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A novel antibiotic effectively inhibiting an unconventional target, Na^+-translocating NADH:ubiquinone oxidoreductase

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Statement of the Problem: The present crisis in antibiotic development and administering was precipitated not only by decades of global misuse of broad-spectrum antibiotics and resulting proliferation of multi-drug resistant strains, but also by a general strategy in antibiotic design, when a very limited set of prokaryotic enzymes and metabolic pathways was ever targeted. The situation calls for urgent intensification of the search for non-traditional antimicrobial targets.

Methodology & Theoretical Orientation: The Na^+-translocating NADH:ubiquinone oxidoreductase (Na^+-NQR) is a key respiratory enzyme in many aerobic pathogens, including a widespread and notoriously difficult to treat *Chlamydia trachomatis*. Inhibition of Na^+-NQR was predicted to arrest bacterial energization and proliferation, and ultimately disrupt the infectious process. To examine this prediction, a new furanone inhibitor of Na^+-NQR, PEG-2S, was designed and assayed for its anti-chlamydial activity in cell culture models of infection.

Findings: The presented work confirms that Na^+-NQR is critical for the *Chlamydia trachomatis* infectious process. A newly designed PEG-2S inhibited intracellular proliferation of *Chl. trachomatis* with a half-minimal concentration in the submicromolar range without affecting the viability of mammalian cells or selected species representing benign intestinal microflora. Infection by *Chl. trachomatis* increased H^+ and Na^+ concentration in the infected mammalian cell. Addition of PEG-2S blocked these changes in ion balance induced by *Chl. trachomatis* infection. PEG-2S also inhibited the Na^+-NQR activity in sub-bacterial membrane vesicles isolated from *Vibrio cholerae* when added at very low (nanomolar) concentrations.

Conclusion & Significance: The obtained results demonstrate that Na^+-NQR is critical for the bacterial infectious process and is susceptible to a precisely targeted bactericidal compound *in situ*. PEG-2S opens a new line of narrowly targeted inhibitors of NQR and is serving as a molecular platform for the development of "individually tailored" anti-NQR remedies narrowly targeting specific pathogens.

Biography

Pavel Dibrov is primarily interested in the molecular mechanisms of the sodium transport, especially in bacterial pathogens. His lab's approach is based upon the combination of methods from membrane bioenergetics, molecular cloning and metagenomic analysis.

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