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Research and development for preparation and preclinical evaluation of novel low-molecular-weight phospha sugar antitumor agents targeting IER5/Cdc25B

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By this research, novel multiple type low-molecular-weight antitumor agents of phospha sugar derivatives, which target IER5/Cdc25B and innovate in chemotheraputic treatment for cancer patients of various type of cancer cells, are developed. Sugar derivatives, whose oxygen atom in the hemiacetal ring is replaced by a nitrogen or a sulfur atom, etc., are called as pseudo sugars and well investigated. Among pseudo sugars phospha sugars in which the oxygen atom in the hemiacetal ring of sugars is replaced by a phosphorus moiety are not so well investigated in spite of important biological activities being expected for the pseudo sugar analogues. We have developed novel synthetic methodologies for preparing phospha sugar derivatives and constructed their compound library, and then preclinical evaluations have been carried out. Among the compound library of the phospha sugar derivatives, branched novel low-molecular-weight di- and tri-bromo deoxyphospha 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 the tumor cell cycles. Therefore, phospha sugar derivatives might induce apoptosis at G2/M stage and inhibit various kinds of cancer cells' growth. *In vivo* evaluation for TBMPP against K562 cell transplanted to a nude mouse was checked visually to be successful. We are expecting that phospha sugars may be developed to be clinically useful novel antitumor agents.

Biography

Mitsuji Yamashita was born in 1944 and has completed his PhD at the age of 27 years from Nagoya University, Japan, and postdoctoral studies from Toyota Science and Chemistry Research Institute, Japan, and Iowa State University, USA. He was a visiting professor of University of Massachusetts at Amherst, USA, and a researcher of Oxford University, UK, in 1994. He was promoted to be a professor of Graduate School of Science and Technology, Shizuoka University, Japan, in 1998 and retired at the age of 65 years old, and he is now a professor emeritus and specially-appointed professor of Shizuoka University, Japan. His research field is now focused on medicinal materials based on chemistry of carbohydrates and heterocycles. He has published more than 175 papers and patents as well as four books. Mitsuji Yamashita is now mainly concentrating in the research and development of phospha sugar antitumor agents and sugar dendritic Gd-DTPA MRI contrast agents for innovating in medical treatment for cancer patients.

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