Impact Objectives

- Use a multidisciplinary approach (biological, chemical, pharmaceutical and clinical) to exploring breakthrough Drug Delivery Systems
- Utilise innovative Fine Droplet Drying (FDD) technology as a novel modality for the treatment of lung disease

A new response to lung disease

***Dr Takashi Sato** at **Yokohama City University** is developing innovative approaches for the treatment of lung disease. He explains his work, which includes a novel strategy for administering existing treatments, and how the administration strategy benefits not only patients but the greater healthcare system of Japan*

Can you talk generally about your background in pulmonology research?

My initial training under the leadership of Dr Ishigatsubo focused on oxidative lung diseases, in particular the role of oxidative stress on disease pathogenesis. My doctoral thesis examined the immunological consequences of silica particle inhalation on the development of silicosis and subsequent lung cancer as oxidative lung disease caused by inhalation of dust containing silica particles. That research fuelled my interest in developing a means to prevent and treat silicotic lung disease.

I pursued that interest during my postdoctoral training at the National Cancer Institute, NIH from 2005 to 2008. My mentor Dr Klinman, is a renowned expert in the field of immunomodulatory oligodeoxynucleotide. He advised me to pursue 'a creative approach to biomedical research'. In particular, Dr Klinman supported my efforts to develop inhalable particles as therapeutic delivery systems. We have continued to collaborate in studying the innovative drug delivery system utilising smart nano/microparticle-incorporated oligodeoxynucleotides first tested in his laboratory for the treatment of lung diseases. My research interest as a pulmonary physician is focused on using the delivery system for the inhalational administration of therapeutic agents.

You are working on a number of projects involving the development of treatment modality for lung diseases. Can you talk briefly about what you hope to learn from this work?

Lung diseases are the major causes of death worldwide. This includes infections such as pneumonia, tuberculosis, chronic obstructive pulmonary disease (COPD) and lung cancer (which were ranked as the third, seventh, fourth and eighth most common causes of death worldwide in 2010). The incidence of these diseases is increasing with lung cancer and is expected to become the sixth greatest cause of death by 2030. Thus, it is important to develop new and better treatment strategies for lung disease. This was established in the successful treatment history of bronchial asthma involving the development of inhaled corticosteroid and bronchodilators. My aim is to pursue the management of other lung diseases using inhalation therapy. As a pulmonary physician for over 15 years, I have considerable experience with patient use of inhalation drugs for bronchial asthma, COPD and influenza virus infection. This experience reinforced my belief that it would be of benefit to expand this simple and well-tolerated treatment modality to additional respiratory (and potentially non-respiratory diseases).

The goal of the current project is to develop a novel means of treating primary lung cancer using a combination of immunostimulatory oligodeoxynucleotides plus additional biologics incorporated into nano/microparticles that can be readily administered via inhalation. We will also examine whether inhalational delivery of small molecule-incorporated nano/microparticles can be used in the treatment of pulmonary fibrosis.

What is the purpose of evaluating these impacts? Why is it important to understand these?

Pulmonary physicians appreciate that limitations imposed by Japan's public medical insurance programmes limits the availability of high dose immune-checkpoint inhibitors for the treatment of some lung cancer patients. The dose, frequency and cost of such therapy could be dramatically reduced if nano-microparticles could be used to deliver these agents directly into the lungs. Decreasing the dose could also reduce the likelihood of immune-related adverse events. Thus, development of the targeted delivery strategy that is the focus of my work could have major public health impacts. Indeed, while initially applied to the delivery of cancer therapeutics, this strategy could also be used in the delivery of a broad range of biologics for a variety of pulmonary diseases. ●

Inhaling to improve prognosis

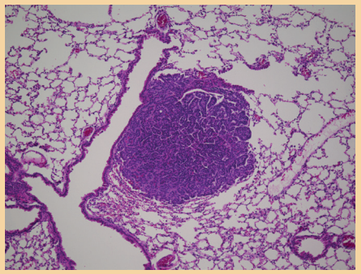
***Dr Takashi Sato** and his colleagues have explored the potential of delivering novel therapies by inhalation for the treatment of pulmonary diseases. Their work has proven to be highly effective at treating lung cancer in murine models thus far and they hope to move this therapy into clinical use in the future*

Millions of individuals worldwide die from lung diseases every year and the number of deaths continues to rise. Now more than ever, medical scientists must strive to provide treatments that are both effective and of sufficiently low cost that governmental and private healthcare providers can utilise them fully.

