Creighton UNIVERSITY
School of Medicine

DR. RICHARD J. BELLUCCI
Translational Hearing Center
Creighton University

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Bellucci Translational Hearing Center Director Recognized by HHF

Director of the BTHC, Peter Steyger, PhD speaks at the 2023 Bellucci Symposium

Bellucci Translational Hearing Center Director, Peter Steyger, PhD was recognized by Hearing Health Foundation (HHF) for being a longtime partner of HHF. Dr. Steyger has been featured numerous times on HHF's blog in Hearing Health magazine. Dr. Steyger joined HHF's Council of Scientific Trustees (CST) in the mid-2000's. CST is the governing body of HHF's Emerging Research Grants (ERG) program. "HHF is dependent on and incredibily grateful to the clinicians and researchers like Peter who volunteer their time and expertise to reviewing grant applications, overseeing the ERG porgram, and informing our mission as the largest private, nonprofit funder of hearing and balance research in the U.S." - Anil K. Lalwani, MD
Dr. Steyger decided to step away from the CST to focus more of his attention on the many other endeavors he has. Anil K Lalwani said, "HHF has benefited from nearly two decades of his service and, while sad to see him go, we wish him all the best." To read more about Dr. Steyger and HHF please visit this link: https://hearinghealthfoundation.org/blogs/our-sincere-thanks-to-peter-steyger-phd

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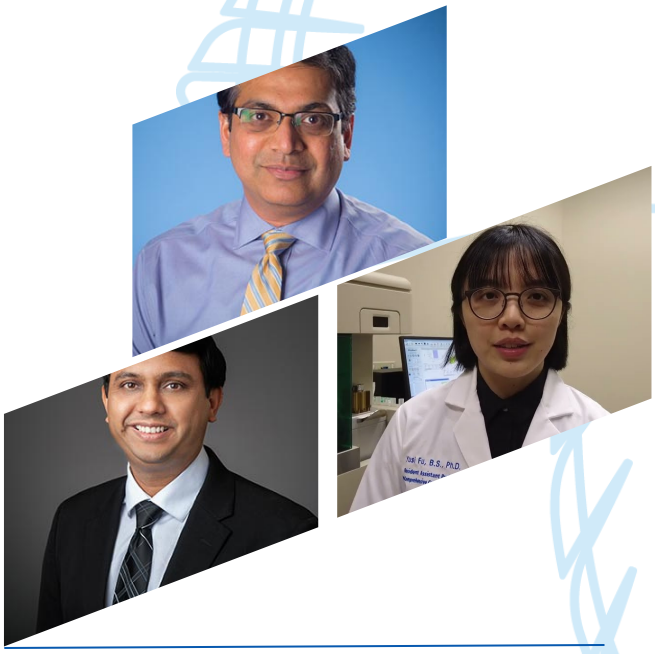
Featured articles

Center Cores Continue to Develop

The Bellucci Translational Hearing Center cores continue to develop exponentially. The Auditory & Vestibular Technology Core is led by Dr. Mike Nichols and operates 4 outstanding sub cores. Electrophysiology (Sarath Vijayakumar), Molecular Biology (Sarath Vijayakumar), Imaging (Anthony Stender), Mass Spectrometry (Molly McDevitt). If you, or someone you know are interested in any of these services please reach out to the respective sub core manager with any questions that you may have. More information regarding the AVT core can be found on our center website here: https://www.creighton.edu/medicine/departments/biomedical-sciences/translational-hearing-center/technology

The Drug Discovery & Delivery Core also continues to experience exponential growth. The DDD core is led by Dr. Patrick Swanson. Dr. Swanson has been a valuable addition to the center as he has taken over leadership of the DDD core. Core manager, Gopal Jadhav has also been excellent in his role to help the development of the DDD core. The DDD core has 4 sub cores, Drug Design, Synthesis and Validation Laboratory (Chunkai Wang), ADMETox Laboratory (Alekha Dash), Zebrafish Laboratory (Linda Goodman), Cell Culture and Tissue Laboratory (Sarath Vijayakumar). If you, or someone you know, are interesting in these services please contact the respective sub core manager to get started. More information regarding the DDD core can be found on our center website here: https://www.creighton.edu/medicine/departments/biomedical-sciences/translational-hearing-center/drug-discovery-delivery-core



Three New Pilot Project Awardees

The center is thrilled to announce the addition of 3 new pilot project awardees. Steven Fernandes, PhD, Sarath Vijayakumar, PhD and Yusi Fu, PhD have all begun their pilot project awards. They will join Gopal Jadhav, PhD as pilots within the center, bringing us to a total of 4 active pilot projects. More informaiton about each pilot project can be found later on in this newsletter.

