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Inhibition of *N*-glycosylation towards novel anti-cancer chemotherapeutics

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The modification of cell surface glycosylation is a characteristic of many cancer cells. Identification of cell type-specific or tissue-specific glycoconjugates (tumor markers) has led to the discovery of new assay systems or diagnosis for certain cancers via immunodetection reagents. Despite the importance of *N*-linked glycans in transformation-associated glycosylation changes for normal cells to develop tumor cells, therapeutic antibodies against *N*-linked glycans have not yet been developed. It may largely be attributable to the lack of specificity of *N*-linked glycans between normal and malignant cells. Abnormal branching of *N*-linked glycans has been observed in certain solid cancer cells. Although it is an extremely challenging subject to discover drug-like glycosyltransferases to block the biosynthesis of specific branching processes in cancer cells, N-glycan biosynthesis can be terminated by inhibition of the first committed enzyme, dolichyl-phosphate N-acetylglucosaminephosphotransferase (DPAGT1) activity. DPAGT1 is an integral membrane protein localized in the ER that catalyzes the transformation from UDP-GlcNAc to N-acetyl-D-glucosaminyl-diphosphodolichol with dolichyl phosphate. Anchored N-acetyl-D-glucosaminyl-diphosphodolichol in the ER membrane is modified by sequential glycosyltransferases to form dolichol-linked oligosaccharide precursors that are transferred to selected asparagine residues of polypeptide chains by oligosaccharyltransferases (OSTs). Selective DPAGT1 inhibitors have the promising therapeutic potential for certain solid cancers that require increased branching of *N*-linked glycans in their growth progressions. We have screened our nucleoside-based chemical libraries against the phosphotransferases, and identified a strong DPAGT1 inhibitor effective in killing a series of solid cancers *in vitro*. The identified DPAGT1 inhibitor displayed strong synergistic effects with FDA-approved anticancer drugs (e.g. taxol).

Biography

Michio Kurosu has completed his PhD in 1995 from Osaka University, Japan and Post-doctoral studies from Harvard University, Chemistry and Chemical Biology. He is a Professor of Pharmaceutical Science at The University of Tennessee Health Science Center. He has published over 85 papers in reputed journals and has been serving as Editorial Board Member of several international journals.

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