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Wei-Chiang Shen

University of Southern California, USA

Human growth hormone–single-chain Fc-dimer fusion protein

During the past decades, many Fc fusion proteins have been successfully produced by biotech companies and approved by FDA to be used as long-acting forms of protein drug. However, there are several limitations on the application of Fc-fusion protein technology to many proteins, especially the stability of Fc-dimerization. In this report, we describe a novel Fc-based drug carrier, single chain Fc-dimer (sc(Fc)₂), which was designed to contain two Fc domains recombinantly linked together via a flexible linker. Since the Fc dimeric structure is maintained through the flexible linker, the hinge region was omitted to further stabilize it against proteolysis and to reduce Fc R-related effector functions. Our results indicate that the recombinant sc(Fc)₂ preserved the neonatal Fc receptor (FcRn) binding capacity. We have prepared a fusion protein consisting human growth hormone (hGH) and sc(Fc)₂ as a model of the novel Fc fusion protein. Compared to the monomeric hGH-Fc fusion protein, hGH-sc(Fc)₂ fusion protein showed a stronger binding affinity to FcRn, a longer *in vivo* plasma half-life of hGH, and a higher hGH-induced plasma IGF-1 level in mice. Our results suggest that sc(Fc)₂ technology has the potential to greatly advance and expand the use of Fc-technology for improving the pharmacokinetics and bioactivity of protein therapeutics.

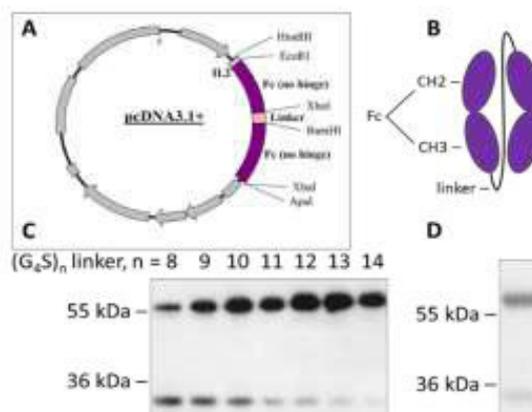


Figure : Production of single-chain Fc-dimer, sc(Fc)₂, in HEK 293 cells. (A) Plasmid of sc(Fc)₂ expression, (B) Structure of sc(Fc)₂, (C) Anti-Fc WB (non-reducing conditions) of sc(Fc)₂ with indicated (G4S)_n linker lengths. (D) Coomassie Blue gel (reducing conditions) of sc(Fc)₂-(G4S)₁₃.

Biography

Wei-Chiang Shen is currently John A Biles Professor in Pharmaceutical Sciences at the University of Southern California, School of Pharmacy. His research interests focus on the development of novel systems for improving peptide and protein drug delivery. He has published 150 papers in different areas of biomedical sciences. He is a Co-author of the textbook, "Immunology for Pharmacy Students", and a Co-editor of the book, "Antibody-Drug Conjugates – the 21st Century Magic Bullets for Cancer". He was elected as Fellow of the American Association of Pharmaceutical Scientists (AAPS) in 1992 and Fellow of the American Association for the Advancement of Sciences (AAAS) in 2000, and was the recipient of the Grand Prize of Eurand Award for Outstanding Novel Research in Oral Drug Delivery from Controlled Release Society in 2002.

weishen@usc.edu