**MOLECULAR MEDICINE: SYNTHESIS AND IN-VIVO DETECTION OF AGENTS FOR
USE IN BORON NEUTRON CAPTURE THERAPY**

Final Report

May 1, 1993 - April 30, 1996

RECEIVED
SEP 04 1997
OSTI

George W. Kabalka

Department of Radiology
The University of Tennessee Medical Center
Knoxville, Tennessee 37920

AUGUST 1997

PREPARED FOR:
THE U.S. DEPARTMENT OF ENERGY
UNDER GRANT NUMBER DE-FG05-93ER61610

MASTER

DISTRIBUTION OF THIS DOCUMENT IS UNLIMITED

dy

DISCLAIMER

This report was prepared as an account of work sponsored by an agency of the United States Government. Neither the United States Government nor any agency thereof, nor any of their employees, make any warranty, express or implied, or assumes any legal liability or responsibility for the accuracy, completeness, or usefulness of any information, apparatus, product, or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any specific commercial product, process, or service by trade name, trademark, manufacturer, or otherwise does not necessarily constitute or imply its endorsement, recommendation, or favoring by the United States Government or any agency thereof. The views and opinions of authors expressed herein do not necessarily state or reflect those of the United States Government or any agency thereof.

DISCLAIMER

**Portions of this document may be illegible
in electronic image products. Images are
produced from the best available original
document.**

I am pleased to report that the DOE Program in Nuclear Medicine at The University of Tennessee has been a productive one. During the period of this project (5/1/93 - 4/30/96), eleven Journal articles appeared in print along with fifteen published abstracts. In addition, twenty one invited lectures were presented on discoveries made in the course of this research project. Our research results are summarized in the following sections.

1. MRI IMAGING

(a) Boron MRI/MRS

During the early stages of this DOE-U.T. BNCT project, we developed the first whole-body boron MRI technique.^{1,2} We found that, for the first time, information concerning both the location and the quantity of boron present in living tissues could be obtained through the use of magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS) respectively. However, it was also discovered that boron MRI was not without problems.

Both naturally occurring isotopes of boron (boron-10 and boron-11) possess magnetic moments, making them amenable to MR detection. We found that there are difficulties in obtaining boron MRI images which are a consequence of the inherently poor magnetic resonance characteristics of the boron nucleus. The magnetogyric ratios of both boron-10 and boron-11 are smaller than those of hydrogen, which makes boron much less sensitive to magnetic resonance detection.³ In addition, both isotopes of boron possess nuclear electric quadrupole moments which serve to shorten their magnetization relaxation times; this causes the MR signal to broaden and decay rapidly, often before the receiver coils can collect the MR information. The rapid rate of signal decay is enhanced in biological systems which leads to further signal loss and a decrease in the signal to noise ratio (SNR). We observed this broadening in all our studies; an example of this phenomenon is evident in the magnetic resonance spectrum (MRS) of sodium μ -disulfido-bis(undecahydro-closo-dodecaborate) (BSSB) in tissue which is compared to the MRS of the same agent, at the same concentration, in solution as shown in Figure 1.⁴ (Next Page)

Figure 1. MRS of $\text{Na}_4\text{B}_{24}\text{H}_{22}\text{S}_2$ (BSSB) in (a) an aqueous solution and (b) in an intact rat both at concentrations of $80 \mu\text{g}$ of boron-11 per gram of sample. Experiments were conducted using a clinical 2-T, 90 cm-bore, whole-body MRI unit operating at 26 MHz for boron-11.

The rapid relaxation rates of both boron-10 and boron-11 negated the use of standard pulsing sequences to obtain boron MRI of BNCT agents in clinical MRI units operating at 2T or less. In the standard gradient encoding techniques used in clinical MRI units, the signal cannot be detected in less than one millisecond after the nuclei are excited by a radiofrequency pulse. For boron-11, the transverse relaxation time (T_2) in tissue is less than one millisecond, so that the MR signal has decayed before the receiver can be placed in the observe mode. The situation may be worse for the boron-10.^{5,6,7}

Consequently, our initial MRI and MRS studies utilized natural abundance boronated agents (80% boron-11).

To overcome the problem of total loss of the resonance signal before it could be observed, we developed a filtered back-projection method for generating boron-11 MRI, which led to the first boron-11 MR image of a BNCT agent which had been infused into a rat, **Figure 2.**⁸

Figure 2. Boron-11 image of a Fisher 344 rat that had been infused with 250 mg of boron per gram of body weight using BSSB. Image highlights liver which was shown to have a boron concentration of 80 μ g of boron per gram of body weight.

