HARNESSING THE POWER OF PROTONS

Photo 1:
Prof. Paweł Olko under the "gantry", with part of this construction holding the magnets that curve the proton beam visible

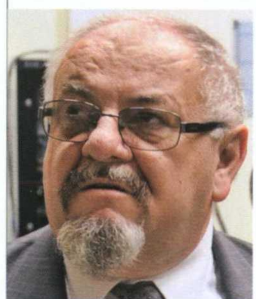
The Cyclotron Center, delivering proton therapy for certain types of cancer, opened recently in Bronowice, Kraków. We talk to **Prof. Marek Jeżabek**, Director of the Niewodniczański Institute for Nuclear Physics, PAS, and **Prof. Andrzej Kawecki**, radiotherapist, clinical oncologist and vice-chairman of the Scientific Board at the Marie Skłodowska-Curie Institute of Oncology.

AKADEMIA: **How did the idea of physicists working alongside doctors at your cyclotron center first arise?**

MAREK JEŻABEK: The PAS Institute for Nuclear Physics has a tradition of collaborating with medical researchers, dating back decades. It all started with the Institute buying and importing a cyclotron from the Soviet Union. We used it to deliver radiation therapy to cancer patients in the form of neutron beams. Such therapy was abandoned due to its low precision, although we revived it in the 1990s with the aim of treating ocular melanoma with protons accelerated using the AIC-144 cyclotron designed by our staff. Unfortunately the protons it delivered were of insufficient energy. For protons to travel a distance of 30 mm through water – the equivalent of a human eyeball – they must be accelerated to an energy of 60 MeV, while we were only capable of generating 40 MeV. Fortunately we convinced the decision-makers that we had a viable way to adapt the AIC-144 cyclotron, and we received funding to modernize the accelerator and procure a therapeutic chair. In 2009, we were ready to start administering therapy for ocular cancer.

Conducting several rounds of successful treatment for ocular melanoma helped us obtain significant funding for the construction of the Bronowice Cyclotron Center. Originally our intention was to transfer ocular therapy from the by-then quite old AIC-144 to new equipment, but as work progressed, we developed a more ambitious plan: to construct a gantry. A gantry is a massive cylindrical structure holding huge magnets, weighing a total of 20 metric tons, curving the proton beams. It guides the beam around the patient, allowing us to deliver the radiation from different directions.

Following a lengthy application process, we secured the necessary funding for the project. The first gantry models with a scanning beam appeared at around the same time. The way they work can be compared to electron beams in old-type kinescopes – they irradiate an entire transverse section, pixel by pixel, specifically tracing out the shape of the tumor at the selected depth. Precision of 1 mm or higher is key here, since the method works by destroying the DNA in cancer cells. The proton beam has sufficient energy to penetrate up to 30 cm into the body, allowing it to reach almost any tissue, as well as being adjustable to perfectly match the shape of a tumor. The Institute for Nuclear Physics has acquired two such devices, thereby making the suburban Kraków district of Bronowice home to one of the most advanced proton therapy centers in the world.



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What are the benefits of using such proton radiation, instead of conventional radiotherapy using electromagnetic waves?

The way protons interact with matter is that the maximum biological effect appears at the end of their path. This means that by selecting the energy and range, we are pinpointing the precise location where the protons reach their maximum therapeutic properties.

Radiation loses energy gradually as it penetrates tissue. For electromagnetic radiation, the relationship between ionization (and the resulting biological effect) and the path travelled within the patient's body is a wide curve, largely corresponding to a high dose in front of the tumor being targeted and behind it. The situation is completely different for protons: starting from a relatively low value, there is a narrow maximum (known as the Bragg peak) then a rapid fall almost to zero. This means that if we select the energy correctly, we can adjust the radiation beam so that it doesn't damage organs in front of or behind the tumor. For example, when we're dealing with an ocular tumor which is spatially separate from the optical nerve, we can direct the beam in such a way as not to damage the optical nerve. For tumors outside the eyeball, we can select the beam to achieve an optimal fit to the tumor's shape.

