Cincinnati Children's

2015 Research Annual Report

Plastic Surgery

RESEARCH AND TRAINING DETAILS

Click to view members

Faculty	13
Joint Appointment Faculty	1
Research Fellows	1
Research Students	4
Support Personnel	1
Direct Annual Grant Support	$470,667
Direct Annual Industry Support	$25,000
Peer Reviewed Publications	18

CLINICAL ACTIVITIES AND TRAINING

Clinical Staff	3
Staff Physicians	9
Clinical Fellows	1
Other Students	3
Inpatient Encounters	794
Outpatient Encounters	6,122

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Research Highlights

Early Correction of Craniofacial Bone Defects

John van Aalst, MD, transferred his National Institutes of Health (NIH)-funded lab to Cincinnati Children's and published work on the large animal model for the alveolar cleft and is actively working on novel stem cell-based solutions for this large animal model in anticipation of clinical trials in children.

The Role of Primary Cilia in Craniofacial Development

Samantha Brugmann, PhD, was awarded a Research Innovation Program (RIP) Funding grant from Basic Science Research Committee (BSRC) entitled “Using the Developing Embryo to Identify Factors that Influence the Primary Ciliome.”

Elizabeth N. Schock, a four-year graduate student in the Brugmann Lab, was awarded an F31 grant from the National Institute of Dental and Craniofacial Research (NIDCR), NIH, entitled “The role of ectodermal primary cilia in murine orofacial development.”

Understanding Mechanisms of Cleft Palate Pathogenesis

To understand the cellular mechanisms of palate development, Yu Lan, PhD, has established a mouse model for cleft palate research using ENU mutagenesis and exome sequencing approaches. Lan was awarded a grant from the National Institute of Dental and Craniofacial Research (NIDCR) for her work investigating the role of Golgi function in cleft palate syndrome.

In addition, Lan and Rulang Jiang, PhD, in the Division of Developmental Biology have generated multiple mutant mouse models for cleft palate research using targeted gene knockout/knockin approaches. They also have an R01 grant from NIDCR investigating the molecular mechanisms patterning mammalian dentition.

Improving Outcomes of Cleft Lip and Palate Surgery

Thomas Sitzman, MD, received a Place Outcomes Research Award to improve measurement of outcomes after cleft palate repair for the division. The award will also support a multicenter pilot study testing the effect of surgeon-directed feedback on outcomes of cleft palate repair. This award extends Sitzman’s current work on clinical outcomes and burden of care of children with cleft lip and cleft palate.

Ron Hathaway, DDS, co-chairs the Global Cleft Team Network Task Force of the International Confederation for Cleft Lip and Palate and Related Craniofacial Anomalies where cohort centers study clinical treatment outcomes for narrowly defined phenotypic expressions of the clefting condition.

FRET Emission and Cytoskeletal Deformation

Fluorescence Resonance Energy Transfer (FRET) cassettes are protein-based strain sensors that can be transfected into living cells. Donna Jones, PhD, has calibrated applied cellular strain and fluorescent emission to validate this system for future biomechanical cell studies. Results were presented at the 59th annual meeting of the Biophysical Society, February 2015.

Muscle Force and Growing Mandibles

Working with mouse mandibles, Donna Jones, PhD, has shown that muscle forces affect bone shape by altering bone deposition and resorption, particularly during early growth. She presented findings in September 2014 at the national meeting of the American Society for Bone and Mineral Research.

Treatment of Obstructive Sleep Apnea

Elhadi Babiker, MD, works in a multidisciplinary unit consisting of the divisions of Otolaryngology, Pulmonary Medicine, Radiology, Newborn Intensive Care Unit and Human Genetics. The team developed an algorithm for the management of children with obstructive sleep apnea. This should help streamline the delivery of care to these children and optimize their outcomes. We also conducted a survey for the families who have kids with pediatric obstructive sleep apnea (OSA) aimed at assessing family preferences, experiences and attitudes regarding treatment of persistent pediatric OSA. Our conclusion is that families prefer the team approach provided by the Upper Airway Center at Cincinnati Children's and that they would like more education on OSA. This resulted in a manuscript that has been submitted to an ENT journal. The team also conducted research to determine whether the decision making done at the UAC is based on current clinical practices or the clinician's past experiences, which also resulted in a manuscript that has been submitted.

Research to Improve Reconstruction

Christopher Gordon, MD; Alessandro DeAlarcon, MD; and Michael Rutter, MD, have produced a tissue-engineered neotrachea. The grafts appear fully mucosalized with ciliated respiratory epithelium, crucial to translating this technology to a human model. Gordon also is pursuing tissue-engineered mandible reconstruction as an alternative to microsurgical reconstruction.

