

# **Fundamental Biomedical Technologies**

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Aleš Prokop · Yasuhiko Iwasaki  
Atsushi Harada  
Editors

# Intracellular Delivery II

Fundamentals and Applications

*Editors*

Aleš Prokop  
Chemical and Biological Engineering  
Vanderbilt University  
Nashville, TN  
USA

Atsushi Harada  
Department of Applied Chemistry  
Osaka Prefecture University  
Osaka  
Japan

Yasuhiko Iwasaki  
Chemistry and Materials Engineering  
Kansai University  
Osaka  
Japan

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# Contributors

**Kazunari Akiyoshi** Department of Polymer Chemistry, Graduate School of Engineering, Kyoto University, Kyoto, Japan; JST-ERATO, Tokyo, Japan

**Helene Andersen** Nanomedicine Research Group, Faculty of Health and Medical Sciences, Department of Pharmacy, Centre for Pharmaceutical Nanotechnology and Nanotoxicology, University of Copenhagen, Copenhagen, Denmark

**Eva Bártová** Institute of Biophysics, Academy of Sciences of the Czech Republic, Brno, Czech Republic

**Fedor Čiampor** Institute of Virology, SAS, Bratislava, Slovak Republic

**Pierpaolo Ceci** CNR—National Research Council of Italy, Institute of Molecular Biology and Pathology, Rome, Italy

**Yung Chang** R&D Center for Membrane Technology, Department of Chemical Engineering, Chung Yuan Christian University, Chung-Li, Taoyuan, Taiwan

**Petr Cigler** Laboratory of Synthetic Nanochemistry, Institute of Organic Chemistry and Biochemistry AS CR v. v. i., Prague 6, Czech Republic

**Dušan Cmarko** 1st Faculty of Medicine, Institute of Cellular Biology and Pathology, Charles University in Prague, Prague, Czech Republic

**Kateřina Dědková** Nanotechnology Centre, VSB—Technical University of Ostrava, Ostrava, Poruba, Czech Republic

**Elisabetta Falvo** CNR—National Research Council of Italy, Institute of Molecular Biology and Pathology, Rome, Italy

**Marcela Foglarová** Contipro Biotech s.r.o, Dolní Dobrouč, Czech Republic

**Eleonore Fröhlich** Center for Medical Research, Medical University of Graz, Graz, Austria

**Jie Han** Department of Electrical and Computer Engineering, University of Alberta, Edmonton, AB, Canada

**Jan Havlik** Laboratory of Synthetic Nanochemistry, Institute of Organic Chemistry and Biochemistry AS CR v. v. i., Prague 6, Czech Republic

**Kateřina Horská** Department of Nanobiotechnology, Institute of Nanobiology and Structural Biology of GCRC, České Budějovice, Czech Republic

**Jian Ji** MOE Key Laboratory of Macromolecule Synthesis and Functionalization of Ministry of Education, Department of Polymer Science and Engineering, Zhejiang University, Hangzhou, China

**Xiaoyan Jiang** Terry Fox Laboratories, British Columbia Cancer Agency, Department of Medical Genetics, University of British Columbia, Vancouver, BC, Canada

**Qiao Jin** MOE Key Laboratory of Macromolecule Synthesis and Functionalization of Ministry of Education, Department of Polymer Science and Engineering, Zhejiang University, Hangzhou, China

**Yoshiki Katayama** Faculty of Engineering, Department of Applied Chemistry, Kyushu University, Nishi-ku, Fukuoka, Japan; Center For Future Chemistry, Kyushu University, Nishi-ku, Fukuoka, Japan

**Won Jong Kim** Center for Self-Assembly and Complexity, Institute for Basic Science (IBS), Department of Chemistry Polymer Research Institute, Pohang University of Science and Technology (POSTECH), Pohang, South Korea

