

EXCLUSIVE LICENSE
BETWEEN
THE BOARD OF REGENTS OF THE UNIVERSITY OF TEXAS SYSTEM
AND
DALLAS BIOMEDICAL CORPORATION

THIS LICENSE is made as of the 15th day of April, 1991 between the Board of Regents ("Regents") of The University of Texas System (hereinafter referred to as "Licensor") for and on behalf of The University of Texas Southwestern Medical Center at Dallas and Dallas Biomedical Corporation, a Texas corporation (hereinafter referred to as "Licensee").

RECITALS

WHEREAS, Licensee and Licensor have co-sponsored certain research pursuant to the terms of a Sponsored Research Agreement by and between Licensor and Licensee, dated August 1, 1989, and entitled Development of Cell-reactive Antibody Toxin Conjugates For Killing Unwanted Cells in vivo, Including Immunodeficiencies, Auto-immune Diseases, Transplantation and Neoplasia, with Drs. Jonathan Uhr and Ellen Vitetta as Principal Investigators and as amended by the First, Second, Third, Fourth and Fifth Amendments to the Sponsored Research Agreement, dated August 14, 1989, June 1, 1990 and August 1, 1990, October 23, 1990 and December 31, 1990, respectively, a copy of each which is attached hereto and made a part of this Agreement for all purposes ("Sponsored Research Agreement");

WHEREAS, Licensee has previously obtained an option to exclusive license rights to all patents and technology developed during the course of such Sponsored Research Agreement with a view to profitable commercialization of such patents and technology for the benefit of the people of the State of Texas, the researchers, Licensor and Licensee;

WHEREAS, Licensor desires to grant to Licensee, pursuant to the exercise of Licensee's option contained in Article VIII of the Sponsored Research Agreement, the license hereinafter set forth;

NOW THEREFORE, in consideration of the mutual covenants and provisions herein contained, Licensor and Licensee agree as follows:

I. EFFECTIVE DATE

This License shall be effective as of April 15, 1991, subject only to any necessary approvals by the Board pursuant to the Regents' Rules and Regulations for the University of Texas System.

II. DEFINITIONS

As used in this Agreement, the following terms shall have the meanings indicated:

2.1 The terms defined in the Sponsored Research Agreement shall have the same meanings herein, unless otherwise defined herein.

2.2 "Licensed Products" shall mean any product or material covered by Patents or otherwise incorporating any Invention or

Licensed Technology licensed hereunder and combinations of Licensed Products with other products, materials, structures or apparatus.

2.3 "Patent" shall mean any and all patents included within Patent Rights.

2.4 "Transfer" shall mean any and all assignments or sublicenses of this License by Licensee or other disposition (by sale, lease or otherwise) of the Technology by Licensee.

III. LICENSE

3.1 Subject to the provisions of Sections 6.1 and 7.1 hereof, Licensor hereby grants and agrees to grant to Licensee the full and exclusive, world-wide, assignable license and authority ("License") under the Patent Rights, the Technology Rights and the Pre-Existing Rights to make, have made, use, lease, import, vend, sell or otherwise dispose of Licensed Products and to practice and use any Invention and to practice and use any Technology made, developed or discovered, in whole or in part, during the course of the Research Program, in all fields of use. This License shall also include the right to grant sublicenses. The foregoing grant shall include, without limitation, the Patents and/or applications set forth on Attachment A hereto.

3.2 The term of the License under Technology Rights, as to all unpatented Technology and Inventions, shall be for a period of twenty (20) years from the Effective Date. Licensee shall have the option to extend such term for additional five (5) year periods, as provided in Section 3.4 hereof. The term of License under each

Patent shall be for the life of such Patent and all renewals, extensions, continuations, continuations-in-part, divisionals, re-examinations, re-issues, substitutions and additions thereof or thereto.

3.3 This License may only be revoked or terminated upon the occurrence of the following events of default:

(a) Licensee shall have failed to commercialize or cause to be commercialized the licensed technology as provided in Article VI hereof; or

(b) Licensee shall have defaulted in its obligations to Licensor as provided in Article IV hereof; provided Licensor shall have first given Licensee and each of its assignees and sublicensees of which Licensor has been given notice, at least ninety (90) days prior written notice of its intent to terminate the License and neither Licensee nor any of such assignees or sublicensees shall have cured such default prior to the expiration of such ninety (90) day period.

3.4 Licensee's option to renew and extend the term of the License, as to all unpatented Technology and Inventions for successive five-year periods shall be conditioned only upon: (i) Licensee's giving Licensor written notice thereof at least ninety (90) days prior to the expiration of such License, and (ii) in the event Licensor shall have received a bonafide and binding and definitive written offer from an unaffiliated third-party to license the same Technology and Inventions, Licensee shall agree to amend this License so that the compensation level to which Licensor

is thereafter entitled shall be equal to any greater compensation level to which it would be entitled pursuant to such offer. For example, if Licensee is receiving a six-percent royalty hereunder, to which Licensor is entitled to one-half, or three-percent, and the bonafide third-party offer contemplates a four-percent royalty, the renewal hereof shall be conditioned upon Licensee agreeing to pay Licensor a four-percent royalty.

3.5 Without limiting the scope of this License, it is anticipated that Patent Rights and Technology Rights to be furnished to Licensee under this License will be used by the sublicensee(s) of Licensee in making and selling pharmaceutical products. **EXCEPT AS PROVIDED IN SECTION 5.2 HEREOF, LICENSOR MAKES NO REPRESENTATIONS, EXTENDS NO WARRANTIES OF ANY KIND, EITHER EXPRESSED OR IMPLIED, AND ASSUMES NO RESPONSIBILITIES WHATEVER WITH RESPECT TO THE USE, SALE, OR OTHER DISPOSITION BY LICENSEE OR ANY OTHER PERSON OF THE PATENT RIGHTS AND TECHNOLOGY RIGHTS OR INFORMATION RESULTING FROM THE SAME FURNISHED UNDER THIS LICENSE.** Licensee agrees to obtain the written agreement of each sublicensee and assignee (i) to hold Licensor, Regents, UT Southwestern, its officers, agents and employees harmless against all liabilities, demands, damages, expenses or losses arising out of the use, sale or other disposition by Licensee or by third parties acquiring through Licensee, including sublicensee(s), or any Licensed Technology furnished under this License, and (ii) if requested, to defend Licensee, Regents, UT Southwestern, its officers, agents and

employees against any and all claims arising out of such use, sale or other disposition.

IV. COMPENSATION AND REPORTS

4.1 Licensee shall transfer to Licensor 400,000 shares of Series A Preferred Stock of Texcellon Inc., plus:

(a) An amount equal to one-half of the royalty income received by Licensee from each and every Transfer; and

(b) One-half of any shares of, or interest in, capital stock or other equity or convertible security or participations received by Licensee upon each and every Transfer.

Such compensation may also include any special compensation arrangement mutually agreed to by the parties hereto.

4.2 Licensor shall also be entitled to receive and Licensee shall cause Texcellon Inc. to issue to Licensor an additional 400,000 shares of Series A Preferred Stock after approval of the Product License Application by the FDA for Imtox 22 unless the Board of Directors of Texcellon determines that an earlier issuance, in whole or in part, is necessary or desirable. Licensee waives any interest it may have in such shares.

4.3 Licensee shall have no liability to transfer to Licensor any portion of any dividends or other distributions received by, or accruing to, Licensee as a holder of any securities or participations of the same entity after the date of such transfer.

4.4 During the term of this License and for one (1) year thereafter, Licensee shall keep complete and accurate records of the consideration received by it from each Transfer made by it, in sufficient detail to enable the compensation under Section 4.1 to be determined. Licensee shall permit Licensor, or its representatives, at Licensor's sole cost and expense, to examine on a semi-annual basis, its records of the consideration received by it from each Transfer made by it, during regular business hours for the purpose of and to the extent necessary to verify any report required under this License. Licensor shall be bound by the provisions of Article VII of the Sponsored Research Agreement as to all information received by it during any such examination and shall cause each of its representatives to be similarly bound.

4.5 If during any calendar quarter during the term of this License, Licensee has made any Transfer(s) or received any consideration from Transfer(s), it shall, within thirty (30) days after the end of that quarter send to Licensor a true and accurate report of such Transfer(s) and the consideration received therefrom.

4.6 The only deductions which Licensee shall make from the consideration received from Transfer(s) before determining Licensor's one-half share of such consideration shall be the following:

(a) Licensee's actual costs of collection of such consideration, including court costs and attorneys' fees; and

(b) Licensee's actual costs incurred in obtaining or maintaining any cross-license from a third party which Licensee deems necessary or appropriate in order to secure for itself, and its assignees or sublicensees, the benefits of the License or rights under patents or other rights it reasonably believes to be dominant over the Patents or Technology Rights.

4.7 Licensee shall cause Texcellon Inc. to pay to each of Jonathan Uhr, M.D., Ellen Vitetta, Ph.D., and Philip Thorpe, Ph.D. a royalty of 1% of Net Royalty Sales by Texcellon of products which include Royalty Bearing Items. Such royalty payments shall be made within one hundred twenty (120) days of the end of each calendar quarter based on Net Royalty Sales for such quarter. Net Royalty Sales shall mean the gross price as received by Texcellon, less all packaging, insurance and freight, storage, transportation and similar costs; all trade discounts, quantity discounts, damaged, outdated or returned goods and all other related costs; all value added, sales, use or excise taxes, tariffs, export license fees and duties; all amounts repaid or credited by reason of rejections, defects or returns or because of retroactive price reductions; and all other royalties. Royalty Bearing Items shall mean all Patent Rights and commercially valuable Technology created by Jonathan Uhr, M.D., Ellen Vitetta, Ph.D., or Philip Thorpe, Ph.D.

4.8 Should the rules of the National Institutes of Health allow equity ownership by Jonathan Uhr, M.D., Ellen Vitetta, Ph.D. and Philip Thorpe, Ph.D. in the future, Licensor and Licensee shall (and shall cause Texcellon Inc. to) discuss whether equity or

royalties, as provided for in Section 4.7 above, shall be received by the said Jonathan Uhr, M.D., Ellen Vitetta, Ph.D. and Philip Thorpe, Ph.D.

4.9 Licensee shall have no obligation to enforce any assignment or sublicense of this License against any assignee or sublicensee. In the event that any such assignee or sublicensee shall default in its obligations under such agreement with Licensee and Licensee shall fail or refuse to take any action to enforce said obligation, then Licensor, with the written consent of Licensee (which consent shall not be unreasonably withheld), shall have the right to enforce such obligation against such assignee or sublicensee at its sole cost and expense. Licensee shall be entitled to one-half of any amount recovered by Licensor after deduction of Licensor's actual expenses of collection thereof (including attorneys' fees).

4.10 (a) Licensee shall, within thirty (30) days of execution of this Agreement, reimburse to UT Southwestern the amount of Forty Seven Thousand Nine Hundred Seventy Dollars and Twenty-Four Cents (\$47,970.24), Licensor's out-of-pocket expenses thus far incurred in filing, prosecuting and maintaining in foreign jurisdictions Patent Rights and Pre-existing Rights exclusively licensed hereunder.

