

# HARVARD

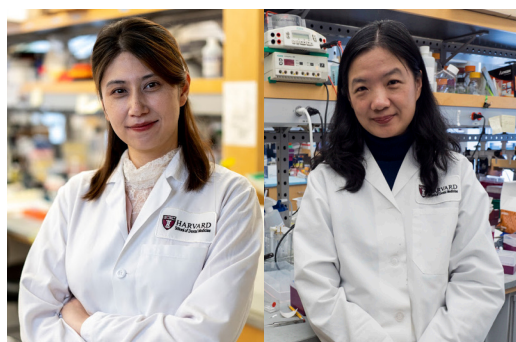
## School of Dental Medicine

### OFFICE OF RESEARCH

## *Study Reveals How Mechanical Stimuli Control Early Embryonic Growth and Development*

New research out of the Harvard School of Dental Medicine's (HSDM) Yang Lab sheds light on a largely underexplored frontier of developmental biology – how mechanical stimuli control growth and patterning in embryonic development. The findings, reported in [Science Advances](#), could have implications for preventing or treating neural tube birth defects in humans.

Previous studies primarily focused on understanding the complex networks of biochemical signaling pathways that control the development of higher vertebrate embryos and had yet to fully consider the interplay of biophysical stimuli that cells receive.



Drs. Qian Cong (left) and Yingzi Yang (right) recently published research that could help prevent or treat neural tube birth defects.

Mechanical information such as stress, strain, and fluid flow, which are generated by gravity, cell movement, and cell-cell or cell-extracellular matrix interactions are constantly collected by embryonic cells. Yet a functional understanding of mechanotransduction remains limited and it is not clear how biophysical and biochemical stimuli are integrated.

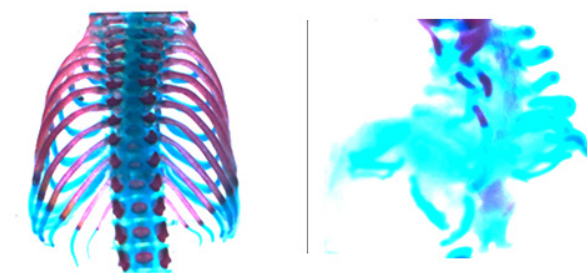
Looking at the formation of the notochord, a central organizer that determines the dorsal-ventral (DV) body plan in early vertebrate development, the researchers found that biophysical stimuli generated during embryonic morphogenesis direct critical growth and patterning of midline structures, including the neural tube, the embryonic precursor of the central nervous system.

At the molecular levels, FoxA2 and Shh are known to be ventrally located key regulators of notochord formation and neural tube DV patterning, but it has been unknown how the regionally restricted expression of FoxA2 and Shh is determined. The findings identify a gradient of mechanical stress and tissue stiffness in the notochord and neural tube generated during morphogenesis. The highest mechanical stress in the notochord and ventral neural tube acts as a crucial initial event that leads to activation of the Yap transcription factor in the notochord and the ventral-most neural tube structure, the floor plate. Activated Yap directly drives FoxA2 and Shh expression.

“Our findings uncover a novel and fundamentally important function of Yap in integrating mechanical stimuli with biochemical signaling activation in establishing signaling centers that guide embryonic growth and patterning,” said Dr. Yingzi Yang, the leading

principal investigator of the project. Yang is a professor of developmental biology and associate dean for research at HSDM.

“We expect that this report will have broad interest and appeal to basic and translational scientists working in the areas of developmental biology, human genetic diseases, neural diseases, stem cell biology, mechanotransduction and Hippo signaling.”



The findings show that Yap is required for Shh expression and formation of the notochord and FP in early embryonic development.

