After 14 years of construction, the Large Hadron Collider, the world’s largest particle accelerator, fired its first beam of protons in September from its home at the European Organization for Nuclear Research (CERN) near Geneva. Now a spinoff technology for treating cancer is also nearing its European debut. The first European center to offer carbon ion therapy—a type of radiation treatment that uses charged particles instead of photons or x-rays—will open in early 2009 in Heidelberg, Germany.

Like its cousin, proton therapy (see JNCI 2008;100:1496-8), carbon ion therapy uses charged particles to deliver more precise, localized radiation to tumors with less exposure to surrounding tissues than x-rays (Therapy using particles—either protons or carbon ions—is called hadron therapy.) But unlike proton therapy, carbon ion therapy causes damage to cancer cells in a way that they cannot repair themselves.

Among European researchers, interest in carbon ion therapy is increasing. The Heidelberg Ion Therapy facility, estimated to cost €100 million, will treat cancer with proton and carbon ion therapy, and late next year, a second center offering similar treatments in Pavia, Italy, near Milan, will open as well. Five more European centers will be built in the next 3-5 years, and another 20 are planned in Europe over the next decade, according to Hirohiko Tsujii, M.D., Ph.D., a carbon ion therapy pioneer at Japan’s National Institute of Radiological Sciences.

Plans for carbon ion therapy in the U.S., on the other hand, are extremely limited. There is more reticence about carbon ions among U.S. researchers because of the high cost—currently about three times the cost of a proton therapy center—and what U.S. investigators consider to be a lack of sufficient evidence of its efficacy.

European Initiatives
“There is a huge momentum in Europe for particle therapy,” said Manjit Dosanjh, Ph.D., CERN’s sole biologist and the driving force behind ENLIGHT, a European network of medical physicists and radiation oncologists focusing on carbon ion therapy. Just as particle physics research gravitated to Europe about 15 years ago with the planning and building of CERN’s Large Hadron Collider, Europe is leading the initiative for carbon ion therapy. Encouraged by promising preliminary data, other European centers are planning to test and offer carbon ion and proton therapy, in Lyon, France; Uppsala, Sweden; Marburg and Kiel in Germany, and Wiener Neustadt, near Vienna, Austria.

In addition to funding ENLIGHT, the EU is supporting particle therapy by recently naming it as one of six areas deemed a scientific research priority, said Piero Fossati, M.D., of Milan’s National Center for Oncological Hadron Therapy (CNAO), which is building the Pavia facility. The EU is funding a 4-year, €5.6 million project, coordinated by Dosanjh, to train 25 researchers and post-docs in hadron therapy.

Physics of Carbon Ions
The idea of using hadron therapy to treat cancer was first proposed in 1946 by Robert R. Wilson, Ph.D., a leader of the Manhattan project and head of the Fermi National Laboratory in the 1960s. Experiments using different types of particles have been ongoing since the 1950s, with mixed results.

Of the types of particles tested over the years in physics labs-turned experimental treatment centers, carbon ions seem to have more theoretical advantages and fewer drawbacks than neon, helium, and neutrons. “Carbon ions are a compromise particle between heavier ions, which inflict too much damage with high-density energy deposition, and neutrons, which lack a
charge, cannot be easily guided, and do
damage all along their pathway,” said
Harvard University professor emeritus of
radiation oncology, Michael Goitein, Ph.D.

Since the 1990s, researchers have treated
about 5,000 patients with carbon ions in
Japan and about 440 patients in Germany. A
range of tumor types have been treated
experimentally: tumors for which surgery
was not an option, those which are tradi-
tionally radioresistant to conventional treat-
ment, and cancers located very close to vital
organs. Few head-to-head comparisons
between carbon ions and protons or
x-rays have been done, but there are
some prospective and retrospective stud-
ies comparing outcomes.

X-rays deposit their energy along the
entire path of radiation with most of it
absorbed near the entrance of the beam at
or near the skin’s surface. Protons and
carbon ions, however, deeply penetrate tis-
sue and release most of their energy near
the end of their range where the tumor is.
But carbon ions are even more precise:
They scatter much less than protons and
concentrate their radiation in a smaller
region.

“Because carbon ion beams are extremely
precise with higher energy, they are best
suited to radioresistant tumors and cancers
for which damage to surrounding tissue
must be minimized,” Dosanjh said.