(b) Licensee shall reimburse UT Southwestern, upon monthly invoice from UT Southwestern, or cause Sublicensee to reimburse UT Southwestern, for all Licensor's expenses hereafter to be incurred in filing, prosecuting and maintaining in foreign

jurisdictions Patent Rights and Pre-existing Rights exclusively licensed hereunder, so long as and in such foreign jurisdictions as this License remains exclusive. Licensor shall hereafter seek to obtain Licensee's prior approval as to the selection of foreign jurisdictions and the general scope of activity undertaken and will, upon request of Licensee, provide estimates (if possible) and detailed invoices of expenses incurred. If Licensor fails to respond to Licensee's written inquiry within five (5) working days after receipt thereof by Licensee, Licensor shall have the right to move forward to obtain patent protection in certain foreign jurisdictions. If Licensee fails to make such reimbursement within sixty (60) days after written demand therefor, Sublicensee shall have no rights in that jurisdiction under this License.

V. THE PATENTS

5.1 Licensor shall provide Licensee a copy of any Patent Application filed by it and provide Licensee the opportunity to comment thereon, in accordance with the terms of the Sponsored Research Agreement, and shall not (i) take any action after a Patent has been issued to amend (in substance) or limit the scope of such Patent, or (ii) allow to lapse, or abandon, any Patent or any application therefor, without the written consent of Licensee, but such consent shall not be unreasonably withheld. Licensor will keep Licensee informed as to the progress of applications under Patents and will provide Licensee with copies of any finally issued claims in such applications.

5.2 Licensor represents and warrants that it is the owner of the entire right, title and interest in and to the Patents and the Technology. Licensor has the sole right to grant licenses under such Patents and Technology and has not granted licenses thereunder to any other person, firm, corporation or entity.

5.3 Licensor shall notify Licensee, and Licensee shall notify Licensor, of any infringement by a third party which may come to the attention of Licensor or Licensee.

5.4 Nothing herein shall impose any obligation upon either Licensee or Licensor to defend any action or proceeding in which a claim or counterclaim is made for revocation of, or contesting the validity or scope of, any Patent or to prosecute any action for infringement or alleged infringement of any Patent, but should either Licensee or Licensor (pursuant to Section 5.5 hereof) decide to defend or prosecute any such action it shall do so at its own cost and be entitled to the entire amount recovered therefrom.

5.5 If Licensee fails to bring suit to prevent any infringement or any allegedly infringing use of which it has knowledge within six (6) months after written notice thereof by Licensor, Licensor shall have the right, after notice to Licensee of its intention to do so, to bring suit against the accused infringer in the name of Licensor, and Licensee may join any such suit as a named party.

5.6 Licensee and Licensor shall fully cooperate with the other in defense or prosecution of any such action, whether or not they are a named party thereto.

VI. COMMERCIALIZATION

6.1 Licensee shall have no obligation to Licensor to develop or otherwise commercialize any of the Pre-existing Rights, Patent Rights or Technology Rights licensed hereunder.

6.2 This License is subject to the provisions of 35 U.S.C. § 203.

VII. RESERVATIONS

7.1 Licensor reserves and retains for itself a royalty-free, right and license to practice and use any Patent Rights, Technology Rights, and Pre-Existing Rights, including any licensed Invention or Licensed Technology, exclusively for teaching, traditional academic research or other educational purposes (including the right to transfer specimen biological materials to other academic institutions to the extent required by U.S. PHS regulations solely for non-commercial purposes) but for no other purpose or use whatsoever.

7.2 All rights of the United States of America required to be reserved pursuant to the requirements of Chapter 18 of Title 35 of the United States Code, as in effect on the date hereof, are hereby reserved.

VIII. CONFIDENTIAL INFORMATION

Licensor and Licensee agree to comply with the provisions of Article VII of the Sponsored Research Agreement and will maintain the confidentiality of all unpatented Technology in compliance

therewith. Licensee agrees to obtain the written agreement of any sublicensee and assignee to be bound by the provisions of Article VII of the Sponsored Research Agreement or terms substantially similar thereto.

IX. GENERAL PROVISIONS

9.1 This License and the rights and obligations of the parties hereto shall be governed, construed and enforced in accordance with the laws of the State of Texas.

9.2 This License shall be binding upon and inure to the benefit of the parties hereto, together with their respective successors and assigns. Nothing in this License, express or implied, is intended to confer upon any person or entity other than the named parties or their respective successors and assigns, any rights, remedies, obligations or liabilities under or by reason of this License.

9.3 Licensee shall not be liable for delay in performance or failure to perform in whole or in part its obligations under this License due to labor disputes, strikes, war or acts of war (whether actual declaration of war is made or not), insurrection, terrorism, riot, civil commotion, acts of the public enemy, accident, fire, flood, or of acts of God, acts of any governmental authority, judicial action, compliance in good faith with any applicable foreign or domestic law, governmental regulation or order, whether or not it later proves to be invalid, or other causes beyond the reasonable control of Licensee.

9.4 This License and the Sponsored Research Agreement and Amendments set forth the entire agreement and understanding between the parties with respect to the subject matter hereof and supersedes and replaces all prior understandings, agreements and statements (written or oral). This License may be amended, modified or supplemented only by a written instrument executed by both parties hereto.

9.5 Any inquiry(ies) or notice(s) required or permitted to be given under this License shall be given in accordance with the terms of Section 13.3 of the Sponsored Research Agreement, with copies to:

Jim D. Cook, M.D.
President
Texcellon Inc.
1265 Two Lincoln Centre/LB 36
Dallas, Texas 75240

and

M. D. Sampels, Esq.
Worsham, Forsythe, Sampels & Wooldridge
2001 Bryan Street, Suite 3200
Dallas, Texas 75201

As to Licensor:

Dudley Dobie, Esq.
U.T. System
Office of General Counsel
201 West 7th Street
Austin, Texas 78701

and

Katherine L. Chapman, Esq.
Assoc. VP for Legal Affairs and
Technology Transfer
UT SOUTHWESTERN
5323 Harry Hines Blvd.
Dallas, Texas 75235-9008

The above-listed names, titles and addresses may be changed by written notification to Licensor. Licensee shall provide Licensor with copies of all sublicenses under, and assignments of, this License.

9.6 If any provision of this License is held to be invalid, unenforceable or illegal under present or future laws effective by the term hereof, such provision shall be fully severable and this License shall be construed and enforced as if such illegal, invalid or unenforceable provision never comprised a part hereof, and the remaining provisions hereof shall remain in full force and effect and shall not be effected by the illegal, invalid or unenforceable provision or by its severance herefrom.

9.7 Licensor and Licensee agree to comply with all applicable federal, state and local laws and regulations, particularly those concerning biological materials and necessary testing to obtain approval of the Federal Drug Administration or other Federal agencies concerning the use, sale and export of Licensed Products.

9.8 Licensee shall not use the name of The University of Texas System or any of its component institutions or employees in a commercial context, without the express written consent of Licensor.

9.9 Headings in this License are for convenience only and shall not be used to construe this License.

IN WITNESS WHEREOF, the parties hereto have caused this Exclusive License to be executed as of the date first above written.

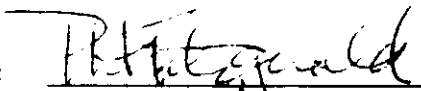
ATTEST:

BOARD OF REGENTS OF THE
UNIVERSITY OF TEXAS SYSTEM

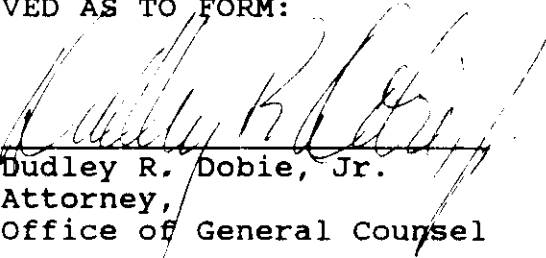
By: _____
Arthur Dilly
Executive Secretary

By: _____
Michael E. Patrick
Executive Vice Chancellor
For Asset Management

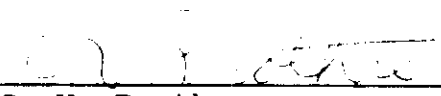
APPROVED AS TO CONTENT:
UT SOUTHWESTERN

By: 
Peter H. Fitzgerald, Ph.D
Executive Vice President
For Business Affairs

APPROVED AS TO FORM:

By: 
Dudley R. Dobie, Jr.
Attorney,
Office of General Counsel

DALLAS BIOMEDICAL CORPORATION

By: 
C. V. Prothro
Chairman of the Board

ATTACHMENT A

<u>INVENTORS</u>	<u>TECHNOLOGY</u>	<u>OUR FILE #</u>	<u>PENDING PATENT SERIAL #</u>	<u>ISSUED PATENT #</u>
Uhr, J. Vitetta, E.	Use of Antigen-Toxin Conjugates to Induce Immunological Tolerance	UTSD:027	465,471 2/10/83	-----
Uhr, J. Vitetta, E.	Anti-Immunoglobulin Toxin Conjugates Useful in Treatment of B Cell Tumors	UTSD:033	498,754 5/27/83	4,792,447 12/20/88
Uhr, J. Vitetta, E.	Immunotoxin Toxin Conjugates Employing Toxin B Chain Moieties	UTSD:034	506,540 6/21/83	4,664,911 5/12/87
Uhr, J. Vitetta, E.	Improved Methods for Screening Antibodies for Use as Immunotoxins	UTSD:130	262,974 10/26/88	-----
Uhr, J. Vitetta, E.	Anti-CD22 & Anti-CD19 Immunotoxins to Treat B Cell Cancer & Auto-Immune Disease	UTSD:131	Know-how	-----
Uhr, J. Vitetta, E.	Vascular Leak Syndrome (VSL), New Methods of Prevention	UTSD:160	To be filed	-----
Uhr, J. Vitetta, E.	Immunotoxin Action: Modified B Chain to Potentiate A Chain Immunotoxins	UTSD:161	To be filed	-----
Uhr, J. Vitetta, E.	Methods & Compositions for the Treatment of HIV-1 Infections: Chloroquine	UTSD:162	To be filed	-----
Uhr, J. Vitetta, E.	Immunoconjugates for the Treatment of AIDS	UTSD:172	To be filed	-----

<u>INVENTORS</u>	<u>TECHNOLOGY</u>	<u>OUR FILE #</u>	<u>PENDING PATENT SERIAL #</u>	<u>ISSUED PATENT #</u>
Uhr, J. Vitetta, E.	Methods & Compositions for the Purification & Preparation of Immunotoxins	UTSD:175	To be filed	-----
Vitetta, E. Thorpe, P.	Sulfated Polysaccharides & Polyanions as Carriers of Drugs	UTSD:165	To be filed	-----
Vitetta, E. Uhr, J. Zolla-Pazner, S.* Gorney, M.* (*NYU)	Methods of Treating HIV Infections Using Immunotoxins	UTSD:147	323,486 3/14/89	-----
Uhr, J. Vitetta, E.	Large Scale Preparation of Immunoconjugate Constructed with Human Recombinant CD4 & Deglycosylated Ricin A Chain	UTSD:179 CIP:172	519,240 5/3/90	Awaiting 1st OA
Uhr, J. Vitetta, E.	Large Scale Preparation of Immunoconjugate Constructed with Human Recombinant CD4 & Dyglycosylated Ricin A Chain	UTSD:250	-----	To be filed
Vitetta, E. Thorpe, P.	Sulfated Polysaccharides & Polyanions as Carriers of Drugs	UTSD:165	-----	Pending

SPONSORED RESEARCH AGREEMENT
BETWEEN
UT SOUTHWESTERN AND DALLAS BIOMEDICAL CORPORATION
IMMUNOTOXINS

THIS SPONSORED RESEARCH AGREEMENT is made by and between The University of Texas Southwestern Medical Center at Dallas (hereinafter referred to as "UT Southwestern"), a component institution of the University of Texas System ("System") governed by a Board of Regents ("Board"), and Dallas Biomedical Corporation, a Texas corporation (hereinafter referred to as "Sponsor").

