Department of Biopharmaceutics and Drug Metabolism

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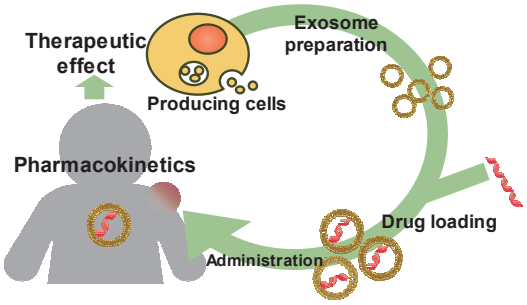
Research Projects:

To realize ideal drug therapy by optimizing drug design and delivery, we are focusing on the studies on the drug-body interaction based on the scientific background of biopharmaceutics, pharmacokinetics and drug delivery system. Our current research projects are listed below.

1) Development of drug delivery system using exosomes: Exosomes are small membrane vesicles secreted from various cells. Exosomes work as endogenous delivery carriers for protein, RNA and DNA, so that they are expected to be delivery system for these molecules. To develop exosome-based delivery systems, we have been trying to establish a method to control the tissue distribution of exogenously administered exosomes. We have succeeded in pharmacokinetic analysis of exosomes by developing methods that can specifically label exosomes. A series of studies also have been conducted to overcome pharmaceutical challenges of exosomes; i.e., selection of exosome-producing cells, preparation methods of exosomes, methods to load drugs onto exosomes, and storage of exosomes. We have also demonstrated that genetically engineered exosome can be useful delivery carriers for tumor antigens targeting antigen presenting cells. Moreover, we have succeeded in the evaluation of not only exosomes collected from *in vitro* cultured cells but also exosomes collected from the blood of mice. Our currently ongoing studies include the regulation of in vivo behavior of exosomes that endogenously exist in the body. Moreover, now we are focusing on various novel types of cell-derived extracellular particles other than exosomes.



Development of exosome-based drug delivery system

2) Establishment of immunotherapy based on gene delivery technology: Recently, immunotherapy using intrinsic immune systems such as immune checkpoint therapy and CAR-T therapy have been attracting a huge amount of attention. Membrane proteins such as MHC and soluble proteins such as cytokines plays major roles in immune system. A method to regulate behavior and activity of proteins of interest is desirable for the development of therapy utilizing immune system and gene delivery of the proteins of interest can be the method. We have succeeded in developing plasmid vectors that express interferon, a cytokine, for a long period of time and proved their efficacy on the treatment for cancer, atopic dermatitis, and multiple sclerosis. We have also succeeded in designing a variety of fusion proteins to control their tissue distribution after in vivo gene transfer.

3) Development of delivery systems of proteins and nucleic acid drugs utilizing nucleic acid-based nanostructures: DNA containing CpG motifs (CpG DNA) induce cytokine production through Toll-like receptor-9 (TLR-9), so CpG DNA is expected to be applied to the treatment of cancer, autoimmune diseases and allergic diseases. We have successfully developed unique DNA assemblies with branches; multiple pods extend from the center of the assembly. We have demonstrated that CpG DNA-induced immune activation is significantly increased by building it up into such branched structures. Dendritic DNA and DNA hydrogels were also prepared by connecting the assemblies. We have also succeeded in the preparation of DNA nanostructures prepared by using long single stranded DNA. Studies are ongoing to develop novel delivery systems using these nucleic acid nanostructures.

4) Development of multifunctional cell therapeutics for in vivo cell therapy: Recent progress in the technology for culture and differentiation of a variety of cells, including induced pluripotent stem cells, has increased the possibility of cell-based therapy. We have been studying on the development of multi-functional cell therapeutics that can be applicable for the next generation therapy. We have established a technology to construct multicellular spheroids, and demonstrated that the spheroid formation is useful to increase the survival of cells transplanted and effective for the treatment of diabetic model mice and the treatment of tumor-bearing model mice.

Recent publications

- Morishita et al. Exosome-based tumor antigens-adjuvant co-delivery utilizing genetically engineered tumor cell-derived exosomes with immunostimulatory CpG DNA. *Biomaterials* **111**, 55-65, 2016.
- Charoenviriyakul C et al. Role of Extracellular Vesicle Surface Proteins in the Pharmacokinetics of Extracellular Vesicles. *Mol Pharm.* **15**, 1073-1080, 2018.
- Umeki et al. Combined encapsulation of a tumor antigen and immune cells using a self-assembling immunostimulatory DNA hydrogel to enhance antigen-specific tumor immunity. *J Control Release* **288**, 189-198, 2018.
- Tanaka et al. Control of polarization and tumoricidal activity of macrophages by multicellular spheroid formation. *J Control Release* **270**, 177-183, 2018.