The technique had the advantage that it avoided the delay inherent in the standard echo protocols because signal acquisition was initiated at the beginning of the free-induction-decay (FID) rather than waiting for a gradient dephasing/rephasing of the signal

into an echo.^{9,10,11,12} Difficulties in MRI detection still remained which were related to the rise time of the frequency encoding gradient, accurate phasing, and spatial resolution limitations resulting from the broad line width of the signal. An alternate approach was developed using a chemical shift imaging (CSI) sequence to generate boron-11 images, and localized spectra.^{13,14} No enhancement in image quality was observed.

The limitations inherent in the projection method (PI) for entire FID data sets led us to utilize a method known as Single Point Imaging (SPI)¹⁵ which we used to map the boron-11 distribution of a BNCT agent in an intact Fischer 344 rat that had been infused with a therapeutic dose of the BSSB agent, **Figure 3**. In both PI and SPI, the free

Figure 3. Hydrogen (left) and boron-11 (right) MRI of a Fisher 344 rat that had been treated with BSSB. Boron image indicates that the boronated agent accumulated in the liver.

induction decay (FID) rather than the echo signal is used, which considerably shortens the pre-acquisition "dead time" during which signal intensity can be lost.^{16,17}

It should be noted that the technology available on clinical MRI scanners of the 1980's generation did not permit us to fulfill the full potential of boron-11 MRI since they lacked fast, powerful gradients and their software was not designed for optimal implementation of PI or SPI imaging. The situation has since improved with the advent of the new, more powerful commercial MRI scanners. A modified 3D back-projection protocol was developed based on our initial studies and very promising images of the distribution of BSH infused into canines have been obtained.¹⁸ The technique has been applied to humans with some success.¹⁹

We also reported that boron-11 MRI can be used to evaluate the pharmacokinetics of BNCT agents *in vivo*. A number of problems were encountered that were related to the increasingly restricted molecular mobility of the boron-containing molecules as they became attached to larger biomolecules. As a consequence, the T2 relaxation became bi-exponential²⁰ and short enough to cause considerable intensity loss, even when PI, CSI or SPI methods were used.

Fortunately, important pharmacokinetic data can still be obtained using a variety of pulsing sequences.^{21,22,23,24} In these experiments, the signal intensities (peak areas) of the boronated agents are monitored over time. The localized spectra are then used to monitor the input and/or washout of the boron agent from various locations in the body. The sensitivity improvement in MRS is achieved mainly by sacrificing spatial resolution. Signal localization in MRS is obtained by the use of surface coils which localize the signal more or less from a hemisphere with a radius of the coil itself. Because MRS uses straightforward "excitation-detection" pulse sequences, the pre-acquisition dead time is minimal which greatly improves the sensitivity and accuracy of detection, even when compared to special MRI techniques such as PI or SPI. An example of some of our MRS pharmacokinetic data is presented in Figure 4, which is representative of the data that we

obtained. Qualitative correlations are then possible through the use of external boron reference standards. The absolute quantitation of boron concentrations in tissue remains an unresolved problem. Even a simple comparison of the boron signal intensities to those of boron standards is complicated by the fact that interactions of boron with the tumor and surrounding tissue can alter the observed signal intensity in an unpredictable manner.

Figure 4. *In vivo* whole body boron-11 nuclear magnetic resonance spectra taken over time of a BSSB treated rat (left), the spectra originated from the entire body of the tumor bearing rat. *In vivo* boron-11 nuclear magnetic resonance spectra of the tumor area of the same BSSB treated rat (right).

Although current MRI units can be upgraded to obtain boron-11 MRI, this is not the ideal solution. As noted, BNCT involves the use of boron-10. Currently, pharmacokinetic and biodistribution data must be obtained using a boron-11 analogue of the BNCT agent.

Using boron-11 MRI, the clinical protocol would involve injection of the boron-11 analogue days (or weeks) prior to injection of the boron-10 BNCT agent. The data from the boron-11 MRI study would then be used to design a BNCT treatment plan based on the accumulation of the boron-11 compound. Although not perfect, this is far superior to the assumptions currently being made using animal studies.

We have also examined a more straightforward approach to improving the performance of boron-11 MRI which involves imaging at the highest possible magnetic field.^{25,26} The sensitivity of *in vivo* NMR detection improves at least linearly with an increase in field strength. Currently, research whole-body MRI systems operating at 3 Tesla or 4 Tesla field strengths are commercially available. Extrapolating from the performance exhibited in **Figures 3 and 4** (which were obtained at 2.0 T), boron-11 MRI at 4 Tesla could be sensitive to local concentrations of boron-11 as low as 9 ppm, at a linear spatial resolution of 7.5 mm. Or, with the same detection sensitivity of 25 ppm, linear resolution could be improved to around 5.5 mm.

