TECHNOLOGY

Targeting NAD biosynthesis in bacterial pathogens

OVERVIEW

The increasing incidence of antibiotic-resistant pathogens is a major health crisis, particularly in hospital settings in the developed world. It has been estimated that ~70% of hospital-acquired infections involve multi-antibiotic resistant organisms, resulting in ~90,000 annual deaths at a cost of 4.5ý6.0 billion per year (Burke, 2003). Recently-developed antibiotics have been hampered by limitations, while funding for new antibiotics has become reduced. The situation is sufficiently dire that many health professionals are considering returning to antibiotics that were previously abandoned due to toxicity concerns (Arias & Murray, 2009). In view of these difficulties, there is an urgent need for new antibiotic treatments. Ideally, these antibiotics would inhibit a vital component of an essential process not be easily circumvented by infectious pathogens. One such target is nicotinate mononucleotide adenylyltransferase (NadD), which is critical for the synthesis of NADH. NADH is an enzyme cofactor essential for redox reactions in all biological systems. NadD, located at the convergence of the only two biological pathways capable of NADH production, performs the penultimate step in the synthesis of NADH. There is no alternative for NADH synthesis. Researchers have identified a new class of antibiotics that specifically target bacterial, but not human, NadD (Sorci et al, 2009). Lead compounds from this study decrease cell growth of E. coli cell cultures. Additional crystallographic studies have characterized the atomic details of this interaction, providing an avenue for the further refinement of lead candidates through structure-based drug design (Huang et al, 2010). This refinement could lead to the production of even more effective antibiotics. These findings permit the development of new antibiotics with widespread utility, which could be critical for the treatment of the ever-growing number of multi-drug resistant pathogens.

APPLICATIONS

New class of antibiotics directed towards a novel target (NadD) that is essential to NAD formation in bacteria Could be used in the treatment of human and veterinary diseases Could be used as a treatment for anthrax exposure Could be incorporated into antibacterial products such as paints and soaps

ADVANTAGES

-In light of the increasing incidence of infectious pathogens displaying multi-drug resistance, it is critical to identify new antibiotics that are specific for novel, biologically essential targets -The novel antibiotics in this invention target bacterial, but not human, NadD. -NadD performs the penultimate, convergent step in the only two biological pathways capable of NADH synthesis. There is no alternative route for NADH production. Bacteria would have to evolve an entirely new NADH synthesis pathway, which is unlikely, or compromise life processes by making potentially devastating changes to the highly evolutionarily conserved NadD to obtain resistance to these drugs.

STAGE OF DEVELOPMENT

-Researchers have found that this new class of antibiotics is toxic to E. coli and B. anthracis, specifically inhibiting NadD of these species -Antibiotics do not appear to bind the human isoforms of NadD -Structure-based drug design on crystal structures to optimize and refine lead candidates (Huang et al, 2010)

R&D REQUIRED

-Efficacy in additional bacterial pathogens needs to be tested -Safety and toxicity studies in animal models of pathogenic infection leading up to human trials -Further efficacy testing prior to clinical trials

LICENSING POTENTIAL

UMB seeks partners for licensing, clinical development, and/or sponsored research to advance this technology into the healthcare field.

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PATENT STATUS

U.S. Patent 8,875,499 issued 7/22/2014

CATEGORIES

- Therapeutics
- Small molecules

INVESTIGATOR(S)

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EXTERNAL RESOURCES

- Targeting NAD biosynthesis in bacterial pathogens: Structure-based development of inhibitors of nicotinate mononucleotide...
- Complexes of bacterial nicotinate mononucleotide adenylyltransferase with inhibitors: implication for structure-based drug...

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