SHARP SHOOTERS

Beams of charged particles can treat cancer more safely and effectively than X-rays. Physicists and biomedical researchers are working to refine the technology for wider use.

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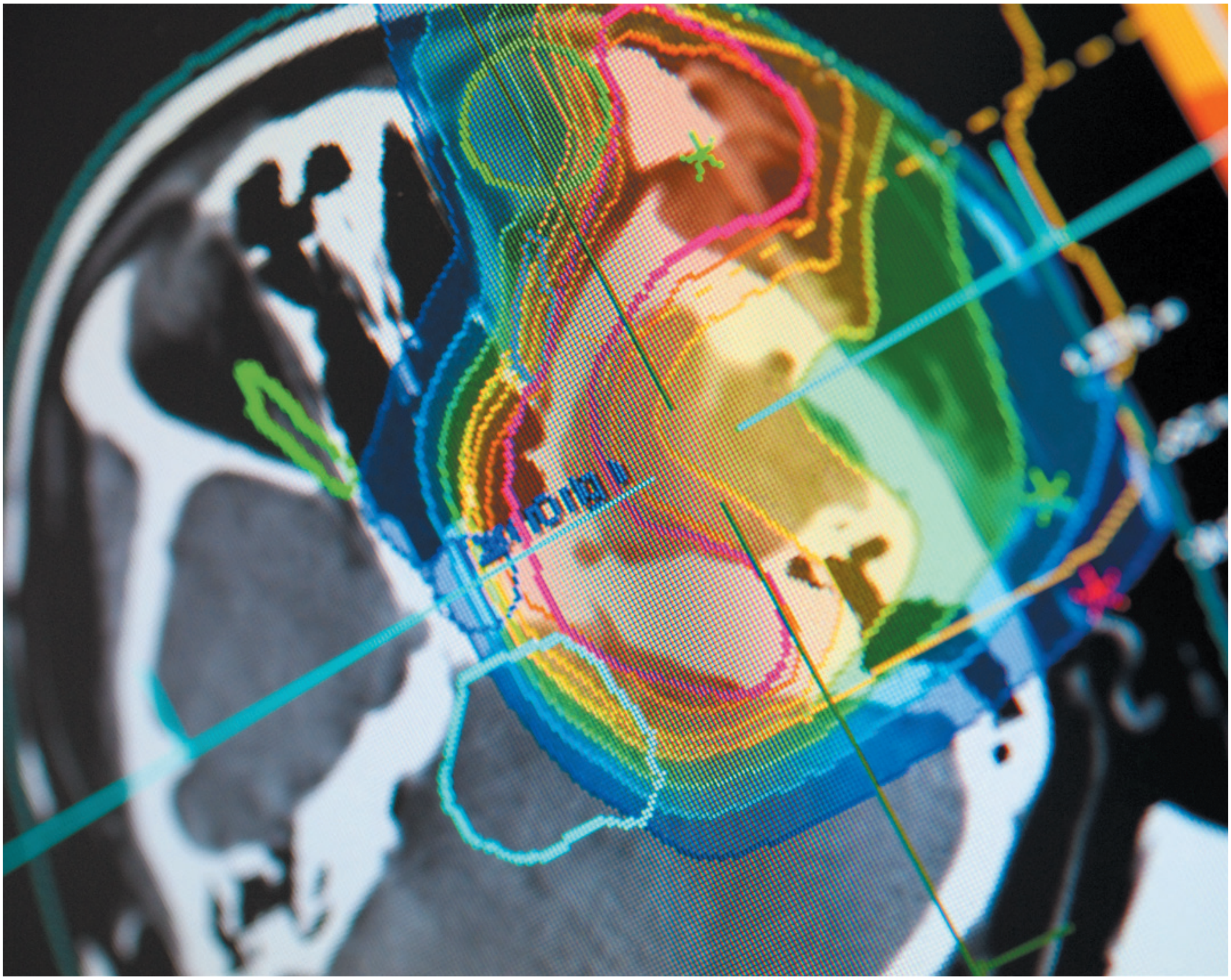


A computed-tomography scan shows a tumour and the ion-beam dosage that will be used to treat it.

