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FUTURE DRUGS RESEARCH PARTNERSHIP

Broker/Dealer Confidential Summary Sheet

1. A total of 66 Limited Partnership units are being offered.

A. Price per unit -- \$150,000 + \$24,250 (interest at 10%) =  
\$174,250.

B. Unit is purchased as follows:

- \* Upon subscription -- \$20,000
- \* April 30, 1983 -- 53,000 (includes interest)
- \* April 30, 1984 -- 54,000 (includes interest)
- \* October 31, 1984 -- 47,250 (includes interest)

(Note -- The installments payable in 1983 and 1984 shall be evidenced by promissory notes bearing interest at the rate of ten percent (10%) per annum. The Promissory Notes must be secured by irrevocable, assignable and transferable letters of credit or other security acceptable to the Partnership.)

C. Closing Date of offering

April 30, 1982

D. Anticipated Tax Deduction (approximate)

	<u>Partnership</u>	<u>Interest</u>	<u>Total</u>
1982	\$60,000	--	\$60,000
1983	61,000	13,000	74,000
1984	5,000	11,000	16,000

E. Purchaser Receives:

\*Pro-rata interest in Partnership revenues (royalty income and/or product sales)

\*Pro-rata interest in Partnership Targeted Pharmaceuticals, Inc. ("TPI") stock (22,720 shares per unit)

F. Sales Agent's commission -- ten percent (10%) per unit;  
payable as follows:

April 30, 1982	--	\$4,545
April 30, 1983	--	2,727
October 31, 1983	--	2,576
April 30, 1984	--	2,576
October 31, 1984	--	<u>2,576</u>
Total		\$15,000

2. Major R&D projects to be developed by TPI on behalf of the Partnership:
  - A. Antibody targeted cancer drugs
  - B. Intratumor immuno-chemotherapy
  - C. Antibody targeted antibiotics
  - D. Diagnostic immunoassays
  - E. Cancer Vaccines and the use of polymers or microspheres for immunopotentialiation
3. Proprietary and/or unique technologies of TPI:
  - A. Microspheres
  - B. Polymeric drug carries with tissue-binding properties
  - C. Special preparations of antibodies and antigens
4. Location of TPI's "satellite" research groups and cooperating investigators:
  - A. University of Florida (Dr. Goldberg)
  - B. George Washington University (Dr. Hollingshead)
  - C. Harvard University (Drs. Grant and Israel)
  - D. Southern Research Institute (Dr. Schabel)
  - E. University of South Carolina (Dr. Fudenberg)
  - F. M.D. Andersen Tumor Institute (Dr. Granatek)
  - G. University of Washington (Dr. Cho-Chou Kuo)
  - H. University of Arizona (Dr. Harrison)
  - I. University of Pittsburgh (Dr. Fisher)
  - J. Brain Tumor Center -- University of California -- San Francisco (Dr. Levin)

K. Weizman Institute -- Israel (Drs. Arnon, Hurwitz, Levy, Trainin)

L. Nottingham Cancer Laboratory -- England (Dr. Baldwin)

5. Opinions:

A. Partnership status/tax:

Schupak, Rosenfeld, Fischbein, Bernstein & Tannenhauser

B. Accounting:

Goldstein, Golub, Kessler & Company

6. To subscribe:

A. Complete subscription documents

B. Make check for \$20,000 payable to:

"Schupak, Rosenfeld, Fischbein, Bernstein & Tannenhauser, Escrow Agent"

C. Mail subscription documents and check to :

Future Drugs Research Partnership

7. A limited number of fractional units may be available. Interested parties should promptly contact the General Partner (also, any questions should be addressed to the General Partner ):

Mr. George M. Stadler  
(Office -- 203-846-9012)  
(Home -- 203-762-7069)

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FUTURE DRUGS RESEARCH PARTNERSHIP

\$9,900,000

Confidential Summary Memorandum

This memorandum summarizes an offering of sixty-six (66) units of Limited Partnership Interest of \$150,000 each in Future Drugs Research Partnership, a Connecticut partnership. A confidential memorandum describing the investment in detail is being made available. This summary memorandum does not constitute an offer to purchase the units described. It has been prepared for the convenience of potential investors and does not purport to set forth all aspects of the offering, and, in particular the risks of the offering. An offering can be made only with a Confidential Memorandum.

The offering of interest in Future Drugs Research Partnership will be made as a private placement under Rule 146.

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THE PARTNERSHIP

FUTURE DRUGS RESEARCH PARTNERSHIP (the "Partnership") is a Connecticut limited partnership organized to engage in reserach and development with respect to targeted anti-tumor drugs, cancer and veneral diseases vaccines, cancer and venereal disease diagnostic assays, antibody targeted antibiotics, novel adjuvants, microsphere technology and polymeric drug technology (the "Technologies"); and exploiting the resulting processes and products, if any. The Partnership will also hold stock of Targeted Pharmaceuticals, Inc., a Nevada Corporation ("TPI"), which will conduct the reserach and development programs for the Partnership. TPI will be initially owned 70% by its Founders, consultants, employees and science advisors; 25% by the Partnership and 5% by the General Partner.

TPI will conduct approximately fifty percent (50%) of the contracted reserach from the Partnership in its own laboratories and will subcontract the remaining reserach to approximately ten to thirteen "satellite" research groups which are associated with major universities and institutes. The Partnership's resources will be initially focused on those aspects of the technologies which should have faster access to the market place. (This should include the diagnostic immuno assays and the antibody drug conjugates for treatment of neoplastic diseases in both humans and animals.)

GENERAL PARTNER

The General Partner of the Partnership will be George M. Stadler. Mr. Stadler holds both a B.S. (Chemistry) and M.S. (Physics) degree from John Carroll University and has done doctoral work at Case Western Reserve University. He is also a registered Patent Agent, admitted to

the U.S. Patent Bar in 1975.

Mr. Stadler's business experience consists of teaching, research, research administration, technology assessment, patent prosecution and licensing, and R&D partnership and new company formation and start-up. From 1972 to 1976 he was Assistant Director of Research Admin. at Case/Reserve University and from 1976 to 1980 Assistant to the President of University Patents, Inc. In 1980 he organized University Genetics, Co. and DNA Limited Partnership which has provided the initial funds for University Genetics, Co.'s operations.

#### THE OFFERING

Sixty-six(66) Limited Partnership units of \$150,000 are being offered to a limited number of qualified offerees. Each unit is payable as follows:

Payment Due	Principal Amount	10% Simple Interest on Unpaid Balance	Total Amount Due
A) Upon execution of Subscription Agreement (Closing date 4/30/82)	20,000	--	20,000
B) April 30, 1983	40,000	13,000	53,000
C) April 30, 1984	45,000	9,000	54,000
D) October 31, 1984	<u>45,000</u>	<u>2,250</u>	<u>47,250</u>
Total	\$150,000	\$24,250	\$174,250

The installments payable in 1983 and 1984 shall be evidenced by promissory notes, bearing interest at the rate of 10% per annum, which must be secured by letters of credit or other security acceptable to the Partnership. If sixty subscriptions have not been received by April 30, 1982, all subscriptions will be terminated and funds advanced by subscribers will be returned promptly without interest. Fractional units may be subscribed for when permitted by the General Partner (See attached breakdown - Appendix I).