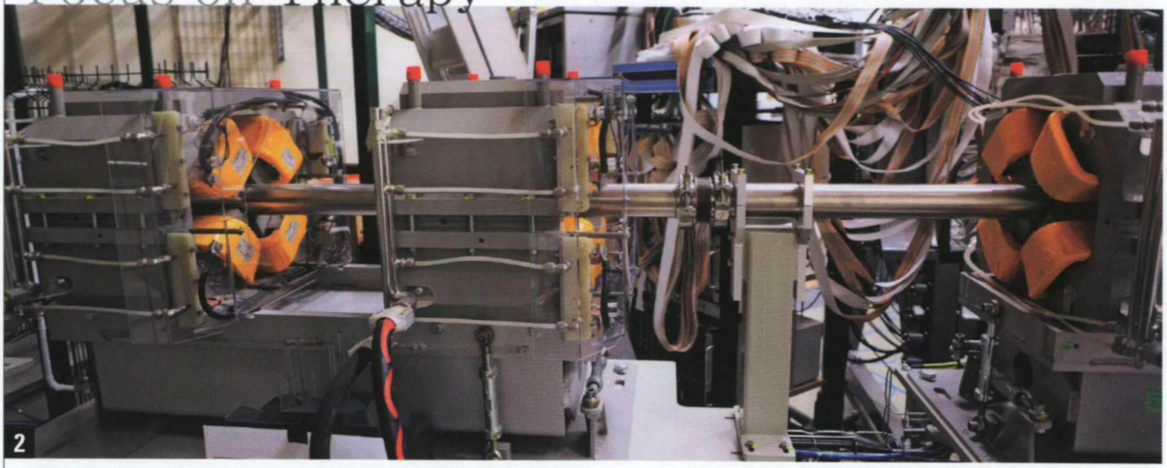
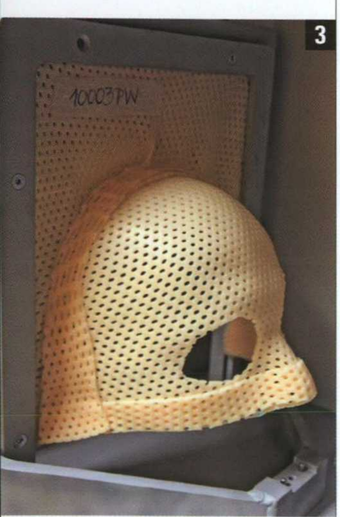


Photo 2:
Section of the ion channel guiding the proton beam from the cyclotron to the station in the experimental lab
Photo 3:
Mask used to position the patient for ocular radiotherapy
Photo 4:
Station with a chair for treating ocular tumors



Does the Institute only treat adults? Certain ocular tumors are more common in children.
The method we use is especially effective in children, since any damage incurred during radiotherapy in a young, growing body has more serious consequences than in adults. Young people are also at a higher risk of side effects, such as tumors caused by radiation; that's why proton therapy is widely regarded as a first-line treatment for many cancers in children. For adults, the situation is made more complicated by funding: the cost of delivering proton therapy to a single patient is approx. 100,000 zlotys, while a similar result can be obtained using other methods costing approx. twenty to thirty thousand. It is a new therapy, and we don't have long-term studies showing results years or decades following treatment, which makes the financial decisions all the more difficult.

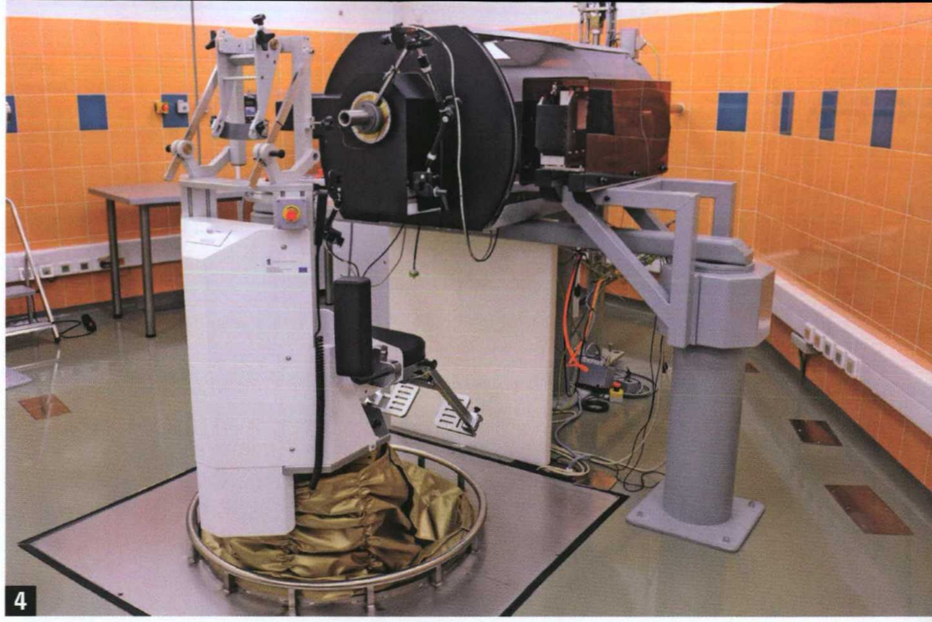
Will the National Health Fund start refunding treatments for patients with other types of tumors?
Obtaining a refund for any medical service has many stages. To start with, the health minister commissions the Agency for Health Technology Assessment and Tariff System to conduct a pricing evaluation of the medical procedure. They then decide whether the procedure can be refunded in Poland, and if the decision is positive, the National Health Fund announces a call for bids. At present, proton therapy is only refunded for ocular tumors. In other cases, the patient can apply for a refund for treatment carried out abroad. The Agency is currently assessing the procedure for the treatment of head and neck cancers.

