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Featured in this issue is Associate Professor Kiyotake Suenaga, whose research focuses on exploration of unknown substances from marine organisms.

Unknown substances from marine organisms are intriguing

Accelerating research for application to pharmaceutical development

How many substances are there on our earth? Associate Professor Kiyotake Suenaga of the Natural Product Chemistry lab makes an almost endless pursuit of unknown substances available from marine organisms, saying: "There must be an incredibly large number of effective substances yet to be discovered." A recent example of his discoveries is a substance isolated from cyanobacteria. It has been found that this substance has an action that is expected to be used for remedies against cancer and osteoporosis, thus opening up the possibilities of application for pharmaceutical development.

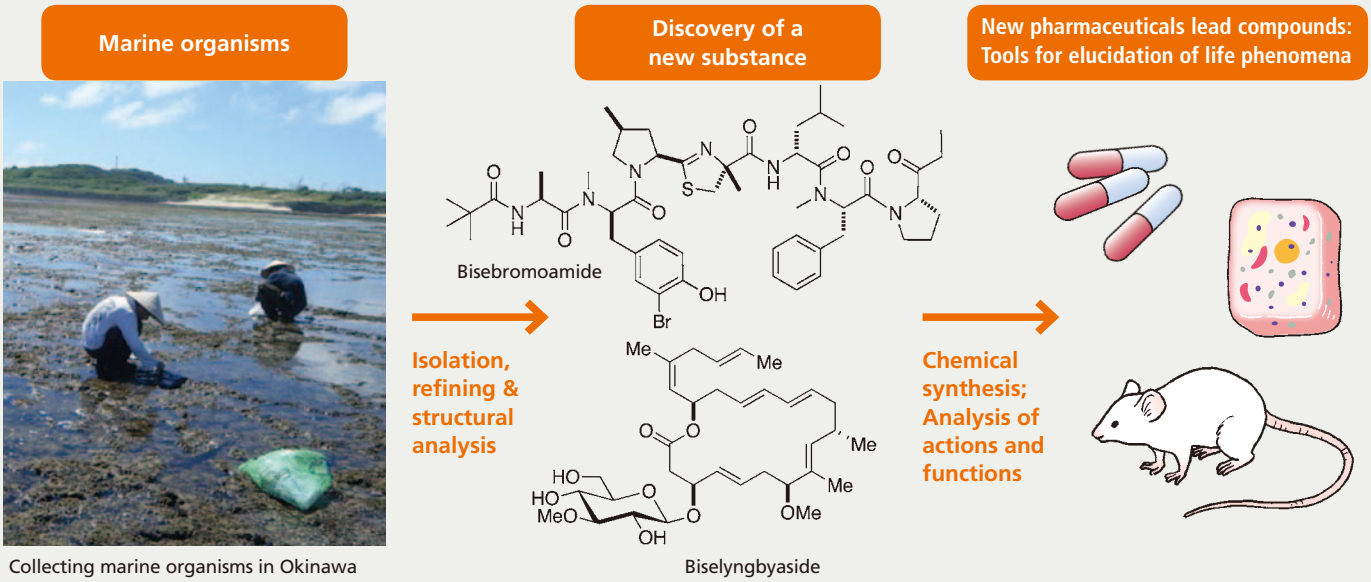
The beginning of the quest for unknown substances

A beach in Okinawa in May . . . A group of people, each wearing a long-sleeved shirt and a hat, was found intently looking for something under the glaring sunlight. This group was Associate Professor Suenaga and his students collecting marine organisms. The quest of unknown substances begins with an incredibly exhaustive work of gathering potential materials (Fig. 1).

Since Dr. Suenaga transferred to Keio University in 2006, he has been mainly collecting marine cyanobacteria. Cyanobacteria are a type of bacteria that have chlorophyll and perform photosynthesis. They are believed to have produced oxygen in the primeval times of the earth. Dr. Suenaga says that he chose cyanobacteria as his objective not because he felt special potential in cyanobacteria. "I had no particular theoretical reason for choosing cyanobacteria as my objective. No one knows that an exciting substance can be found in a particular organism," remarks Dr. Suenaga. Indeed, assumption is a taboo when it comes to exploration of unknown substances.