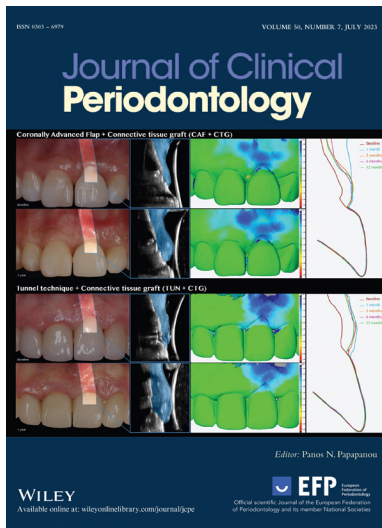
By providing new insights into notochord and neural tube development, these findings present Yap as potential targets for preventing or treating neural tube defects. Neural tube defects are one of the most common birth defects in humans and can result in malformation of the gut, neural tube, vertebrae, and cranial region. Despite limited interventions of surgery corrections and folic acid supplementation during pregnancy, a significant portion of neural tube defects remain unpreventable and/or difficult to treat.

Importantly, these new findings about the critical feed-forward roles of Yap in controlling FoxA2 and Shh expression unify the research team’s previous work. They demonstrated that direct activation of Shh expression by Yap in a completely different and FoxA2-independent context: the disease of heterotopic ossification, which is caused by abnormal osteoblast differentiation in soft tissues in adult human beings.

Drs. Caiqi Cheng and Qian Cong are co-first authors of the paper. Cheng was a visiting student in the Yang Lab and Cong is an instructor in the Yang Lab at HSDM. This work is supported by NIH grants R01DE025866, R01AR070877 and R01CA222571, as well as the DoD grant PR201987 to Yang.

# DEPARTMENT NEWS

## *Oral Medicine, Infection, and Immunity*



**The Journal of Clinical Periodontology** featured a clinical trial conducted by Assistant Professor of Oral Medicine, Infection, and Immunity Lorenzo Tavelli and Dean William Giannobile on its July cover. The research, titled “Coronally advanced flap versus tunnel technique for the treatment of peri-implant soft tissue dehiscences with the connective tissue graft: A randomized, controlled clinical trial” assessed the clinical, volumetric, and ultrasonographic outcomes of connective tissue grafts, either with coronally advanced flap or tunnel technique for the treatment of implant esthetic complications. Results showed that while both approaches showed positive results at one year, coronally advanced flap outperformed tunnel technique in terms of mean defect coverage, volumetric gains, and patient-reported outcomes.

**Ang Cui, faculty member in the Department of Oral Medicine, Infection, and Immunity, participated as a panelist during the 72nd Lindau Nobel Laureate Meeting this June.** Discussing "Artificial Intelligence and Medicine," the panel touched on the progress, challenges, and future opportunities of AI in medicine and medical research. Cui believes that while there has been "tremendous progress of AI in medicine," it has been limited to domain-specific problems, and there remains a need for AI to grow into new spaces and address new opportunities.



## *Oral and Maxillofacial Surgery*



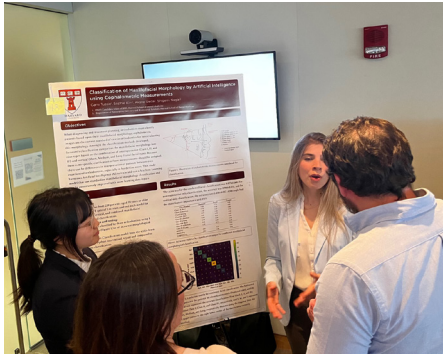
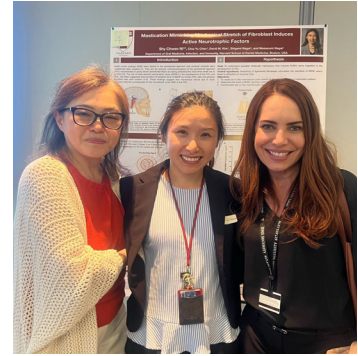
**A group of HSDM students and alumni gathered at the International Conference on Oral and Maxillofacial Surgery in Vancouver, BC this June.** Pictured from left to right is Joshua Yang, DMD25, Gerardo Alvarez, DMD24, Sheridan Danquah, DMD24, Yisi Daisy Ji, DMD18, Jonathan Fillmore, DMD08, Zachary Peacock, DMD04, Brian

Ruggiero, DMD17, and Salvatore Ruggiero, DMD87. Yang, Alvarez, Danquah, and Ji each presented posters on their research and Peacock presented on "Medical Management of Surgical Disease."



