Artificial-molecule evolution, finding drug candidates, extreme early stage cancer diagnosis with PET (positron emission tomography) imaging, generating synthetic antibody substitutes

Masumi TAKI Laboratory

Masumi TAKI

Summary of Research

Developing Smaller Protein/Artificial Molecule Drugs for Fine Targeting and Extermination of Cancer Cells

Some 3 of every 10 deaths in Japan are said to be attributable to cancer, a rate that climbs year after year. Among the most pressing issues facing the medical industry is the early detection and effective extermination of cancer cells. However, it remains all but impossible to detect all metastasized cancer cells or to find cancer cells hidden in places that resist observation. Additionally, conventional chemotherapeutic agents tend to damage both normal and cancer cells, resulting in serious side effects. The antibody-type anti-cancer drugs that have emerged in recent years exterminate cancer cell with remarkable efficacy while dramatically reducing the risk of side effects. However, most of these agents have large molecular structures. In some cases, treatments have failed because the agents failed to reach the targeted cancer cells.

At our laboratory, we take a *chemo-biological* approach, an integration of synthetic organic chemistry and biological techniques supported by physical chemistry. Taking our hints from the antibodies produced by organisms, we seek to develop antibodies that offer functions added by chemical methods. We hope to identify applications in various fields. Specifically, we are currently carrying out research and development on a diagnostic drug whose particles are smaller than the antibodies produced by the body and will be capable of discovering hidden cancer cells, as well as therapeutic drugs that will kill cancer cells without adverse effects on normal cells.

Discovering Small Tumors and Generating Synthetic Peptides/Proteins/Hybrid Artificial Molecules That Bond Only to Cancer Cells

To make cancer cell detection as effective as possible, we take a strategy that involves introducing a non-natural amino acid that will emit positrons for a finite duration to the terminals of proteins or peptides that bind only to cancer cells. Once administered, these proteins/peptides rapidly search out and bind to cancer cells. We can then determine the locations of the cancer cells via positron emission tomography (PET) imaging. This method makes it possible to identify small tumors or cancer cells that would otherwise be overlooked by conventional X-ray diagnosis. (JST Development of Systems and Technology for Advanced Measurement and Analysis Program) As part of our strategy for developing antibody substitutes that affect only cancer cells, we must identify artificial hybrid molecules that bind only to cancer cells, then introduce antibody-derived molecules to their terminals to attract white blood cells. The goal is to administer this synthetic antibody substitute and to have it quickly find and bind to cancer cells. At the same time, the antibody-derived molecule attracts white blood cells, which engulf and isolate both the synthetic antibody and the cancer cell to which it has bound itself.

Continuous dispensing and rinsing apparatus essential when repeating experiments multiple times

This artificial hybrid pharmaceutical is expected to be highly biocompatible and to affect only cancer cells, with little or no adverse effects on healthy cells. (NEDO Grant for Industrial Technology Research)

Keywords

Chemical biology; organic chemistry; optical physics; cancer cells; proteins; peptides; non-natural amino acids; bacteriophage T7 virus; PET; positron emission tomography imaging; the NEXT-A reaction; the 10BASEd-T reaction; pharmacophore generation

Affiliations	Chemical Society of Japan; American Chemical Society; Society of Synthetic Organic Chemistry, Japan; Japanese Peptide Society; Molecular Biology Society of Japan; Japanese Society for Chemical Biology
Member	Masumi Taki, Associate professor

Advantages

A Simple but Powerful NEXT-A/10BASEd-T Reaction

The NEXT-A reaction technique developed by Associate Professor Taki is essential to creating these innovative synthetic proteins. The technique lets us synthesize hybrid molecules by a reaction occurred only at a single terminus of a biomolecule, like protein or peptide. The process involves mixing three biocatalysts in a test tube—L/F-transferase, tRNA (transfer RNA), and aminoacyl tRNA synthetase—and adding the biomolecule and a non-natural amino acid to produce the biomolecule conjugated with the amino acid. This extreme simple, fast-progressing reaction requires just mixing but no heating.

Using bacteriophages makes creating 100 million candidate drugs at the same time remarkably easy—a task that would take years if done manually. Taking advantage of a fundamental feature of biodiversity, wherein a substance (protein/peptide) produced by a virus always has a one-to-one correspondence with a gene, we can dramatically facilitate producing artificial hybrid molecules library (called 10BASEd-T). By using this drug-discovery system and the library, we can evolve the artificial molecule to make a novel pharmacophore. We can also create millions of new drug candidates by combining this procedure with our NEXT-A reaction.

An extensive background in chemistry gives Associate Professor Taki the capacity to design substances from an organic chemical approach; that is, he can use the protein/peptide produced by viruses and hybridize them to generate artificial molecules that bind more readily to cancer cells.

During the process of establishing the NEXT-A reaction, we have also synthesized a fluorescent amino acid excitable by visible lights. This amino acid has now been commercially available as a fluorescent peptide synthesizing reagent by Watanabe Chemical Industries, Ltd.

Future Prospects

Combining of the NEXT-A and the 10BASEd-T reactions

After finding the artificial molecule which can bind cancer via the 10BASEd-T, the artificial molecule can further be labeled by the PET probe via the NEXT-A reaction. Consequently, the artificial molecule would be useful for detection of the cancer at an extreme early stage.

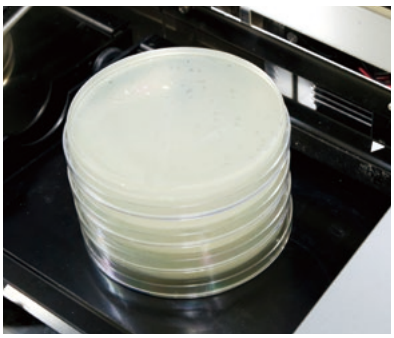
Biological Studies Unique to the University of Electro-Communications

Despite the limits of what we can achieve in the field of biology, we believe we can continue to push these limits forward by strategically combining the disciplines of biology and chemistry and adding human wisdom, thereby creating truly useful substances. The essence of chemistry lies in finding ways to form optimal bonds; from that basis, we hope to create innovative materials.

Having assumed his position at the University of Electro-Communications in 2011, Associate Professor Taki is a relative newcomer to the faculty. Nevertheless, he aspires to pursue research that can only be performed at our university. This includes plans to apply his chemo-biological knowledge to electrical and electronic materials and to elucidate the mechanisms that control information communication networks and transmission within the living body. His ultimate goal is to achieve success in biological studies unique to the University of Electro-Communications.

Centrifuge used to purify phage viruses and synthetic compounds

An ultraviolet-visible spectrophotometer that performs instantaneous multi-sample measurements



Culturing a phage virus infected with *E. coli*

Synthetic proteins and organisms (specimens) stored at -78 °C.