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Review

Boron Tracedrugs Challenge for Neutron Dynamic Therapy

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Abstract. *In this short review we describe our innovative boron tracedrugs and drugs for neutron dynamic therapy (NDT), as a newly emerging challenge beyond conventional drug treatments.*

The Real Drug Discovery Crisis for Medicinal Chemists

In the present situation of drug discovery, most medicinal chemists in pharmaceutical companies, universities, and institutes continue to create new entities using the conventional strategies and tactics of medicinal chemistry. Given that most diseases are currently usually diagnosed in well-developed symptomatic or terminal stages, *i.e.* when multiple parts of a biological system are dysfunctional, it is little wonder that most of the molecularly targeted therapies have limited influence on the actual course of the disease. A recent article in Nature Reviews Drug Discovery (1) states: "Research and development (R&D) is the ultimate source of the economic value that the pharmaceutical industry creates. It is therefore not surprising that the evidence of a major decline in R&D productivity has lead to a sense of crisis." The authors further comment that "Various solutions have been proposed, ranging from calls to re-engineer the R&D process to the radical suggestion that large pharmaceutical companies abandon internal R&D altogether. However, although decades of improvements to the R&D process and the introduction of new technologies, such as high-throughput screening, have substantially improved the efficiency of discrete steps in the R&D process, they have not been able to counteract the market and the institutional forces that underlie the decline in R&D productivity." We, as 'old-fashioned' medicinal chemists, think that the traditional medicinal chemistry dogma, that drugs should be designed to have specific chemical characteristics, contributes greatly to the real drug discovery crisis. Thus, a radically different way of thinking is needed that can lead to breakthroughs, through chemical-interaction-based drug discovery.

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Boron Tracedrugs Innovation

We recently proposed our concept of boron tracedrugs as 'wonder drugs', based on our drug design of B-10-carrier (2-5) for boron neutron capture therapy (BNCT) (6, 7). We proposed these not just as a new drug-class with broad potential, but also as the next-generation pharmaceutical drugs (8, 9). In this report we explain here boron tracedrugs briefly. We believe that frequently failed clinical trials, over the last decade were due to intrinsic chemical characteristics rather than pharmacological characteristics of drugs designed by traditional drug design methodology. Since drugs, even molecularly-targeted drugs, possess no intrinsic rational targeting mechanism associated with their chemical characteristics, they generally affect multitargets leading to multiple pharmacological effects. A further important point is that management of traceable data associated with the flow of goods, information and other resources is integral to present logistics information systems. However, many materials, such as drugs themselves, as yet, have no general tags which enable their traceability. When these drugs need to be traced, the only option for tracking them is to analyze them by the appropriate analytical method, or by using custom-made radioisotope-labeled synthetic compounds. For tracking drug data-management, we propose our strategy and tactics of boron tracedrugs as next-generation pharmaceuticals.

The key design element of boron tracedrugs consists of their containing multiple boron atoms firmly embedded in their scaffold or skeleton at a position that will have little or no influence on other functional group(s) and pharmacophore(s). The traceability of boron tracedrugs is based on the neutron capture activity of the stable isotope boron-10 embedded in the drug. Thus, newly designed boron tracedrugs would be novel pharmaceuticals, the structures of which would always include natural boron (B-11, 80.4%; B-10, 19.6%), as tracers, embedded deeply in their skeletons or scaffolds, as shown in Figure 1.

