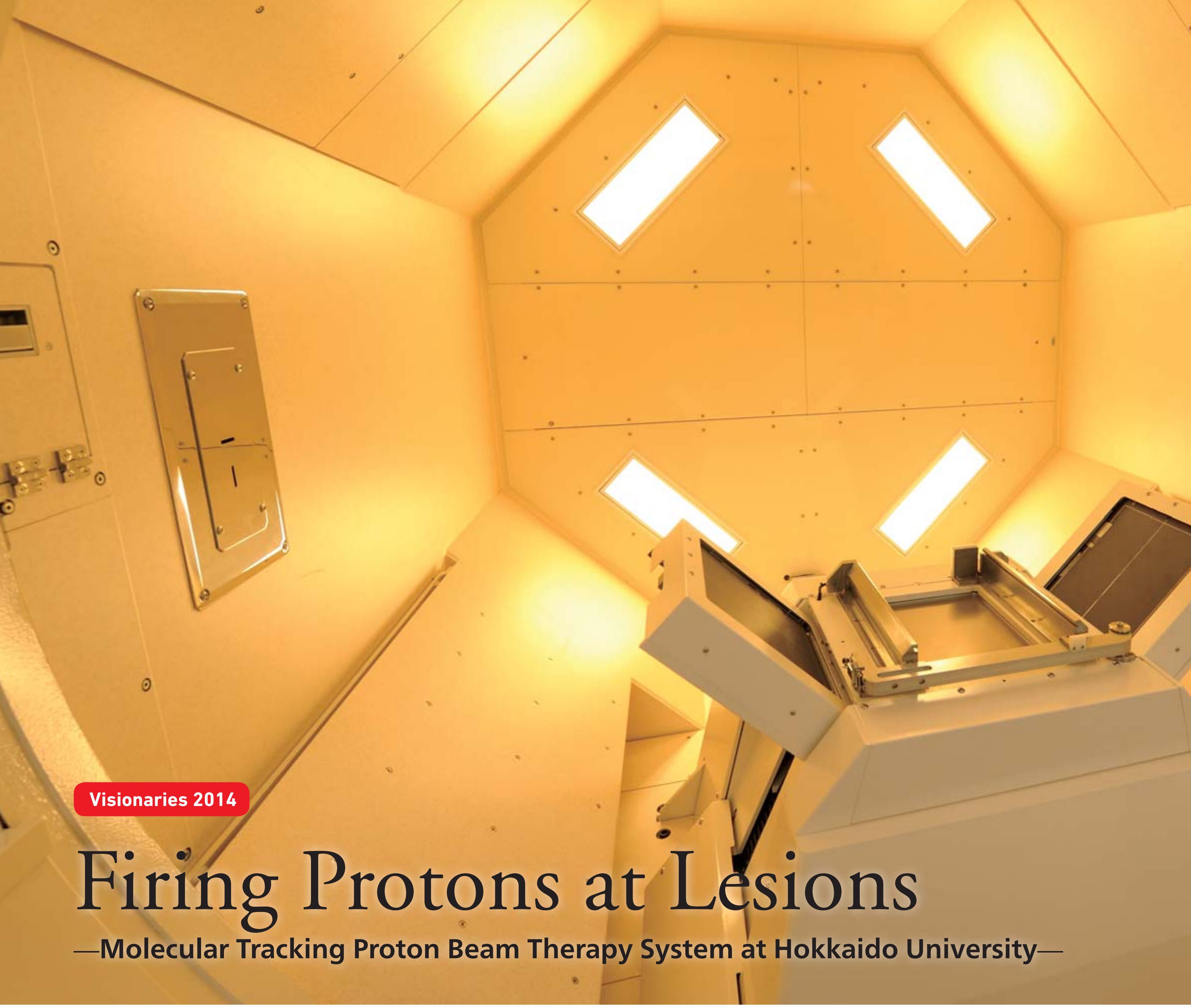


Visioneries 2014

Firing Protons at Lesions

—Molecular Tracking Proton Beam Therapy System at Hokkaido University—

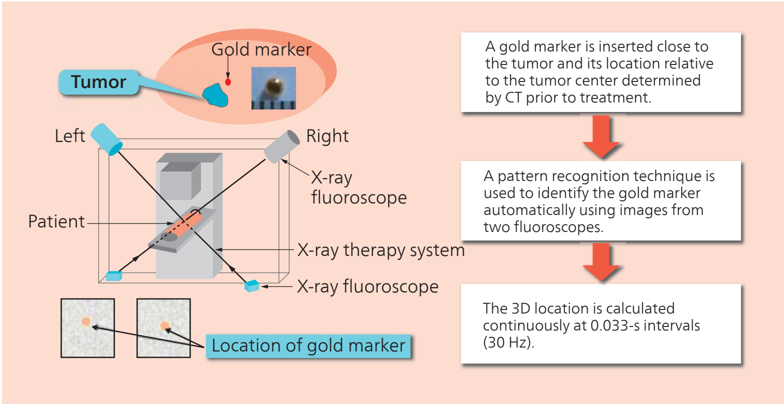
**Radiotherapy is widely used as a treatment for cancer (malignant tumors) that has minimal side effects and imposes only minimum stress on the body.
Despite this, the remaining challenges include the effects it has on healthy tissue and the problems of dealing with large tumors or ones that move about due to respiration or other bodily movement.
Hokkaido University and Hitachi, Ltd. have jointly developed a molecular tracking proton beam therapy system that can treat large tumors in internal organs that move.
The result of a decade of collaboration between the two partners, the new system is smaller and less expensive than previous proton beam therapy systems. It has attracted interest from around the world due to the improved cancer cure rates it offers and the potential to broaden the appeal of particle beam therapy.**

Keeping Track of Movement

Passing through the entrance to the hospital that occupies a corner of Hokkaido University's sprawling campus and looking straight ahead past the main hospital building, a brand new building is visible with a prominent sign identifying it as the Hokkaido University Hospital Proton Beam Therapy Center*. This leading-edge facility for molecular tracking proton beam therapy has been constructed jointly by Hokkaido University and Hitachi, Ltd. since 2010. Work on finishing the light-brown interior decoration and on commissioning the various equipment and systems in preparation for the commencement of treatment in March 2014 is now proceeding at a rapid pace.

A major feature of the system is its combination of techniques for accurately tracking a moving lesion and techniques for targeting the proton beam with high precision. Professor Hiroki

