Development of systemic drug delivery technology for proteins and siRNA

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It would not be an overstatement that the market value of high molecular weight compounds such cytokines are dependent on the launch of controlled-release products which are introduced into the market in order to minimize the frequency of drug administration given to the patients. Since there is a limit for new cytokines introduced from the pharmaceutical industry, the improvement of delivery technology becomes more important. In the past decade, the development and market of pegylated proteins such as IFNα, G-CSF, EPO and TNFα are well recognized as successful product market. These products have been developed for the improvements of patient compliance, quality of life and pharmacoeconomics. The tendency toward sustained-release of cytokines will continue to increase in the future development. However, the products are now faced with the generic market in the bio-similar manner. The main characteristics of delivery technology for such proteins are almost satisfied with stability or sustained-release of drug in the blood circulation.

On the other hand, the delivery technology is essential for the high molecular weights nucleic acids such as siRNA due to the drug's rapid degradation and elimination from the body. For siRNA delivery, not only stability/sustained-release technology, but the both drug penetration into the target cell and proper drug release into the cytoplasm are required. It is not easy to deliver the naked siRNA with normal activity to cytoplasm by the use of conventional technology.

NanoCarrier has recently performed extensive studies on the delivery of protein as well as siRNA in vitro and in vivo by using innovative micellar nanoparticle technology.

NanoCap™ system

The NanoCap™ system is the micellar nanoparticle composed of polyethyleneglycol(PEG)-poly(amino acid) block copolymer, in which PEG constitutes the hydrophilic ouster shell of the micelles, and drugs are either physically incorporated

into hydrophobic inner core or electrostatically entrapped by counter ionic inner poly(amino acid).

For the treatment of neutropenia often occurred in cancer patients given by anti-cancer drugs, G-CSF is commonly used at hospitals. In order to reduce the necessity of daily injections of G-CSF, PEG-G-CSF such as Neulasta® has been developed, which has led to a success in the market.

NanoCarrier has also developed long sustainable delivery of G-CSF by using NanoCap™ system. The release of G-CSF test from NaoCap™ system was first confirmed by ELISA after the incubation in 80% bovine serum at 37℃ followed by gel filtration. Block copolymer was optimized for G-CSF, and PK profile and pharmacological activity were evaluated in rat compared with those of G-CSF solution and Neulasta®. The effect of administration route (i.v. and s.c.) on the PK profile was also evaluated.

NanoCap™ system for G-CSF was characterized as micellar nanoparticles with average 70 nm diameter containing G-CSF at 0.1-5.0%. Consequently we observed 5.1 times higher AUC value and 7.4 times higher MRT value than those for G-CSF solution after i.v. administration. For s.c. administration, 7.4 times lower AUC value, 1.6times higher t1/2 and 2.0 times higher MRT values than those for i.v. administration were observed. As pharmacological activity, NanoCap™ system showed significant increase in neutrophil counts for a prolonged time compared with G-CSF solution, the same level of activity as Neulasta®. We obtained the similar results for IFN-α, Somatotropin and the other proteins.

NanoCap™ system for siRNA demonstrated more than 100 times higher AUC value than that for naked siRNA. I would like to introduce some date if available.

References

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