Steven Fernandes, PhD

Steven Fernandes Recognized as Top 2% in AI & Image Processing by Stanford University

To read more about Bellucci Translational Hearing Center member Steven Fernandes being recognized as top 2% in AI & image processing by Stanford university please click here: https://elsevier.digitalcommonsdata.com/datasets/btchxktzyw/5

2023 Bellucci Symposium

The 2023 Bellucci Symposium was a massive success. The 2023 symposium was focused on hair cell development and regeneration. Jaime García-Añoveros, PhD was the 2023 Bellucci Prize winner as well as the keynote address speaker. The 2023 trainee awardee was Nesrine Benkafadar, PhD, PharmD. We were able to welcome speakers and attendees from all over the country. The center would like to thank everyone who was able to participate in the symposium both virtually and in-person. We are excited to welcome everyone back for the 2024 Bellucci Symposium. The date for the 2024 symposium is set for May 17th. We are also thrilled to announce that the 2024 symposium will continue to be held both virtually and in-person. If you have any questions regarding the 2024 symposium please reach out to Charles Klinetobe charlesklinetobe@creighton.edu.

Left to right, Peter Steyger, PhD, Nesrine Benkafadar, PhD PharmD, Jamie García-Añoveros, PhD, Litao Tao, PhD

Our New Pilot Project Awardees

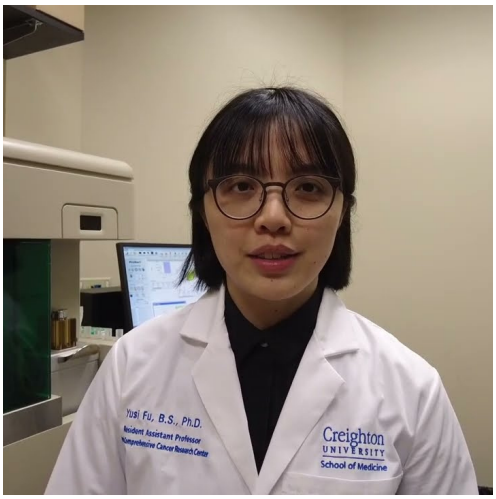
Steven Fernandes, PhD

Hearing loss affects more than 1.5 billion people globally, comprising approximately 20% of the global population. Of these, 430 million people have disabling hearing loss, a number expected to rise to 700 million by 2050. Children with hearing loss often do not receive the same level of schooling as their peers, and adults with hearing loss are more likely to face higher unemployment rates or occupy lower-level jobs. Therefore, according to the WHO, unaddressed hearing loss incurs an annual global cost of US$ 980 billion, including the costs of hearing devices, educational support, productivity losses, and societal impacts. When hair cells are lost, sound is not readily converted into neural activity in the cochlea. To mitigate this issue, we intend to develop a deep learning-based method for detecting auditory hair cells (HCs) along the entire length of the cochlea. We propose to use two main algorithms in our deep learning model to analyze microscopy images of cochlear HCs: iFS-RCNN for HC detection and EM-net for HC segmentation. Unlike traditional Faster R-CNN, which requires a large volume of labeled data, iFS-RCNN is designed to learn new classes using just a few labeled examples. iFS-RCNN incorporates memory-augmented components for efficient feature storage, making it more memory-efficient than traditional Faster R-CNN methods. For HC segmentation, we will use EM-net to analyze the fluorescent signal in HCs along the cochlea's length. We will also optimize the spatial embeddings of cells for instance segmentation. Pixels that belong to a cell are projected from their spatial locations through predicted embedding vectors, forming clusters around centroid object instances. To identify clusters of pixels and predict segmentation masks for missing cells, we will employ Deep Embedded Subspace Clustering, known for its robustness against noise and scalability.

Sarath Vijayakumar, PhD

Cystic fibrosis (CF) is an autosomal recessive genetic disorder with a prevalence of over 40,000 children and adults in the U.S. and an estimated 105,000 people worldwide. It is the most common fatal genetic disease in the United States. The reduced or null function of the cystic fibrosis transmembrane conductance regulator (CFTR) protein predisposes patients to frequent pulmonary bacterial infections, pancreatic exocrine insufficiency, and gastrointestinal complications. Although the arsenal of antibiotics has expanded, aminoglycosides, especially tobramycin —selected for its anti-P. aeruginosa activity—remain pivotal for managing acute pulmonary exacerbations in patients with CF. Notably, while many aminoglycosides manifest ototoxic effects predominantly either in the cochlea or the vestibular system, tobramycin impacts both systems. In the inner ear, CFTR observed in the basolateral membrane of the cochlear outer hair cells and it has been shown to interact directly with prestin, the cochlear outer hair cell electromotility protein. Furthermore, pendrin and CFTR mRNA transcripts co-localize in the mitochondria-rich cells of the mouse endolymphatic sac. While CFTR's role in vestibular physiology has been implied, its exact expression pattern within the vestibular organs remains elusive. In this proposed study, we postulate: 1) the higher incidence of vestibular impairment in patients with CF is due to CFTR mutation affecting the ionic homeostasis and normal function of the vestibular organs 2) CFTR channel dysfunction sensitizes the vestibular organs to aminoglycoside ototoxicity. Our investigative approach will involve 1) mapping the cellular distribution of the CFTR channel across both vestibular and auditory organs, and 2) detailing the vestibular and auditory