Careful adjustments are being made at the Proton Beam Therapy Center in preparation for the commencement of patient treatment.



Realtime tumor-tracking radiotherapy developed by Professor Shirato' s research group. The technique can significantly reduce effects on healthy tissue when irradiating a tumor at a moving site.

Shirato (Department of Radiation Medicine of the Hokkaido University Graduate School of Medicine), who is the project leader, described the development process as follows.

"**Radiotherapy**[a] is a form of non-surgical treatment that can preserve the form and function of the organ being treated, and has a low level of side effects on the patient's body. A major challenge, however, is how to deal with moving tissue. The pin-point irradiation of lung or liver tumors, for example, is made more difficult by the fact that they are in continuous motion due to respiration and digestive system movement."

Hokkaido University Hospital is located in a corner of the university' s sprawling campus near Sapporo Station.

In response, Professor Shirato's research group developed a technique for **realtime tumor-tracking radiotherapy**[b] in 1998.

This succeeded in significantly reducing the effect of radiation on healthy tissue.

Because X-ray dosage gradually attenuates as the rays penetrate deeper into the body, being at its highest at the point of entry, it has a significant impact on healthy cells upstream of the tumor. Intensity-modulated radiation therapy was developed in response to this problem. It is a technique for improving cure rates and expanding the scope of application of the therapy by maximizing the dosage applied to the tumor while using a computer to manage and control the radiation dosage received by healthy tissue. When combined with realtime tumor-tracking radiotherapy, it allows radiotherapy to be used on moving tumors.