We are beginning to develop protocols which could be used to detect boron-10 enriched BNCT agents *in vivo*. One method involves the use of MRI and MRS to detect hydrogens present in the BNCT agents. We demonstrated the feasibility of this method in an experiment in which BSSB was detected in a mouse melanoma tumor xenograft.^{27,28}

Many advances have been made in the short time that boron MRI has been in existence. It is clear that further study will be necessary before the technique becomes routine.

(b) Synthesis of New BNCT Agents

Carborane reagents are extremely important in the BNCT field because they deliver ten boron atoms per molecule. Significant research effort has been focused on the

preparation of the next generation of boron rich BNCT agents and they often contain the carborane nucleus, **Figure 5**.^{29,30,31,32,33,34}

[Where $\bigcirc$ =BH, $\bullet$ =CH]

Figure 5: The Isomeric Carboranes

We have focused our synthetic efforts on developing new chemical transformations for functionalizing the carboranes so that they can be utilized to prepare more complex physiologically active agents. These new routes include a study of the functionalization of alkenyl side chains via hydroboration reactions, **Scheme 1**,³⁵ and the coupling of

SCHEME 1.

[Where $n = 1,2,3,4,5$]

o-carboranes to alkenyl derivatives via a lithium iodide-catalyzed coupling reaction,³⁶ **Scheme 2**. These synthetic manipulations led to the synthesis of a series of carboranyl

SCHEME 2

nucleosides in which the carborane moiety was attached via a linear acetylenic linkage.³⁷ The compounds were prepared, as shown in the retrosynthetic scheme outlined in **Scheme 3**. They were supplied to Dr. Soloway at the Ohio State University and to Dr. Peter Bendel of the Weizmann Institute for evaluation of their ability to intercalate in DNA strands.

SCHEME 3

2. Positron Tomography

(a) Synthesis of PET Agents

Positron emission tomography, PET, now makes it possible to quantitatively evaluate the pharmacokinetics of a variety of physiologically active agents. Over seven thousand PET scans have been performed at The University of Tennessee Biomedical Imaging Center since 1988. The DOE Program at The University of Tennessee has emphasised the development of new, efficient synthesis of physiologically active agents for clinical use.^{38,39,40,41} Interestingly, most of these new methods involved boron reagents which has led to the development of a great deal of expertise in the preparation of boron containing, pharmacologically active agents.⁴²

We also developed extensive expertise in the preparation and use of amino acids for evaluating tumors. For example 1-aminocyclobutane-1- ^{11}C carboxylic acid (^{11}C ACBC) has been utilized at the University of Tennessee Medical Center for clinical PET studies of brain tumors for almost five years. ^{11}C ACBC is selectively taken up by intracranial tumors but not by normal brain tissue and we have found ^{11}C ACBC studies to be extremely useful in evaluating patients for tumor recurrence. This selectivity is illustrated in the FDG and ACBC PET scans of 66 y.o. female with a history of a right

occipital glioma are presented in **Figure 6**. The scans were obtained ten months after she had been treated with surgery and external beam irradiation. The image on the right is the $2\text{-}[^{18}\text{F}]\text{FDG}$ PET scan showing a defect from previous treatment in the right occipital lobe and a rim of $2\text{-}[\text{F-18}]\text{FDG}$ uptake in the deep left parietal white matter. The image on the left shows a markedly abnormal $1\text{-}[\text{C-11}]\text{ACBC}$ PET scan with the intense uptake in the same location. This proved to be a glioma on biopsy. Of particular interest in this image is the high tumor-to-normal brain concentration ratio of ACBC.

Figure 6. FDG (right) and ACBC (left) PET scans of a glioblastoma patient.

We then utilized our experience with both boron chemistry and positron labeled agents to prepare the fructose complex of fluorine-18 labeled *p*-boronophenylalanine

(FBPA-F) that is an analog of the fructose complex of boronophenylalanine (BPA-F) which is currently being used in Phase I/Phase II clinical trials at Brookhaven National Laboratory and at M.I.T., **Scheme 4**.

Scheme 4

(b) Preliminary PET Patient Data

The product, FBPA-F, was prepared and injected into a patient and kinetic data of the normal brain tissue and the brain tumor were collected and analyzed.

The tissue uptake data was also evaluated using the graphical Gjedde-Patlak method and compartmental model analysis. The Patlak analysis is distinct from individual rate constant determinations. The normalized, or equivalent time was computed from the analytically fit C_p . Least squares fitting of C_{pet}/C_p versus $\int C_p/C_p$ in the longer equivalent time region of the plots gives the desired straight line slopes (accumulation rates) for use

in characterizing tumor uptake.

The preliminary data are presented in **Figures 7 and 8**. **Figure 7** is the PET image after administration of the ^{18}F -BPA-F complex. The distribution of the agent indicates that the uptake is primarily by amino acid transport.