effects of tobramycin-induced ototoxicity using a CF mouse model harboring the prevalent CFTR ΔF508 mutation. This investigation aims to enrich our comprehension of the CFTR channel's physiological role in vestibular and auditory organs. From a public health perspective, this research would elucidate molecular underpinnings and associated risks of irreversible ototoxicity in CF patients undergoing tobramycin therapy.



Yusi Fu, PhD

Drug-induced ototoxicity is a leading cause of acquired hearingloss. Intravenous administration of aminoglycoside antibiotics is used to treat individuals with cystic fibrosis (CF) hospitalized with respiratory infections, which can lead to sensorineural hearing loss (SNHL) in a dose-dependent manner.Yet, there is substantial variability in the degreeof hearing loss among individuals of similar age and cumulative aminoglycoside dosing, suggestive of genomic influences that contribute to susceptibility to Aminoglycoside-Induced Hearing Loss (AIHL). To uncover susceptibility-related genes, other researchers are conducting genome-wide association studies (GWAS) by genotyping ~700 patients with CF using microarrays and their corresponding audiograms by audiologists. GWAS focus on statistical associations to identify associated loci instead of the tfunctional gene. Thus, a major challenge posed by GWAS is the exploration of the functional consequences of nearby variants of identified loci. Although the array-based imputation strategy enables us to investigate more than 90% of the common loci (minor allele frequency, MAF ≥ 0.5%),it cannot be applied to rare variants(MAF < 0.5%) that make up the vast majority of human genetic variations. Whole genome sequencing (WGS) can determine almost the entireDNA sequence of a singleindividual at a singlebase resolution and is efficient for evaluating rare genetic variants.WGS enables the profiling of exon regions and regulatory non-coding sequences (e.g., promoters and enhancers), which can also contribute to altering the transcription and expression of genes. With the reduced cost of sequencing, WGS has become more popular when determining the risk variants associated with traits and diseases, as it guarantees that real functional variants are sequenced. WGS can identify rare genetic variants and better understand complex traits. WGS can identify rare variants with high confidence, with a substitution error rate of 10-5 to 10-4/bp. Based on sequencing results from 1000 genome projects, WGS can detect 4-5 million rare variants in each individual. Studies have shown that, both analytically and numerically, extreme phenotype sampling (EPS) increases the presence of rare causal variants in various settings. For this study, we will utilize WGS of extreme phenotypes to potentially identify rare variants that modulate susceptibility to AIHL. The results can be used to curate a list of candidate genes for testing in a future study with a larger sample size. Impact - This study can potentially identify candidate causal genes for AIHL susceptibility and provide a list of variants for test in future studies. The results will help identify patients with CF at risk for AIHL and improve the quality of life of patients treated with aminoglycosides.

Pilot Project Awardee Renewal

Centers for Disease Control and Prevention (CDC) states noise induced hearing loss (NIHL) as one of the prevalent health issues in the U.S. Currently, there are no FDA approved treatments for NIHL. Therefore, a search to identify novel druggable targets for NIHL is required. Recently, inflammation has proved to be an attractive target for novel drug discovery against NIHL and associated ototoxicity. TREM1 is a primary target responsible for exaggerating various inflammatory disorders by manipulating human immune system. Its pharmacological inhibition by LR12 in the subversion of various disease models, suggest that it might be used as a template to design TREM1 inhibitory agents, provided derivatives devoid mainly of proteolytic... Read more here: Pilot Project Awardees (creighton.edu)

Gopal Jadhav, PhD

Our Current Research Project Leaders

Jeffery North, PhD

Aminoglycosides (AG) have broad antibiotic spectra against aerobic gram-positive and gram-negative bacteria and mycobacterial pathogens. AG toxicities include kidney tubular necrosis, vertigo, and, most notably, hearing loss. AG are used to treat multidrug-resistant tuberculosis (MDR-TB) and *Mycobacterium abscessus* complex (MABSC) infected patients (e.g. cystic fibrosis, bronchiectasis or chronic obstructive pulmonary disease). Studies have shown that 55-58% of patients infected with MDR-TB who received amikacin as part of their therapy, experienced hearing loss due to its ototoxic effects. Likewise, up to 27% of cystic fibrosis patients infected with *M. abscessus* who received AG therapy experienced hearing loss. Read more here: Research Project Leaders (creighton.edu)

