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Addressing liver fibrosis with lipid-based drug carriers targeted to hepatic stellate cells

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appendix II



The adventure in Japan

Joanna E. Adrian
GUIDELines October 2005

Early morning: before the alarm clock rings, trucks coming to the small factory behind the house wake me up. The house is situated in a rather interesting neighbourhood, with a small paddock in front of the house, a large gambling palace and highway to the left, the aforementioned factory behind it and a quaint apartment building to the right. There's a small river running through this scene, in which a couple of turtles live. After the night on the futon, my muscles and bones are slightly sore. The bed is thin and rather cool, but this is not all that unpleasant given the warm nights here in Osaka. This is one of Japan's largest ports, and the heart of a metropolitan area second only to the megalopolis of Tokyo several hundred kilometres to the north. Not that my small apartment in the far north of the city really gives the impression of being located in a buzzing and relevant city. It's mainly the trucks that do the buzzing here.



South gate of the Suita campus of Osaka University



Graduate School of Medicine in Suita campus of Osaka University

After a quick shower and some breakfast, it is time to leave for the lab. It is sunny and rather hot already this morning. In the middle of the day, it will be 30 degrees. The Suita campus of Osaka University, my destination now, is 25 min by foot from my house. I walk uphill along a smelly highway, where the newest branch of the Osaka City Monorail is under construction. Its concrete tracks with magnetic propulsion system tower high above the road. Land is very expensive here, so it was cheapest to just build this futuristic rollercoaster above the road that the city already owned. On the ground, Osaka is a town designed for cars and not for bikes and pedestrians. The first have broad highways, spanning two levels or more where necessary. The last have to share narrow and bumpy pavements. Entering Suita campus itself brings relief though, it is quiet here. Only cars with special (and expensive) permission are allowed to enter the campus, and the institutes are surrounded by half wild ponds, patches of bamboo forest and, naturally, cherry trees. It is amazing how many of these there are around here. They grow everywhere, but you really notice them during the cherry

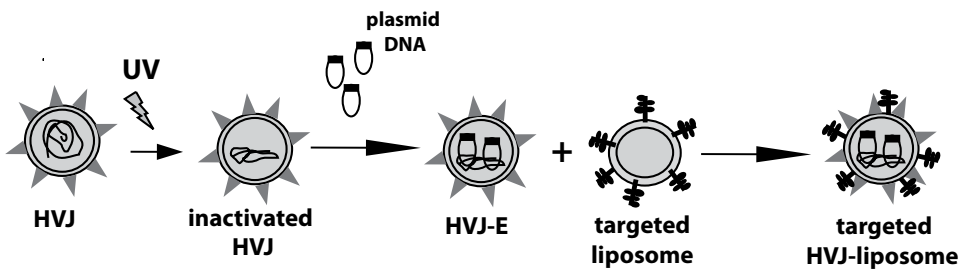
blossom time. It lasts only around a week, and Japanese people celebrate it by having mandatory parties on the grass below the cherry blossoms.

The institutes on the Suita campus are all related to the beta sciences and engineering. It is here, also, that one finds the Osaka University Hospital, the largest hospital of Osaka, and its Graduate School of Medicine, reputedly the best medical school in Japan. Within the rather monumental looking building of the Graduate School, I take the elevator to the tenth floor, the left wing of which houses the Division of Gene Therapy Science of Professor Yasufumi Kaneda.

The research of this group focuses on using the Hemagglutinating virus of Japan (HVJ,

or Sendai virus) as vectors for gene therapy. The major advantages of HVJ are its high transfection activity in various types of tissues and its being non-infectious for humans, which makes HVJ vectors potentially usable for medical purposes. HVJ enters the cell by fusing with the cell membrane, a process which is mediated by the virus' membrane proteins. Reports from the laboratory of Professor Kaneda showed that HVJ can also fuse with liposomes (lipid vehicles) containing plasmid DNA. As a result of this fusion, viral proteins are introduced into the membrane of liposomes, significantly increasing transfection activity of these liposomes.

For my PhD project, under the supervision of Klaas Poelstra and Jan Kamps, I'm working in two departments: the Department of Pharmacokinetics and Drug Delivery, and the Medical Biology section. The aim of this project is the development of liposomes targeted to the hepatic stellate cells in the fibrotic liver. In a diseased organ, these cells produce large amounts of collagen, making them attractive targets for anti-fibrotic therapy. One of the approaches to the treatment of fibrotic livers would be gene therapy. In November 2004, I wrote a mail to Professor Kaneda, proposing a research project which combines the high transfection efficiency of HVJ with the targeting properties of our liposomes. Professor Kaneda accepted my proposal, and invited me to perform experiments in his laboratory. Since HVJ vectors lack cell specificity, the aim of the study was to investigate whether fusion of HVJ with our targeted liposomes will form HVJ liposomes characterised by both specific interaction with certain cell types and good transfection activity.



