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NANOTECHNOLOGY IN MEDICINE

1. Application of magnetic bio-nanoparticles to the control of stem cell behavior

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Cell therapy using stem cells is a promising method to treat inveterate diseases like myocardial infarction and spinal cord injury. But there are some obstacles in the stem cell therapy, which include the problems in homing and fixing myocardial stem cells to desired site and guiding neurite extension of neural stem cell to specific direction. In this study, magnetic nanoparticles were used to overcome these challenges in therapeutic application of stem cells. A magnetic bacteria strain, *Magnetospirillium magneticum* AMB-1, contains magnetic nanoparticles in it, which have 40–50 nm diameter and lipid bilayer on their surface (Matsunaga, 1991). The magnetic bacterial strain and magnetic nanoparticles have been used for various researches (Seong and Park, 2001; Kim et al., 2005). The magnetic bio-nanoparticles were harvested from the bacteria and introduced into stem cells. It was observed that magnetic nanoparticle introduced cells moved to a specific direction on external magnetic field and fixed at the desired site.

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2. Production and characterization of bioceramic nano-powders of natural-biological origin

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Living in the era of life control and prolongation, calcium phosphate-based biomaterials such as hydroxyapatite (HA) and beta-tricalcium phosphate (beta-TCP) are considered as promising bioceramics for both delivering drugs and increasing bone mass. HA are very popular for hard tissue (e.g., bone) restorations because they accelerate bone growth around the implant (Rocha et al., 2005). Having a calcium–phosphorus ratio similar to natural bone mineral, low-density, highly porous beta-TCP have been proposed as potential bone defect fillers where they fill the void and gradually dissolve away due to their resorbable nature, being replaced by bone. For preparing nano-powders of calcium phosphates, nacres are considered as suitable natural materials for dental and bone restorations. Besides their worldwide availability and low cost, they are able to initiate and induce mineralized tissue formation by human osteoblasts in vitro and also exhibit osteogenic and osteoinductive features by developing bonds with bones (Lemos et al., 2006). The present work aims at preparing inexpensive nano-sized HA and beta-TCP particles from various raw materials of natural-biological origin. These materials include the bones of cuttlefish *Sepia officianalis*, Chinese sweet water Pearl Powder, the Pacific Kumamoto oyster *Crassostrea sikamea*, the bivalve mollusc *Venus verrucosa* collected from Turkish and Portuguese beaches and the common European oyster *Ostrea edulis*. Each sample was reduced to sub100 μm particle size and Differential thermal analysis (DTA/TG) was employed to determine their exact $CaCO_3$ content. The morphology of HA and beta-TCP powders was

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examined by a scanning electron microscope. The crystalline phases of the nano-powders were identified by a high resolution X-ray diffraction analyzer and Fourier transform infrared spectroscopy (FTIR). The effect of calcining temperature on the formation of calcium phosphates was also investigated by analyzing the XRD spectra of the samples obtained at a temperature range between 800 and 1250 °C. Besides the classical method of Hydrothermal transformation followed by sintering, the process parameters of a sonochemical synthesis method were also optimized for each sample.

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3.
Characterization and *in vitro* permeation study of behenic acid nanoparticles containing hinokitiol

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The objective of this work is to develop a novel formulation of hinokitiol (HKL) for its efficient transdermal delivery. Lipid nanoparticles were reported to solubilize triptolide, an anti-inflammatory agent, and they enhance the transdermal delivery and the anti-inflammatory activity of the drugs. In this study, hinokitiol-loaded lipid nanoparticles (HKL-LN) were prepared by a melt-emulsification method. Behenic acid was used as a lipid for the matrix material of the nanoparticle. The physicochemical properties and the *in vitro* permeability of HKL-LN were investigated. The size of HKL-LN was determined by a dynamic light scattering spectrophotometer (DLS, Brookhaven Instrument Co.). The size ranged from 30 to 200 nm. Energy filtering transmission electron microscopy image (EF-TEM, LEO-912AB OMEGA) showed that the HKL-LN was spherical. Microelectrophoresis revealed that the surface potential of HKL-LN decreased with pH and the values were negative at acidic conditions and positive at neutral and alkali condition. Since HKL dose not have an ionizable group, the zeta potentials of HKL-LN depend mainly on behenic acid. Because the carboxyl groups of free fatty acids have a pK of approximately 5, fatty acids will be deprotonated at higher pHs. COO^- of the fatty acids would account for the negative values of the zeta potentials. When HKL-LN was scanned on a differential scanning calorimeter (DSC, TA instruments DSC 2010), no endothermic peak of HKL was observed. It means that HKL in the lipid matrix of the nanoparticles is in a dissolved state. In a 18 h permeation study using hairless mouse skin mounted on a diffusion cell, HKL encapsulated in the nanoparticles was transported into the receptor cell even more than HKL dissolved in either ethanol or propylene glycol was. This is possibly because they perturb the ordered structure of skin by the hydrophobic interaction with skin lipid. The permeations of the SLN into skins were observed using a confocal laser scanning microscope (CLSM, LSM510 META NLO). In addition, the stability against solubilization in either an alcoholic solution or a surfactant solution was investigated. The results in our study revealed that HKL-LN may be a prospective drug carrier for transdermal delivery of HKL.

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4.
A novel approach to ultrasensitive diagnosis using protein nanoparticles

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We report on the ultrasensitive protein nanoprobe system that specifically captures disease marker (heat labile enterotoxin of enterotoxigenic *E. coli* (ETEC) in this case) with attomolar sensitivity. The system relies on supramolecular protein nanoparticles that bind a specific antigenic marker, heat labile enterotoxin. The ultrasensitive detection of ETEC during the early phase of infection is important because clinical onset occurs only after ETEC concentration reaches 107–109 cells per 1 mL. For the purpose of using the specific interaction between B domain of *Staphylococcal* protein A and constant domain of antibody, the chimera genes encoding B domain in the middle of capsid of hepatitis B virus were expressed in *E. coli* cytoplasm, and supramolecular nanoparticles with uniform diameters (28-30 nm were produced), owing to self-assembly activity of capsid. Each nanoparticle, formed by intermolecular self-assembly between the chimera protein molecules, is subjected to carrying a large number of antibody bindig domain on the surface of capsid with a homogeneous and stable conformation per antibody and marker binding, thereby allowing substantial enhancement of sensitivity. The sensitivity was finally boosted to 100 attomolar concentration of the disease marker, 4–9 orders of magnitude more sensitive than conventional immunoassays.

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