There are many boron compounds that have been used in drug development. These include such classes as borinic esters and oxazaborolidines with antibacterial activity, and benzoxaborole which is being studied for onychomycosis. Certain alpha-animoboronic acids and related agents have anticancer, hypolipidemic, and antifungal activity; diazaborines are antimalarial, and others are protease and proteosome inhibitors, such as bortezomib (10, 11). Thus, boron chemistry falls within the interest of synthetic organic chemists and medicinal chemists. Our concept of boron tracedrugs evolved from our previous drug design studies on the development of hypoxia-targeting B-10 carrier compounds described above. In particular, the pharmacokinetics of neutron-induced prompt gamma-ray spectroscopy (NIPS) allows for the measurement of B-10 concentration within a few minutes. We envisioned that if new pharmaceuticals, all contained B-10 embedded in their molecular skeleton or scaffold, research and developmental facilities would be simplified and 'green chemistry' would be facilitated. Although boron is not an element commonly found in natural products or drugs, several bioactive boron-containing compounds are known. Although the creation of a boron tracedrug seemed to be a simple concept for researchers who are working on BNCT with prompt gamma ray spectroscopy, a search of the literature using PubMed and other tools, revealed no previous reports of this application. Thus, this represents an unexplored area with much potential in next-generation neutron-related industrial development.

We, here, should explain the difference between our boron tracedrugs and previously developed BNCT B-10 carrier drugs such as BSH and BPA. Boron tracedrugs usually do not need to use B-10-enriched boron reagents, which are prepared custom-made and are very expensive. Thus boron tracedrugs can interact with a drug target both chemically (mainly by B-11 and partly by B-10) and physically (only by B-10 with a natural abundance of ca. 20%), as shown schematically in Figure 2.

We suggest that boron tracedrugs will have major impact on the process of clinical drug development and open a new era in medicinal chemistry without radioisotope technology. Research using such technology can be carried out in conventional laboratories without legal regulations, except those related to the measurement of pharmacokinetics using

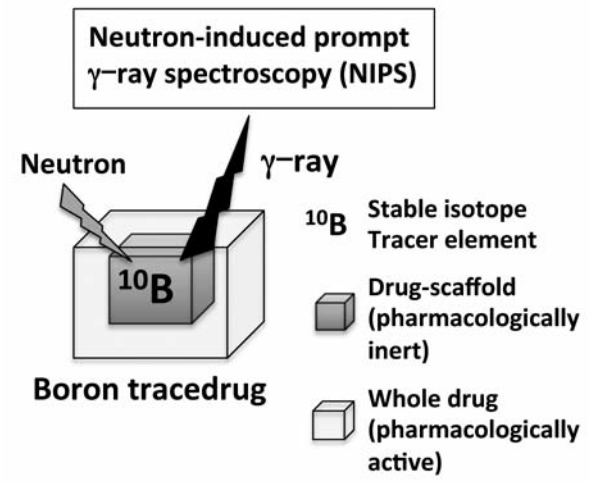

Figure 1. *A conceptual image of boron tracedrugs.*

prompt gamma-ray analysis using neutrons in nuclear reactors and accelerators, including BNCT (^{18}F-BPA-PET) (12), now under development. Boron tracedrugs can also be fitted into the era of tailor-made or personalized medicine development because of a less stringent requirement during the evaluation of absorption, distribution, metabolism, excretion, and toxicity (ADME/Tox) properties in early clinical drug development. Generally, at this stage of drug development, only a few drug candidates, selected based on their preclinical investigation, should be applied to pharmacological assays. Boron tracedrugs have the added potential of being a new class of drugs based on their destructive physical powers acquired by weak thermal neutrons used in BNCT. Possible applications include destruction of extracellular amyloid-beta deposits in the brain, the hallmark lesions of Alzheimer disease, and other aberrant macromolecules in degenerative diseases frequently occurring in elderly patients.

Research in boron tracedrugs offers opportunities for research in engineering fields, in particular in nuclear engineering and neutron engineering, to develop human-friendly atomic power reactors as neutron generators. In the chemical and in the chemical engineering fields, boron tracedrugs could help the pharmaceutical industry to design diversity-oriented libraries of boron-containing organic compounds. The importance of traceability of synthetic materials, modified natural products, and biomolecules such as proteinaceous drugs/antibody drugs, of RNA interference for gene transfer system, of nanomaterials, and micromachines, is apparent. However, there are no ethical discussions on the traceability of medicine(s) in patients except for a limited number of cases where drug accidents have occurred. Providing patients with drugs which have high traceability is a priority for the entire field of pharmaceutical research and development in health care.

