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Tumor targeted pro-drugs

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Matrix Metalloproteinases (MMPs) play a significant role in degrading the extra- cellular matrix in cancer development and metastasis. Overexpression of MMPs in tumor tissues relative to normal tissues has been exploited as a target for peptide-based therapeutics, to improve therapeutic index of currently used agents. The stability of MMP-activated pro-drugs in normal tissue or organs is a significant challenge for their success in the clinic. In an in vitro study, the stability of 26 pro-drugs was studied in mouse liver, kidney, lung and tumor homogenates using HPLC and LC/MS. Selected agents were studied in vivo. Each pro-drug has a characteristic amino acid sequence with dominant FITC N-terminal end cap. All pro-drugs were conjugated to a colchicine derivative (ICT 2552) which is a vascular disrupting agent causing tumor vasculature shutdown and consequently, tumor necrosis. ICT 3146, ICT 3019, ICT 3120 and ICT 3115 pro-drugs showed significant stability in normal tissues and considerable activation in certain tumor tissues compared to the lead compound ICT 2588. Also, the selectivity of promising pro-drugs to the MMP family was confirmed by using leupeptin (serine, cysteine and threonine protease inhibitor), pepstatin A (aspartate protease inhibitor), phosphoramidon (neprilysin inhibitor), ilomastat (metalloproteinase inhibitor) and BML-P115 (matrix metalloproteinase inhibitor). Moreover, members of the MMP family responsible for cleaving the selected pro-drugs were identified using recombinant MMP enzymes. Furthermore, a LC/MS-MS method was developed to specifically detect and quantify MMP-16 protein expression in H460 tumor. MMP-16 was responsible for the cleavage of ICT 3146 and ICT 3115. Therefore, MMP-activated pro-drugs could be a useful therapeutic approach to avoid off-site toxicities of currently used anti-tumor agents.

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