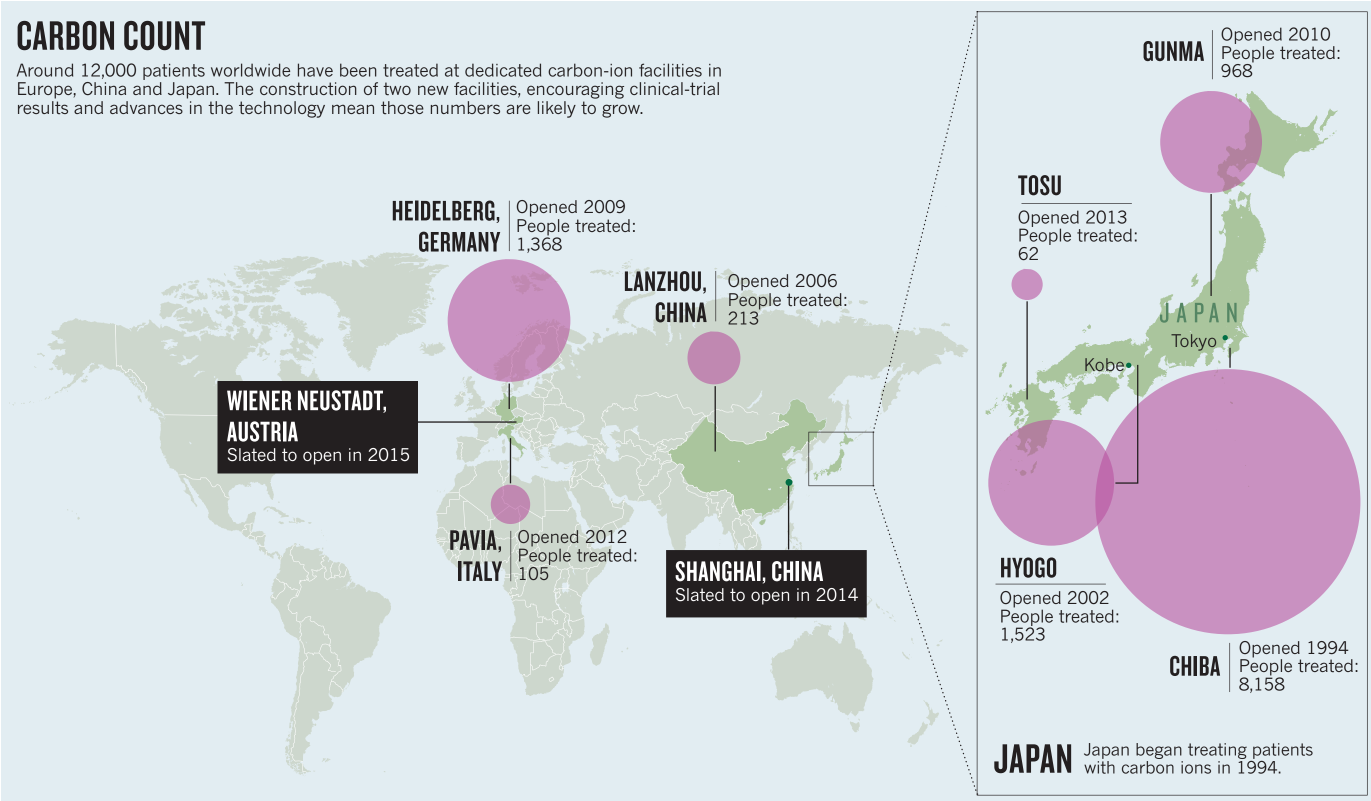
BY VIVIEN MARX

Clinicians attack cancer with many types of weapon, ranging from scalpels to physically remove all or most of a tumour to drugs that kill the tumour cells where they are. In about half of people with cancer, doctors go after the malignant cells with ionizing radiation.

Classic radiation treatment involves mainly X-rays. But because these lose energy all along their path through the body — damaging healthy cells as they go — clinicians and researchers are increasingly paying attention to beams that use charged particles such as protons and carbon ions[1]. Charged particles can deposit most of their lethal energy mainly at the tumour site, largely sparing the healthy tissue. Protons are slightly more lethal to cancer cells than X-rays, and carbon ions seem to be around 2–3 times as deadly.

