Development of a Small-Molecule AdipoR Agonist AdipoRon as Exercise Mimetics

TOSHIMASA YAMAUCHI*1) 2)

*1) Department of Diabetes and Metabolic Diseases, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan, *2) Sportology Center, Juntendo University Graduate School of Medicine, Tokyo, Japan

In obesity, plasma adiponectin is reduced, which causes insulin resistance and atherosclerosis. We identified its receptors AdipoR1 and R2, and showed that they exert antiaging effects via activation of AMPK/SIRT1 and PPAR-α pathways, respectively, leading to increased mitochondria as well as decreased ectopic fat accumulation, oxidative stress and inflammation. Recently, we identified orally active small-molecule AdipoR agonist AdipoRon, which bound to AdipoR, showed very similar effects to adiponectin in muscle and liver, such as increased exercise endurance and energy expenditure, and ameliorated insulin resistance via AdipoR in obese mice, leading to healthy longevity. Most recently, we determined and reported the crystal structures of human AdipoR, which will facilitate the understanding of novel structure–function relationships and the optimization of AdipoRon as exercise mimetics.