**Kateřina Knotková** Contipro Biotech s.r.o, Dolní Dobrouč, Czech Republic

**Tomohiro Konno** Department of Bioengineering, School of Engineering, The University of Tokyo, Bunkyo-ku, Tokyo, Japan

**Petr Král** Department of Chemistry, University of Illinois at Chicago, Chicago, IL, USA

**Gabriela Kratošová** Nanotechnology Centre, VSB—Technical University of Ostrava, Ostrava, Poruba, Czech Republic

**Breanne Landry** Faculty of Engineering, Department of Chemical and Materials Engineering, University of Alberta, Edmonton, AB, Canada

**Jinghang Liang** Department of Electrical and Computer Engineering, University of Alberta, Edmonton, AB, Canada

**Zdeňka Maděrová** Department of Nanobiotechnology, Institute of Nanobiology and Structural Biology of GCRC, České Budějovice, Czech Republic

**Deniz Meneksedag-Erol** Faculty of Medicine and Dentistry and Engineering, Department of Biomedical Engineering, University of Alberta, Edmonton, AB, Canada

**S. Moein Moghimi** Nanomedicine Research Group, Faculty of Health and Medical Sciences, Department of Pharmacy, Centre for Pharmaceutical Nanotechnology and Nanotoxicology, University of Copenhagen, Copenhagen, Denmark



**Takeshi Mori** Faculty of Engineering, Department of Applied Chemistry, Kyushu University, Nishi-ku, Fukuoka, Japan; Center For Future Chemistry, Kyushu University, Nishi-ku, Fukuoka, Japan

**Eva Muchova** Laboratory of Synthetic Nanochemistry, Institute of Organic Chemistry and Biochemistry AS CR v. v. i., Prague 6, Czech Republic

**Nobuhiro Nishiyama** Chemical Resources Laboratory, Polymer Chemistry Division, Tokyo Institute of Technology, Midori-ku, Yokohama, Japan

**Jindřich Novák** Contipro Biotech s.r.o, Dolní Dobrouč, Czech Republic

**Takashi Ohtsuki** Department of Biotechnology, Okayama University, Okayama, Japan

**Ladan Parhamifar** Nanomedicine Research Group, Faculty of Health and Medical Sciences, Department of Pharmacy, Centre for Pharmaceutical Nanotechnology and Nanotoxicology, University of Copenhagen, Copenhagen, Denmark

**Stanislav Petřík** Institute for Nanomaterials, Advanced Technologies and Innovation, Technical University of Liberec, Liberec 1, Czech Republic

**Marek Pokorný** Contipro Biotech s.r.o, Dolní Dobrouč, Czech Republic

**Kristýna Pospíšková** Regional Centre of Advanced Technologies and Materials, Palacký University, Olomouc, Czech Republic

**Helena Raabova** Laboratory of Synthetic Nanochemistry, Institute of Organic Chemistry and Biochemistry AS CR v. v. i., Prague 6, Czech Republic

**Ivan Raška** 1st Faculty of Medicine, Institute of Cellular Biology and Pathology, Charles University in Prague, Prague, Czech Republic

**Ivan Rehor** Laboratory of Synthetic Nanochemistry, Institute of Organic Chemistry and Biochemistry AS CR v. v. i., Prague 6, Czech Republic

**Eva Roblegg** Department of Pharmaceutical Technology, Institute of Pharmaceutical Sciences, Karl-Franzens-University of Graz, Graz, Austria

**Jana Růžicková** Contipro Biotech s.r.o, Dolní Dobrouč, Czech Republic

**Ivo Šafařík** Department of Nanobiotechnology, Institute of Nanobiology and Structural Biology of GCRC, České Budějovice, Czech Republic; Regional Centre of Advanced Technologies and Materials, Palacký University, Olomouc, Czech Republic

**Mírka Šafaříková** Department of Nanobiotechnology, Institute of Nanobiology and Structural Biology of GCRC, České Budějovice, Czech Republic

**Gurusamy Saravanakumar** Institute for Basic Science (IBS), Center for Self-Assembly and Complexity, Department of Chemistry Polymer Research Institute, Pohang University of Science and Technology (POSTECH), Pohang, South Korea

**Shin-ichi Sawada** Department of Polymer Chemistry, Graduate School of Engineering, Kyoto University, Kyoto, Japan; JST-ERATO, Tokyo, Japan

