Development of Calciprotein Particle Growth Inhibitors Utilizing Human Serum Proteins and Bisphosphonates Derivatives

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論 文 名　：Development of Calciprotein Particle Growth Inhibitors Utilizing Human Serum Proteins and Bisphosphonates Derivatives (ヒト血清タンパク質とビスホスホン酸誘導体を用いるカルシプロテイン粒子成長阻害剤の開発)

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論 文 内 容 の 要 旨

Vascular calcification, an important pathological, is associated with the conversion of primary calciprotein particles CPPI to secondary calciprotein particles CPPII. In the current strategy, CPP maturation is focused on being inhibited by different classes of inhibitors, which include multi-phosphates and bisphosphonates. While multi-phosphates are subject to enzymatic degradation, the P-C-P backbone of bisphosphonates is enzymatically stable. However, bisphosphonates have a critically short plasma half-life, limiting their therapeutic effects. To surmount these hurdles, this thesis investigates the application of protein-conjugated bisphosphonates as next-generation CPP maturation inhibitors.

In Chapter 2, the author designed a bisphosphonate derivative that can bind to Cys34 of HSA to further enhance the CPP maturation inhibition effect. The prepared molecule exhibited excellent inhibition of CPP maturation. Binding with HSA further improved the suppression. The protein-drug conjugate also prevented macrophage uptake, indicating a potential pharmacokinetic advantage for the fabricated compound.

In Chapter 3, HSA direct modification with bisphosphonate (alendronate, ALN) was carried out. The HSA-ALN conjugates respectively showed increased inhibition of CPP with an increased modification ratio. While organ distribution of the conjugates was in line with that of intact HSA, plasma half-life was dependent on the ratio of ALN modification, and moderate modifications were shown to give similar half-lives as intact HSA.

In Chapter 4, the relationship of protein surface charge to CPP inhibition was examined. Negatively charged antibody-ALN (Ab-ALN) were designed using acetylation and succinylation procedures, this alteration improves CPP binding and inhibits them better than neutral Ab-ALN. Despite these developments, the clearance of systemic CPP clearance in vivo was still undetermined.

Together, the study lays the groundwork for the rational design of bisphosphonate-protein conjugation and highlights their potential as effective inhibitors of CPP maturation, paving the way for improved therapeutic strategies against vascular calcification.