UC San Diego
JACOBS SCHOOL OF ENGINEERING
NanoEngineering

UC SAN DIEGO NANOENGINEERING SEMINAR

Wednesday, January 30th, 2019
Seminar Presentation: 11:00am – 12:00pm
SME 248

"Boosting Intracellular Delivery of mRNA Therapeutics"

Dr. Gaurav Sahay
Assistant Professor
College of Pharmacy
Oregon Health and Science University

Abstract: Intracellular delivery of messenger RNA for the therapeutic production on proteins can transform modern medicine. While lipid-based nanoparticles (LNPs) remain in the forefront of delivery of nucleic acids, there endosomal sequestration remains a formidable barrier for cytosolic delivery. In studies with siRNA, even the most potent cationic lipids (the active ingredients within LNPs) enable a mere <2% release of nucleic acid to its cytosolic target. We have identified novel naturally occurring lipid that can enhance cytosolic delivery of nucleic acids and decoded structural activity relationships using analogues of these lipids to reveal the nature of endosomal escape processes. We found that these inclusions of these endosomal escape agents can lead to LNP mediated mRNA delivery (eLNPs) to about ~200-fold. Cryo-TEM, X-ray scattering, and state-of-the-art imaging were used to interrogate nanoparticle shape, internal structure, and intracellular trafficking, respectively. eLNPs were of polyhedral morphology with a disordered internal structure, in contrast to the spherical LNPs, which possessed an inverse hexagonal phase. 3D-Dynamic Photon Localization Tracking showed that eLNPs had improved diffusivity inside cells as compared to LNPs which remain in a mostly immobile state suggesting endosomal entrapment. eLNP-delivered mRNA also exhibited substantial cytosolic localization as visualized through single-molecule RNA-FISH, confirming that these agents guide in overcoming endosomal barriers by inducing structural polymorphism within LNPs. In this talk, I will further discuss the application of LNPs based mRNA therapeutics for the treatment of lung and eye disorders. Understanding the overall structure of nanoparticles and their internal networks will enable new designs that lead to the improved subcellular release of cargo and boost gene delivery.

Biosketch: Gaurav Sahay is an Assistant Professor in the College of Pharmacy at Oregon State University in Portland, Oregon. Dr. Sahay works at interface of nanotechnology, cell biology and drug delivery. Gaurav completed his postdoctoral research with Prof (s). Robert Langer and Daniel Anderson at Koch Institute for Integrative Cancer Research at MIT and his PhD with Dr. Alexander Kabanov at the University of Nebraska Medical Center. Dr. Sahay's lab has unlocked the molecular mechanisms involved in the intracellular delivery of nanoparticles and has used fundamental insights to design new materials that can effectively deliver nucleic acids to their subcellular targets. Sahay Lab has deployed non-viral vectors for treatment of rare genetic disorders like cystic fibrosis and disorders of the eye. He has over 30 publications in top tier journals including Nature Biotechnology, Nano Letters, Nature Nanotechnology, PNAS, Journal of Controlled Release, ACS Nano etc. Dr. Sahay is the winner of 2013 AAPS Postdoctoral Fellow Award, 2015 CRS T. Nagai Post Doc Award and New Investigator Awards from AACP and was the Chair of 2018 International Nanomedicine and Drug Delivery Symposium (nanoDDS2018) and serves on the Scientific Advisory Board of Oncorus Therapeutics. Sahay Lab has received funding from the NIH, Cystic Fibrosis Foundation, Medical Research Foundation of Oregon, OSU Foundation and several biotech companies.