

## 2011 Tsuneji Nagai Postdoctoral Fellowship Year Reflections

*Soo Hyeon Lee, Ph.D.*

*Postdoctoral Fellow, Jean-Christophe Leroux Laboratory, Swiss Federal Institute of Technology Zurich (ETH Zurich)*

### Previous Studies for Clinical Applications of RNAi

In 2006, when Andrew Fire and Craig C. Mello received the Nobel Prize in Physiology or Medicine for their work on RNA interference (RNAi), I started my Ph.D. about small interfering RNA (siRNA) delivery at the Korea Advanced Institute of Science and Technology (KAIST) under the supervision of Prof. Tae Gwan Park. To obtain a balance between cytotoxicity and delivery efficiency, we developed various siRNA delivery carriers and modified siRNAs chemically by conjugating with polymers or crosslinking siRNA molecules.

After finishing my Ph.D., I realized that there are still important unmet needs for the clinical application of siRNAs as therapeutics, despite the tremendous efforts in this field. To devote myself to solving the current delivery problems of new drugs, I wanted to apply for a postdoctoral position in the laboratory of Prof. Jean-Christophe Leroux at the Swiss Federal Institute of Technology Zurich (ETH Zurich).

### Reflections from the Fellowship Year

The Drug Formulation and Delivery Laboratory headed by Prof. Leroux belongs to the Institute of Pharmaceutical Sciences in the Department of Chemistry and Applied Biosciences. Within this department, many experts from different fields—for example, pharmacology and chemistry—are collaborating actively to develop drug delivery systems for clinical application. It is worth noting that defining the problem of conventional therapies from a pharmaceutical point of view and designing a novel system with various knowhow about chemical synthesis should not be considered separately. Based on my knowledge and experience acquired in cancer therapy and gene delivery during my Ph.D., I was greatly interested in joining this group to study at a world-class university and train myself as an independent researcher.

With Prof. Leroux, we designed a new research project and applied for the postdoctoral fellowship. Fortunately, I was selected as the recipient of the 2011 Tsuneji Nagai Postdoctoral Fellowship from the CRS Foundation. This honorable prize motivated me to dedicate myself in this field as well as gave me a great opportunity to join the group of Prof. Leroux and broaden my expertise for my future career. This fellowship also gave me the opportunity to meet

and discuss the project with a very precious academic mentor, Prof. Tsuneji Nagai.

Prof. Leroux's laboratory focuses on developing drug delivery systems not only for life-

threatening diseases such as cancer but also for rare diseases such as celiac disease or inflammatory bowel disease (IBD). Prof. Leroux is an expert in the fields of gastroenterology and drug delivery systems. Thanks to support and help from Prof. Leroux and my colleagues, I could set up my experiments immediately and focus on the research project, entitled "Inflammatory Bowel Disease Therapy with Nucleic Acid Drugs via Oral Administration."

### Research Project

IBD is a group of chronic inflammatory disorders of the colon and small intestine. Patients usually are treated with anti-inflammatory drugs such as mesalazine to alleviate the immune response in the colon. However, the drug efficacy varies in patients, and long-term immunosuppressant therapy can cause severe side effects to the whole body. While the deteriorated intestine sections can be excised by surgery, there are still many problems such as relapses and inconvenience to the patient. To improve the quality of the patient's life, we need to develop new therapeutics with fewer side effects and higher efficiencies, relieving the symptoms and eventually curing the disease. Even though the main cause of IBD has not yet been defined, many factors—for example, genetic, infectious, immunologic, and psychological reasons—can influence the development of IBD.

Recent clinical studies with IBD patients have revealed that genetic properties can predispose people to develop IBD. The comparison of microRNA (miRNA) expression levels between patients and healthy people showed that certain miRNAs were abnormally under- or overexpressed in a group of patients, and the recovery of these problematic genes to express at the normal level elicited some therapeutic effect, suggesting that gene therapy could provide a breakthrough by replacing the conventional IBD therapy. As a target tissue, the colon is one of the most accessible sites via oral administration, in comparison with other tissues. Oral delivery to the colon has several advantages, namely, higher dose tolerated, convenience for the patient, and minimal systemic exposure, which usually causes undesirable side effects. However, the harsh conditions in the gastrointestinal tract (e.g., pH and digestive enzymes) should be considered in designing an efficient delivery system.