"Unfortunately, this still left the problems that X-rays are not particularly effective for some types of cancer cell, and that they are difficult to use to treat large tumors of more than 6 cm," said Professor Shirato.

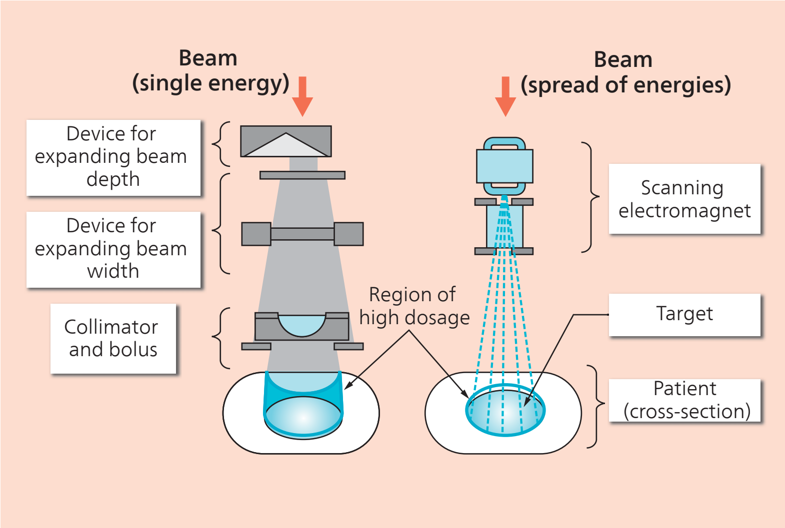
Bringing into Focus

Particle beam therapy systems have been

Professor Hiroki Shirato

(a) Radiotherapy
Along with surgery and chemotherapy, radiotherapy is a form of cancer treatment that uses either a photon beam (X-rays or gamma rays), electron beam, or particle beam (beams of protons or carbon ions).

(b) Realtime tumor-tracking radiotherapy
A technique for targeting radiotherapy beams. The location of a gold marker inserted close to the tumor is determined using two X-ray fluoroscopes and the beam only turned on when it is within a few millimeters of its intended position.



Spot scanning can accurately target the proton beam on tumors, even those with complex shapes.

(c) Spot scanning
A technique that interrupts the particle beam to irradiate sites point-by-point. It requires technology for generating a uniform proton beam and for controlling the beam with high accuracy.

(d) Funding Program for World-Leading Innovative R&D on Science and Technology
A research funding program for advanced research that seeks to lead the world, with the aims of enhancing Japan's international competitiveness over the medium to long term and delivering the fruits of research and development back to people and society. A request for submissions was issued by the Council for Science and Technology Policy of the Cabinet Office in 2009 and the top 30 of the 565 proposals received were selected.

attracting attention for offering a new generation of radiotherapy. Unlike X-rays, which are a form of electromagnetic radiation, matter particles have a low level of intensity after entering the body. Instead, the dosage is at its maximum (called the Bragg peak) at a depth determined by the energy of the accelerated protons. Because the dosage attenuates rapidly after this peak, it is easy to concentrate the dosage on the tumor and keep the effect on surrounding healthy cells to a very low level. Nevertheless, the radiation can kill cancer cells or destroy their ability to reproduce, even in large tumors.

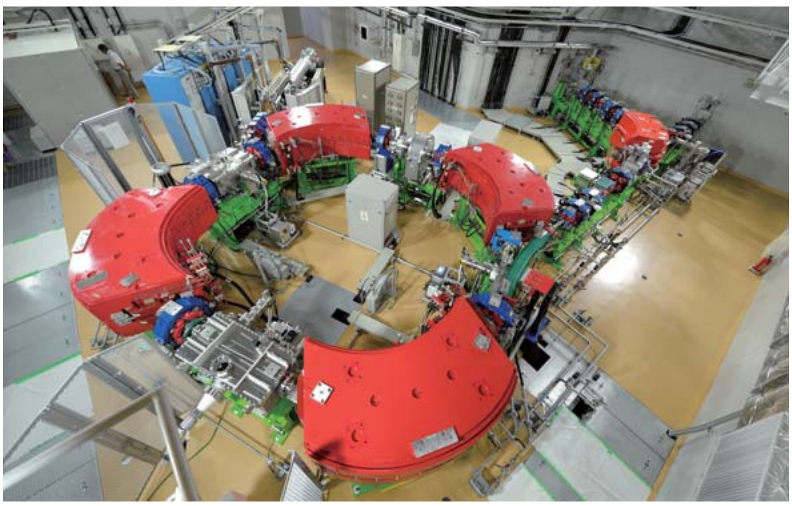
Professor Shirato's research group started studying particle beam therapy systems around 2000. He commented as follows.

