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Self-assembly PEGylation Retaining Activity (SPRA) technology via an interaction between cyclodextrin and adamantane: Application for insulin, lysozyme and bromelain

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Polyethylene glycol (PEG) modification (PEGylation) is one of the best approaches to improve the stabilities and blood half-lives of protein drugs; however, PEGylation dramatically reduces the bioactivities of protein drugs. Here, we present "self-assembly PEGylation retaining activity" (SPRA) technology via a host–guest interaction between PEGylated β-cyclodextrin (PEG-β-CyD) and adamantane-appended (Ad)-proteins. Firstly, we prepared SPRA-insulin and SPRA-lysozyme. Both SPRA-proteins showed high stability against heat and trypsin digest, comparable with that of covalently PEGylated protein equivalents. Importantly, the SPRA-lysozyme possessed ca. 100% lytic activity, whereas the activity of the covalently PEGylated lysozyme was ca. 23%. Additionally, SPRA-insulin provided a prolonged and peak-less blood glucose profile when compared with insulin glargine. It also showed no loss of activity. In contrast, the covalently PEGylated insulin showed a negligible hypoglycemic effect. Next, we prepared SPRA-bromelain, because bromelain is known to degrade the extracellular matrix (ECM) in pancreatic cancer and increase the penetration of antitumor agents, although the blood half-life of bromelain is short. SPRA-bromelain showed high *in vitro* ECM-degrading activity, and enhanced not only the accumulation of FITC-dextran (2 MDa) in the tumor, but also the *in vivo* antitumor activities of doxorubicin and DOXIL. These findings indicate that SPRA technology has the potential as a generic method, surpassing conventional PEGylation methods for proteins.

Recent Publications

1. Higashi T, Hirayama F, Misumi S, Arima H, Uekama K (2008) Design and evaluation of polypseudorotaxanes of PEGylated insulin with cyclodextrins as sustained release system. Biomaterials 29:3866-3871.
2. Higashi T, Li J, Song X, Zhu J, Taniyoshi M, Hirayama F, Iohara D, Motoyama K, Arima H (2016) Thermoresponsive formation of dimethyl cyclodextrin polypseudorotaxanes and subsequent one-pot synthesis of polyrotaxanes. ACS Macro Lett. 5:158-162.
3. Hirotsu T, Higashi T, Abu Hashim II, Misumi S, Wada K, Motoyama K, Arima H (2017) Self-assembly PEGylation Retaining Activity (SPRA) technology via a host-guest interaction surpassing conventional PEGylation methods of proteins. Mol. Pharm. 14:368-376.
4. Hirotsu T, Higashi T, Motoyama K, Arima H (2017) Cyclodextrin-based sustained and controllable release system of insulin utilizing the combination system of self-assembly PEGylation and polypseudorotaxane formation. Carbohydr. Polym. 15:42-48.

Biography

Taishi Higashi took part in a half-year internship of Evonik Röhm GmbH & Co., Darmstadt, Germany in 2008. Then, he obtained PhD (Pharmaceutical Sciences) at Kumamoto University, Japan in 2009. In 2009-2011, he became a Research Scientist of Taisho Pharmaceutical Co., Ltd, Japan, and engaged self-medication business such as oral solid formulation. From 2011, he works as a Research Associate in the Department of Physical Pharmaceutics, Graduate School of Pharmaceutical Sciences at Kumamoto University, Japan. In 2013-2014, he became a Guest Researcher at Faculty of Engineering, National University of Singapore. From 2016, he holds the additional post as a Technical Adviser in CyDing Co., Ltd. His research topic is "supramolecular pharmaceutical sciences" which combines Pharmaceutical Sciences and Supramolecular Chemistry.

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