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In This Issue

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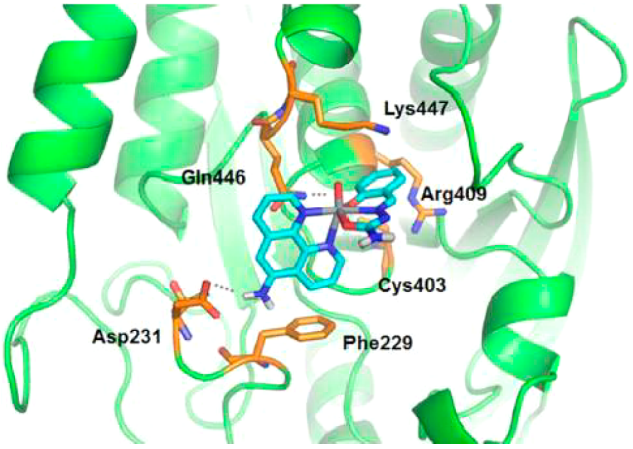
INHIBITING BACTERIAL TYROSINE PHOSPHATASE

Functional cell signaling mediated by the enzymatic activity of phosphatases and kinases is required to maintain cellular homeostasis. Pathogenic bacteria belonging to the genus *Yersinia* produce a phosphatase, YopH, which is injected into the host cell. Once inside the host, YopH interferes with host cell signaling and helps the bacteria evade the immune system. Selective inhibition of YopH presents a novel strategy for development of antimicrobials against *Yersinia* species.

In this Featured Letter, Martins et al. (DOI: 10.1021/acsmedchemlett.5b00267) describe novel oxidovanadium(IV) complexes capable of potent inhibition of YopH. The authors use several biochemical techniques, as well as molecular modeling, to identify the mechanism of YopH inhibition of these complexes. The complexes described here present not only a new antimicrobial strategy for treatment of *Yersinia* but also potential new leads in the search for potent phosphatase inhibitors.



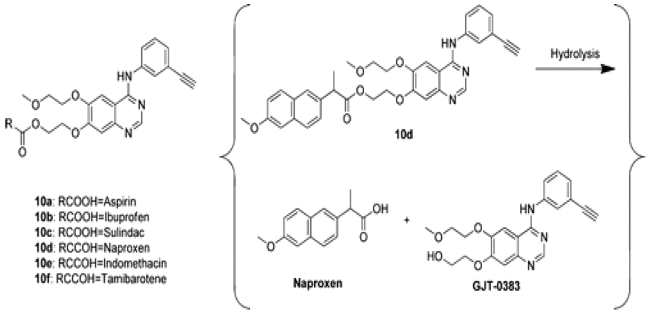
SIMPLIFYING COMBINATION THERAPY

Non-small cell lung carcinoma (NSCLC) is associated with poor prognosis. Current therapy for NSCLC includes the use of epidermal growth factor receptor tyrosine kinase inhibitors such as erlotinib; however for many cancers, targeting a single mechanism is often insufficient. A combination drug with multiple targets presents an opportunity for maximizing efficacy while minimizing side effects.

Here, Zhang et al. (DOI: 10.1021/acsmedchemlett.5b00286) prepare and evaluate conjugates of NSAIDS and erlotinib for improved efficacy over erlotinib alone. The authors demonstrate that the new conjugates have potential as a new class of chemotherapeutic agents with multiple targets with improved efficacy for NSCLC and a simple dosing regimen compared to other combination therapies.

STOPPING DIGITOXIN NEOGLYCOSIDES AT THE BLOOD–BRAIN BARRIER

Digitoxin and digitoxin neoglycosides have been extensively investigated as potential cancer therapeutics; however, potent derivatives tend to be neurotoxic and cardiotoxic. Reducing the ability of these compounds to cross the blood–brain barrier could help to reduce the neurotoxicity of these compounds. As amino sugars do not readily cross the blood–brain barrier, synthesis of amino sugar derivatives of digitoxin neoglycosides presents promising new drug leads with anticancer activity and reduced neurotoxicity.



In this issue, Thorson et al. (DOI: 10.1021/acsmedchemlett.5b00120) report the synthesis and biological evaluation of a set of digitoxin neoglycosides containing amino sugar regioisomers. In addition, the authors put forth a computational model to serve as a blueprint for further steroidal glycoside optimization.

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