Cincinnati Children's

2015 Research Annual Report

Developmental Biology

RESEARCH AND TRAINING DETAILS

Click to view members

Faculty	**23**
Joint Appointment Faculty	**25**
Research Fellows	**45**
Research Students	**59**
Support Personnel	**63**
Direct Annual Grant Support	**$6,827,339**
Peer Reviewed Publications	**38**

CLINICAL ACTIVITIES AND TRAINING

Clinical Fellows	**2**
Other Students	**37**

Download Report in PDF Format Visit Developmental Biology

Research Highlights

Worlds first human stomach tissue from stem cells

The laboratory of Jim Wells, PhD, established methods to grow the first human stomach tissue in a dish from stem cells. By manipulating extracellular signaling pathways in a temporal manner that recapitulates normal embryonic development of the stomach, Wells and colleagues directed the *in vitro* differentiation of human pluripotent stem cells (hPSCs) into three-

dimensional human gastric organoids (hGO) or mini stomachs. They used hGO cultures to identify novel signaling mechanisms that regulate early endoderm patterning and gastric endocrine cell differentiation upstream of the transcription factor NEUROG3. In collaboration with researchers at the University of Cincinnati College of Medicine, they went on to model pathogenesis of gastric disease caused by H. pylori bacteria infection, a major cause of peptic ulcer disease and stomach cancer. This is important because the embryonic development, architecture and physiology of animal stomachs are very different from man, making animal models suboptimal for studying human stomach organogenesis and pathogenesis. This breakthrough in generating hGOs, reported in the journal *Nature*, presents new opportunities for drug discovery, modeling early stages of stomach cancer and studying some of the underpinnings of obesity related diabetes.

Significant Publications

McCracken KW, Cata EM, Crawford CM, Sinagoga KL, Schumacher M, Rockich BE, Tsai YH, **Mayhew CN**, Spence JR, Zavros Y, **Wells JM**. Modelling Human Development and Disease in Pluripotent Stem-Cell-Derived Gastric Organoids. *Nature*. 2014 Dec 18;516(7531):400-4.

> Species differences in embryonic development and architecture of the adult stomach make animal models suboptimal for studying human stomach organogenesis and pathogenesis. Here we report the *de novo* generation of three-dimensional human gastric tissue *in vitro* through the directed differentiation of human pluripotent stem cells (hPSCs). By manipulating extracellular signaling pathways in a temporal manner that recapitulates stomach development, human gastric organoids (hGOs) progressed through molecular and morphogenetic stages that were nearly identical to the developing antrum of the mouse stomach. We used hGO cultures to identify novel signaling mechanisms that regulate early endoderm patterning and gastric endocrine cell differentiation upstream of the transcription factor NEUROG3 and to model pathogenesis of gastric disease caused by *H Pylori* infection.

McCauley HA, Liu C-Y, Attia A, Wikenheiser-Brokamp KA, Zhang Y, Whitsett JA, **Guasch G**. TGFβ signaling inhibits goblet cell differentiation via SPDEF in the conjunctival epithelium. *Development.* 2014 Dec;141(23):4628-39.

> This manuscript highlights findings into the understanding of goblet cell differentiation. In studying TGFβ signaling, a crucial regular of cell growth and differentiation in many cell types, we discovered that loss of this pathway in epithelial cells resulted in goblet cell metaplasia in the ocular surface. To our knowledge, this is the first report of TGFβ signaling controlling goblet cell differentiation in any system. Moreover, our findings unveil a hitherto unrecognized role for TGFβ signaling in controlling goblet cell differentiation via a common regulator (SPDEF) of goblet cells, revealing new insights into how goblet cells might be deregulated in disease states. The novel findings in our paper will have broad appeal to the TGFβ field, and those interested in goblet cell biology, and open the door for many potential applications.

Ren W, Zhang Y, Li M, Wu L, Wang G, Baeg GH, You J, Li Z, **Lin X**. Windpipe Controls Drosophila Intestinal Homeostasis by Regulating Jak/Stat Pathway Via Promoting Receptor Endocytosis and Lysosomal Degradation. *PLoS Genet.* 2015 Apr 29:11(4):e1005180.

> In this paper, investigators identified *windpipe (wdp)* as a novel negative feedback regulator of the JAK/STAT pathway during intestinal development. They found that expression of *wdp* was induced by high levels of JAK/STAT signaling, and loss of Wdp leads to loss of midgut homeostasis as well as increased proliferation of intestinal stem cells. Furthermore, they demonstrated that Wdp in turn negatively regulates JAK/STAT signaling activity through promoting domeless receptor endocytosis and lysosomal degradation. In this way, high levels of JAK/STAT signaling is switched off by Wdp. All together, this paper provides a new mechanism by which over-proliferated intestinal stem cells return to the homeostatic state after tissue damage.

Liu Z, Brunskill E, Boyle S, Chen S, Turkoz M, Guo Y, Grant R, **Kopan R**. Second-Generation Notch1 Activity-Trap Mouse Line (N1ip::Crehi) Provides a More Comprehensive Map of Cells Experiencing Notch1 Activity. *Development.* 2015 Mar 15;142(6):1193-202.

Cells probe their immediate environment using notch receptors. When neighboring cells “shakes hands” they engage a ligand with the receptor. Notch undergoes proteolysis sending a part of the molecule to the nucleus. The paper describes a tool designed to capture information describing which cells received a notch signal. The Kopan Lab produced several Notch1 activity-trap mouse lines, termed N1IP::CreLO, N1IP::CreHI and N1IP::CreERT2, that respond to the “hand shake” by releasing an enzyme (Cre) that can rearrange a reporter from an “off: to an ”on” state. The cells and all its descendants will be marked. These trap lines form a complementary series: N1IP::CreHI is a sensitive line, mapping weak and strong Notch1 activation patterns *in vivo.* N1IP::CreLO traps only the stronger interactions (Figure), and N1IP::CreERT2 maps strong interaction but only when the investigator adds a drug to activate the enzyme released by the molecular “hand shake”. These new lines reveal variations in Notch1 signal strength define different notch-dependent decision across developmental time. For example, early- versus late-born cortical neurons, or anterior versus posterior stem cells along the intestine, experience different “strength”. The tools generated in this study can be used to address the question whether an increase in signal strength as the consequence of genetic or pharmaceutical intervention can impact pathology or physiology in a desired manner.

Brunskill EW, **Park JS**, Chung E, Chen F, Magella B, **Potter SS**. Single Cell Dissection of Early Kidney Development: Multilineage Priming. *Development.* 2014 Aug;141(15):3093-101.

Developmental biologists seek to understand the gene expression programs that drive the formation of organs. In the long run this will allow the regeneration or repair of diseased or damaged organs. In this paper a high resolution technique was used that allowed the analysis of gene expression patterns in single cells of the developing kidney. Surprisingly, it was found that a principle referred to as multilineage priming was employed. Individual cells actively express genes of multiple differentiated cell types before deciding on a single developmental direction. In previous studies, examining ensemble averages of pools of cells, this effect had been blurred out.

Division Publications

1. Andersen J, Urban N, Achimastou A, Ito A, Simic M, Ullom K, Martynoga B, Lebel M, Goritz C, Frisen J, Nakafuku M, Guillemot F. **A transcriptional mechanism integrating inputs from extracellular signals to activate hippocampal stem cells**. *Neuron*. 2014; 83:1085-97.

2. Broering TJ, Wang YL, Pandey RN, Hegde RS, Wang SC, Namekawa SH. **BAZ1B is dispensable for H2AX phosphorylation on Tyrosine 142 during spermatogenesis**. *Biol Open*. 2015; 4:873-84.

3. Brunskill EW, Park JS, Chung E, Chen F, Magella B, Potter SS. **Single cell dissection of early kidney development: multilineage priming**. *Development*. 2014; 141:3093-101.

4. Brunskill EW, Potter SS. **Pathogenic pathways are activated in each major cell type of the glomerulus in the Cd2ap mutant mouse model of focal segmental glomerulosclerosis**. *BMC Nephrol*. 2015; 16:71.

5. Cha J, Bartos A, Park C, Sun X, Li Y, Cha SW, Ajima R, Ho HY, Yamaguchi TP, Dey SK. **Appropriate crypt formation in the uterus for embryo homing and implantation requires Wnt5a-ROR signaling**. *Cell Rep*. 2014; 8:382-92.

