High-density lipoprotein engineering for treatment of age-related macular degeneration

ShT-05.2-2

T. Murakami[I], R. Fukuda[I], N. Mahmuda[II], S. Kasirawat[III], R. Kawakami[I], R. Shima[I], Y. Mizukami[I], S. Shibukawa[I], Y. Tada[I], F. Kawanishi[I], M. Ogura[IV], K. Matsuki[V], Y. Nagai[I], E. Nakano[VI], K. Suda[VI], A. Tsujikawa[VI]

[I]Toyama Prefectural University, Imizu, Japan, [II]Independent University, Bangladesh, Dhaka, Bangladesh, [III]Chiang Mai University, Chiang Mai, Thailand, [IV]Juntendo University, Urayasu, Japan, [V]Hirosaki University Graduate School of Medicine, Hirosaki, Japan, [VI]Kyoto University Graduate School of Medicine, Kyoto, Japan

Age-related macular degeneration (AMD) is a leading cause of blindness in people aged 60 years or older worldwide. The current major treatment for AMD is intravitreal injection of biopharmaceuticals that inhibit neovascularization. While they have revolutionized the AMD therapy, the route of their administration is highly invasive. Eye drops have been desired, but none have been clinically approved yet.
The main pathological mechanisms of AMD are dyslipidemia, chronic inflammation, oxidative stress, and neovascularization, which are similar to those of atherosclerosis. In contrast, high-density lipoprotein (HDL) is well known for its anti-atherosclerotic effects. This coincidence led us to hypothesize that HDL could also show anti-AMD activities. Although reconstituted HDL (rHDL) nanoparticles have been clinically tested as drugs, their eye drops had never been tested for any purposes at that time. Considering the poor corneal/conjunctival absorption of rHDL due to the rapid tear clearance, we decided to develop an engineered rHDL library with various types of cell-penetrating peptides and phospholipids and by changing the size from 10 to 25 nm and to screen it for the efficiency of posterior delivery of a fluorescent cargo molecule via eye drop instillation. The best rHDL, designated as engineered lipoprotein 1 (eLP1), showed therapeutic efficacy in a mouse model of AMD (Suda, K. et al., J. Control. Release, 2017). Recently, we reported that this efficacy was dramatically improved by attaching the AsnGlyArg tripeptide to eLP1 (Fukuda, R. et al., Adv. Therap., 2023). In this congress, we will present the structure, HDL biological activities, and the therapeutic activity of this second-generation eye drop, eLP2. Our study demonstrates that eLP2 is a novel and promising eye drop for AMD treatment, which potentially overcomes the limitations of current therapies and provides a non-invasive and effective option for patients.