F-18-BPA-F PET in Glioblastoma Multiforme

Figure 7. PET scan of glioblastoma patient.

The time activity curve shown in **Figure 8** exhibits an accumulation pattern supportive of intracellular trapping.^{43,44}

Figure 8. Time activity curve for glioblastoma patient whose PET scan is presented in Figure 7.

The data clearly demonstrate that the BNCT agent concentrates in the tumor tissue in sufficient quantities for successful therapy. Further studies are planned in which uptake values are compared pre and post debulking surgery in an effort to decide whether debulking prior to BNCT is a preferred therapeutic route.

3. Students Trained

One of the goals of the DOE-U.T. BNCT program is to provide training for students (predoctoral and postdoctoral). Since 1993 three postdoctoral and two graduate students have received support and training under the auspices of this program.

STUDENT	DEGREE/YEAR	RESEARCH AREA
Reddy, N. Kesavulu	Postdoctoral-Current	Carboranyl Uracil Derivatives
Narayana, Chatla	Postdoctoral-1994	Alkylation of Carboranes
Anderson, Charles	Postdoctoral-1993	Development of MRI Protocols
Hondrogiannis, George	Ph.D. - 1995	Hydroboration of Alkenyl Carboranes
Dyke, Jon	Ph.D. - 1996	MRI of BNCT Agents

4. BIBLIOGRAPHY OF PUBLICATIONS

(a) Journal Articles

1. Kabalka, G. W.; Tang, C.; Bendel, P. "The Role of Boron MRI in Boron Capture Therapy." *J. Neuro. Onco.* **1997**, 33, 153.
2. Kabalka, G. W.; Reddy, K. N.; Narayana, C. "Synthesis of Boronated Uridine Derivatives for Boron Neutron Capture Therapy" in "Cancer Neutron Capture Therapy" Plenum, Inc. New York, **1996**, 256.
3. Bendel, P.; Zilberstein, J.; Salomon, Y.; Kabalka, G. W., "Non Invasive In-Vivo Detection of Boron-10 By Magnetic Resonance: Application To Mouse Melanoma and Prospects for Humans", in "Cancer Neutron Capture Therapy", Plenum Inc., New York, **1996**, 157.
4. Kabalka, G. W. "In Vivo Biodistribution and Pharmacokinetics of BNCT Agents Using PET and MRI", *Quart. J. Nucl. Med.*, **1995**, 39, 30.
5. Daniel, G. B.; Edwards, D. F.; Harvey, R. C.; Kabalka, G. W. "Communicating Hydrocephalus in Dogs with Congenital Ciliary Dysfunction", *Developmental Neuroscience*, **1995**, 17, 230.
6. Hondrogiannis, G.; Kabalka, G. W. "Hydroboration of Alkenylcarboranes: A Regiochemical Investigation", *Tetrahedron Lett.* **1995**, 36, 4365.
7. Rafeiro, E.; Leeder, R. G.; Brien, J. F.; Kabalka, G. W.; Chatla, N.; Massey, T. E. "Comparison of the *In Vivo* Pulmonary Toxicity of Amiodarone and Des-Oxo-Amiodarone in the Hamster", *Toxic. Appl. Pharmac.*, **1994**, 127, 275.

8. Kabalka, G. W.; Narayana, C.; Reddy, N. K. "Nickel Catalyzed Hydroboration with Catecholborane", *Synth. Commun.* **1994**, 24, 1019.
9. Kabalka, G. W.; Cheng, -Q. C.; Anderson, C. L.; Bendel, P.; Micca, P.; Slatkin, D. N. "In Vivo Pharmacokinetics of a Boron Neutron Capture Agent in a Tumor-Bearing Rat Via Boron-11 MRS and MRI", In: Barth, R. F. and Soloway, A.H. "Advances in Neutron Capture Therapy" *Plenum Press* NY, **1993**, 491.
10. Yang, D. T. C.; Evans, T. J.; Yamazaki, F.; Narayana, C.; Kabalka, G. W. "Sodium Perborate: A Convenient Oxidative Cleavage of α -Diketones", *Synth. Commun.* **1993**, 23, 1183.
11. Bockisch, A.; Daniel, G.; Harvey, R. C.; Davis, M. A.; Kabalka, G. W. "MRI Contrast Enhancement of the Lung Using Gd-DTPA Aerosol", *Radiologica. Diagnostica.* **1993**, 34, 21.