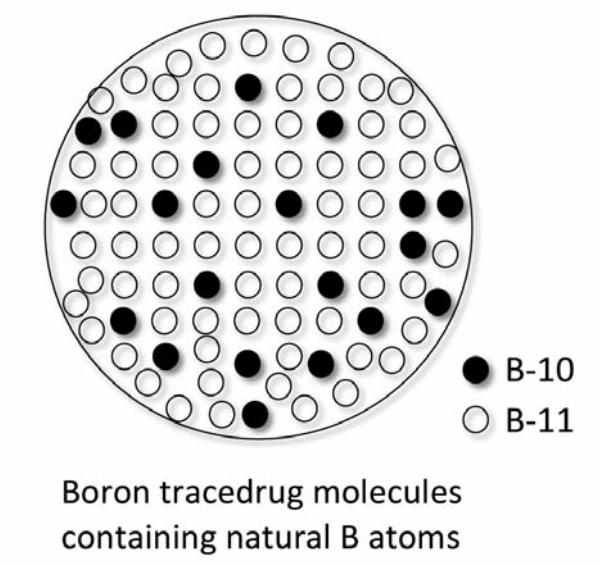

Figure 2. *A schematic molecular image of a boron tracedrug constructed with natural boron atoms.*

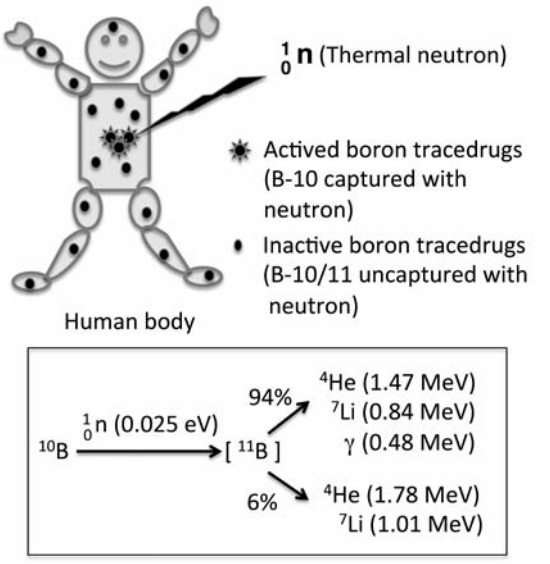

Figure 3. *A conceptual image of a boron tracedrug for neutron dynamic therapy (NDT).*

Boron Tracedrugs for Neutron Dynamic Therapy (NDT), as Doctor-friendly Tools

We now propose 'new-fashioned' physics-based drugs, named boron tracedrugs, for NDT, powered by neutron beams, as shown in Figure 3. These boron tracedrugs for NDT are chemicals with different characteristics from those used as tracers. When administered, they interact weakly with drug targets and endogenous molecules surrounding the microenvironment, like prodrugs (13). Only by capturing a neutron beam ('on-demand' or '*honnête homme*' signals) are they transformed to their active drug form to destroy drug targets by their great amount of energy (about 2.5 MeV generated from a thermal-neutron energy of 0.025 eV). Boron tracedrugs are designed to have persistent traceability at any time during their lifetime. Physics-based drugs, similar to our idea, are employed in radioimmunotherapy using radioisotopes for cancer treatment. Radioimmunotherapy involves the administration of radiolabeled monoclonal antibodies that are directed specifically against tumor-associated antigens. Clinical success has so far been achieved mostly with radiolabeled antibodies against CD20 (I-131-tositumomab and Y-90-ibritumomab tiuxetan), for the treatment of lymphoma (14). We are sure this NDT with the use of stable isotope B-10 has great advantage over radioimmunotherapy with radioisotopes especially with regard to convenience.

We also describe our idea of the neutron generator for NDT. As the neutron source for BNCT, experimental nuclear reactors for clinical use are commonly available. An accelerator-driven neutron source for BNCT is planned to be installed at some Institutes and Universities. In 2009, the Kyoto University Research Reactor Institute (Osaka, Japan) installed accelerator-based intense neutron source for BNCT. We propose portable and mobile neutron generators as the neutron source for the clinical use of boron tracedrugs for NDT, instead of nuclear reactors and accelerators.