The concept of creating new targeted particles. After inactivation of viral genome with UV light, to HVJ envelop (HVJ-E) plasmid DNA is incorporated. In the next step HVJ-E is fused with targeted liposomes. Protein which is covalently coupled on the surface of liposomes provides specific recognition of these liposomes by the target cells. In the final step cell targeted HVJ-liposomes are formed. They contain protein from liposomes and virus as well as plasmid DNA, and can efficiently transfect target cells.

Every morning, when I enter the lab, I'm greeted by a cheerful *ohaiyo gozaimas!* (good morning!) from Okuno-san, one of the technicians. In this group, there are between 30 and 40 people, but only two technicians. Here, everybody is doing all their experiments by themselves. In spite of the grandeur of the building on the outside, the laboratories themselves are small and filled to the absolute limit with people, laboratory animals, equipment and chemicals. It all looks rather chaotic and there isn't much free space, like most of Osaka. But it's the people that matter more than things, and the people here are very friendly. Their hospitality is great and they are always willing to help. Fortunately, they have a lot of opportunities to help me. It is not just that it is a new lab for me – it is a

Japanese lab to boot! This means manuals, protocols and software are most often written in unreadable Japanese, just like catalogues, forms, ordering systems, group seminars and many other large and small things (like labels on waste containers). It was sure to make working here a lot of fun, of the confused and adventurous sort. Unfortunately, not all people in the group speak much English either. On the other hand, working here can be fast and efficient, mainly because of the very short delivery times of ordered items (often only one or two days) and the free access to all kinds of equipment.

Lunch time is around one o'clock in the afternoon, when I buy a sandwich in the shop and join some colleagues that are eating in the seminar room. The typical Japanese lunch consist of rice or noodles with some fish or sea weeds or other kind of sea animal and a bit of vegetable. To drink, green tea is most popular. It can be bought everywhere, even from vending machines, and several kinds are usually available. After lunch, I have a meeting with Professor Kaneda. Although he is very busy person, he has time for me whenever I need it, and provides me with all the help he is able to give. Our discussion is short, but contrite and interesting as usual. He has been educated as a medical doctor, and his opinions are therefore often coming from different point of view as mine, or those of my supervisors in Groningen. I learnt a lot from him.



Sweets eaten before drinking traditional green tea

I work until six o'clock, when I walk to the large cafeteria at the centre of the campus for dinner. I can try Japanese dishes here, and it is actually cheaper then cooking by myself.



Kiomizudera temple, Kyoto

Luckily, the menu is exhibited on the wall and each dish is described by names in both Japanese and Latin writing, and accompanied by a picture. This time, I take *tamagodon* (a bowl of rice, with scrambled eggs and vegetable on top) and *miso suru* (a kind of soup, based on fermented soybeans). After dinner, I go back to the lab. Early in the evening, it is still hot and almost dark. The night comes very fast here, even in the middle of summer. Of course, the laboratory is still full of people. The atmosphere is good here, everybody seems to enjoy being at work and nobody is in a hurry to go back home. I chat a bit with a colleague about the lab party which took place yesterday in the luxurious apartment of one of the associate professors. She, like some other people in the lab, is a medical doctor and she works in the hospital as well. Sometimes she needs to recuperate during the long day at work, and then she sleeps on her desk for about half an hour. She's always a bit worried that the professor will see her sleeping like that, because it is important, in the hierarchy of the lab, for your superiors to have a favourable impression of you. Of course, the professor knows, but he is understanding enough to pretend never to notice. Around ten o'clock it's rush hour on the campus and people are going back home.

On my way home, I pass a supermarket to buy some breakfast for tomorrow. As usual, I walk through the big section of sea food, which is like a free visit to the aquarium full of weird sea monsters. A bit frozen perhaps, but still quite interesting. The shops here have long opening hours, and if you forget something there are plenty of convenient stores that are open all night. However, this convenience is not quite extended to financial matters. For such an advanced economy, Japan is remarkably cash-oriented and one shouldn't expect to be able to pay with plastic anywhere. And unlike the stores, ATM's are open strictly during the day and one should be careful not to be too late for them.

Before I go to sleep, I talk with my mother using Skype. In Poland, it is now four in the afternoon. Tomorrow will be a Saturday, and I'm planning to visit some temples in Kyoto. The former capital of Japan is only thirty minutes by train from Osaka, but its character is totally different. It is a historic and cultural city, with some two thousand temples. On Sunday, I'm going to relax in an *onsen*, a traditional Japanese bath, and have a dinner in the neighbourhood restaurant where they serve the Osaka speciality of *okonomiyaki*, a small pancake of Japanese potatoes with oyster sauce, cabbage and bonito flakes. There's always something interesting to do here.

If I had to make the decision once again, I would again decide to go for a short research project to Japan. This experience belongs to those that happen only once in your life.

March-July 2005

