BIOGRAPHICAL SKETCH

NAME: Klein, Ophir D

eRA COMMONS USER NAME (agency login): OPHIRKLEIN

POSITION TITLE: Professor of Orofacial Sciences & Pediatrics

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date	FIELD OF STUDY
University of California, Berkeley	BA	06/1993	Cum Laude, Spanish
Yale University School of Medicine	PhD	06/1999	Genetics
Yale University School of Medicine	MD	06/2000	
Yale University School of Medicine	Resident	06/2003	Pediatrics
University of California, San Francisco	Resident	06/2007	Medical Genetics

A. PERSONAL STATEMENT

I am a developmental biologist as well as a pediatrician and medical geneticist, and I am interested in understanding developmental mechanisms in order to lay the groundwork for regenerative medicine. My clinical efforts center on patients with craniofacial anomalies, and my lab is focused on using the mouse as a model for understanding the genetic regulation of development and regeneration. We have focused in general on understanding how stem cells function during normal homeostasis as well as during injury and repair. One of my main areas of interest has been to elucidate the mechanisms that regulate adult stem cells in the mouse incisor as a first step toward being able to regenerate teeth and other craniofacial structures, and my laboratory has published a number of key discoveries in this field. Over the past few years, I have devoted considerable effort to building the craniofacial community at UCSF. I am the founding Director of the research Program in Craniofacial Biology; I serve as Chair the Division of Craniofacial Anomalies and, as of April 2016, Chief of the Division of Genetics in the Department of Pediatrics. In addition to our craniofacial work, my laboratory has invested a significant amount of effort of late into studying epithelial stem cells in the intestine. Our first foray into this field led to an exciting publication that investigated the identity of stem cells in the intestine. More recently, we have investigated how signaling pathways interact in the regulations of intestinal stem cells.

1. Tian H, Biehs B, Warming S, Leong KG, Rangell L, **Klein OD***, de Sauvage FJ*. A reserve stem cell population in small intestine renders Lgr5-positive cells dispensable. Nature. 2011 Sep 18;478(7368):255-9. PMID: 21927002; PMCID: PMC4251967.
2. Biehs B§, Hu JK§, Strauli NB, Sangiorgi E, Jung H, Heber RP, Ho S, Goodwin AF, Dasen JS, Capecchi MR, **Klein OD**. BMI1 represses Ink4a/Arf and Hox genes to regulate stem cells in the rodent incisor. Nat Cell Biol. 2013 Jul;15(7):846-52. PMID: 23728424; PMCID: PMC3735916.
3. Harjunmaa E, Seidel K, Häkkinen T, Renvoisé E, Corfe IJ, Kallonen A, Zhang ZQ, Evans AR, Mikkola ML, Salazar-Ciudad I, **Klein OD***, Jernvall J*. Replaying evolutionary transitions from the dental fossil record. Nature. 2014 Aug 7;512(7512):44-8. PMID: 25079326; PMCID: PMC4252015.
4. Prochazka J, Prochazkova M, Du W, Spoutil F, Tureckova J, Hoch R, Shimogori T, Sedlacek R, Rubenstein JL, Wittmann T, **Klein OD.** Migration of founder epithelial cells drives proper molar tooth positioning and morphogenesis. Dev Cell. 2015 Dec 21;35(6):713-24. PMID: 26702830; PMCID: PMC4710359.

B. POSITIONS AND HONORS

Positions and Employment

2007 - 2011	Assistant Professor of Orofacial Sciences & Pediatrics, University of California, San Francisco
2009 -	Director, Program in Craniofacial Biology, University of California, San Francisco
2011 - 2015	Associate Professor of Orofacial Sciences & Pediatrics, University of California, San Francisco
2013 -	Chair, Division of Craniofacial Anomalies, University of California, San Francisco
2013 -	Medical Director, Craniofacial Center, University of California, San Francisco
2014 - 2016	Chair, Division of Orthodontics, University of California, San Francisco
2015 -	Professor of Orofacial Sciences & Pediatrics, University of California, San Francisco
2016 -	Chief, Division of Medical Genetics, University of California, San Francisco

