BIOGRAPHICAL SKETCH

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NAME: HSU, Wei

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

POSITION TITLE: Professor & Senior Member of Staff

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Tamkang University, Taipei	B.S.	06/1989	Chemistry/Biochemistry
Mount Sinai School of Medicine, New York City	Ph.D.	05/1994	Signal Transduction & Cancer Biology
Columbia University, College of Physicians & Surgeons, New York City	Postdoctoral Fellow	12/1997	Mammalian Genetics & Developmental Biology

A. Personal Statement

My research career started as a graduate student focusing on transcription factors regulated by interleukin-6 in response to lymphocyte differentiation and viral infection at Mount Sinai Medical Center. I was fascinated by the dynamics of embryonic development and the advancement of mouse genetics in the early 90' so decided to do my postdoctoral training in the lab of Frank Costantini, a pioneer in developmental genetics at Columbia University. Since then, I have established my independent research lab first at the University of Rochester, and now at Forsyth Institute/Harvard for the past two decades. I have concentrated on the genetic control of cellular signaling pathways in mammalian development and disease. As a developmental geneticist, I have established my lab capable of generating mouse mutant strains by pronuclear injection of DNA, blastocyst injection of ES cells and CRISP-Cas9 targeted DNA editing. Using these advanced methods, several new mouse models highly valuable for our research programs are developed. My lab has made significant contributions to our knowledge base of signaling interplays in the development of tissue-specific stem cell niches and lineages, and the disorders associated with these processes. Our most well-known discovery includes the elucidation of the mechanism underlying Wnt signal production and transduction, particularly the identification and characterization of Axin family genes and Gpr177/Wntless (*PNAS* 2009). Our work has also directed us to small ubiquitin-related modifiers in various aspects of development and disease (*PLOS Biology* 2008). Recently, our identity and purification of mouse and human skeletal stem cells and the interplay of skeletogenic signaling pathways in lineage commitment have also been well recognized in the field of craniofacial and skeletal research (*Nature Communications* 2016 and *Science Translational Medicine* 2021).

I have been actively promoting gender and minority/ethnic diversity in science and education. I have mentored ~30 female students and postdocs, and 3 trainees from racial/ethnic minorities (Dr. Natalie Hernandez, John Martinez, Andrea Akwiwu). My trainees were from culturally diverse backgrounds around the world. As a first-generation immigrant in the US, I have firsthand experience of how the environment could be unfair, challenging sometimes. I wholeheartedly understand the challenge that disadvantaged groups are facing and how important it is to create an inclusive learning environment. As the Chair of this Forsyth Symposium, I have taken every possible step to enhance and implement Diversity Equity Inclusion.

Ongoing and recently completed projects that I would like to highlight include:
NIH R01DE026936 HSU (PI) 6/1/2018-5/31/2023
Title: Stem Cells for Craniofacial Bone Repair and Regeneration
This proposal studies newly identified and isolated stem cells essential for craniofacial bone development and disease and their ability to repair the damaged skeleton via direct engraftment. Role: PI

NIH R01DE015654 HSU (PI) 7/1/06-02/29/24
Title: Genetic Regulatory Network in Craniofacial Development

This proposal continues our efforts to elucidate the genetic regulatory network underlying the interplay of Wnt, FGF, and BMP signaling pathways in calvarial morphogenesis and craniosynostosis. Role: PI

NIH R21DE028696 MARUYAMA (PI) 3/1/2019-2/28/2021
Title: The Essential Role of miR-27a in Craniofacial and Body Skeletons
The main objective is to examine the function of miR-27a in skeletal development and remodeling and explore the preventive and therapeutic treatment for osteoporosis. Role: Co-Investigator

Citations:

1. Fu J, Jiang M, Mirando AJ, Yu HI and **Hsu W** (2009). Reciprocal regulation of Wnt and Gpr177/mouse Wntless is essential for embryonic axis formation. ***Proc Natl Acad Sci USA***, 106, 18598-18603. PMID: 19841259, PMCID: PMC2773984
2. Chiu, S, Asai N, Costantini F and **Hsu W** (2008). SUMO-specific protease 2 is essential for modulating p53-Mdm2 in development of trophoblast stem cell niches and lineages. ***PLOS Biology***, 6(12): e310. PMID: 19090619, PMCID: PMC2602722
3. Maruyama T, Jeong J, Sheu TJ and **Hsu W** (2016). Stem cells of the suture mesenchyme in craniofacial bone development, repair and regeneration. ***Nature Communications***, 7:10526. PMID: 26830436
4. Takamitsu Maruyama, Ronay Stevens, Alan Boka, Laura DiRienzo, Connie Chang, H-M Ivy Yu, Katsuhiko Nishmori, Clinton Morrison, and Wei Hsu (2021). BMPR1A maintains skeletal stem cell properties in craniofacial development and craniosynostosis. ***Science Translational Medicine***, 13, eabb4416. PMID: 33658353

