

The rational design of intestinal targeted drugs

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Abstract

Intestinal targeting of drugs is an effective means of increasing the therapeutic index of certain therapies by increasing the local concentration of drug in the intestine while minimizing the concentration of drug elsewhere in the body. The potential for unwanted side-effects can be reduced by minimizing the amount of drug available to bind to off-targets or the on-target in anti-tissues, which would have undesired consequences. Several approaches to attain intestinal targeted, or non-systemic, small molecule drugs exist. Physicochemical properties can be optimized to access large, polar chemical space, which can lead to low intestinal absorption. Alternatively, driving properties towards lipophilic chemical space can increase first-pass clearance and reduce systemic exposure. Designing substrates for either uptake or efflux transporters in the gut epithelia, or at the hepato-biliary interface, is another strategy. Finally, low absorption prodrugs have been shown to be effective for intestinal targeting, often relying on bacterial conversion to the active substance. These strategies will be discussed, using known examples of drugs and drug candidates to highlight the attributes and liabilities of each approach. Emerging data around the remission of type 2 diabetes after gastric bypass surgery and new appreciation of the gut microbiome in disease, as two examples, suggest that gut targets will continue to be an important area of research.

Biography

Kevin J. Filipski is a Senior Scientist at Pfizer Worldwide Research & Development in Cambridge, MA. He has worked in the Cardiovascular, Metabolic, and Endocrine Diseases Chemistry department at Pfizer for 14 years following schooling at the University of Rochester and the University of Michigan. He has published 22 journal articles and book chapters and is a co-inventor on six patents. Highlights of his career include the advancement of seven development candidates into clinical trials, including three into Phase 2 studies. He also co-invented and first synthesized the oral antithrombotic Factor Xa inhibitor eribaxaban, which completed Phase 2b clinical trials.