6. Craig MP, Grajevskaja V, Liao HK, Balciuniene J, Ekker SC, Park JS, Essner JJ, Balciunas D, Sumanas S. **Etv2 and fli1b function together as key regulators of vasculogenesis and angiogenesis**. *Arterioscler Thromb Vasc Biol*. 2015; 35:865-76.

7. Deans AR, Lewis SE, Huala E, Anzaldo SS, Ashburner M, Balhoff JP, Blackburn DC, Blake JA, Burleigh JG, Chanet B, Cooper LD, Courtot M, Csosz S, Cui H, Dahdul W, Das S, Dececchi TA, Dettai A, Diogo R, Druzinsky RE, Dumontier M, Franz NM, Friedrich F, Gkoutos GV, Haendel M, Harmon LJ, Hayamizu TF, He Y, Hines HM, Ibrahim N, Jackson LM, Jaiswal P, James-Zorn C, Kohler S, Lecointre G, Lapp H, Lawrence CJ, Le Novere N, Lundberg JG, Macklin J, Mast AR, Midford PE, Miko I, Mungall CJ, Oellrich A, Osumi-Sutherland D, Parkinson H, Ramirez MJ, Richter S, Robinson PN, Ruttenberg A, Schulz KS, Segerdell E, Seltmann KC, Sharkey MJ, Smith AD, Smith B, Specht CD, Squires RB, Thacker RW, Thessen A, Fernandez-Triana J, Vihinen M, Vize PD, Vogt L, Wall CE, Walls RL, Westerfeld M, Wharton RA, Wirkner CS, Woolley JB, Yoder MJ, Zorn AM, Mabee P. **Finding our way through phenotypes**. *PLoS Biol*. 2015; 13:e1002033.

8. Delloye-Bourgeois C, Jacquier A, Charoy C, Reynaud F, Nawabi H, Thoinet K, Kindbeiter K, Yoshida Y, Zagar Y, Kong Y, Jones YE, Falk J, Chedotal A, Castellani V. **PlexinA1 is a new Slit receptor and mediates axon guidance function of Slit C-terminal fragments**. *Nat Neurosci*. 2015; 18:36-45.

9. Demehri S, Yockey LJ, Visness CM, Jaffee KF, Turkoz A, Wood RA, O'Connor GT, Kattan M, Gern JE, Gergen PJ, Holtzman M, Bloomberg G, Kopan R. **Circulating TSLP associates with decreased wheezing in non-atopic preschool children: data from the URECA birth cohort**. *Clin Exp Allergy*. 2014; 44:851-7.

10. Dye BR, Hill DR, Ferguson MA, Tsai YH, Nagy MS, Dyal R, Wells JM, Mayhew CN, Nattiv R, Klein OD, White ES, Deutsch GH, Spence JR. **In vitro generation of human pluripotent stem cell derived lung organoids**. *Elife*. 2015; 4.

11. Gilbert S, Nivarthi H, Mayhew CN, Lo YH, Noah TK, Vallance J, Rulicke T, Muller M, Jegga AG, Tang W, Zhang D, Helmrath M, Shroyer N, Moriggl R, Han X. **Activated STAT5 confers resistance to intestinal injury by increasing intestinal stem cell proliferation and regeneration**. *Stem Cell Reports*. 2015; 4:209-25.

12. Gregory J, Cannell J, Kofron M, Yeghiazarian L, Nistor V. **Functionalization of hybrid poly(n-isopropylacrylamide) hydrogels for Escherichia coli cell capture via adsorbed intermediate dye molecule**. *Journal of Applied Polymer Science*. 2015; 132:nfp-nlp.

13. Gu Z, Imai F, Kim IJ, Fujita H, Katayama K, Mori K, Yoshihara Y, Yoshida Y. **Expression of the immunoglobulin superfamily cell adhesion molecules in the developing spinal cord and dorsal root ganglion**. *PLoS One*. 2015; 10:e0121550.

14. Gupta A, Bischoff A, Pena A, Runck LA, Guasch G. **The great divide: septation and malformation of the cloaca, and its implications for surgeons**. *Pediatr Surg Int*. 2014; 30:1089-95.

15. Hu YC, Namekawa SH. **Functional significance of the sex chromosomes during spermatogenesis**. *Reproduction*. 2015; 149:R265-77.

16. Hufnagel RB, Arno G, Hein ND, Hersheson J, Prasad M, Anderson Y, Krueger LA, Gregory LC, Stoetzel C, Jaworek TJ, Hull S, Li A, Plagnol V, Willen CM, Morgan TM, Prows CA, Hegde RS, Riazuddin S, Grabowski GA, Richardson RJ, Dieterich K, Huang T, Revesz T, Martinez-Barbera JP, Sisk RA, Jefferies C, Houlden H, Dattani MT, Fink JK, Dollfus H, Moore AT, Ahmed ZM. **Neuropathy target esterase impairments cause Oliver-McFarlane and Laurence-Moon syndromes**. *J Med Genet*. 2015; 52:85-94.

17. Ilagan MX, Kopan R. **Monitoring Notch activation in cultured mammalian cells: luciferase complementation imaging assays**. *Methods Mol Biol*. 2014; 1187:155-68.

18. Ilagan MX, Kopan R. **Monitoring Notch activation in cultured mammalian cells: transcriptional reporter assays**. *Methods Mol Biol*. 2014; 1187:143-54.

19. Ji H, Zhang X, Oh S, Mayhew CN, Ulm A, Somineni HK, Ericksen M, Wells JM, Khurana Hershey GK. **Dynamic transcriptional and epigenomic reprogramming from pediatric nasal epithelial cells to induced pluripotent stem cells**. *J Allergy Clin Immunol*. 2015; 135:236-44.

20. Karpinka JB, Fortriede JD, Burns KA, James-Zorn C, Ponferrada VG, Lee J, Karimi K, Zorn AM, Vize PD. **Xenbase, the Xenopus model organism database; new virtualized system, data types and genomes**. *Nucleic Acids Res*. 2015; 43:D756-63.

21. Kumar S, Xu J, Kumar RS, Lakshmikanthan S, Kapur R, Kofron M, Chrzanowska-Wodnicka M, Filippi MD. **The small GTPase Rap1b negatively regulates neutrophil chemotaxis and transcellular diapedesis by inhibiting Akt activation**. *J Exp Med*. 2014; 211:1741-58.

22. Liu H, Xu J, Liu CF, Lan Y, Wylie C, Jiang R. **Whole transcriptome expression profiling of mouse limb tendon development by using RNA-seq**. *J Orthop Res*. 2015; 33:840-8.

23. Liu Z, Brunskill E, Boyle S, Chen S, Turkoz M, Guo Y, Grant R, Kopan R. **Second-generation Notch1 activity-trap mouse line (N1IP::CreHI) provides a more comprehensive map of cells experiencing Notch1 activity**. *Development*. 2015; 142:1193-202.

24. McCauley HA, Liu CY, Attia AC, Wikenheiser-Brokamp KA, Zhang Y, Whitsett JA, Guasch G. **TGFbeta signaling inhibits goblet cell differentiation via SPDEF in conjunctival epithelium**. *Development*. 2014; 141:4628-39.

25. McCracken KW, Cata EM, Crawford CM, Sinagoga KL, Schumacher M, Rockich BE, Tsai YH, Mayhew CN, Spence JR, Zavros Y, Wells JM. **Modelling human development and disease in pluripotent stem-cell-derived gastric organoids**. *Nature*. 2014; 516:400-4.

26. McGrath PS, Wells JM. **SnapShot: GI tract development**. *Cell*. 2015; 161:176-176 e1.

27. Nolan K, Kattamuri C, Luedeke DM, Angerman EB, Rankin SA, Stevens ML, Zorn AM, Thompson TB. **Structure of neuroblastoma suppressor of tumorigenicity 1 (NBL1): insights for the functional variability across bone morphogenetic protein (BMP) antagonists**. *J Biol Chem*. 2015; 290:4759-71.

28. Pooya S, Liu X, Kumar VB, Anderson J, Imai F, Zhang W, Ciraolo G, Ratner N, Setchell KD, Yoshida Y, Jankowski MP, Dasgupta B. **The tumour suppressor LKB1 regulates myelination through mitochondrial metabolism**. *Nat Commun*. 2014; 5:4993.

29. Rankin SA, Thi Tran H, Wlizla M, Mancini P, Shifley ET, Bloor SD, Han L, Vleminckx K, Wert SE, Zorn AM. **A Molecular atlas of Xenopus respiratory system development**. *Dev Dyn*. 2015; 244:69-85.