B. Positions, Scientific Appointments, and Honors

Faculty Positions

2021	Senior Member of the Staff, Forsyth Institute, Cambridge, MA
2021	Professor of Developmental Biology, Faculty of Medicine of Harvard University
2021	Affiliate Faculty Member, Harvard Stem Cell Institute
2017	Co-Director, NIH/NIDCR T90/R90 Training Program, University of Rochester, NY
2015	Dean's Professor, University of Rochester Medical Center, Rochester, NY
2012	Professor, Department of Biomedical Genetics, Center for Oral Biology, James P. Wilmot Cancer Institute, University of Rochester Medical Center, Rochester, NY
2007	Member, University of Rochester Stem Cell & Regenerative Medicine Institute
2006	Associate Professor, Department of Biomedical Genetics, Center for Oral Biology, James P. Wilmot Cancer Center, University of Rochester Medical Center, Rochester, NY
2005	Assistant Professor, James P. Wilmot Cancer Center, University of Rochester Medical Center
2002	Assistant Professor, Department of Biomedical Genetics, University of Rochester, NY
1998	Associate Research Scientist, Genetics & Development, Columbia University, New York City

Scientific Appointment – Professional Memberships

2021	Member, NIH, Special Emphasis Panel, ZRG1 IDIA-W (02) M
2021	Member, NIH, Special Emphasis Panel, ZDE1 JK (04)
2020	Member, NIH, Musculoskeletal, Oral, and Skin Sciences (MOSS-R 02M) Study Section
2020	External Reviewer, Swiss National Science Foundation (SNSF)
2019	Member, NIH, Special Emphasis Panel/Scientific Review Group, ZRG1 IDM-W (02) M
2017	Reviewer, Japan Society for the Promotion of Science (JSPS)
2015-2019	Member, NIH, Skeletal Biology Development and Disease (SBDD) Study Section
2015	Member, NIH, Special Emphasis Panel, NIH/ZRG1 MDCN-Q (03) Study Section
2014-2015	Ad hoc, NIH, Skeletal Biology Development and Disease (SBDD) Study Section
2014	Member, NIH, Special Emphasis Panel, ZRG1 MOSS T-90 Study Section
2014	Reviewer, BBSRC, Great British Bioscience, UK
2013-Date	Member, American Society Bone, and Mineral Research
2013, 2019	Reviewer, Research Grant for Developmental Biology, Medical Research Council, UK
2013	Member, NIH, Special Panel, ZRG1 F05-D: Cell Biology & Developmental Biology Study Section
2013	Member, NIH/NICHD, ZHD1 DSG-D (40)-Mechanisms of Human Structure Birth Defects
2012	Member, NIH, Special Panel, ZRG1 F05-R: Cell Biology and Development Study Section
2012	Reviewer, Patton Trust Grant Program, Kansas City Area Life Sciences Institute
2012	Reviewer, Research Grant for Regenerative Medicine, Medical Research Council, UK