WHEREAS, UT Southwestern, through Drs. Jonathan Uhr and Ellen Vitetta have been developing cell-reactive antibody-toxin conjugates for killing unwanted cells in vivo, targeting Immunodeficiencies, Auto-immune diseases, and Transplantation; (hereinafter referred to as "Research Program");

WHEREAS, Sponsor and its Scientific Advisory Committee, as well as UT Southwestern have determined that Stage I of the Research Program (hereinafter defined) entitled: Development Of A More Relevant Mouse Model For Use In Immunotoxins As Therapeutic Agents warrants project funding by Sponsor and UT Southwestern in order to further develop the science and technology being developed thereby with a view to its commercial use;

WHEREAS, Sponsor desires that UT Southwestern, under the direction of Principal Investigators, Jonathan Uhr, M.D. and Ellen Vitetta, Ph.D. perform such research and related work as hereinafter described and is willing to advance certain funds to co-sponsor such Research Program;

WHEREAS, UT Southwestern desires to co-sponsor such Research Program on a matching funds basis through funds supplied to UT Southwestern as a grant by the John Hartford Foundation (hereinafter referred to as "Foundation");

WHEREAS, Sponsor desires to obtain exclusive license rights to Pre-existing Rights (as herein defined) patents and technology developed during the course of such Research Program with a view to profitable commercialization of such patents and technology for the benefit of the people of the State of Texas, the researcher and the parties hereto; and

WHEREAS, UT Southwestern is willing to perform such research and to grant to Sponsor, on behalf of the Board, exclusive license rights to such Pre-existing Rights and such patents and technology;

NOW, THEREFORE, in consideration of the mutual covenants and promises herein contained, UT Southwestern and Sponsor agree as follows:

I. EFFECTIVE DATE

This Agreement shall be effective as of August 1, 1989, subject only to any necessary approval by the Board pursuant to the Regents' Rules and Regulations for the System.

II. RESEARCH PROGRAM

2.1 UT Southwestern will use its best efforts to conduct the Research Program (herein so called) described in Attachment "A" and will furnish the facilities necessary to carry out such Research Program. UT Southwestern delegates its responsibility for the day-to-day management of the Research Program, which will be conducted at UT Southwestern, to Jonathan Uhr, M.D. and Ellen Vitetta, Ph.D. or their successors as mutually agreed to by the parties hereto (hereinafter referred to as the "Principal Investigators").

2.2 The Research Program shall be performed during the period from August 1, 1989 through and including January 31, 1990 (unless earlier terminated pursuant to the terms of this

Agreement). Sponsor shall have the option of extending the term of the Research Program upon terms mutually agreeable to both parties. Sponsor shall have the right to terminate the Research Program at any time, as provided in Article XI of this Agreement.

2.3 Sponsor understands that UT Southwestern's primary mission is education and advancement of knowledge, and, consequently, the Research Program will be designed with a view to carry out that mission, and also to develop rights to patents and technology for Sponsor with commercially viable possibilities and to protect Sponsor's exclusive rights under such patents and technology. Except as expressly provided herein, the manner of performance of the Research Program shall be determined solely by the Principal Investigators. UT Southwestern does not guarantee specific results, and the Research Program will be conducted only on a best efforts basis.

2.4 UT Southwestern will keep accurate financial and scientific records relating to the Research Program and will make such records available to Sponsor and its authorized representatives during normal business hours upon reasonable notice.

2.5 Sponsor understands that UT Southwestern may be involved in similar research through other researchers on behalf of itself and others. UT Southwestern represents and warrants to Sponsor that after due inquiry it is not aware of the existence of any such similar research on the date hereof other than as disclosed to Sponsor in writing. UT Southwestern will use its best efforts to notify Sponsor of any such similar research of which it becomes aware after the date hereof. UT Southwestern may continue all such research, provided that it is conducted separately and by a different investigator from the Research Program herein defined, and Sponsor shall not gain any rights by way of this Agreement to any such other research. UT Southwestern will not convey, nor permit the acquisition of, any rights with respect to this Research Program by way of its agreements with the sponsors of such other research, except as

provided in Section 8.4. In the event that any part of the basic research upon which the Research Program may be based was funded by grants from the National Institute of Health ("NIH"), UT Southwestern represents that it has complied with all regulations necessary to obtain rights from NIH and has obtained, or agrees to use its best efforts to obtain, such rights.

2.6 UT Southwestern does not guarantee that any patent rights will result from the Research Program, that the scope of any patent rights obtained will cover Sponsor's commercial interests, or that any such patent rights will be free of dominance by other patents, including those based upon inventions made by other inventors in the System independent of the Research Program.

III. PAYMENT OF EXPENSES OF THE RESEARCH PROGRAM

3.1 (a) During the six (6) month term of the Research Program, Sponsor agrees to pay a total of \$50,000 in two (2) equal payments of \$25,000 each. Payments shall begin on August 1, 1989, and shall be made within fifteen (15) days of the first day of each calendar quarter in the term. Each of these quarterly payments represents one-half of the total direct costs in such quarter for the Research Program, as determined in accordance with the budget forming part of Attachment "B" (the "Budget"). In addition to the Sponsor's share of the total direct costs, Sponsor shall pay UT Southwestern on the same quarterly schedule, a total of \$5,000, an amount equal to ten percent (10%) of Sponsor's share of the direct costs for allocation to UT Southwestern's indirect or overhead costs. Each quarterly payment for the term shall be \$2,500.

(b) During the term of the Research Program, UT Southwestern agrees to transfer each quarter, to the account of the Research Program, commencing August 1, 1989 (within fifteen (15) days of the first day of such quarter) an amount, out of funds made available to it by the Foundation, equal to the

remaining one-half of the total direct costs to be incurred in such quarter for the Research Program.

(c) Sponsor and UT Southwestern may, by mutual agreement, alter the amount and timing of such payments as they may deem necessary or advisable under the circumstances.

3.2 UT Southwestern shall maintain all Research Program funds in a separate account and shall expend such funds for operating expenses in connection with the Research Program in accordance with the Budget. However, UT Southwestern has authority to make transfers within Budget categories as the Principle Investigators determine such transfer is needed. UT Southwestern will monitor, control and account for the disbursement of all funds from such account in accordance with prudent internal documentation, verification and audit procedures. At the conclusion or termination of the Research Program, UT Southwestern will return to Sponsor any unexpended and uncommitted funds remaining in such account paid to UT Southwestern by Sponsor under this Agreement.

3.3 UT Southwestern shall retain title to any equipment purchased and/or fabricated by it with funds provided by Sponsor, or otherwise furnished by Sponsor, under this Agreement, except as mutually agreed to the contrary.

IV. CONSULTATION AND REPORTS

4.1 Sponsor's Designated Representative (herein so called) for consultation and communications with the Principal Investigators shall be A. Devon Giacalone, or such other person as Sponsor may from time to time designate in writing to UT Southwestern and the Principal Investigators.

4.2 During the period of this Agreement, Sponsor's Designated Representative may consult informally with UT Southwestern's representatives regarding the Research Program, both in person and by telephone. Access to work carried on in UT Southwestern laboratories in the course of the Research Program

shall be entirely under the control of UT Southwestern personnel and shall be available to Sponsor's Designated Representative on a reasonable basis.

4.3 The Principal Investigators will make up to four (4) oral reports each year as requested by Sponsor's Designated Representative, including reports to Sponsor's Scientific Advisory Committee, or in lieu thereof, will participate in whatever format and frequency of communication with Sponsor as may be mutually agreed upon. Upon reasonable request, Principal Investigators will participate (at Sponsor's expense) in presentations by Sponsor of the research results to third parties as may be necessary to promote the appropriate commercialization of the resulting technology.

4.4 Semi-annually, within thirty (30) days from the end of each six-month period, the Principal Investigator shall submit to Sponsor a written report containing the information set forth in Items (a) through (c) below. The Principal Investigator shall also submit a comprehensive final written report within 120 days of termination of this Agreement, which shall contain, but which need not be limited to, the following information:

(a) A detailed summary of income and expenses by Budget categories from funds provided pursuant to this Agreement for the Research Program for the prior six-month period.

(b) A budget setting forth anticipated income and expenses for the current fiscal year and for the next two years thereafter, or until the expiration date of this Agreement, if less than two years.

(c) A statement setting forth (i) the activities undertaken by UT Southwestern under the Research Program during the prior six-month period; (ii) the nature and extent to which progress has been made in relation to the development of viable commercial application; and (iii) any changes in the Research Program that are recommended as a result of the activities undertaken to date.

V. PUBLICITY

Except as required by the Texas Open Records Act, no press release or other written statements in connection with work performed under this Agreement intended for use in the public media, having or containing any reference to Sponsor, shall be made by UT Southwestern without approval of Sponsor. UT Southwestern, however, shall have the right to acknowledge Sponsor's support of the investigations under this Agreement in scientific publications and other scientific communications, without Sponsor's prior approval. In any such statements, the parties shall describe the scope and nature of their participation accurately and appropriately.

VI. PUBLICATION AND ACADEMIC RIGHTS

In order to avoid loss of patent or other rights as a result of premature public disclosure through oral presentation or publication in academic or professional journals of patentable or other proprietary or confidential information, UT Southwestern will submit any materials to Sponsor for review at least thirty (30) days prior to planned submission for publication or oral presentation. Sponsor shall notify UT Southwestern within (30) days of receipt of such materials: (1) whether it desires UT Southwestern to file patent applications on any inventions contained in the materials (in which case UT Southwestern shall, upon receipt thereof, promptly proceed to file all appropriate patent applications and shall refrain from publication or presentation of such material until appropriate patent filings have been accomplished), or (2) whether such materials contain information obligated to be held in confidence under the provision of Article VII following. Sponsor shall have the right to reasonably request that any commercially prejudicial information be deleted from the materials or that portions thereof be rewritten to be less prejudicial. UT Southwestern will comply in good faith with any such reasonable request. UT

Southwestern shall have the final authority to determine the scope and content of any publication, provided that such authority shall be exercised with reasonable regard for the commercial interests of Sponsor and not arbitrarily or recklessly.

VII. CONFIDENTIALITY OF INFORMATION

Sponsor and UT Southwestern may, from time to time, in connection with work contemplated under this Agreement, disclose confidential information to the other's personnel. Confidential or proprietary information may also result from the Research Program. For purposes of this Agreement, such confidential information shall include, without limitation, all confidential technical or commercial information and trade secrets in oral, written or physical form. Sponsor and UT Southwestern will use all reasonable efforts to prevent the disclosure to third parties of any confidential information of the other, and will use such information only for the purposes expressed in this Agreement during the term of this Agreement and for a period of five (5) years thereafter, provided that the parties' obligations hereunder shall not apply to information that:

(1) is not in written or physical form or reduced to written or physical form and appropriately identified within thirty (30) days of disclosure or designated as such by the disclosing party;

(2) is already in the receiving party's possession at the time of initial disclosure thereof;

(3) is or later becomes part of the public domain through no fault of the receiving party;

(4) is received from a third party having no obligations of confidentiality to the disclosing party;

(5) is independently developed by the receiving party;

(6) is required to be disclosed under the laws of the United States of America or the State of Texas provided that the parties shall first exhaust all measures available to protect the confidentiality of such information upon disclosure;

(7) is permitted to be disclosed by UT Southwestern pursuant to Article VI hereof, but only with respect to such manner and degree of disclosure as may be expressly permitted thereunder; or

(8) is disclosed by Sponsor in the furtherance of its rights under any license granted pursuant to Article VIII hereof.

