Development of PCBP2 siRNA Nanocomplex for the Treatment of Alcoholic Liver Fibrosis

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Abstract

Alcoholic liver fibrosis is characterized by the excessive accumulation of extracellular matrix (ECM). Type I collagen is the major component of ECM and its accumulation is primarily due to an increase in the half-life of its mRNA. We recently discovered a PCBP2 siRNA to silence the αCP2 protein, which accounts for the stabilization of type I collagen mRNA. The PCBP2 siRNA exhibits promising activity in reversing alcohol-induced collagen expression in rat hepatic stellate cells HSC-T6. Moreover, the siRNA reverses the fibrogenesis effects of alcohol and pro-fibrogenic cytokines in primary rat hepatic stellate cells. However, poor stability and lack of target-ability are the primary obstacles in achieving therapeutic activity of the PCBP2 siRNA. We therefore aimed to develop an avidin-based nanocomplex to protect the siRNA from degradation and specifically deliver the siRNA to hepatic stellate cells. We evaluated avidin, streptavidin, and neutravidin and discovered that neutravidin is the best carrier for siRNA delivery. We also discovered a peptide ligand for IGF2R, which is overexpressed in activated hepatic stellate cells. We have conjugated the IGF2R-specific peptide to the avidin-based nanocomplex to specifically deliver the PCBP2 siRNA to hepatic stellate cells. The peptide modified siRNA nanocomplex exhibits high uptake in hepatic stellate cells and fibrotic liver. Anti-fibrotic activity study demonstrated that the PCBP2 siRNA nanocomplex efficiently silenced the target genes in the firbrotic liver and subsequently reversed liver fibrogenesis in the rats with CCl_4-induced liver fibrosis.

Biography

Dr. Kun Cheng is a Professor of Pharmaceutical Sciences in the School of Pharmacy at the University of Missouri-Kansas City (UMKC). Dr. Cheng received his B.S./M.S. from China Pharmaceutical University (1996/1999) and another M.S. from Nationa University of Singaprore (2001). He was a research scientist at the Brightfuture Pharmaceutical Company in HongKong prior to joining the University of Tennessee Health Science Center, where he received his Ph.D. in Pharmaceutical Sciences (2007). He joined UMKC as an Assistant Professor and was promoted to Associate Professor with tenure in 2013 and to Full Professor in 2017.

Dr. Cheng's research focuses on the development of novel drug delivery systems for small-molecule and macromolecular drugs; identification of artificial ligands for targeted drug delivery and tumor imaging; development of peptide-modified prodrugs for chemotherapy; development of novel immunotherapy; and therapeutic applications of siRNA for the treatment of breast cancer, prostate cancer, and liver fibrosis. His research has been continuously supported by the Department of Defense (DoD), the National Institutes of Health (NIH), American Cancer Society (ACS), and the American Association of Pharmaceutical Scientists (AAPS). He is a grant reviewer for various study sections at NIH, DOD and other agencies.

Dr. Cheng is the recipient of the 2011 AAPS New Investigator Grant Award in Pharmaceutics and Pharmaceutical Technology. He is also the recipient of the UMKC Chancellor's Early Career Award for Excellence in Teaching (2013), the UMKC Trustees Faculty Scholar Award (2013), and the UMKC Trustees Faculty Fellowship Award (2018). He received the American Cancer Society (ACS) Research Scholar Grant Award in 2015 to support his siRNA research for breast cancer therapy. Dr. Cheng has been actively engaged in extramural professional activities. He has edited two theme issues for *Molecular Pharmaceutics* and *Pharmaceutical Research* as a guest editor. He has also edited two books entitled "Advanced Delivery and Therapeutic Applications of RNAi" and "Advanced Drug Delivery" for Wiley.