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Novel multiple type and wide spectral molecular targeted antitumor agents: Preparation and preclinical evaluation of IER5/Cdc25B targeted phospha sugar derivatives as well as attempts of computer aided drug designing

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Novel multiple type and wide spectral low-molecular-weight molecular targeted antitumor agents of phospha sugar derivatives, which target IER5/Cdc25B and innovate in chemo-therapeutic treatments against various type of cancer cells, were investigated. We have developed novel synthetic methodologies for preparing phospha sugar derivatives, in which the oxygen atom in the hemiacetal ring of Haworth structure is replaced by a phosphorus moiety, and constructed their compound library, and then preclinical evaluations and mechanistic investigations have been carried out. Among the compound library of the phospha sugar derivatives, branched deoxybromo-phospha sugar derivatives (DBMPP and TBMPP) as well as some substituted phospha sugar analogues were found to exert novel, potential, and wide spectral antitumor activities by MTT *in vitro* evaluation method. The characterization and mechanism elucidation of these phospha sugar derivatives by flow cytometry and Western blotting showed that phospha sugars DBMPP and/or TBMPP enhanced the expression of cancer suppressors and suppressed the expression of cancer accelerators. Phospha sugar derivative TBMPP enhanced the expression of IER5 and then suppressed the expression of Cdc25B, which is the common and essential factor to act at the mitosis stage of tumor cell cycles. Therefore, phospha sugar derivatives might induce apoptosis at G2/M stage and inhibit the proliferation of various kinds of cancer cells. *In vivo* evaluation for TBMPP against K562 cells transplanted to a nude mouse implied successful cure of cancer. Based on the preclinical research and computer aided drug designing we are expecting that phospha sugars may be developed to be clinically useful novel antitumor agents.

Biography

Mitsuji Yamashita has completed his PhD from Nagoya University, Japan, and Postdoctoral studies from Iowa State University, USA. He was a Visiting Professor of University of Massachusetts at Amherst, USA, and a Visiting Researcher of Oxford University, UK, in 1994. He was promoted to be a Professor of Shizuoka University, Japan, in 1996 and retired to be a Professor Emeritus of Shizuoka University, Japan. His research field is now focused on medicinal materials based on chemistry of carbohydrates and phosphorus compounds regarding phospha sugar antitumor agents and sugar dendritic Gd-DTPA MRI contrast agents for innovating in cancer therapy. He has published more than 180 papers and patents as well as four books.

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