A major potential advantage of carbon
ions is that, unlike x-rays and protons, they
do not require oxygen to work and can,
therefore, reach and kill hypoxic areas of
tumors, which are notoriously hard to
treat.

Another difference is that carbon ions
cause more irreparable damage to the can-
cer cells. Protons and x-rays have about the
same relative biological effectiveness, or
RBE—which is a measure of the damage
from ionizing radiation—whereas the RBE
of carbon ions is three times higher, said
Ugo Amaldi, Ph.D., a CERN physicist and
professor of medical physics at the
University of Milan. The higher RBE of
carbon ions means they damage DNA in a
way that is double-stranded and not repair-
able, giving them a possible edge in treat-
ing radioresistant, slow-growing tumors,
which are typically resistant to both x-rays
and protons. Conventional radiation is
given over many sessions to overcome the
cancer cells’ ability to repair radiation dam-
age and to allow hypoxic areas of tumors to
re-oxygenate. But carbon ion therapy can
be given in fewer doses.

“The real difference between x-rays, pro-
tons, and carbon ions is that damage by
x-rays and proton therapy is based on chem-
istry—chemical damage to DNA,” Amaldi
said. Both require oxygen to work, produc-
ing indirect DNA damage through the cre-
ation of free radicals. Such cellular damage is
repairable by the body 50%-60% of the
time, which is why 30 doses of radiation may
be necessary to treat certain tumors with
x-rays, he explained.

“In contrast, carbon ion therapy
works through physics, directly producing
double-stranded DNA
breakage in cells that the
body cannot repair.”

“Moving from x-rays to protons is not a
quantum leap, whereas moving from either
x-rays or protons to carbon ions is,” Fossati
said.

Ready for the Clinic?

While carbon ions have much potential,
we don’t think that everyone should be
treated with them,” Amaldi said. But they
do plan to test carbon ions in a variety of
settings.

In Germany, carbon ion therapy has
been used as a “booster” treatment with
x-rays and proton radiation at a pilot facil-
ity in Darmstadt, at GSI (the Helmholtz
Center for Heavy Ion Research), according
to Gerhard Kraft, Ph.D., a researcher at
GSI and emeritus professor of biophysics at
Darmstadt University.

“Conceivably, protons or photons
could also be used for a large area of can-
cer, if there is a concern for metastasis or
for lymph nodes at risk, and carbon ions
could be used for tumors themselves,”
Fossati said. “CNAO plans to use carbon
ions as part of a combination treatment,
and also as a boost after protons or x-rays,”
he said.

Carbon ions can also be used before sur-
gery to shrink a tumor or immediately after
surgery because, unlike x-rays or protons,
they don’t damage the skin. Other potential
uses include inoperable tumors, such as
sacral chordomas or sarcomas, for which
no other treatment is available, Fossati
added. CNAO is also planning clinical trials
to treat early lung cancer, liver, and head
and neck cancers with carbon ions.

In Heidelberg, the plan is to conduct
clinical studies using both proton and car-
on ions, because both
have benefit, depend-
ing on the type of
tumor’s repair capac-
ity. “For deep tumors
without clearly defined
shapes, one approach
would be to give a
high-dose carbon ion
radiation ‘boost’ at the
solid and well-defined center, and photons
for the gross volume of a tumor and the
margins,” Kraft said. “This ‘boost’ tech-
nique was already done with great success
in some salivary cancer patients at GSI.
There, tumor control was increased from
25% without the carbon [ion] boost, to
close to 80% with a boost.” But this is not
likely to happen with all tumor types, Kraft
said.

In the short-term, Amaldi estimated
that only 3% of tumors will be treated
with carbon ions, but this could change
as studies provide more data. “We need to
define 2-3 tumors that cannot be treated
with protons, which should be tested in
phase II trials,” he said. Radioresistant
tumors located near vital organs are good
contenders for trials, such as those in
the salivary gland, liver, and lung, he added.
CNAO will treat prostate tumors with both protons and carbon ions, in combination and as booster treatments, which will require fewer beams than the standard radiation therapy.

U.S. Reticence
Some serious technical challenges remain for carbon ions, including software problems that have been plaguing the Heidelberg facility and the question of how to treat moving organs. U.S. researchers interested in Europe’s progress are waiting until studies show a definite advantage for carbon ion treatment over protons and x-rays, before considering a financial commitment to testing carbon ions.

