A Novel Phospholipid-Based Prodrug Strategy for the Treatment of IBD

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Technology

We propose a novel targeted prodrug approach that may address drug localization issue by using phospholipase A2 (PLA2), an enzyme that hydrolyses the sn-2 position of phospholipids (PL) and is overexpressed in the inflamed tissues of IBD patients. The prodrug contains three main components: the PL, the drug moiety, and a carbonic linker that connects them through the sn-2 position of the PL; we have shown that depending on the suitability of the linker design and length, PLA2 enzyme is capable of activating this prodrug, liberating the free drug from the complex. Therefore, orally delivered PL-based prodrugs will release the free drug specifically at the diseased site(s), effectively targeting the regions of intestinal inflammation. We have shown proof-of-concept for this novel drug targeting approach for PL-diclofenac prodrugs. In addition, we have developed a state of the art computational approach to simulate the PLA2-mediated activation of different PL-based prodrugs. Further, we have successfully synthesized variety of PL-drug conjugates with different drugs and linkers. We then showed effective PLA2-mediated activation of the optimal prodrugs in-vitro, with excellent correlation between the computational simulations and the in-vitro results. Finally, we were able to demonstrate high in-vivo activation of the PL-Drug conjugates in a rat IBD model vs. minimal drug release in healthy control animals.

Advantage

The global inflammatory bowel diseases (IBD) drug market is estimated at $8.5bn in 2016 and $9.5bn in 2020.Novel therapies are expected to be the main drivers of growth in the IBD drug market according to the forecast period. Current IBD therapies target a particular segment in the gastrointestinal tract (GIT), generally the colon, regardless of where the inflammation is actually localized, thereby having a less optimal activity with high none specific effect. The technology is based on an approved drug with validated activity. The same rationale can be applied to other drugs for IBD. A diversified team comprising pharmaceutical scientist and IBD clinicians.