

The NuPECC logo is rendered in a bold, white, sans-serif font. The 'N' and 'u' are connected, as are the 'P' and 'E'. The 'c' is a simple, rounded shape. The background of the entire cover is a dark blue with abstract, glowing blue lines and several glowing blue spheres, some of which are clustered together, resembling a molecular or atomic structure.

NuPECC

NUCLEAR PHYSICS **FOR MEDICINE**

How nuclear research is improving human health

The logo for the European Science Foundation is a green circle containing the text 'EUROPEAN SCIENCE FOUNDATION' in white, stacked vertically. The 'E' is significantly larger than the other letters.

EUROPEAN
SCIENCE
FOUNDATION

THE RISE OF NUCLEAR MEDICINE AND RADIATION THERAPY

Procedures employing nuclear particles and radiation to understand, diagnose and cure disease are becoming an ever-more important component of critical life-saving healthcare

Tens of millions of medical procedures, based on particle and radiation emissions from nuclear reactions, are carried out annually at more than 10,000 hospitals across the world. Much of the underpinning research and development is carried out in institutes devoted to nuclear physics studies – in identifying suitable radiological materials and sources, and in devising new procedures and advanced technologies that can be transferred to the clinic.

Increasingly, nuclear physics laboratories have dedicated facilities that provide the infrastructure for treatments. This brochure explains the techniques and technologies upon which modern nuclear medicine and radiation therapy are based, and describes some of the recent exciting advances.

What is nuclear physics?

Nuclear physics is the study of the core of the atom – the nucleus – in all its many forms and complexities. Atomic nuclei consist of various combinations of component particles called protons and neutrons. The chemical elements, such as carbon, oxygen or copper, are defined by the number of the protons in their nuclei, while variants within each element, with differing numbers of neutrons, are called **isotopes**. Those belonging to the same element have the same chemical properties but different masses and different nuclear properties.

Many isotopes are not stable and decay by either breaking up (fission) or emitting particles and electromagnetic radiation. These emissions include **alpha particles** (helium nuclei – two protons and two neutrons), **beta particles** (electrons, both normal negatively charged electrons and their antimatter versions – positively-charged **positrons**) and **gamma-rays** (high-energy electromagnetic radiation).

Nuclear physicists make and study a large variety of both stable and radioactive isotopes in order to understand how the fundamental forces of Nature bind the nuclear components together, and generate the amazing structural and behavioural complexity

seen in nuclei. Most of the studies are carried out at moderately high energies using large machines – **accelerators** – that fire beams of particles such as protons and nuclei at a target to generate often unusual isotopes, and study their properties. **Nuclear reactors** dedicated to scientific research are also employed to make particular nuclear species, using the neutrons that are emitted in uranium fission.

The research reactor at the Institut Laue-Langevin, Grenoble, France is used to explore new radioisotopes, some with clinical potential



Proton therapy is carried out at the INFN Laboratory in Catania, Italy using a superconducting cyclotron to deliver the particle beam



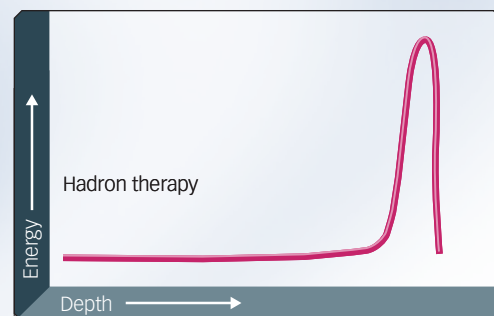
Applications in the clinic and in medical research

Nuclear medicine and radiation therapy encompass several aspects:

- The emissions from radioactive isotopes can be employed as **diagnostic tools** by creating images of a patient's tissues and organs to reveal details of both the structure and function. To provide images of target cells or living processes, these isotopes are chemically combined with molecules known to bind to specific biomolecules.
- Radioisotopes are also used as tracers in **pharmaceutical research** to study the behaviour of drugs in the body.
- Beams of nuclei, as well as emissions from radioisotopes, can be targeted so as to **kill cancer cells** that are otherwise inaccessible or difficult to destroy by other means.