VIII. PATENTS, COPYRIGHTS AND TECHNOLOGY RIGHTS

8.1 The following terms shall have the indicated meanings when used in this Article VIII:

(a) "Patent Rights" shall mean any patent application or patent covering any invention made during the course of the Research Program, including any continuations, continuations-in-part, divisionals, reissues, reexaminations, substitutions, extensions or additions thereto, and any corresponding foreign patent application or patent based on such application or patent.

(b) "Technology" shall mean all unpatented inventions, software, know-how, and other technology and commercially valuable information developed during the Research Program.

(c) "Technology Rights" shall mean the Board's and UT Southwestern's rights under State and Federal laws, including the laws of copyright, mask works, trade secret, and unfair competition in Technology.

(d) "Invention" shall mean any discovery, concept, or idea, whether or not patentable or copyrightable, made during the Research Program, including but not limited to processes, methods, software, tangible research products, formulas and techniques, improvements thereto, and all know-how related thereto.

(e) "Domestic Patent Expenses" shall mean any expenses, including reasonable attorney's fees, incurred in the searching, filing, prosecuting or maintaining a patent or patent application in the United States.

(f) "Foreign Patent Expenses" shall mean any expenses, including reasonable attorney's fees, incurred in the

searching, filing, prosecuting or maintaining a patent or patent application in any country other than the United States.

(g) "Pre-existing Rights" shall mean all those previously uncommitted rights of the Board and UT Southwestern relating to the subject matter of the Research Program which existed before the Effective Date and which are necessary for Sponsor to practice the exclusive license granted pursuant hereto, including without limitation those items listed on Attachment "D."

Except for the rights granted in Section 8.4 below, any Patent Rights and Technology Rights, including Inventions or copyrightable works made, developed or discovered during the course of the Research Program either solely by UT Southwestern personnel or jointly by UT Southwestern and Sponsor personnel shall be the property of the Board and UT Southwestern. Rights shall be deemed to have arisen during the Research Program if they are either conceived or reduced to practice during such Research Program.

8.3 After consultation with Sponsor, UT Southwestern will prepare and file appropriate United States and foreign patent applications on Inventions made during the course of the Research Program. UT Southwestern will provide Sponsor a copy of any such application filed and any documents received or filed during prosecution thereof (including correspondence with its patent attorneys) and will provide Sponsor the opportunity to comment thereon. On any application as to which an employee of Sponsor is a co-inventor, Sponsor will cooperate in obtaining execution by its employees of any documents deemed necessary by UT Southwestern's patent attorneys for protecting UT Southwestern's rights to such invention.

8.4 UT Southwestern grants to Sponsor an option to obtain a worldwide, exclusive and assignable license under Patent Rights and Technology Rights to practice and use any and all Inventions, and use and practice any and all Technology made, developed or discovered in the course of the Research Program, and said option will also include all Pre-Existing Rights related to Research Program. Sponsor shall pay to UT Southwestern for such option

One Thousand Dollars (\$1000) within ninety (90) days of execution of this Agreement. Such option shall be exercisable at any time by Sponsor during the period commencing on the Effective Date of this Agreement and ending on the date one (1) year from the termination of this Agreement. Until the expiration of the option period for an item within Patent Rights and Technology Rights, such as an invention disclosure, patent, patent application, or identifiable piece of unpatented technology, UT Southwestern shall neither offer nor convey these rights to any third party or take any action which at a later date might preclude or limit the exercise of Sponsor's option with respect to any rights.

8.5 UT Southwestern shall bear all Domestic Patent Expenses, including the costs of any prior activities investigating patentability, such as search and opinion for patentability that may have been performed by UT Southwestern. It is contemplated that, in the majority of instances, Sponsor will be asked to determine whether it will exercise its option prior to the filing of the first foreign patent application. In the event Sponsor elects to exercise its option as to such item, it shall be obligated to pay all Foreign Patent Expenses for such item.

8.6 Sponsor may exercise its option on Pre-Existing Rights, Patent Rights and/or Technology Rights by informing The University of Texas System Intellectual Property Office, 201 W. Seventh St., Austin, Texas 78701, (512) 499-4462, of the identity of the item(s) within Pre-Existing Rights, Patent Rights and/or Technology Rights and by providing a written statement of its intention to develop the item, i.e. inventions, technology or software, for public use as soon as practicable, consistent with sound and reasonable business practices and judgment.

8.7 Upon exercise of each such option, the parties shall enter into a license agreement granting Sponsor a license to manufacture, have made, use and sell products based on the foregoing rights, and to grant sublicenses, which agreement shall be substantially in the form of the Model Exclusive License, a copy of which is attached to this Agreement as Attachment "C."

Both parties agree to negotiate in good faith to enter into a license agreement as soon as reasonably practicable after the exercise of such option. If such a license agreement is not executed by the parties within 6 months following Sponsor's exercise of such option (or within such additional time as may be mutually agreed upon by the parties) and such failure to execute a license agreement is not attributable to UT Southwestern's delay, then all rights shall remain with Board as if said option has not been exercised by Sponsor.

8.8 UT Southwestern grants Sponsor a fully paid-up license under its copyrights to copy and prepare derivative works from any writer report prepared and delivered to Sponsor in accordance with this Agreement. Such license shall be exclusive except with respect to internal dissemination of such materials for administrative and educational purposes within UT Southwestern and in compliance with the provisions of Article VII of this Agreement.

IX. LIABILITY

9.1 Sponsor agrees to indemnify and hold harmless the System, the Board and UT Southwestern, and, their respective Regents, officers, agents and employees from any liability, loss or damage they may suffer as a result of claims, demands, costs or judgments against them arising out of negligent acts or omissions arising from the obligations of this Agreement and the use of Sponsor of the results obtained from the activities performed by UT Southwestern under this Agreement.

9.2 UT Southwestern shall, to the extent authorized under the Constitution and laws of the State of Texas, hold Sponsor harmless from liability resulting from UT Southwestern's negligent acts or omissions within the terms of this Agreement; provided, however, UT Southwestern shall not hold Sponsor harmless from any claims, demands, or causes of action arising in favor of any person or entity, growing out of, incident to, or resulting directly or indirectly from negligence (whether sole, joint, concurring or otherwise) of Sponsor its officers, agents,

representatives, or employees, or any person or entity not subject to UT Southwestern's supervision or control.

9.3 Both parties agree that within fifteen (15) days of the receipt of a notice of claim or action arising out of the Research Program, or any related Patent License Agreement that party will notify the other. Sponsor agrees, at its own expense, to provide attorneys to defend against any actions brought or filed against UT Southwestern, System, their Regents, officers, agents and employees with respect to the subject of the indemnity contained herein, whether or not such claims or actions are rightfully brought or filed, provided however, that UT Southwestern, System and Board reserve the right to defend themselves (at their own expense) in such actions. Sponsor and UT Southwestern agree to fully cooperate (each at its own expense) in the defense of any such claim or action.

X. INDEPENDENT CONTRACTOR

10.1 For the purposes of this Agreement and all services to be provided hereunder, the parties shall be, and shall be deemed to be, independent contractors and not agents, employees, partners or joint venturers of the other party. No party shall have authority to make any statements, representations or commitments of any kind, or to take any action which shall be binding on the other party, except as may be explicitly provided for herein or authorized in writing.

10.2 UT Southwestern and Sponsor may from time to time enter into agreements similar to this Agreement in connection with other research projects. Each such project shall be completely independent of all others and this Research Project shall be governed exclusively by the terms of this Agreement.

XI. TERM AND TERMINATION

11.1 This Agreement shall commence with the Effective Date hereof and extend until the end of the Research Program as

described hereinabove, unless sooner terminated in accordance with the provisions of this Section.

11.2 This Agreement may be terminated at any time by the mutual agreement of both parties.

11.3 This Agreement may be terminated at any time by either party upon sixty (60) days written notice to the other party.

11.4 Termination of this Agreement shall not affect the rights and obligations of the parties accrued prior to termination. Sponsor shall pay UT Southwestern for all reasonable expenses incurred or committed to be expended as of the effective termination date, including salaries for term appointees for the remainder of their terms of appointment.

11.5 Any provisions of this Agreement which by their nature extend beyond termination hereof shall survive such termination.

XII. ATTACHMENTS

Attachments A, B, C and D are made a part hereof for all purposes.

XIII. GENERAL

13.1 This Agreement may not be assigned by any party without the prior written consent of the other party; provided, however, that Sponsor may assign this Agreement to any purchaser or transferee of all or substantially all of Sponsor's business upon prior written notice to UT Southwestern if such purchaser or transferee agrees in writing to be bound to the terms and conditions hereof to the same extent as Sponsor. Nothing in this Agreement, express or implied, is intended to confer upon any person or entity other than the named parties hereto or their respective successors and assigns (to the extent assignment is permitted hereinabove) any rights, remedies, obligations or liabilities under or by reason of this Agreement.

13.2 This Agreement constitutes the entire and only agreement among the parties relating to the Research Program, and all prior negotiations, representations, agreements and

understandings are superseded hereby. No agreements altering or supplementing the terms hereof may be made except by means of a written document signed by the duly authorized representatives of the parties.

13.3 Any notice required by this Agreement shall be given by prepaid, first class, certified mail, return receipt requested, addressed in the care of UT Southwestern to:

University of Texas Southwestern Medical
Center at Dallas
5323 Harry Hines Boulevard
Dallas, Texas 75235-9013
Attn: Peter Fitzgerald, Ph.D.
Vice President for Business Affairs

with a copy to:

Office of General Counsel
The University of Texas System
201 West Seventh Street
Austin, Texas 78701

Attn: System Intellectual Property Office

or in case of SPONSOR to:

Dallas Biomedical Corporation
1265 Two Lincoln Centre
5420 LBJ Freeway
Dallas, Texas 75240

Attn: A. Devon Giacalone, President

or at such other addresses as may be given from time to time under the terms of this notice provision.

13.4 This Agreement shall be construed and enforced in accordance with the laws of the State of Texas.

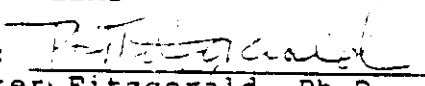
13.5 If one or more provisions of this Agreement are held to be void or unenforceable under applicable law, such provisions shall be excluded from this Agreement and the balance of the

Agreement shall be interpreted as if such provision were so excluded and shall be enforceable in accordance with its terms.


IN WITNESS WHEREOF, the parties have caused this Agreement to be executed by their duly authorized representatives.