Other Experience and Professional Memberships

2003 -	Member, American Society of Human Genetics
2004 -	Member, American College of Medical Genetics
2007 -	Member, International and American Associations for Dental Research
2008 -	Member, American Cleft Palate-Craniofacial Association
2009 -	Member, Society for Craniofacial Genetics
2009 -	Member, Society for Developmental Biology
2009 -	Director (2009-2012); Vice president (2013-2014); President-elect (2014-2015); President (2015-16) Craniofacial Biology Group, International Association for Dental Research
2010 -	Editorial Board, Frontiers in Craniofacial Biology
2010 - 2010	Grant reviewer, Medical Research Council, UK
2011 - 2011	Ad hoc member, NIH study section (ODCS and RG1 MOSS SEP)
2012 -	Editorial Board, Molecular Genetics and Genomic Medicine
2012 - 2012	Grant reviewer, Research Foundation - Flanders
2012 - 2012	Chair, Society for Craniofacial Genetics Annual Meeting, San Francisco, CA
2012 - 2012	Ad hoc member, NIH study section (SBDD)
2012 - 2013	Guest Editor, PNAS
2013 -	Editorial Board, International Journal of Oral Science
2013 - 2013	Grant reviewer, Biotechnology and Biological Sciences Research Council (BBSRC), UK
2013 - 2013	Ad hoc member, NIH study section (BMBI)
2013 - 2013	Grant reviewer, The Wellcome Trust, UK
2014 - 2014	Grant reviewer, Danish Council for Independent Research
2014 - 2014	Ad hoc member, NIH special emphasis panel (ZHD1 DRG-H [NK] 2)
2014 - 2014	Ad hoc member, NIDCR Board of Scientific Counselors
2014 - 2015	Guest Editor, Journal of Dental Research Special Issue on Craniofacial Stem Cells
2014 - 2017	Member, American Society of Human Genetics Annual Meeting Program Committee
2014 - 2018	Vice chair (2016) and Chair (2018), Craniofacial Gordon Research Conference
2014 - 2020	Standing member, NIH study section (DSR)

Honors

1989	Chancellor's Scholarship, University of California, Berkeley
1993	NIH Medical Scientist Training Program, NIH
1999	Dean’s Distinguished Thesis Commendation, Yale University Graduate School
2004	Fellow, American Academy of Pediatrics
2004	Fellow, Pediatric Scientist Development Program, NICHD
2005	David W. Smith Pediatric Trainee Research Award, Western Society for Pediatric Research
2005	Young Investigator Research Grant Award, American Academy of Pediatrics
2005	Fellow Research Award, Society for Pediatric Research
2008	United States Bone and Joint Decade Young Investigator
2008	Elected member, Society for Pediatric Research
2008	New Faculty Award, California Institute of Regenerative Medicine (CIRM)
2008	Scholar, Culpeper Foundation
2009	March of Dimes Basil O’Connor Starter Award, March of Dimes Foundation
2009	Harold M. Frost Young Investigator Award, American Society for Bone and Mineral Research
2009	Elected member, Western Society for Pediatric Research
2010	Director’s New Innovator Award, NIH
2013	Elected member, American Society for Clinical Investigation
2013	CIRM Physician Scientist Award, CIRM
2013	Outstanding Faculty Mentorship Award, UCSF Graduate Students Association
2014	Larry L. Hillblom Distinguished Professor in Craniofacial Anomalies, UCSF
2015	Fellow, American Association for the Advancement of Science (AAAS)
2015	E. Mead Johnson Award, Society for Pediatric Research
2015	Faculty Research Lecturer Award, UCSF School of Dentistry
2016	Charles J. Epstein Professor of Human Genetics

