Ribozyme, quorum sensing... Opening the way from heresy to a leading edge through friendly competition

Interviewer: Hiroshi Murakami, research associate

——Professor Suga, you often tell me about your philosophy for research. Let me first ask you about your research philosophy because without discussing this it would be difficult to go into the details of research.

My philosophy is to do things that are heretical as much as possible. Be heretical. And when the level of consciousness of many people catches up, what has been considered to be heretical evolves into a leading edge. But it is very difficult to find things heretical and move ahead with them. When you do things heretical, you must be absolutely conscious that you are being heretical and you must be confident that your heretical attempt will eventually turn into a leading edge. Otherwise, you would not be able to carry on with your heretical endeavor.

Of course, I am sure that there are a number of people embracing heretical ideas. We must elevate our heretical idea and turn it into a leading edge before other people do so. That is our mission. Or I should say that it is the starting point of my research activities.

——Starting from there, how have you proceeded with your research?

I continued to study in Japan till I earned a master's degree from a graduate school. After that, I left for the United States. The biggest reason I went to the US was because at that time Japan had very few researchers who were studying both chemistry and biology at the same time, or those who were getting into the filed of biochemistry. I moved to the US in 1989. In the US, many researchers began to study both chemistry and biology from around 1985 and 1986, and this type of study already became a trend by mid-1995. Now, you can probably take such an approach in Japan. Back then in Japan, however, there were very few researchers who would consciously try to integrate knowledge and ideas from different domains to create something new.

——At that time, chemistry and biology were considered to be two completely different things, weren't they?

In the 1980s, that was how things were supposed to be in Japan. So, I went to the US and the first thing I did was research on catalytic antibodies. I began to work on the development of an enzyme, using antibodies. The late Professor Satoru Masamune, under whom I studied at the Massachusetts Institute of Technology (MIT), was a researcher specialized in organic chemistry. He had very aggressive ideas about biology or science in general and I learned lots of philosophy of science from him, that is, we must keep on trying something new. He was not at all interested in collaboration between industry and academia, though. Rather he was quite satisfied as long as he was doing things he was interested in and if these things were novel. Indeed, he was someone who truly deserved the title of scientist. Unfortunately, he passed away last year. In undertaking my research, I am sort of proclaiming myself as being his successor to carry on his will.

——And then afterward, you became a postdoctoral fellow.

I served as a postdoctoral fellow at Harvard Medical School / Massachusetts General Hospital (MGH). There I studied under Professor Showstack. The professor is specialized in biology but quite interested in chemistry, which I would say is the

point of our common interests. This is the ninth year since I became independent. But even today, what I studied over there in Boston remains the main theme of my study. That is catalytic ribonucleic acids (RNAs). The focus of my research has shifted from catalytic antibodies to catalytic RNAs, that is, from antibodies to nucleic acids, and to a technique to create artificial enzymes using nucleic acids. In this sense, my interests have been consistent. When I was studying under Professor Showstack, he was hardly known to those specialized in chemistry. In the field of biology, however, he was quite famous and has been often cited as a Nobel Prize candidate. He is only 10 years older than I am. But he had done a number of excellent works by the time I met him. Indeed, I found him very bright and brilliant. He is a kind of person who freely shifts from one domain to another and in this respect I was quite influenced by him.

Creation of a catalytic RNA is to explore the origin of life

——Now, let me turn to the evolution of catalytic RNAs. Professor Suga, could you tell me specifically how you set up and develop this theme?

After serving as a postdoctoral fellow, I moved to the State University of New York at Buffalo, where I took up an academic post and set up a laboratory. The project idea came from what I had in mind when I was a postdoctoral fellow at Professor Showstack' s laboratory. While I was a postdoctoral fellow, I could not achieve the goal I had set for myself. So, I was feeling compelled to attain that goal.

The goal was to artificially create a catalytic RNA or a ribozyme. Among various possible catalytic agents, I wanted to discover the one that enables a ribozyme to recognize a specific amino acid and induce the aminoacylation of a transfer-RNA (tRNA), i.e. to bind the specific amino acid with an RNA via an ester linkage. My original chemical interest in the creation of a catalytic RNA stems from my interest in the origin of life. Thus the project, in a sense, was an attempt to experimentally explore the origin of life.