Using a reconstruction algorithm, a computer can then produce a 3D image from the data. The most commonly used radioisotope is technetium-99m. It accounts for about 80 per cent of medical radioisotope usage today. It is extremely suitable because it has an intermediate half-life of six hours, and the gamma-rays have an energy well suited for imaging. It can also be made available even in remote locations by being generated from a longer-lived isotope (see p.7) made in accelerators or reactors elsewhere. Over the decades, methods have been developed to bind technetium to a variety of inorganic and organic compounds, enabling it to reach many different kinds of target tissues.

Another imaging technique that has gained popularity since 2000 is **positron emission tomography, PET**. It employs positron-emitting



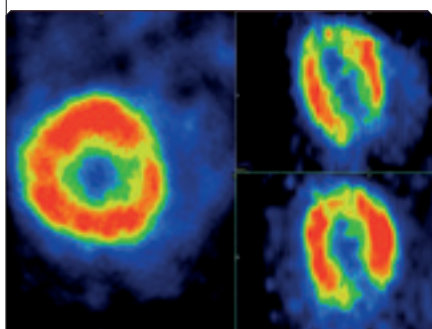
In hadron therapy, all the energy of an ion beam is delivered to a precise target location – the tumour – without damaging surrounding tissues

A patient being treated with carbon-ion therapy at the Heidelberger Ionenstahl-Therapiezentrum, Heidelberg University Hospital



IMAGING

The most used nuclear imaging technique is **single-photon computed tomography**, or **SPECT**, in which the gamma-rays, emitted in all directions by a radioisotope that has been injected into the body, are detected by a special gamma camera. The camera scans the patient, or organ site, from all angles, collecting data on the location of the points of emission.



PET images of a rat heart using a specialised state-of-the-art small-animal scanner

MTA Atomki, Hungary/ ST Microelectronics/ Philips/ ENIAC CSI

isotopes, which are injected in the same way. The positrons emitted annihilate when they come into contact with ordinary matter to release a pair of gamma-rays that fly off in opposite directions along a so-called line of response (LOR). The pairs can be identified because they reach detectors positioned on opposite sides almost simultaneously; their point of origin can then be ascertained along the LOR. Again, an image can be reconstructed. The positron-emitting isotope most commonly used is fluorine-18 combined with a glucose derivative that is easily distributed in the body. Because it has a short half-life of just under two hours, the radiation dose is low.

THERAPY

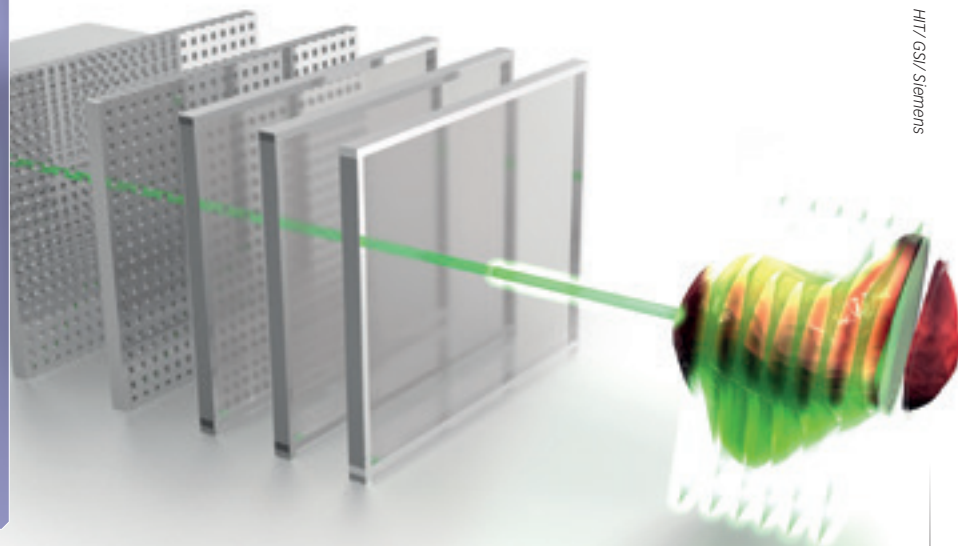
A direct spin-off from nuclear physics research is the use of accelerated beams of nuclear particles (hadrons) to treat cancer. Thin pencil-like beams of protons, and more recently carbon-12 nuclei (as ions), are used to selectively irradiate

a tumour in the same way as in conventional X-ray 'teletherapy'. The energetic hadrons break up the DNA strands within the tumour cells so that they die. The advantage of **hadron therapy**, is that most of the particle energy is deposited within a small volume inside the tumour, thus sparing healthy tissue. This makes it ideal for treating tumours close to organs at risk and those in children, for which exposure to radiation should be minimised. Since its launch in 1954, about 100,000 hadron-therapy procedures have been carried out across the world, of which approximately 10,000 are with carbon ions. It is still quite an undeveloped clinical procedure with considerable potential for expansion.