C. Contribution to Science ([§] = co-first authors; * = co-senior authors)

1. The intestine is one of the most regenerative tissues in our bodies, and understanding the identity and behavior of the stem cells that drive this renewal is of great interest. When we began our work in this field, two stem cell populations had been postulated in the small intestine epithelium. The central and unexpected finding in our first paper studying intestinal renewal was that one group of progenitor cells can repopulate the epithelium in the absence of another group. Our findings demonstrated that an alternative, more slowly cycling cell population in the small intestine is able to compensate for loss of fast-cycling stem cells under both homeostatic and pathological conditions, providing an important general paradigm for epithelial stem cell biology. We have gone on to study the signaling pathways that regulate intestinal stem cells, as well as to use in vitro models of intestinal renewal.
   a. Tian H, Biehs B, Warming S, Leong KG, Rangell L, **Klein OD***, de Sauvage FJ*. A reserve stem cell population in small intestine renders Lgr5-positive cells dispensable. Nature. 2011 Sep 18;478(7368):255-9. PMID: 21927002; PMCID: PMC4251967.
   b. Nusse YM, **Klein OD**. If a stem cell dies in the crypt, and no one is around to see it…. Cell Stem Cell. 2013 Apr 4;12(4):389-90. PMID: 23561439.
   c. Tian H[§], Biehs B[§], Chiu C, Siebel CW, Wu Y, Costa M, de Sauvage FJ*, **Klein OD***. Opposing activities of notch and wnt signaling regulate intestinal stem cells and gut homeostasis. Cell Rep. 2015 Apr 7;11(1):33-42. PMID: 25818302; PMCID: PMC4394041.
   b. Belinson H, Savage AK, Fadrosh D, Kuo YM, Lin D, Valladares R, Nusse Y, Wynshaw-Boris A, Lynch SV, Locksley RM, **Klein OD**. Dual epithelial and immune cell function of Dvl1 regulates gut microbiota composition and intestinal homeostasis. JCI Insight 2016 July 7;1(10):e85395. doi:10.1172/jci.insight.85395. PMID: 27525310; PMCID: PMC4979554.
2. The maintenance, repair and growth of adult organs depend on tissue-specific populations of stem cells. Unlike human teeth, the mouse incisor grows continuously throughout the life of the animal, providing a model for understanding how adult stem cells contribute to dental renewal. A major research accomplishment of my group has been the identification and characterization of stem cells in the continuously-growing rodent incisor. We have investigated the regenerative capacity of these cells by combining lineage tracing and functional analyses with evolutionary and comparative approaches. Our work has led to an understanding of how these epithelial stem cells function. Specifically, we have found markers of the stem cells, identified Sonic Hedgehog and Fibroblast Growth Factor signaling as critical regulators of the stem cells and their progeny, and discovered that E-cadherin maintains stem cells in their niche. We have also developed techniques for isolation and culture of incisor stem cells, and we have collaborated with other groups to study the roles of several signaling pathways, microRNAs and transcription factors in the incisor stem cell system. Thus, in a relatively short period of time, we have led the way in opening up a new field in mammalian stem cell biology.
   a. Seidel K[§], Ahn CP[§], Lyons D, Nee A, Ting K, Brownell I, Cao T, Carano RA, Curran T, Schober M, Fuchs E, Joyner A, Martin GR, de Sauvage FJ*, **Klein OD***. Hedgehog signaling regulates the generation of ameloblast progenitors in the continuously growing mouse incisor. Development. 2010 Nov;137(22):3753-61. PMID: 20978073; PMCID: PMC3049275.
   b. Li CY, Cha W, Luder HU, Charles RP, McMahon M, Mitsiadis TA, **Klein OD**. E-cadherin regulates the behavior and fate of epithelial stem cells and their progeny in the mouse incisor. Dev Biol. 2012 Jun 15;366(2):357-66. PMID: 22537490; PMCID: PMC3690274.
   c. Juuri E, Saito K, Ahtiainen L, Seidel K, Tummers M, Hochedlinger K, **Klein OD**, Thesleff I, Michon F. Sox2+ stem cells contribute to all epithelial lineages of the tooth via Sfrp5+ progenitors. Dev Cell. 2012 Aug 14;23(2):317-28. PMID: 22819339; PMCID: PMC3690347.
   d. Biehs B[§], Hu JK[§], Strauli NB, Sangiorgi E, Jung H, Heber RP, Ho S, Goodwin AF, Dasen JS, Capecchi MR, **Klein OD**. BMI1 represses Ink4a/Arf and Hox genes to regulate stem cells in the rodent incisor. Nat Cell Biol. 2013 Jul;15(7):846-52. PMID: 23728424; PMCID: PMC3735916.
3. Much of our knowledge about mammalian evolution comes from examination of dental fossils, because the highly calcified enamel that covers teeth causes them to be among the best-preserved organs. As mammals entered new ecological niches, many changes in tooth number and shape occurred, presumably as adaptations to new diets. We have found that altering genetic dosage of signaling molecules can recapitulate ancestral dental characters, and we have also studied how stem cells evolved in teeth. In a recent paper, we created rodent teeth that harken back in evolutionary time. We achieved this by adding