The key structural feature of boron tracedrugs consists of their having multiple boron atoms firmly embedded in their scaffold or skeleton and located at a position that will have little or no influence on other functional group moieties or pharmacophoric descriptors. Boron tracedrugs have unique characteristic physical effects due to their B-10 atoms and their chemical and/or drug-like effects, are responsible for their pharmacodynamic characteristics. Marc Kirschner said, in his vision for Initiative Systems Pharmacology at Harvard University: "In the past, the issues that caused drugs to fail were mainly off-target effects, but in many cases now, toxicity problems are on-target effects and the lack of efficacy in phase II and III trials is just unexplainable. So the question becomes: Could we develop a better way of predicting whether a drug will work or have an intolerable side-effect." (15). Our answer is yes, we can supply boron tracedrugs for NDT as a better way of predicting whether a drug will work or have intolerable side-effects.

We present our recent results of boron tracedrugs for NDT (16), shown schematically in Figure 4. In order to explore their destructive dynamic effects when bombarded by weak thermal neutrons, we performed thermal neutron irradiation of bovine serum albumin (BSA), a typical model bio-macromolecule, treated with the boron tracedrugs. Boron

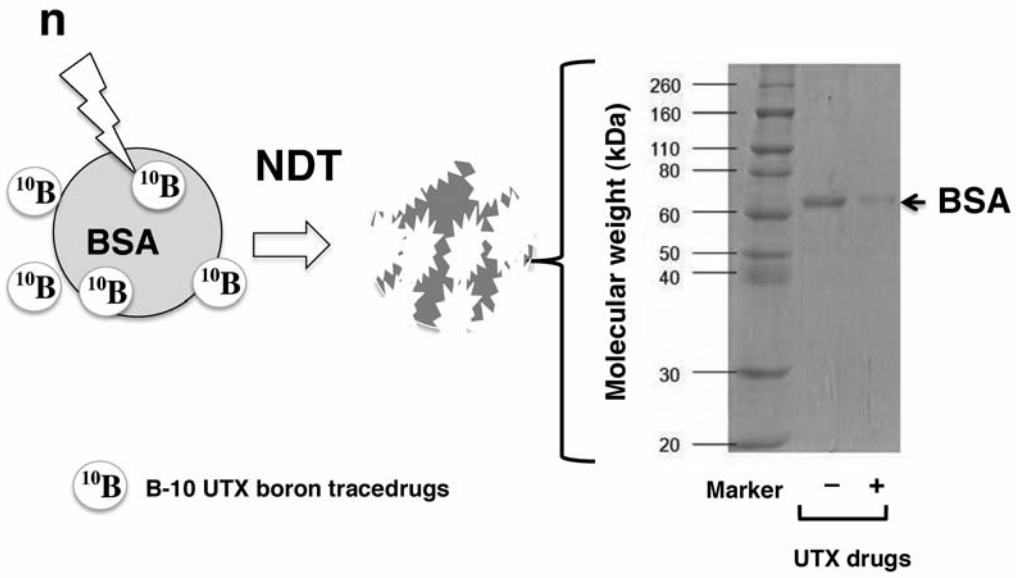

Figure 4. *A schematic image of neutron dynamic therapy (NDT) using a boron tracedrug for bovine serum albumin (BSA) as a model macromolecule.*