What's the therapy like from the patient's point of view?
The radiation is delivered in several doses. In the case of ocular cancer therapy, this means four radiation doses delivered on consecutive days. The radiation process itself lasts less than a minute, although it takes around half an hour to set up the patient and the equipment so that the beam is targeted precisely at the affected area. Treatment of other cancers generally requires the delivery of dozens of doses.

The therapy is conducted under the banner of the National Hadron Radiotherapy Center. Why is that?
When we were applying for funding for a cancer treatment center, we were aware that the project is important not only for the Institute for Nuclear Physics, but for the entire country. Additionally, it was essential for us to work closely together with other centers to implement it. In 2006, we were aware that our Institute was not able to meet the challenge alone, which resulted in the creation of the National Hadron Radiotherapy Center consortium. We initially assumed that the Institute for Nuclear Physics would use protons, while more ambitious and expensive procedures would be conducted in Warsaw. At the time we were considering not just proton therapy but also carbon ion therapy. The protons and neutrons that form the atomic nucleus are types of strongly interacting particles, known as hadrons, hence the name of the consortium.

Tell us more about carbon ion therapy.
Our understanding of it has improved vastly since 2006, when the Center was first being discussed, and the original hopes have faded somewhat. However, the therapy has not been fully abandoned, and it is being successfully delivered at the renowned oncology center in Heidelberg in Germany. The problem is that the type of gantry needed for carbon ions is significantly larger and more expensive than the proton equivalent. We have had to put the idea on hold for now, although it wasn't an easy decision.

What other research do you do, apart from delivering radiotherapy? The Center also has an experimental lab.



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Our cyclotron can be used with several stations. One line actually runs to an experimental lab, where we have been conducting basic nuclear physics research for the last two years. We are also testing the resistance of electronics to radiation, which is a major issue during space flights, since protons are what cosmic radiation consists of. We also study scintillators – a new type of crystal used in detectors applied in particle physics, and we are starting a research program in radiobiology.

The cyclotron has a proton beam with energy of 230 MeV, which means we have become an attractive lab for nuclear physics research. We have two detectors; we obtained one from the Netherlands, and largely built the other ourselves. They allow us to study interactions of very high numbers of nucleons, which is a key topic in theoretical nuclear physics. Although outside the world of physics we are best known for our cancer therapies, basic research is actually the Institute's main activity and it drives our scientific ranking: we have the A+ category and the status of a Leading National Research Center.

We have 550 staff and 70 doctoral students. Some are involved with proton radiotherapy, but they also work in other branches of physics. We are also in the final stages of fitting out a huge brand new laboratory for basic research and imaging using physical methods.

Do you also conduct research in biological sciences?

Absolutely. We are developing a process of irradiating various biological samples with protons of different energies. We also use the old AIC-144 cyclotron and a Van Der Graaf accelerator generating microbeams, which allows us to target protons in a selected fragment of the atomic nucleus. We also use microbeams of X-rays. The PAS Institute for Nuclear Physics has unique capabilities of studying interactions of different types of radiation with living matter and biological objects.

Participants in the National Hadron Radiotherapy Center include many medical institutions. Tell us about your work with medical professionals.

We treat patients referred by the Department of Ophthalmology and Ocular Oncology at the Jagiellonian University Hospital, which is one of our three main partners. We also work with the University Children's Hospital in Prokocim – as I already mentioned, childhood cancer is the main indication for proton therapy. Our third partner is the Kraków Division of the Marie Curie-Skłodowska Institute of Oncology, although we actually work with the Center as a whole, including the divisions in Warsaw and Gliwice. Additionally, the Medical University in Katowice and the Świętokrzyskie Oncology Center in Kielce have expressed an interest in working with us.