Their wait-and-see attitude is mainly due to the high cost, relative scarcity of data, difficulty in predicting long-term effects, and lack of head-to-head trials, experts say. “Some questions with respect to its power, lack of biological models to predict effects, including long-term effects, and a variable RBE in different tissues like neutrons, means that I’d like to see more research,” said Harald Paganetti, Ph.D., associate professor of radiation oncology at Harvard. “Because of a lack of data, I don’t see a lobby for it in the U.S.

“For now the NIH is not convinced carbon ions are the way to go,” Paganetti said. “But I am confident that within a few years, [as randomized trials are conducted and data emerge], that will change.”

The NCI is not supporting carbon ion research, “having funded a number of initiatives in particle therapy for 25 years and being less than enthused with the results,” said James Deye, Ph.D., NCI’s medical physics program director.

Many U.S. researchers are skeptical about carbon ion therapy due to negative experiences with neutrons, which have some physical similarities to carbon ions, said James D. Cox, M.D., head of the division of radiation oncology at the University of Texas M. D. Anderson Cancer Center.

Neutrons were tested before World War II at the University of California, Berkeley and at the UK’s Hammersmith Hospital in the late 1960s, but this work was halted due to poor distribution of the radiation, and because the high doses needed to reach tumors caused severe side-effects, such as severe late-onset necrosis, Cox said. “Neutron therapy also produced toxicities and very different results in humans than it had in lab and animal studies,” said Cox. “In addition, neutrons have different RBEs in different tissues, so that it affected nerves, bone, and soft tissues very differently.”

While there is some interest in the U.S., cost is a major barrier, said Paganetti. “Would I want to have it here to do trials? Yes. But I’m not sure how realistic it is now. It takes a lot of money, and there is not a lot of proof that carbon ions provide the best treatment for patients, and then there’s the question of reimbursement. Some questions need answering before it’s ready for primetime.”

Randomized controlled trials comparing protons with carbon ions may answer some of questions, he said. “While many of the trials in Japan show great results, such as for lung cancer, the use of much higher doses makes the outcomes unclear to me,” he said. “Are they due to more aggressive fractionations or the carbon ions themselves?”

Carbon ion therapy is generally three times as expensive as proton therapy, which in turn is 2–3 times more than x-rays, because these ions currently cannot be produced in smaller proton cyclotrons—charged particle accelerators—but require a magnet that is 80-times larger. Centers with extant proton therapy facilities, which are proliferating in the U.S., cannot easily or inexpensively add a carbon ion capability, so U.S. institutions with proton facilities are not currently considering carbon ions. However, one U.S. company is developing a smaller particle accelerator, which will be able to initially produce protons and later, with an add-on, carbon ions.

Some U.S. investigators believe it’s too soon to focus on carbon ions. “There is still a great amount of work to be done with protons,” Cox said. “I’d like to see more research with protons and chemotherapy,” he said. “Currently, we [at M. D. Anderson] are the only institution doing such combination trials, which indicate lower toxicity with protons than x-rays.

A few U.S. institutions, such as the Mayo Clinic, believe there is enough information on carbon ions to invest in it. “Our interest in carbon ion therapy is based on the science, and potential benefit shown in pilot studies, which makes it a compelling treatment,” said Robert Miller, M.D., assistant professor of radiation oncology at Mayo. “It is very hard, as a doctor, not to want to make carbon ion treatment available to my patients.” But he, too, cited cost as the biggest barrier.

Vanderbilt University’s Dennis Hallahan, M.D., echoes both sentiments. Right now, Vanderbilt can only fund a proton center, but looking toward the future, it is planning to build a “carbon-ready” facility, following Hallahan’s visit to GSI to investigate feasibility. “We became interested in carbon ions when encouraging reports were published on treatments for lung cancer and hepatocellular carcinoma, two diseases where we do a terrible job with outcomes.” Even if outcomes are similar, he believes there will be less morbidity with carbon ions because of their ability to reach deep, radioreistant tumors with less damage to surrounding tissue.

Touro University in California plans to build a facility that will treat patients with protons starting in 2010 and carbon ions in 2012, said president Bernard Lander, Ph.D. “I visited Heidelberg twice and witnessed first-hand what carbon ions can do,” said Lander. “While we need research to establish if it is more effective than other radiation, heavy ions such as carbon can theoretically have more effect on cancer than protons.”

Over the next 5 years, as new data begins accumulating from new clinical trials with carbon ions, proponents and skeptics alike will have a better understanding of how best to use this new technology for patients in need of better treatments.

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