(b) Published Abstracts

1. "Boron-11 MS of Borocaptate in vitro and in Melanoma Bearing Mice," P. Bendel, A. Franted, J. Zilberstein, Y. Solomon and B. W. Kabalka, Fourth Magnetic Resonance Meeting , New York, NY (April 1996).
2. "Synthesis of of Boronated Agents Labeled with Positron Emitting Isotopes for Use in Boron Neutron Capture Therapy," G. W. Kabalka, C. Longford, N. Reddy, R. Srivasitava, and C. Narayana, Boron-USA Meeting, Guanajuato, Mexico (May 1996).
3. "Synthesis of Carboranyl Alynyl Uridine and Deoxyuridine Derviatives," N.K. Reddy, C. Narayana and G. W. Kabalka, Boron-USA Meeting, Guanajuato, Mexico (May 1996).
4. "Kinetics of F-18 BPA in Glioblastoma Multiforme", K. Hubner, G. W. Kabalka, G.T. Smith, W.S. Reid, N Reddy, C. Longford, T. Roberts, E. Buonocore, Society of Nuclear Medicine Meeting, Denver, CO (June 1996).
5. "4-[¹⁰B]Borono-2-[¹⁸F]fluoro-L-phenylalanine-fructose Complex for Use in Timing Boron Neutron Capture Therapy (BNCT)", N. K. Reddy, G. W. Kabalka, C. P. D. Longford, T. G. Roberts, XI International Symposium on Radiopharmaceutical Chemistry, Vancouver, B. C. Canada (August, 1995).
6. "A New Application of Nuclear Magnetic Resonance Microscopy: The Boron-11 MRS and MRI of Boron Neutron Capture Agents", Hoechst-Celanese Research Symposium, Knoxville, TN (February, 1995).

7. "The ZAP (Zero Alternate Phase) Sequence in Magnetic Resonance Imaging", D. F. Vaslow, G. -Z. Cheng, C. L. Anderson, H. W. Bond, G. W. Kabalka and G. T. Smith. 80th Annual Meeting, Radiological Society of North America, Chicago, IL (November, 1994)
8. "Synthesis of 5(4'-carboranyl-1'-butanyl)uridine", G. W. Kabalka, N. K. Reddy and C. Narayana, Sixth International Symposium on Neutron Capture Therapy, Kobe Japan (November, 1994).
9. "Non-Invasive In-Vivo Detection of Boron-10 in Mouse Melanoma by Magnetic Resonance Spectroscopy (MRS)", P. Bendel, J. Zilberstein, Y. Salomon and G. W. Kabalka, Sixth International Symposium on Neutron Capture Therapy, Kobe Japan (November, 1994).
10. "Proton-Observed ^{10}B -Edited In-Vivo Detection of a Boron-Neutron-Capture Agent in Mouse Melanoma", P. Bendel, J. Zilberstein, Y. Salomon, G. W. Kabalka, XVIth International Conference on Magnetic Resonance in Biological Systems, Veldhoven, The Netherlands (August, 1994).
11. "The Boron-11 MRS and MRI Study of the Boron Neutron Capture Agents BSSB and VCDP at 9.4 Tesla", C. L. Anderson, G. W. Kabalka, P. Bendel, G.-Q. Cheng, P. Micca, and D. N. Slatkin, Society of Magnetic Resonance 2nd Annual Meeting, San Francisco, CA (August, 1994).
12. "The High Resolution of ^1H MRI Investigation of the Soybean (Glycine Max L.) Root System", G. W. Kabalka, C. L. Anderson, and P. M. Gresshoff, Southeast Regional American Chemical Society Annual Meeting, John City, Tennessee (October 1993).
13. "Boron MRI for Use in BNCT", G. W. Kabalka, NIH Workshop on Biological Evaluation of Compounds for BNCT:, Washington, D.C. (September 1993).
14. "The Boron-11 MRS and MRI Studies of the Boron Neutron Captures Agents BSSB and VCDP at 9.4 Tesla. A New Application of NMR Microscopy", G. W. Kabalka, C. L. Anderson, P. Bendel, and G. -Q. Cheng, American Chemical Society Annual Meeting, Nucl 156, Chicago, Illinois (August 1993).
15. "Synthesis of Functionally Diverse Amino Alcohols Via Allylboration", G. W. Kabalka, and R. D. Pace, Eighth International Meeting on Boron Chemistry, Knoxville, Tennessee (July 1993).