back absent proteins to produce the step-wise transitions observed in the fossil record. Surprisingly, the experiments recapitulated many of the known transitions of tooth evolution. By making a molar that mimics features found in an ancestral rodent that roamed the earth 60 million years ago, we demonstrated a new way to explore how genetic changes affect mammalian development.

a. Charles C, Lazzari V, Tafforeau P, Schimmang T, Tekin M, **Klein O***, Viriot L*. Modulation of Fgf3 dosage in mouse and men mirrors evolution of mammalian dentition. Proc Natl Acad Sci U S A. 2009 Dec 29;106(52):22364-8. PMID: 20018768; PMCID: PMC2799759.

b. Charles C§, Hovorakova M§, Ahn Y, Lyons DB, Marangoni P, Churava S, Biehs B, Jheon A, Lesot H, Balooch G, Krumlauf R, Viriot L, Peterkova R, **Klein OD**. Regulation of tooth number by fine-tuning levels of receptor-tyrosine kinase signaling. Development. 2011 Sep;138(18):4063-73. PMID: 21862563; PMCID: PMC3160100.

c. Harjunmaa E, Seidel K, Häkkinen T, Renvoisé E, Corfe IJ, Kallonen A, Zhang ZQ, Evans AR, Mikkola ML, Salazar-Ciudad I, **Klein OD***, Jernvall J*. Replaying evolutionary transitions from the dental fossil record. Nature. 2014 Aug 7;512(7512):44-8. PMID: 25079326; PMCID: PMC4252015.

d. Tapaltsyan V§, Eronen JT§, Lawing AM, Sharir A, Janis C, Jernvall J*, **Klein OD***. Continuously growing rodent molars result from a predictable quantitative evolutionary change over 50 million years. Cell Rep. 2015 May 5;11(5):673-80. PMID: 25921530; PMCID: PMC4426059.

4. A principal research emphasis in my group involves studying components of the signaling pathways responsible for embryonic development and regeneration. Such signaling occurs via soluble molecules that are members of the FGF, HH, TGF-β, Notch and WNT families. We have shown that inactivating mutations in antagonists of FGF signaling, known as Sprouty genes, result in several developmental abnormalities. Ongoing efforts in this area of investigation include genetic and biochemical approaches to analysis of positive and negative regulators of signaling. We are studying the roles of these signaling regulators in the patterning and outgrowth of teeth and other craniofacial structures, including taste papillae and the facial skeleton, as well as in the genital tubercle, temporomandibular joint, appendicular skeleton, and gastrointestinal tract.

   a. Metzger RJ, **Klein OD**, Martin GR, Krasnow MA. The branching programme of mouse lung development. Nature. 2008 Jun 5;453(7196):745-50. PMID: 18463632; PMCID: PMC2892995.

   b. Petersen CI§, Jheon AH§, Mostowfi P, Charles C, Ching S, Thirumangalathu S, Barlow LA, **Klein OD**. FGF signaling regulates the number of posterior taste papillae by controlling progenitor field size. PLoS Genet. 2011 Jun;7(6):e1002098. PMID: 21655085; PMCID: PMC3107195.

   c. Castillo D§, Seidel K§, Salcedo E, Ahn C, de Sauvage FJ, **Klein OD*,** Barlow LA*. Induction of ectopic taste buds by SHH reveals the competency and plasticity of adult lingual epithelium. Development. 2014 Aug;141(15):2993-3002. PMID: 24993944. PMCID: PMC4197660.

   d. Jheon AH*, Prochazkova M, Meng B, Wen T, Lim YJ, Naveau A, Espinoza R, Cox TC, Sone ED, Ganss B, Siebel CW, **Klein OD*.** Inhibition of notch signaling during mouse incisor renewal leads to enamel defects. J Bone Miner Res. 2016 Jan;31(1):152-62. PMID: 26179131.