## HSDM at AADOCR Boston

**A number of students past and present represented the School at this year's American Association for Dental, Oral, and Craniofacial Research (AADOCR) Boston Section Spring Meeting.** From the Department of Oral Medicine, Infection, and Immunity, Shy Ni, DMSc23, presented a poster titled "Mastication mimicking mechanical stretch of fibroblasts induces active neurotrophic factors."



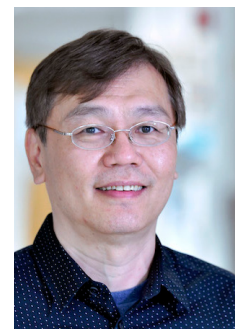
**Cami Tussie, DMD25, and Sophie Kim, DMD25, were also at the AADOCR Boston meeting representing the Department of Restorative Dentistry and Biomaterial Sciences.** The two presented a poster titled "Classification of Maxillofacial Morphology by Artificial Intelligence using Cephalometric Measurements."

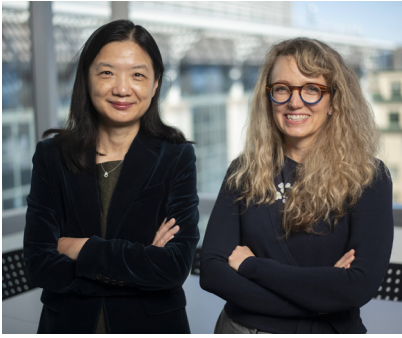
## GRANTS AND AWARDS



**The National Center for Equitable Care for Elders (NCECE), led by HSDM Associate Professor of Oral Health Policy and Epidemiology Christine Riedy, received renewed funding from the Health Resources and Services Administration.** Established in 2017, NCECE develops and shares culturally competent models of care, interprofessional training and educational resources, and technical assistance to health centers caring for the country's growing population of older adults. This three-year award totaling \$1.6 million is the third time the Center's funding has been renewed. It will be put towards furthering NCECE's mission to advocate for the needs of older adults and address issues in our nation's health centers.

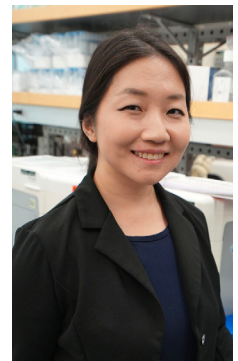
**Dr. Wei Hsu, a professor of developmental biology at HSDM, has been granted a \$2.7 million NIH/NIDCR R01 award to investigate tooth development and regeneration.** The project aims to elucidate the mechanisms underlying the regulation of odontogenesis to better understand tooth agenesis. Based on past human genetic studies of tooth agenesis that indicate a number of significant causative genes involved in Wnt signaling, Hsu will explore new functions of  $\beta$ -catenin, a multifaced protein responsible for transducing canonical Wnt signaling. The goal of the project is to uncover important insights into next-generation therapy for dental restoration.





**Drs. Yingzi Yang and Jennifer Gibbs were presented Distinguished Scientist Awards at the 101st General Session of the International Association for Dental, Oral, and Craniofacial Research (IADR).** Yang was honored with the 2023 IADR Distinguished Scientist Basic Research in Biological Mineralization Award for her significant work in the field of oral health research. Gibbs was honored with the 2023 IADR Distinguished Scientist Award for Pharmacology/Therapeutics/Toxicology Research for her contribution to the novel pharmacologic approaches of controlling dental pain.

