Union of Compact Accelerator-Driven Neutron Sources (UCANS) III & IV

The Pros and Cons of Preliminary R&D of Boron Neutron Capture Therapy Based on Compact Neutron Generators: A Plan of Collaboration

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Abstract

The characteristics of boron neutron capture therapy (BNCT) for cancer treatment demand, in addition to sufficient fluxes of epithermal neutrons, proper conditions of the neutron sources—compact layout, flexible operation, compatibility with hospital setting, etc. These requirements are best satisfied by compact accelerator-driven sources (CANS). We discuss the trade-offs among different CANS options and the needed R&D in order to advance BNCT to an acceptable level of practical prevalence and cancer treatment scope. We focus our attention on compact neutron generators (CNGs) which are the most compact and least expensive. We argue that the usefulness of D-D CNGs for preliminary studies, in spite of the substantial lower fluxes, can be augmented by high-performance beam-shaping assemblies and discoveries of superior $^{10}$B-containing cancer-cell seeking drugs. The plausibility of BNCT treatment of breast cancer using neutrons from a DD-109 CNG (Adelphi Technology, Inc.) is assessed by calculating the distribution of photon equivalent dose on a breast phantom using Monte-Carlo (MCNPX) simulations.

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1. Introduction

Boron neutron capture therapy (BNCT) which bases a cancer treatment on the neutron-capture reaction of $^{10}$B(n, $\alpha$) $^{7}$Li is by far the most researched modality among all the possible neutron-capture therapeutic processes. The emitted $\alpha$-particle and $^{7}$Li nucleus from each neutron capture have high linear energy transfer (LET) of ~100 times of those of X-, $\gamma$- and $\beta$-rays and a short mean range, ~9 and ~5 $\mu$m, respectively, that is comparable to the typical dimension (~10 $\mu$m) of a cell. If sufficient amount of $^{10}$B can be delivered and concentrated on the surface or preferably in the interior of only the cancerous tumor cells, neutron irradiation on the cancer will generate a superlative relative biological effectiveness (RBE) on killing the tumor cells while preserving the normal tissue. Clearly, BNCT is a complex, multi-disciplinary enterprise, encompassing the fields of neutron sources and neutronics, pharmaceuticals, medical imaging, radiobiology, and clinical planning and implementation. In spite of a long history of research first conceived in 1930s and of experimentation in early 1950s, progress of BNCT so far has fallen behind the photon- and ion-beam therapies in practical prevalence and treatment scope. For example, preclinical trials and treatments to date have taken place only at improvised neutron-delivery stations at fission-reactor sources that devote not entirely to medical purposes. Only two $^{10}$B-carrying drugs have been approved for treating head and neck cancers. The lack of proper neutron sources that can be integrable to the infrastructure of hospital or clinical facilities is a major problem.

The use of accelerator-driven neutron sources in lieu of nuclear reactors in principle offers several favorable characteristics such as the fissile-material-free operation, easy on/off switch of neutron production, and neutron energies adjustable to treat cancers in different organs. Moreover, recent advances in accelerator and neutronics technologies have led to the realization of increasingly compact, relatively low cost, reasonably intense neutron sources, readily to lend themselves to a variety of applications including BNCT. Therefore, opportunities now exist for the development of innovative compact accelerator-driven neutron sources (CANS) commissioned to a broad scope of cancer treatments by BNCT. This paper first discusses the trade-offs between several plausible CANS options with respect to the BNCT characteristics and requirements and then focuses on the newly improved compact neutron generators (CNGs) that are based on the deuteron-deuteron (D-D) fusion reaction. We note that the not yet sufficient neutron flux of CNGs can be augmented by improvements of the neutron moderator design and beam optics as well as discoveries of novel, high $^{10}$B-content cancer-cell seeking drugs so that proof-of-principle studies and preliminary testing of BNCT treatment of breast cancer can commence. Naturally, networking the research communities and commercial enterprises toward a unified goal is a key factor for the success due to the multidisciplinary nature of BNCT.

