Development of a new family of drugs for cystic fibrosis patients with non-tuberculous mycobacterial infection

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Abstract

Cystic fibrosis (CF) is an autosomal recessive disease affecting over 100,000 people worldwide. The disease is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, which codes for a cell-surface chloride ion channel. These mutations lead to a lack of CFTR protein in the cell membrane or a reduction in the activity of the CFTR protein, lowering chloride ion secretion, thickening the mucus in the airways of CF individuals, and thereby promoting bacterial infection. Chronic lung infections caused by non-tuberculous mycobacteria (NTM) are becoming more common in CF patients. This trend is concerning because most morbidity and mortality in CF patients is due to microbial lung infections. There are no reliable and effective therapies for NTM, therefore it is necessary to develop antibiotics or adjuvant therapies against these bacteria. To solve this problem, we are studying a new family of chemical compounds from the National Institute of Health for their potential against NTM. Our lab selected this family of chemical compounds via screening an NIH compound library, and we further evaluated their strength against *Mycobacterium abscessus* (*M. abscessus*) and *Mycobacterium avium* (*M. avium*), the two most common NTM species found in CF patients. We determined the compounds' toxicity to host cells, their effect on NTM growth in bacterial broth, and their anti-mycobacterial efficacy in macrophages. To better understand the mechanism of action of this family of chemical compounds, we used an artificial intelligence (AI)-based drug-docking technology and determined the interaction of drug candidates with their mycobacterial targets. We found that one of the compounds (named Cpd #3), with the best attracting cavity score, binds to the ATP-binding domain of *M. abscessus* DNA Gyrase subunit B, an essential protein for mycobacterial growth. This finding correlates with our data that Cpd #3 has the best antimycobacterial activity against *M. abscessus*. Our results suggest that Cpd #3 could be potentially used as a new antibiotic for CF patients with NTM lung infections. We plan to further test this possibility by testing Cpd #3 in combination with CLR in a PK/PD study in preclinical CF mice with NTM lung infections.