#### PARTNERSHIP AGREEMENT

The Partnership Agreement allocates 98% of the revenues and losses to the Limited Partners and 2% of the revenues and losses to the General Partner. The Capital Contribution of the General Partner will not be made in cash, but in common stock of TPI. The contribution from the General Partner will be valued in his capital account at one ninety-eighth of the total capital contributions of the Limited Partners.

## PARTNERSHIP TPI STOCK

There will be no initial public market for the Partnership's TPI stock, and it is expected that it will be retained as a Partnership asset. In the event of a public offering of TPI stock by TPI, the Partnership may distribute some or all of its TPI shares to the Partners (a maximum of 22,720 shares per unit). Sale by the individual Partners would then have to find exemptions such as private sale, Rule 144, etc. Alternatively, there could be a TPI/Partnership Agreement that the Partnership's shares, or a portion thereof, would be included in the TPI public offering. This may be with lower priority, (i.e., last shares sold) so as to not interfere with the basic TPI offering.

## PARTNERSHIP/TPI R&D CONTRACT

The Partnership will enter into two eighteen month R&D contracts with TPI, one in 1982 for \$3,850,000.00 and one in 1983 for \$4,000,000.00, pursuant to which TPI will undertake a Research and Development program into target drugs, immuno-diagnostic assays and vaccines. It is anticipated that this program will include some of the following objectives:

### I. Targeted Drugs

- A. Tumor-specific monoclonal and polyclonal antibody targeted drugs for localized cancer therapy.
  - 1. Human breast cancer
  - 2. Feline leukemia
- B. Fetal antigen targeted antibody drugs for localized cancer therapy.
  - 1. Human breast cancer
- C. Intratumor immuno-chemotherapy of cancer in animals.
  - 1. Canine mammary carcinomas
  - 2. Equine sarcoids
- D. Tissue binding drugs for localized intratumor or intracavitary immuno-chemotherapy.
  - 1. Human Breast cancer
  - 2. Canine mammary carcinomas
- E. Microsphere-drug preparations for localized intratumor or intracavitary immuno-chemotherapy.
  - 1. Human breast cancer
  - 2. Canine mammary carcinomas
- F. Pathogen-specific antibody targeted drugs for infectious disease.
  - 1. Ophthalmic and ENT pseudomonas infections

## II. Immunodiagnostic Assays

- A. Chlamydia assay for venereal infections using pathogen-specific monoclonal and polyclonal antibodies.
- B. Cancer detection and monitoring using monoclonal and polyclonal antibodies to tumor-associated antigens
  - 1. Breast Cancer
  - 2. Colon Cancer
  - 3. Lung Cancer

## III. Vaccines

- A. Tumor-associated antigen vaccines for cancer therapy and prophylaxis.
  - 1. Breast Cancer
  - 2. Microsphere adjuvant preparations
  - 3. Polymer-antigen preparations

TPI will conduct approximately fifty (50%) of this contracted research in its own laboratories and will subcontract the remaining research to "satellite" research groups:

- 1. University of Florida (Dr. Eugene Goldberg)
- 2. George Washington University (Dr. Arid Hollingshead)
- 3. Harvard University (Dr. Chris Grant)
- 4. Southern Research Institute (Dr. Frank Schabel)
- 5. University of South Carolina (Dr. Hugh Fudenberg)
- 6. M. D. Andersen Tumor Institute (Dr. Christine Granatek)
- 7. University of Washington (Dr. Cho-Chou Kuo)
- 8. University of Arizona (Dr. Robert Harrison)
- 9. University of Pittsburgh (Dr. Bernard Fisher)
- 10. Harvard University (Dr. Merv Israel)
- 11. Brain Tumor Center University of California--San Francisco (Dr. Victor Levin)
- 12. Weizman Institute--Israel (Drs. Arnon, Hurwitz, Levy, Trainin)
- 13. Nottingham Cancer Laboratory--England (Dr. Robert Baldwin)

(Note--a more complete description of the proposed research objectives and function of the "satellite" research groups can be found in the attached summary of TPI -- Appendix II.)

As a condition for entering into this commitment to perform a concentrated and intensive research and development effort, including the necessary commitment of staff and facilities by TPI and TPI's "satellite" research groups, TPI shall require payment of the full contract amounts, when issued, in cash at the beginning of the contract. The Partnership shall borrow in 1982 (and 1983) the additional money (above and beyond the Limited Partners' initial capital contribution) necessary to make full contract payments in 1982 and 1983 to TPI. The borrowing, not to exceed the face amount of his promissory note to the Partnership, will be reduced and repaid out of the Limited Partner's future payments to the Partnership in 1983 and 1984.

Except for the cost of organizing and managing the Partnership and selling the Partnership units, all of the Partnership funds shall be expended on the R&D contracts. (For additional details see the attached cash flow projections -- Appendix III.)

#### PARTNERSHIP/TPI LICENSING AGREEMENT

The Partnership will enter into a Licensing Agreement with TPI, pursuant to which the Partnership will be entitled to fifty percent (50%) of any and all gross royalties received by TPI from unaffiliated third parties on any products, processes, treatments, etc. resulting from the research efforts funded by the Partnership and/or a royalty equal to six percent (6%) of the sales price of any products, processes, treatments, etc. that are manufactured and/or sold by TPI (or a subsidiary or joint venture partner of TPI) until the Partnership receives cumulative revenues (gross royalties and/or sales) in an amount such that the Limited Partners share is equal to the total capital (less interest) contributed by them to the Partnership. Thereafter, all gross royalties will be shared twenty-five percent (25%) to the Partnership and seventy-five percent (75%) to TPI and a royalty equal to three percent (3%) of the sale price of manufactured products by TPI.

TPI shall have a purchase option, exercisable no earlier than four (4) years from the date the Partnership is formed and not later than ten (10) years after the date of formation of the Partnership, to purchase the interest of all the Partners for a price equal to:

1. \$360,000 for the General Partner's interest and the Limited Partners will receive two (2) times their cash investment if the option is exercised before the expiration of the fifth (5th) year following the formation of the Partnership; or
2. \$540,000 for the General Partner's interest, and the Limited Partners will receive three (3) times their cash investment if the option is exercised after the fifth (5th) year.



The purchase price shall be payable in cash and/or in stock of TPI. In the event all or a portion of the purchase price is to be paid with TPI stock, then the consent of the holders of at least 51% of the Limited Partnership interests shall be required. TPI shall be entitled to a credit against the purchase price equal to any revenues previously distributed to the Limited Partners pursuant to the Licensing Agreement between the Partnership and TPI.

#### FEDERAL INCOME TAX CONSEQUENCES

The majority of Partnership Capital will be expended in contracting for research and development, and this is expected to result in losses to the Partnership during at least the early years of operation which should result in tax deductions to the Partners, under Section 174 of the Internal Revenue Code. If there is no income to the Partnership from exploitation of the technologies through the end of 1984, tax deductions to the Limited Partners per unit are expected to be as follows:

<u>Year</u>	<u>Investment</u>	<u>Approximate Deduction</u>
1982	\$20,000	\$60,000
1983	40,000	61,000
1984	<u>90,000</u>	<u>5,000</u>
Total	\$150,000	\$126,000

If the Partnership's future operations are not profitable, each Limited Partner may be entitled to additional deductions up to the aggregate amount of his investment.