Ann Schwentker, MD; Brian Pan, MD; and Bruce Aronow, PhD, are investigating the impact of autologous and cultured adipocyte injections in a porcine model of hypertrophic burn scarring.

John van Aalst, MD, has committed to being a part of the Cincinnati Children's institute-wide initiative to build a deep partnership with the UAE.

Division Publications

1. 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.
2. 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; 141:3003-12.
3. Kosnik-Infinger L, Gendron C, Gordon CB, Pan BS, van Aalst JA, Vogel TW. **Enzyme replacement therapy for congenital hypophosphatasia allows for surgical treatment of related complex craniosynostosis: a case series**. *Neurosurg Focus*. 2015; 38:E10.
4. Lacina L, Casper T, Dixon M, Harmeyer J, Haberman B, Alberts JR, Simakajornboon N, Visscher MO. **Behavioral observation differentiates the effects of an intervention to promote sleep in premature infants: a pilot study**. *Adv Neonatal Care*. 2015; 15:70-6.
5. 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.
6. Nathan J, Pan B, Tiao G. **Arterial Reconstruction in Children**. In: MJ Englesbe, MW Mulholland, eds. *Operative techniques in transplantation surgery*. Philadelphia: Wolters Kluwer Health; 2015:193-200.
7. Pan BS, Babiker HE, Billmire DA. **Craniofacial Trauma**. In: DS Wheeler, HR Wong, TP Shanley, eds. *Pediatric Critical Care Medicine*. New York: Springer; 2014:221-228.
8. Pan BS, Rapp SJ, Vu A, Uribe-Rivera A, Billmire DA, Gordon CB. **Evolution in minimal-incision palatoplasty:**

surgical technique and outcomes in 67 consecutive cases. *Plast Reconstr Surg*. 2014; 134:102-11.

9. Rapp SJ, Pan BS, Yakuboff KP. **Flail extremity resulting from constriction band syndrome: Neurovascular implications and surgical management**. *Case Reports in Plastic Surgery and Hand Surgery*. 2014; 1:29-32.
10. Rapp SJ, Rumberg A, Visscher M, Billmire DA, Schwentker AS, Pan BS. **Establishing a Reproducible Hypertrophic Scar following Thermal Injury: A Porcine Model**. *Plast Reconstr Surg Glob Open*. 2015; 3:e309.
11. Runyan CM, Uribe-Rivera A, Karlea A, Meinzen-Derr J, Rothchild D, Saal H, Hopkin RJ, Gordon CB. **Cost analysis of mandibular distraction versus tracheostomy in neonates with Pierre Robin sequence**. *Otolaryngol Head Neck Surg*. 2014; 151:811-8.
12. Saal HM, Prows CA, Guerreiro I, Donlin M, Knudson L, Sund KL, Chang CF, Brugmann SA, Stottmann RW. **A mutation in FRIZZLED2 impairs Wnt signaling and causes autosomal dominant omodysplasia**. *Hum Mol Genet*. 2015; 24:3399-409.
13. Sitzman TJ, Sillah NM, Hanson SE, Gentry LR, Doyle JF, Gutowski KA. **Validation of Clinical Criteria for Obtaining Maxillofacial Computed Tomography in Patients With Trauma**. *J Craniofac Surg*. 2015; 26:1199-202.
14. Visscher MO, Adam R, Brink S, Odio M. **Newborn infant skin: physiology, development, and care**. *Clin Dermatol*. 2015; 33:271-80.
15. Visscher MO, Bailey JK, Hom DB. **Scar treatment variations by skin type**. *Facial Plast Surg Clin North Am*. 2014; 22:453-62.
16. Visscher MO, Lacina L, Casper T, Dixon M, Harmeyer J, Haberman B, Alberts J, Simakajornboon N. **Conformational positioning improves sleep in premature infants with feeding difficulties**. *J Pediatr*. 2015; 166:44-8.
17. Vu AT, Patel PA, Chen W, Wilkening MW, Gordon CB. **Pediatric frontal sinus fractures: outcomes and treatment algorithm**. *J Craniofac Surg*. 2015; 26:776-81.
18. Yoshida H, Taguchi H, Hachiya A, Kitahara T, Boissy RE, Visscher MO. **The natural trait of the curvature of human hair is correlated with bending of the hair follicle and hair bulb by a structural disparity in the root sheath**. *J Dermatol Sci*. 2014; 75:195-9.

