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Development of bacterial β-glucuronidase specific inhibitors to reduce chemo-induced intestinal toxicity and diarrhea

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The direct inhibition of bacterial β-glucuronidase (βG) activity is expected to reduce the reactivation of glucuronide-conjugated drugs in the intestine, thereby limiting drug toxicity. In this study, we report on the effects of pyrazolo[4,3-c]quinoline derivatives acting as bacterial βG-specific inhibitors. These inhibitors exhibited potent inhibition of E. coli βG (eβG), but not human βG (hβG). The binding modes revealed that the inhibitors bound in the active site of eβG and formed a hydrogen bound relatively strong and stable interaction compared to hβG. Notably, the inhibitors acted effectively against endogenous βG in E. coli, and also had low cytotoxicity to the bacterial cells. The oral administration of one inhibitor, TCH-3511, reduced intestinal βG activity in mice in general, in addition to suppressing intestinal morphology damage in chemotherapeutic CPT-11-treated mice. Finally, CPT-11 treatment combined with the administration of TCH-3511 alleviated diarrhea while maintaining the anti-tumor efficacy in tumor-bearing mice. These results suggest a novel and potent bacterial βG-specific inhibitor, TCH-3511, that would allow this inhibitor to be used for the purpose of reducing drug toxicity.

Biography

Kai-Wen Cheng received her BS degree in 2007 from Kaohsiung Medical University, Taiwan, with a major in Biomedical Science and Environmental Biology and MSc degree in 2009 from the Graduate Institute of Oral Biology at National Taiwan University. In 2011, she received the Master of Science degree in Cancer Immunology and Biotechnology from the University of Nottingham, UK. She is currently a PhD student at the Institute of Biomedical Sciences in National Sun Yat-Sen University, working in the laboratory of Prof. Tian-Lu Cheng for development of bacterial β-glucuronidase specific inhibitor. Her research interest is Antibody Therapy and Drug Discovery.

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