Worldwide, around 100,000 people have received proton treatments for cancer. Japan, China, Germany and Italy have built ion-beam facilities that have treated some 12,000 patients with carbon ions, the majority in Japan and Germany (see 'Carbon count').

Carbon ions are heavier than protons, so the facilities to deliver them are pricier. The charged-particle facilities in Germany and Japan cost between US$130 million and $200 million each to build. Nonetheless, there has been a spike in research and ▶



CARBON COUNT

Around 12,000 patients worldwide have been treated at dedicated carbon-ion facilities in Europe, China and Japan. The construction of two new facilities, encouraging clinical-trial results and advances in the technology mean those numbers are likely to grow.

SOURCES: PARTICLE THERAPY COOPERATIVE GROUP; NIRS JAPAN; HEIDELBERG UNIV. HOSPITAL

clinical activity to use charged particles more broadly for cancer treatment, and a hope that as the technology evolves, the price will come down.

Clinical trials and new types of radiobiology assay are under development to study the molecular effects of carbon ions as well as helium, lithium and oxygen ions, often referred to in cancer research as 'heavy' ions because they are heavier than protons. Advancing this approach to patient treatment will require further development of particle-accelerator and beam-delivery technology. An international community of clinicians, researchers and technology developers are working to make it happen.

The United States began treating patients with protons in the 1950s and has funded research in this area[2], but it has lagged behind Japan and Germany in advancing other ion therapies. The United States now has 14 facilities for proton treatment and none for carbon-ion treatment.

In Japan, radiation oncologist Hirohiko Tsujii of the National Institute of Radiological Sciences (NIRS) in Chiba has devoted his career to advancing carbon-ion therapy. Chiba is home to the first of Japan's four carbon-ion facilities, all of which the NIRS oversees, and treated its first patient in 1994. In Germany, the Heidelberg Ion-beam Therapy Center (HIT) has been treating patients since 2009 with protons and carbon ions[3].

In both countries, the development and construction of these facilities was helped along by public funding for physics-based facilities ,as well as investments from large companies such as Siemens Healthcare, based in Erlangen, Germany, and Hitachi, Mitsubishi, Sumitomo and Toshiba, all based in Tokyo.

The published clinical results from patients in Germany and Japan are causing the United States to shift its stance, Tsujii says. The US National Cancer Institute (NCI) now wants to fund domestic research on carbon ions and other ion species, and to help fund an international clinical trial.

FIRE AWAY

Standard radiation treatment involves firing a barrage of X-rays at tumours in the hope of stunting their growth by breaking their cells' DNA. But some areas of tumours seem to be resistant to X-ray damage, and those that are not can often repair it. And many X-rays pass through tumour cells without hitting the DNA, leaving the cells unscathed. X-ray beams can also hit tissue adjacent to a tumour, which can set off molecular events leading to tumour formation. For example, children who survive cancer after radiation treatment face a heightened risk of secondary cancers later in life.

This kind of collateral damage has been reduced by advances in radiation oncology, such as the ability to deliver beams from different angles and with varying intensities so that they converge on the tumour. But improvement is still needed. For example, when treating head and neck cancers with conventional radiation, "we do a reasonable job", says Stephen Hahn, a radiation oncologist at the Perelman School of Medicine at the University of Pennsylvania in Philadelphia — but the X-rays can harm healthy tissues nearby, such as the heart, oesophagus or lung.

Charged particles, by contrast, can mostly avoid healthy tissue. Stripped of their electrons and accelerated to some 70% of the speed of light, they pass through healthy tissue without interacting strongly with the atoms there. Once their speed drops to a certain level, however, they abruptly deposit almost all of their energy in "a dramatic bam", says Arnold Pompoš, a physicist at the University of Texas Southwestern Medical Center in Dallas.

This deposition of energy is known as the Bragg peak, named after physicist William Henry Bragg, who discovered the behaviour in 1903. Charged-particle beams can be tuned so that particles reach their Bragg peaks right at a tumour, where they do the maximum damage.

READY, AIM, SCAN

The researchers at the HIT use — and are continuing to develop — an approach called raster scanning, in which a source readies one or several types of ion that are then accelerated. Next, the beams are extracted slowly in bunches, each of which has hundreds of individual Bragg-peak positions tailored to deposit radiation throughout the tumour.