Another therapeutic approach is to inject radioisotopes chemically attached to molecules that are preferentially taken up by cancer cells. **Targeted radionuclide therapy** is best used to reach cancer cells that have spread and distributed metastases that cannot be reached with surgery or external radiation therapy.

HADRON THERAPY

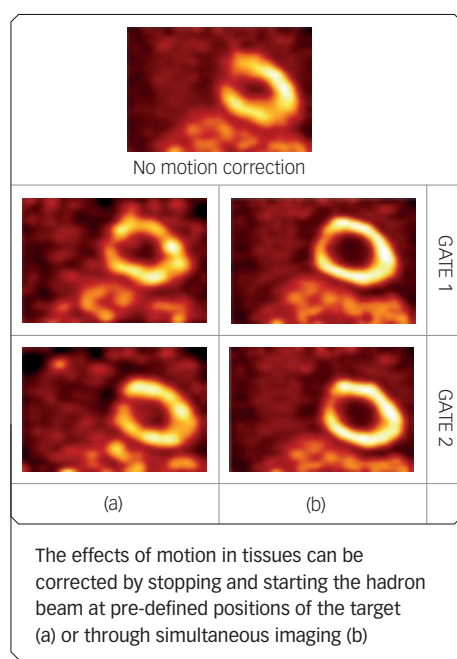
Huge progress is being made in advancing the benefits of hadron therapy – in which nuclear physics research plays an important role



HIT / GSI / Siemens

In hadron therapy, the ion beam is scanned across the tumour in 'slices'

Hadron therapy has several advantages over X-ray therapy. It can accurately deliver a highly controlled dose of radiation to the tumour, while sparing surrounding healthy tissue. It is more effective at treating highly-resistant tumours. Moreover, the reduced exposure of the normal tissue makes it possible to reduce the number of treatments.



area at different depths. Tumour tissue is not homogeneous, and dose-painting ideally allows the amount of radiation reaching different parts of the tumour to be modified. Progress and outcomes can be monitored through imaging. This means that doses can be delivered in fewer treatments, which is cheaper and aids patient recovery.

MOVING TARGETS

A major issue in any treatment is the fact that tumours and normal organs move, and so compensatory scanning methodologies are being developed that can take account of, for example, breathing or bowel movement. The target can be scanned more than once to average out the motion (re-scanning), or the beam can be stopped and started to coincide with a pre-defined position of the target ('gating'). Another promising option is to track the motion using simultaneous imaging to guide the beam (tracking). Charged particles generate positron-emitting isotopes in the patient, which can be exploited as a PET imaging agent, both in treatment monitoring and beam guidance. Such techniques will allow clinicians to treat tumours in the lung, the rectum, and in the left breast (without affecting the heart).

THE IDEAL PROCEDURE

A state-of-the-art set-up would consist of a compact accelerator (see p.7), which can deliver highly tuneable beams to a patient lying in front of a gantry that is rotated to accommodate different beam arrangements.

A crucial part of the procedure is the treatment planning. The target tissues are imaged in 3D using X-ray CT scanning, magnetic resonance imaging and/or PET (see opposite). The images are taken in sequential segments to identify the target volume and the position of the organs at risk. Computer simulation is then carried out to determine the energies and orientation of the beams that will achieve the correct level and distribution of the radiation dose, together with the number of treatments needed.

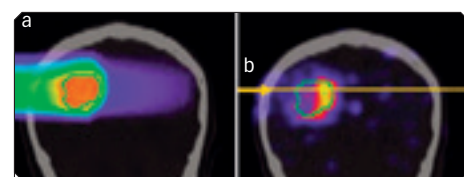
The computed dosage is then delivered by 'painting' the beam across the target

COMBINED THERAPIES

An important part of cancer therapy is to assess the type and range of treatments needed. Particle therapy can not only shrink or kill the main tumour, but also boost an immune response, which can then be amplified by immunotherapy (using target antibodies that attack cancer cells). Such combined treatments would also target metastases, leading to much improved survival prospects for cancer sufferers.