30. Ren W, Zhang Y, Li M, Wu L, Wang G, Baeg GH, You J, Li Z, Lin X. **Windpipe controls Drosophila intestinal homeostasis by regulating JAK/STAT pathway via promoting receptor endocytosis and lysosomal degradation**. *PLoS Genet*. 2015; 11:e1005180.

31. Schumacher JA, Zhao EJ, Kofron MJ, Sumanas S. **Two-color fluorescent in situ hybridization using chromogenic substrates in zebrafish**. *Biotechniques*. 2014; 57:254-6.

32. Simon M, Richard EM, Wang X, Shahzad M, Huang VH, Qaiser TA, Potluri P, Mahl SE, Davila A, Nazli S, Hancock S, Yu M, Gargus J, Chang R, Al-Sheqaih N, Newman WG, Abdenur J, Starr A, Hegde R, Dorn T, Busch A, Park E, Wu J, Schwenzer H, Flierl A, Florentz C, Sissler M, Khan SN, Li R, Guan MX, Friedman TB, Wu DK, Procaccio V, Riazuddin S, Wallace DC, Ahmed ZM, Huang T, Riazuddin S. **Mutations of human NARS2, encoding the mitochondrial asparaginyl-tRNA synthetase, cause nonsyndromic deafness and Leigh syndrome**. *PLoS Genet*. 2015; 11:e1005097.

33. Sinagoga KL, Wells JM. **Generating human intestinal tissues from pluripotent stem cells to study development and disease**. *EMBO J*. 2015; 34:1149-1163.

34. Sun Y, Florer J, Mayhew CN, Jia Z, Zhao Z, Xu K, Ran H, Liou B, Zhang W, Setchell KD, Gu J, Grabowski GA. **Properties of neurons derived from induced pluripotent stem cells of Gaucher disease type 2 patient fibroblasts: potential role in neuropathology**. *PLoS One*. 2015; 10:e0118771.

35. Van Battum EY, Gunput RA, Lemstra S, Groen EJ, Yu KL, Adolfs Y, Zhou Y, Hoogenraad CC, Yoshida Y, Schachner M, Akhmanova A, Pasterkamp RJ. **The intracellular redox protein MICAL-1 regulates the development of hippocampal mossy fibre connections**. *Nat Commun*. 2014; 5:4317.

36. Wells JM. **Developmental biology. Regional identity of gut stem cells--one gene to rule them all**. *Nat Rev Gastroenterol Hepatol*. 2015; 12:125-6.

37. Young SM, Liu S, Joshi R, Batie MR, Kofron M, Guo J, Woods JC, Varisco BM. **Localization and stretch-dependence of lung elastase activity in development and compensatory growth**. *J Appl Physiol (1985)*. 2015; 118:921-31.

38. Zeng X, Han L, Singh SR, Liu H, Neumuller RA, Yan D, Hu Y, Liu Y, Liu W, Lin X, Hou SX. **Genome-wide RNAi screen identifies networks involved in intestinal stem cell regulation in Drosophila**. *Cell Rep*. 2015; 10:1226-38.

Faculty, Staff, and Trainees

Faculty Members

Raphael Kopan, PhD, Professor
Leadership Division Director
Research Interests Notch signaling, mouse.

Nadean Brown (end 8/31/14), PhD, Adjunct
Research Interests Eye development, mouse and drosophila.

Kenneth Campbell, PhD, Professor
Leadership Co-Associate Director; Director, Basic Science Research in Surgical Services
Research Interests CNS patterning, mammal.

Sang-Wook Cha, PhD, Assistant Professor
Research Interests Early vertebrate development.

Chieh Chang (end 8/15/14), PhD, Assistant Professor
Research Interests Nervous system, C. elegans.

Chiou-Fen Chuang, PhD, Adjunct
Research Interests Nervous system, C. elegans, laterality.

Vaughn Cleghon, PhD, Associate Professor
Research Interests Kinase function in development; signaling.

Tiffany Cook, PhD, Associate Professor
Research Interests Eye development, drosophila.

Brian Gebelein, PhD, Associate Professor
Research Interests Transcriptional regulation, drosophila; body patterning; nervous system.

Geraldine Guasch (adjunct 5/1/15), PhD, Assistant Professor

Research Interests Stem cells in epithelial tissues and their role in tumorigenesis; transitional epithelium and anorectal malformations.

Rashmi S. Hegde, PhD, Professor
Leadership Director, Molecular and Developmental Biology Graduate Program
Research Interests Protein structure/function.

Yueh-Chiang Hu, PhD, Assistant Professor
Leadership Director, Transgenic Core
Research Interests Transgenic mouse model.

Rulang Jiang, PhD, Professor
Research Interests Genetic basis and developmental mechanisms of structural birth defects; mammalian organogenesis.

J. Matthew Kofron, PhD, Assistant Professor
Leadership Confocal Imaging Core Director
Research Interests Ectodermal organ development in vertebrates; Xenopus.

Hung-Chi Liang, PhD, Instructor
Research Interests Gene expression core manager

Xinhua Lin, PhD, Professor
Research Interests Cell signaling, drosophila.

Christopher Mayhew, PhD, Assistant Professor
Leadership Co-Director, Pluripotent Stem Cell Core
Research Interests Human ES biology and differentiation.

Masato Nakafuku, MD, PhD, Professor
Research Interests Nervous system patterning and stem cells, mammal.

S. Steven Potter, PhD, Professor
Leadership Director, Gene Expression Core
Research Interests Transcription regulation and kidney development, mammal.

Saulius Sumanas, PhD, Assistant Professor
Research Interests Vascular development, zebrafish.

James M. Wells, PhD, Professor
Leadership Co-Director, Pluripotent Stem Cell Core
Research Interests Vertebrate gut development, stem cells, mammal.

Yutaka Yoshida, PhD, Assistant Professor
Research Interests Nervous system, cell migration, mammal, chicken.

Aaron Zorn, PhD, Professor
Leadership Co-Associate Director
Research Interests Vertebrate gut development, Xenopus, mammal.

Joint Appointment Faculty Members

Bruce Aronow, PhD, Professor (Pediatric Bioinformatics)
Research Interests Bioinformatics.

Samantha Brugmann, PhD, Assistant Professor (Plastic Surgery)
Research Interests Molecular basis for craniofacial development and disease.

Steven Crone, PhD, Assistant Professor (Neurosurgery)
Research Interests Spinal circuit development and repair.

Tony DeFalco, PhD, Assistant Professor (Reproductive sciences)
Research Interests Gonad development, mammal.

Sudhansu Dey, PhD, Professor (Director, Reproductive Sciences)
Research Interests Reproductive biology.

Prasad Devarajan, MD, Professor (Director, Nephrology and Hypertension)
Research Interests Urinary tract differentiation, mammal.

Fumika Hamada, PhD, Assistant Professor (Pediatric Ophthalmology)
Research Interests Molecular and neural mechanisms of circadian rhythm and temperature sensation in drosophila.

Chris Hong, PhD, Assistant Professor (Mol Cell Physiology (UC))
Research Interests Systems biology.

Stacey Huppert, PhD, Associate Professor (Gastroenterology, Hepatology, and Nutrition)
Research Interests Hepatic development and regeneration.

Vladimir Kalinichenko, MD PhD, Associate Professor (Pulmonary Biology and Neonatology)
Research Interests Transcriptional regulation of lung embryonic development.

Yu Lan, PhD, Associate Professor (Plastic Surgery)
Research Interests Genetic control of craniofacial development, mutant mouse models.

Richard A. Lang, PhD, Professor (Pediatric Ophthalmology)
Research Interests Visual system development, mammal.

Richard Lu, PhD, Professor (Exp Hem & Cancer Biology)
Research Interests Molecular mechanisms of glial development and brain tumorigenesis.

Jun Ma, PhD, Professor (Pediatric Bioinformatics)
Research Interests Transcriptional regulation, drosophila.

Douglas Millay, PhD, Assistant Professor (Mol Cardio Biology)
Research Interests Development and regeneration of skeletal muscle.

Takahisa Nakamura, PhD, Assistant Professor (Endocrinology)
Research Interests Obesity-induced metabolic diseases.

Satoshi Namekawa, PhD, Assistant Professor (Reproductive Sciences)
Research Interests Germ cells; epigenetics; reproduction, mouse.

