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Synthetic small molecule epigenetic modulators as antitumor agents

Patrick M. Woster
Medical University of South Carolina, US

Histone demethylases such as lysine-specific demethylase 1 (LSD1) mediate an important cellular mechanism for epigenetic control of gene expression. In particular, histone H3 dimethyl lysine 4 (H3K4me2) is a transcription activating chromatin mark at gene promoters, and aberrant demethylation of this mark by LSD1 may broadly repress the expression of tumor suppressor genes that are important in human cancer. We, and others, have conducted studies verifying that LSD1 is an exciting new therapeutic target. We reported a series of (bis)guanidines and (bis)biguanides that are potent inhibitors of recombinant human LSD1. These inhibitors significantly increase H3K4me2 levels, initiate chromatin remodeling and induce the re-expression of tumor suppressor genes. The potent LSD1 inhibitor 2d promoted re-expression of multiple, aberrantly silenced genes important in the development of colon cancer, including members of the secreted frizzle-related proteins (SFRPs) and the GATA family of transcription factors. We were the first to demonstrate the antitumor effects of LSD1 inhibitors *in vitro* and have recently demonstrated their significant antitumor effects *in vivo*. Based on this lead, and on a recently conducted virtual screen, we have now identified additional LSD1 inhibitors and begun to elucidate structure/activity relationships for inhibition of LSD1. In this presentation, the syntheses leading to these analogues, their characterization as LSD1 inhibitors, their cellular effects and their evaluation as antitumor agents will be discussed.

Biography

Patrick M. Woster received a B.S. in Pharmacy from the University of Nebraska Medical Center in 1978, and a Ph.D. in Medicinal Chemistry from the University of Nebraska - Lincoln in 1986. Following postdoctoral work in chemistry at Rensselaer Polytechnic Institute (1986), and in medicinal chemistry at the University of Michigan (1987), he joined the Wayne State University Faculty of Pharmacy in 1988. In 2011, he was appointed Professor and Smart State™ Endowed Chair in Drug Discovery at the Medical University of South Carolina. He also serves as Director of the MUSC Drug Design and Synthesis Core. Ongoing research projects in the Woster laboratories include the synthesis of alkylpolyamines as antitumor or antiparasitic agents, design and synthesis of mechanism-based enzyme inhibitors, synthesis of inhibitors of chromatin-remodeling enzymes such as histone deacetylases and histone demethylases, and studies aimed at elucidating the cellular mechanisms of epigenetic modulators.

woster@musc.edu