LOCATION OF THERAPY CENTRES

Proton therapy is available in 42 centres worldwide with more than 30 being planned. Carbon-ion therapy is carried out in eight centres in Germany, Italy, Japan and China.

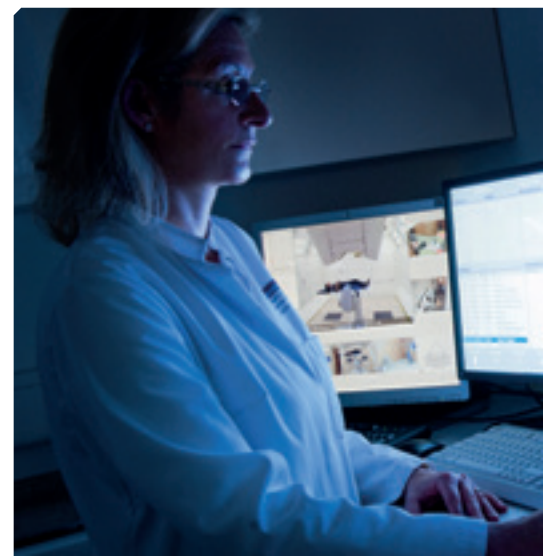


Bauer / 2013

Carbon-ion therapy (a) can be combined with PET imaging (b) using positron-emitting isotopes generated in the irradiated tissue after the delivery of the treatment dose

NEW TREATMENTS

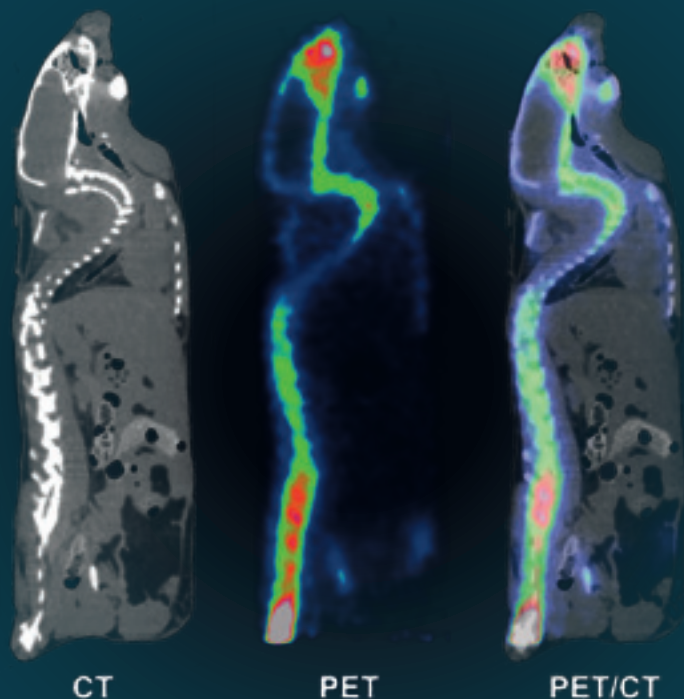
Protons and carbon ions are not the only particles that can be used in therapy. Helium ion beams might offer a lower-dose, better-targeted treatment than protons for young cancer sufferers, because these ions scatter less than protons. Oxygen-16 ion beams are being studied as a more effective alternative for treating hypoxic tumours such as those characterising pancreatic cancer, which are very radiation-resistant and for which the therapeutic outcomes are currently poor.



MEDICAL IMAGING

Nuclear imaging techniques, SPECT and PET, are invaluable tools both in the clinic and the pharmaceutical research laboratory

A combined PET/CT image of a mouse gives optimised information about its internal organs



CT

PET

PET/CT

SPECT and PET are both capable of visualising the physical functioning of tissues and biomolecular changes by attaching the isotope to a selected molecule. For example, metabolic activity in the brain can be followed with the PET fluorine-18 tracer, fluorodeoxyglucose (FDG). Although SPECT is still better established than PET, interest in the latter is increasing because it offers twice as high spatial resolution – at about 4 mm.

THE NEED FOR HIGHER RESOLUTION

Both imaging techniques are entering a new era, driven by the need for higher resolution and improved molecular specificity. Small-animal imaging is an essential component of biomedical research, in particular in following the uptake of drugs. However, a resolution of better than 1 mm is needed to study the brain of a mouse, for example. More advanced instrumentation is therefore required that is capable of imaging smaller structures. The early diagnosis of disease at the molecular level, radiotherapy planning, and the simultaneous imaging of moving organs to guide treatment (see opposite), also demand the highest resolution possible.

