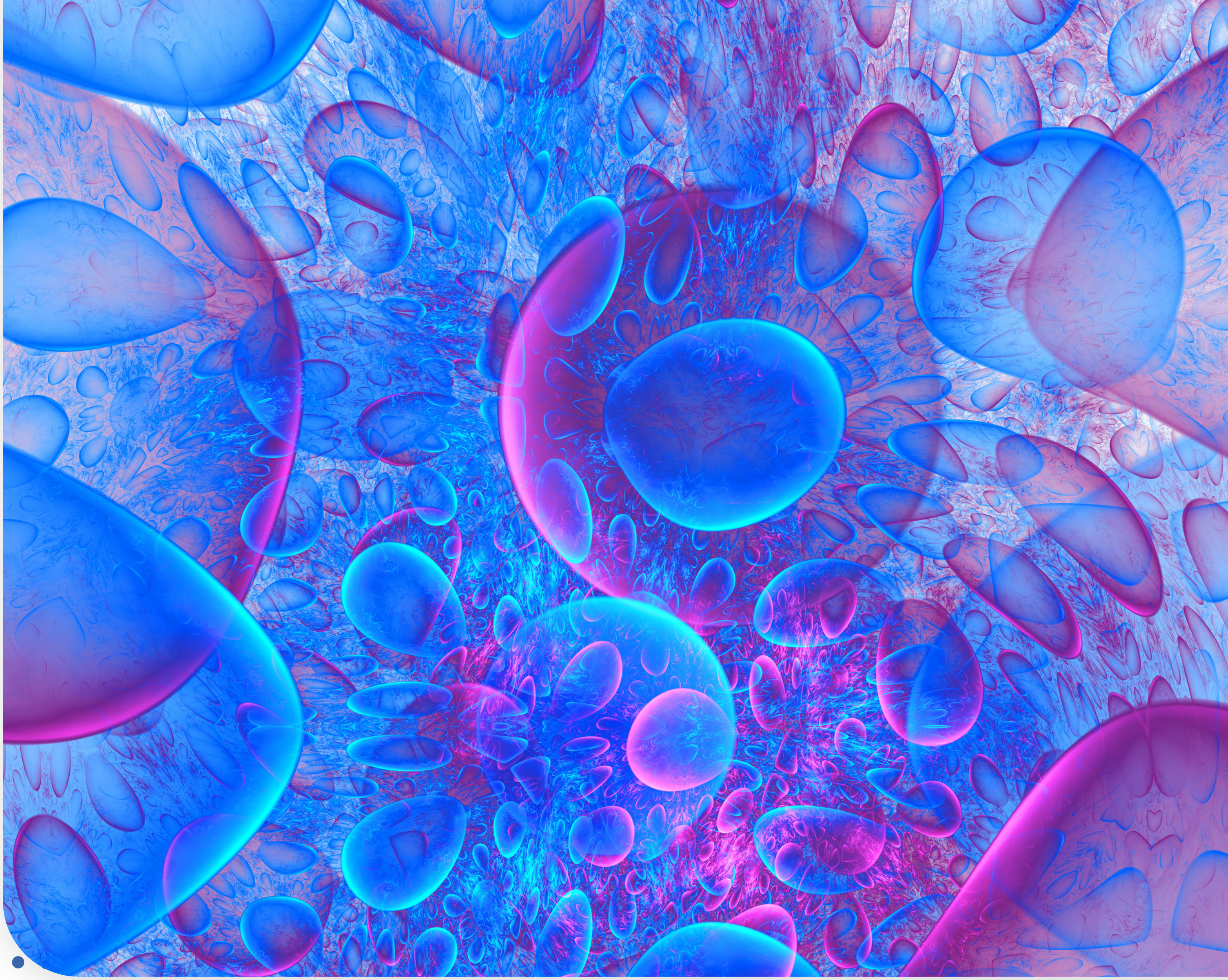

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Biologically Targeted Tumor Specific Particle Therapy

Expanding Radiotherapy's Reach: Dealing with Resistant Tumors

Radiation therapy is a cornerstone of modern cancer treatment. Clinically efficient and cost-effective, conventional radiation therapy has played a significant role in broad improvements to patient survival rates and disease control. Today, conventional radiation therapy is used to treat approximately 50% to 60% of all cancer patients.

Yet conventional radiation therapy—including protons—is not an effective or practical option for many patients and many cancers. Conventional radiation therapy cannot be used to treat radioresistant and recurrent cancers. Its application is also limited by the high incidence of collateral damage to surrounding healthy tissue.

This is where a biologically targeted radiation therapy—boron neutron capture therapy, or BNCT—shows transformative promise: effectively treating the most difficult cancers, including brain cancer, head and neck cancers, and melanoma, while significantly reducing collateral damage and resulting side effects.