(c) Invited Presentations

1. "New Imaging Techniques for BNCT", Central U.S. Meeting of the International Isotope Society, Chicago, IL (June, 1996).
2. "New Boron Neutron Capture Agents", Brookhaven National Laboratory, Upton, NY (April, 1996).
3. "The Design and Synthesis of New Medical Imaging Agents", West Virginia University, Morgantown, WV (April, 1996).
4. "Synthesis of Agents for Use in Nuclear Medicine", University of Louisville, Louisville, KY (February, 1996)
5. "Boron Neutron Capture Therapy", Northern Kentucky University, Highland Heights, KY (February, 1996).
6. "Design and Synthesis of Medical Imaging Agents", Western Kentucky University, Bowling Green, KY (December, 1995).
7. "Advances in Boron Neutron Capture Therapy", University of the South, Sewanee, TN (December 1995).
8. "Synthesis of Agents for Use in Therapy", University of California-Davis, Davis, CA (August 1995).
10. "The Detections of BNCT Agents Using PET and MRI", University of Michigan, Ann Arbor, MI (June 1995).
11. "Advances in Medical Imaging", Governor's School, University of Tennessee, Knoxville, TN (June 1995).
12. "*In Vivo* Detection of BNCT Agents", DOE Workshop on BNCT, Williamsburg, VA (May, 1995).
13. "Preparation of BNCT Agents", University of Illinois, Champaign/Urbana, IL (April, 1995).
14. "Modern Medical Imaging", University of Tennessee Mini Medical School, Knoxville, TN (March, 1995)
15. "Boron Neutron Capture: New Perspectives", University of Illinois, Champaign-Urbana, Illinois, (March, 1995).

16. "Design of Medical Imaging Agents" Spellman College, Atlanta, GA (January, 1995).
17. "PET and MRI as Tools for Imaging Cancer", Veterinary Cancer Society, 14th Annual Conference, Townsend, Tennessee (October, 1994).
18. "The Design and Synthesis of BNCT Agents", DOE Workshop on BNCT, Washington, D.C., (October, 1994).
19. "Modern Medical Imaging", University of Tennessee Mini Medical School, Knoxville, TN (September, 1994).
20. "Boron in Nuclear Medicine", DOE Symposium on BNCT, Atlanta, GA (February, 1994).
21. "Boron MRI and MRS for Use in BNCT", National Institution of Health Workshop on Neutron Capture Therapy, Washington, DC (September 1993).

F. LITERATURE CITED

1. Kabalka, G. W.; Davis, M.; Bendel, P.; "Boron-11 MRI and MRS of Intact Animals Infused With a Boron-Neutron-Capture Agent." *J. Magn. Reson. Med.* **1988**, *8*, 231.
2. Kabalka, G. W.; Bendel, P.; Davis, M.; Slatkin, D. N.; Micca, P. L.; "Boron-11 Magnetic Resonance Imaging and Spectroscopy: Tools for Investigating Pharmacokinetics for Boron Neutron Capture Therapy." In: Fairchild, R. G.; Bond, J. P. (eds) *Clinical Aspects of Neutron Capture Therapy*, Plenum Press, New York, **1989**, pp 243.
3. Harris, R. K.; Mann, B. E. "NMR and the Periodic Table." Academic Press, London, **1978**. p 91.
4. Kabalka, G. W.; Cheng, G. Q.; Bendel, P. "Boron-11 MRI and MRS." In: Blümich B, Kuhn W (eds) *Magnetic Resonance Microscopy, Methods and Application in Materials Science, Agriculture and Biomedicine*. VCH, Weinheim. **1992**. p. 533.
5. Kabalka, G. W.; Davis, M.; Bendel, P. "Boron-11 MRI and MRS of Intact Animals Infused With a Boron-Neutron-Capture Agent." *J. Magn. Reson. Med.* **1988**, *8*, 231.