2012 Member, NIH/NICDR, ZDE1 JR (18)-Molecular Characterization of Salivary Gland Tumors
2012 Reviewer, A*STAR Biomedical Research Council, Research Partnership Grant, Singapore
2011 External Member, Grant Review Session, Telethon Foundation, Italy
2011 Reviewer, Scientific Advisory Board, Dutch Cancer Society, Netherlands
2011 Member, NIH/NICHD, ZHD1 DSR-Y (50)-Mechanisms of Human Structure Birth Defects
2011 Ad hoc, NIH/NICHD, Developmental Biology Grant Review Committee, CHHD Study Section
2010-2012 Reviewer, Bankhead-Coley Cancer Research Program, Florida Department of Health
2010-2011 Reviewer, James & Esther King Biomedical Research Program, Florida Department of Health
2010-2011 Member, Grant Review Panel for CDMRP, BCRP, Department of Defense
2010 Ad hoc, NIH/NCI, Tumor Microenvironment Study Section
2010 Ad hoc, Developmental Systems, Developmental Mechanisms, National Science Foundation
2008-2014 Member, Alzheimer's Association Research Grant Review Committee, Chicago, IL
2008 Ad hoc, Career Development Grant Review Panel for CDMRP, OCRP, Department of Defense
2008 Ad hoc, NIAMS, Musculoskeletal Repair & Regeneration P&F, Hospital for Special Surgery, NYC
2007 External Member, Grant Review Committee, Research Council of University of Ghent, Belgium
2006-2011 Ad hoc, NIH/NICHD, Developmental Biology Grant Review Committee, CHHD Study Section
2006-2007 Member, Basil G. Bibby Fellowship Award Committee, Eastman Dental Center, Rochester, NY
2005-Date Member, Society for Craniofacial Genetics
2005 Chair, Basil G. Bibby Fellowship Award Committee, Eastman Dental Center, Rochester, NY
2004 Member, Award Committee, American Association for Dental Research, Rochester, NY
2001-Date Member, Society for Developmental Biology
1995-1997 Fellow, National Kidney Foundation
1995-Date Member, New York Academy of Sciences
1995-2010 Member, American Society for Microbiology
1992-Date Member, American Association for the Advancement of Science

Scientific Appointment – Other Experience

Journal Referee

2018-2021 Editorial Board: Journal of Dental Research
2013-2018 Associate Editor: PLOS Genetics
2011-Date Editorial Board: Human Genetics & Embryology, Hereditary: Current Research, Transcriptomics, JSM Regenerative Medicine
2009-2014 Editorial Board: Breast Cancer-Targets and Therapy
2008-2013 Editorial Board: Cancer Management and Research, International Journal of Women's Health
2001-Date Reviewer: Nature, Nature Communications, EMBO Reports, Science Translational Medicine, Science Signaling, Development, PNAS, Disease Models & Mechanisms, Developmental Biology, PLOS Genetics, PLOS One, Cell Death & Differentiation, Cell Research, Cancer Research, Oncogene, Nucleic Acid Research, Journal of Investigative Dermatology, Nature Bone Research, Journal of Dental Research, BioTechniques, Bone, etc.

Invited Talks/Lectures

Conferences

Cold Spring Harbor Meetings, Northeast Regional Developmental Biology Meeting, WNT Meeting 2001, American Dental Association for Dental Research, Society of Craniofacial Genetics, ASO International Symposium – Japan, Emerging Information and Technology – Toronto, EITA –Cornell University, American Society for Bone & Mineral Research Annual Meeting – Baltimore, Cold Spring Harbor Asia Conference 2016.

Seminars

Harvard University, U Penn, Weil Medical College of Cornell University, Mount Sinai School of Medicine, Mayo Clinic, UCLA, UC Davis, Boston University, New York University, Albert Einstein Medical College, University of Massachusetts, UT Austin, UT Southwestern, UT Houston, Baylor College of Medicine, University of Maryland, Indiana University, Georgetown University, the University of Alabama at Birmingham, Roswell Park Cancer Institute, Ohio State University, University of Hawaii Cancer Center, Texas A&M Health Science Center, University at Albany, Georgia Health Sciences University, Academia Sinica-Taiwan, RIKEN Center for Developmental Biology – Japan, National Health Research Institutes – Taiwan, National Yang-Ming University – Taiwan, Hangzhou Normal University – China, Wuhan University – China, Chinese Academy of Sciences/Shanghai Institute of Biological Sciences – China, etc.

Awards & Honors

2020	Nominee, AAAS Fellow
2015	Dean's Professorship, University of Rochester School of Medicine and Dentistry
2013	Advisor/Senior Author for the 2013 ASBMR Raisz-Drezner Award honoring first authors of meritorious scientific reports published in the Journal of Bone and Mineral Research
2012	Distinguished Alumni Award, Taipei Fuhsing Private School, Taiwan
2012	Pathways to Excellence – Visiting Professorship, Texas A&M Health Science Center, Dallas
2007-2010	Idea Award, Breast Cancer Research Program, US Department of Defense
1997	Traveling & Research Award, Northeast Region, Society for Developmental Biology
1995-1997	Postdoctoral Fellowship, National Kidney Foundation
1991&1993	Traveling & Research Award, Molecular Biology Center, Mount Sinai School of Medicine