"Our fundamental idea was that particle beam therapy systems would become part of general medicine, just like X-ray therapy systems. Because the equipment back then was so large and expensive, it was not easy to install. Accordingly, our aim was to create a system that could be installed in the limited space available in a hospital, and to minimize its up-front and operating costs."

To this end, they embarked on basic research in conjunction with Hitachi. As part of this work, they looked at a proton beam therapy system that Hitachi supplied to The University of Texas MD Anderson Cancer Center (MDA) in the USA. The MDA system uses a new technique called **spot scanning**[c] that focuses on the tumor and progressively targets it with repeated short bursts of a tight beam of protons. Compared to the double scattering method used in the past, it can target the proton beam on tumors with high accuracy, even those with complex shapes. In addition to minimizing the effect on nearby healthy cells and not requiring the production of patient-specific items (collimators and boluses), its features include making efficient use of the proton beam with minimal extraneous radiation. The objective now is to combine this with realtime tumor-tracking radiotherapy to develop a new generation of proton beam therapy systems that can deliver accurately targeted radiation treatment even for large lung or liver cancers with volumes of 1 L or more.

Meanwhile, the **Funding Program for World-Leading Innovative R&D on Science and Technology**[d], a national project that seeks to deliver world-leading results, issued a call for submissions in 2009. With Professor Shirato as lead researcher, Hitachi participated in a proposal entitled "Sustainable Development of Molecular-Tracking Radiotherapy System" that was selected among the top 30.

Unfortunately, the government funding budget was subsequently cut by more than half, leaving Professor Shirato with the job of cancelling the project. However, Hitachi at that time was looking at the prospects for bringing the world-first spot scanning system that had been implemented at MDA to Japan. For the project to be cancelled would be a major setback. Presented with this situation, Fumito Nakamura (General Manager, Particle Therapy Division, Power Systems Company, Hitachi, Ltd.), who manages the proton beam therapy system business, made the decision to continue with the work despite the tight budget.



A synchrotron (shown here) uses electromagnetic force to accelerate protons obtained from hydrogen and deliver them to the treatment room.

Change of Thinking

With the primary objective of the joint research being to produce a compact and low-cost proton beam therapy system, it was felt that making further cost reductions within the short three-year development schedule would be difficult. What made it possible was the reduction in size of the synchrotron (accelerator) unit at the core of the

View from the rear of the treatment room as the gantry rotates. A comprehensive review of the design succeeded in downsizing the unit.

system and the rotating gantry.

Masumi Umezawa (Senior Researcher, Department of Applied Energy Systems Research, Energy and Environment Research Center, Hitachi Research Laboratory, Hitachi, Ltd.), the leader of the development unit that works on proton beam therapy systems, explained as follows.

"At the time, Hitachi Research Laboratory was working on research aimed at shrinking the size of synchrotrons. By building a unit specifically intended for spot scanning, we estimated that we could reduce the 23-m circumference of the previous model down to 18 m by changing from a hexagonal to a quadrilateral synchrotron."

The rotating gantry, meanwhile, is a large device that allows the proton beam to be directed at the patient from any direction. The design and development department investigated how it could be made smaller and came up with ideas for achieving this. Although there were concerns that making the gantry smaller would restrict access to its interior, this problem was overcome by adopting a robot arm treatment platform. As a result, the unit's approximate dimensions of 11-m maximum circumference and 3.5-m internal diameter were shrunk down to approximately 9 m and 2.5 m respectively.