Planning and monitoring hadron therapy
at Heidelberg Ionenstahl-Therapiezentrum



RECENT ADVANCES

Fortunately, nuclear and particle-physics research is providing a range of developments that is benefiting medical imaging.

- New photodetectors based on miniaturised semiconductor chip designs have been developed to enable compact, higher-resolution instruments to be designed for small-animal PET.
- To pair up the back-to-back annihilation gamma-rays in PET requires being able to measure detection times with a precision of half a billionth of a second. Image quality can be improved by narrowing the location of the annihilation. This is achieved by measuring the time difference of arrival at the detectors of the two gamma-rays (each will have travelled different distances and passed through differing tissues). This requires dedicated reconstruction algorithms, which are developed in nuclear physics laboratories.
- A further potential improvement in localisation that is creating great interest could be obtained using a new class of PET isotopes in which a third, additional gamma-ray is emitted by the daughter nucleus of the positron-emitting isotope. This can be detected by a gamma-ray camera, and again, by measuring the time after the annihilation event, its trajectory used to triangulate the point of origin.



An advanced combined PET/MRI system recently developed

A. Del Guerra / 2013

In addition, nuclear reactions induced in tissues by a therapeutic hadron beam (such as carbon-12 ions) may generate positron-emitting nuclei (such as carbon-11), which can then be used to generate PET images with a suitable detector.

All these processes require a deep knowledge of nuclear processes, as well as the facility to design ultra-fast position-sensitive detectors, and optimised simulation and reconstruction software.

COMBINATION IMAGING

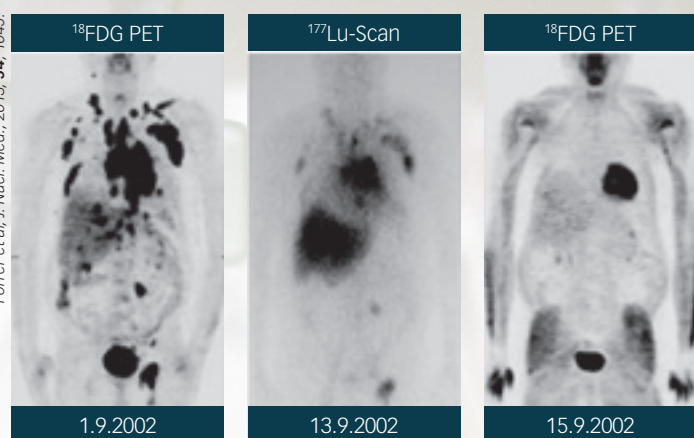
Today, SPECT or PET are generally combined with X-ray CT scanning in order to provide structural information that renders a more quantitatively accurate image. To obtain even more valuable complementary information, the option of additional magnetic resonance imaging (MRI) would be preferable. However, the high magnetic field associated with MRI presents challenges for traditional PET and SPECT instrumentation – which is being addressed through the development of a new generation of solid-state detectors.

RADIOISOTOPES FOR MEDICINE

Identifying and producing new economically and medically useful radioisotopes is an important research area in nuclear physics

Virtually all radioisotopes have to be produced by the artificial transmutation of stable elements via nuclear reactions first investigated at nuclear physics facilities. During recent decades, more than 3000 radioactive isotopes have been discovered in this way. While many are very short-lived or extremely difficult to produce, several dozen have properties that make them potentially useful for medical applications.

Forrer et al, J. Nucl. Med., 2013, 54, 1045.



The effectiveness of radio-immunotherapy using lutetium-177 on a patient with widespread lymphoma: left shows the initial PET scan; the distribution of the radioisotope is shown in the middle image; and right shows complete remission after the radiotherapy

A medical isotope must:

- for imaging, emit long-range, medium-energy radiation so that it can be detected outside the patient's body;
- not emit (non-beneficial) high-energy radiation that would require excessive radiation shielding or isolation protocols;
- for therapy, emit short-range radiation that deposits the maximum amount of energy in a defined target tissue volume;
- have a half-life long-enough to be delivered, but short enough not to cause unnecessary radiation exposure for the patient or present waste-disposal problems;
- have appropriate chemical properties so that it can, for example, seek out target tissues, or be coupled to molecules that preferentially bind to specific tissues;
- decay or be expelled from the body within a suitable period;
- be produced in large enough amounts for clinical use at an economic cost.