Litao Tao, PhD

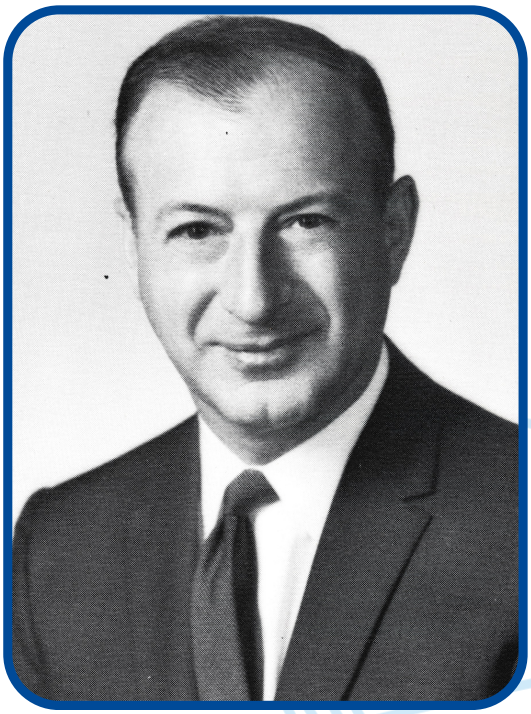
Transcription factor POU4F3 is indispensable for the differentiation and homeostasis of sensory hair cells, the essential cell type converting mechanical vibrations into electrical signals for hearing function. During hair cell differentiation, the pioneer factor activity of POU4F3 is required for ATOH1 to access many inaccessible elements to up-regulate hair cell genes. In mature hair cells, reduction of POU4F3 transcription activity due to mutations in one allele leads to hair cell death and hence progressive hearing loss (DFNA15,autosomal dominant non-syndromic hearing loss 15). It remains unclear how the expression of POU4F3 gene is regulated at different developmental stages... Read more here: Research Project Leaders (creighton.edu)

Padmashri Ragunathan, PhD

Exposure to alcohol during pregnancy produces fetal alcohol spectrum disorders (FASD) that are associated with sensory and cognitive deficits. Individuals with FASD have impaired auditory processing and also frequently exhibit atypical auditory behaviors. It is therefore important to determine the molecular mechanisms that govern auditory processing in normal and developmentally abnormal brain. We will examine auditory processing in mice prenatally exposed to alcohol, perform in vivo imaging in the primary auditory cortex to track AMPARs α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid.) and dendritic spines over days, and perform electrophysiological recordings... Read more here: Research Project Leaders (creighton.edu)

Translational Hearing Center Renamed to Honor Alumnus and Pioneering Surgeon Richard J. Bellucci, MD

DR. RICHARD J. BELLUCCI Translational Hearing Center Creighton University



Bellucci is best known for his work on stapedectomy, a surgery where a prothesis is inserted into the middle-ear to improve hearing. He expanded the use of microscopes in surgery and invented the Bellucci Micro Ear Scissors--which remain a standard instrument for otological surgeons.

He was president of the American Otological Society and volunteered his expertise in Haiti. He received the Italian *Cavaliere de Merito*, the Legion of Merit Award, for his work treating World War II veterans suffering from hearing loss.

About Creighton University

Creighton University, founded in Omaha, Nebraska, in 1878, is one of 27 Jesuit colleges and universities in the U.S. The Omaha campus has more than 8,000 undergraduate, graduate, and professional students among nine schools and colleges. No other university its size offers students such a comprehensive academic environment with personal attention from faculty-mentors. The new health sciences campus in Phoenix, which will accommodate nearly 1,000 students by 2025, is the largest expansion outside of Omaha in Creighton's history and positions the University as one of the largest Catholic health professions educators in the country. Creighton is ranked in the top third of National Universities by U.S. News & World Report.

More About Richard J. Bellucci, MD

Dr. Bellucci's mission in starting the Bellucci DePaoli Family Foundation was to ensure the important work of hearing preservation and restoration continues. The Foundation offers funding to impressive PhD candidates and post-doctoral fellows making important contributions in auditory research, plus support for acquiring necessary research equipment. During the procedure, the stapes (a tiny bone in the ear) is removed and replaced by a prosthetic device, gifting patients with certain types of hearing loss to regain their hearing. Dr. Bellucci was Chair of Otolaryngology at the Manhattan Eye, Ear & Throat Hospital (1963-79) and Chairman of Otolaryngology at New York Medical College (1966-80), completing his residency at the former. He trained many ear, nose, and throat specialists who practice today throughout the United States, Canada, and beyond. Dr. Bellucci was also the Director of several impressive residency programs. In addition to running his own private practice and serving as a longtime president of the American Otological Society, he volunteered time and services in his later years at the Hopital de Sacre Coeur in Milot, Haiti, exemplifying the Jesuit spirit of service.

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