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Editorial

Intracellular Delivery

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Many potentially highly effective drugs possess low cellular permeability and require special delivery systems to enhance their cellular uptake. Such systems can be further modified to simultaneously fulfill multiple tasks including: targeted delivery of active ingredients to specific organs, tissues, cells and cellular organelles; limitation of systemic toxicity of their payload; and prevention or suppression of cellular drug resistance, etc. The present theme issue contains papers describing different approaches for intracellular drug delivery of diverse therapeutic components and examines important mechanisms of cellular responses for various treatments.

Dr. Discher and coauthors describe the results of the comparison of two types of micelles with different morphologies, classical spherical and worm-like micelles, prepared from the same amphiphilic diblock copolymer as carriers for hydrophobic drugs. Both types of empty micellular drug carriers showed far less toxicity when compared with the solubilizers that are currently used. Loaded with the hydrophobic anticancer drug paclitaxel, both micelles were five-times more toxic for cancer cells compared to the traditional paclitaxel solubilizer. The authors found that the worm-like micelles (filomicelles) load and solubilize twice as much drug as spherical micelles. Therefore, worm-like filomicelles appear to be promising drug carriers with distinct advantages over spherical micelles and traditional paclitaxel formulations.

Two different targeting approaches for intracellular delivery to macrophages and cancer cells are proposed by Dr. Sinko and the coauthors and Dr. Minko and coauthors respectively in two separate papers. Both teams developed nanocarriers that allow for conjugating several copies of active ingredients to one carrier and used special targeting moieties to facilitate the intracellular uptake of entire delivery system by specific types of cells. It was found by Dr. Sinko and coauthors that N-Formyl-Methionyl-Leucyl-Phenylalanine as a targeting moiety increased the accumulation of poly(ethylene glycol) nanocarriers in major macrophage-residing tissues (liver, kidney and spleen) and caused opposite effects on the pharmacokinetic properties of smaller and larger carriers. The proposed macrophage-targeting approach can be useful for HIV treatment where macrophages represent a major site for the accumulation of the virus. Dr. Minko and coauthors showed that targeting of the drug to cancer cells and an increase in the number of copies of a targeting moiety and an anticancer drug per molecule of a carrier substantially enhanced the cellular internalization and cytotoxicity of the drug.

Dr. Torchilin and coauthors employed liposomal carriers in order to enhance the intracellular delivery of exogenous Coenzyme Q10 (CoQ10) and examined the possibility to use this liposomal formulation to limit the fraction of the irreversibly damaged myocardium in rabbits with an experimental myocardium infarction. The results showed that liposomal CoQ10 effectively protected the heart muscle from ischemic damage. Consequently, proposed liposomal CoQ10 has the potential to be effective in pharmacological prevention and in the treatment of cellular damages caused by different pathological conditions accompanied by severe tissue hypoxia and ischemia.

Dr. Ghandehari and coauthors studied an influence of concentration, generation number and surface charge of PAMAM dendrimers on their cellular internalization, intracellular trafficking and distribution. The authors labeled dendrimers with a fluorescent label and observed colocalization of these delivery systems with markers of endocytosis by a confocal microscopy. The influence of different dendrimers on the morphology of microvilli was also studied. The results of the study provide a visual evidence of an involvement of endocytosis in intracellular uptake and trafficking of dendrimers and document possible cytotoxic effect of high concentrations of cationic dendrimers. The proposed dendrimers after careful selection of their generation number, concentration and surface charge might be used for the enhancement of para- and transcellular oral delivery of drugs with poor bioavailability.