The position, size and intensity of these collections of beams are measured around 100,000 times a second to ensure safety and precision. The beams fill the tumour's contours as a hand fills a glove, says Thomas Haberer, chief technology officer of the HIT, who developed the technology while working at the GSI

Helmholtz Centre for Heavy Ion Research in Darmstadt, Germany. (The HIT is a spin-out of that centre.)

"Clinically, we use protons and carbon-ion radiation as is needed from one patient to the next," says Haberer. He and his team are working to add oxygen, helium and other ions to the mix. The researchers also want to increase the number of ion species they use, because the heavier ones stay focused even when travelling deep into the body, as in the treatment of prostate cancer, he says. The heavier the ion, the greater the possible damage to solid tumours.

For tumours that contain a mix of healthy and diseased cells, the HIT team chooses protons to avoid injuring the healthy ones.

During particle-beam treatment, a patient lies on a couch wearing a stiff plastic garment that positions them with millimetre-scale precision in reference to a computed-tomography image of the tumour, says Haberer. A tumour can shift as the patient breathes, so the system must also adjust to account for this change.

In collaboration with several research groups, Haberer and his colleagues are working on ways to use the raster-scanner approach to refine how a tumour can be tracked during treatment. "In the lab, the prototype is working well," he says. "It will take a while for it to reach clinical application, at least a few years."

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Gantries to direct charged-particle beams weigh as much as 600 tonnes.

At the HIT, clinicians have applied carbon-ion therapy to tumours in the brain and at the base of the skull, and to head and neck cancers. And they have begun treating cancers of the liver and pancreas, recurrent rectal and prostate cancers, and paediatric bone cancer. Children are regularly treated with proton beams, and the team wants to launch clinical trials of carbon ions for paediatric cancers, says Haberer.

When treating cancers of organs in the torso, clinicians use 'spacers', which can be made from a variety of materials, to physically shift healthy tissue adjacent to the tumour out of the way of the Bragg peak. For example, Tsujii says, in carbon-ion therapy for colon cancer, "we put a spacer between the tumour and the intestines".

Tsujii points to the expanding range of tumour types that have been treated in Japan with carbon ions. When people with rectal cancer are treated with surgery, he notes, around 15% develop recurrence within 3–5 years. Another surgery is an option for only 10–40% of them. When these patients are treated with carbon ions, only 10% of them develop a second recurrence, compared with 30–70% of those treated with X-rays. Patients eventually succumb to metastases, but Tsujii nonetheless finds the results so far promising.

Another study under way in Japan is looking at combined chemotherapy and carbon-ion therapy to treat people who have inoperable pancreatic tumours, and at pre-operative carbon-ion therapy for pancreatic cancer that can be removed surgically. Carbon-ion therapy may take less toll on the patient and reduce treatment times — for liver cancer and early-stage lung cancer, carbon ions are delivered in one or two sessions over as many days, compared with 10–30 sessions over many days or weeks for X-ray therapy.

GROWING THE TECHNOLOGY

Protons hinder the growth of some tumours better than X-rays, says Herman Suit, a proton-therapy pioneer at Massachusetts General Hospital in Boston[4]. Some of the published results from carbon-ion treatment centres in Japan and Germany are "impressive", he adds, such as those for tumours at the base of the skull, renal cancer and mucosal melanoma of the head and neck. He would like to see clinical trials comparing protons and carbon ions.

Carbon-ion therapy has so far been used mainly on tumours that are difficult to remove surgically and risky to treat with classic radiation. Tumours at the base of the skull, for example, are near nerves, brain tissue and the cochlea of the inner ear, where X-ray exposure could cause debilitating damage.

Hahn says that some charged particles deliver "a more powerful punch" to tumours and that he and most of his colleagues now accept that carbon-ion therapy performs well on the most challenging tumours. The next step is to see whether charged particles are right for more common diseases such as lung cancer.