Yuya Ogawa, PhD, Assistant Professor (Reproductive Sciences)
Research Interests Long noncoding RNA-mediated transcriptional regulation in mammals.

Joo-Seop Park, PhD, Assistant Professor (Urology)
Research Interests Molecular biology; genetics.

Rolf Stottmann, PhD, Assistant Professor (Human Genetics)
Research Interests Genetic approaches to understanding human congenital defects affecting the face and forebrain.

Ronald Waclaw, PhD, Assistant Professor (Experimental Hematology)
Research Interests Forebrain progenitor cell differentiation.

Joshua Waxman, PhD, Assistant Professor (Molecular Cardiovascular Biology)

Research Interests Molecular genetics of cardiovascular development.

Matt Weirauch, PhD, Assistant Professor (Autoimmune Genomics and Etiology)
Research Interests Transcription factors; computational biology; functional genomics; bioinformatics.

Jeffrey A. Whitsett, MD, Professor (Chief, Section of Neonatology, Perinatal, and Pulmonary Biology)
Research Interests Respiratory system, mammal.

Chunyue Yin, PhD, Assistant Professor (Gastroenterology, Hepatology, and Nutrition)
Research Interests Liver development and diseases.

Trainees

- **Masaki Ueno, PhD**, Vis Ob, Osaka University
- **Kristina Baltrunaite, PhD**, Vis Re, VU Institute of Biotechnology, Lithuania
- **Ok Hee Chai, PhD**, Vis Re, Chonbuk National University, Republic of Korea
- **Emmanuel Tadjuidje, PhD**, Vis Re, University of Göttingen, Germany
- **Cai Zhang*, PhD**, Vis Re, Tongji Medical College
- **Tatyana Belenkaya, PhD**, Res. A, Russian Academy of Science
- **Eric Brunskill, PhD**, Res. A, University of Maryland
- **Kevin Burns, PhD**, Res. A, University of Cincinnati
- **Yinhuai Chen, PhD**, Res. A, University of Massachusetts
- **Eunah Chung*, PhD**, Res. A, Cornell University
- **Lisa Ehrman*, PhD**, Res. A, University of Cincinnati
- **Tadahiro Goda*, PhD**, Res. A, Kyushu University
- **Christina James-Zorn, PhD**, Res. A, University of Queenland, Australia
- **Matthew Hass, PhD**, Res. A, Harvard University Medical School
- **Yasuko Kato*, PhD**, Res. A, Kyoto Institute of Technology, Japan
- **Han Liu, PhD**, Res. A, University of Rochester
- **Junbo Lui*, PhD**, Res. A, Fudan University, China
- **Michael Mucenski, PhD**, Res A, University of Cincinnati
- **Athanasia Nikolaou*, PhD**, Res. A, University of Melbourne, Australia
- **Virgilio Ponferrada, PhD**, Res. A, Wright State University
- **Jennifer Schumacher, PhD**, Res. A, University of Pennsylvania
- **Huirong Xie, PhD**, Res. A, Vanderbilt University
- **Nian Zhang, PhD**, Res. A, University of Edinburgh
- **Sarah Beckman*, PhD**, Res. F, University of Pittsburgh

- **Ching-Fang Chang*, PhD**, Res. F, University of Alabama
- **Mark Charlton-Perkins, PhD**, Res. F, University of Cincinnati (end 5/14/15)
- **Michael Craig, PhD**, Res. F, University of Cincinnati
- **Sharina Desai, PhD**, Res. F, University of Cincinnati (end 8/1/14)
- **Ashley Driver*, PhD**, Res. F, University of Wisconsin-Madison
- **Tarsis Ferreira, PhD**, Res. F, Universidade Federal de Sao Paulo, Brazil (end 7/25/14)
- **Tadahiro Goda, PhD**, Res. F, Kyushu University, Fukuoka, Japan
- **Zirong Gu, PhD**, Res. F, University of Cincinnati
- **Shuang Guo, PhD**, Res. F, Case Western Reserve University
- **Yi-Wen Hsieh, PhD**, Res. F, University of California, Los Angeles (end 8/15/14)
- **Fumiyasu Imai, PhD**, Res. F, Yokohama City University of Medicine, Japan
- **Shihai Jia, PhD**, Res. F, Shanghai Institute for Biological Sciences, China (end 9/30/14)
- **Taishi Kimura*, PhD**, Res. F, Osaka University, Japan
- **Vikram Kohli*, PhD**, Res. F, University of Alberta, Canada
- **Hyuk-Jae Kwon, PhD**, Res. F, Yonsei University, Korea
- **Alejandro Lopez Juarez*, PhD**, Res. F, University of Mexico
- **Jaya Mallela, PhD**, Res. F, University of Mississippi
- **Pamela Mancini, PhD**, Res. F, University of Pisa, Italy
- **Paloma Merchan Sala, PhD**, Res. F, University of Murcia, Spain
- **Ajit Muley*, PhD**, Res. F, Anna University, India
- **Jorge Munera, PhD**, Res. F, University of California, San Diego
- **Minh-Thanh Nguyen*, PhD**, Res. F, University of Florida
- **Yoshinobu Odaka*, PhD**, Res. F, Louisiana State University
- **Craig Park*, PhD**, Res. F, McGill University, Canada
- **Shannon Romer*, PhD**, Res. F, Wright State University
- **Kaushik Roychoudhury, PhD**, Res. F, Jadavpur University, India
- **Gowri Sarangdhar*, PhD**, Res. F, University of Sussex, UK
- **Jacqueline Schiesser, PhD**, Res. F, Monash University, Australia
- **Ankur Sharma, PhD**, Res. F, Indian Institute of Science
- **Xin Tang*, PhD**, Res. F, Vanderbilt University

- **Jumpei Terakawa*, PhD**, Res. F, Yamaguchi University, Japan
- **Quynh Ton, PhD**, Res. F, Lehigh University
- **Mustafa Turkoz, PhD**, Res. F, Washington University
- **Yujiro Umezaki*, PhD**, Res. F, Okayama University, Okayama, Japan
- **Shruti Vemaraju*, PhD**, Res. F, Texas A&M University
- **Guolun Wang, PhD**, Res. F, Graduate University of Chinese Academy of Sciences
- **Yuhua Wang, PhD**, Res. F, Sun Yat-Sen University, China
- **Marcin Wlizla, PhD**, Res. F, University of Chicago (end 6/30/15)
- **Jingyue Xu, PhD**, Res. F, Nanjing University, China
- **Norishige Yamada*, PhD**, Res. F, Kagoshima University, Japan
- **Eun-Jin Yeo*, PhD**, Res. F, Seoul National University, South Korea
- **Jia You, PhD**, Res. F, University of Cincinnati
- **Celvie Yuan*, PhD**, Res. F, Case Western Reserve University
- **Jing Zhou, PhD**, Res. F, Shanghai Institute for Biological Sciences, China (end 9/30/14)
- **Jonathan Howell, MD PhD**, Clin., Indiana University
- **Alan Kenny, MD PhD**, Clin., University of Rochester, School of Medicine and Dentistry
- **Yetki Aslan,** , Grad., University of Denis Diderot, France
- **Douglas Brown*,** , Grad., University of Cincinnati - College of Medicine
- **Samantha Chery,** , Grad., Paris Diderot University, France
- **Michael Craig,** , Grad. , University of Cincinnati (end 5/29/15)
- **Anne Heritier,** , Grad., University of Paris, Diderot (end 8/29/15)
- **Meina Huang,** , Grad., Chinese Academy of Sciences (end 6/23/15)
- **Rosalina Lam,** , Grad., University of Paris Diederot, France
- **Baptiste Martin,** , Grad., Polytech Marseille, France (end 8/8/14)
- **Julie Treguier,** , Grad., Polytech, Marseille, France
- **Morgan Albert,** , Underg, University of Rochester
- **Christopher Anglin,** , Underg, Xavier University (end 5/27/15)
- **Brittany Bayne,** , Underg, University of Cincinnati (end 8/6/14)
- **Matthew Carter,** , Underg, Miami University, Oxford, OH (end 8/22/14)
- **Emily Cata,** , Underg, Xavier University (end 5/8/15)

