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論　文　内　容　要　旨

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学位論文題目	Synthesis of New Protection-free Symmetrically Branched Oligoglycerols that Conjugate with Target in One Step Under Mild Conditions (温和な条件下に一工程で標的化合物と結合する新しい無保護型対称分岐オリゴグリセロールの合成)

Protection-free Symmetrically Branched Oligoglycerols (BGL) can covalently connect with desired molecules to enhance their water affinity. These BGLs have no asymmetric center, and several free alcoholic groups are present on the minimum carbon backbone. To demonstrate the various properties of BGLs, there are remaining challenges to synthesize new protection-free BGL. Although previous BGLation has often required two steps to conjugate with desired targets, newly protection-free BGL can conjugate with desired targets in one step under favorable chemical conditions. In my doctoral research work, these newly synthesized protection-free BGLs has been covalently connected with desired targets in one step under mild reaction conditions to investigate their physico-chemical properties.

A thiol possessing polyols is suitable to prepare a stable and neutral water-affinitive metal surface. Also, thiol coating powerfully stops the undesired chemical reactions on the surface. Therefore, I have designed to prepare protection-free branched glyceryl trimer thiol (BGL003–SH) and branched glyceryl heptamer thiol (BGL007–SH) named as BGLated thiol. All the synthetic steps were carried out from the starting material branched glycerol trimer (BGL003) to the protection free BGLated thiol with a reasonable high chemical yield. By treating with these BGLs (BGL003–SH and BGL007–SH) on the metal surface shown a lower contact angle than the original metal surface.

BGLation protocols require pure functionalized BGL reagents, which can be synthesized by simple and efficient procedures and maintain a level of chemical reactivity with protein and peptide drugs functional groups under mild reaction conditions. Considering this idea, a new apex of protection-free branched glyceryl trimer alkoxyamine (BGL003–ONH_2), branched glyceryl heptamer alkoxyamine (BGL007–ONH_2), and branched glyceryl heptamer isothiocyanate (BGL007–NCS) were synthesized. Drug molecules that contain acyl functionality possessing carbon or hydrogen substitutions and the functionality will react with protection-free branched glyceryl alkoxyamine BGL003–ONH_2 and BGL007–ONH_2. SN-38 (7-ethyl-10-hydroxycamptothecin, an active metabolite of irinotecan) is very insoluble in water. This drug was properly conjugated with the assistance of the apex of protection-free branched glyceryl heptamer alkoxyamine (BGL007–ONH_2) *via* a diazo linker 4-formylbenzene diazonium hexafluorophosphate (FBDP). After BGLation, hydroxyl functionality remains in SN-38, and it forms a very stable water-affinitive compound, an SN-38–BGL007 conjugate.

Nucleophilic attack of branched glyceryl heptamer isothiocyanate (BGL007–NCS) by amino group of peptide or protein forms a stable bond, which has a more water-affinity than the original peptide or protein. Branched glyceryl heptamer isothiocyanate (BGL007–NCS) will be used for the selective reaction of amino group modification to increase their water-affinity. I presume utilizing this BGL007 modified drug will be increase more water-affinity and more consumption in the human body. The adaptability (*in vitro and in vivo*) of this modified drug will be examined consecutively.

I hope that the above newly synthesized protection-free BGLated thiol will introduce a new coating method on the metal surface and the functionalization of BGL as BGLated alkoxyamines, isothiocyanates conjugation with targets will be established in a new format in the field of drug delivery systems to human to save lives.