COMPARING BEAMS

According to the NCI, the first international clinical trial on charged particles is now being planned. Slated to last 3–5 years, the randomized phase III trial, which will examine efficacy and dose, will compare X-rays, protons and carbon ions in the treatment of cancers of the pancreas, liver, head and neck, as well as bone and soft-tissue tumours and recurrent rectal cancer. The NCI will contribute funding for the trial and is soliciting proposals from US institutions and from carbon-ion facilities in Japan, Germany, Italy and China.

The trial presents many logistical challenges in addition to that of obtaining the necessary scientific review and approval. Facilities for charged-particle therapy are much less common than those for X-ray treatment, so patients will need to travel further to reach them, especially the carbon-ion centres.

The NCI also wants to fund domestic research into charged-particle therapy. James Deye, a programme director for extramural radiation research at the NCI, and his colleagues are poring over project applications from institutions vying to set up the first US research centre for particle-beam radiation therapy. The NCI funds research, not construction, Deye says, so applicants must find the money to build, over the next 5–10 years, a research facility that can handle treatments with protons, carbon ions and other ion species. Grant recipients will be announced later this year.

One of the applicants is the University of Texas Southwestern Medical Center, where radiation oncologist Hak Choy wants to put classic radiation, protons and heavy ions all under one roof. A new X-ray facility is set to open by 2016; a proton-therapy suite is slated for 2017; and Choy hopes to have a carbon-ion facility by 2021. The project is under review with the Texas state government, and Choy is hopeful about receiving support so that construction can begin.

ACCELERATE AND DELIVER

Accelerators and beam-delivery systems are crucial components in directing charged particles at patient tumours, but their size and operation costs are some of the factors hindering their widespread use. To help to make the use of this technology more feasible, some scientists are trying to make these systems more compact.

One overhaul researchers are targeting is of the gantry, a massive rotating platform that delivers ion beams to patients at any angle. To achieve different angles, the gantry directs the ions with huge, powerful magnets, which weigh it down and raise its electricity use. The gantry at the HIT is as tall as a commercial passenger aircraft and weighs around 600 tonnes. Because carbon ions have more momentum and charge than protons, a beam of them is around 2.5 times harder to bend than a proton beam, says Stephen Peggs, an accelerator physicist at Brookhaven National Laboratory in Upton, New York.

> ***"Compared to X-rays, charged particles deliver 'a more powerful punch' to tumours."***

Using stronger magnets on the gantry would be beneficial, he says. Superconducting magnets could be an option, he adds, because they are not limited to a magnetic strength of 1 Tesla, as conventional magnets are, and could have strengths closer to 4 or 5 Tesla. That boost could reduce the gantry size, because the greater the force the magnet exerts on the beam, the more readily the beam can be bent in a smaller radius, reducing the size of the system.

Peggs and his team are also working to improve the accelerator itself. Charged-particle therapy accelerators could be more compact, he says, if they cycled more quickly.

The Brookhaven scientists are building a prototype of a rapid-cycling accelerator, which extracts beams more often than the slow-cycling accelerators now used in carbon-ion treatment facilities[5]. In the new system, fewer ions travel around the accelerator track at any given time, and these doses are extracted cyclically and delivered to the patient.

The use of fewer ions and more frequent extraction reduces the size of the beam pipe and the other system components, including the conventional magnets used on the accelerator to direct the beam. Such design changes also cut power use relative to that of slow-cycling systems.

The Brookhaven researchers are testing this concept by building a fast-cycling accelerator to deliver multiple ion species, including lithium, neon, helium and carbon. It will be able to deliver a salvo of one ion species and then quickly switch energy levels and deliver another, Peggs says.

The scientists are building the system components but want to assemble them at a location — not yet determined — where they can be applied to biomedicine. The prototype could be used as a radiobiology research facility to continue maturing the technology for charged-particle therapy, Peggs says.