Fig. 1 Marine natural product chemistry

Some marine organisms contain substances that have a unique chemical structure and bioactivity unavailable from terrestrial organisms. Discovery of such substances is extremely important, not merely as discovery of new substances, but also because they can contribute to pharmaceutical development and shed light on living phenomena.



He continues: "If I dare to give a reason, it's perhaps because cyanobacteria were attached to seaweeds which were the food of sea hares I was studying as a college student." Sea hares are known to have a unique substance, which is considered to be their food origin. That's why cyanobacteria have weighed on his mind since then.

Anticancer activity as a bench mark

The total amount of cyanobacteria that has been gathered in the past five years is approximately 150 kilograms, from which essence is extracted, allowing a "target" substance to be isolated. Isolation is a process of purifying (Fig. 2), making full use of chromatography*1 and other sophisticated techniques in the state where no substances other than the target are mixed. The bench mark for Dr. Suenaga to choose a target is whether the substance in question has an anticancer activity *2 or not. Therefore, most of the substances Dr. Suenaga has chosen thus far have an anticancer activity.

Then he proceeds with the examination of the target substances based on their chemical structures. Use of a nuclear magnetic resonance spectrometer (NMR)

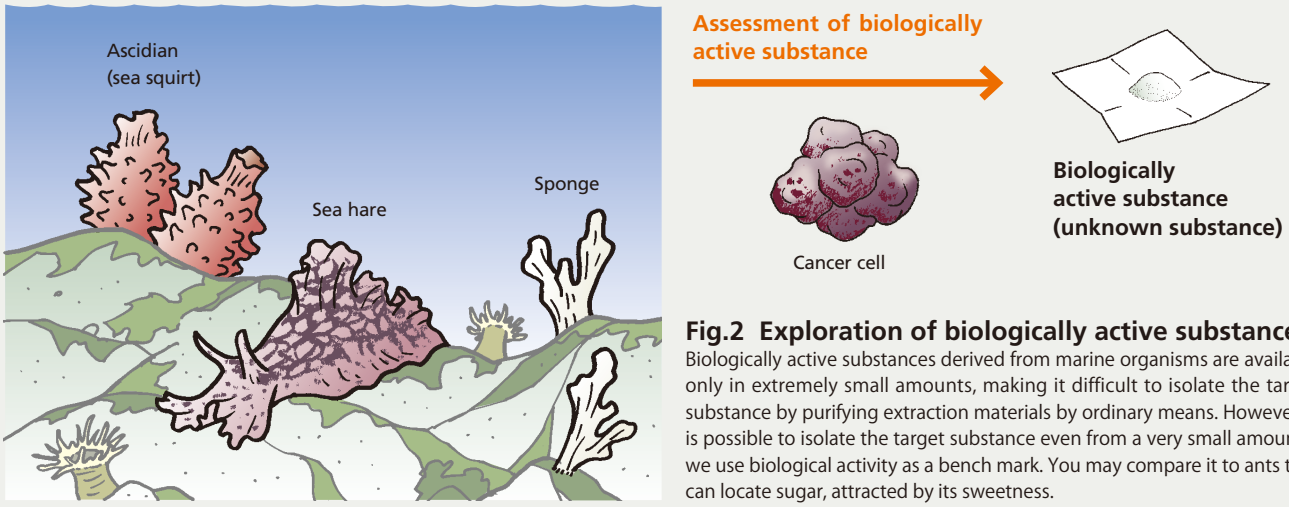


Fig.2 Exploration of biologically active substances
Biologically active substances derived from marine organisms are available only in extremely small amounts, making it difficult to isolate the target substance by purifying extraction materials by ordinary means. However, it is possible to isolate the target substance even from a very small amount if we use biological activity as a bench mark. You may compare it to ants that can locate sugar, attracted by its sweetness.

installed at the Keio campus enables a substance's chemical structure to be identified in a short period of time. If the chemical structure of a given substance is too complex, an NMR with higher resolution, available outside the campus, may be used. More specific aspects of the substances are determined based on their reactivity and crystal structure analysis. Once the structure has been identified, you can determine whether the substance is really unknown.