Then, why does it have to be an amino acid? My interest centered on what bridges the "world of RNAs" and the "world of RNAs and protein" in the process in which the latter is born from the former. And I wanted to discover an enzyme that can serve as a catalyst in aminoacylation reactions, a process in which an RNA meets with an amino acid for the first time. Furthermore, I was thinking about the possibility of technical application to develop it into a catalyst to bind a non-natural amino acid with a tRNA. These are the reasons why I took up this topic as my research theme.

For the first two years or so after setting up the independent laboratory, things were very tough, for instance, with the physical space of the laboratory very limited. In 2000, however, we were able to publish in "Natural Structural Biology," for the first time in the world, the result of our experiment in which we were able to evolve a ribozyme that can catalyze the aminoacylation of a t-RNA. In 2001, we succeeded to evolve another ribozyme, which has the same catalytic function as the previous one but has a simpler mechanism, and we announced the findings in the "EMBO Journal." Then, in 2002, we succeeded to isolate another ribozyme in an experiment focusing on a different concept and we published the result in "Nature Biotechnology." As such, for three years in row after becoming independent, I was able to announce research achievements in major science publications, thereby making my name known to those engaged in this particular field of science.

In terms of evolution, we were coming closer to the completion of an ideal ribozyme. But we still wanted to further expand the technical aspects of the ribozyme. It was around that time that you, Mr. Murakami, joined us as a postdoctoral fellow at my laboratory. With your help, we made a major progress in developing technical applications. And now, we are here at the University of Tokyo to explore further development. For the moment, I am working with you, Mr. Murakami, and other staff at my laboratory on what I believe is a heretical project.

Also, we introduced a ribozyme that is capable of catalyzing oxidation reduction reactions in "Nature Structural Biology" in 2003 and we are currently trying to expand this idea to evolve yet another new ribozyme.

Quorum sensing, an interesting mechanism of bacteria

I am also engaged in another research project focusing on applications. This has nothing to do with RNAs and catalysts. This is an attempt to discover a new drug that can inhibit intercellular communication in gram-negative bacteria. This intercellular communication is called quorum sensing in scientific language. Pathogenic bacteria, such as Pseudomonas aeruginosa which is one of pathogens responsible for hospital-acquired infection, would not start doing any harm immediately after getting into the human body. Instead, they quietly increase in number. When the cell density reaches a certain level, however, they suddenly discharge toxin and attack the host, namely, the human body. For bacteria, quorum sensing is a gene manifestation control mechanism which they have acquired in the process of evolution in order to evade the immune system of human. On the other hand, seen from human infected with such pathogens, quorum sensing is a very troublesome system that enables bacteria to determine the best timing for an attack. In the US, research on such mechanism became a boom from around 1996 and a report to this effect was made shortly before I got the post at the State University of New York. Then, from around 1999, it became widely recognized that this mechanism is related to various aspects of pathogenicity. At my laboratory, we launched this quorum sensing project in 1998. We began to produce results from around 2002. Then, in 2003, we published two reports in succession in the January and June editions of "Chemistry & Biology." After returning to Japan, I have been working on this project jointly with a private-sector company in the form of

industry-academia collaboration. We will continue to work on the project through collaboration with our corporate partner, focusing on the development of a new drug as our ultimate goal.

——Professor Suga, I understand that you started this project, not with the intention of developing technical applications of quorum sensing or for the purpose of inventing a new drug, but out of your pure interest in the mechanism of quorum sensing. Am I correct?

As it turned out, the development of a new drug has become the ultimate goal. But yes, what prompted me to launch this research was my pure scientific interest in the very fact that bacteria have such an intercellular system. I believe that I am among the first group of chemists who have jumped on this subject. In this regard, I think that I started as a heretic and have been able to become a leading edge.

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Curriculum Vitae

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Associate Professor (2002-2003), Dep. of Chemistry, University at Buffalo.

Assistant Professor (1997-2002), Dep. of Chemistry, University at Buffalo.

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Links

Chemical Biology and Biotechnology laboratory
http://www.cbl.rcast.u-tokyo.ac.jp/

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Recent Publications

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