- **Calyn Crawford,** , Underg, Xavier University
- **Jacob Enriquez,** , Underg, Xavier University
- **Mackenzie Gauck,** , Underg, University of Cincinnati
- **Emily Grigg,** , Underg, Xavier University
- **Nicholas Ingram,** , Underg, University of Cincinnati (end 11/21/14)
- **Cameron Ingram,** , Underg, University of Cincinnati
- **Sarah Kastner,** , Underg, Cincinnati State (end 4/26/15)
- **Risako Kimura,** , Underg, Brown University
- **Mishi Liang,** , Underg, University of Cincinnati (end 12/1/14)
- **Kelsey Lin,** , Underg, Ohio State University (end 8/12/14)
- **Julia Madzia,** , Underg, University of Cincinnati (end 12/31/14)
- **Madhulika Mamidi,** , Underg, University of Cincinnati (end 11/6/14)
- **Kyle Mackenzie,** , Underg, Cincinnati State Tech and Community College
- **Mhadhumithan Naresh,** , Underg, University of Cincinnati (4/9/15)
- **Cory Newland,** , Underg, University of Cincinnati
- **Thanh Phan,** , Underg, University of Cincinnati (end 11/6/14)
- **Katherine Philo,** , Underg, Xavier University
- **Carolyn Stevenson,** , Underg, University of Cincinnati
- **William Stone,** , Underg, University of Cincinnati
- **Jon Vardanyan,** , Underg, Xavier University
- **Austin Wanek,** , Underg, University of Cincinnati (end 11/6/14)
- **Ian Campbell,** , HighS, Turpin High School
- **Kristen Martin,** , HighS, Oak Hills HIgh School (end 9/26/14)

Grants, Contracts, and Industry Agreements

Grant and Contract Awards **Annual Direct**

Campbell, K / Gebelein, B

Roles of Gsx Factors in Telencephalic Neurogenesis

National Institutes of Health

R01 NS044080	3/15/2014-2/28/2019	$350,906

Cha, S

Wnt/PCP Signaling in the Intestinal Epithelium

National Institutes of Health

K01 DK101618	4/15/2014-2/28/2019	$119,422

Cook, T

Molecular Networks Controlling Subtype Specification of Color Photoreceptors

National Institutes of Health

R01 EY022687	8/1/2014-6/30/2018	$225,000

Defining Glial Programs That Support Adult Photoreceptor Form And Function

National Institutes of Health

R21 EY024405	4/1/2014-3/31/2016	$122,500

Gebelein, B

Hox Control of Cell-Specific EGF Signaling During Development

National Institutes of Health

R01 GM079428	8/9/2013-5/31/2017	$190,000

Guasch Grangeon, G

Regulated Morphogenesis of Human Sebaceous Glands

National Institutes of Health

R21 AR064341	9/1/2014-5/31/15	$105,185

Hegde, R

Mechanism Of Action Of Retinal Determination Proteins

National Institutes of Health

R01 EY014648	4/1/2014-3/31/2018	$220,500

EYA in Retinal Angiogenesis

National Institutes of Health

R01 EY022917	8/1/2013-7/31/2017	$245,000

EYA in the Treatment of Peripheral Vascular Disease and Pulmonary Arterial Hypertension

National Institutes of Health (The Cleveland Clinic Lerner Coll of Medicine)

U54 HL119810	3/01/2015-2/29/2016	$50,000

Jiang, R

Molecular Patterning of Mammalian Dentition

National Institutes of Health

R01 DE018401	9/12/2013-6/30/2018	$337,777

Molecular Genetic Analysis of Craniofacial Development

National Institutes of Health

R01 DE013681	7/1/2011-6/30/2015	$413,359

Kopan, R

Assessing the Therapeutic Window for Future Anti-Notch Dimerization Agents

National Institutes of Health

R01 CA163653	7/1/2013-4/30/2018	$211,676

Imaging Notch Interactions with Members of Its Pathway

National Institutes of Health (Washington University)

P50 CA094056	1/1/2014-12/31/2015	$112,445

Lin, X

Regulation of Wingless (Wg) Signaling and Morphogen Gradient Formation

National Institutes of Health

R01 GM063891	4/1/2012-3/31/2016	$200,000

Mayhew, C

Digestive Health Center: Bench to Bedside Research in Pediatric Digestive Disease - Stem Cell Core

National Institutes of Health

P30 DK078392	6/1/2012-5/31/2017	$25,907

Munera, J

Human Intestinal Organoids As A Model Of Ulcerative Colitis

Crohn's & Colitis Foundation of America

	7/1/2014-6/30/2017	$58,250

Nakafuku, M / Campbell, K

Molecular Control of Neurogenesis in the Adult Subventricular Zone

National Institutes of Health

R01 NS069893	4/1/2015-3/31/2020	$309,376

Potter, S

Recombineering Based Analysis of Hox Function in Kidney Development

National Institutes of Health

R01 DK099995	8/8/2014-4/30/2018	$217,500

Transcriptome Atlases of the Craniofacial Sutures

National Institutes of Health (Mount Sinai Medical Center)

U01 DE024448	5/1/2014-4/30/2019	$9,663

Generating Molecular Markers that Selectively Label Urothelial Sub-Populations

National Institutes of Health (Columbia University Medical Center)

U01 DK094530	9/30/2011-8/31/2016	$28,089

Digestive Health Center: Bench to Bedside Research in Pediatric Digestive Disease - Gene Expression Core

National Institutes of Health

P30 DK078392	6/1/2012-5/31/2017	$33,048

Critical Translational Studies in Pediatric Nephrology

National Institutes of Health

P50 DK096418	9/21/2012-8/31/2017	$258,400

Potter, S / Wells, J

Single Cell/RNA-Seq Dissection of Human iPS Cell Development into Intestine

National Institutes of Health

R01 DK098350	9/20/2013-7/31/2017	$217,500

Potter, S / Whitsett, J

"Lung MAP" Atlas Research Center

National Institutes of Health

U01 HL122642	6/15/2014-4/30/2019	$510,804

Sumanas, S

Molecular Mechanisms of Arterial-Venous Differentiation in Zebrafish

National Institutes of Health

R01 HL107369	4/1/2011-3/31/2016	$246,250

Inhibition of Etv2 Function as a Novel Strategy to Prevent Tumor-Induced Angiogenesis

Ohio Cancer Research Associates

	7/1/2013-6/30/2015	$27,273

Ton, Q

Validation of Aneurysm Associated Genes in a Zebrafish Model

National Institutes of Health

F32 HL124889	12/1/2014-11/30/2017	$49,850

Wells, J

Human Endocrine Cell Development

National Institutes of Health

R01 DK092456	4/7/2012-2/28/2017	$297,412

Generating Human Intestinal Organoids with an ENS

National Institutes of Health

U18 TR000546	7/24/2012-6/30/2015	$100,000

Intestinal Organoids as a Model System for Studying Enteric Disease

National Institutes of Health (University of Cincinnati)

U19 AI116491	3/01/2015-2/29/2020	$175,000

Yoshida, Y

Axon Die-back and Regeneration

Craig Neilson Foundation

	7/1/2014-6/30/2016	$136,364

Mechanism of Neural Circuit Reorganization for Homeostasis after CNS Injury

Japan Science and Technology Corporation

	10/1/2013-3/31/2017	$100,784

Semaphorin Signaling and Regeneration of Corticospinal Activity

New Jersey Commission on Spinal Cord Research (Rutgers, The State University of New Jersey)

	6/15/2015-6/30/2017	$89,091

Xenbase: the Xenopus Model Organism Database		
National Institutes of Health		
P41 HD064556	6/1/2015-5/31/2016	$230,692
Molecular Basis of Digestive System Development in Xenopus		
National Institutes of Health		
R01 DK070858	4/1/2014-3/31/2018	$223,719
Production, Validation and Distribution of the Xenopus ORFeome		
National Institutes of Health (University of Virginia)		
R01 HD069352	8/1/2011-5/31/2016	$55,078
Deciphering the Gene Regulatory Network Controlling Vertebrate Endodermal Fates		
National Institutes of Health(Regents of University of California)		
R01 HD073179	5/1/2013-4/30/2018	$80,000
Systematic Improvement of Xenopus Gene Annotations and Reference Genomes		
National Institutes of Health (University of California-Berkeley)		
R01 HD080708	8/1/2014-4/30/2018	$28,985
Osr Transcription Factors Regulate Embryonic Lung Development		
National Institutes of Health		
R01 HL114898	8/10/2012-6/30/2017	$407,000
Collaborative Research: Ontology-Enabled Reasoning across Phenotypes from Evolution and Model Organisms		
National Science Foundation (University of South Dakota)		
	7/1/2011-6/30/2015	$7,534
	Current Year Direct	**$6,827,339**
	Total	**$6,827,339**

Additional Information
Molecular And Developmental Biology Graduate Program

The Graduate Program in Molecular and Developmental Biology is an interdepartmental program within the University of Cincinnati that offers the PhD degree. It has been based in the Department of Pediatrics for over 40 years. Drs. Rashmi Hegde and Rulang Jiang served as directors of the program with associate directors Drs. Jeffrey Whitsett (finance), Aaron

Zorn (curriculum), Rolf Stottmann (admissions), Edith Markoff (recruitment), Yi Zheng (faculty membership) and John Shannon (graduate studies).