**Dr. Ang Cui, a faculty member in the Department of Oral Medicine, Infection, and Immunity, has been awarded the Christina Fleischmann Award for Excellence in Cytokine & Interferon Research.** Presented by the International Society for Interferon and Cytokine Research (ISICR), the award is dedicated in memory of ISICR member and outstanding interferon research scientist Christina Fleischmann. Cui is the director of the Systems Immunology laboratory at HSDM and Harvard Medical School (HMS). She has developed massively high-throughput experimental and computational approaches to decipher the complex in vivo immune responses to cytokines.



**Dr. David Kim, associate professor of Oral Medicine, Infection, and Immunity, has been awarded the A. Clifford Barger Excellence in Mentoring Award.** Created by HMS, the award was created to recognize the value of quality mentoring relationships and the impact they have on professional development and career advancement in basic/clinical medicine, research, teaching, and administration.

**Two graduates from the Class of 2023 Doctor of Medicine in Dentistry (DMD) program were recognized for their research contributions at this year's commencement ceremony.** Ariana Aram (left) and Bradley Bousquet (right) both graduated with Honors in Research for their thesis projects that went above and beyond a typical scholarly project. In addition to their Honors degrees, the two received research awards at this year's Graduate Recognition Award Ceremony. Aram received the Harvard Odontological Society Award for excellence in research and Bousquet earned the Grace Milliken Award for an outstanding thesis on the general subject of dental health.



# NEW RESEARCH STAFF AND PROMOTIONS



**Dr. Lakmali Silva began her new appointment in June as assistant professor in the Department of Oral Medicine, Infection, and Immunity.** Silva joins HSDM from the National Institute of Dental and Craniofacial Research (NIDCR), where she completed her postdoctoral training. Her research centers around inflammatory regulation in the periodontal microenvironment and was recognized by the NIDCR in 2021 with a K99/R00 Pathway to Independence Award.

**After completing his Periodontology Residency and Doctor of Medical Sciences in Oral Biology this spring, Dr. David Wu began his new role at HSDM as a part-time lecturer and post-doc fellow in the Department of Oral Medicine, Infection, and Immunity.** This position allows Wu to continue his research exploring how biomaterial mechanical properties can tune stem cell behavior for tissue regeneration and medical device development, while also practicing and teaching one day per week.



**Dr. Sung Eun Choi in May was promoted to assistant professor of oral health policy and epidemiology.** Formerly an instructor in the department, Choi's work focuses on areas of disease simulation policy modeling and health services research in oral healthcare. In her new role, she is creating a research portfolio aimed at promoting the adoption of high-value interventions and policies to reduce oral health disparities utilizing mathematical modeling.

**Dr. Jennifer L. Gibbs recently became an associate professor in the Department of Restorative Dentistry and Biomaterials Sciences.** In addition to her professorship, Gibbs serves as the division head of endodontics, the program director of the Advanced Graduate Education Program in Endodontics, and as a practicing clinician in endodontics at HSDM. Her research seeks to understand the neurobiological mechanisms of orofacial pain with a focus on the nociceptors of the dental pulp.



**The Department of Restorative Dentistry and Biomaterials Sciences also recently promoted Dr. Sang Lee to the position of associate professor.** Lee concurrently serves as the Assistant Dean of Clinical Affairs at HSDM and is the medical director of the Harvard Dental Center practices in Longwood and Cambridge. His research interests include the development and application of digital dental technology from treatment planning, implant placement, and restoration.





**The Office of Research has welcomed Dr. Christine Riedy (left) as the director of oral health workforce innovation and population health.** In this newly created position, Riedy will develop a comprehensive research agenda to expand and educate the oral health workforce, addressing oral health disparities and improving oral health in the general population. Riedy has stepped down from her former position as Chair of the Department of Oral Health Policy and Epidemiology, where she served for six years. Succeeding

Riedy as Department Chair is Dr. Catherine Hayes (right), who also serves as the program director of the dental public health advanced graduate education program at HSDM. She has been actively involved in research and policy initiatives related to oral health disparities and inequities throughout her career and has published numerous articles and book chapters in the field of dental public health and epidemiology.

