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Therapeutic Delivery

'Close-to-ideal' tumor boron targeting for boron neutron capture therapy is possible with 'less-than-ideal' boron carriers approved for use in humans

"Optimizing the targeting of ^{10}B compounds approved for use in humans is a cost- and time-effective way to hit the bull's eye of boron neutron capture therapy."

Keywords: boron compounds approved for use in humans • boron neutron capture therapy (BNCT) • BPA • GB-10 • optimization of boron tumor targeting

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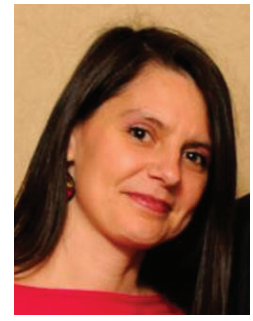

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"A bird in the hand is worth two in the bush"– J. Capgrave (at least for the time being!).

Boron neutron capture therapy (BNCT) is classically described as a binary treatment modality for cancer that involves the selective accumulation of boron carriers in tumors followed by irradiation with a thermal or epithermal neutron beam. The high linear energy transfer α particles and recoiling ^{7}Li nuclei emitted during the capture of a thermal neutron by a ^{10}B nucleus have a range of 5–9 μm in tissue and are known to have a high relative biological effectiveness. In this way, BNCT would potentially target neoplastic tissue selectively, while preserving healthy tissue [1]. Since BNCT involves biochemical rather than geometrical targeting, it is also ideally suited to treat undetectable micrometastases [2].

An ideal boron carrier (if such a dream were to come true one day!) will be nontoxic at therapeutic dose levels, will accumulate selectively in tumor cells, will target all tumor cells homogeneously and will deliver ^{10}B to tumor efficiently. Preferential accumulation of boron in tumor contributes to the therapeutic advantage of BNCT for tumor versus normal tissue. The importance of homogeneous targeting of boron to tumor lies in the fact that tumor cells poorly loaded with boron will be less responsive or altogether refractory to treatment and will lead to therapeutic failure. Absolute boron content in tumor tissue must be high enough (10^{9} atoms ^{10}B/cell) to allow sufficient ^{10}B(n,α)^{7}Li capture reactions to occur for the effect to be lethal. More so, high absolute tumor ^{10}B concentration maximizes the tumor-specific boron component of the dose and allows shorter irradiation times, with the concomitant reduction in the background dose that affects tumor and healthy tissue alike. An ideal boron carrier will clear rapidly from blood and normal tissues but will persist in tumor long enough to allow for neutron irradiation. Finally, the microdistribution of the ideal ^{10}B carrier will place the ^{10}B atoms close to a therapeutically useful target such as DNA. The short ranges of α and lithium particles make the microdistribution of the boron relative to the subcellular target of critical radiobiological significance [3,4]. Developing an ideal boron compound that fulfills all these requirements is, unfortunately, easier said than done!

Maximizing/optimizing the delivery of boron to tumor is the most effective way to optimize BNCT. In contrast, increasing exposure to neutrons increases the nonspecific background dose with no net gain in the therapeutic ratio. Within this context, much effort and resources have been expended – and still are – to search for the 'ideal' ^{10}B compound that would potentially replace the three 'imperfect' compounds currently authorized for use in man, in other words, boronophenylalanine (BPA), sodium borocaptate (BSH) and decahydrodecaborate (GB-10). Although these compounds delivered as single agents in the traditional way (as a single intravenous injection prior to a single

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neutron irradiation) have shown therapeutic potential for different pathologies [5–10], there is undoubtedly room for improvement. Presently, no other ^{10}B compounds have reached the stage for evaluation in a clinical biodistribution study. If and when a new ^{10}B carrier is identified as promising from cell culture studies, it still faces many hurdles, beginning with biodistribution studies in appropriate animal tumor models and *in vivo* evaluation of toxicity. Translation of experimental biodistribution data to clinical biodistribution studies is costly, of no direct benefit to participants, and must comply with the stringent requirements of regulatory agencies [11].

Optimizing the delivery of the ^{10}B compounds currently authorized for use in man is an excellent short- and medium-term strategy. It will help to bridge the gap between research and clinical application. The knowledge gained will also be applicable to potentially 'more perfect' ^{10}B compounds if and when they are developed.

Different strategies have been developed by our group and other groups to optimize tumor boron targeting employing ^{10}B carriers authorized for use in man.

It has been shown that even when a ^{10}B compound is not selectively taken up by tumor it can still target tumors homogeneously and produce a selective effect on tumors by preferential effects on the aberrant tumor vasculature. Such is the case of GB-10 in an experimental model of oral cancer in the hamster in which the cheek pouch is cancerized with the carcinogen dimethyl-1,2-benzanthracene to give rise to exophytic tumors (squamous cell carcinomas) surrounded by field-cancerized tissue. These findings show that selective tumor lethality can result from a selective effect on aberrant tumor blood vessels rather than from selective tumor uptake of the boron compound [5]. This example of a new paradigm in BNCT radiobiology emerging from *in vivo* BNCT studies stresses the importance of actual radiobiological studies in appropriate experimental models to determine the therapeutic efficacy of boron carriers/administration protocols. Although boron biodistribution studies are orientative, a boron carrier that would be ruled out based solely on biodistribution studies might prove successful in actual BNCT studies.