2. Neutron-generating reactions of CANS

Because thermal neutrons are efficiently captured by $^{10}$B and fast neutrons impose negative biological effects to healthy cells over a long penetrative distant, BNCT should be administered with epithermal neutrons (eV to keV range). Consequently, a consideration of the neutron yields and emission energies of various neutron-generating reactions, as given in Table 1, leads to the conclusion that the reactions of $^{7}$Li(p, n)$^{7}$Be, $^{9}$Be(p, n)$^{9}$B, $^{9}$Be(d, n)$^{10}$B, and $^{13}$C(d, n)$^{14}$N are most favorable. The design and engineering of CANS based on these reactions for BNCT have to confront a variety of technical issues. For superficial cancers (~5 cm deep), an ideal situation would be operating a CANS at a projectile energy just above the threshold energy of the reaction, if any, so as to produce a maximum amount of ‘soft’ epithermal neutrons in the forward direction (in the laboratory frame of reference) with minimum $\gamma$-radiation, fast neutrons, and daughter nuclei in the beam. This implies the $^{7}$Li(p, n)$^{7}$Be reaction being the best candidate. However, the flammable and low-melting-point Li target presents a number of technical challenges such as heat...
removal and protecting the target from radiation damage by the proton beam, which have yet to be overcome. The second best option is the $^7\text{Li}(p,n)^7\text{Be}$ reaction which is founded on a proven accelerator-target technology to produce a good neutron fluxes. Proton linac systems designed for BNCT application are available commercially (e.g., by AccSys, USA). More details about a BNCT facility based on this proton accelerator-beryllium neutron target currently under construction in Japan can be found in an accompanying paper in this proceedings [1]. The alternative of using deuterons as projectile on a beryllium target is suboptimal in terms of neutron flux production. The option of deuterons on carbon targets is a future possibility pending more technical development.

In general, the technologies of the front-end proton or deuteron accelerators are well established although their compactness and efficiency can be improved. But the neutron target system and the beam-shaping assembly (BSA) require substantially more research. The operation of CANS requires no nuclear-facility qualification and the compactness of the entire system including the mandated measures for radiation protection affords uncomplicated installation and routine running at hospitals or medical centers (see Table 1).

| Reaction       | $E_{\text{projectile}}$ (MeV) | $E_{\text{threshold}}$ (MeV) | $<E_{\text{neutron}}>$ (MeV) | Neutron yield (n/mA/s) | Accelerator/target; approx. linear dimension & cost |
|----------------|-------------------------------|------------------------------|-----------------------------|------------------------|---------------------------------------------------|
| $^7\text{Li}(p,n)^7\text{Be}$ | 2.5                           | 1.88                         | ~0.6                        | 9.09 $\times 10^{11}$  | p-linac/lithium (technical challenging); ~5 m & ~$5+M$ |
| $^9\text{Be}(p,n)^9\text{B}$  | ~4-20                         | 2.06                         | ~1.6-8                      | 0.5-1.2 $\times 10^{12}$ | p-linac/beryllium (achievable); ~5-10 m & ~$5-10M$ |
| $^9\text{Be}(d,n)^{10}\text{B}$ | 1.5                           | 0                            | 1.66                        | 3.3 $\times 10^{11}$   | p-linac/beryllium (achievable); ~5 m & ~$5M$      |
| $^2\text{H}(d,n)^3\text{He}$   | 0.15                          | 0                            | 2.5                         | ~2 $\times 10^{9}$     | neutron generator/d-Ti; ~1m & ~$0.2M$             |
| $^3\text{H}(d,n)^4\text{He}$   | 0.15                          | 0                            | 14.1                        | ~5 $\times 10^{10}$    | neutron generator/d-Ti; ~1m & ~$0.3M$             |
| $^{11}\text{C}(d,n)^{14}\text{N}$ | 1.5                           | 0                            | 1.08                        | 1.9 $\times 10^{11}$   | under study                                       |
| $^{12}\text{C}(d,n)^{15}\text{N}$ | 1.5                           | 0.33                         | 0.55                        | 6 $\times 10^{10}$     | under study                                       |

3. Compact neutron generators

A CANS operating in the energy range of a few MeVs usually employs the radio-frequency quadrupole (RFQ) accelerator to build up the kinetic energy, at a typical rate of ~1 MeV per meter of RFQ segment, of the projectile particles generated by the ion source. This allows the overcome of reaction threshold, if any, and attaining the desirable neutron yield at a high projectile energy of the (p/d, xn) reaction. But the associated complexity, necessitating high RF power, high-vacuum beam transport and optics, a neutron target-moderator-reflector (TMR) station, the associated interfaces, and heavy shielding enclosing the beam path, engenders an intertwined structure which demand considerable capital investment and operation overhead (see Table 1).