For this reason, we selected chemically and enzymatically stable peptide nucleic acids (PNAs) as a nucleic acid drug, to eventually modulate the abnormal expression levels of miRNA in the colon. Because PNAs have a high molecular weight and neutral charge, they do not penetrate easily through the cell membrane. Therefore, previous studies have chemically conjugated cell-penetrating peptides (CPPs) for intracellular delivery of PNAs. Based on the previous studies about CPP-mediated oligonucleotide delivery, we selected 12 different CPPs to deliver PNAs into the cell to show the silencing effect on the target protein. We have successfully synthesized CPP-PNA conjugates and treated colon cancer



*Soo Hyeon Lee and Prof. Tsuneji Nagai.*

cells. With several potent CPPs for the efficient cytosolic delivery of PNA, we are currently modifying our potential drugs to provide colon tissue specificity. We hope that this work will result in a novel gene delivery system with high efficacy and safety for IBD, ultimately improving the patients' quality of life and informing the design of other drug delivery systems.

Even though the CRS Tsuneji Nagai Postdoctoral Fellowship has ended, I will never forget the numerous great moments that

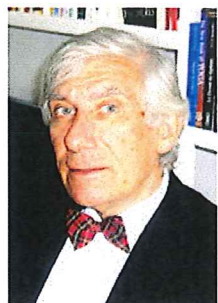
I had during the past year. This fellowship provided me lots of opportunities to develop my international visibility and experience to become a world-leading researcher. I greatly enjoyed working with Prof. Jean-Christophe Leroux, Dr. Bastien Castagner, and all my colleagues in the Drug Formulation and Delivery Laboratory at ETH Zurich. I appreciated their insightful comments and helpful guidance. I also deeply thank the CRS Foundation and, in particular, Prof. Tsuneji Nagai. ■

## Building a Delivery Science Legacy



The objective of the CRS Foundation is to support the future of delivery science and honor those who have made outstanding contributions to the field. Now is the time to plan for 2014, build the endowment, and celebrate the CRS Foundation's early successes.

### 2014 Alexander Florence Postdoctoral Fellowship



Alexander Florence

In 2014 the CRS Foundation will give a \$30,000 postdoctoral fellowship named to honor CRS past president Alexander "Sandy" Florence, former dean and current emeritus professor of the School of Pharmacy, University of London. He is editor-in-chief (Europe) of the *International Journal of Pharmaceutics* and was founding coeditor of the *Journal of Drug Targeting*. Author of hundreds of papers and multiple books, and recipient of numerous awards, Prof. Florence's expertise

in pharmaceutical nanotechnology, drug delivery systems, physical pharmaceutical chemistry, novel dendrimers, and surface chemistry has added greatly to drug delivery research.

### Build the Endowment in 2013

The CRS Foundation Board is focusing its 2013 time and resources to build the endowment for future sustainability. Your contribution matters. Please help build the endowment and support the next postdoctoral fellowship by making a generous year-end donation on the CRS Foundation website, [www.controlledreleasesociety.org/about/foundation](http://www.controlledreleasesociety.org/about/foundation).

### Celebrate the Advances of 2009–2012

Thanks to the generosity of CRS members and the delivery science community, the CRS Foundation has awarded postdoctoral fellowships of \$30,000 each to four exceptional young delivery scientists since 2009. With each fellowship, CRS honors exemplary delivery scientists and supports the training of its future leaders.



Tram Dang

### 2012 Sung Wan Kim Postdoctoral Fellowship

#### Tram Dang

Engineering high-throughput *in vitro* systems for the investigation of immunological interaction

*Ali Khademhosseini Laboratory  
Brigham and Women's Hospital  
Harvard Medical School*



Soo Hyeon Lee

### 2011 Tsuneji Nagai Postdoctoral Fellowship

#### Soo Hyeon Lee

Design of novel macromolecular conjugates for delivery of antisense oligonucleotides to the colonic mucosa

*Jean-Christophe Leroux Group  
ETH Zurich*



Qun Wang

### 2010 Jorge Heller Postdoctoral Fellowship

#### Qun Wang

Use of intestinal stem cells to treat colorectal cancer through regenerative medicine

*Robert Langer Laboratory  
MIT and Harvard Medical School*



David Nguyen

### 2009 Joseph R. Robinson Postdoctoral Fellowship

#### David Nguyen

Medical school and immunology research with novel vaccine adjuvants

*David Lewis Laboratory  
Stanford University* ■