Bisebromoamide was the first substance discovered from an extract of cyanobacteria through such an exploration process. "We named it 'Bisebromoamide' because it was an amide containing bromine (Br) and found in cyanobacteria which were gathered in the seaside Bise district of Okinawa," says Dr. Suenaga. He makes it a rule to give a substance he has discovered a name based on the place of discovery and/or the main characteristic of its molecule. Bisebromoamide was successively followed by the discovery of biselyngbyaside and leptolyngbyolides. And even a fourth substance is likely to be discovered before long.

That said, each of these substances is available in only an extremely small amount (several milligrams to several tens of milligrams). This makes it difficult to make detailed investigation into properties and actions of these substances. As a solution to obtain sufficient amount of substances, Dr. Suenaga is attempting artificial chemical synthesis. Synthesis methods for bisebromoamide and biselyngbyaside are expected to be established soon.

Key points for successful research

Dr. Suenaga's research work now appears to be progressing smoothly. But he could not find any promising substance at all in the first two years. There are countless marine organisms. Why didn't he switch to other organisms? "To tell the truth, I had been dealing with other marine organisms in my early years, but I couldn't achieve visible results. That's why I switched to cyanobacteria. Therefore, the idea of giving up cyanobacteria in a mere two years or so didn't occur to me at all." It seems that exploration of unknown substances also requires tenacity and toughness.

A turning point came to him when he began collecting cyanobacteria of different varieties from what he had been focusing on. "When talking about cyanobacteria, we tend to think, first and foremost, of those outstanding ones like impressive green algae. Having spent two years looking only at cyanobacteria, however, I suddenly noticed that cyanobacteria also exist that are plain and less conspicuous," he remarks. This change in approach fueled his advance.

Substances derived from marine organisms: a focus of attention

"Among the many substances I know, bisebromoamide is unique in that it contains D-amino acid, bromine (Br) and t-butyl group." Substances derived from marine organisms are intriguing not merely because of their structures. Dr. Suenaga continues, "Recently I'm often asked by researchers of my acquaintance, 'Do you have any interesting substance?' So I send a sample. Later on, I receive a report from that researcher saying that he/she found a particular action." For example, Prof. Je-Tae Woo of Chubu University informed him of the possibility that biselyngbyaside might become an effective remedy for osteoporosis.

Osteoporosis is a disease for which no effective remedy has been found to date. So biselyngbyaside has come to the fore as the key substance for an osteoporosis remedy. Dr. Suenaga humbly says, "Although I can gather and isolate unknown substances, I'm not in an environment where I can examine all of them in detail as to what actions these substances have. So I really appreciate other researchers' efforts and support in this regard." Despite his humble comment, it may not be an exaggeration to say that such a co-research framework can exist only because the substances discovered by Dr. Suenaga have been intriguing enough.

On March 23, 2011, the *Chemical Daily* ran an article reporting that full-scale pharmaceutical development endeavors would be undertaken using the substance discovered by Dr. Suenaga. Adding "Pharmaceutical development requires the highest possible safety and efficacy," he appears to be not placing too much expectation on the proposed pharmaceutical development and is determined to steadily pursue his research work. Yet, at the same time, he proudly says "Should it fail to come to fruition as a new drug, the significance of continuing in-depth quest of unknown substances remains unchanged because it will eventually help to shed light on mysteries of life phenomena."

"Many marine organisms have no shells to protect themselves and are slow in moving, making them apparently defenseless. Despite that, they are surviving. Decades ago, some scientists thought that such organisms must have a certain kind of defensive substance that enables them to survive despite their apparent weakness. This is believed to be the starting point of exploration of unknown substances peculiar to marine organisms. I'm not sure if this hypothesis is true or not, but as far as my research endeavors are concerned, I can confidently say that marine organisms do have many intriguing substances that are not yet known to us," concluded Mr. Suenaga. Natural product chemistry is bound to attract more and more attention in the years to come.

(Reporter & text writer: Akiko Ikeda)

*1: One of the methods to isolate a substance utilizing differences in affinity with the carrier.
*2: An action that inhibits growth of cancer cells.