Contribution ID: **15** Type: **Poster only**

Poster #15: Guide amplification bootstraps immune specificity in a bacterial Argonaute

Monday, 5 October 2026 20:38 (1 minute)

Bacteria face constant invasion by mobile genetic elements such as plasmids and phages, and many have evolved guide-directed nucleases related to eukaryotic Argonaute proteins to combat these threats. How such systems achieve specific recognition of foreign, supercoiled plasmid DNA without simply guessing based on guide sequence has been a longstanding puzzle. Here we describe a short prokaryotic Argonaute system that solves this problem in an unexpected way: rather than encoding specificity in the guides themselves, the system generates its own specificity dynamically, through a feedback process triggered by target recognition. This self-reinforcing behavior allows the system to home in on supercoiled plasmid targets while leaving the host chromosome untouched. We present structural, biochemical, and *in vivo* data that together reveal this mechanism, and discuss its implications for how specificity can emerge in nucleic-acid-guided immune systems more broadly, with intriguing parallels to amplification-based immunity in other domains of life.

Reference #1

Reference #2

Reference #3

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Session Classification: Poster-Session