(UT SOUTHWESTERN)

THE UNIVERSITY OF TEXAS
SOUTHWESTERN MEDICAL CENTER
AT DALLAS

By: 
Peter Fitzgerald, Ph.D.
Executive Vice President
for Business Affairs

DALLAS BIOMEDICAL
CORPORATION
(SPONSOR)

By: 
A. Devon Giacalone
President

ATTACHMENT A RESEARCH PROGRAM

Introduction

Drs. Jonathan Uhr, Chairman of Microbiology at The University of Texas Southwestern Medical Center at Dallas and a member of the National Academy of Sciences and Dr. Ellen Vitetta, Professor of Microbiology and Director of the Cancer Immunobiology Center, have been working for the past decade at UT Southwestern with collaborators to develop cell-reactive antibody-toxin conjugates for killing unwanted cells in vivo. This work has been initially targeted toward B-cell lymphoma; however, it has now been expanded to develop immunotoxins to treat other cancers, auto immune diseases, immunodeficiencies and transplantation problems.

Scientific Background and Rationale

For the past decade, Drs. Ellen Vitetta and Jonathan Uhr have led a group developing cell-reactive antibody-toxin conjugates for killing unwanted cells in vivo. Drs. Uhr and Vitetta have used the A chain of the plant toxin, ricin, conjugated to tumor-reactive antibodies primarily in a mouse model of human leukemia/lymphoma (BCL). This is an excellent model of the prolymphocytic form of chronic lymphocytic leukemia in man. Killing of these tumor cells in vivo has been the major yardstick by which the chemistry of the conjugates has been altered to yield second generation conjugates. These conjugates have a bond between the toxin and antibody which is more stable in vivo. They also had certain carbohydrates removed from the toxins so that the conjugate is not diverted to the liver. Drs. Uhr and Vitetta have utilized Fab fragments of the conjugate as well as intact antibody to have both small and larger forms of the conjugate. The smaller form is sometimes preferable when penetration into a tumor is a problem. These second generation conjugates are highly effective at killing tumor cells in vivo and display very little nonspecific toxicity. On the basis of in vitro, experimental mouse studies and pharmacokinetic and toxicity-studies in Rhesus monkeys, material has been prepared for clinical trials.

Drs. Vitetta and Uhr have developed a scale-up laboratory for purification of the conjugates that is highly effective, semi-automated and can produce gram amounts of FDA-quality material. They have obtained FDA approval for two INDs to investigate two second generation conjugates for the treatment of refractory B cell lymphomas in man. They are presently in a Phase I/II trial and have treated fourteen patients with one or the other of these conjugates. The side effects have been extremely modest and even

in the Phase I/II trial, tumor regression has been observed. In particular, only one of the fourteen patients in their lymphoma clinical trial have made antibodies to either the A chain or mouse immunoglobulin. Furthermore, the one patient had pre-existing anti-A chain antibodies. Hence, repeated courses of therapy with the conjugates may be possible.

In addition, they have obtained in collaboration with New York University, two human monoclonal antibodies specific to the gp41 envelope glycoprotein of the human immunodeficiency virus. This is a relatively conserved envelope protein in contrast to gp120, which varies from one strain to another. They have prepared conjugates of these antibodies with A chain. The conjugates are highly effective in killing HIV-infected lymphocytes and monocytes (infected with five different divergent strains of HIV) *in vitro*, but do not kill uninfected cells. Since A chain-conjugates have very little nonspecific toxicity in humans, it is planned to only perform a small number of additional *in vitro* tests with this new anti-AIDS drug (e.g., to prove that cells killed by the immunotoxin do not release infectious virus. Preliminary results suggest that live virus is not released. Furthermore, in vivo clearance studies, tissue localization studies and histopathology studies have been carried out in mice. The first dose to be used in humans will be tested in rhesus monkeys. Then we will perform scale-up and toxicity studies needed for an FDA approval of IND for a Phase I/II clinical trial of these reagents. The rationale is to reduce the cellular reservoir of virus to return the HIV-infected patient to an earlier stage of the disease. It is unlikely that these immunosuppressed patients will form antibody to the A chain of human IgG.

PROPOSAL FOR STAGE I
OF IMMUNOTOXIN RESEARCH PROGRAM

For the past 10 years, we have been developing conjugates of tumor-reactive antibody and toxins (immunotoxins) in order to kill tumor cells *in vivo*. The rationale is to provide a new pharmacologic approach to cancer chemotherapy which exploits the exquisite specificity of antibody as a delivery vehicle for toxin moieties. We have used the toxic chain (A chain) of the plant toxin, ricin, that inhibits protein synthesis in all eukaryotic cells at extraordinarily low concentrations. Most of our work has been done *in vitro*, or using a murine lymphoma model *in vivo*. This model helped us to choose the type of immunotoxin to be used in the clinical trials, in particular, the type of disulfide bond between the toxin and antibody. This bond is critical in determination of target cell cytotoxicity and the stability of the immunotoxin *in vivo*. However, this model did not help us to select the specificity of the antibody to be used in clinical trials which must be directed to human B cells. Therefore, our decision concerning the specificity of the antibody was based on availability of anti-human B cell antibodies and the *in vitro* potency of immunotoxins prepared from such antibodies using human neoplastic B cell lines. As a result of these studies, we selected a mouse monoclonal anti-CD22 antibody for clinical use. About 1 year ago, we began a phase I/II clinical trial using two immunotoxins for treatment of patients with refractory B cell lymphomas. One immunotoxin uses an Fab fragment and the other an intact IgG.

A major problem in developing these immunotoxins is the need for a relevant animal model. Thus, it is not possible to study important variables systematically in the human. Since the reagents that we develop react with human but not mouse tumor cells, we need an experimental model for human tumors. The nude

2

mouse injected with human tumor cells has been the most widely used model of this type. It is not a satisfactory model, however, for several reasons: (1) only some human tumor cells grow in nude. (2) those tumors that grow do so very slowly; and, (3) the tumors usually grow only at the injection site (i.e., they rarely metastasize). These latter two features are quite different from cancer in humans, in which the tumor cells grow rapidly, are invasive, and usually metastasize to other sites.

Recently, we have developed a new model which we believe will prove extremely important in further developing immunotoxins as therapeutic agents. We have found that mice with severe combined immune deficiency disease (SCID mice) that are injected with a human B cell lymphoma (Daudi) develop widespread tumors that grow progressively and rapidly until the mouse dies. This particular tumor cell displays the vast majority of molecules on its surface that are present on other human B cell tumors and, therefore, represents an excellent candidate for testing out our reagents for human use. The purpose of this study is to develop this mouse model of human tumors further in order to make it a useful one.

Specific Objectives:

1. Define the natural history of the Daudi tumor in SCID mice, i.e., define the kinetics of tumor growth at the primary and metastatic sites.
2. Define the dose-growth response of the tumor. This is important in establishing a biological assay for determining the percentage of viable tumor cells remaining after treatment with immunotoxins.

3. Compare the two major constructs of immunotoxins that are being used in the human in this experimental system, namely, intact antibody linked by SMPT to deglycosylated A chain (IgG-SMPT-dgA) and Fab antibody linked by the natural cysteines to A chain (Fab'-dgA). Compare each of these at a similar percentage of maximally tolerizable dose (MTD) and the combination of the two together at the same total dosage. Determine the optimal regimen for administration, i.e., test fractionated vs. single doses and the length of the intervals between doses.
4. Test each immunotoxin in combination with conventional chemotherapy. We predict potentiation of these two therapeutic modalities because *in vitro* there is marked synergy.

Approach:

1. Groups of 48 mice will be injected with 10^6 Daudi cells intravenously. Groups of 6 mice will be sacrificed twice a week and their organs examined grossly and histologically for tumor infiltration. All the mice will be dead by 1 month. The organs will be used for immunofluorescent analysis of cell surface phenotype, tumor cell growth *in vitro*, and histologic study of fixed sections. We will determine the kinetics of appearance of the primary subcutaneous tumor, kidney nodules, bone infiltration, bone fractures, leukemia, and lung metastases.
2. Groups of 6 mice each will be injected with 10^1 to 10^6 Daudi cells in ten-fold increments. In this experiment, we will again determine the appearance of tumor. We will plot the dose against the appearance of tumor in each

of the different organ sites mentioned above to determine which is the most reliable indicator of the dose of tumor cells that was injected. This will establish a standard dose-response curve to be used in the future as a biological assay for the quantification of viable tumor cells remaining in a treated animal. This experiment will have to be repeated at least 2X in order to verify the reproducibility of the curve.

3. We will use already purified and characterized anti-CD22 (RFB-4)-SMPT-dgA and RFB4-Fab-dgA immunotoxins. These immunotoxin react with an antigen, CD22, present on 70% of B cell lymphomas. The reagents are sterile, free of endotoxin and are over 90% pure. We will inject these into mice that have well established Daudi cell tumors. Thus, 7-14 days after a subcutaneous dose of 10^6 Daudi cells, mice have tumor nodules in the kidney, bone marrow, and fat tissue. We will treat such mice with 10, 15, and 20% of the MTD dose of each of the two ITs or a mixture of the two containing the same percentage of MTD. We will assay one group of animals 48 hours after the injection to determine immediate cell killing and one week later to determine any late killing induced by the immunotoxins. This latter consideration is important because there is suggestive evidence from our own clinical trials and more decisive evidence from clinical trials of others utilizing monoclonal anti-B cell antibody (without toxins) that a host immune response induced by the injected antibody can cause tumor regression.
4. We will treat groups of mice with cyclophosphamide, immunotoxins or both as described above. We will determine whether there is summation or potentiation of anti-tumor effects of these two therapeutic modalities.

Justification of Personnel:

M. Ghetie will supervise the project under our direction. Mr. Tucker will prepare injections, remove organs, and monitor tumor growth and side effects. Ms. Jones will grow cells, do FACS analyses, and prepare immunotoxins. All work with SCID mice is done in our UT sterile SCIDK mouse facility.

Justification of Materials:

Costs of supplies are based on current expenses.

DALLAS BIOMEDICAL CORPORATION

1265 Two Lincoln Centre LB36 5420 LBJ Freeway Dallas, Texas 75240 (214) 490-6711 Telex 205753 Fax (214) 490-4051

BUDGET (1 YEAR)

IMMUNOTOXINS

Jonathan W. Uhr, M.D., Ph.D. and Ellen S. Vitetta, Ph.D.

August 1, 1989 through July 31, 1990

PERSONNEL

Research Scientist	\$19,120	
Fringe Benefits (27.5%)	5,258	
Research Assistant II	20,880	
Fringe Benefits (27.5%)	<u>5,742</u>	
Total Personnel Costs		\$51,000

EQUIPMENT

40 SCIDS/mo x 12 s \$30 for housing and purchase	\$27,000	
Slide preparation (tissue sectioning)	2,500	
Fluorescent activated cell sorter analysis	6,200	
Tissue culture medium, plasticware	5,000	
Immunotoxin preparation and testing	500	
Isotopes for IC ₅₀ determinations	1,000	
Miscellaneous publication costs	<u>1,500</u>	
Total Equipment		49,400

Total Direct Costs \$100,000

Hartford Share of Project Costs	<u>\$50,000</u>	
Dallas Biomedical Share of Project	\$50,000	
10% Overhead Costs	<u>5,000</u>	
	\$55,000	
		<u>\$105,000</u>

NOTE: Salaries category based on 1 year; other direct costs based on 6 months.

ATTACHMENT "B"

ATTACHMENT C

(MODEL) EXCLUSIVE LICENSE

THIS LICENSE is made as of the day of _____, 19____, between the Board of Regents ("Regents") of The University of Texas System (hereinafter referred to as "Licensor") for and on behalf of The University of Texas Southwestern Medical Center at Dallas and Dallas Biomedical Corporation, a Texas corporation (hereinafter referred to as "Licensee").