Dr Takashi Sato is a researcher at the Department of Pulmonology, Yokohama City University in Japan. He is working in conjunction with collaborators, Dr Shimosato from Shinshu University, Japan and Dr Klinman from the National Cancer Institute of the National Institutes of Health (NIH), to develop and improve technologies for the delivery of cost-effective inhalational therapies for pulmonary diseases. Their current focus is on therapy that can thwart lung cancer.

STARTING STRONG

Sato and his colleagues developed their broad understanding of pulmonology over many years of research and study. They use their creativity and knowledge of the field to develop novel treatment options for lung disease. Sato became interested in this therapeutic strategy while studying how oxidative stress (the strain put on the body from inhaling certain harmful chemicals) supported the development of silicosis, a lung disease caused by inhaling silica particles. When training with Klinman, Sato developed the idea of using particles of similar size (but without pathogenic particles) to treat rather than cause pulmonary disease. He recognised that inhalational therapy might be used to treat both pulmonary and non-pulmonary diseases. This marked the beginnings of his effort to develop inhalable nano/microparticles containing immunomodulatory oligodeoxynucleotides. He postulated that these could be harnessed to treat a variety of immune-mediated diseases as well as diseases that would benefit from enhanced immunity (such as cancer). 'Findings from this work would contribute to the real-world health care with less needles; just inhale deeply, even in the lethal malignant diseases like lung cancer,' Sato says.



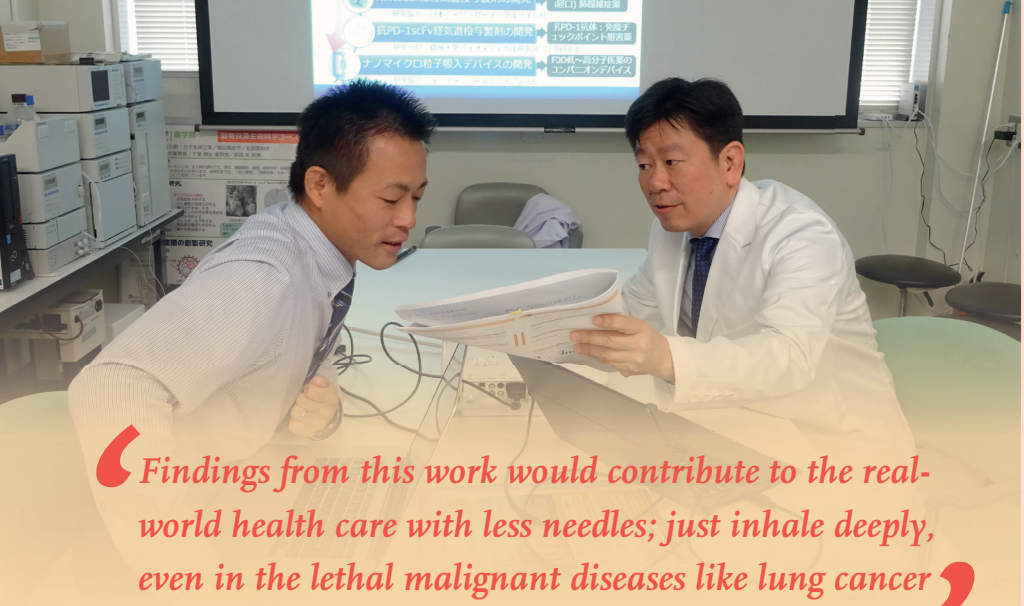
Lung tumour: the target for inhalation therapy

In the past ten years, Sato focused his research efforts on improving and broadening the scope of inhalation therapies. He synthesised biodegradable polymer nanoparticles carrying oligodeoxynucleotides that could be used for immunotherapy. 'I also established that the effect of these particles could be readily monitored in murine models, showing that the nanoparticles reached inflammatory lesions in the lungs and caused them to regress when delivered by intratracheal instillation,' explains Sato. Published studies by Sato, Shimosato and Klinman document the promise of this strategy. One of their projects began with 'Nintedanib (OFEV® Boehringer Ingelheim GmbH)', a medicine in pill form used to treat Idiopathic Pulmonary Fibrosis, a disease which causes scarring to the lungs. The team was able to create a particle form of the medication suitable for inhalation treatment. Based on the favourable preclinical results, they are moving forward towards human trials.

CONFRONTING CHALLENGES

While effective for delivery of immunostimulatory oligos to the lungs, inhalational therapy is not optimal for delivery elsewhere in the body. Sato's team is therefore interested in developing nano/microparticles that can deliver these oligodeoxynucleotides orally. While uptake through the gastrointestinal tract has been achieved, dosage remains a problem. Thus, this approach remains potentially useful for the delivery of oligos to cells lining the gastrointestinal tract but remains problematic for systemic therapy.