Faculty, Staff, and Trainees

Faculty Members

John van Aalst, MD, Professor
Leadership Director, Pediatric Plastic Surgery

David Billmire, MD, Professor
Leadership Director Emeritus

Samantha Brugmann, PhD, Assistant Professor
Research Interests Craniofacial Development

Haithem Elhadi, MD, Assistant Professor

Christopher Gordon, MD, Associate Professor

Ronald Hathaway, DDS, Professor

Donna Jones, PhD, Assistant Professor

Yu Lan, PhD, Associate Professor

Brian Pan, MD, Assistant Professor

Ann Schwentker, MD, Associate Professor

Marty Visscher, PhD, Associate Professor
Leadership Director, Skin Sciences Program
Research Interests Skin Science

Kevin Yakuboff, MD, Professor
Leadership Co-Director, Hand and Upper Extremity Center

Thomas Sitzman, MD, Assistant Professor

Joint Appointment Faculty Members

Rulang Jiang, PhD, Professor (Developmental Biology)

Clinical Staff Members

- **Dawn Rothchild, RN, PNP**
- **Stacey Ruth, RN, MSN, CFNP**
- **Lynn Olberding, RN, PNP**

Trainees

- **Christopher Runyan, MD, Resident**, 2009, Cleveland Clinic, PGY-9
- **Darlene Sparkman, MD, Resident**, 2010, Mayo Clinic, PGY-5
- **Sarah Evans, MD, Resident**, 2006, Duke University, PGY-8
- **Anthony Vu, MD, Resident**, University of Vermont Medical School, PGY-4
- **Binh Nguyen, MD, Resident**, University of Texas Southwestern Medical Center, PGY-7
- **Jillian Morrison, MD, Resident**, University of Toledo Medical School, PGY-3
- **Fernando Ovalle, MD, Resident**, Vanderbilt University School of Medicine, PGY-2
- **Christopher van Belle, MD, Resident**, University of California, San Francisco School of Medicine, PGY-1
- **Ching-Fang Chang, PhD, Research Fellow**, 2012, University of Alabama at Birmingham
- **Betsy Shock, Graduate Student**, University of Cincinnati
- **Rebecca Rice, Graduate Student**, University of Cincinnati
- **Grethel Millington, Graduate Student**, University of Cincinnati

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Grants, Contracts, and Industry Agreements

Grant and Contract Awards		Annual Direct
Brugmann, S		
The Role of Primary Cilia in Craniofacial Development		
National Institutes of Health		
R00 DE019853	2/1/2011-1/31/2015	$9,384
The Role of Primary Cilia in Murine Craniofacial Development		
National Institutes of Health		
R01 DE023804	12/13/2013-11/30/2018	$250,000
Lan, Y		
Golgb1 in Craniofacial Development		
National Institutes of Health		
R03 DE023864	12/13/2013-11/30/2015	$75,000
van Aalst, J		
Large Animal Model for Novel Autologous Treatments of Alveolar Clefts		
National Institutes of Health		
K08 DE023124	9/1/2014-8/31/2016	$120,250
Implanted Bioreactor to Direct Development of Engineered Cartilage in Mice		
The Plastic Surgery Foundation		
	9/1/2014-12/31/2015	$16,033
	Current Year Direct	**$470,667**

Industry Contracts		
Visscher, M		
The Procter and Gamble Company		$25,000
	Current Year Direct Receipts	**$25,000**
	Total	**$495,667**

Whole-Genome Sequencing Confirms Avian Model of Human Disease

Ching-Fang Chang, PhD

Samantha Brugmann, PhD

RESEARCH AND TRAINING DETAILS

Faculty	10
Joint Appointment Faculty	1
Research Fellows	1
Research Students	2
Support Personnel	1
Direct Annual Grant Support	$325,000
Direct Annual Industry Support	$147,572
Peer Reviewed Publications	20

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 talpid^2. *Development*. 2014;141(15):3003-3012.

PUBLISHED AUGUST 2014
Development

For more than 60 years, developmental biologists have studied a naturally occurring avian mutant called talpid^2 because of its interesting phenotypes, including cleft lip/palate, oral dysmorphologies and limb defects. However, talpid^2 has been of limited utility because researchers did not know what caused the mutation — until now.