RECITALS

WHEREAS, Licensee and Licensor have co-sponsored certain research pursuant to the terms of that certain Sponsored Research Agreement by and between Licensor and Licensee, dated as of _____, 19____ ("Sponsored Research Agreement");

WHEREAS, Licensee has previously obtained an option to exclusive license rights to patents and technology developed during the course of such research with a view to profitable commercialization of such patents and technology for the benefit of the people of the State of Texas, the research, Licensor and Licensee;

WHEREAS, Licensor desires to grant to Licensee, pursuant to the exercise of Licensee's option contained in Article VIII of the Sponsored Research Agreement, the license hereinafter set forth;

NOW THEREFORE, in consideration of the mutual covenants and provisions herein contained, Licensor and Licensee agree as follows:

I. EFFECTIVE DATE

This License shall be effective as of _____, 19____, subject only to any necessary approvals by the Board pursuant to the Regents Rules and Regulations for the University of Texas System.

II. DEFINITIONS

As used in this Agreement, the following terms shall have the meanings indicated:

2.1 The terms defined in the Sponsored Research Agreement shall have the same meanings herein, unless otherwise defined herein.

2.2 "Licensed Products" shall mean any product or material covered by Patents or otherwise incorporating any Invention or Licensed Technology licensed hereunder and combinations of Licensed Products with other products, materials, structures or apparatus.

2.3 "Patent" shall mean any and all patents included within Patent Rights.

2.4 "Transfer" shall mean any and all assignments or sublicenses of this License by Licensee or other disposition (by sale, lease or otherwise) of the Technology by Licensee.

III. LICENSE

3.1 Subject to the provisions of Sections 6.2 and 7.1 hereof, Licensor hereby grants and agrees to grant to Licensee the full and exclusive, world-wide, assignable license and authority ("License") under the Patent Rights, the Technology Rights and the Pre-Existing Rights to make, have made, use, lease, import, vend, sell or otherwise dispose of Licensed Products and to practice and use any Invention and to practice and use any Technology made, developed or discovered, in whole or in part, during the course of the Research Program, in all fields of use. This License shall also include the right to grant sublicenses. The foregoing grant shall include, without limitation, the following Patents and/or applications:

3.2 The term of the License under Technology Rights, as to all unpatented Technology and Inventions, shall be for a period of twenty (20) years from the Effective Date. Licensee shall have the option to extend such term for additional five (5) year periods, as provided in Section 3.4 hereof. The term of License

under each Patent shall be for the life of such Patent and all renewals, extensions, continuations, continuations-in-part divisionals, re-examinations, re-issues, substitutions and additions thereof or thereto.

3.3 This License may only be revoked or terminated upon the occurrence of the following events of default:

(a) Licensee shall have failed to commercialize or cause to be commercialized the licensed technology as provided in Article VI hereof; or

(b) Licensee shall have defaulted in its obligation to pay to Licensor the compensation as provided in Section 4.1 hereof; provided Licensor shall have first given Licensee and each of its assignees and sublicensees of which Licensor has been given notice, at least ninety (90) days prior written notice of its intent to terminate the License and neither Licensee nor any of such assignees or sublicensees shall have cured such default prior to the expiration of such ninety (90) day period.

3.4 Licensee's option to renew and extend the term of the License, as to all unpatented Technology and Inventions for successive five-year periods shall be conditioned only upon: (i) Licensee's giving Licensor written notice thereof at least ninety (90) days prior to the expiration of such License, and (ii) in the event Licensor shall have received a bonafide and binding and definitive written offer from an unaffiliated third-party to license the same Technology and Inventions, Licensee shall agree to amend this License so that the compensation level to which Licensor is thereafter entitled shall be equal to any greater compensation level to which it would be entitled pursuant to such offer. For example, if Licensee is receiving a six-percent royalty hereunder, to which Licensor is entitled to one-half, or three-percent, and the bonafide third-party offer contemplates a four-percent royalty, the renewal hereof shall be conditioned upon Licensee agreeing to pay Licensor a four-percent royalty.

IV. COMPENSATION AND REPORTS

4.1 Licensee shall pay to Licensor and/or its designees compensation in an amount equal to one-half of the consideration received by Licensee upon each and every Transfer by Licensee, for example:

- (a) An amount equal to one-half of the royalty income received by Licensee from each and every Transfer;
- (b) One-half of any shares of, or interest in, capital stock or other equity or convertible security or participations received by Licensee upon each and every Transfer;
- (c) Such compensation may also include any special compensation arrangement mutually agreed to by the parties hereto.

4.2 Licensee shall pay or transfer, as the case may be, such consideration to Licensor when, as and if received by Licensee, within thirty (30) days of such receipt.

4.3 In the event that Licensee transfers equity securities or participations to Licensor pursuant to Section 4.1, then Licensee shall have no liability to transfer to Licensor any portion of any dividends or other distributions received by, or accruing to, Licensee as a holder of any securities or participations of the same entity after the date of such transfer.

4.4 During the term of this License and for one (1) year thereafter, Licensee shall keep complete and accurate records of the consideration received by it from each Transfer made by it, in sufficient detail to enable the compensation under Section 4.1 to be determined. Licensee shall permit Licensor, or its representatives, at Licensor's sole cost and expense, to examine on a semi-annual basis, its records of the consideration received by it from each Transfer made by it, during regular business hours for the purpose of and to the extent necessary to verify any report required under this License. Licensor shall be bound

by the provisions of Article VII of the Sponsored Research Agreement as to all information received by it during any such examination and shall cause each of its representatives to be similarly bound.

4.5 If during any calendar quarter during the term of this License, Licensee has made any Transfer(s) or received any consideration from Transfer(s), it shall, within thirty (30) days after the end of such quarter send to Licensor a true and accurate report of such Transfer(s) and the consideration received therefrom.

4.6 The only deductions which Licensee shall make from the consideration received from Transfer(s) before determining Licensor's one-half share of such consideration shall be the following:

(a) Licensee's actual costs of collection of such consideration, including court costs and attorneys fees; and

(b) Licensee's actual costs incurred in obtaining or maintaining any cross-license from a third party which Licensee deems necessary or appropriate in order to secure for itself, and its assignees or sublicenses, the benefits of the License or rights under patents or other rights it reasonably believes to be dominant over the Patents

or Technology Rights.

4.7 Licensee shall have no obligation to enforce any assignment or sublicense of this License against any assignee or sublicensee. In the event that any such assignee or sublicensee shall default in its obligations under such agreement with Licensee and Licensee shall fail or refuse to take any action to enforce said obligation, then Licensor, with the written consent of Licensee (which consent shall not be unreasonably withheld), shall have the right to enforce such obligation against such assignee or sublicensee at its sole cost and expense. Licensee shall be entitled to one-half of any amount recovered by

Licensor after deduction of Licensor's actual expenses of collection thereof (including attorneys fees).

V. THE PATENTS

5.1 Licensor shall provide Licensee a copy of any Patent Application filed by it and provide Licensee the opportunity to comment thereon, in accordance with the terms of the Sponsored Research Agreement, and shall not (i) take any action after a Patent has been issued to amend (in substance) or limit the scope of such Patent, or (ii) allow to lapse, or abandon, any Patent or any application therefor, without the written consent of Licensee, but such consent shall not be unreasonably withheld. Licensor will keep Licensee informed as to the progress of applications under Patents and will provide Licensee with copies of any finally issued claims in such applications.

5.2 Licensor represents and warrants that it is the owner of the entire right, title and interest in and to the Patents and the Technology. Licensor has the sole right to grant licenses under such Patents and Technology and has not granted licenses thereunder to any other person, firm, corporation or entity.

5.3 Licensor shall notify Licensee, and Licensee shall notify Licensor of any infringement by a third party which may come to the attention of Licensor or Licensee.

5.4 Nothing herein shall impose any obligation upon either Licensee or Licensor to defend any action or proceeding in which a claim or counterclaim is made for revocation of, or contesting the validity or scope of, any Patent or to prosecute any action for infringement or alleged infringement of any Patent, but should either Licensee or Licensor (pursuant to Section 5.5 hereof) decide to defend or prosecute any such action it shall do so at its own cost and be entitled to the entire amount recovered therefrom.

5.5 If Licensee fails to bring suit to prevent any infringement or any allegedly infringing use of which it has knowledge within six (6) months after written notice thereof by Licensor, Licensor shall have the right, after notice to Licensee

of its intention to do so, to bring suit against the accused infringer in the name of Licensor, and Licensee may join any such suit as a named party.

5.6 Licensee and Licensor shall fully cooperate with the other in defense or prosecution of any such action, whether or not they are a named party thereto.

VI. COMMERCIALIZATION

6.1 Licensee (and, to the extent applicable, its sublicensees and assignees) agree to exert its (or their) best efforts to commercialize or cause to be commercialized the Licensed Technology as rapidly as practicable, consistent with sound and reasonable business practices and judgment.

6.2 In the event that Licensee has failed to commercialize, or cause to be commercialized, the Licensed Technology within _____ () years from the date hereof, Licensor shall have the right to notify Licensee in writing that this License is subject to termination upon the expiration of nine (9) months from the date of such notice if at such time the Licensed Technology has not then been commercialized or (in the event that such Technology is not reasonably capable of such commercialization within such period) if Licensee is not diligently pursuing a course of action reasonably calculated to commercialize or cause the commercialization of such Technology at the earliest practicable date.

6.3 If Licensee or any sublicensee or assignee has an ongoing and active research, developmental, manufacturing, marketing or licensing Program, as appropriate, directed toward the production and sale of Licensed Products, the same shall be deemed to be sufficient evidence that Licensee has commercialized the Licensed Technology.

VII. RESERVATIONS

7.1 Licensor reserves and retains for itself a royalty-free right and license to practice and use any Patent Rights,

Technology Rights, and Pre-Existing Rights, including any licensed Invention or Licensed Technology, exclusively for teaching, traditional academic research or other educational purposes but for no other purpose or use whatsoever.

7.2 All rights of the United States of America required to be reserved pursuant to the requirements of Chapter 18 of Title 35 of the United States Code, as in effect on the date hereof, are hereby reserved. (IF APPLICABLE)

VIII. CONFIDENTIAL INFORMATION

Licensor and Licensee agree to comply with the provisions of Article VII of the Sponsored Research Agreement and will maintain the confidentiality of all unpatented Technology in compliance therewith. Licensee agrees to obtain the written agreement of each sublicensee and assignee to be bound by the provisions of Article VII of the Sponsored Research Agreement or terms substantially similar thereto.

IX. GENERAL PROVISIONS

9.1 This License and the rights and obligations of the parties hereto shall be governed, construed and enforced in accordance with the laws of the State of Texas and shall be enforceable in Dallas County, Texas.

9.2 This License shall be binding upon and inure to the benefit of the parties hereto, together with their respective successors and assigns. Nothing in this License, express or implied, is intended to confer upon any person or entity other than the named parties or their respective successors and assigns, any rights, remedies, obligations or liabilities under or by reason of this License.

9.3 Licensee shall not be liable for delay in performance or failure to perform in whole or in part its obligations under this License due to labor disputes, strikes, war or acts of war (whether actual declaration of war is made or not), insurrection, terrorism, riot, civil commotion, acts of the public enemy, accident, fire, flood, or of acts of God, acts of any governmental authority, judicial action, compliance in good faith with any applicable foreign or domestic law, governmental

regulation or order, whether or not it later proves to be invalid, or other causes beyond the reasonable control of Licensee.