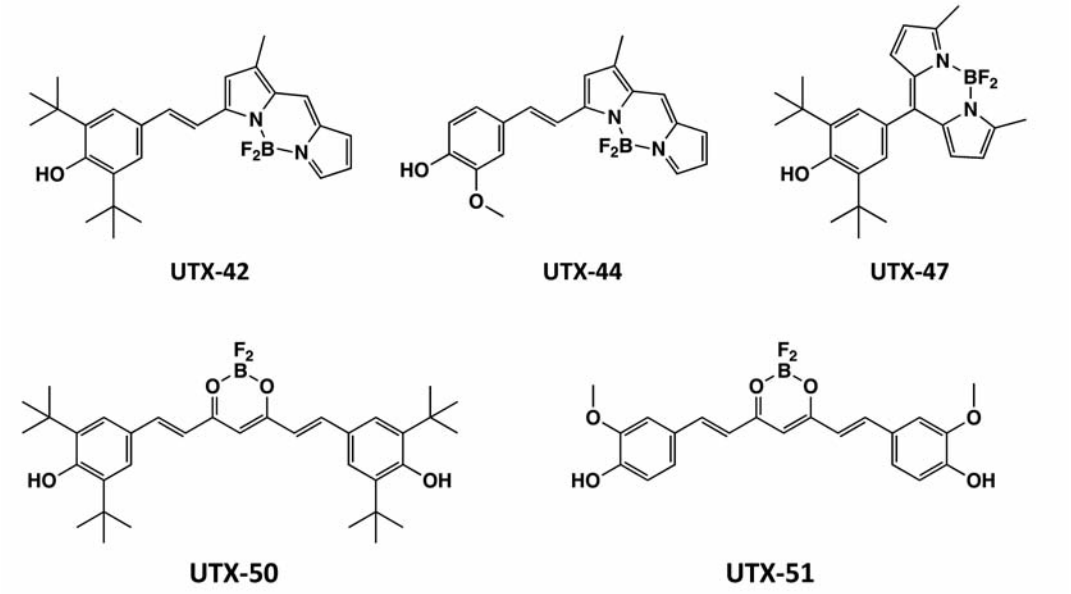

Figure 5. *Designed boron tracedrugs for neutron dynamic therapy (NDT).*

tracedrugs, including the boron dipyrromethene (BODIPY)-containing compounds UTX-42, UTX-44, and UTX-47, and the curcuminoid compounds UTX-50 and UTX-51, were designed for NDT, based on their molecular orbital calculations (Figure 5).

Sodium dodecyl sulfate–polyacrylamide gel electrophoresis (SDS-PAGE) was performed to detect decomposition by thermal neutron irradiation of the BSA treated with these boron tracedrugs. The combination of 1.0 μM BSA with 100 μM of each of the boron tracedrugs showed a decrease in band intensity after irradiation, as shown schematically in Figure 5, based on our results (16). All tested boron tracedrugs caused destructive dynamic damage of BSA during thermal neutron irradiation, the mechanism of which should be elucidated by further investigation. We speculate the mode of action of boron tracedrugs for NDT as follows. The nontoxic thermal neutron (0.025 eV), irradiated through the neutron source in the nuclear reactor, reacts with the B-10 atom contained in the boron

tracedrug (UTX drug tested here), and is embedded in and in the environment of BSA. After B-10 has captured a neutron, a nuclear reaction takes place to release two heavy particles, an alpha particle (He-4) and a lithium ion (Li-7) (see Figure 3). According to the great energies, the alpha particles and Li-7 nuclei can be regarded as short-range particles since they travel less than 10 μm in a microenvironment containing large numbers of macromolecules. The macromolecule is destroyed when the alpha or Li particle causes their structural breakdown.

Conclusion

In this short review we describe our concept of boron tracedrugs including their applications for NDT. We consider this a potentially far-reaching new drug-class that should challenge the current predominance of conventional drugs that rely only on chemical interactions, particularly if this approach were to be extended to a wide range of drug types. Boron tracedrugs could be ideal medicines of the future, with applications in diagnotherapeutics, as drugs possessing properties of both diagnostics and therapeutics. This would derive from the information related to pharmacokinetics that would be available directly from the drugs themselves, without the need for additional treatments. These drugs could also be useful in the future where autopsy imaging and virtopsy (virtual biopsy), will be available for medical assessment, in the detection of the cause of disease and death. In the near future, physics-based NDT using boron tracedrugs, as drugs possessing destructive physical powers, could be applied for all macromolecule-related diseases, against which conventionally pharmacodynamics-based, or chemical interaction-based, designed drugs have not had success.

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