**Adam Schröfel** 1st Faculty of Medicine, Institute of Cellular Biology and Pathology, Charles University in Prague, Prague, Czech Republic

**Yu-Ju Shih** Department of Chemical Engineering, R&D Center for Membrane Technology, Chung Yuan Christian University, Chung-Li, Taoyuan, Taiwan

**Asako Shimoda** Department of Polymer Chemistry, Graduate School of Engineering, Kyoto University, Kyoto, Japan; JST-ERATO, Tokyo, Japan

**Jitka Slegerova** Laboratory of Synthetic Nanochemistry, Institute of Organic Chemistry and Biochemistry AS CR v. v. i., Prague 6, Czech Republic

**Chongbo Sun** Faculty of Engineering, Department of Mechanical Engineering, University of Alberta, Edmonton, AB, Canada

**Katarzyna Szuszkiewicz** Contipro Biotech s.r.o, Dolní Dobrouč, Czech Republic

**Hiroyasu Takemoto** Chemical Resources Laboratory, Polymer Chemistry Division, Tokyo Institute of Technology, Midori-ku, Yokohama, Japan

**Tian Tang** Faculty of Engineering, Department of Mechanical Engineering, University of Alberta, Edmonton, AB, Canada

**Lemmuel L. Tayo** Department of Chemical Engineering, R&D Center for Membrane Technology, Chung Yuan Christian University, Chung-Li, Taoyuan, Taiwan

**Ching-Wei Tsai** Department of Chemical Engineering, R&D Center for Membrane Technology, Chung Yuan Christian University, Chung-Li, Taoyuan, Taiwan

**Hasan Uludag** Faculty of Medicine and Dentistry and Engineering, Department of Biomedical Engineering, University of Alberta, Edmonton, AB, Canada  
Department of Chemical and Materials Engineering, Faculty of Engineering, University of Alberta, Edmonton, AB, Canada; Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, AB, Canada

**Juliana Valencia-Serna** Faculty of Medicine and Dentistry, Department of Biomedical Engineering, University of Alberta, Edmonton, AB, Canada

**Luca Vannucci** Institute of Microbiology, Academy of Sciences of the Czech Republic (ASCR), v.v.i, Prague, Czech Republic

**Ivo Vávra** Nanotechnology Centre, VSB—Technical University of Ostrava, Ostrava, Poruba, Czech Republic; Institute of Electrical Engineering, Slovak Academy of Sciences, Bratislava, Slovak Republic

**Vladimír Velebný** Contipro Biotech s.r.o, Dolní Dobrouč, Czech Republic

**Lela Vuković** Department of Chemistry, University of Illinois at Chicago, Chicago, IL, USA

**Kazunori Watanabe** Department of Biotechnology, Okayama University, Okayama, Japan

**Peican Zhu** Department of Electrical and Computer Engineering, University of Alberta, Edmonton, AB, Canada

# Editorial and Introduction

This book features a special subsection of Nanomedicine, an application of nanotechnology to achieve breakthroughs in healthcare. The Nanomedicine exploits the improved and often novel physical, chemical, and biological properties of materials only existent at the nanometer scale. As a consequence of small scale, nanosystems in most cases are efficiently uptaken by cells and appear to act at the intracellular level. Nanotechnology has the potential to improve diagnosis, treatment and follow-up of diseases, and includes targeted drug delivery and regenerative medicine; it creates new tools and methods that impact significantly existing conservative practices. This book more specifically targets using nanotechnology in the area of drug delivery and tissue engineering, i.e., the application of various nanoparticulates based on natural or synthetic, organic or inorganic materials as drug carriers and tissue regenerative support, first of all to deliver substances and drugs inside cells.

