Potential prodrugs based on PLA_2 for IBD

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Technology

Prof. Dahan developed novel targeted prodrugs that may address drug localization issue by using phospholipase A_2 (PLA_2), an enzyme that hydrolyses the sn-2 position fatty acyl bond of phospholipids (PL). By replacing the sn-2 positioned fatty-acid with a drug, PLA2 may be exploited as a prodrug activating enzyme, liberating the free drug from the PL-complex. PLA2 expression/activity is significantly elevated in the inflamed intestinal tissues of patients with inflammatory bowel disease (IBD), Crohn's disease (CD) and ulcerative colitis (UC). Therefore, orally delivered PL-based prodrugs will release the free drug specifically at the inflamed sites, effectively targeting the regions of intestinal inflammation, while minimizing unnecessary systemic drug exposure. 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. Prof. Dahan's team 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. One of the advantageous of this core technology is that it may be applied to numerous drug candidates; they have already shown proof-of-concept with several small organic molecule (indomethacin, diclofenac, etc.) and larger molecules such as the cyclic peptide cyclosporine. Advanced computational simulations were used to predict the PLA2-mediated activation of different prodrug structures. Four PL-cyclosporine prodrugs were synthesized, differing by their linker length between the PL and the drug moiety. To study the prodrug activation, a novel enzymatically enriched model was developed, the colonic brush border membrane vesicles (cBBMVs); in this model, tissue vesicles were produced from colitis-induced (vs. healthy) rat colons. PLA2 overexpression (3.4-fold) was demonstrated in diseased vs. healthy cBBMVs. Indeed, while healthy cBBMVs induced only marginal activation, substantial prodrug activation was evident by colitis-derived cBBMVs. Together with the PLA2 overexpression, these data validate the offered drug targeting strategy. In the diseased cBBMVs, quick and complete activation of the entire dose was obtained for the 12-carbon linker prodrug, while slow and marginal activation was obtained for the 6/8-carbon linkers. The potential to target the actual sites of inflammation and treat any localizations throughout the GIT, together with the extended therapeutic index, makes this orally delivered prodrug approach an exciting new therapeutic strategy for IBD treatment.

Application

Prodrug technology for treatment of IBD – CD & UC. The drug can be orally administrated.

Advantages

- Platform for prodrug for treatment of IBD -CD &UC
- Orally administrated
- Target to site of inflammation - minimize drug absorption, maximize drug levels in the diseased area, and minimize drug levels in the blood

Patent

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