# ORS Recognizes Loiselle, Young Investigators for Research Excellence

The February Orthopaedic Research Society Annual Meeting was an eventful one for CMSR: Alayna Loiselle, PhD, received the Adele L. Boskey PhD Award, given to mid-career researchers who have made significant contributions in mentoring young researchers in orthopaedics, musculoskeletal science, and engineering; and three early-career investigators earned recognition for their presentations.

Out of 41 finalists, Rahul Alenchery, PhD, and Himanshu Meghwani, PhD, were two of the ten who received New Investigator Recognition Awards (NIRA), and Emmanuela Adjei-Sowah received a Podium Award. They shared their work with fellow researchers, post-doctoral students, and physician-researchers at the meeting in Long Beach, California.

The NIRA award recognizes the innovative contributions of early-career investigators who exhibit exceptional potential in advancing orthopaedic science and practice. Recipients who present the findings of their research papers are recognized for demonstrating originality, scientific merit, and potential impact. The Podium Award recognizes high-quality presentations about research topics and presenters' ability to express complex concepts clearly and impactfully to audiences.

## Mapping the Entire Injury/Healing Pathway

Alenchery presented his paper, *Unraveling The Role Of mTOR In Tendon Fibrosis: Implications For Targeted Therapies And Scar-free Healing.*

Alenchery, who has been with CMSR for more than five years and studies in the Hani Awad Lab, focuses his research on mapping the complete signaling pathway of tendon repair and fibrosis, revealing the pivotal role of the mTOR signaling pathway in these processes. His study further examined how the mTOR pathway affects inflammatory peritendinous adhesions in injured flexor tendons; how regulation of mTOR signaling changes over time in various populations of cells involved in tendon repair; and whether inhibition of mTOR signaling improves repair of the injured tendons.

In his study on mice with partial tendon injuries, Alenchery discovered that certain cells react in a remarkable way, showing shifts in key markers linked to healing and scarring, such as α-SMA, γH2AX, and Ki-67, alongside heightened immune activity and disruptions in tissue structure. By administering a 10-day treatment of Rapamycin, a well-known mTOR inhibitor and a drug commonly used as an immune suppressor in liver transplant patients, the injured tendons demonstrated significant improvements in genetic and protein markers, as well as a 50% increase in biomechanical strength.

"Blocking activity of this pathway for a transient period allows the body to not be overreactive in terms of inflammation, and healing improves," Alenchery said. His findings support the search for a pharmacological treatment to improve tendon healing. "Rapamycin is well-established as a drug that inhibits this pathway, but we haven't yet used it for treating injuries. Since mTOR inhibitors are in clinical trials as disease-modifying agents for pulmonary fibrosis, the association between mTOR signaling and poor outcomes of tendon injury makes mTOR a novel and promising therapeutic target for fibrotic adhesions."

## Boosting the Immune System to Fight a Devastating Bone Infection

Meghwani presented his paper, *CCL20/CCR6 Limits The Disease Severity in Staphylococcus Aureus Osteomyelitis by Increasing Th17 and Macrophage Recruitment at The Site of Inflammation.*

Meghwani is pursuing his post-doctoral fellowship and studies in the Gowrishankar Muthukrishnan lab. His paper focused on his research in osteomyelitis following implant surgery; 75 percent of these bone infections are caused by *Staphylococcus aureus*.

"We wanted to see, other than antibiotics, what we can do to prevent infection; my work looks at how human immune cells behave in countering the infection," Meghwani said.

Meghwani's research aims to develop an immune-based theory that can boost the human immune system before bone infection develops. He collected serum from patients infected with *S. aureus*-associated osteomyelitis and performed Luminex assays to see which chemokines in the serum were changing in these patients. Using the Luminex assay, he gauged the quantity of CCL20, a chemokine involved in recruitment or migration of leukocytes to the site of inflammation from the blood vessels.

"It's high in the patients who are diagnosed with *S. aureus*-induced osteomyelitis," Meghwani said. "We wanted to know what happens when we alter the amount of CCL20, so we started more experiments using in vitro and mouse models; we found when we reduced or knocked out the CCL20, or its receptor, CCR6, the infection severity increases in mice. We determined that CCL20 and CCR6 are essential for limiting infection severity. In the future, we plan to run more experiments where we administer more CCL20 before the infection develops and see if it reduces infection severity. The ultimate goal is to translate the result in human patients."

## Targeted Drug Delivery Using Nanoparticles

Adjei-Sowah's presentation detailed her work in developing a nanoparticle-based, tendon-targeting drug delivery system to pharmacologically modulate tendon healing.

"Traditional methods for repairing tendon injuries involve suturing but it heals with so much scar tissue," she said. "As a new approach in the field of tendon injury, we want to pivot from using suturing alone as the gold standard to incorporating therapeutics. Currently, there are no therapeutics available to promote regenerative tendon healing, and no effective mechanisms to target these treatments to the tendon. But there are very novel things done in that space now thanks to advances in multi-omics, and it was striking for the audience at ORS to learn about drug delivery methods using nanoparticles."

Adjei-Sowah, now in her fourth year as a PhD trainee, has been working with Alayna Loiselle and Danielle Benoit since her first year on efforts to load the drug Niclosamide into nanoparticles and inject into mouse models to target the tendon.

Previous work from her labmate showed that a 50 percent reduction in s100a4 gene expression resulted in improved mechanical and functional outcomes in a genetic mouse model. To recapitulate these results in a more translational manner, Adjei-Sowah used Niclosamide, a transcriptional inhibitor of S100a4. Using mouse models that had complete transection and surgical repair of a tendon, Adjei-Sowah injected mice on day 7 post-surgery, which resulted in high accumulation of the drug at the injury site; the free drug group had minimal accumulation at the injury site.

She observed significant inhibition of s100a4 gene expression compared to controls and significantly lower s100a4 protein expression levels, demonstrating that the nanoparticle drug delivery model efficiently achieved s100a4 inhibition to a much greater extent than the systemic free drug treatment.

Adjei-Sowah observed significantly increased flexion angle and lower gliding resistance at days 14 and 28 post-injury, indicating consistent improvements in functional restoration and range of motion. She also observed higher max load at failure and stiffness at both d14 and d28, indicating improved mechanical outcomes after targeted niclosamide treatment.

“Our development of a highly translational tendon-targeting drug delivery model, which helps improve tendon healing by delivering a drug directly to the injury site, is possible because we leveraged transcriptomics as a mechanism to both identify potential therapeutic targets, and perhaps more importantly, to identify strategies for high-efficiency tendon targeting of systemic treatments,” Adjei-Sowah said.

Targeting the tendon was so effective that the improved outcomes were possible with just one treatment, she noted.

“Our future work will define how broadly this system can be used both for other tendon pathologies and tendon aging, as well as potentially in other contexts of soft tissue fibrosis. The beauty of this system is that it can be loaded with different kinds of drugs to target different molecular processes or pathways.”