During the last decade, intracellular drug delivery has become an emerging area of research in the medical and pharmaceutical field. Many therapeutic agents can be delivered to a particular compartment of a cell to achieve better activity. In Volume 1 of this series, we investigated various means of delivering cargo, via endocytosis. Various carriers have been investigated for efficient intracellular delivery, either by direct entry to cytoplasm or by escaping the endosomal compartment. These include cell-penetrating peptides, and carrier systems such as liposomes, cationic lipids and polymers, polymeric nanoparticles, etc. Various properties of these carriers, including size, surface charge, composition, and the presence of cell-specific ligands, alter their efficacy and specificity toward particular cells. Also included were various aspects of targeted intracellular delivery of therapeutics including pathways, mechanisms, and approaches.

This Volume 2, a continuation of Volume 1 (not numbered this way), is a collection of **authoritative reviews**.

The Part I of this volume deals with *Novel Nanocarrier Design and Processing*, listing some new designs and chemistry. The very first chapter deals with a survey of production methods of nanofibers, as exemplified by proprietary and successful Nanospider<sup>TM</sup> technology developed by Technical University Liberec, Czech Republic, licensed to Elmarco (Liberec, Czech Republic) ([www.elmarco.com](http://www.elmarco.com)). This technology has also been licensed in several countries with applications in different fields as well as in biomedicine. It should be stressed that nanofibers are

readily taken up by cells (e.g. Che et al. 2011). Other four chapters describe several different new designs for nanoparticles, with emphasis on responsiveness to different external stimuli.

Part II deals with *Nanocarrier Characterization and Function*. The first chapter of this section describes, in some details, how nanoparticles (NP) enter the cells and how they are distributed within the cell interior, while the subsequent chapter describes specific problems related to delivery to mucus. Following are two chapters which cover rather physical methods of nanocarrier characterization, the rest of this section introduces novel delivery vehicles for specific sites or specific cargo.

Part III is entirely a new section; it covers *Simulation for Delivery and Function*. Future applications in nanotechnology are likely to require this level of sophisticated control in order to form precisely ordered structures, with specific chemical and physical properties. Theoretical understanding of the fundamental principles of self-assembly and the design rules for creating new self-assembling materials.

Based on a paper by Vauthier and Bouchemar (2009) two out of about ten different methods of nanoparticle production are (a) formation of polyelectrolyte complexes and (b) production of nanogels. Self-assembly processes typically, both or colloidal building blocks above combine spontaneously to form ordered structures and that without guidance or control from an outside source. Resulting from a disordered system of pre-existing components is an organized structure or pattern as a consequence of specific, local interactions among the components themselves. Self-assembly can be classified as either static or dynamic process. In *static* self-assembly, the ordered state forms as a system approaches equilibrium (thermodynamic stability). In *dynamic* self-assembly, patterns of pre-existing components organized by specific local interactions are not commonly described as “self-assembled” (characterized by the presence of long-range repulsive and short-range attractive forces), whereas they should, in fact, be denoted as “self-organized” (Wikipedia).

New computational simulation tools are required to describe the self-assembly, and to apply them to understand the structures and their thermodynamics and dynamics of both biological and synthetic self-assembling systems (Frenkel and Smit 2002). We envisage that in the future it would be possible to tailor nanoparticles to deliver cargoes at the right subcellular compartment through the use of signaling signatures and pathways. This will improve the magnitude and duration of the drug effects. It is a challenging task due to the complexity of multiple compartments such as endosomes and nuclei, which themselves are dynamic and can undergo fusion and fission and exchange their content (Csukas et al. 2011). The result is to guide further experimental efforts in determining most sensitive parameters. Moreover, there is still much room for building knowledge about the interactions of NPs with proteins and membrane structures on the cell surface. Taking advantage of computer simulations and current developments in interactomics, it would certainly be of great use to know the molecules that interact with the NPs, as well as the nature of this interaction. We emphasize this effort as the literature is relatively scarce in this direction.