C. Contributions to Science

1. Skeletal development & deformity: stem cell and signaling regulation

Skeletogenic mesenchyme mediates the formation of the craniofacial and body skeletons through two distinct mechanisms – intramembranous and endochondral ossifications, respectively. These processes are initiated by the commitment of the skeletogenic mesenchyme to osteogenic or chondrogenic lineage. Endochondral ossification requires chondrogenic condensation to form cartilage templates while mesenchymal stem cells directly differentiate into osteoblasts during intramembranous ossification. The suture is the equivalent of growth plates in the long bone and serves as the growth center for the healthy development of the craniofacial skeleton. Aberrant suture closure results in craniosynostosis, one of the most common congenital deformities affecting 1 in 2,500 individuals. Our characterization of mice with disruption of Axin2 exhibiting synostosis phenotypes has initiated our longstanding project in skeletal development and deformity. We found that Axin2-mediated regulation of Wnt signaling is essential for the regulation of skeletogenic precursors in cell proliferation and differentiation (*Development*, 2005). Further investigations revealed that Wnt signaling directly controls the stem cell population by regulating its renewal and proliferation, and indirectly modulates lineage specification by setting the balance of the FGF and BMP pathways (*Science Signaling*, 2010). The findings led to a hypothesis on the existence of stem cells present in the suture midline and our search for these suture stem cells. We were able to identify and characterize this Axin2+ cell population as genuine stem cells capable of long-term self-renewal, clonal expansion, and differentiation into skeletogenic cell types during skeletal development, homeostatic maintenance, and injury repair (*Nature Communications*, 2016). Our findings provide the first evidence for isolation of this skeletal stem cell population and demonstrate their innate capacities to regenerate bones at ectopic sites and replace the damaged skeleton in cell-based therapy (Nature Communications, 2016; featured at NIDCR News). Using unbiased proteomic and genomic approaches, we have identified downstream effectors of Axin2 that regulates signaling crosstalk of Wnt, BMP, and FGF during skeletal development and isolated human skeletal stem cells residing in the suture mesenchyme (*Science Translational Medicine*, 2021).

a. Yu HI, Jerchow B, Sheu TJ, Liu B, Costantini F, Puzas JE, Birchmeier W, **Hsu W** (2005). The role of Axin2 in calvarial morphogenesis and craniosynostosis. ***Development***, 132, 1995-2005. PMID: 15790973
b. Maruyama T, Mirando AJ, Deng CX and **Hsu W** (2010). The balance of WNT and FGF signaling influences mesenchymal stem cell fate during skeletal development. ***Science Signaling***, 3, ra40. PMID: 20501936, PMCID: PMC2902546
c. Maruyama T, Jeong J, Sheu TJ, **Hsu W**. Stem cells of the suture mesenchyme in craniofacial bone development, repair and regeneration (2016). ***Nature communications***, 7:10526.
d. Maruyama T, Stevens R, DiRienzo L, Boka A, Chang C, Yu H-M I, Nishmori K, Morrison C, and **Hsu W**. Skeletal stem cell stemness in development and congenital deformity. ***Science Translational Medicine***, 13, eabb4416.

2. Wnt signal production and transduction in development and disease

My contribution to our understanding of Wnt signaling begins with the cloning of the gene responsible for neural developmental defects associated with mouse *Fu*^{Fu}, *Fu*^{Ki,} and *Fu*^{Kb} alleles. The *Fu* locus encodes Axin1, a scaffold protein required for inhibition of the Wnt pathway (*Cell*, 1997). Axin1 is essential for the formation of a disruption complex, modulating phosphorylation and subsequent degradation of β-catenin (*JBC*, 1999). This seminal discovery has led to a paradigm shift in numerous fields of biomedical sciences, e.g. stem cell, developmental, and cancer biology. Furthermore, compared to an enormous wealth of knowledge on the

events in signal-receiving cells, we know very little about the maturation, sorting, and secretion of Wnt in signal-producing cells. My lab identified *Gpr177* as the mouse orthologue of *Drosophila Wntless* (*Wls/Evi/Srt*) required for the determination of the anterior-posterior axis during early embryogenesis (*PNAS*, 2009). Our findings suggest that Gpr177-mediated Wnt secretion cannot be substituted in a wide variety of developmental and pathogenic processes, e.g. gastrulation, craniofacial deformities, skeletal development (*JBMR*, 2013), hair follicle induction, tooth morphogenesis, pulmonary vasculogenesis, and mammary tumorigenesis. The Gpr177 studies have profound impacts on cellular signaling research in development and disease.