BNCT is not new. Discovered nearly a century ago, it has been studied clinically since the 1950s, progressively accumulating a strong and wide body of data supporting its safety and efficacy in treating patients with a variety of advanced tumors. Promisingly, BNCT is now becoming an accessible and practical reality, thanks to important new technical advances that can bring it closer to patients and into the hands of skilled medical teams.

Today,
RADIATION THERAPY IS USED TO TREAT
50-60%
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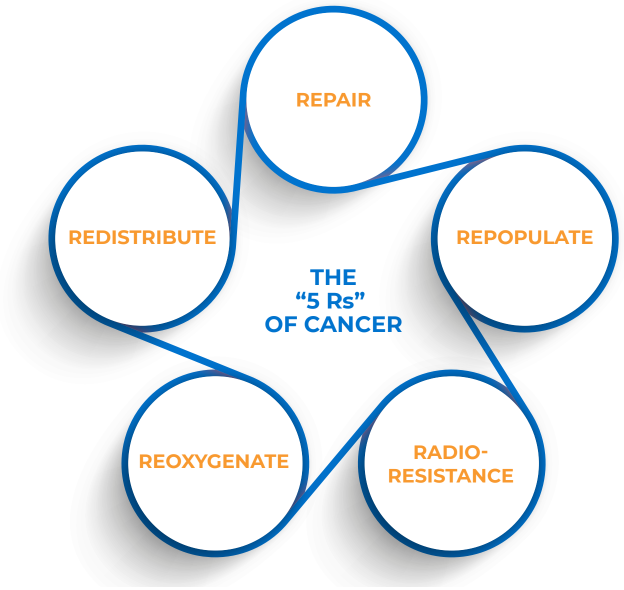
Resolving the Challenges of Radioresistant Cancers



Radiotherapy traditionally follows evaluation and treatment of cancers according to the "5 Rs": the ability of cancer cells to repair, redistribute, repopulate and reoxygenate, as well as their intrinsic radioresistance. Radiotherapy aims to cause enough damage to tumor cells that they cannot accomplish any of the above. However, conventional radiotherapy is often limited by the capability of some tumors to resist damage from therapeutic dose levels. One approach to resolving radioresistance is the use of multiple or fractionated treatments, delivered over a period of days or weeks.

Conventional approaches to resolving radioresistance typically present increased risk of harm to normal tissues from the radiation treatment itself. As photon radiation passes through the body on its way to tumors, it can irradiate healthy tissue and even turn some stem cells from non-cancerous to cancerous. This transition has been noted for glioblastoma and breast cancer.

Ideally, destroying cancer cells requires severe cell damage, including a double strand break of the DNA. But due to the hazards of higher therapeutic doses, conventional radiotherapy isn't always able to achieve a high level of damage at the outset. As a result, the cancer cells often have a chance to repair themselves over time, and certain cells are even able to repair double strand breaks.

Limitations of Conventional Radiation Therapy

The promise of BNCT is best understood against the backdrop of the state of conventional radiotherapy. These conventional radiation therapies deliver beams of very high-energy photons (X-rays) to kill the targeted cancer. While advances have made the therapy more precise and cost-effective over time, these changes have been incremental. Challenges remain and there are inherent limits to what can be achieved with conventional photon beam radiotherapy.

For example, as mentioned, the need to balance tumor-killing dosage against toxicities to surrounding tissues can hinder the ability to fully destroy a tumor. Safely delivering higher doses also demands complex geometrical calculations because the process involves multiple overlapping beams. Successful delivery of high-dose radiation to the target can be affected by movement such as breathing, swallowing, and even digestion, making it a complicated and error-prone procedure.

Tumor identification and targeting presents another challenge with conventional radiotherapy. Clinicians depend on imaging to precisely deliver high-dose radiation to the tumor, while sparing surrounding healthy tissues. But imaging quality and targeting precision may vary depending on the technique used and how technicians define the volume to be irradiated. Mitigation of these challenges is possible with image-guidance (i.e., MRI-guided radiotherapy or MR-Linacs) to some degree. But supplementary and highly specialized technologies can be expensive, and their complex and labor-intensive operation limits their application and practicality.

Particle Therapies: A Novel Approach

Proton and carbon ion therapies offer a novel approach to achieve the ideal treatment objective of destroying the tumor while not harming healthy tissue. These technologies enable the beams to be more precisely shaped and directed. The particles also move more slowly through the body, mitigating damage to healthy tissue. Because both types of particles possess an electrical charge, magnetic fields can be used to bend the particles into a well-defined beam focused on the tumor area. Beam delivery can match the tumor depth and more reliably deposit the energy only at the tumor location.