**Associate Professor of Oral Health Policy and Epidemiology Dr. Brittany Seymour has taken on a new role as HSDM's first associate professor of faculty affairs.** Seymour is well-known at HSDM and across Harvard for her work in global and community health and as a leader in advancing oral health initiatives around the world. With experience creating her own unique faculty path in global and community health, and inspiring her students to pursue roles in academia, Seymour will be a crucial collaborator with department chairs in support of their work to guide and mentor faculty of all academic ranks and promotion pathways.



## UPCOMING EVENTS



### Faculty Research Day

Wednesday, September 6

6:00 p.m. to 8:00 p.m.

HMS Courtyard Café

The HSDM Office of Research is pleased to host the second iteration of its Faculty Research Day. The event introduces DMD and AGE students to the breadth of ongoing studies performed at HSDM and affiliated sites, and is critical in helping students identify projects and mentors aligned with their research interests.

## **Osteology Research Academy Boston**

Tuesday, September 19 to Thursday, September 21 at HSDM

This three-day program, titled "Research Design and Methodology - How to plan and run a research project from A to Z," will provide attendees with the skills needed to effectively carry out a study of dental medicine. The course will feature lectures from leading experts, interactive case studies and ample opportunities to collaborate with instructors and peers. To learn more about the event and register, visit the Research Academy page on the [Osteology Foundation's](#) website.

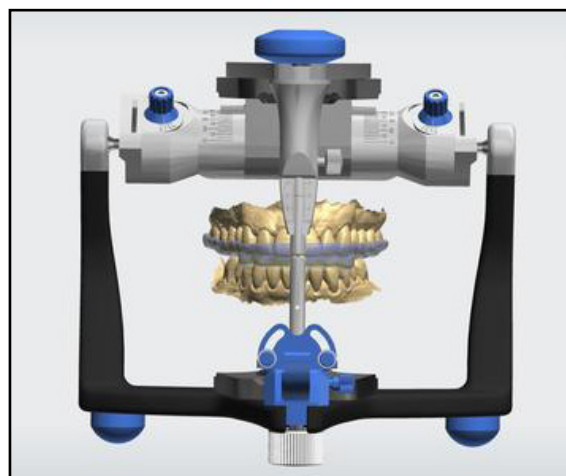
## **The New Age of Occlusal Rehabilitation: Harmony for Teeth and Implants**

Saturday, October 28

9:00 a.m. to 3:00 p.m.

HSDM Campus

Course participants will have in-depth learning opportunities regarding dental occlusion from a board-certified prosthodontist and dental sleep medicine specialist. The program will present an ideal occlusal scheme as well as therapy to treat patients with malocclusion, temporomandibular disorder, and other related occlusal disorders. Visit the HSDM calendar event webpage to register for the course.



## **2023 Paul Goldhaber Award and Lecture**

Tuesday, October 17

3:00 p.m. to 5:30 p.m.

REB Auditorium, HSDM



Established in 1989, the Goldhaber Award is HSDM's highest research honor, which recognizes a recipient who is held in international esteem in their field relating to oral health. This year's awardee is Dr. Yang Chai, a professor and the George and MaryLou Boone Chair in Craniofacial Biology at the University of Southern California. His research on craniofacial development and birth defects has transformed the field and led to the successful rescue of cleft palate in mouse embryos. The event will feature a school-wide reception with light refreshments followed by a lecture from Dr. Chai and an award ceremony.



## GLOBAL SYMPOSIUM ON ARTIFICIAL INTELLIGENCE IN DENTISTRY

Held at the Harvard University Science & Engineering Complex on November 3-4, the event will bring together dental researchers, scholars, and industry leaders from around the world for dynamic presentations and a lively exchange of ideas about the impact of rapidly changing technological innovations in the field of health care and dentistry. To register or to submit an abstract, visit the [University's event website](#).

# PUBLICATIONS

## Developmental Biology

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