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
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” 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.”

In response, Professor Shirato’s research group developed a technique for realtime tumor-tracking radiotherapy 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
Policy of the Cabinet Office

565 proposals received were
back to people and society.
international competitiveness
2009 and the top 30 of the
of research and development
selected.

It requires technology for
generating a uniform proton
beam and for controlling the
beam with high accuracy.

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

Attracting beam with high accuracy, even those with complex shapes.

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

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

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

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(d) 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.

Change of Thinking
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our aim was to create a system that could be

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.

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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

Masumi Umezawa

Toshie Sasaki

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

**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.**
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.”
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.

“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.

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*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.*