A phase III clinical trial was performed to examine whether systemically administered immunostimulatory CpG oligodeoxynucleotide combined with chemotherapy could improve survival of patients with advanced non-small cell lung cancer. 'The results showed that patients receiving CpG oligodeoxynucleotide plus chemotherapy did better that those receiving chemotherapy alone, although the benefit was modest,' outlines Sato. Those findings support continued work on the use of oligodeoxynucleotides to treat lung cancer, particularly if their activity could be increased by delivering them directly to the lungs. 'Indeed, work by Klinman's laboratory showed that injection of CpG oligos into the tumour bed was considerably more effective than systemic administration as it shifted the immune milieu surrounding the tumour from suppressive to tumoricidal,' ▶



'Findings from this work would contribute to the real-world health care with less needles; just inhale deeply, even in the lethal malignant diseases like lung cancer'

summarises Sato. 'So far we have learned that local immunotherapy with immunostimulatory oligodeoxynucleotide-containing microparticles contributes to changing the immunosuppressive tumour microenvironment and maintaining long-term tumour immunity that prevents cancer recurrence.'

Sato is interested in broadening the scope of the inhalable delivery system. He and his collaborators seek to develop particles suitable for inhalational delivery of additional agents including antibodies and small molecules that can be used as immune-checkpoint inhibitors or to block the activation of immune cells. Many immunotherapies have some efficacy but because they are administered systemically they have serious side effects, such as including the induction of type one diabetes, interstitial lung diseases, endocrine disorders, colitis and arthritis. Sato hopes that his strategy of focusing on inhalational delivery of these agents will have multiple benefits. By focusing treatment where it is required in the lung, this approach will lower the dose required, thereby lowering the cost of treatment while enhancing efficacy and reducing adverse side effects.

'We are still facing challenges but our efforts to collaborate with experts from particle technology, surface engineering and chemical engineering could help us fulfil our requirements soon,' states Sato. Through their journey, the research team has worked through challenges and continues to move forward with their promising developments.

NOVEL TECHNOLOGY

Presently, Sato and colleagues are examining a new approach to generating particles of appropriate size for inhalational therapy. This involves using the Fine Droplet Drying (FDD) technology by RICOH Co., Ltd, a technology used for ink-jet printing. 'Through our previous lung cancer study, we realised that the uniformity of particle size would be critical for clinical inhalation use,' explains Sato, and this is precisely what FDD offers: particle sizes of approximately two to three micrometres, ideal for inhalation. However, Sato's group needs to modify the technology to meet the exacting needs of human therapy. 'The FDD provides a variety of advantages for the researchers' needs including amorphous, spherical solid dispersion; narrow particle size distribution; good stability in higher temperatures; constant and prolonged drug release; and improved dissolution,' he says. Use of this technology could improve the absorption, distribution, metabolism and excretion of therapeutic nano/microparticles, which are properties especially important when applied to inhalation. FDD might also provide the answer in the team's relentless search for the perfect carrier for administering immunostimulatory oligodeoxynucleotide via the oral route.

BEYOND PARTICLES

The immunotherapy of lung cancer causes a wide range of adverse effects whose treatment adversely impacts the Japanese government's overall healthcare expenditure. The delivery system being developed by Sato and his team should deliver a number of benefits, including: drive down the initial cost of therapy; reduce the frequency of costly side effects; and allow for the self-administration of therapy by non-invasive inhaler, thereby engaging the patient in self-care and eliminating the need for health care providers to deliver the medications by injection. Perhaps of greatest importance, local delivery should improve the efficacy of lung cancer therapy.

Sato and his colleagues hope that their projects will enable not only targeting of respiratory diseases but be expanded to use nano/microparticles (administered by inhalation or orally) to treat many additional illnesses. ●

Project Insights

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- RICOH Co., Ltd
- Boehringer Ingelheim GmbH

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BIO

Dr Takashi Sato's research examining the effect of silica particles on the lungs was the subject of his PhD degree from Yokohama City University Graduate School of Medicine, Japan in 2006. He worked in collaboration with Dr Shimosato under the guidance of Dr Klinman at the US National Cancer Institute, NIH, from 2005 to 2008 and from 2012 to 2014. During that period, Sato developed and tested the concept of using nano/microparticles as smart drug carriers for the delivery of drugs to the lungs. In 2014, Sato moved back to Yokohama City University to assume leadership of the project 'Development of a newly treatment modality for lung diseases by using innovative particle formation technology'.