9.4 This License and the Sponsored Research Agreement set forth the entire agreement and understanding between the parties with respect to the subject matter hereof and supersedes and replaces all prior understandings, agreements and statements (written and oral). This License may be amended, modified or supplemented only by a written instrument executed by both parties hereto.

9.5 Any notice required or permitted to be given under this License shall be given in accordance with the terms of Section 13.3 of the Sponsored Research Agreement. Licensee shall provide Licensor with copies of all sublicenses under, and assignments of, this License.

9.6 If any provision of this License is held to be invalid, unenforceable or illegal under present or future laws effective by the term hereof, such provision shall be fully severable and this License shall be construed and enforced as if such illegal, invalid or unenforceable provision never comprised a part hereof; and the remaining provisions hereof shall remain in full force and effect and shall not be effected by the illegal, invalid or unenforceable provision or by its severance herefrom.

9.7 Licensor and Licensee agree to comply with all applicable federal, state and local laws and regulations, particularly those concerning biological materials and necessary testing to obtain approval of the Federal Drug Administration or other Federal agencies concerning the use, sale and export of Licensed Products.

9.8 Licensee shall not use the name of The University of Texas System or any of its component institutions in a commercial context, without the express written consent of Licensor.

9.9 Headings in this License are for convenience only and shall not be used to construe this License.

IN WITNESS WHEREOF, the parties hereto have caused this Exclusive License to be executed as of the date first above written.

ATTACHMENT D

<u>INVENTORS</u>	<u>TECHNOLOGY</u>	<u>OUR FILE #</u>	<u>PENDING PATENT SERIAL #</u>	<u>ISSUED PATENT #</u>
Uhr, J. Vitetta, E.	Use of Antigen-Toxin Conjugates to Induce Immunological Tolerance	UTSD:027	465,471 2/10/83	- - - - -
Uhr, J. Vitetta, E.	Anti-Immunoglobulin Toxin Conjugates Useful in Treatment of B Cell Tumors	UTSD:033	498,754 5/27/83	4,792,447 12/20/88
Uhr, J. Vitetta, E.	Immunotoxin Toxin Conjugates Employing Toxin B Chain Moieties	UTSD:034	506,540 6/21/83	4,664,911 5/12/87
Uhr, J. Vitetta, E.	Improved Methods for Screening Antibodies for Use as Immunotoxins	UTSD:130	262,974 10/26/88	- - - - -
Uhr, J. Vitetta, E.	Anti-CD22 & Anti-CD19 Immunotoxins to Treat B Cell Cancer & Auto- Immune Disease	UTSD:131	Know-how	- - - - -
Uhr, J. Vitetta, E.	Vascular Leak Syndrome (VSL), New Methods of Prevention	UTSD:160	To be filed	- - - - -
Uhr, J. Vitetta, E.	Immunotoxin Action: Modified B Chain to Potentiate A Chain Immunotoxins	UTSD:161	To be filed	- - - - -
Uhr, J. Vitetta, E.	Methods & Compositions for the Treatment of HIV-1 Infections: Chloroquine	UTSD:162	To be filed	- - - - -
Uhr, J. Vitetta, E.	Immunoconjugates for the Treatment of AIDS	UTSD:172	To be filed	- - - - -

<u>INVENTORS</u>	<u>TECHNOLOGY</u>	<u>OUR FILE #</u>	<u>PENDING PATENT SERIAL #</u>	<u>ISSUED PATENT #</u>
Uhr, J. Vitetta, E.	Methods & Compositions for the Purification & Preparation of Immuno- toxins	UTSD:175	To be filed	- - - - -
Vitetta, E. Thorpe, P.	Sulfated Polysaccha- rides & Polyanions as Carriers of Drugs	UTSD:165	To be filed	- - - - -
Vitetta, E. Uhr, J. Zolla-Pazner, S.* Gorney, M.* (*NYU)	Methods of Treating HIV Infections Using Immunotoxins	UTSD:147	323,486 3/14/89	- - - - -

FIRST AMENDMENT TO SPONSORED
RESEARCH AGREEMENT
(IMMUNOTOXIN: STAGE II)

This amends the Sponsored Research Agreement ("the Agreement") between the University of Texas Southwestern Medical Center at Dallas ("UT Southwestern") and Dallas Biomedical Corporation ("DBC"), dated August 1, 1989 for a Research Program entitled: Development of Cell-reactive Antibody Toxin Conjugates for Killing Unwanted Cells in vivo, Targeting Immunodeficiencies, Auto-immune Diseases and Transplantation (Drs. Jonathan Uhr and Ellen Vitetta).

I.

The title to the Research Program in the Agreement shall be changed to be: Development of Cell-reactive Antibody Toxin Conjugates For Killing Unwanted Cells in vivo, Including Immunodeficiencies, Auto immune Diseases, Transplantation and Neoplasia.

II.

Paragraphs 2.1 and 2.2 of the Agreement shall be deleted and replaced with the following:

2.1 UT Southwestern will use its best efforts to conduct Stage I and II of the Research Program (herein so called) described respectively in Attachments "A" and "E" and will furnish the facilities necessary to carry out such Research Program. UT Southwestern delegates its responsibility for the day-to-day management of the Research Program, which will be conducted at UT Southwestern, to Jonathan Uhr, M.D. and Ellen Vitetta, Ph.D. or their successors as mutually agreed to by the parties hereto (hereinafter referred to as the "Principal Investigators").

2.2 Stage I of the Research Program shall be performed during the period from August 1, 1989 through and including January 31, 1990 (unless earlier terminated pursuant to the terms of this Agreement); Stage II of the Research Program shall be performed during the one year period from September 1, 1989 through and including August 31, 1990. Sponsor shall have the option of extending the term of the Research Program upon terms mutually agreeable to both parties. Sponsor shall have the right to terminate the Research Program at any time, as provided in Article XI of this Agreement. All other terms of the Agreement remain unaltered by this Amendment.

III.

Attachment F shall be added as an additional budget to run simultaneously with Stage I of the Research Program during the periods they overlap and for the additional period of time reflected in Paragraph 2.2.

IV.

Attachment E and F are attached hereto and made a part of this Amendment for all purposes.

V.

Paragraphs 3.1(a) and 3.1(b) shall be deleted and replaced with the following:

3.1(a) During the six (6) month term of the Stage I of the Research Program, Sponsor agrees to pay a total of \$50,000 in two ((2) equal payments of \$25,000 each. Payments shall begin on August 1, 1989, and November 1, 1989. Each of these payments represents one-half of the total direct costs in such quarter for Stage I of the Research Program, as determined in accordance with the budget forming part of Attachment "B" (the "Stage I Budget"). In addition to the Sponsor's share of the total direct costs, Sponsor shall pay UT Southwestern on the same schedule, a total of \$5,000, an amount equal to ten percent (10%) of Sponsor's share of the direct costs for allocation to UT Southwestern's indirect or overhead costs. Each payment for the term shall be \$2,500.

During the twelve (12) month term of Stage II of the Research Program, Sponsor agrees to pay a total of \$200,000 in four (4) equal payments of \$50,000 each. Payments shall begin on September 1, 1989 and shall be made within (15) days of the first day of each calendar quarter in the term. Each of these quarterly payments represents one-half of the total direct costs in such quarter for Stage II of the Research Program, as determined in accordance with the budget forming part of Attachment "F" (the "Stage II Budget"). In addition to the Sponsor's share of the total direct costs for Stage II, Sponsor shall pay UT Southwestern on the same quarterly schedule, a total of \$20,000, an amount equal to 10% of Sponsor's share of the direct cost for allocation to UT Southwestern's indirect or overhead costs. Each quarterly payment for the term shall be \$5,000.

3.1(b) During the term of Stage I of the Research Program, UT Southwestern agrees to transfer each quarter, to the account of the Research Program, commencing August 1, 1989 (within fifteen (15) days of the first day of such quarter) an

amount, out of funds made available to it by the Foundation, equal to the remaining one-half of the total direct costs to be incurred in such quarter for Stage I of the Research Program.

During the term of Stage II of the Research Program, UT Southwestern agrees to transfer each quarter, to the account of the Research Program, commencing September 1, 1989 (within fifteen (15) days of the first day of such quarter) an amount, out of funds made available to it by the Foundation, equal to the remaining one-half of the total direct costs to be incurred in such quarter for Stage I of the Stage II Research Program.

VII.

Paragraph 8.1(g) shall be deleted and replaced with the following:

(g) "Pre-existing Rights" shall mean all those previously uncommitted rights of the Board and UT Southwestern relating to the subject matter of the Research Program which existed before the Effective Date and which are necessary for Sponsor to practice the exclusive license granted pursuant hereto, including without limitation those items listed on Attachment D (and any U.S. and/or foreign patents or patent applications pertaining to such items).

This Amendment shall take effect August 14, 1989.

IN WITNESS WHEREOF, the parties have caused this First Amendment to Sponsored Research Agreement to be signed by their duly authorized officers on the dates written below.

Dallas Biomedical
Corporation

Devon Giacalone
Devon Giacalone
President

Sept 21, 1989
Date

The University of Texas
Southwestern Medical
Center at Dallas

Peter Fitzgerald
Peter Fitzgerald, Ph.D.
Executive Vice President for
Business Affairs

9/26/89
Date

IMMUNOTOXIN PROJECT

Stage II

August 21, 1989

INTRODUCTION

This proposal is to fund the second stage of the immunotoxin project. Stage I of the project was devoted to optimizing the immunotoxin constructs for *in vivo* use and initiating two Phase I clinical trials. Stage II will expand upon these efforts. Specifically, we request \$400,000 to:

- Finish the ongoing Phase I trials for B cell lymphoma
- Begin to construct immunotoxins for a proposed Phase I Trial of Lupus to be done with the Director of Rheumatology (division in the Department of Internal Medicine), Dr. Peter Lipsky
- Begin to construct immunotoxins for a proposed Phase I clinical trial of Hodgkin's Disease in Cologne, Germany

BACKGROUND AND RATIONALE

For the past decade, Drs. Jonathan Uhr and Ellen Vitetta have led a group developing cell-reactive antibody-toxin conjugates (immunotoxins) for killing unwanted cells *in vivo*.

Drs. Uhr and Vitetta have used the A chain of the plant toxin, ricin, conjugated to tumor-reactive antibodies primarily in a mouse model of human leukemia/lymphoma (BCL₁). This is an excellent model of the prolymphocytic form of chronic lymphocytic leukemia in man. Killing of these tumor cells *in vivo* has been the major yardstick by which the chemistry of the conjugates has been altered to yield second generation immunotoxins. These immunotoxins have a bond between the A chain of the toxin and the Fab' fragment of the intact antibody or the intact antibody itself which is more stable *in vivo*. They also had certain carbohydrates removed from the A chain so that the immunotoxin is not diverted to the liver. Drs. Uhr and Vitetta have utilized Fab' fragments of the immunotoxin as well as intact antibody to have both small and larger forms of the conjugate. The smaller form is sometimes preferable for penetration into tumor masses. The larger form is more potent and long-lived. These second generation conjugates are highly effective at killing tumor cells *in vivo* and display very little nonspecific toxicity. On

ATTACHMENT "E"

the basis of *in vitro* and *in vivo* experimental mouse studies and pharmacokinetic- and toxicity-studies in Rhesus monkeys, material has been prepared for clinical trials.