There are 86 faculty members in the program. During the past year, there were 59 pre-doctoral students in the program, eight of whom are pursuing MD/PhD degrees. Students and faculty continue to be productive as measured by their numbers of publications, presentations at meetings, honors and awards received. Grant support to faculty remains high.

During the past year, the University of Cincinnati continued to support the program by providing University Graduate Assistantships and funds appropriated from the dean's office to support five first-year students. The remaining students are supported through a variety of sources including Albert J. Ryan Fellowships (1), American Heart Association Fellowships (2), NIH training grants (5), external grants to their advisors (50) and funds from the Children's Hospital Research Foundation to the graduate program (3).

The MDB Program provides an excellent research educational experience for students and has an excellent record in the placement of its graduates in scientific careers.

Molecular and Developmental Biology Graduate Program Students

Student	Faculty Mentor	Admission
Thomas Acciani	Timothy Le Cras	2009
Amel Alqadah	Chiou-Fen Chuang	2010
Aria Attia	Rolf Stottmann	2010
Kristin Bell	Noah Shroyer	2010
Katie Bezold	Louis Muglia	2011
Gregory Bick	Paul Andreassen	2010
Markaisa Black	Tanya Kalin	2012
Satish Casie Chetty	Rotating	2014
Adam Burr**	Jeffery Molkentin	2009
Jason Cowan	Stephanie Ware	2009
Angela (Matthews) Damen	Katherine Yutzey	2011
Andrew DiStasio	Rolf Stottmann	2013
Tracy Dohn	Joshua Waxman	2009
Caitlin Dunn-Fletcher**	Louis Muglia	2013
Ming Fang	Katherine Yutzey	2010
Margaret Gardner	Kathryn Wikenheiser-Brokamp	2010
Vicky Gomez	Katherine Yutzey	2011
Zirong Gu	Yutaka Yoshida	2008
Lu Han	Aaron Zorn	2011

Jamie Havrilak	John Shannon	2008
Michael Hester	Steve Danzer	2009
Jillian Hufgard	Charles Vorhees	2012
Jed Kendall**	Nancy Ratner	2011
Andrew Kim**	Katherine Yutzey	2014
Andrew Koenig	Saulius Sumanas	2012
Yi Kuang	Rotating	2014
Jeff Kuerbitz**	Kenneth Campbell	2012
Julie Lander**	Stephanie Ware	2011
Chaochang Li	Rotating	2014
Shan Lin	James Mulloy	2009
Mariana Louza Stevens	Aaron Zorn	2010
Bliss Magella	Steve Potter	2011
Amrita Mandal	Joshua Waxman	2011
Kate Maurer	Nadean Brown	2009
Heather McCauley	Geraldine Guasch	2009
Patrick “Sean” McGrath	James Wells	2012
David Milewski	Tanya Kalin	2013
Grethel Millington	Samantha Brugmann	2013
Edward “David” Muench	H. Leighton Grimes	2012
Shenyue Qin	Kenneth Campbell	2011
Rebecca Rice	Rotating	2014
Stephen Riffle	Rashmi Hegde	2013
Megan Rost	Saulius Sumanas	2008
Ariel Rydeen	Joshua Waxman	2011
Betsy Schock	Samantha Brugmann	2012
Moen Sen	Kathryn Wikenheiser-Brokamp	2011
Katie Sinagoga	James Wells	2012
Shatrunjai Singh	Steve Danzer	2010
Sneha Sitaraman	Timothy Weaver	2013
Yuntao “Charlie” Song	Rotating	2014

Jun Su	Rotating	2014
Stephen Trisno**	James Wells	2014
Angela White	Lionel Chow	2013
Michael Workman	James Wells	2012
Arya Zandvakili**	Brian Gebelein	2013
Inuk Zandvakili**	Yi Zheng	2009
Xinghao Zhang	Rotating	2014
Xuzhe Zhang	Louis Muglia	2012
Zheng Zhang	Aaron Zorn	2008

Students Completing PhD Work

Thomas Acciani – "EGF Signaling and Diesel Exhaust Particle Exposure in Asthma Pathogenesis," September 5, 2014.

Adam Burr – "Sodium Dysregulation Coupled with Calcium Entry Leads to Muscular Dystrophy in Mice," July 25, 2014.

Tracy Dohn – "Roles of Wnt Signaling and Nr2f1a during Zebrafish Cardiac Development," February 6, 2015.

Zirong Gu – "Building Corticospinal Circuits for Skilled Behavior," February 24, 2015.

Jamie Havrilak – "The Role of Endothelial Cells during Early Lung Development," February 27, 2015.

Michael Hester – "mTOR Regulation of Hippocampal Granule Cell Pathology in Temporal Lobe Epilepsy," August 1, 2014.

Kate Maurer – "Notch Signaling and bHLH Transcription Factor Regulation of Early Retinal Neurogenesis," July 10, 2014.

Megan Rost – "The Roles of Vegf and Stabilin-2 Signaling during Arterial-venous Differentiation," November 11, 2014.

Zheng Zhang – "Function of Frizzled-7/Syndecan-4 Signaling in Foregut Organ Development," January 9, 2015.

Students Completing MS Work

Angela Damen – "In Vivo Characterization of Non-Myocyte Heterogeneity during the Postnatal Development of the Cardiac Interstitium," November 5, 2014.

Margaret Gardner – "Cell and Developmental Stage Specific Role of Dicer1 during Lung Development," February 4, 2015.

Michael Workman – "Generating 3D Human Intestinal Organoids with an Enteric Nervous System," October 28, 2014.

Student Publications

During the past year, students from the Program authored or co-authored 33 articles:

Accornero F, Kanisicak O, Tjondrokoesoemo A, **Attia AC**, McNally EM, Molkentin JD. **Myofiber-specific inhibition of TGFβ signaling protects skeletal muscle from injury and dystrophic disease in mice.** *Hum Mol Genet.* 2014 Dec 20;23(25):6903-15.

Bell KN, Shroyer NF. **Krüpple-like factor 5 is required for proper maintenance of adult intestinal crypt cellular proliferation.** *Dig Dis Sci.* 2015 Jan;60(1):86-100.

Chang KH, Nayak RC, Roy S, Perumbeti A, Wellendorf AM, **Bezold KY**, Pirman M, Hill SE, Starnes J, Loberg A, Zhou X,

Inagami T, Zheng Y, Malik P, Cancelas JA. **Vasculopathy-associated hyperangiotensinemia mobilizes haematopoietic stem cells/progenitors through endothelial AT_2R and cytoskeletal dysregulation.** *Nat Commun.* 2015 Jan 9;6:5914.

Cheng XH, **Black M**, Ustiyan V, Le T, Fulford L, Sridharan A, Medvedovic M, Kalinichenko VV, Whitsett JA, Kalin TV. **SPDEF inhibits prostate carcinogenesis by disrupting a positive feedback loop in regulation of the Foxm1 oncogene.** *PLoS Genet.* 2014 Sep 25;10(9):e1004656.

Burr AR, Molkentin JD. **Genetic evidence in the mouse solidifies the calcium hypothesis of myofiber death in muscular dystrophy.** *Cell Death Differ.* 2015 Sep;22(9):1402-12.

Cowan JR, Ware SM. **Genetics and genetic testing in congenital heart disease.** *Clin Perinatol.* 2015 Jun;42(2):373-93, ix.

Pavlicev M, Hiratsuka K, Swaggart KA, **Dunn C**, Muglia L. **Detecting endogenous retrovirus-driven tissue-specific gene transcription.** *Genome Biol Evol.* 2015 Mar 11;7(4):1082-97.

Fang M, Alfieri CM, Hulin A, Conway SJ, Yutzey KE. **Loss of β-catenin promotes chondrogenic differentiation of aortic valve interstitial cells.** *Arterioscler Thromb Vasc Biol.* 2014 Dec;34(12):2601-8.