If the Partnership operations are profitable and make cash distributions out of profits to its Limited Partners, each Limited Partner will be entitled to his pro-rata share of the income from the Partnership's revenues, a portion of which may be taxed at capital gains rates.

#### TARGETED PHARMACEUTICALS, INC.

Appendix II contains a description of TPI's (a Nevada corporation formed in 1981) integrated research program, proprietary technologies (microspheres; polymeric drug carriers with tissue-binding properties; and antibodies and antigens), management and commercial projections for successfully marketed products resulting from its research programs.

#### INVESTOR SUITABILITY

The offering is limited to investors who: (i) have a net worth of at least \$500,000 or three times their proposed investment (exclusive of certain personal assets), and are in a Federal income tax bracket of 50% or higher, or (ii) have a net worth of at least \$750,000 or four times their proposed investment. Net worth shall not include homes, furnishings and automobiles. (These standards may be somewhat lower for the purchaser of a fractional unit.)

LIMITED LIQUIDITY

The Limited Partnership interests may not be transferred without the consent of the General Partner and without registration under applicable securities laws, unless an exemption is available.

OPINIONS

## Partnership Status/Tax

Schupak, Rosenfeld, Fischbein, Bernstein & Tannenhauser  
555 Madison Avenue  
New York, New York 10022  
(Contact: Robert Tannenhauser, Esq.)

## Accounting

Goldstein, Golub, Kessler & Company  
245 Park Avenue  
New York, New York  
(Contact: Mr. Martin Greif, C.P.A.)

INFORMATION

To obtain a Confidential Offering Memorandum and/or answers to any questions, please contact the General Partner or Sales Agent:

Mr. George M. Stadler  
General Partner of Future Drugs Research Partnership  
537 Newtown Avenue  
Norwalk, CT 06851  
(203-846-9012)

or

APPENDIX I

Future Drugs Research Partnership

1. Capitalization

66 units at \$150,000/unit = \$9,900,000

could be raised as:

49 units at \$150,000/unit =	7,350,000
34 (1/2 units) at \$75,000/unit =	<u>2,550,000</u>
	9,900,000

or

53 units at \$150,000/unit =	\$7,950,000
17 (1/2 units) at \$75,000/unit =	1,275,000
18 (1/4 units) at \$37,500/unit =	<u>675,000</u>
	\$9,900,000

2. Equity in TPI (Approximate):

6,000,000 shares of TPI issued:

TPI	
(Founders, Management, etc.)	4,200,000 shares (70%)
FDR Partnership	1,500,000 shares (25%)
General Partner	<u>300,000 shares (5%)</u>
Total	6,000,000 shares

## TARGETED PHARMACEUTICALS, INC.

## BACKGROUND AND COMPANY OBJECTIVES

Targeted Pharmaceuticals, Inc. will conduct cancer and infectious disease research aimed at development of new drug therapies and new diagnostic methods. A common theme for the Company's specialty pharmaceuticals research and development is biological TARGETING; taking advantage of the exquisitely selective recognition processes which we now know exist between certain biological molecules and using this specificity for *localizing cancer drug action, for early diagnosis of cancer and venereal infections, and for development of vaccines* to prevent disease. The highly specific interactions of the giant chain-like molecules (biopolymers) which are involved in all life processes (i.e. enzymes and antibodies) have been employed increasingly in biological research during the past few years, especially for improved analytical methods (e.g. affinity chromatography). New methods have also been recently developed to produce many synthetic biopolymers and to chemically couple synthetic and natural biological molecules to alter biological activity. Additionally, the advent of cell fusion (hybridoma) techniques now enables preparation of large quantities of complex biological molecules capable of highly specific targeting (e.g. monoclonal antibodies) and makes possible new approaches to drug delivery, diagnosis and vaccines. The time is now ripe to combine this knowledge for development of new clinically useful products for targeted *therapeutic, diagnostic and prophylactic* medicine.

The Company's approach will be to marry the innovative ideas of its scientific staff with recent progress in biophysics, immunology, biopolymer chemistry, and hybridoma technology in a uniquely organized and coordinated fashion; via a modest central corporate R & D program strongly coupled to 8-10 external contract research "satellite" programs. These satellite programs will be carefully placed at Universities and Institutes with leading scientists in selected project areas to achieve the targeted medical product goals of the Company.

The key scientists involved in forming the Company (Drs. C. A. McLaughlin, E. P. Goldberg, H. D. Caldwell and G. F. Rowland) combine extensive experience in immunology, biochemistry, biopolymers, biophysics, veterinary medicine, and cancer and venereal disease research. They have conducted pioneering research

## Targeted Pharmaceuticals Program

in the fields of antibody targeting and intratumor injection of cancer drugs, chlamydia immunology and polymeric drug carriers. They have impressive track records demonstrating significant accomplishments in industry, university and government research and product development and have widespread collaborative relationships with international leaders in medical science related to the Company's interests. This provides the basis for an exceptional group of associated contract research satellite programs.

Based upon research already conducted by the key scientists of the Company and their ideas for further studies, plus the accomplishments and planned work of collaborating university scientists, the Company expects to obtain exclusive rights to several potentially important cancer and infectious disease developments (i.e. human and animal tumor-associated antigen and antibody preparations, new microsphere and polymeric drug carrier technologies, chlamydial venereal disease antigen-antibody preparations, and specific pathogen antibody-antibiotic compositions). The Company will engage in projects in the areas of *Targeted Drugs*, *Vaccines*, and *Diagnostic Assays*. The projects are inter-related to the extent that common experimental facilities and procedures will afford significant economies in research and product development costs and time. Projects have also been very carefully selected to achieve a judicious balance between short and long-term developments. Several important product opportunities should thereby be possible within 1-2 years for licensing, joint ventures or commercial development by the Company. The following summarizes the major projects planned by the Company.

