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Vibrio MARTX toxins as effector delivery platforms to promote bacterial pathogenesis

PI4D Seminar
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2:30 pm- 3:30 pm, MRGN 121

MARTX toxins are large proteins (up to 5208 amino acids in size) secreted from many different Gram-negative bacteria, including human pathogens. Conserved MARTX N- and C-terminal repeat regions have been shown to form pores in eukaryotic cell membranes, through which the central region of the toxin is translocated. Upon inositol hexakisphosphate-induced activation of the MARTX cysteine protease domain (CPD) in the eukaryotic cytosol, the central portion of the toxin is autoprocessed to release "effector domains". All total, genome sequence analyses have revealed 10 different MARTX effector domains present in various MARTX toxins, although the presence and organization of the effector domains varies by species and by strain. These effector domains disturb many distinct cellular processes including causing cytoskeleton disassembly, inhibiting of autophagy, disrupting normal protein secretion, and disabling Rho and Ras family GTPases. In the intestinal pathogens *Vibrio vulnificus,* it has been shown that the MARTX effector domain regions induce rapid intestinal barrier dysfunction and increased paracellular permeability. However, the function of the toxin can change due to the combination of effectors and strains within the same species can carry different organizations of their effector domains. In particular the overall pathogenesis can change dependent upon the single factor Ras/Rap1 specific endopeptidase that "disconnects" the RAS-ERK signaling network. The processing of Ras is being investigated as a tool for cancer research and as a therapeutic to treat tumors.

Dr. Karla Satchell (*nee* Karla Fullner) earned her B.S. in Biology at Pacific Lutheran University in Tacoma WA in 1988 and completed a Ph.D. in Microbiology in 1996 at the University of Washington in Seattle. Her graduate dissertation focused on bacterial pathogens of plants. She next conducted post-doctoral training at the University of Pittsburgh studying genetics of *Mycobacterium* spp. and at Harvard Medical School on the pathogenesis of cholera. During her post-doc, Dr. Satchell discovered a novel toxin now known as a representative of a large family of Multifunctional-Autoprocessing RTX toxins, or simply MARTX. Since joining the faculty at the Northwestern University Feinberg School of Medicine in Chicago in 2000, Dr. Satchell has continued to conduct research on the MARTX toxin of *Vibrio cholerae*, building a diverse program including both studies on the mechanism of action of the toxin and the role of the toxin in infection using mouse models. She has since 2008 expanded her research program to include studies of MARTX toxins of other pathogens, including *Vibrio vulnificus,* a bacterium that causes severe sepsis from seafood consumption. Her most recent work utilizes structure biology to understand the mechanism of a protease that cleaves oncogenic Ras. She also directs a multi-site center in high throughput structure determination for pathogens. In these areas, she has published more than 70 research articles. In recognition of her work, Dr. Satchell was awarded tenure in 2008 and was promoted to full professor in 2013. She was the recipient of a Burroughs Wellcome Investigators in Pathogenesis of Infectious Diseases Award in 2006. She has been elected as a fellow for the American Academy of Microbiology and the American Association for the Advancement of Science. She is also active in teaching of graduate students and in 2016 was awarded the Driskill Dean's Award for Excellence in Teaching. She has mentored 10 Ph.D. students and 13 post-doctoral fellows.