Following on from this, a new design concept was put together with modifications being made to more than 100 parts of the overall system to eliminate the unnecessary wherever possible.

Overcoming Differences

After Hitachi's new design concept was put to Professor Shirato, he set about lobbying the university and relevant government agencies to make up the shortfall in funding. As a result, the project was able to proceed with the cooperation of engineering and other disciplines.

"As well as proceeding with the project, we also wanted to pursue radical innovations beyond just downsizing the system," said Professor Shirato.

One of these was the incorporation of cone beam computed tomography (CT). Because this provides a three-dimensional (3D) image indicating the location and condition of the tumor, it can be combined with realtime tumor-tracking radiotherapy to improve targeting accuracy for a variety of different treatment sites. Toshie Sasaki (Senior Engineer, Particle Therapy Systems

Treatment room with molecular tracking proton beam therapy system (prior to completion of installation). The system is designed to be easy for hospital staff to use.

Masumi Umezawa

Toshie Sasaki

Professor Kikuo Umegaki

Application of Engineering Technology from an All-encompassing Medical Perspective

Collaborative medical research by Hokkaido University and Hitachi first started around 2000, subsequently expanding in scope to include joint proposals and participation in important national projects from FY2006 onwards. The Development of the Real-time Tumor-tracking Proton Beam Therapy System with Molecular Imaging project in which Professor Hiroki Shirato of the Graduate School of Medicine was lead researcher was selected by the Japanese Cabinet Office's Funding Program for World-Leading Innovative R&D on Science and Technology and proceeded as a five-year plan starting in FY2009. Professor Kikuo Umegaki (Division of Quantum Science and Engineering, Faculty of Engineering, Hokkaido University), who formerly belonged to a research and development division of Hitachi and who pioneered the establishment of joint research, works on quantum imaging through the Future Drug Discovery and Medical Care Innovation Program, a decade-long industry-academia collaboration that commenced in FY2006, and also acts as a project manager on the Development of the Real-time Tumor-tracking Proton Beam Therapy System with Molecular Imaging project, heading up the medical physics team that brings together the medical and engineering disciplines. He transferred to Hokkaido University in FY2010 where he is working on medical and engineering collaboration. He made the following comment.

"If engineering technology is to have a genuine role in medicine, then it is not enough simply to look at systems on their own. Rather, what is needed, I believe, is a broad-based understanding of radiation medicine with an appreciation of how systems fit in with the overall medical process extending across prevention, diagnosis, treatment, and follow-up, and taking account of the patients, doctors, and others involved in providing treatment.

In this joint development with Hitachi, I have been involved in vigorous debate on what is needed if proton beam therapy systems are to play a central role in cancer treatment in the hospitals of the future, and in incorporating the conclusions into the system design. The combination of spot scanning and realtime tumor-tracking radiotherapy has attracted the attention of the international academic community for providing an advanced form of proton beam therapy for moving tumors. I look forward to Hitachi not only making further enhancements to its proton beam therapy systems, but also to their applying the strengths of the entire Hitachi group to the development of a full range of medical systems, including diagnostic equipment and medical information."

Koji Matsuda

Design Department, Medical Systems and Nuclear Equipment Division, Hitachi Works, Power Systems Company, Hitachi, Ltd.), who worked on the development of the system, explained it as follows.

"Realtime tumor-tracking radiotherapy calculates the location of the moving target based on high-frame-rate X-ray images (30 per second) and controls the proton beam accordingly. Cone beam CT is a technique for generating 3D CT images from X-ray images captured as the gantry is rotated, and can be used to accurately identify the location of the treatment site. Both of these required an advanced level of technology development, and we devoted ourselves to the task because of its potential to provide a new generation of treatments."