6. Richards, T. L.; Bradshaw, K. M. ^{10}B Versus ^{11}B Signal-To-Noise Comparison at 2 Tesla. (Abstract) In: Proceedings of The Society of Magnetic Resonance in Medicine 8th Annual Meeting, **1991**, p 665.
7. Kabalka, G. W. "Boron-11 MRI and MRS of Intact Animals Infused With a Boron-Neutron-Capture Agent." (Abstract) In: Proceedings of the NIH Workshop, Annapolis MD, **1988**.
8. Kabalka, G. W.; Davis, M.; Bendel, P. "Boron-11 MRI and MRS of Intact Animals Infused With a Boron-Neutron-Capture Agent." *J. Magn. Reson. Med.* **1988**, 8, 231.
9. Kabalka, G. W.; Cheng, G. -Q.; Bendel, P. "In *In-Vivo* Boron-11 MRI and MRS Using $(\text{B}_{24}\text{H}_{22}\text{S})^4$ In the Rat." (Abstract) In: Proceedings of The Society of Magnetic Resonance in Medicine Meeting, **1991**.
10. Kabalka, G. W.; Cheng, G. Q.; Bendel, P. *In Vivo* Boron-11 MRI in the Rat." (Abstract) In: Proceedings of The International Isotope Society Meeting, **1991**.
11. Kabalka, G. W.; Bendel, P.; Cheng, G. -Q. "Boron MRI and MRS. (Abstract) In: Proceedings of The International Conference on NMR Microscopy, **1991**.
12. Kabalka, G. W.; Cheng, G. -Q.; Anderson, C. "*In vivo* Pharmacokinetics of a Boron Neutron Capture Agent in a Tumor-Bearing Rat Via Boron-11 MRS and MRI." (Abstract) In: Proceedings of The Boron USA Workshop, **1992**.
13. Bradshaw, K. M.; Richards, T. L. "*In vivo* Chemical Shift Imaging of Canine Brain Tumors After Injection of $\text{Na}_2\text{B}_{12}\text{H}_{11}\text{SH}$." (Abstract) In: Proceedings of The Society of Magnetic Resonance in Medicine 9th Annual Meeting, **1990**, p 1166.
14. Richards, T. L.; Bradshaw, K. M.; Freeman, D. M.; Sotak, C. H.; Gavin, P. R. "Imaging With ^{11}B of Intact Tissues Using Magnetic Resonance Gradient Echoes." *Strahlenther. Onkol.* **1989**, 179.
15. Bendel, P.; Davis, M.; Berman, E.; Kabalka, G. W. "A Method for Imaging Nuclei With Short T2 Relaxation: Application to Boron-11 MR Imaging of a BNCT Agent in an Intact Rat." *J. Mag. Reson.* **1990**, 88, 369.
16. Kabalka, G. W.; Cheng, G. Q.; Bendel, P.; Micca, P. L.; Slatkin, D. N. "*In-vivo* Boron-11 MRI and MRS Using $(\text{B}_{24}\text{H}_{22}\text{S}_2)^4$ In the Rat." *J. Magn. Reson. Imag.* **1991**, 9, 969.
17. Kabalka, G. W.; Cheng, Q. C.; Bendel, P.; Slatkin, D. N.; Micca, P. L. "Boron MRI Method for Imaging BNCT Agents. In: "Progress in Neutron Capture Therapy for Cancer" Plenum Press, New York, **1992**, p 321.

18. Bradshaw, K. M.; Schweizer, M. P.; Glover, G. H.; Hadley, J. R.; Tippets, R.; Tang, P. P.; Davis, W. L.; Heilbrun, M. P.; Johnson, S.; Ghanem, T. "BSH Distributions in the Canine Head and a Human Patient Using ^{11}B MRI." *Mag Reson Med.* **1995**, 34, 48.
19. Glover, G. H.; Pauly, J. M.; Bradshaw, K. M. "Boron-11 imaging with a three-dimensional reconstruction method." *J. Magn. Reson. Imaging.* **1992**, 2, 47.
20. Monoi, H: "Nuclear Magnetic Resonance of Ions With Quadrupole Nuclei in Aqueous Heterogeneous Systems: Basic Theory and Applications." *Rev. Magn. Reson. Med.* **1986**, 1, 73.
21. Kabalka, G. W.; Cheng, G. -Q.; Anderson, C. L.; Bendel, P.; Micca, P.; Slatkin, D. N. "Pharmacokinetics of BNCT Agents Via Boron-11 MRS and MRI." (Abstract) In: Proceedings of The International Symposium on Neutron Capture Therapy, **1992**.
22. Kabalka, G. W.; Cheng, Q. C.; Anderson, C. L.; Bendel, P.; Micca, P.; Slatkin, D. N. "*In vivo* Pharmacokinetics of a Boron Neutron Capture Agent in a Tumor-Bearing Rat Via Boron-11 MRS and MRI." In: Barth R F, Soloway AH (eds) *Advances in Neutron Capture Therapy*. Plenum Press NY, **1993**, p 491.
23. Bradshaw, K. M.; Richards, T. L.; Kraft, S. L. "*In Vivo* Pharmacokinetic Evaluation of Boron Compounds Using Magnetic Resonance Spectroscopy and Imaging." In: Allen, B. J.; Moore, D. E.; Harrington, B. V. (eds) *Progress in Neutron Capture Therapy for Cancer*. Plenum Press, New York, **1992**, p 325.
24. Kabalka, G. W. "*In Vivo* Biodistribution and Pharmacokinetics of BNCT Agents Using PET and MRI." *Quart. J. Nucl. Med.* **1995**, 39, 301.
25. Kabalka, G. W.; Anderson, C. L.; Bendel, P.; Cheng, C. Q. "The Boron-11 MRS and MRI Study of the Boron Neutron Capture Agent BSSB at 9.4 Tesla: A New Application of NMR Microscopy", (Abstract) In: Proceedings of The Eighth International Meeting on Boron Chemistry, Knoxville, Tennessee **1993**.
26. Kabalka, G. W.; Anderson, C. L.; Bendel, P.; Cheng, G. Q. "The Boron-11 MRS and MRI Studies of the Boron Neutron Captures Agents BSSB and VCDP at 9.4 Tesla. A New Application of NMR Microscopy." (Abstract) In: Proceedings of The American Chemical Society Annual Meeting, Nucl 156, **1993**.
27. Bendel, P.; Zilberstein, J.; Salomon, Y.; Kabalka, G. W.; "Non Invasive *In-Vivo* Detection of Boron-10 by Magnetic Resonance: Application to Mouse Melanoma and Prospects for Humans." In: Mishima, Y. (ed) *Cancer Neutron Capture Therapy*. Plenum Inc, in press