Dr. Lim and coauthors and Dr. Rosania and coauthors examined the intracellular fate of internalized gene therapy products and anticancer drugs in corresponding papers. Dr. Lim and team used the protein switch to target active components to subcellular compartments and found that such constructs are exported out of the nucleus by CRM1 receptors. They also concluded that the ligand binding domain in the controlled protein switch constructs plays an important role in maintaining the constructs in the cytoplasm and it re-exports from the nucleus in the absence of the ligand and after the ligand washout. Dr. Rosania and coauthors analyzed the rate of doxorubicin efflux from the nucleus of different human cancer cells. They found that cells with facilitated drug efflux from

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the nucleus possess higher resistance to the anticancer drug. The authors concluded that such an ATP-independent passive diffusion mechanism of drug efflux from cellular nuclei may play a role in the intrinsic resistance of certain cancers to chemotherapy.

I certainly hope that the readers will find this special theme issue interesting and useful.

DR. TAMARA MINKO

Is a professor of Pharmaceutics at, Rutgers, The State University of New Jersey. Her current research interests unclude drug delivery; biopharmaceutics; nanotechnology for cancer detection and treatment; molecular targeting; antisense oligonucleotides, siRNA and peptides in cancer therapy; mechanisms of multidrug resistance; intracullular fate and molecular mechanisms of action of anticancer drugs: apoptosis and necrosis, signal transduction, antiapoptotic cellular defensive mechanisms; use of macromolecules for drug delivery; preclinical evaluation of anticancer drugs; tumor hypoxia; modulation of cell death mechanisms during hypoxia. Professor Minko is an author and co-author of more than 80 peerreviewed papers, 16 book chapters and almost 200 conference proceedings. Her research is supported by grants form National Institutes of Health, American Lung Association and several other national and international sources.

Interview Questions for Dr. Tamara Minko

1. What do you think holds the key to your success as a pharmaceutical scientist?
   – Enthusiasm, intelligence, positive thinking and hard work.
2. What do you consider to be your key research accomplishments?
   – Targeted proapoptotic anticancer drug delivery systems, which consist of:
   (1) Nanocarrier
   (2) Anticancer drug(s)
   (3) Targeting moiety
   (4) Suppressors of pump and nonpump resistance
3. What was the turning point in your career?
   – The move from Molecular and Cellular Physiology to Pharmaceutical Science.
4. Who are the individuals who most influenced your research career?
   – Dr. J. Kopecek, Dr. P. J. Sinko, Dr. J. L. Colaizzi and my husband, Dr. V. P. Pozharov.
5. Pharmaceutical scientists are faced with the dilemma of having to publish in biomedical or basic science journals. Does it mean cutting edge science will not likely be featured in the Pharmaceutical Research?
   – I am sure that cutting edge pharmaceutical science will be featured in the Pharmaceutical Research.
6. Where is the field of Intracellular Delivery going, and how do the articles in the theme section fill the gap?
   – Multifunctional nanocarriers are the most promising direction in Intracellular Delivery.
   – The articles in the theme section will make a substantial impact on the field of Intracellular Delivery
7. What are the challenges for intracellular drug delivery and how can they be overcome?
   – Challenges: Low cellular permeability of active ingredients (drugs, peptides, antisense oligonucleotides, siRNA, etc.); adverse side effects on healthy cells; resistance to therapy
   – Approaches to overcome: Appropriate intracellular delivery system; targeting to specific cells, intracellular organelles, molecules, etc.; suppression of pump and nonpump cellular resistance.
8. What is the key to developing successful collaborative relationships?
   – Common research interests and approaches, ability to work as a team and trust.
9. What is your philosophy of educating graduate students?
   – According to my philosophy, graduate students should learn how to:
   (1) Perform all required techniques from drug development to biological testing *in vitro* and *in vivo*
   (2) Follow the rules of scientific ethics
   (3) Work as a team player
10. What are the challenges facing the pharmaceutical sciences?
    – Lack of funding
    – Switch from BS to Pharm D. programs in most leading pharmacy schools. As a result, students with Pharm. D. do not apply to Ph.D. graduate program in Pharmaceutical Science.
11. What is the place for collaboration with industry in academia?
    – The entire education and research processes.

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