Drs. Uhr and Vitetta are currently completing FDA-approved Phase I clinical trials with a B cell lymphoma product. To date the results of the trial look promising:

- The maximally tolerated dose has not been reached and patients are not experiencing serious side effects
- Even with sub-optimal dose, over 40% of the patients have shown mass shrinkage of tumor. Other patients have responded with partial tumor regressions.
- Patients do not typically make antibodies to the immunotoxins

In order to complete the Phase I trial, Drs. Uhr and Vitetta will require approximately 15 to 20 more patients in order to complete the trial.

PROJECT PLAN

In Stage II of this project we plan to:

- Complete the B cell lymphoma trials. We currently estimate that seven to ten more patients will be required to assess the maximal tolerable dose of each of the immunotoxins.
- We have agreed to initiate two lupus Phase I trials with Dr. Peter Lipsky, an expert in autoimmune disease, and the Director of the Department of Rheumatology Division at the University of Southwestern Medical Center at Dallas. We will be employing Dallas Biomedical Corporation funds only for the preparation of the materials.
- We have agreed to initiate an immunotoxin, Phase I clinical trial for Hodgkin's Disease trial in Cologne, Germany with Drs. Phil Thorpe and Volker Diehl, both experts in this field. DBC funds will be spend to prepare the materials for the trial.

DALLAS BIOMEDICAL CORPORATION

1265 Two Lincoln Centre LB36 5420 LBJ Freeway Dallas, Texas 75240 (214) 490-6711 Telex 205753 Fax (214) 490-4051

BUDGET (1 YEAR)

IMMUNOTOXINS STAGE II

Jonathan W. Uhr, M.D., Ph.D. and Ellen S. Vitetta, Ph.D.
September 1, 1989 through August 31, 1990

PATIENT COSTS FOR LYMPHOMA

Supplies	\$68,000
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LUPUS TRIALS

Supplies	\$217,000
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HODGKINS TRIALS

Supplies	\$115,000
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TOTAL ESTIMATED COST	<u>\$400,000</u>
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Hartford Share of Project	<u>\$200,000</u>
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Dallas Biomedical Share of Project	\$200,000
10% Overhead Costs	<u>20,000</u>
	<u>\$220,000</u>

ATTACHMENT "F"

SECOND AMENDMENT TO
SPONSORED RESEARCH AGREEMENT

This amends the Sponsored Research Agreement (SRA) between The University of Texas Southwestern Medical Center at Dallas ("UT Southwestern"), and Dallas Biomedical Corporation ("DBC"), dated August 1, 1989, for a research program entitled: Development of Cell-reactive Antibody Toxin Conjugates for Killing Unwanted Cells in vivo, Including Immunodeficiencies, Auto-immune Diseases, Transplantation and Neoplasia to be directed by Ellen Vitetta, Ph.D. and Jonathan Uhr, M.D.

I.

Paragraph 9.1 shall be deleted in its entirety and shall be replaced with the following new Paragraph 9.1:

9.1 Sponsor agrees to indemnify and hold harmless the System, the Board and U.T. Southwestern, and their respective Regents, Officers, agents and employees from any liability, loss or damage they may suffer as a result of claims, demands, costs or judgments against them arising out of negligent acts or omissions, or alleged acts of patent infringement, in this or in a foreign country, arising from the obligations of this Agreement or the use of Sponsor by the results obtained from the activities performed by U.T. Southwestern under this Agreement.

In consideration for this Amendment the University agrees to (1) forbear in seeking termination under Paragraph 11.3 of the SRA; and (2) release DBC from its obligation of best efforts to commercialize any Pre-Existing Rights, Patent Rights, or Technology Rights under the SRA and its amendments.

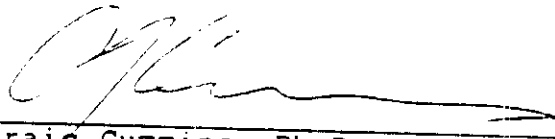
Paragraph 3.1 shall be changed to add the following:

(d) The Principal Investigator may rebudget into any budget category a total of \$5,000 on a cumulative basis. The President of UT Southwestern or his designee may approve any rebudgeting over this amount.

All other terms of the SRA and the First Amendment remain unaltered by this Second Amendment.

This amendment shall take effect June 1, 1990.


DALLAS BIOMEDICAL CORPORATION



Craig Cummins, Ph.D.
President

6/18/90
Date

THE UNIVERSITY OF TEXAS
SOUTHWESTERN MEDICAL CENTER
AT DALLAS



Peter H. Fitzgerald
Executive Vice President
For Business Affairs

8/16/90
Date

**THIRD AMENDMENT TO
SPONSORED RESEARCH AGREEMENT**

This amends the Sponsored Research Agreement (SRA) between The University of Texas Southwestern Medical Center at Dallas ("UT Southwestern"), and Dallas Biomedical Corporation ("DBC"), dated August 1, 1989, for a research program entitled: Development of Cell-reactive Antibody Toxin Conjugates for Killing Unwanted Cells in vivo, including Immunodeficiencies, Auto-Immune Diseases, Transplantation and Neoplasia to be directed by Ellen Vitetta, Ph.D. and Jonathan Uhr, M.D.

Paragraph 2.2 shall be deleted in its entirety and shall be replaced with the following new Paragraph 2.2:

2.2. The Research Program shall be performed during the period from August 1, 1989 through and including December 31, 1990 (unless earlier terminated pursuant to the terms of this agreement). Sponsor shall have the option of extending the term of the Research Program upon terms mutually agreeable to both parties. Sponsor shall have the right to terminate the Research Program at any time, as provided in Article XI of this Agreement.

All other terms of the SRA and the First and Second Amendment remain unaltered by this Third Amendment.

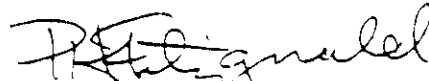
This amendment shall take effect August 1, 1990.

DALLAS BIOMEDICAL CORPORATION

THE UNIVERSITY OF TEXAS
SOUTHWESTERN MEDICAL CENTER
AT DALLAS



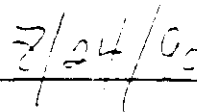
Craig Cummins, Ph.D.
President



Peter H. Fitzgerald
Executive Vice President
For Business Affairs



Date



Date

FOURTH AMENDMENT TO
SPONSORED RESEARCH AGREEMENT

This amends the Sponsored Research Agreement between The University of Texas Southwestern Medical Center at Dallas ("UT Southwestern"), and Dallas Biomedical Corporation ("DBC"), dated August 1, 1989, for a research program entitled "Development of Cell-reactive Antibody Toxin Conjugates for Killing Unwanted Cells in vivo, Including Immunodeficiencies, Auto-immune Diseases, Transplantation and Neoplasia" directed by Drs. Jonathan Uhr and Ellen Vitetta.

Article III shall be changed to add \$2,750, including 10% indirect costs, to Phase II of the Research Program for a new Phase II total amount of \$202,750.


Article XII shall be deleted in its entirety and shall be replaced by the following new Article XII:

"Attachments A, B, C, D, E, F and F-1 are made a part hereof for all purposes."

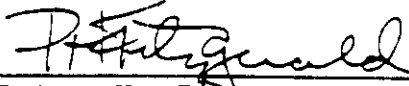
All other terms and conditions remain unchanged.

DALLAS BIOMEDICAL CORPORATION

THE UNIVERSITY OF TEXAS
SOUTHWESTERN MEDICAL CENTER
AT DALLAS



Dr. Jim Cook
President



Peter H. Fitzgerald
Executive Vice President
for Business Affairs

Date

10/23/90

Date

ATTACHMENT "F-1"

BUDGET

IMMUNOTOXINS
STAGE II

Jonathan W. Uhr M.D., Ph.D. and Ellen S. Vitetta, Ph.D.
September 1, 1989 through December 31, 1990

Supplies	\$5,000
TOTAL ESTIMATED COST	\$5,000
Hartford Share of Project	<u>\$2,500</u>
Dallas Biomedical Share of Project	\$2,500
10% Overhead Costs	250
	<u>\$2,750</u>

4-15-91

THE UNIVERSITY OF TEXAS
Southwestern Medical Center
AT DALLAS

Office of Contracts Management

April 10, 1991


Dr. Jim Cook
President
Dallas Biomedical Corporation
1265 Two Lincoln Centre/LB36
5420 LBJ Freeway
Dallas, TX 75240

Dear Dr. Cook:

Enclosed are three (3) copies of Amendment No. 5 to the Sponsored Research Agreement between The University of Texas Southwestern Medical Center at Dallas and Dallas Biomedical Corporation concerning the Immunotoxin Project for Drs. Uhr and Vitetta. This amendment adds \$82,500 for a new Phase II total amount of \$305,250 and extends the agreement through December 31, 1991. All other terms and conditions remain unchanged.

After you have signed, please return two (2) fully executed, manually signed copies to me for official institutional records.

Sincerely,


Gerald Mussey
Director

js
Enc.

cc: Dr. Jonathan Uhr
Dr. Ellen Vitetta

FIFTH AMENDMENT TO
SPONSORED RESEARCH AGREEMENT

This amends the Sponsored Research Agreement between The University of Texas Southwestern Medical Center at Dallas ("UT Southwestern"), and Dallas Biomedical Corporation ("DBC"), dated August 1, 1989, for a research program entitled "Development of Cell-reactive Antibody Toxin Conjugates for Killing Unwanted Cells in vivo, Including Immunodeficiencies, Auto-immune Diseases, Transplantation and Neoplasia" directed by Drs. Jonathan Uhr and Ellen Vitetta.

Paragraph 2.2 shall be deleted in its entirety and shall be replaced with the following new Paragraph 2.2:

"2.2 Stage I of the Research Program shall be performed during the period from August 1, 1989 through and including January 31, 1990 (unless earlier terminated pursuant to the terms of this Agreement); Stage II of the Research Program shall be performed during the period from September 1, 1989 through and including December 31, 1991. Sponsor shall have the option of extending the term of the Research Program upon terms mutually agreeable to both parties. Sponsor shall have the right to terminate the Research Program at any time, as provided in Article XI of this Agreement. All other terms of the Agreement remain unaltered by this Amendment."

Article III shall be changed to add \$82,500, including 10% indirect costs, to Phase II of the Research Program for a new Phase II total amount of \$305,250.

Article XII shall be deleted in its entirety and shall be replaced by the following new Article XII:

"Attachments A, B, C, D, E, F, F-1 and F-2 are made a part hereof for all purposes."

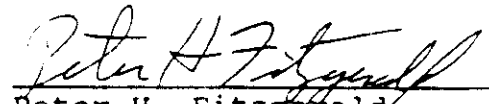
All other terms and conditions remain unchanged.

This amendment shall take effect December 31, 1990.

DALLAS BIOMEDICAL CORPORATION

THE UNIVERSITY OF TEXAS
SOUTHWESTERN MEDICAL CENTER
AT DALLAS

Dr. Jim Cook
President



Peter H. Fitzgerald
Executive Vice President
for Business Affairs

Date

APR 12 1991

Date

ATTACHMENT "F-2"

BUDGET

IMMUNOTOXINS
STAGE II

Jonathan W. Uhr M.D., Ph.D. and Ellen S. Vitetta, Ph.D.
September 1, 1989 through December 31, 1991

Supplies	\$75,000	
TOTAL ESTIMATED COST	\$75,000	
Hartford Share of Project		<u>\$75,000</u>
Dallas Biomedical Share of Project		\$75,000
10% Overhead Costs		7,500
		<u>\$82,500</u>