5. Our studies in mice have provided important insights into mammalian tooth morphogenesis, a process that is controlled by interactions between the oral epithelium and the neural crest-derived mesenchyme. These interactions are mediated by signaling pathways, such as the receptor-tyrosine kinase pathway initiated by the FGFs. We have discovered novel mechanisms by which tooth number and shape are controlled, as well as how the mineralized components of the dentition form.

   a. **Klein OD**, Minowada G, Peterkova R, Kangas A, Yu BD, Lesot H, Peterka M, Jernvall J, Martin GR. Sprouty genes control diastema tooth development via bidirectional antagonism of epithelial-mesenchymal FGF signaling. Dev Cell. 2006 Aug;11(2):181-90. PMID: 16890158; PMCID: PMC2847684.

   b. Jheon AH, Mostowfi P, Snead ML, Ihrie RA, Sone E, Pramparo T, Attardi LD, **Klein OD**. PERP regulates enamel formation via effects on cell-cell adhesion and gene expression. J Cell Sci. 2011 Mar 1;124(Pt 5):745-54. PMID: 21285247; PMCID: PMC3039019.

   c. Prochazka J, Prochazkova M, Du W, Spoutil F, Tureckova J, Hoch R, Shimogori T, Sedlacek R, Rubenstein JL, Wittmann T, **Klein OD.** Migration of founder epithelial cells drives proper molar tooth positioning and morphogenesis. Dev Cell. 2015 Dec 21;35(6):713-24. PMID: 26702830; PMCID: PMC4710359.

d. Li CY[§*], Hu J[§], Lu H, Lan J, Du W, Galicia N, **Klein OD***. aE-catenin inhibits YAP/TAZ activity to regulate signalling centre formation during tooth development. Nat Commun. 2016 Jul 13; 7:12133. PMID: 27405641; PMCID: PMC4947177.

Complete List of Published Work in My Bibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/ophir.klein.1/bibliography/40450360/public/?sort=date&direction=descending

D. RESEARCH SUPPORT

Active

R35-DE026602 (PI: Klein) 9/22/16-6/30/24 Effort: 32.80%, 3.94 calendar
NIDCR $400,000 direct costs/$7,845,750 total award
Harnessing natural stem cell-based strategies for mammalian dental renewal
The major goal of this project is to understand how stem cells enable dental renewal.

U01-DK103147 (PI: Klein) 9/5/14-8/31/19 Effort: 10.00%, 1.20 calendar
NIDDK $256,546 direct costs/$1,882,188 total award
Regulation of distinct pools of intestinal stem cells
The major goal is to study how the interaction between signaling pathways regulates behavior of adult stem cells.

U01-DE024440 (PI: Spritz/Klein) 5/16/14-4/30/19 Effort: 4.00%, 0.48 calendar
NIDCR $131,830 direct costs/$987,063 total award
Developing 3D Craniofacial Morphometry Data and Tools to Transform Dysmorphology
The major goal of this project is to use morphometrics to diagnose syndromes.

RN3-06525 (PI: Klein) 4/1/13-3/31/18 Effort: 30.00%, 3.60 calendar
California Institute of Regenerative Medicine $400,000 direct costs/$3,084,000 total award
Stem cell therapy for inflammatory bowel disease
The major goal of this project is to utilize stem cells for generation of intestinal organoids to identify new therapies for inflammatory bowel disease.

R01-DE024988 (PI: Klein) 7/1/15-6/30/17 Effort: 15.20%, 1.82 calendar
NIDCR $250,000 direct costs/$792,500 total award
The role of Hippo and YAP/TAZ in dental renewal
The major goal of this grant is to study the role of Hippo signaling in renewal of the rodent incisor.