Wagh PK, **Gardner MA**, Ma X, Callahan M, Shannon JM, Wert SE, Messinger YH, Dehner LP, Hill DA, Wikenheiser-Brokamp KA. **Cell- and developmental stage-specific Dicer1 ablation in the lung epithelium models cystic pleuropulmonary blastoma.** *J Pathol.* 2015 May;236(1):41-52.

Wirrig EE, **Gomez MV**, Hinton RB, Yutzey KE. **COX2 inhibition reduces aortic valve calcification in vivo.** *Arterioscler Thromb Vasc Biol.* 2015 Apr;35(4):938-47.

Gu Z, Imai F, Kim IJ, Fujita H, Katayama Ki, Mori K, Yoshihara Y, Yoshida Y. **Expression of the immunoglobulin superfamily cell adhesion molecules in the developing spinal cord and dorsal root ganglion.** *PLoS One.* 2015 Mar 31;10(3):e0121550.

Rankin SA, Thi Tran H, Wlizla M, Mancini P, Shifley ET, Bloor SD, **Han L**, Vleminckx K, Wert SE, Zorn AM. **A Molecular atlas of Xenopus respiratory system development.** *Dev Dyn.* 2015 Jan;244(1):69-85.

Ren X, Ustiyan V, Pradhan A, Cai Y, **Havrilak JA**, Bolte CS, Shannon JM, Kalin TV, Kalinichenko VV. **FOXF1 transcription factor is required for formation of embryonic vasculature by regulating VEGF signaling in endothelial cells.** *Circ Res.* 2014 Sep 26;115(8):709-20.

Havrilak JA, Shannon JM. **Branching of lung epithelium in vitro occurs in the absence of endothelial cells.** *Dev Dyn.* 2015 Apr;244(4):553-63.

Hester MS, Danzer SC. **Hippocampal granule cell pathology in epilepsy – a possible structural basis for comorbidities of epilepsy?** *Epilepsy Behav.* 2014 Sep;38:105-16.

Mann EA, Alam Z, **Hufgard JR**, Mogle M, Williams MT, Vorhees CV, Reddy P. **Chronic social defeat, but not restraint stress, alters bladder function in mice.** *Physiol Behav.* 2015 Oct 15;150:83-92.

de Bruin C, Mericq V, Andrew SF, van Duyvenvoorde HA, Verkaik NS, Losekoot M, Porollo A, Garcia H, **Kuang Y**, Hanson D, Clayton P, van Gent DC, Wit JM, Hwa V, Dauber A. **An XRCC4 splice mutation associated with severe short stature, gonadal failure, and early-onset metabolic syndrome.** *J Clin Endocrinol Metab.* 2015 May;100(5):E789-98.

McCauley HA, Liu CY, **Attia AC**, Wikenheiser-Brokamp KA, Zhang Y, Whitsett JA, Guasch G. **TGFβ signaling inhibits goblet cell differentiation via SPDEF in conjunctival epithelium.** *Development.* 2014 Dec;141(23):4628-39.

Brunskill EW, Park JS, Chung E, Chen F, **Magella B**, Potter SS. **Single cell dissection of early kidney development: multilineage priming.** *Development.* 2014 Aug;141(15):3093-101.

Mandal A, Waxman J. **Retinoic acid negatively regulates dact3b expression in the hindbrain of zebrafish embryos.** *Gene Expr Patterns.* 2014 Nov;16(2):122-9.

Maurer KA, Riesenberg AN, Brown NL. **Notch signaling differentially regulates Atoh7 and Neurog2 in the distal mouse retina.** *Development.* 2014 Aug;141(16):3243-54.

McGrath PS, Wells JM. **SnapShot: GI tract development.** *Cell.* 2015 Mar 26;161(1):176-176.e1.

Cumaraswamy AA, Lewis AM, Geletu M, Todic A, Diaz DB, Cheng XR, Brown CE, Laister RC, **Muench D**, Kerman K, Grimes HL, Minden MD, Gunning PT. **Nanomolar-Potency Small Molecule Inhibitor of STAT5 Protein.** *ACS Med Chem Lett.* 2014 Sep 19;5(11):1202-1206.

Palencia-Desai S, **Rost MS**, Schumacher JA, Ton QV, Craig MP, Baltrunaite K, **Koenig AL**, Wang J, Poss KD, Chi NC, Stainier DY, Sumanas S. **Myocardium and BMP signaling are required for endocardial differentiation.** *Development.* 2015 Jul 1;142(13):2304-15.

Rydeen A, Voisin N, D'Aniello E, Ravisankar P, Devignes CS, Waxman JS. **Excessive feedback of Cyp26a1 promotes cell non-autonomous loss of retinoic acid signaling.** *Dev Biol.* 2015 Sep 1;405(1):47-55.

Schock EN, Chang CF, Struve JN, Chang YT, Chang J, Delany ME, Brugmann SA. **Using the avian mutant talpid2 as a disease model for understanding the oral-facial phenotypes of oral-facial-digital syndrome.** *Dis Model Mech.* 2015 Aug 1;8(8):855-66.

Chang CF, **Schock EN**, **Attia AC**, Stottmann RW, Brugmann SA. **The ciliary baton: orchestrating neural crest cell development.** *Curr Top Dev Biol.* 2015;111:97-134.

Chang CF, **Schock EN**, O'Hare EA, Dodgson J, Cheng HH, Muir WM, Edelmann RE, Delany ME, Brugmann SA. **The cellular and molecular etiology of the craniofacial defects in the avian ciliopathic mutant talpid2.** *Development.* 2014 Aug;141(15):3003-12.

Sinagoga KL, Wells JM. **Generating human intestinal tissues from pluripotent stem cells to study development and disease.** *EMBO J.* 2015 May 5;34(9):1149-63.

McCracken KW, Catá EM, Crawford CM, **Sinagoga KL**, Schumacher M, Rockich BE, Tsai YH, Mayhew CN, Spence JR, Zavros Y, Wells JM. **Modelling human development and disease in pluripotent stem-cell-derived gastric organoids.** *Nature.* 2014 Dec 18;516(7531):400-4.

Jonatan D, Spence JR, Method AM, Kofron M, **Sinagoga K**, Haataja L, Arvan P, Deutsch GH, Wells JM. **Sox17 regulates insulin secretion in the normal and pathologic mouse β cell.** *PLoS One.* 2014 Aug 21;9(8):e104675.

Nolan K, Kattamuri C, Luedeke DM, Angerman EB, Rankin SA, **Stevens ML**, Zorn AM, Thompson TB. **Structure of neuroblastoma suppressor of tumorigenicity 1 (NBL1): insights for the functional variability across bone morphogenetic protein (BMP) antagonists.** *J Biol Chem.* 2015 Feb 20;290(8):4759-71.

Zandvakili I, Davis AK, Hu G, Zheng Y. **Loss of RhoA Exacerbates, Rather Than Dampens, Oncogenic K-Ras Induced Lung Adenoma Formation in Mice.** *PLoS One.* 2015 Jun 1;10(6):e0127923.

Student Honors

Black, M. – NIH Training Grant Appointee (Lung and Cardiovascular Development and Disease Pathogenesis Training Program).

Fang, M. – Cover Art Award granted by the Editorial Board in *Arteriosclerosis, Thrombosis and Vascular Biology.*

Gomez, M. V. – American Association of Anatomists Langman Graduate Student Platform Presentation Award, First Place; American Association of Anatomists Student Travel Award; University Research Council Summer Research Fellowship, University of Cincinnati.

Han, L. – Best Question Award, Endoderm Lineages in Development and Disease Keystone Meeting.

Havrilak, J. – Selected for Platform Presentation, Federation of American Societies for Experimental Biology Meeting.

Hufgard, J. – University of Cincinnati Graduate Student Governance Association Research Fellowship; NIH Training Grant Appointee (Teratology).

Koenig, A. – NIH Training Grant Appointee (Understanding Cardiovascular Disease Mechanisms).

Lin, S. – American Society of Hematology Abstract Achievement Award; CancerFree Kids Pediatric Cancer Research Alliance Funding Support.

Millington, G. – NIH Training Grant Appointee (Teratology).

Riffle, S. – CancerFree Kids Pediatric Cancer Research Alliance, Cincinnati Bell Research Grant.

Stevens, M. – NIH Training Grant Appointee (Lung and Cardiovascular Development and Disease Pathogenesis Training Program); Underrepresented Trainee Scholarship, Endoderm Lineages in Development and Disease Keystone Meeting.