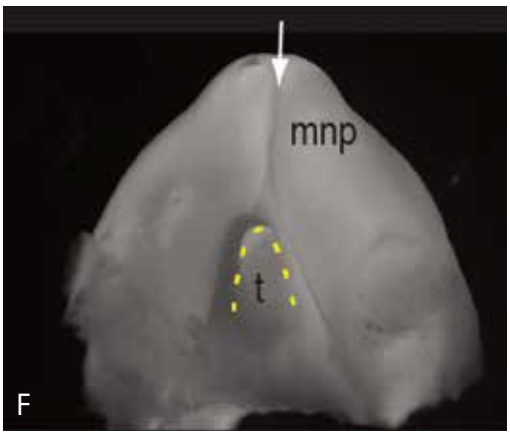
The solution came from the lab of Samantha Brugmann, PhD, which cracked the genetic, molecular and cellular code on how and why the talpid^2 mutation occurs. Their findings appeared in the August 2014 issue of *Development*.

Using whole-genome sequencing, a group of researchers from Cincinnati Children's and four other universities traced the talpid^2 mutation to a ciliary gene called C2CD3, which causes a significant reduction in the number of cells that extend a primary cilium. The team also identified molecular disruptions that occur in the Hedgehog (Hh) signaling pathway, leading to the facial and limb abnormalities associated with talpid^2.

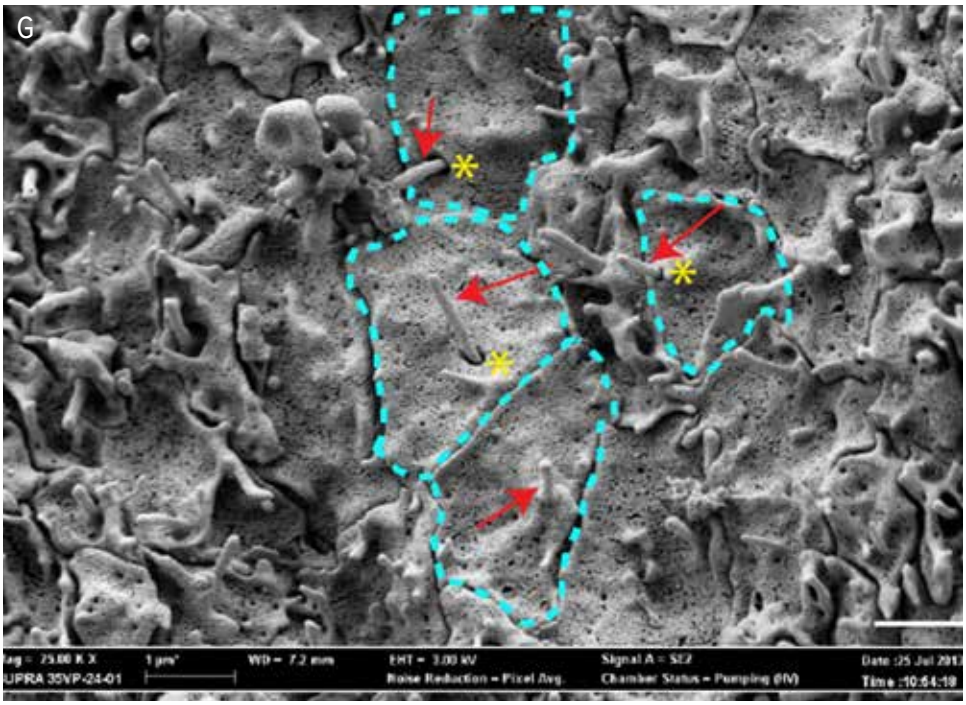
"Recently, the study of primary cilia has exploded because of the identification of a large class of human diseases called ciliopathies," Brugmann says. "Now that we know what gene causes this defect in chickens — as well as the molecular and cellular pathway that is involved — we have an avian model for human disease."

An accompanying *Development* editorial, titled "talpid^2: A Mystery Finally Solved," states: "Identification of the talpid^2 locus has been long awaited, and although there is still much to understand about how C2CD3 regulates cilia formation and function, and SHH signaling, these data provide an important step in this direction."

This prediction has come to fruition as the group, in a subsequent publication (Schock et al., 2015, in *Disease Models & Mechanisms*), has shown that talpid^2 is a bona fide model for the human ciliopathy called Oral-facial-digital Syndrome.



"Now that we know what gene causes this defect in chickens — as well as the molecular and cellular pathway that is involved — we have an avian model for human disease."



Primary cilia are disrupted in talpid[2] mutants as shown in scanning electron microscope images of the ventricular surface of the neuroectoderm. Blue lines outline cells; red arrow indicates axoneme; yellow asterisks mark ciliary pockets.