CNGs produce fast neutrons from the $^2\text{H}(d, n)^3\text{He}$ (D-D) or the $^3\text{H}(d, n)^4\text{He}$ (D-T) fusion reactions. A CNG accommodates the ion source, electron shield, acceleration structure and a target in a single housing, see layout in Fig. 1. Thus they are substantially smaller and less expensive (by factors of 1/50 to 1/1000) than accelerators/reactors. The drawback is the production of fast neutrons at considerably lower neutron
fluxes. The modern target uses a deuterium (D⁺) or tritium (T⁺) absorbing material such as titanium backed by liquid cooled copper. The titanium readily absorbs the D⁺ or T⁺ ions forming a titanium hydride. Succeeding D⁺ or T⁺ ions strike these embedded ions and fuse, resulting in (d, d), (T, d) or (t, t) reactions and releasing fast neutrons.

![Fig. 1. A schematic layout of an Adelphi D-D CNG.](image)

Traditionally, Penning ion sources are used in most neutron generators. Adelphi neutron generators utilize the electron cyclotron resonance as a more efficient way of ionizing the deuterium gas. Such sources have been greatly improved in the last decade by K. Leung and his collaborators at the Lawrence Berkeley National Laboratory (LBNL) in the US [2]. A more modern source, the ECR ion source (ECRIS) can achieve plasma densities much higher than Penning or RF-driven ion sources at similar operation pressures (0.5–5 mT) and power consumption. The ECRIS is easy to use with no complicated ignition procedures, requiring pressure or matching network adjustments. The source’s low operation pressure prevents voltage breakdown in the acceleration region, resulting in more stable operation. The ECRIS production of high fraction (80–98%) atomic ions makes it possible for the generators to push the envelope of the available neutron yields above those of Penning-driven neutron generators. Since the microwaves are confined within the waveguide and the ion source cavity, no EMI noise, typical to the RF-driven ion sources, is present. With these new ion sources the operation of the generators has become simpler, making them more attractive for medical, industrial and security applications since trained technicians are in general not needed to operate the generator.

Compact fusion generators offer perhaps the most inexpensive method for generating neutrons for BNCT. The individual D-D, single-ion beam generator is limited to a global yield of the order of 10¹¹ n/s, while that of the D-T fusion generator can have a factor of 100 more yield for the same amount of high voltage power and ion-beam current. Neutron yield limitations are primarily due to target heating and high voltage power requirements to achieve higher yields. However, the D-D neutron generator offers a number of benefits that make it more useful and safer for a clinical setting. It uses non-radioactive deuterium gas, can be actively vacuum pumped, has a long lifetime and can be easily repaired; whereas, a D-T generator uses radioactive tritium, must be sealed, has a short lifetime and components in the generator head that cannot be easily repaired or replaced (they are tritium contaminated).

The preference to ‘soft’ epithermal neutrons is good for superficial cancers like tumors in the brain and the neck. For deeper cancers, for example, to reach a depth of ~10 cm, neutrons of energies ~1 MeV are needed [3]. Therefore, the moderately high energy neutrons (2.45 MeV before moderation) from a D-D CNG become useful, better than the very fast neutrons (14.1 MeV) from a D-T CNG.
4. Neutronics performance for BNCT using an Adelphi DD-109 CNG

Cancer in humans is an assortment of more than 200 diverse diseases that can arise in all tissues and organs. According to United States Cancer Statistics (USCS) of year 2100, breast cancer tops 18% of all cancer incidence in females. More alarming is the high risk of acquiring breast cancer in a lengthy period over the life span (from 20 year of age up). Here, we report an assessment of the photon equivalent dose on breast cancer treatment by BNCT with neutrons supplied by an Adelphi DD-109 CNG in conjunction with a BSA optimized by computer simulations using the Monte Carlo radiation transport code (MCNPX).