Richard A. Akeson Fellowship Fund

The Richard A. Akeson Fellowship and Memorial Lectureship Fund continues to support the Annual Richard Akeson Memorial Lectureship and travel by students in our graduate program to relevant courses and meetings in which they are presenting results of their research. Dr. Cliff Tabin presented the Nineteenth Annual Richard Akeson Memorial Lectureship in conjunction with the annual Molecular and Developmental Biology Graduate Student Symposium in 2014.

The following students received funding from the Richard A. Akeson Fellowship and Memorial Fund for travel in 2014 - 2015:

Student	Meeting	Location	Presentation	Date
Ming Fang	AHA Basic Cardiovascular Sciences Scientific Sessions	Las Vegas, Nevada	Poster	July 2014
Lu Han	Society for Developmental Biology 73rd Annual Meeting	Seattle, Washington	Poster	July 2014
Bliss Magella	Society for Developmental Biology 73rd Annual Meeting	Seattle, Washington	Poster	July 2014
Tracy Dohn	Society for Developmental Biology 73rd Annual Meeting	Seattle, Washington	Poster	July 2014
Ariel Rydeen	Society for Developmental Biology 73rd Annual Meeting	Seattle, Washington	Poster	July 2014
Amrita Mandal	Society for Developmental Biology 73rd Annual Meeting	Seattle, Washington	Poster	July 2014

Jamie Havrilak	FASEB: The Lung Epithelium in Health and Disease	Saxtons River, Vermont	Poster	July 2014
Zheng Zhang	15th International Xenopus Conference	Pacific Grove, California	Poster	August 2014
Vicky Gomez	London Heart Valve 2014	London, United Kingdom	Poster	September 2014
Andrew Koenig	NAVBO – Vascular Biology 2014	Monterey, California	Poster	October 2014
Shatrunjai Singh	Society for Neuroscience	Washington, DC	Poster	November 2014
Shenyue Qin	Society for Neuroscience	Washington, DC	Poster	November 2014
Jeff Kuerbitz	Society for Neuroscience	Washington, DC	Poster	November 2014
Sean McGrath	Endoderm Lineages in Development and Disease	Keystone, Colorado	Poster	February 2015
Katie Sinagoga	Endoderm Lineages in Development and Disease	Keystone, Colorado	Poster	February 2015
Katie Bezold	Society for Reproductive Investigation	San Francisco, California	Poster	March 2015
Arya Zandvakili	Annual Drosophila Research Conference	Chicago, Illinois	Poster	March 2015
Jillian Hufgard	International Behavioral Neuroscience Society	Victoria, British Columbia, Canada	Poster	June 2015
Satish Casie Chetty	2015 Midwest Zebrafish Conference	St. Louis, Missouri	Poster	June 2015
Amel Alqadah	2015 C. elegans International Meeting	Los Angeles, California	Poster	June 2015

Breakthrough Stomach Organoids Open Doors for New Insights into Ulcers, Cancer, Diabetes and Other Diseases

James Wells, PhD

RESEARCH AND TRAINING DETAILS

Faculty	23
Joint Appointment Faculty	25
Research Fellows	70
Research Students	64
Support Personnel	53
Direct Annual Grant Support	$6.2M
Peer Reviewed Publications	46

McCracken KW, Cata EM, Crawford CM, Sinagoga KL, Schumacher M, Rockich BE, Tsai YH, Mayhew CN, Spence JR, Zavros Y, Wells JM. Modelling human development and disease in pluripotent stem-cell-derived gastric organoids. *Nature*. 2014;516(7531):400-404.

PUBLISHED ONLINE OCT. 29, 2014
Nature

In 1984, Australian physician Barry Marshall resorted to drinking a petri dish brimming with *H. pylori* bacteria and then treated himself with antibiotics to prove that ulcers were caused by an infection, not by stress, spicy foods or stomach acid.

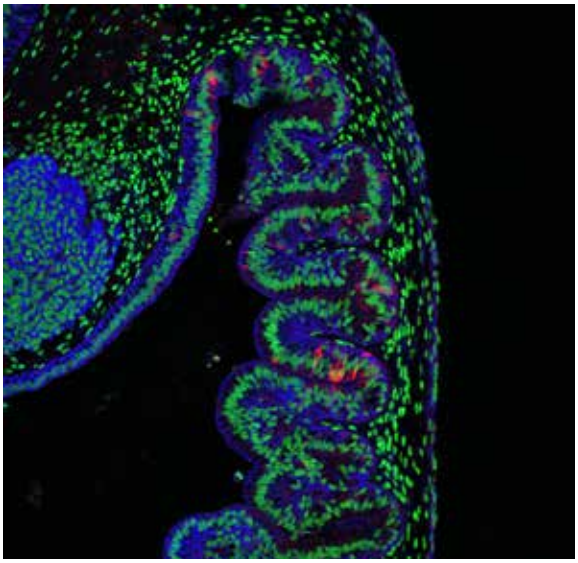
Thirty years later, James Wells, PhD, and fellow researchers with the Divisions of Developmental Biology and Endocrinology are using human pluripotent stem cells as building blocks to create functional, three-dimensional, architecturally complex stomach tissues in the laboratory. Their anatomical breakthrough will enable researchers to study stomach development and a wide range of diseases including peptic ulcer disease, cancer and diabetes — without resorting to Marshall's drastic solution.

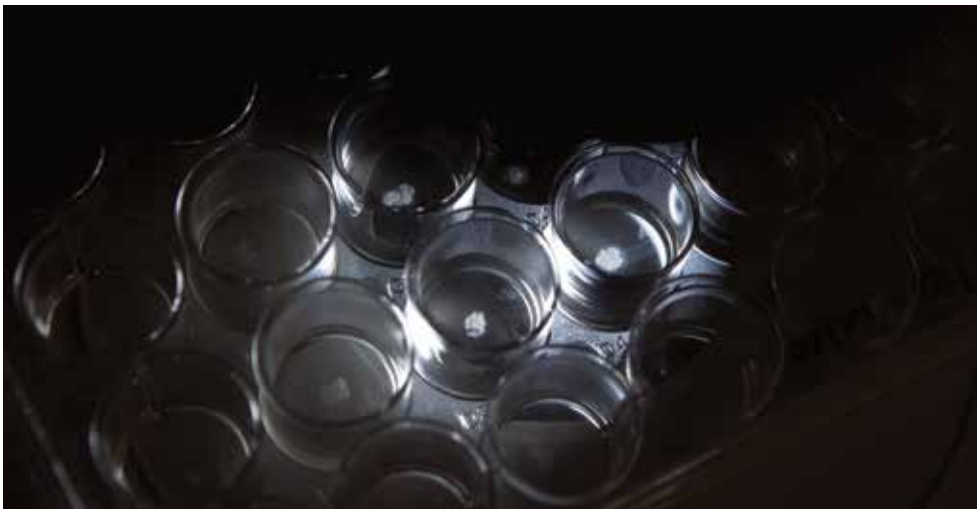
Until Wells' team's discovery, experimental models of human stomach tissue did not exist, and mouse stomachs and other animal tissues have not been ideal models for studying stomach diseases in humans.

In a study published online Oct. 29, 2014, in *Nature*, Wells described how his team performed a series of manipulations of the growth environment to guide human pluripotent stem cells (hPSCs) — stem cells that can grow into any type of tissue — into forming tiny, pea-sized human stomachs, dubbed "human gastric organoids" (hGOs).

In collaboration with colleague Yana Zavros, PhD, at the University of Cincinnati, Wells demonstrated the hGOs can be used to study how the bacteria *H. pylori* causes peptic ulcers and stomach cancer, as the team was able to observe cellular and tissue changes associated with the bacterial infection.

The team's accomplishment represents the first time that researchers have produced a 3-D model of the human stomach. The team plans to use a similar approach to develop other "mini-organs," including the lungs and esophagus. It also creates possibilities for studying new drugs, building tissue models of stomach cancer and investigating the underpinnings of obesity-related diabetes.





Researchers plan to use a similar approach to develop other "mini-organs."

Drs. James Wells, Yana Zavros, and Kyle McCracken received national attention for their work using differentiation of human pluripotent stem cells to generate 3-D human gastric tissue. The confocal microscope image (top) shows a functioning cross section of the lining of the stomach organoid. The next image shows the organoids growing *in vitro* in the Wells laboratory.