In parallel with work on these radical innovations, it was also important that a more complete working system be produced that would be suitable for use in hospital treatment. Project manager Koji Matsuda (Senior Engineer, Particle Therapy Systems Design Department, Medical Systems and Nuclear Equipment Division, Hitachi Works, Power Systems Company, Hitachi, Ltd.) explained as follows.

"We consulted directly with hospital staff on questions such as whether the adoption of a smaller gantry, for example, would leave enough space for doctors and radiotherapists to move around, and whether treatment could still be performed efficiently."

Even after this, there were more than a few problems that arose because of the dual objectives of research and development and clinical treatment. Masato Osawa (Particle Beam Therapy Project Section, Particle Therapy Division, Power Systems Company, Hitachi, Ltd.), who was involved in the project, worked on collating the circumstances in meticulous detail to identify solutions.

Professor Shirato commented, “That we were able to overcome the crisis was thanks to the trust built up with Hitachi through 10 years of working together. While Hokkaido University has been involved in medical-engineering and industry-academia collaborations since the time of Professor Goro Irie, another major factor is that we have cultivated a research culture that seeks to overcome differences of perspective or professional demarcations to reach the forefront of our field.”

Working toward an Ideal

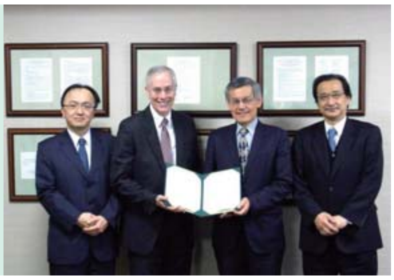
In this way, the world’s first molecular tracking proton beam therapy system commenced treating patients in March 2014.

After MDA, another early adopter of the spot scanning system was Quality Life 21 Johoku in Nagoya. The newly developed compact system, meanwhile, is to be installed at the Mayo Clinic, a major general hospital, and St. Jude Children’s Research Hospital in the USA. In particular, the St. Jude system will also include cone beam CT.

With demand for compact and reasonably priced proton beam therapy systems on the rise internationally since the global financial crisis, the Hitachi and Hokkaido University system has attracted significant interest from hospitals as far afield as Europe, Asia, and the Middle East.

Professor Shirato said, “For the people in the healthcare workplace, having a fully working system is only the beginning. Our role is to deliver high-quality research findings from treatment using world-first techniques for dealing with moving tumors, and to share the data we acquire with people in the healthcare field around the world. To say that our ultimate goal is to save all of the patients that we have been unable to treat in the past may sound grandiose, yet by being bold enough to express this aim out loud, I hope we can make at least some progress toward that ideal.”

In January 2014, a research team made up of doctors, radiotherapy specialists, medical physicists, biologists, and others at Stanford University in the USA embarked on joint research with Hokkaido University. This can be seen as a consequence of the opportunities opened up by the world-leading molecular tracking proton beam therapy system. Along with his determination to strive toward establishing a world-class clinical facility, Professor Shirato expressed his expectations for Hitachi as follows.



Numerous interested visitors from overseas have come to view the facility at Hokkaido University.

Sites that have ordered or taken delivery of proton or carbon ion beam systems from Hitachi. The systems have been adopted by some of the world’s most well-known medical institutions.

“Along with remaining a front-runner in the field of proton beam therapy systems, I hope that Hitachi will support international collaboration on clinical research with the world’s leading facilities such as MDA. Once the number of spot scanning therapy systems supplied to hospitals around the world reaches double figures or more, I believe it may well become a truly self-sustaining revolution in cancer treatment.”

There are many other illnesses besides cancer that cause people suffering and pain, and the battle against these adversaries will continue into the future. Nonetheless, people now have an effective new weapon in their arsenal in the form of the molecular tracking proton beam therapy system.

Masato Osawa

* This facility was built as part of the Sustainable Development of Molecular-Tracking Radiotherapy System project of the Funding Program for World-Leading Innovative R&D on Science and Technology. The research was funded through the Japan Society for the Promotion of Science by the Funding Program for World-Leading Innovative R&D on Science and Technology, a funding program devised by the Council for Science and Technology Policy.