### *Targeted Drugs*

1. Tumor-Specific Monoclonal and Polyclonal Antibody Targeted Drugs for Localized Cancer Therapy.
  - a) Human Breast Cancer
  - b) Feline Leukemia
2. Fetal Antigen Targeted Antibody Drugs for Localized Cancer Therapy.
  - a) Human Breast Cancer
3. Intratumor Immuno-Chemotherapy of Cancer in Animals.
  - a) Canine Mammary Carcinomas
  - b) Equine Sarcoids

## Targeted Pharmaceuticals Program

4. Tissue Binding Drugs for Localized Intratumor or Intracavitary Immuno-Chemotherapy.
  - a) Human Breast Cancer
  - b) Canine Mammary Carcinomas
5. Microsphere-Drug Preparations for Localized Intratumor or Intracavitary Immuno-Chemotherapy.
  - a) Human Breast Cancer
  - b) Canine Mammary Carcinomas
6. Pathogen-Specific Antibody Targeted Drugs for Infectious Disease.
  - a) Ophthalmic and ENT *Pseudomonas* Infections

### *Immunodiagnostic Assays*

7. Chlamydia Assay for Venereal Infections Using Pathogen-Specific Monoclonal and Polyclonal Antibodies.
8. Cancer Detection and Monitoring Using Monoclonal and Polyclonal Antibodies to Tumor-Associated Antigens and Serum Proteins.
  - a) Breast Cancer
  - b) Colon Cancer
  - c) Lung Cancer
  - d) Prostate

### *Vaccines*

9. Tumor-Associated Antigen Vaccines for Cancer Therapy and Prophylaxis.
  - a) Breast Cancer
  - b) Lung Cancer
  - c) Microsphere Adjuvant Preparations
  - d) Polymer-Antigen Preparations

## Targeted Pharmaceuticals Program

THE MAJOR PROGRAMS OF THE COMPANY: *TARGETED DRUGS, IMMUNODIAGNOSTICS, VACCINES*

### A. *Targeted Drugs*

Most drugs today are given systemically and are relatively nonspecific. In many cases, especially in cancer chemotherapy, there are serious toxic side effects which make effective treatment very hazardous. Since the pioneering work of Paul Ehrlich at the turn of the century and his "Magic Bullet" concept for delivering drugs to the precise tissues or organs requiring treatment, there has been an awareness of the potential of this approach. However, there has been relatively little clinical success for this "guided missile" drug delivery approach to the present time.

Only a few relatively unsophisticated examples now exist for commercial clinically useful pharmaceuticals which work in a highly localized fashion. They include: (1) controlled release of contraceptive hormones in the uterus from inserted IUDtype plastic devices to avoid the systemic problems of the "pill" (2) injections of cortisone for local anti-inflammatory activity (3) aerosol inhalers for localization of bronchial dilators and steroids to avoid systemic problems (4) release of pilocarpene from polymer inserts in the eye to treat glaucoma, and (5) topical application of 5-fluorouracil ointment to skin cancers (the only significant example of localized treatment of solid tumors with chemotherapy today). However, these examples are trivial in comparison to the enormous opportunities which exist.

A major theme of our research and development program will therefore be development of clinically useful new pharmaceuticals which may be targeted or localized in the specific areas of the body to be treated. Emphasis will be upon cancer therapy because cancer is responsible for 20% of all mortality and because chemotherapy remains highly hazardous, unpleasant and relatively ineffective for the most lethal forms of cancer (lung, breast and colon).

Conventional cancer therapy is systemic and kills normal healthy cells as well as tumor cells. Indeed, the clinical oncologist frequently walks a fine line between killing the patient with chemotherapy and attempting a cure. Unfortunately, solid tumors of the lung, breast and colon, which readily metastasize throughout the body, remain resistant to

conventional chemotherapy and account for one half of the 420,000 cancer deaths in the U.S. in 1981. The potential economic and social impact of even moderately more effective therapy is *enormous* since one of every four persons, 2 of 3 families and 55 million individuals are affected by cancer. Cancer treatment is now estimated to be a \$40 *billion* business annually.

The research philosophy adopted by Drs. McLaughlin, Goldberg and Rowland has been to develop less toxic and more effective therapeutic methods by confining the cell killing action of drugs to tumor cells and to also assist or stimulate the natural immune system to much greater tumor cell killing activity and so help reject the tumor cell invasion.

A-1. Antibody Targeted Cancer Drugs [Projects 1,2]

During the past decade, advances in tumor immunology have shown that tumor cells possess specific, though complex, antigenic groups (tumor associated antigens). These tumor antigens are crucial in mobilizing the immune defense and because they are uniquely located on tumor cells they are logical homing sites for "guided missile" drug targeting. Antibodies produced naturally by these antigens bind or stick very specifically to the antigens.

*Tumor specific antibody-drug compositions* therefore hold great promise for more effective cancer therapy. However, one must first have the specific antibodies and antigens in order to use them to synthesize targeted drug compositions and they are required in sufficient quantity to be practical. The Company will therefore contract with those groups which today are at the forefront of human and animal tumor associated antigen and antibody preparation and will coordinate drug modification studies, laboratory evaluations and animal and human clinical trials. Initial emphasis will upon *human breast cancer*. This cancer type was selected because of high incidence (110,000 new cases in U.S. in 1981) and high mortality (37,000 deaths in U.S. in 1981) and because it is a physically accessible human solid tumor type which may be most readily susceptible to all of the localized therapy approaches of the Company (i.e. antibody targeting, intra-tumor injection, systemic plus local therapy, local chemo-immunotherapy plus surgery). Furthermore, there is probably a larger statistical data base regarding breast cancer treatment



than for any other cancer site. Based upon studies to date there is a high probability for successful development of tumor-associated antigen antibody and fetal antigen-antibody preparations through planned collaborations with the leading research groups in this field at the University of Nottingham, George Washington University, M.D. Anderson Hospital and U. South Carolina. These preparations will also be utilized for inter-related immunodiagnostic and vaccine development projects.

In addition, *feline leukemia* will receive project attention for antibody directed therapy. This animal cancer has both important commercial significance in veterinary medicine for treatment of pets (~60,000 new case/yr.) as well as research significance relative to human cancer. It is one of the few cancers for which the cause (a virus) has been clearly established. Furthermore, through planned collaboration with one of the leading feline leukemia research groups (at Harvard), the Company expects to have specific antibody and antigen preparations for antibody targeted drug development and clinical studies.

Although a coordinated program of (1) antibody preparation, (2) drug-antibody and drug-polymer-antibody chemical coupling, (3) laboratory and animal testing and (4) human clinical trials may appear to be straightforward, it is a fact that few, if any, pharmaceutical companies have thus far devoted the multi-disciplinary effort required; nor have the research activities supported by the National Cancer Institute and the American Cancer Society been focused to date in this area of research. Only now, for example, is a drug targeting program beginning to be developed at the NCI. It is the Company's view that a highly creative, multidisciplinary, uniquely coordinated and managed program can indeed prove successful at this time using the combined new technologies which have become available in tumor immunology and biopolymer synthesis.

A-2. Intratumor Immuno-Chemotherapy [Projects 3,4,5]

Drug targeting will also be explored using an approach pioneered by Dr. Goldberg's group - the synthesis of *tissue binding drugs*. These are drugs which are incorporated into microspheres (analogous to time release capsules) or are modified to possess groups on the molecules which promote binding or immobilization in tissue at the site of injection. In this manner, drugs for chemotherapy or immunotherapy may be directly

injected into a solid tumor. The potential value of this type of drug localization is manifold: to regress tumors without surgery, to use in combination with surgery, to use as a post-surgical tumor cavity coating to kill residual tumor cells, to stimulate immunological activity and the killing of cells which have spread from the primary tumor, and to use in combination with systemic chemotherapy or immunotherapy.

