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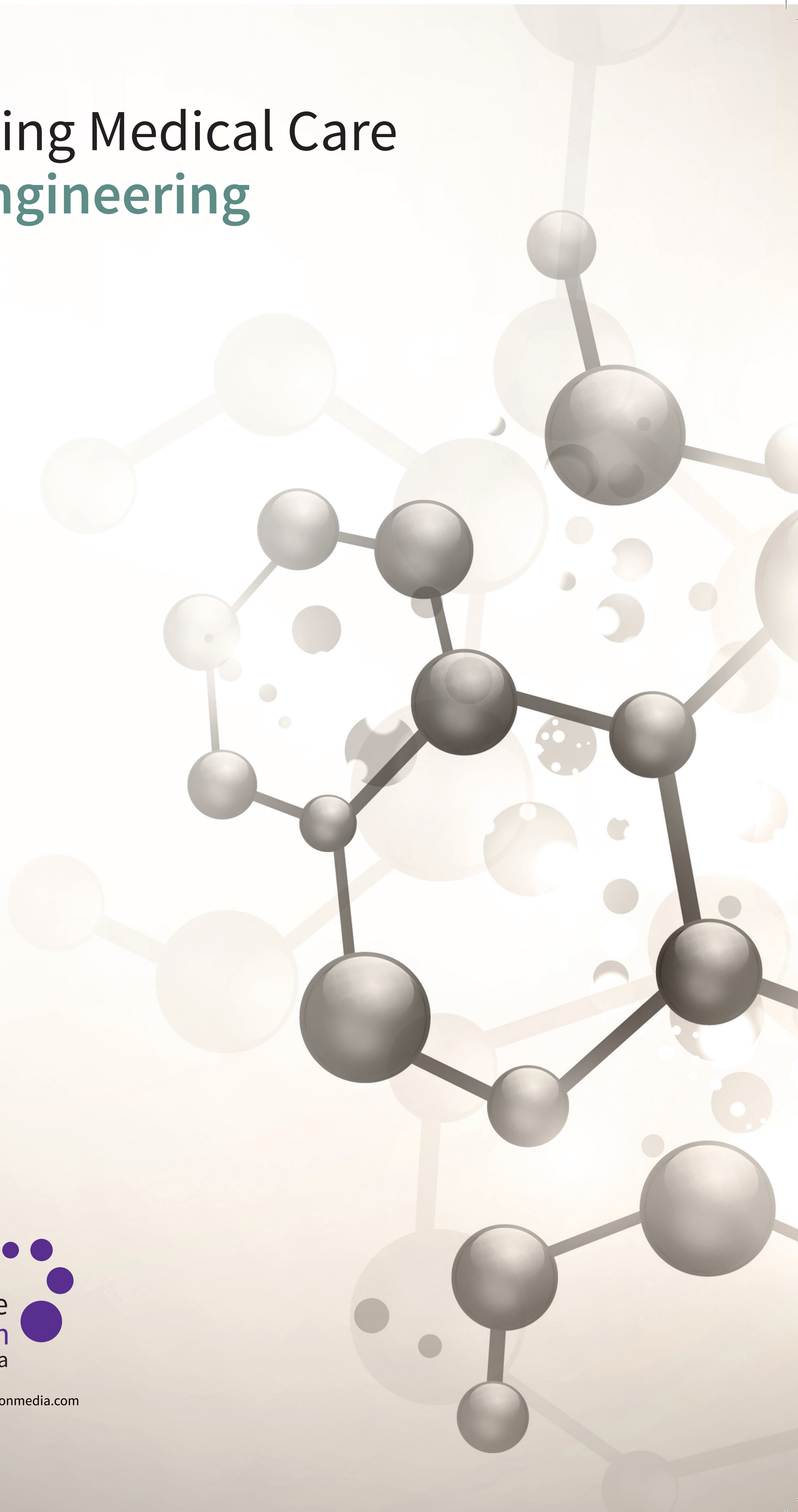
Improving Medical Care with Engineering

Professor Hiroshi Ueda



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Improving Medical Care with Engineering

Professor Hiroshi Ueda is a researcher at the Ueda Laboratory of the Tokyo Institute of Technology. Here he describes his work developing Quenchbody, a fluorescent dye-labeled antibody that can detect antigen for fast diagnosis of illnesses.

Ueda Laboratory members

To start, when did you develop an interest in biochemistry?

Since my father was a medical doctor, I have been interested in the working mechanisms of the human body since my high school days. However, I chose my major in chemical engineering, since I was also interested in engineering. I also happened to meet a very interesting professor, who had been a radical anti-pollution activist but had just started a career teaching biotechnology. Since then, I focused my studies on the biochemistry and biotechnology of antibodies. This interest was a gift from the professor, and is my life's work. Fortunately, antibodies continue to be one of most useful proteins in this area, in view of diagnostics and therapeutics.