RECENT SUCCESSES FROM NUCLEAR PHYSICS

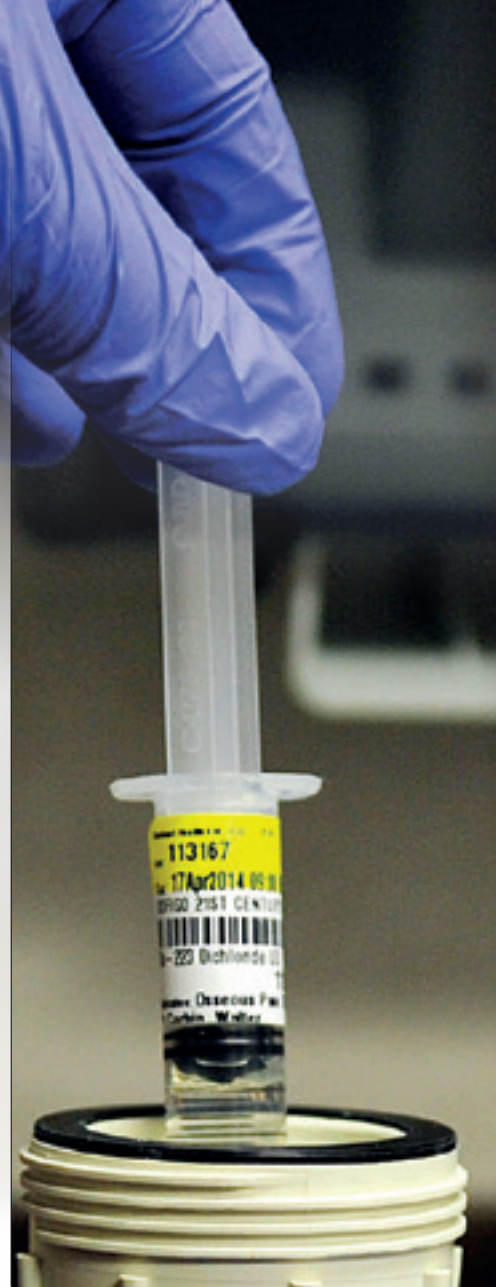
Very short-lived isotopes are accessible in the clinic from the decay of longer-lived 'generator' isotopes. The PET isotope, **rubidium-82**, which is a promising agent for studying the blood flow in

heart muscle, has a half-life of only 75 seconds. It is generated from strontium-82, which can be made only in the larger accelerators based in nuclear physics centres. To meet rising demand, new dedicated machines are now coming online.

Such machines can also make the long-lived generator isotope, germanium-68. Its decay produces the PET isotope, **gallium-68**. Via chemical compounds called chelators, it can be attached to a large variety of cancer-specific molecules, such as peptides that bind to certain cell receptors found in neuroendocrine tumours, to produce successful PET scans.

Lutetium-177 can also be attached via chelators to large organic molecules, and its nuclear decay properties (half-life one week, low-energy, short-range beta radiation) make it ideal for the targeted radionuclide therapy of neuroendocrine and other tumours. The side-effects are much milder than for chemotherapies, so its use is rapidly growing.

Isotopes that emit **alpha particles** offer a new type of targeted radiotherapy that is now coming to the fore. As in hadron therapy, all the energy is deposited within a short range. The first alpha-emitting radiopharmaceutical based on **radium-223** has now been approved and is used to treat otherwise difficult-to-treat bone metastases.



Radium-223 marketed as 'Xofigo' is the first available alpha emitter for targeted radiotherapy

THERANOSTICS

The planning of cancer treatments is hampered by the fact that – depending on their cell biochemistry – patients respond differently to chemo- or immunotherapy. Nuclear physics can offer a more personalised approach known as theranostics. Using 'matched pairs' of diagnostic and therapeutic isotopes (for example, **copper-64** and **copper-67**, that combine with the same targeting vector), clinicians can tailor the radiation dose needed to maximise success. Just recently, nuclear physicists even identified and produced a matched quartet of **terbium isotopes**, which provide a set of decay characteristics producing excellent tumour visualisation and therapeutic efficacy. Theranostics is also possible in teletherapy, using high-energy proton beams for simultaneous proton radiography and treatment. Collaborative work is underway to establish economic methods of production.