Drs. McLaughlin and Goldberg have shown that direct intratumor injection therapy using conventional drugs such as adriamycin or mitomycin can cure metastatic disease in a guinea pig tumor model. They have also shown increased efficacy using combined local chemotherapy and immunotherapy with BCG-type cell wall preparations. However, the small drug molecules quickly become distributed throughout the body. Tissue-binding drugs which remain fixed in tumor tissue for prolonged periods may therefore be important for more effective therapy. Overall, it seems most likely that local therapy combined with surgery or with systemic targeted chemo- or immuno-therapy will prove most effective. These combinations will be investigated by the Company. In addition, there is potential for the use of tissue-binding drugs for intracavitary therapy (prolonged drug release in the surgical cavity following tumor removal) which will be studied for breast and brain (glioma) tumors.

Because of the need to more effectively translate animal experiments to human clinical application, as well as the important opportunities in veterinary medicine, these studies will address the treatment of tumors in pets (canine mammary) and horses (equine sarcoids) as well as human breast cancer (projects 3,4,5). This approach will generate important animal data while taking advantage of excellent commercial opportunities for new drugs which exist in veterinary medicine.

#### A-3. Antibody Targeted Antibiotics [Project 6]

*Antibody targeting of antibacterial drugs* will be studied by the Company. The exciting possibilities for antibodies in cancer treatment seem to have obscured perhaps equally intriguing opportunities (using antibodies to pathogenic bacteria) for treating common infectious diseases far more thoroughly than by the conventional shot-gun administration of massive doses of antibiotics. In many cases, such treatments are not effective. This is particularly true for continuing (chronic) low grade infections of the moist cavities of the body (mouth, ear, throat, bronchia,

genital tract, etc.). There are especially serious problems in bacterial and fungal infections of the eye. Dr. Goldberg's group is currently exploring an antibody targeted antibiotic system for safer treatment of the most common type of bacterial infection of the cornea (*Pseudomonas*). If this model study is successful, it could open up a major new field of pharmacology for the general treatment of infectious diseases. The Company will emphasize development of anti-*pseudomonas* drugs for ENT use. For ophthalmic infections alone, this development could result in a market of 2-5 million drug doses per year (\$10-30 million annually).

B. *Diagnostic Immunoassays* [Projects 7,8]

A multi-million dollar industry has already evolved from the use of antibodies to detect a long list of substances such as drugs, allergy-causing pollens, specific components of blood, microorganisms, and cancer cells. Antibodies are produced by animals and humans in response to foreign substances that are called antigens. The antibody molecules can sort through a multitude of antigens to find a single antigen and thereby identify a specific disease-causing agent; an immunoassay.

A technological explosion occurred in the late 1960s in the application of immunoassays to several fields of biomedical science. The sensitivity of immunoassays for quantitative detection of antigenic substances was magnified several fold by the introduction of radioisotopes into the assay procedures (radioimmunoassays) or through the use of enzymes coupled either to the antigen or to the antibody molecules (enzyme-linked immunoassays). These assay systems are unrivaled in their convenience, sensitivity, and ease of application in a multitude of circumstances.

In 1975, the introduction of a new procedure for production of antibodies revolutionized immunology and immunoassays. This procedure entails the laboratory creation of one cell (a hybrid) from two different individual cells. One of the individual cells is obtained from an animal (or human) immunized with a particular antigen (or many antigens). The second cell is derived from a laboratory culture of special tumor cells. The fused hybrid cell will produce a continuous large quantity of unique, highly specific antibody directed against the particular antigen used for immunization. The new antibody-producing cell line of hybrid cells is called a hybridoma. The antibody molecules that are produced are termed monoclonal antibodies. In contrast, the antibodies produced by humans or animals and collected from their blood sera are called polyclonal antibodies.

The Company intends to use the specific binding properties of antibodies not only for drug targeting but also for two immunoassays projects: (project-7) *diagnosis of venereal diseases caused by chlamydia micro-organisms* and (project 8) *cancer detection*. Each of these projects is unique, but the basic technology to be applied is the same. Immunoassays (either radio-immunoassays or enzyme-linked immunoassays) using polyclonal and monoclonal antibodies will be used.

Chlamydial infection has become the most prevalent venereal disease. The availability of an immunoassay for improved *diagnosis of chlamydial venereal disease* and pneumonitis in infants could displace presently used diagnostic tests. Immunoassays for chlamydia would insure much more rapid and effective treatment thereby reducing the increasing incidence of infant deaths from chlamydial infections. Dr. Caldwell is perhaps the world's leading authority today on chlamydia. His research holds out the promise of achieving successful results with both polyclonal and monoclonal antibody immunoassays within 1-2 years.

The early detection and monitoring of all forms of cancer remains one of the most significant medical challenges. Many research groups are currently interested in such analyses. However, using tumor-specific antigens and antibodies from our contract research collaborating groups we hope to enjoy a special position with a variety of unique preparations for new *cancer detecting immunoassays*. The commercial opportunities for sensitive, simple, safe, reliable cancer diagnostic methods are obviously very great. Each test for a specific cancer type would provide the basis for a multi-million dollar product. The Company will emphasize the detection of the major solid tumors: breast, lung, colon/rectal.

C. *Cancer Vaccines and the Use of Polymers or Microspheres for Immuno-potential* [Project 9].

Preventive or prophylactic medicine through vaccination of animals and humans has been one of the major advances produced by modern biomedical research. Vaccines are usually prepared from live or killed microorganisms. The use of killed microorganisms or their cell components has the obvious advantage of eliminating the chance of disease arising from multiplication of live microorganisms. In recent years, an explosion has occurred in

the development of vaccines composed of well defined substances isolated from microorganisms and from synthetic compounds which mimic these natural substances. These essential substances in vaccines are called antigens or immunogens and provoke an immune reaction upon administration which confers a specific immune resistance.

Despite the rapid development of improved antigen preparations, a pressing need remains for better carriers to enhance the immune response. This is especially true for vaccine-like preparations for cancer immunotherapy. The enhancing vehicles are termed adjuvants. The most commonly used adjuvant for human and animal vaccines is a so-called "complete Freund's adjuvant"; an emulsion of mineral oil, water, and dead bacteria mixed with the antigen to which an immune response is desired. Unfortunately such adjuvant systems often have very undesirable side effects. Injections are painful and cause ulcers at the site of injection. Although recent studies have shown that complete Freund's adjuvant can be replaced in certain immunization schemes with adjuvants that do not produce these undesirable effects, There is still no adjuvant system that is as uniformly successful and as widely applicable as the Freund's adjuvant. A major breakthrough in vaccine preparation would be the development of an antigen-carrier-adjuvant system which avoids the harmful side-effects of the mineral oil emulsion.

Clinical trials by Dr. Hollinshead and others with whom the Company will collaborate are now in progress wherein tumor-associated antigens mixed with complete Freund's adjuvant are given to cancer patients. The prophylaxis and may yield a major advance in the treatment of cancer in humans. New adjuvant-immunogen carriers (i.e. based on polymer-antigen or antigen-microsphere technology) could prove more effective immunologically and also avoid the painful ulcers which often occur with this type of therapy.