a. Zeng L, Fagotto F, Zhang T, **Hsu W**, Vasicek TJ, Perry III WL, Lee JJ, Tilghman SM, Gumbiner BM and Costantini F (1997). The mouse *Fused* locus encodes Axin, an inhibitor of the Wnt signaling pathway that regulates embryonic axis formation. ***Cell***, 90, 181-192. PMID: 9230313
b. **Hsu W**, Shakya R and Costantini F (2001). Impaired mammary gland and lymphoid development caused by inducible expression of Axin in transgenic mice. ***Journal of Cell Biology***, 155, 1055-1064. PMID: 11739413
c. Fu J, Jiang M, Mirando AJ, Yu HI and **Hsu W** (2009). Reciprocal regulation of Wnt and Gpr177/mouse Wntless is essential for embryonic axis formation. ***Proc Natl Acad Sci USA***, 106, 18598-18603. PMID: 19841259, PMCID: PMC2773984
d. Takamitsu Maruyama, Ming Jiang and **Wei Hsu** (2013). Gpr177, a novel locus for bone mineral density and osteoporosis, regulates osteogenesis and chondrogenesis in skeletal development. ***Journal of Bone and Mineral Research***, 28, 1150-9, Epub Nov 27, 2012. PMID: 23188710, PMCID: PMC3593783

3. SUMO-specific protease 2 in development and disease

SUMO-specific proteases are known to reverse sumoylation in many defined systems, their importance in mammalian development and pathogenesis remains largely elusive. Our proposed investigation here stems from my cloning of SUMO-specific protease 2 (SENP2) which interacts with Axin1 in the yeast 2-hybrid system in the late 90'. Using genetic approaches, we have begun to assess its function and elucidate its regulatory network. Work from my graduate student was the first to functionally characterize SENP2 in mammalian development (*PLOS Biology*, 2008). Disruption of SENP2 in mice reveals its essential role in the development of trophoblast stem cell niches and lineages. SENP2 specifically regulates the G1-S transition in mitotic and endoreduplication cell cycles through modulation of Mdm2-p53. Further exploration by a former postdoctoral fellow Ming Jiang identified a specific isoform of SENP2 necessary and sufficient to regulate the p53-induced stress responses. Our findings lead us to propose a mechanism underlying genome integrity mediated by SENP2 (*Cell Death & Differentiation*, 2011). The embryonic lethality associated with the global deletion of SENP2 led to our establishment of two new mouse strains permitting conditional deletion. Targeted disruption of SENP2 in the epiblasts (whole embryonic but not extra-embryonic tissues) showed that it's dispensable for embryogenesis, suggesting placental expression of SENP2 is necessary and sufficient for embryonic development. Our findings (*Scientific Reports*, 2016) argue against a previous report in *Molecular Cell* (Kang et al, 2010) showing a requirement of SENP2 in embryonic heart development. The heart defects associated with the global knockout are not primary but secondary defects due to placental insufficiency. Although dispensable for embryogenesis, SENP2 is required for postnatal development. Mice with neural-specific disruption of SENP2 exhibit severe neurodegeneration where Drp1-mediated mitochondrial dynamics are dysregulated (*PLOS Genetics*, 2014). This work provides a causal link of SUMO modification enzymes to neural cell survival, suggesting a new pathogenic mechanism for neurodegeneration.

a. Chiu, S, Asai N, Costantini F and **Hsu W** (2008). SUMO-specific protease 2 is essential for modulating p53-Mdm2 in development of trophoblast stem cell niches and lineages. ***PLOS Biology***, 6(12): e310. PMID: 19090619, PMCID: PMC2602722
b. Jiang M, Chiu S and **Hsu W** (2011). SUMO-specific protease 2 in Mdm2-mediated regulation of p53. ***Cell Death and Differentiation***, 18, 1005-1015. PMID: 21183956, PMCID: PMC3081924
c. Fu, J, Yu HI, Chiu S, Maruyama EO, Mirando AJ, Cheng J and **Hsu W** (2014). Disruption of SUMO-specific protease 2 induces mitochondria mediated neurodegeneration. ***PLOS Genetics***, 10(10): e1004579. PMID: 25299344, PMCID: PMC4191884
d. Maruyama EO, Lin H, Chiu S, Yu HI, Porter GA and **Hsu W**. Extraembryonic but not embryonic SUMO-specific protease 2 is required for heart development. ***Scientific Reports***, 6: 20999. PMID: 26883797

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