

Platform to Incorporate Selectivity into Prodrug Linkers

A major limitation of protease-activated prodrugs (PAPs) is that linkers are traditionally designed to target one or two proteases. This is challenging because the human genome codes for more than 600 proteases, and there is no guarantee that any one protease will be present in sufficient concentration to release the drug. The fact that only three different protease-cleavable linkers exist on the market is testament to the lack of innovative and effective strategies for linker discovery. Instead of navigating the specificities of 600 individual human proteases, we simplify the problem by considering the collection of proteases present in a microenvironment as a single protease. Analogous to a single protease, each biological mixture has a unique proteolytic signature because of the combined activity from associated proteases. *Our novel strategy enables us to identify a linker that cleaves selectively in one set of microenvironments while remaining stable in others.* We demonstrate an application of this platform for the development of antibiotic prodrugs that combat resistant infections. As more infections emerge that are resistant to all current therapies, innovation in this area is direly needed. The ultimate goal of our linker discovery program will be to expand the platform to improve prodrugs for multiple diseases, including diverse cancers.