The use of suspensions of minute injectable and biodegradable tumor-associated antigen containing spheres (i.e. microspheres prepared from albumin or dextran) offers the potential for a new type of adjuvant system to replace the complete Freund's adjuvant. It is known that chemically synthesized units of antigens and adjuvants that are linked together are more potent than antigens and adjuvants simple mixed together

## Targeted Pharmaceuticals Program

before injection. Microspheres could be prepared in which antigens and adjuvants are chemically coupled to enhance the immune response. Microspheres could also be designed to prolong release of the antigen and adjuvant in a manner similar to a "time-release capsule". Such prolonged release, as well as appropriate presentation of the antigen-adjuvant complex, would be likely to produce stronger, more lasting and more effective immunity. The goal would be to accomplish this without the undesirable effects of the complete Freund's adjuvant. Microsphere vaccines may also be advantageous by reducing the frequency of immunization and may permit the use of relatively unstable immunogens and adjuvants which are not now practical (made possible by the protective environment of the microsphere). The Company will utilize the microsphere and polymer-binding technology being developed in Dr. Goldberg's laboratory for development of human breast cancer antigen vaccines. These preparations will utilize tumor-associated antigens or fetal antigens which will be available from our collaborating groups at George Washington University, Nottingham University, M.D. Anderson Hospital and the University of South Carolina.

### UNIQUE TECHNOLOGIES AVAILABLE TO THE COMPANY

#### 1. *Microspheres*

Although methods have been available for many years to prepared minute spherical particles of such potential drug carrier materials as albumin, these preparations have been complicated and produce microspheres which have had limited medical utility to date for drug or vaccine applications. Research at U. Florida in Dr. Goldberg's group has achieved a simple and highly versatile new procedure which enables preparation of albumin, dextran and other microspheres with good control of particle size and microsphere structure. Such microspheres may be easily modified chemically in many ways to produce unusual drug carriers or antigen-adjuvant compositions and may be made biodegradable so that they will disappear over different time periods in the body as required. Unique hydrophilic (water wettable) albumin microspheres containing both physically mixed and chemically attached anti-tumor drugs have been made which disperse in water for injection without the need for surfactants. This is an important new technology for development of drug, vaccine and diagnostic products related to the Company's interests.

2. *Polymeric Drug Carriers with Tissue-Binding Properties*

Giant natural chain-like molecules, termed biopolymers, are at the heart of all life processes and synthetic chain molecules (polymers) form the basis of today's enormous plastics industry. In recent years there has been an intermixing and bridging of the science of both natural and synthetic polymers. As a result, a growing field of "polymeric drugs" is newly emerging. Combinations of polymers and drug molecules can often produce less toxic, more effective and more stable compositions.

Dr. Goldberg's research group has pioneered the use of polymeric molecules as carriers and modifiers for drugs and for biological molecules such as enzymes and antibodies. Dr. Rowland has also been among the leaders in preparing polymer-drug systems for cancer drug targeting. As a result, an extensive inventory of chemical methods and water soluble polymer carrier materials is available to the Company for drug targeting, vaccine-adjuvant and immunoassay development. One important new concept has also been developed recently; that of designing polymeric carriers for drugs or proteins with tissue-binding groups. The objective is to fix the injected substance in place at the site of an injection (i.e. a tumor) and so localize its biological activity. Numerous tissue-binding polymer compositions based upon chemical binding or physical complexing with tissue cell surfaces have now been produced at U. Florida. This technology is therefore available for the preparation of new tissue-binding drug, vaccine, or diagnostic compositions to help achieve the Company's objectives for development of tissue-targeted or localized pharmaceutical products.

3. *Antibodies and Antigens*

Special preparations of natural substances, particularly specific tumor antigens and antibodies (both monoclonal and polyclonal) will be available from contracting research groups around the world. Furthermore, Dr. Caldwell has already identified specific new chlamydia antigen-antibody preparations and methods applicable to venereal disease diagnostic developments to be exploited by the Company.

PATENTS AND PROPRIETARY INFORMATION OF THE COMPANY

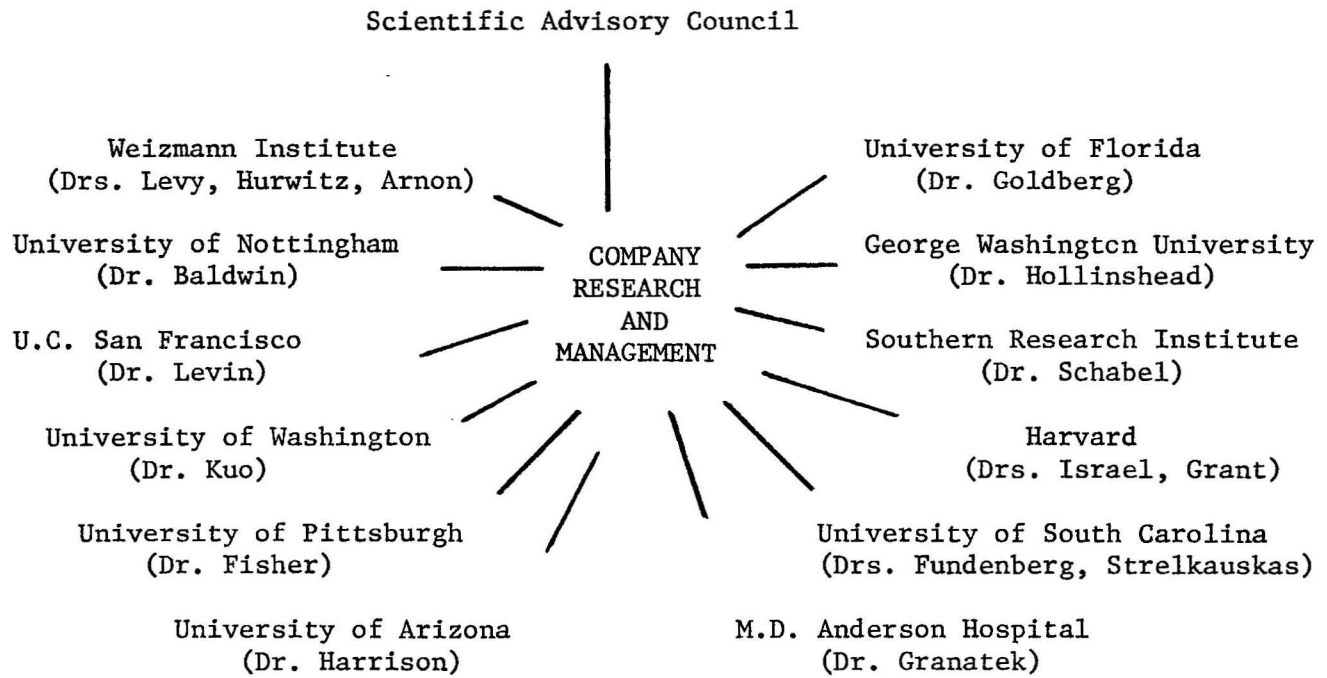
All internal developments and know-how of the Company will be vigorously protected and covered by patent applications as appropriate. Contracted research at Universities will be undertaken on the basis that the Universities will provide first refusal options for exclusive patent licensing arrangements. Letters of intent for such arrangements with the principal university contract groups are expected in the near future. All collaborators have been agreeable to this type of arrangement.