Can you tell me more about the Ueda Laboratory? How and why was it established?

I was given my "Protein Engineering" lab as a PI about 12 years ago in the School of Engineering, University of Tokyo. There I worked for 10 years, and moved to my current affiliation (Chemical Resources Laboratory, Tokyo Tech) 2 years ago. One of my key interests has been the effect of antigens on the stability of antibody fragments. In many antibodies, when the antigen binds to it, the antibody structure is stabilized through the bridging effect of its two (heavy and light) chains. Based on this phenomenon, I found that antigen concentration can be measured by measuring the interaction strength of the two chains. This principle also constitutes the background of our new biosensor "Quenchbody (Q-body)".

Do you or your research team have any plans to help disseminate Quenchbody into hospitals or other medical facilities?

Not yet at this moment. However, since we are developing Q-bodies to several diagnostic markers in collaboration with a diagnostic company, it is probable that our team will go for this direction in near future.

Who funded the Quenchbody research? Did you have any difficulties gaining funding?

The Q-body was first discovered during the academia-industrial collaborative "Metropolis Area" project funded by the Japanese government about 6 years ago. At that time, we were collaborating with a small venture company "Proteinexpress" that has a specialty in site-specific chemical labelling technology using a cell-free protein synthesis system. However, the problem was that the company was not making enough profit due to small sales of reagents. After the end of the project, a most difficult time followed. What happened was that the key collaborator (Dr. Ryoji Abe) in the company could not get a salary for months, and a researcher in my lab (Dr. Hiroyuki Ohashi) had to quit the lab due to the same reason. Afterwards, the company found an angel who decided to buy the Q-body division of the company, and the R&D of Q-body has been funded and continued by the angel (Ushio Inc.) to date.

Do you have any key collaborators? What has been their involvement?

As already written, Ryoji and Hiroyuki are now working with Ushio Inc., and we are collaborating mutually in order to develop practical Q-body assays and associated technologies for the sake of our bright future. I think the keys to success exist both in science (biochemistry and chemical biology) and in the market. It is quite an exciting challenge. Hopefully, we can find more collaborators for the latter aspect.

Do you have plans for future projects? If so, can you say what they are?

The future of Q-body is a secret for now :-). However, I am also interested in bioluminescent protein-based sensors. The concept is to divide the enzyme (luciferase) reaction into two by introducing mutations, not by the dissection of polypeptide, to make two mutants. Based on this novel concept, I already published two papers for protein-protein interaction detection in *Analytical Chemistry*. I hope this concept is utilized to regulate the activity of many other enzymes.

Is there anything else you would like to add?

About 16 years ago, I was a visiting researcher in Cambridge, MRC-LMB, UK, for two years under the guidance of Dr Sir Gregory Winter (One of the founders of human antibody technology and also Master of Trinity College now). Although my work at that time was not very successful, to be honest, I really enjoyed the academic and also innovative atmosphere of the lab and the Cambridge area. This attitude constitutes the backbone of my research going forward.

Quenching Patient Doubts

The Ueda Laboratory at the Tokyo Institute of Technology, with funding from Ushio Inc., recently developed a new, award-winning biosensor that uses fluorescence quenching to quickly detect antigens. Its speed has the potential to greatly reduce stress for patients who may need a diagnosis.

WHAT IS FLUORESCENCE QUENCHING?

Scientists have discovered certain dyes that fluoresce, or glow, when they undergo certain chemical reactions or while traveling through the human body. In medical science, they are often attached to specific molecules so that the molecules' progress through the body can be tracked. When the molecules get physically close to a certain substance, or substances, the fluorescence is "quenched", or weakened, and does not glow as brightly as it previously did. With the knowledge of where and when quenching occurred, scientists and doctors can determine what is happening inside a patient's body. Fluorescence quenching happens one of two ways; it is caused either by energy transfer or electron transfer. In the case of energy transfer, two dyes of different colours are tracked as they travel through the body. Where the two dyes interact or get very close to each other, the fluorescence reduces and it is possible to directly see their interaction or measure the distance between the dyes all the way down to the nanometre level. Electron transfer, on the other hand, is only possible with molecules that give electrons to other molecules or receive electrons from other molecules through chemical reactions. Electron transfer is measured at the angstrom level. Angstroms are typically used to express the size of single atoms or molecules, making these measurements very small and precise.