I think that in the next few years, we'll be able to treat up to 700 patients each year using both gantry stations; for ocular melanoma this meets the national demand for this type of therapy. For oncologists, it's obviously excellent news that Poland will be able to conduct state-of-the-art proton radiotherapy. ■

How does it work?

Prof. Paweł Olko (photo on p. 4), Bronowice Cyclotron Center, PAS Institute for Nuclear Physics in Kraków during a lecture held as part of the PAS Wszechnica initiative:

As physicists, our task was to facilitate the construction of the cyclotron and prepare it for therapeutic applications. When we were installing the cyclotron, we brought Kraków traffic to a standstill, and we had to demolish the gateway to the Institute property to actually deliver it. Everything is working as it should now, and we are ready to start treating patients.

Radiotherapy aims to destroy the DNA of cancer cells. In contrast to photons, most of the energy of the proton beam is released at the very end of its path, which prevents radiation damage to tissues along the way. The beam needs to be accelerated to allow it to reach the required depth. This is achieved using the cyclotron, which works a bit like a swing. An electrical field accelerates the proton beam, and a magnetic field curves its path and prevents it from escaping. Although we don't need especially high energy to accelerate the beam, it needs to be applied at precisely the right points. The next issue is matching the beam to the shape and location of the tumor. We first irradiate the deepest part of the tumor with a beam with the highest dose; the dose is then reduced to irradiate the section closer to the surface, and so on. We use massive magnets to manipulate the beam by curving its path. The gantry we use for this weighs 100 metric tons and has a diameter of 11 meters, yet it allows us to achieve a precision of around half a millimeter. We can monitor the results of the radiotherapy using positron emission tomography (PET) imaging, since as the proton beam passes through tissue, it induces the formation of radioactive isotopes with short half-lives. This allows us to check straight away whether the therapy was successful.

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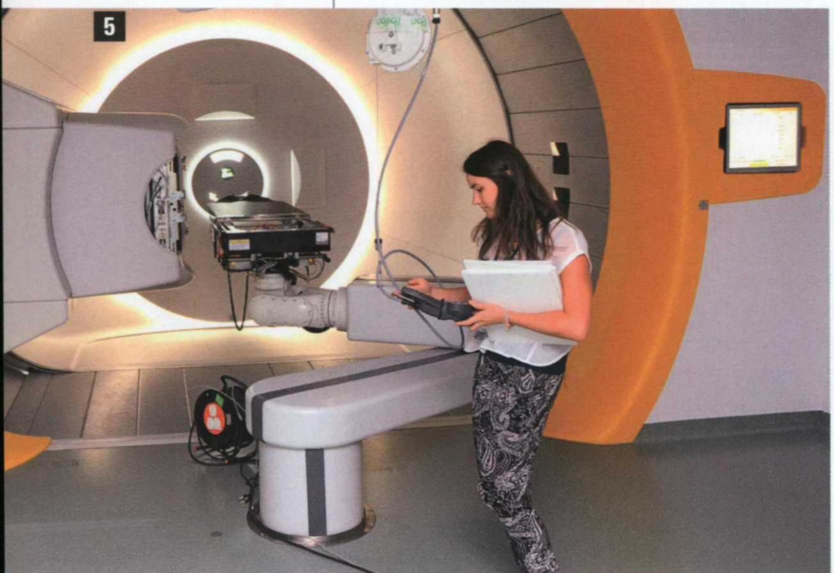
ACADEMIA: **As a doctor, what is your view on proton therapy?**

ANDRZEJ KAWECKI: It's shrouded in many myths, with the main one claiming it is more effective than conventional radiotherapy. The truth is that both methods have a similar effect on cancer cells. The advantage of proton therapy is that it provides a higher level of protection for critical organs – healthy tissues which are sensitive to radiation. The specific physical properties of proton beams reduce the risk of severe side effects in situations when the radiation beam passes through a critical organ.

Is the method well regarded by oncologists and radiotherapists?

Of course! For example, the US alone aims to run 20 centers conducting proton therapy by 2020. There are many such institutions in Europe, too. Work is ongoing on developing recommendations for best practice, so it can't be said that the method is a gimmick or ineffective. But, equally, we can't claim that it's a revolution in oncology. We should remember that proton therapy has limitations, and keep things in a balanced perspective when reporting on it to the public. All new medical technologies stir hope in patients, but they also bring demand, even from people who don't qualify for them.