ORGANIZATION AND MANAGEMENT OF THE COMPANY

The principals involved in forming the Company are Dr. Eugene P. Goldberg, Dr. Charles A. McLaughlin, Dr. Harlan D. Calwell, Dr. George F. Rowland and Mr. Jon E. Cobain. It is anticipated that the principals will retain a 70% equity position in the Company. Brief biographical sketches and descriptions of Company activities follow (CVs are appended). In brief, the Company will operate via a small corporate R & D staff and central facility which will complement and integrate the activities 12-13 "satellite" contract research groups. A prestigious (and operationally useful) *Scientific Advisory Council* will be used to advise management on the scientific and technological merit of Company activities. This overall organization is probably quite different from that of most industrial or research institute operations. The Company believes that this arrangement (shown schematically on the following page) will afford unusual economies, and rapid decision making in a coordinated, efficient and well focused manner. There is a synergistic objective in this arrangement and there is great economic leverage in supporting the majority of projects externally at carefully selected Universities and Institutes.



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\* Note that most but not all collaborating groups have expressed intent to participate to date. Funding levels and specific research tasks have not been finalized and are contingent upon further detailed discussions and Company financing.

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RESEARCH CONTRACTS WITH UNIVERSITIES AND INSTITUTES

1. University of Florida: Dr. Eugene Goldberg

- |               |   |
|---------------|---|
| \$550,000 (1) | -Polymeric Drug Carriers                        |
| 575,000 (2)   | -Microsphere Drug Carriers                      |
|               | -Antibody Targeted Chemoimmunotherapy           |
|               | -Antibody Targeted Antibiotics                  |
|               | -Tissue Binding Drugs                           |
|               | -Microsphere Adjuvants and Immunoassay Carriers |

2. George Washington University: Dr. Ariel Hollinshead and Dr. T. Stewart  
(University of Ottawa)

- |                           |   |
|---------------------------|---|
| \$480,000 (1)             | -Human Tumor-Associated Antigens to Colon,              |
| 500,000 (2) (Hollinshead) | Breast, Melanoma, Gliomas, Lung, Ovarian<br>Cancer      |
|                           | -Specific Monoclonal and Polyclonal Tumor<br>Antibodies |
| 300,000 (1)               | -Clinical Trials  |
| 300,000 (2) (Stewart)     | -Adjuvants and Vaccines                                 |

Dr. Hollinshead has one of the most advanced programs in the world in antigen vaccine treatment of human cancer. She would supply antigens and antibodies for the Florida program, for the central Company laboratory and would continue her lab and clinical tests with emphasis on breast cancer therapy. Her preparations would be used for all types of cancer diagnostic assays and microsphere adjuvant development. Funds allocated to Dr. Tom Stewart at U. Ottawa will be for collaborative clinical trials of lung cancer vaccine preparations.

3. Southern Research Institute: Dr. Frank Schabel

- |               |   |
|---------------|---|
| \$180,000 (1) | -Mouse and Guinea Pig Tumor Models            |
| 200,000 (2)   | -Animal Studies of Company's Antitumor Agents |

Dr. Schabel is one of the foremost experts in the world in antitumor drug evaluations in animal models. His group is recognized as probably the most accomplished in the U.S.

Targeted Pharmaceuticals Program

4. University of South Carolina: Dr. Hugh Fundenberg, Dr. Anthony Strelkauskas

- \$150,000 (1) -Human Hybrid Monoclonal Antibodies
- 150,000 (2) -Tumor-Associated Antigens to Major Human  
Cancer Types
- Clinical Studies

Dr. Fundenberg's group is among the best in the world in tumor immunology. Drs. Strelkauskas and Fundenberg will provide breast cancer tissue and monoclonal antibody preparations for antibody-polymer-drug conjugate preparation at U. Florida and the Central Laboratory and for other therapeutic, vaccine and immunoassay developments.

5. M.D. Anderson Tumor Institute: Dr. Christine Granatek

- \$100,000 (1) -Tumor Associated Fetal Antigens and
- 100,000 (2) Antibodies

Dr. Granatek has pioneered the isolation of tumor-associated fetal antigens and produced their antibodies. Both are potentially important for treatment of human tumors; the antigens for active specific immunotherapy and the antibodies for immunodiagnosis and drug targeting. Her preparations will be used at Florida and in the Central Laboratories.

6. Harvard: Dr. Chris Grant

- \$65,000 (1) -Feline Leukemia Antigens and Antibodies
- 75,000 (2)

Dr. Grant has monoclonal and polyclonal antibodies to viral and tumor-associated feline leukemia antigens. These will be used to prepare vaccines and drug conjugates for treatment of feline leukemia.

7. University of Washington: Dr. Cho-Chou Kuo

- \$25,000 (1) -Purified Chlamydiae Preparations
- 25,000 (2)

Targeted Pharmaceuticals Program

8. University of Arizona: Dr. Robert Harrison

\$50,000 (1)	-Clinical Evaluations of Chlamydiae
50,000 (2)	-Immunodiagnostic Assays in Collaboration with Dr. Kuo and Dr. Caldwell

9. University of Pittsburgh: Dr. Bernard Fisher

\$100,000 (1)	-Breast Cancer: Antigen Preparations,
100,000 (2)	Therapeutic Protocols and Clinical Studies

Dr. Fisher is perhaps the foremost authority on breast cancer clinical experience. He has developed the primary data base for this cancer type and is responsible for directing new clinical studies in breast cancer therapy.

10. Nottingham (England) Cancer Laboratory: Dr. Robert Baldwin

\$150,000 (1)	-Breast Cancer Antigen and Monoclonal Antibodies
150,000 (2)	-Intratumor Immunotherapy

Dr. Baldwin is an international authority on localized tumor therapy. His antigen-antibody preparations will be used in Florida and in the Central Laboratory. He also has interests in drug targeting and polymer modified drugs.

11. Harvard: Dr. Merv Israel

\$40,000 (1)	-Antitumor Drug Pharmacology
40,000 (2)	-Drug Modifications

Dr. Israel has one of the finest laboratories for studying the metabolic fate of drugs *in vivo* and for mechanistic tumor cell biology studies.

#### FACILITIES

The Company will occupy central R & D laboratories and offices located near a major university center for medical and veterinary research - probably in Seattle, Washington. A modest but well equipped facility of approx. 12,000 sq. ft. is considered adequate. A leased space arrangement costing ~\$50,000/yr. is believed to be feasible in the Seattle area. For the major research contract at the University of Florida, leased space of 8-10,000 sq. ft. is contemplated. The cost of this space at Florida (if any) will be negotiated with the University or the University Research Park and will be part of the contract award.

