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Multi-targeted proteostatic collapse as an antimicrobial strategy against multi-resistant Escherichia coli

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We here present a novel designer antibiotics paradigm that exploits protein aggregation to kill pathogenic E. coli by widespread proteostatic collapse. In order to induce multi-targeted protein aggregation, we designed P2, a synthetic peptide containing a short aggregation-nucleating sequence that is highly redundant in the E. coli proteome. P2 is readily internalized by E. coli, inducing rapid formation of large polar inclusions resulting from co-aggregation between P2 with bacterial proteins containing similar aggregation prone sequences, resulting in a lethal aggregation cascade involving over 300 proteins connected through a network of associated APRs. P2 is active against clinical isolates that are resistant to multiple antibiotics and is effective in reducing bacterial load in bladder infection in mouse. Our results indicate slow development of resistance, suggesting that aggregation of redundant APRs constitutes a tight proteostatic deadlock. Exploiting this finding could be useful as a novel therapeutic approach against drug-resistant bacteria.

Biography

Ladan Khodaparast has completed her PhD from KU Leuven from Department of Immunology and Microbiology in 2017 and she currently works at the Faculty of Medicine, Switch Laboratory VIB-KU Leuven Centre for Brain & Disease Research Department of Cellular and Molecular Medicine, University of Leuven. She has published more than 8 papers in reputed journals.

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