The last chapter of this section seeks to emphasize an importance of theoretical background, as provided by Systems Biology, to guide the researcher in the process of discovery. That is, guide the drugs/reagents to an appropriate site. Targeting, localized and intracellular delivery present still a key challenge to effective delivery. To establish an effective fight against diseases, we have to have the ability to selectively attack specific cells, while saving the normal tissue from excessive burdens of drug toxicity. However, because many drugs are designed to simply kill specified cells, in a semi-specific fashion, the distribution of drugs in healthy organs or tissues is especially undesirable due to the potential for severe side effects. Consequently, systemic application of these drugs often causes severe side effects in other tissues (e.g., bone marrow suppression, cardiomyopathy, neurotoxicity), which greatly limits the maximal allowable dose of the drug. In addition, rapid elimination and widespread distribution into nontargeted organs and tissues requires the administration of a drug (in a suitable carrier) in large quantities, which is often not economical and sometimes complicated due to nonspecific toxicity. This vicious cycle of large doses and the concurrent toxicity is a major limitation of many current therapies. Thus, the benefit of nanocarrier design.

Part IV covers *Nanocarriers for Drug Discovery and Treatment*, listing specific applications in biology and medicine. Of a special interest should be a proprietary technology of Contipro s.r.o. (Dolní Dobruška, Czech Republic; [www.contipro.com](http://www.contipro.com)) employing low-molecular weight hyaluronate to assemble highly biocompatible nanofibers using a technology based on needle-less electrostatic filament principle. The company's main emphasis is in wound healing and other applications.

## References

- Che H-L, Muthiah M, Ahn Y et al (2011) Biodegradable particulate delivery of vascular endothelial growth factor plasmid from polycaprolactone/polyethylenimine electrospun nanofibers for the treatment of myocardial infarction. *J nanosci Nanotechnol* 11(8):7073–7077
- Csukas B, Varga M, Prokop A (2011) Simulation based analysis of nanocarrier internalization: Exciting challenges with a new computational tool, In: Prokop A (ed)., *Intracellular delivery: fundamentals and applications book series: fundamental biomedical technologies Vol 5*, pp 125–154
- Frenkel D, Smit B (2002) *Understanding molecular stimulation: From Algorithms to Applications*, 2nd ed. Academic Press, New York
- <http://en.wikipedia.org/wiki/Self-assembly>, accessed October 29, 2013
- Vauthier C, Bouché K (2009) Methods for the Preparation and Manufacture of Polymeric Nanoparticles. *Pharm Res.* 26:1025–1058

## Editorial Plan

- **Novel Nanocarrier (NC) Design and Processing**

- Silica-based
- Nanofiber design/biological
- Multifunctional NC
- Templating
- Hybrid NC
- Core-shell NC
- New Cationic NC
- Colocalization (dual-label)
- Stimuli-responsive NC
- Scale-up

- **Nanocarrier Characterization and Function**

- Physical
- Biological/toxicity
- Stem cell tracking
- Compartmental delivery/trafficking
- NC uptake
- Gene silencing
- Pharmacokinetics and compartmentalization

- **Simulation for Delivery and Function**

- Modeling of self-assembly and molecular modeling
- Payload simulation
- Simulation of release
- Simulation of ligand function/binding energy
- NC dynamics
- Regulation and simulation of NC uptake/endocytosis/exocytosis/disregulation
- NC and pharmacokinetics
- Computational understanding of nanoparticle interface and interaction

- **Nanocarriers for Drug Discovery and Treatment**

- NC imaging
- Imaging/Delivery to brain
- Spinal injury

The Editors would like to profoundly thank all contributors to this volume for their cooperation and enthusiasm, and also, for their reviewing of colleagues' chapters, which served as a basis of internal review process. Finally, we invite contributions from different researchers to this series.

In future volumes, the emphasis will be more on pharmacokinetic aspects as they control the ultimate application and utility. As pointed by Karel Petrak (personal communication on 10/28/2013), “Although I understand the importance of having ‘enabling technology’ available, the issue of ‘promises, promises and more promises’ being made about ‘new delivery systems’ that are never delivered only to be replaced by new promises. To me the central issue is to recognize that the systems must focus on modifying the drug’s pharmacokinetics and pharmacodynamics to be optimal for the given disease target.” This volume, unfortunately, does not spell out this emphasis clearly. Thus, this eminent topic is sought for future volumes.

Aleš Prokop  
Yasuhiko Iwasaki  
Atsushi Harada