28. Bendel, P.; Zilberstein, J.; Salomon, Y.; *In Vivo* Detection of a Boron-Neutron-Capture Agent In Melanoma by Proton Observed ^1H - ^{10}B Double Resonance." *Mag Reson Med.* **1994**, 32: 170.
29. Yamamoto, Y.; Seko, T.; Nakamura, H.; Nemoto, H. "Synthesis of Carboranes Containing Nucleoside Bases." *Heteroat. Chem.* **1992**, 3, 239.
30. Wyzlic, I. M.; Soloway, A. H.; "A General Convenient Way to Carborane Containing Amino Acids for Boron Neutron Capture Therapy." *Tetrahedron Lett.* **1992**, 33, 7489.
31. Tjarks, W.; Anisuzzaman, A. K. M.; Soloway, A. H. "Synthesis of 1,3-Di-O-acetyl-5-O-benzoyl-2-O-(o-carboran-1-ylmethyl)-D-ribofuranose. A General Precursor for the Preparation of Carborane Containing Nucleosides for Boron Neutron Capture Therapy." *Nucleosides Nucleotides* **1992**, 11, 1765.
32. Prashar, J. K.; Moore, D. E. "Synthesis of Carboranyl Phenylalanine for Potential Use in Neutron Capture Therapy of Melanoma." *J. Chem. Soc., Perkin Trans. 1* **1993**, 9, 1051.
33. Scobie, M.; Mahon, M. F.; Threadgill, M. D. "Tumor-Targeted Boranes. Part 2. Coupling of *Closo*-Carboranes to Substituted 2-Nitroimidazoles via 1,3-Dipolar Cycloaddition." *J. Chem. Soc., Trans 1* **1994**, 2, 203.
34. Dreschel, K.; Lee, C. S.; Leung, E. W.; Kane, R. R.; Hawthorne, M. F. "Synthesis of New Building Blocks for Boron-Rich Oligomers in Boron Neutron Capture Therapy (BNCT)." *Tetrahedron Lett.* **1994**, 35, 6217.
35. Hondrogiannis, G.; Kabalka, G. W. "Hydroboration of Alkenylcarboranes: A Regiochemical Investigation", *Tetrahedron Lett.* **1995**, 36, 4365.
36. Kabalka, G. W.; Reddy, N. K.; Narayana, C. "Lithium iodide-catalyzed alkylation of Carboranes." *Tetrahedron Lett.*, **1992**, 33, 8.
37. Kabalka, G. W.; Reddy, K. N.; Narayana, C. "Synthesis of Boronated Uridine Derivatives for Boron Neutron Capture Therapy" in "Cancer Neutron Capture Therapy" Plenum, Inc. in press.
38. Kabalka, G. W.; Green, J. F.; Goodman, M. M.; Maddox, J. T.; Lambert, S. J. "The Synthesis of Oxygen-15 Butanol Via the Oxidation of Tributylborane Adsorbed on Solid Surfaces", *J. Labelled Compd, Radiopharm.* **1994**, 35, 186.
39. Kabalka, G. W.; Goodman, M. M.; Green, J. F.; Marks, R.; Longford, D. "Synthesis of Nitrogen-13 Labeled Amines Using Organoborane Polymers." *J. Labelled Compd. Radiopharm.* **1993**, 32, 165.

40. Kabalka, G. W. "Synthetic Approaches to the Preparation of Oxygen-15 Labeled Compounds," *Int. J. Rad. Appl. Instrum. [A]* **1988**, 39, 557.
41. Kabalka, G. W.; Lambrecht, R. M.; Sajjad, M.; Fowler, J. S.; Kunda, S. A.; McCollum, G. W.; MacGregor, R. "Synthesis of ^{15}O -Labeled Butanol Via Organoborane Chemistry," *Int. J. Appl. Rad. Isot.* **1985**, 35, 853.
42. Kabalka, G. W.; Varma, R. S. "The Synthesis of Radiolabeled Compounds Via Organometallic Intermediates," *Tetrahedron* **1989**, 45, 6601.
- 43.
- 44.