Particle therapy research began in the late 1930s—around the same time that BNCT was first studied. Clinical research in the 1950s showed proton therapy to deliver an equivalent effect to standard radiation, but at a higher cost. Nonetheless, activity continued and new centers began to spring up for patient treatment.

Carbon ion radiotherapy was developed in 1975 as a means to achieve results superior to proton therapy. However, the research and application of carbon ion therapy quickly stalled due to the significant expense and the need for patients to be treated at a nuclear reactor facility, which was used as the source for the ions.

Despite this slow start, particle therapies are resurging today: Research has advanced far enough to offer improved imaging, measurement, and delivery methods that make particle therapies more practical. Moreover, particle therapies gained renewed traction as possible solutions for difficult-to-target and radioresistant cancers. Led by Japan, modern particle therapies, including BNCT, which was approved for treating recurrent head and neck cancers in 2020, are being used in patient treatment and seeing increased clinical adoption and research funding.

Late 1930s	1950s	1975	2020
Particle therapy research begins	**Clinical research shows equivalent effect as radiation**	**Carbon ion radiotherapy is developed**	**BNCT is approved for treating head & neck cancers**

Particle Therapy Challenges

The primary challenge of proton and carbon ion therapy is selection and definition of the target volume. This requires advanced image guidance systems to calculate the shape and location of the mass, and to ensure the beam’s path covers all of the tumor while avoiding neighboring healthy tissue. Technicians may also need to allow for an additional margin around the tumor target area to help ensure that microscopic metastatic cancer cells are also destroyed.

In addition to patient movement challenges in geometric targeting mentioned earlier (breathing, swallowing), the tumor itself may also grow or shrink during the course of treatment. Ideally, this requires medical technicians to develop adaptive plans. Unfortunately, research shows that such plans are rarely initiated or implemented due to technology, time, and workflow constraints.

Proton beam therapy, in particular, still uses high-energy particles that fully pass through the body, exiting on the other side. While the particles can be shaped into a beam to avoid scattering, the energy level of the protons is such that when they do traverse healthy tissue, they can cause damage and side effects.

Finally, clinical research concludes further work is needed to improve the accuracy of radiation dose calculations for particle beam therapies. Research teams are still assessing the stopping power by various materials, including surgical or dental implants and even tissue inhomogeneities.

BNCT Technology Selectively Targets Cancer Cells

BNCT is a high linear energy transfer (LET) radiation therapy and falls into the same category of particle therapy as proton and carbon ion therapies, but offers several clinically and economically significant advantages.

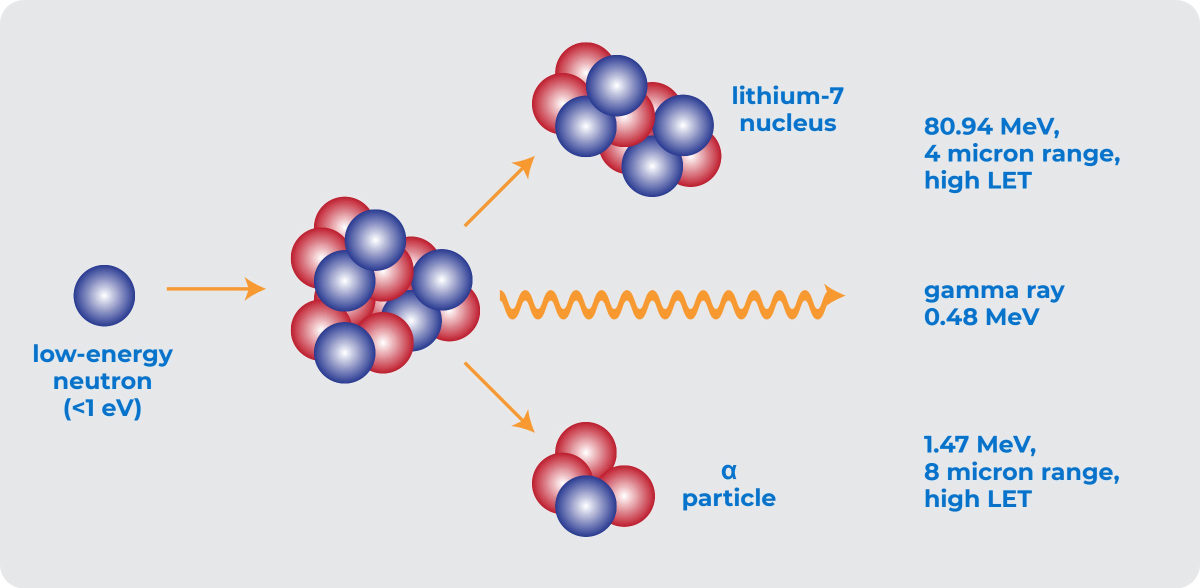
First envisioned right after the discovery of the neutron, the potential of BNCT was obvious. The tantalizing prospect of combining a focused low-energy neutron beam with a target drug to create a “homing system” has kept researchers working on development and refinement of such a solution since the 1970s.