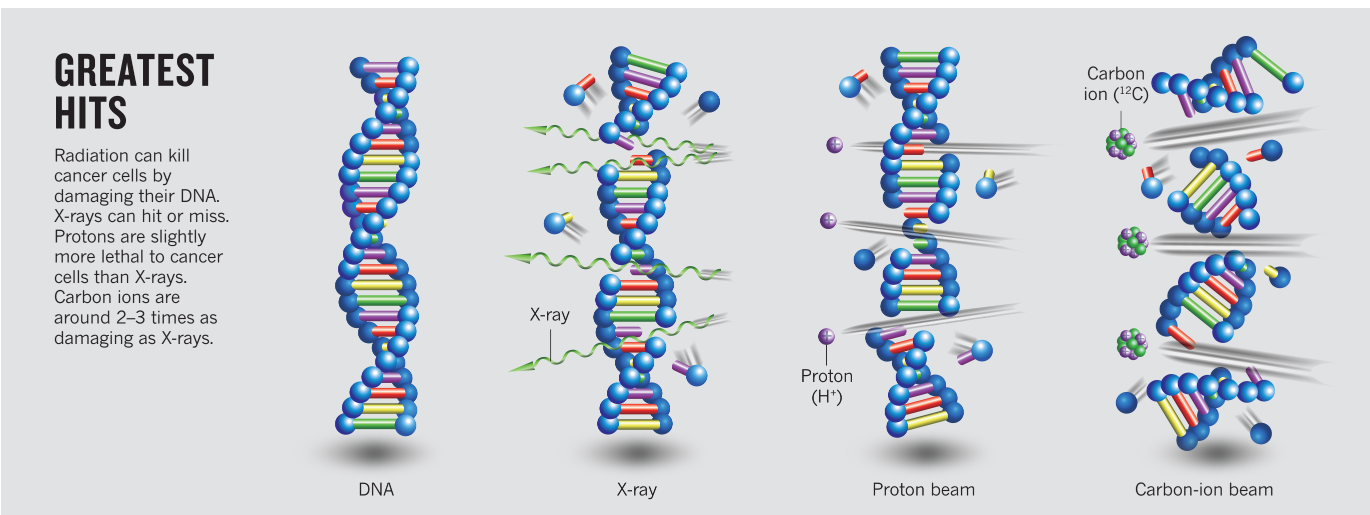
To help with technology transfer, the Brookhaven scientists have partnered with Best Medical, a company in Springfield, Virginia, that builds radiation facilities. Krishnan Suthanthiran, the company's chief executive, sees a market for a rapid-cycling system.

His company has spent around $5 million on the partnership thus far and expects it will take another $10 million to $15 million to build a working system by 2016. This year, he is applying for approval from the US Food and Drug Administration to build a facility. He estimates that a therapeutic centre will cost between $30 million and $100 million, depending on how many treatment rooms it has. It may or may not need a gantry and will probably require less radiation shielding than current carbon-ion facilities, reducing cost and footprint.

BROOKHAVEN NATIONAL LAB

Stephen Peggs is building a fast-cycling accelerator.

Haberer says that he likes Peggs' concept because of its robust, steady way of cycling, which is perhaps even more stable than that of a slow-cycling system. But until a rapid-cycling system is built and used in therapy, it will not be easy to compare systems, he says. Superconducting magnets would allow the facility's dimensions to be reduced, but they do not yet work quickly enough. "At present, these magnets are slow — which would mean fewer patients could be treated, impinging on the facilities' sustainability," Haberer says. And, he notes, a rapid-cycling accelerator is better able to extract the exact dose at the right time, but it could be difficult to monitor the beams extracted to ensure their dose and



