Johns Hopkins University

Department of Biology Seminar Series

Thursdays, 4:00pm

For more information go to: *https://bio.jhu.edu/events*

Zoom link: *https://zoom.us/j/97925356454?pwd=bjNuTlY1dU9BcXcvRFdleis2TVNadz09*

Mudd Room 100 - December 1st, 2022

Joshua Modell

Molecular Biology & Genetics

Johns Hopkins University School of Medicine

Host: Bob Johnston

"CRISP-Cas9 autoregulation balances phage defense and autoimmunity"

CRISPR-Cas systems provide bacteria with adaptive immunity against foreign genetic elements, including bacterial viruses or "phages". As with any immune system, CRISPR-Cas expression comes with the risk of autoimmunity against self elements, in this case the bacterial chromosome. How CRISPR-Cas systems are regulated to enhance immunity against phages while minimizing autoimmunity is poorly understood. We discovered that in many type II CRISPR-Cas systems, which encode Cas9 homologs that have been adopted as gene editing tools, a natural single-guide RNA (tracr-L) reprograms Cas9 from a nuclease of foreign DNA into a transcriptional repressor of its own promoter. CRISPR-Cas expression is thus maintained at low levels to prevent autoimmunity. In cells lacking tracr-L, CRISPR-Cas expression and phage defense are dramatically increased. We show that tracr-L repression can be naturally relieved to allow CRISPR-Cas induction (1) in direct response to a phage infection and (2) preceding a phage infection in a subpopulation of cells with promoter mutations. We believe that such intrinsic control strategies may explain how CRISPR-Cas systems are so frequently spread by horizontal transfer between prokaryotic hosts, and our ongoing work explores how widely Cas9 has been deployed as a transcriptional regulator in nature.