The combined administration of ^{10}B compounds with different properties and uptake mechanisms contributes to more homogeneous tumor targeting and helps to overcome the potential toxicity of higher doses of each of the compounds given alone. Combinations of agents may be superior to any single agent [12,13]. Strategies in this hamster oral cancer model such as combining aberrant tumor blood-vessel targeting with GB-10 and tumor cell targeting with BPA as in BNCT mediated by (BPA+GB-10) yielded 93% tumor response with no normal tissue toxicity and only mild mucositis in dose-limiting field-cancerized tissue [5]. Sequential BNCT (BPA–BNCT followed by GB-10–BNCT, 24 h or 48 h later) achieved >90% tumor response with no normal tissue toxicity and only mild mucositis in field-cancerized tissue [14]. Sequential BNCT benefits from the use of two boron carriers. Since they are administered separately, each application can be modulated with appropriate methods tailored for each boron carrier. In addition, the first application of BNCT would reduce tumor interstitial fluid pressure, thus improving the distribution of blood-borne therapeutic agents such as GB-10 for the second application. The interval between applications, which is short enough to preclude tumor cell repopulation, would favor targeting of tumor cells that were refractory to the first application.

> "Blood-vessel normalization seeks to distribute drugs effectively to a larger proportion of tumor cells rather than increase total drug uptake."

Another effective strategy to improve the delivery of boron carriers to tumor and increase therapeutic efficacy consists in fixing the flawed delivery system in tumors. The abnormal structure and function of tumor blood vessels compromise blood flow and hinder effective convective fluid transport, resulting in impaired distribution of blood-borne therapeutic agents [15]. Tumor blood-vessel normalization by tailored administration of antiangiogenic agents that downregulate overexpressed VEGF would lead to less leaky, less dilated and tortuous blood vessels, decreased interstitial fluid pressure and improved penetration of drugs in tumors. Within this context, reversible tumor blood-vessel normalization and administration of the boron compound in the established 'window of normalization' has been shown to improve boron targeting. Blood-vessel normalization seeks to distribute drugs effectively to a larger proportion of tumor cells rather than increase total drug uptake. Hence, pretreatment to normalize aberrant tumor blood vessels prior to administration of BPA did not increase gross boron concentration in tumor but did enhance tumor control from 67 to 84% [16]. This increase in therapeutic efficacy is attributed to a rise in homogeneity in tumor boron microdistribution. The combined treatment with tumor blood-vessel normalization followed by sequential BNCT achieved, for the first time, in the hamster cheek pouch oral cancer model, 100% tumor response with 87% complete tumor remission, with no normal tissue toxicity and no cases of severe mucositis in field-cancerized tissue [4].

An additional strategy that has enhanced therapeutic efficacy is the double application of BNCT mediated by BPA or by the combined administration of BPA+GB-10 with 4–6 weeks interval between applications. We successfully employed this strategy to inhibit the development of second primary tumors in field-cancerized tissue in a model of precancer in the hamster cheek pouch [17]. This is an issue of great clinical relevance given that locoregional recurrences and the development of second primary tumors is often the cause of therapeutic failure. Double applications of BNCT enable boron retargeting of tumor and/or field-cancerized tissue, the delivery of higher total doses to target tissue without exceeding radiotolerance of dose-limiting tissues, and in the case of large solid tumors, reduction of tumor volume after the first application and the associated improved dose distribution for the second application.

In addition to the strategies described above, additional approaches to improve tumor boron uptake and distribution in experimental models and human subjects have been examined with varying success by different groups. Some examples include the combined administration of BPA and BSH [12], blood–brain barrier disruption and convection-enhanced delivery for BPA administration in the case of brain tumors and slow infusion of BPA to improve boron targeting of infiltrating tumor cells [11], electroporation and sonoporation to improve BSH uptake [18], preloading with structural analogs such as L-DOPA or L-tyrosine to improve BPA uptake [19] and mild temperature hyperthermia to increase tumor blood flow [20].

Optimizing the targeting of ^{10}B compounds approved for use in humans is a cost- and time-effective way to hit the bull's eye of BNCT.

Future perspective

The recent initiation of BNCT clinical trials employing hospital-based accelerators rather than nuclear reactors as the neutron source will conceivably pave the way for new and more numerous clinical trials, leading up to the much needed randomized trials. This, in turn, should prompt further exploration of new targets for BNCT and favor research into novel 'closer-to-ideal' boron carriers. In the meantime, optimizing delivery strategies of the boron compounds already approved for their use in humans will provide stepping stones to move forward.

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