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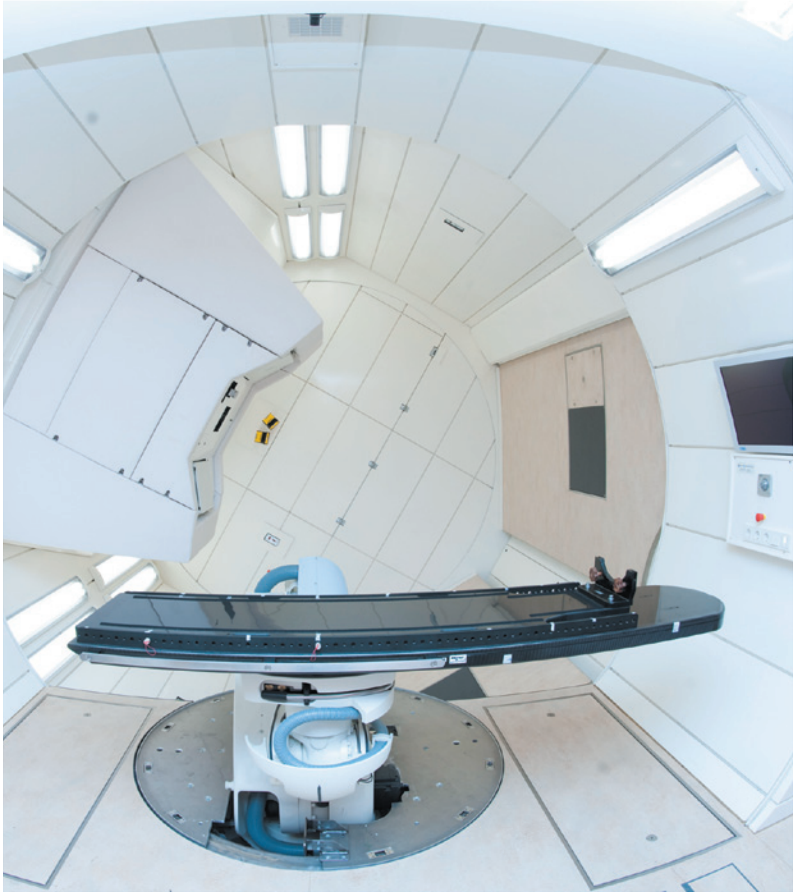

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The treatment area of an ion-beam facility (left). Patients are carefully positioned (right) to ensure that the particle beam hits the tumour accurately.

directionality.

To further explore the potential uses and ideal dosages for charged-particle therapy, scientists want to expand basic radiobiology research. Scientists perform this work at charged-particle therapy centres and in facilities such as the NASA Space Radiation Biology Lab at Brookhaven, for example.

Kathryn Held, a radiobiologist at Massachusetts General Hospital in Boston is working on ways to get molecular information about the effects of different ion species on tumour cells — information that could help researchers to develop dosage regimens.

New approaches to studying cell survival, changes in cell cycle and cell death will help researchers to explore why charged particles have more tumour-killing power than X-rays.

Measures such as standard 'clonogenic assays', in which scientists irradiate cells and then see whether they continue to grow and form colonies, suggest that protons are slightly more effective than X-rays at killing cells, whereas carbon ions are about 2–3 times more effective. Scientists have a number of hunches about why this is so.

One is related to the fact that X-rays tend to be spread out, meaning that many of them pass through the cell without hitting DNA, says Held. Ions such as carbon are heavier and bigger than protons, have a greater positive charge and move more slowly through tissue or cells, creating a thicker track of ionization. This track seems to produce clusters of damage, such as breaks in one or both strands of DNA, and damage to neighbouring nucleotides (see 'Greatest hits').

When one strand of DNA breaks, repair enzymes use the sequence of the other, intact strand as a template to fix the helix's rails and rungs. But double-strand breaks are harder to repair accurately, because there is no intact template from which to reconstitute the DNA.

"Assays that specifically measure types of possible clustered DNA damages would be very useful."

A cluster of damage adds to the challenge. All of this helps to explain why carbon ions are more lethal, says Held.

Indirect evidence — computer simulations or the use of antibodies to detect DNA-repair enzymes — helps to explain the type of injury that charged particles inflict on tumour cells. "However, we do not have good assays to quantify, or identify the composition of, those clustered lesions," Held says. "DNA assays that more specifically measure the various types of possible clustered DNA damages would be very useful."

Another reason charged particles may pack more punch to cancerous cells is related to tumour physiology. As tumours grow, oxygen-poor regions develop, and these areas seem to be resistant to classic radiation treatment. That is because X-rays kill cells by producing free radicals — reactive molecules formed from the water in cells and tissues — which then react with DNA to produce other destructive radicals. More oxygen exacerbates the damage these radicals can cause, and less oxygen weakens their effect. Researchers think that charged particles such as carbon ions may not lose their destructive power in low-oxygen regions.

Basic radiobiology research on charged particles can feed into clinical practices in current and future facilities. Radiation oncologist Anders Brahme at the Karolinska Institute in Stockholm, who has spent his career working on charged-particle therapy, says that he sees great potential for cancer treatment in such therapies and is excited that they are drawing global interest. In his view, charged particles offer the chance for radiation oncology to move from a cancer treatment to a cancer cure. ■

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