ACS Infectious Diseases

In This Issue

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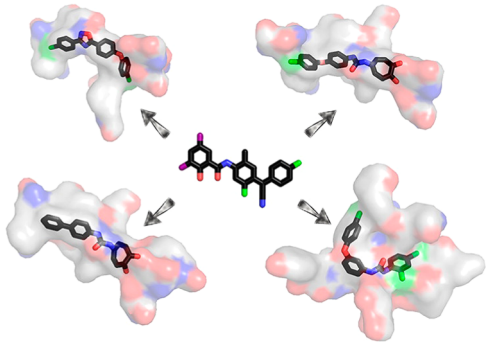
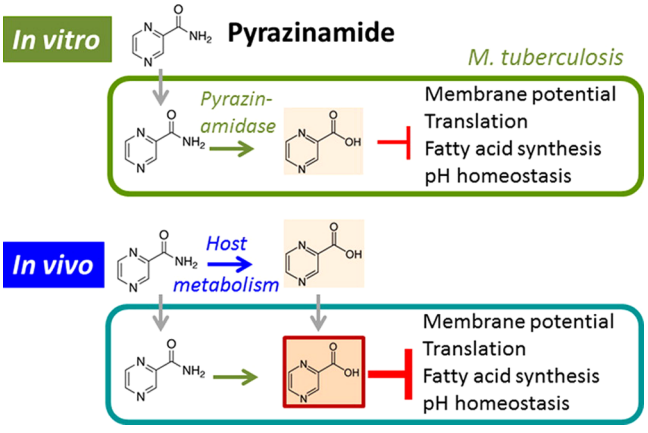
LEAD HOPPING TO FIND ONCHOCERCIASIS INHIBITORS



Onchocerciasis affects over 37 million people worldwide. It is an infectious disease caused by the parasitic nematode *O. volvulus*. There is a great need for novel targets and therapeutic strategies against the disease as current efforts to eliminate parasite transmission are met with challenges and limitations.

Here, Gooyit et al. (DOI: 10.1021/acsinfecdis.5b00017) describe a "lead hopping" strategy to identify novel structures with chitinase inhibitory activity. Their efforts resulted in the identification of analogues with improved potency against chitinase and serve as promising inhibitors of *O. volvulus* L3 molting. These findings are significant for the development of macrofilaricidal drugs and strategies toward the elimination of onchocerciasis.

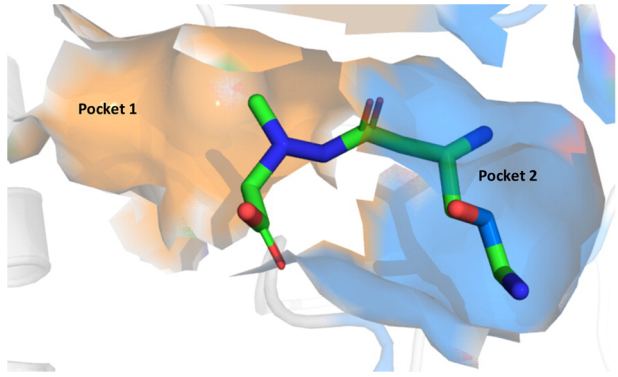
PHARMACOKINETIC EXPLANATIONS FOR AN OLD DRUG PUZZLE



Tuberculosis kills more than 1.5 million people each year and requires months of daily multidrug therapy. Pyrazinamide is a prodrug that has played a critical role in shortening therapy against drug-sensitive and drug-resistant tuberculosis. Despite widespread recognition of its therapeutic importance and being around for 60 years, pyrazinamide's outstanding clinical efficacy remains an enigma given its rather poor activity in a test tube.

As featured on the cover, Via et al. (DOI: 10.1021/id500028m) show that bioactivation of pyrazinamide is achieved not only by the pathogen but also by the host and that the resulting pool of active metabolites distributes effectively from the blood compartment to the site of infection. Furthermore, the group demonstate that oral administration of pyrazinoic acid leads to good exposure, which can be further boosted by coadministration of the FDA-approved gout drug, allopurinol.

NEGAMYCIN'S HIGH AND LOW UPTAKE ROUTES



Negamycin, a natural product antibacterial, has previously been shown to inhibit protein synthesis. The molecular mechanism of inhibition has pointed to negamycin's binding to ribosome, which was recently demonstrated in structural studies. Still, the precise mechanism of action remains unclear, and the route of cellular entry of this polar molecule continues to confound researchers.

In this issue, McKinney et al. (DOI: 10.1021/acsinfecdis.5b00027) show how negamycin enters the *Escherichia coli* cytosol and identified two modes of entry, a high and a low transport route. The group synthesized the four negamycin stereoisomers and investigated how each isomer utilizes the two transport routes. These results provide a strong rationale for improved negamycin to maintain utilization of the low-affinity uptake route and thus minimize clinical resistance due to transport-related mutations.

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