BNCT holds tremendous promise for certain hard-to-treat cancers, especially those that typically offer more radioresistance either intrinsically or by virtue of support from their microenvironment. These include head and neck cancers, melanomas, sarcomas, certain brain cancers and cancers that have not responded to conventional radiation treatment. Clinical evidence suggests that particle therapies offer advantages over photon therapy for radioresistant tumors in close proximity to at-risk organs. And BNCT provides an option that resolves many of the challenges and limitations of proton and carbon ion particle therapies.

How BNCT Works

BNCT is a unique, biologically targeted, non-invasive, two-step procedure. A patient is first infused with a non-toxic, non-radioactive boron-10 drug, which preferentially accumulates in tumor tissue. After the infusion, the tumor is irradiated with low-energy neutrons, which generates a reaction inside the cells.

This neutron capture reaction yields an alpha and a lithium particle. The alpha particle destroys the tumor cell (apoptosis) through a double DNA strand break, while sparing the surrounding healthy tissue cells that contain no boron-10. In fact, increasing the number of boron-10 molecules in cancer cells can actually produce a higher dose to the targeted tumor without impacting the healthy tissue.



BNCT Delivers Significant Clinical and Economic Advantages

Through its biological targeting, BNCT also has the potential to treat undetected metastases in the local region of the tumor during the same treatment session. This broad efficacy is difficult to achieve with conventional radiotherapy because it requires the treatment volume to be enlarged, delivering too much radiation to healthy cells. This makes BNCT an ideal treatment option for tumors that are not good candidates for surgery or conventional radiation because of their infiltrative nature or location near sensitive organs. BNCT's biological targeting also alleviates the need for the strict motion control that must be applied during irradiation using existing photon and other particle therapies.

BNCT may treat
UNDETECTED METASTASES
in the local region of the tumor

Studies have shown that BNCT treatments can be carried out in one or two treatment fractions—with no long-term hospitalization—as opposed to 30 or more treatment sessions common in conventional and proton radiotherapy. This shortened treatment cycle can help ensure that cancer cell redistribution and repopulation does not occur. Additionally, this efficiency stands to make treatments easier and less costly for patients, healthcare providers, and payors—and to streamline hospital scheduling and enable increased patient throughput.

Cancer-killing radiation in
1 – 2 TREATMENTS
instead of
20 – 30 TREATMENT SESSIONS
with conventional radiotherapy

~~30~~

To date, most BNCT clinical studies have used boronophenylalanine (BPA) as the boron-10 target drug. BPA is a passively targeted drug that relies on higher uptake in rapidly dividing tumor cells. Although shown to be effective, BPA has limitations in achieving sufficient tumor cell targeting and boron-10 delivery at therapeutic levels that work for all cancer types and patients. The full potential of BNCT will largely be driven by the development of new, high-performance boron target drugs that provide higher uptake of boron-10 in tumors, lower uptake in normal cells, rapid clearance after treatment, and lower toxicity.

With BNCT, Revolutionary Treatment Is Already Here

Facing the frustrating reality that some of the most deadly and difficult-to-treat cancers, including brain metastases, are becoming more prevalent, it's clear that revolutionary—rather than evolutionary—therapy modalities are needed. These modalities must reduce the risk to the patient's healthy tissue, more selectively destroy cells and tumors, including breakaway metastatic cells, shorten the treatment cycle without hospitalization, and improve the patient's quality of life. To be truly revolutionary, these therapies must be accessible and practical in a hospital setting without requiring patient travel to a nuclear reactor facility.

While a new generation of particle therapies is seeing rapid advancement, these modalities—when used by themselves—require greater research on how the particles travel through tissue. As well as requiring expensive and sophisticated technology for precise identification, geometric targeting and treatment of the tumor mass. In the case of carbon ion therapy, patients will need to travel to one of only a dozen facilities around the world, which limits access.

BNCT already offers the advantage of activating cancer cells for biological targeting, reducing the need for advanced mapping and imaging as well as tumor motion control. As new drug compounds are developed that can carry more boron-10 to cancerous cells, medical teams will increasingly be able to adjust the strength of treatment accordingly.

Perhaps most critically, recent technological advances promise to enable BNCT to more easily proliferate in hospitals. A new breed of small-footprint neutron accelerators make in-hospital treatment economically practical and clinically efficient, and leading medical teams are looking forward to deploying and actively using hospital-based accelerators as soon as this year.

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*TAE Life Sciences drug and neutron beam technology is in development and only available for investigational use and not available commercially.

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