellow, American Association of Anatomists (elected 2017); 2017 Henry Gray Scientific Achievement Award, American Association of Anatomists; 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).

Advisory Committee Service: Utah Genome Project Scientific Advisory Board (2015-present); Society for Developmental Biology Public Affairs Committee (2017-present); FASEB Science Policy Committee (2014-2016); Chairman, National Public Affairs Committee, American Association of Anatomists (2012-2016); 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 Member: 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 (2001-2005;1996-2000); 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).

External Reviewer: Welcome Trust Fund, UK; Medical Research Council, UK; National Science Foundation; Israel Science Foundation, Israel Academy of Sciences and Humanities; Natural Sciences and Engineering Research Council of Canada; Medical Research Council of Canada; March of Dimes; Pennsylvania Dept Health; An Bord Taighde Sláinte, Ireland; Volkswagen Stiftung, Germany; Human Frontier Science, EU.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 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 pathways that convey LR information throughout the embryo.
   a. Yost HJ. Regulation of vertebrate left-right asymmetries by extracellular matrix. *Nature.* 1992 May 14;357(6374):158-161.
   b. Danos MC, Yost HJ. Role of notochord in specification of cardiac left-right orientation in zebrafish and Xenopus. *Dev Biol.* 1996 Jul 10;177(1):96-103. (featured on journal cover)
   c. Hyatt BA, Lohr JL, Yost HJ. Initiation of vertebrate left-right axis formation by maternal Vg1. *Nature.* 1996 Nov 7;384(6604):62-65.
   d. 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.

2. **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, Roberts syndrome, Li-Fraumeni syndrome and colon cancer.
   a. Tsai IC, Woolf M, Neklason DW, Branford WW, **Yost HJ**, Burt RW, Virshup DM. Disease-associated casein kinase I delta mutation may promote adenomatous polyps formation via a Wnt/beta-catenin independent mechanism. *Int J Cancer.* 2007 Mar 01;120(5):1005-1012.
   b. 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
   c. Nash D, Arrington CB, Kennedy BJ, Yandell M, Wu W, Zhang W, Ware S, Jorde LB, Gruber PJ, **Yost HJ**, Bowles NE, Bleyl SB. Shared Segment Analysis and Next-Generation Sequencing Implicates the Retinoic Acid Signaling Pathway in Total Anomalous Pulmonary Venous Return (TAPVR). *PLoS One.* 2015;10(6):e0131514. PMCID: PMC4485409
   d. Percival SM, Thomas HR, Amsterdam A, Carroll AJ, Lees JA, **Yost HJ**, Parant JM. Variations in dysfunction of sister chromatid cohesion in esco2 mutant zebrafish reflect the phenotypic diversity of Roberts syndrome. *Dis Model Mech.* 2015 Aug 01;8(8):941-955. PMCID: PMC4527282

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 (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 Next Generation Sequencing datasets. While 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. All these tools are freely available on our lab website.

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. 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.
d. Lyozin GT, Bressloff PC, Kumar A, Kosaka Y, Demarest BL, **Yost HJ**, Kuehn MR, Brunelli L. Isolation of rare recombinants without using selectable markers for one-step seamless BAC mutagenesis. *Nature Methods.* 2014 Sep;11(9):966-970. PMCID: PMC4149595

4. **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

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. Our work has 16 foundational publications, with the top five accumulating over 500 citations. Discovering how these codes are regulated and how they are utilized in biology will 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: http://www.ncbi.nlm.nih.gov/sites/myncbi/1FoQh-V7G3CQM/bibliography/44577036/public/?sort=date&direction=ascending

D. Research Support

Ongoing Research Support

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
This genomics program explores 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.

U01HL098160 (NIH / NHLBI) 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 biologists, cardiac physiologists, experts in epigenomics, proteomics, genome-wide gene network profiling, bioengineering and bioinformatics at the University of Utah, as part of the national Cardiovascular Development Consortium within the NIH Bench-to-Bassinet (B2B) Consortia.

T32HD007491 (NIH / NICHD) 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.

U01HL131698 (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.

U01 HL098188 (NIH / NHLBI) King (PI); Yost (subcontract PI) 06/01/2011-12/31/2020
CvDC Genomic Data Sharing Hub
This subcontract establishes a national data-sharing hub for the CvDC consortium, including server hardware and web-based bioinformatics software at the University of 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.

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

Society for Developmental Biology Yost/Neugebauer (MPI) 04/15/2016 – 04/14/2017
BioEYES Utah
BioEYES is an outreach program to inspire under-represented groups to envision themselves as scientists, by offering hands-on science education and by bringing zebrafish into the classroom. To date, BioEyes taught >3000 students and 25 teachers in Salt Lake City School District.

P01 HD048886 (NIH/NICHD) Yost (Project 2 PI) 12/01/2006-02/28/2013
Patterning and Morphogenesis of Kupffer's Vesicle (KV)
This multidisciplinary team project elucidated complex regulatory interactions, based on four transcription factor genes, ntl, spt, rfx2 and hfh4, which coordinate the formation, ciliogenesis and function of KV.

5R01HL066292 (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, using zebrafish genetics and *Xenopus* embryology.