Firstly, we configure a neutron production zone in the simulation by adopting the dimensions of the cylindrical vacuum chamber of Adelphi’s DD-109 CNG, with a Ti-target emits isotopically 2.45-MeV neutrons at the center [4]. Next, we model the BSA that consists of a sleeve made of iron around the neutron production zone, a connecting block made of AlF₃, and an enclosing structure of lead, as shown schematically in Fig. 2. This rationale of a two-stage neutron slowing-down, first by Fe and then by AlF₃, in conjunction with the Pb as a reflector and gamma shield was tested by the MCNPX simulations. The calculated neutronic performance was monitored as the dimensions of the Fe, AlF₃ and Pb components are varied until an optimal performance was achieved. No beam collimator was implemented but a layer of Li was added as additional thermal neutron delimiter of the exit beam. The final thickness of the Fe and AlF₃ structure is 10 and 25 cm, respectively (see Fig. 2). Fig. 3 shows the leakage neutron spectrum per unit lethargy (logarithmic energy decrement) tallied at the position of 10 cm from the Li layer (inside the phantom, see Fig. 2). It shows that the BSA is successful in the slowing-down of the 2.45-MeV fast neutrons, resulted in a neutron energy distribution peaked at ~10 keV with a sharp suppression of fast neutrons at high energies.

Finally, we conduct a rudimentary calculation of the dosimetry on a breast phantom placed at the exit of the beam (Fig. 2). The elemental composition of the breast tissue phantom (density: 1.02 g/cm³ with H 10.6%wt, C 33.2%wt, N 3.0%wt, and O 52.7%wt) was taken from the ICRU 46 report [5]. The ¹⁰B concentration in the tumor and the healthy tissue was assumed to be 60 ppm and 12 ppm, respectively. The CBE (compound biologic effectiveness) factors, 1 for gamma dose, 3.2 for nitrogen, carbon, and oxygen, and the fast neutron dose, 1.3 for boron in healthy tissue and 3.8 for tumor, were applied. The dosage in terms of RBE Gy as a function of depth in the breast tissue (phantom) is shown in Fig 4. Assuming a tumor depth that matches the peak total dose, the maximum dose in the tumor, about 3.6 × 10⁻¹² RBE Gy/h/ DD neutron/s, is about three orders of magnitude higher than the dose in the normal tissue. This maximum dose corresponds to 72 RBE Gy of one-hour irradiation by a DD neutron source with a monimal intensity of 2 × 10¹³ n/s, which is comparable to the maximum dose per hour (66.8 RBE Gy) for recurrent breast cancer reported in [7]. Therefore, the current neutron flux (~2 × 10⁹ n/s) of the DD-109 CNG is about 10,000 times lower than the ideal condition for treatment of breast cancer.
5. Conclusion and outlook

The cost of cancer in terms of human suffering and economic impairment is enormous. By any measure revealed by cancer statistics such as the data collected by the National Cancer Institute (NCI) of the US, very little progress has been made in cancer treatment and prevention, let alone of gaining the upper hand on the War on Cancer that was declared by the National Cancer Act of 1971. BNCT is one of the promising weapons deserving honing for the fight against cancer to which advance in CANS will be a key contributing factor. We focus on the fusion-based D-D CNGs mainly for the reasons of i) the recent improvement on the device, ii) their compactness, transportability and commercial availability, and iii) the substantial saving in capital investment and operation overhead. All of these point to a plausible fast-track approach of a BNCT research program. The readiness of neutron supply by CNGs, albeit of a moderate flux, will permit a concentrating effort on improving neutronic performance of the BSA,
dosimetry measurements, and drug effectiveness evaluation. Furthermore, the research data can be scaled up to provide an assessment of future high-flux neutron experiments.

We are working with a number of research partners at universities, government labs, and high-tech companies on various fronts of BNCT treatment of breast cancer: i) R&D of higher-flux CNGs, including an approach of multi-beam configuration (Adelphi Technology, Inc.) [4], ii) Building the BSA and experimental platform in collaboration with computer simulations (in-house engineering & IoP-CAS), iii) development of novel $^{10}$B-containing drugs (Jinan University & Sun Yat-Sen University) [7], iv) dosimetry and health physics studies (The University of Hong Kong and University of Utah) [8], and v) a discussion of a new protocol of clinical management for BNCT (International BNCT Society) [9]. The last three items (iii-iv) have produced encouraging results although they are not rigorous enough to present here. It is our hope that these combined efforts will lead to expedient preclinical trials of BNCT for an expanded scope of cancer treatments.

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