Professor Hiroshi Ueda's lab at the Tokyo Institute of Technology recently used this concept to develop an extremely useful new biosensor device, named Quenchbody, which is a fluorescent dye-labeled antibody, detecting antigen. Medical tests that look for the presence of certain molecules are called "immunoassays", and they are often used to detect antigens. Antibody-based diagnoses are advantageous to medical professionals because they can be used to prepare personalized medicines that target specific, disease-related molecules. Antibodies interact strongly with other molecules, and the reactions are very specific, making antibodies good for the disease they are attempting to fight. Currently, however, the immunoassay process takes hours to complete and receive results. Not only are there multiple steps to complete the tests, but they also require a long incubation period to wait for certain chemical reactions to complete. Waiting for a diagnosis can be an incredibly stressful life event, so a quick test result goes a long way to improving the health care experience for patients. It also frees doctors from the laborious, time-consuming testing process, allowing them to spend more time with patients or on more difficult projects.

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QUENCHBODY

Quenchbody operates using electron transfer fluorescence quenching. It allows doctors or researchers to detect the binding of an antigens to an antibody fragment. Antigens are substances that cause the body to produce antibodies. In this case, tracking which antibody the antigen becomes attached to indicates a certain disease. Quenchbody can detect both small and large molecules like proteins, so the biosensor will be able to diagnose a very wide range of illnesses. In theory, it can detect most of the commonly diagnosed diseases today, so its potential application and impact on the medical system is tremendous. What used to take hours now only takes seconds or minutes, so diagnoses can be made desk-side or bedside, while the patient is with their doctor.

One or more dyes are chemically attached very near to the antigen binding site of an antibody. The dyes are placed on specific spots depending on what antigens need to be tracked. If no antigen attaches to the site, the dye stays where it was chemically placed, and will be quenched by tryptophan residues in the antibody. If an antigen binds, the dye gets "kicked off" the antibody molecule, because the antigen stabilizes the antibody and displaces the dye molecules. When the dye is expelled, it emits fluorescence. Tracking the activity of the dye allows medical professionals to quickly determine what antigens are attaching to which antibodies. Different colours can be used for different antibodies to distinguish between them, for example, or a single Quenchbody test can determine the presence or absence of a single antigen.

In addition to diagnosing disease, collaborator and project funder Ushio Inc. has used Quenchbody to detect and identify many drugs including narcotics and toxins. The potential applications of Quenchbody are enormous, and may improve the day-to-day operations of many different medical industries.

AWARD-WINNING TECHNOLOGY

Quenchbody has already won the Student Award at the annual meeting held by the Society of Chemical Engineers. The prize was awarded to Takuya Kawamura, a student of the Ueda Laboratory. The project specifically focused on the detection of a cancer-related membrane protein, called claudin, by Quenchbody. The project was originally developed by Professor Masuo Kondoh, a collaborator of Professor Ueda's who specializes in claudin research. The two met at the Antibody Engineering meeting held in San Francisco three years ago, while Professor Ueda's student was working unsuccessfully on a very similar project. He subsequently decided to change his research plan to focus on claudin. With help from Professor Kondoh's group, who provided antibody clones and generously shared previous work with Kawamura. Now, doctors helping patients who may have cancer can simply stain the claudin antigen on the cells just be applying Quenchbody to the supernatant (the supernatant is the liquid that cells are suspended in during culture and growth). Quenchbody claudin tracking does not require any washing steps, a process that significantly slowed previous immunoassay diagnosis tests. In addition, Ushio Inc. and Ueda Lab members recently received an Innovative Technology Award from a Japanese press Fuji Sankei Business I (July, 2015). In the ceremony they received the prize from Hisako, a Japanese Imperial family member who recently addressed the IOC, delivering Tokyo's opening speech of the presentation.

It is not surprising that Quenchbody has already begun receiving awards. Its ability to relieve patient stress is significant. Even in the event of a positive diagnosis, patients can begin treatment as opposed to waiting in suspense. More significant, however, may be its impact on medical professionals. Expertise is a resource that should not go to waste, and time-consuming testing procedures take up valuable time, especially when there is a better option available. In addition, doctors and patients can be together for the few seconds or minutes it takes for the results to appear, allowing for more communication between the two and relieving patient stress even further. The Ueda Laboratory and their collaborators quickly and competently reacted to the needs of the medical community, and their continuing contributions will play an important part in shaping the future of medicine.

Researcher Profile

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Professor Hiroshi Ueda studied at The University of Tokyo, where he earned his PhD in chemical engineering. He has received both the Research Award and Promotion Award from the Society of Chemical Engineers in Japan, the Hot Article Awards from the Japan Society for Analytical Chemistry, and the Nagase Science and Technology Promotion Award. He currently teaches at the Tokyo Institute of Technology where he specializes in protein engineering of antibody and other molecules with the aim of biosensing and diagnostics. Professor Ueda is also an expert in immunoassay, bioluminescence, and combinatorial technology.

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