A modern compact cyclotron used for making medical radioisotopes

Nuclear medicine and radiation therapy offer some highly effective strategies for combating disease, but their application is limited by the current availability of dedicated infrastructures to provide radioisotopes or ion beams for therapy. The demand for radioisotopes is increasing rapidly, and there are supply bottlenecks for some well-established radioisotopes, such as the generator of technetium-99m – molybdenum-99, as well as some new isotopes with clinical potential.

The development of hadron therapy is also curtailed by the fact that the accelerators needed to generate the beams are large and expensive. The most serious obstacle, hampering the worldwide spread of hadron-therapy centres, is the high cost. Should it drop enough to match that of X-ray therapy, hadron therapy could become the dominant – if not the sole – radiotherapy offered.

A major challenge for nuclear physicists, therefore, is to develop economic methods of production and delivery. New generations of affordable, more compact accelerators (see opposite) are now being developed that could considerably expand the curative value of nuclear particles and radiation.

THE IMPORTANCE OF COLLABORATION

Nuclear medical research is extremely interdisciplinary, and nuclear physicists aim to work closely with other specialists:

- chemists and life scientists – in the optimisation of nuclear medical procedures;
- instrument specialists and software engineers – in developing optimised instrumentation such as detectors, electronics and computer programs;
- clinicians – in designing effective treatment strategies;
- and commercial instrument companies – in developing cost-effective treatment systems.

Enabling nuclear technologies for medicine

Many non-invasive diagnostic techniques take advantage of devices and technologies that were originally developed for research in subatomic physics. These include:

- superconducting magnets required for MRI, itself a technique based on nuclear physics;
- X-ray digital detectors called charge-coupled devices;
- a new generation of advanced chips for detecting high-energy radiation;
- computer algorithms for data-processing in nuclear physics, also applied to treatment planning.

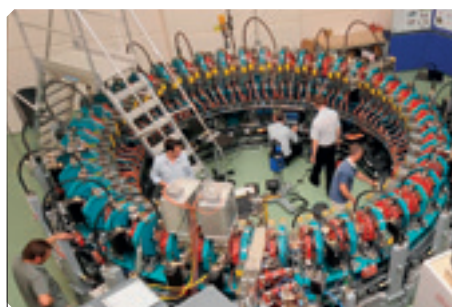
GOALS AND CHALLENGES

The future of nuclear medicine and radiation therapy is extremely promising



Novel accelerator schemes

One of the first accelerators developed was the cyclotron, in which charged particles travel in a spiral controlled by magnetic fields, while being accelerated by a radio-frequency electric field. Small, low-energy cyclotrons are in use today to make medical isotopes on-site, and for proton therapy. However many isotopes must be made at higher energies, requiring other types of circular and linear machines that are in operation only in central research facilities. The same argument applies to the production of ion beams for therapy. A great deal of work is going into developing novel compact accelerators – which might even be installed directly in a treatment room.



The EMMA proof-of-principle FFAG accelerator developed in the UK

• THE FIXED FIELD ACCELERATING GRADIENT (FFAG) ACCELERATOR

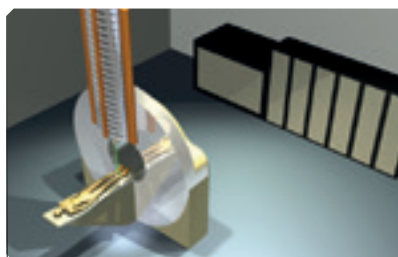
Work is being undertaken on a compact circular accelerator that is similar to a cyclotron but with an advanced magnetic-field configuration, enabling higher energies to be reached in smaller dimensions.

• THE DIELECTRIC WALL ACCELERATOR

A very compact device, which employs a linear electromagnetic wave travelling down a tube made of insulating material to accelerate particles, is now being developed for proton therapy. The design has the advantage that the energy and intensity of the beam can be modulated to deliver a precise dose to a tumour.

• LASER ACCELERATION

Another concept that is developing fast, though still far from clinical use, is that of laser-driven acceleration in which a plasma of charged particles rides the wake of an intense table-top laser beam.



An artist's concept of a compact proton therapy system based on the dielectric wall accelerator

LINAC/Tomotherapy/University of California, Davis

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