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So who does qualify?

Indications are quite well defined. Proton therapy is recommended to treat tumors near the base of the skull, which is the location of many critical organs such as the optical nerve and the brainstem. Another indication is cancers of the spinal cord, where it is also essential to protect critical organs, certain head and neck cancers which require repeated irradiation, and most of all childhood cancers. Since children's bodies are developing rapidly, it is essential to reduce the risk of side effects. The main advantage of proton radiotherapy is that it reduces side effects on a longer time scale, that is over six months after completion of the treatment.

However, in other cases, such as lung cancer, prostate cancer and breast cancer, no advantages of proton therapy over conventional radiotherapy have been found. Still, the list of indications for proton therapy is growing, so it's quite possible that in years to come it will be recommended for a wider range of cancers.

I hope that we will have at least two proton therapy centers in Poland, although it's simply not true that around eight to ten thousand patients require this type of treatment every year. The real figure is significantly lower.

While we're on the subject of statistics, how many people do you refer for proton therapy every year?

The Cyclotron Center in Bronowice is currently waiting for Poland's Health Technology Assessment and Tariff System Agency to evaluate the cost of proton therapy, so patients requiring the treatment are currently being sent abroad, mainly to Germany. As regional consultant for the Mazowsze region, I have been referring around 20 patients per year, although the numbers of patients who potentially need proton therapy are significantly higher. They are estimated to be between 500 and 1500 patients per year, and personally I lean towards an estimate of 1200-1500. Current recommendations mean that the majority of the patients are children. Once we start offering proton therapy in Poland, we will be able to conduct wide-reaching tests and controlled clinical studies in order to determine new indications and to improve the technology.

Prof. Jeżabek mentioned that this is an ambition of the Medical University of Warsaw, one of the participants in the consortium.

That's right. The plan for developing proton therapy in Poland, laid out back in 2005 and 2006, calls for two therapy centers to be opened. The center at the Institute for Nuclear Physics in Bronowice is the first. It has a state-of-the-art cyclotron with two gantry stations, therapeutic exits implementing the latest technologies, and radiation beams with adjustable intensity. The second stage was going to be opening a hadron therapy center in Warsaw. Originally, ten years ago, there were plans to locate it at the Oncology Center, but in 2009 it was decided to open it at the Medical University of Warsaw. So far everything remains at the planning stage.

The Institute for Nuclear Physics isn't a medical center. Logistically speaking, how do you work together?

It's true that it's unusual for therapy equipment to be located somewhere which isn't a hospital or a radiotherapy center. Close cooperation with an oncology center, and more specifically the Oncology Center in Kraków, is therefore crucial. This is not a question of science but of routine clinical practice. Ideally, oncology centers in Poland should refer patients to Bronowice, since it should be easier and I hope cheaper for them to do so.

In any case, we really need a team of expert physicists, since they are qualified to set up and maintain the correct technical parameters of the radiation aimed at the target determined by the doctor.

Radiotherapy involves a cycle of doses. How does it actually proceed?

Conventional radiation therapy is delivered daily between Monday and Friday, and the weekend break is essential to minimize radiation toxicity. Depending on the cancer, the cycle takes between four and seven weeks. If the patient is in overall good health and we aren't expecting them to have severe side effects, the therapy can be delivered on an outpatient basis.

What are the prospects for research into new radiotherapy methods being conducted at centers such as Bronowice?

Evidence-based medicine means that all new technologies must be backed by results of highly reliable, controlled clinical trials before they are brought into use. In oncology, the most reliable studies are randomized trials, that is those comparing results obtained in patients randomly assigned to be treated using conventional or experimental methods. If the results show the experimental therapy to be more effective, it becomes the new standard course of treatment. Unfortunately it's difficult to conduct randomized trials on proton therapy, since they require large patient populations. Accessibility is also a barrier, as is the fact that the therapy is frequently used to treat rare types of cancer. There is also the question of ethics. As such, we make decisions on the basis of evidence with a third degree of reliability, using results obtained at a single center or retrospective analysis. As more proton therapy centers start treating patients, more data will become available. Having the capacity for proton therapy in Poland means we will be able to join controlled international studies, so we must strive to develop and expand the Bronowice Center. It is very much in the interests of Polish oncology.

Photo 5:
Therapeutic station with the patient's bed in the gantry

Photo 6, 7:
Staff training at the Bronowice Cyclotron Center – patient being prepared for a CT scan

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