#### SCIENTIFIC ADVISORY COUNCIL

A group of five notable scientists will be selected to advise the Company on scientific matters, evaluate progress and recommend future directions for research. They will be expected to meet with the research staff 2-3 full days per year and would receive consulting compensation of \$5,000/yr. plus expenses (plus possible stock options). They will be selected from the following tentative candidates:

Frank Schabel - SRI - Tumor Animal Models  
Ariel Hollinshead - G.W.U. - Tumor Immunology  
Robert Baldwin - Nottingham - Tumor Immunology  
Donald Morton - UCLA - Lesional Immunotherapy  
Bernard Fisher - Pittsburgh - Clinical Oncology Breast Cancer  
James Holland - Mt. Sinai, N.Y. - Chemotherapy  
Hugh Fudenberg - U. South Carolina - Tumor Immunology  
Tom Frey - Sidney Farber Inst. - Chemotherapy  
T. Ghose - Dalhousie U. - Antibody Therapy

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FINANCIAL SUMMARY\*

	<u>1st 18 mos.</u> <u>(1982-83)</u>	<u>2nd 18 mos.</u> <u>(1983-84)</u>
Salaries**	395,000	540,000
Travel (including moving and living expenses)	105,000	105,000
Scientific Advisory Council	55,000	55,000
Laboratory Equipment and Instrumentation	450,000	175,000
Laboratory Lease	75,000	75,000
Laboratory Supplies	75,000	75,000
Utilities/Phone/Waste Disposal	60,000	60,000
Experimental Animals and Maintenance	130,000	175,000
Computer/Accounting/Legal/Graphics	<u>80,000</u>	<u>90,000</u>
	1,425,000	1,350,000
Overhead (10%)	410,000	410,000
University and Institute Contracts***	<u>2,265,000</u>	<u>2,340,000</u>
	4,100,000	4,100,000

\*3 Year Funding: Two 1-1/2 yr. \$4.1M contracts; Total \$8,200,000

\*\*No individual salary will exceed \$60,000 in the 1st year (1982). A staff of about 12 is planned for 1982.

\*\*\*Contract funds indicated in the following section are tentative and include institutional overheads. Specific allocations to contracts will depend upon negotiations with individual institutions. Any unexpended funds or funds saved by favorable overhead negotiations will be applied to Central Laboratory operations or additional contracts.

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12. Brain Tumor Center U.C. - San Francisco: Dr. Victor Levin

\$25,000 (1) -Localized Therapy of Brain Tumors-Gliomas

25,000 (2)

Dr. Levin's groups has pioneered localized irradiation therapy of brain tumors. He will collaborate in evaluations of new tissue-binding drugs for glioma treatment, especially studying intracavitary therapy.

13. Weizmann Institute (Israel): Drs. Arnon, Hurwitz, Levy, Trainin

\$50,000 (1) -Polymeric Antitumor Agents

50,000 (2) -Antibody-Drug Preparations

Drs. Arnon and Hurwitz have been among the leaders in antibody targeting and polymer modified anti-tumor drugs. Dr. Levy heads the Division of Applied Polymer Science and has collaborated with Dr. Goldberg in biopolymer studies. The Weizmann group would work closely with Company projects at Florida and the Central Laboratories.

COMMERCIAL POTENTIAL FOR COMPANY DEVELOPMENTS

The Company's products will be new scientific knowledge, technological know-how, and patentable discoveries in the major areas of R & D described herein; i.e. *targeted anti-tumor drugs, for breast cancer; cancer and chlamydia venereal disease diagnostic assays; pseudomonas antibody targeted antibiotics; novel adjuvants, microsphere technology and polymeric drug technology for cancer drugs and immunoassays.* In all cases there are major commercial opportunities for both human and veterinary medicine. One significant break-through in the field of breast cancer chemotherapy or immunotherapy from the Company's program would have market potential of several hundred million dollars per year. It should be further emphasized that because of the unusual risk-benefit ratio for cancer therapy, FDA and human clinical trial constraints are less stringent than for conventional new drug developments. It may therefore be possible to commercialize cancer drugs relatively rapidly and with less investment. Commercial potential is probably even greater for cancer diagnostic assays. Although this field will be much more competitive. Assuming a reasonable success ratio in the Company's R & D projects \$100 million/yr in product sales within 5 years of commercialization appears possible.

Although the Company may choose to license its discoveries or enter into joint ventures on specific products, it may also choose to establish subsidiaries or new companies for commercial exploitation of specific inventions and technological developments; doing so by additional private or public capitalization as deemed most appropriate.

There is a calculated balance of shorter term and longer range projects in the Company's program as indicated in the brief project financial summaries which follow.



Targeted Pharmaceuticals Program

Human Breast and Lung Cancer Therapy Program  
 [Projects 1,2,4,5,9]

Development of antigen-vaccine and intratumor immuno-chemotherapy drugs and therapeutic protocols for lung and breast cancer is the major targeted drug program of TPI embracing activities in five projects with major research emphasis at six contract research institutions. It has both short and long range aspects in that clinical trials with lung tumor antigen-vaccines will commence during the first year. Breast cancer vaccine and intratumoral or intracavitary drug clinical studies could begin within two years. Program costs from the various projects are estimated on a shared basis with cancer immunoassay studies since similar specific antigen-antibody preparations will be used in diagnostic immunoassay developments.

Market potential is based upon American Cancer Society lung cancer estimates of 120,000 new cases, 105,000 deaths, and about 200,000 under medical care in 1981. The incidence of lung cancer has tripled since 1950 and continues to increase. For breast cancer, estimates are 110,000 new cases in 1981 with a continuing annual population of about 200,000 under medical care. Mortality was 37,000/1981. Breast cancer remains the foremost cause of cancer death among women. There has been virtually no change in the age-adjusted death rate for this disease since 1950.

	<u>Six Year Estimate</u> <u>(\$ in thousands)</u>					
	<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>6</u>
Product Sales:	0	0	500	6,000	22,600	46,000
Development Costs:	1,150	1,150	1,150	5,000	10,000	10,000
Total Profit (loss):	(1,150)	(2,200)	(3,350)	(2,350)	10,250	46,250

Year-3: Introduction of lung vaccine  
 0.5% of market (1,000 patients); \$500/patient

Year-4: Development of lung vaccine market  
 5% (10,000 patients); \$500/patient

Introduction of breast vaccine  
 0.5% of Mkt (1,000 patients); \$500/patient

Introduction of targeted drug therapy  
 0.5% (1,000 patients); \$500/patient

Year-5: Lung Vaccine therapy: 20%/ \$400 treatment  
 Breast vaccine therapy: 5%/ \$500 treatment  
 Drug therapy: 2%/ \$400 treatment

Year-6: Lung Therapy: 40%/ \$400  
 Breast therapy: 20%/ \$400  
 Drug therapy: 5%/ \$400

## Targeted Pharmaceuticals Program

### Feline Leukemia/Viremia Program [Project 1]

This project is aimed at the population of 30 million pet cats in the U.S. Incidence of leukemia is 1/1000 and viremia is 1/100. Leukemia market potential is 30,000 cases at \$50/treatment; viremia is 300,000 cases at \$20/treatment. Development costs are modest. It is felt that there is a high probability of developing successful treatment using antibody-drug therapy within 2-3 years. Furthermore, much can be learned relative to treatment of human disease.

	Six Year Estimate (\$ in thousands)					
	<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>6</u>
Product Sales:	0	0	75	750	1,500	2,500
Development Costs:	90	90	90	300	500	500
Total Profit (loss)	(90)	(180)	(195)	255	1,255	3,255

Year-3: Introduction of antibody-drugs  
1% of \$7.5m market.

Year-4: 10% of market

Year-5: 20%

Year-6: 33%

## Targeted Pharmaceuticals Program

### Intratumor Immuno-Chemotherapy of Canine Mammary and Equine Sarcoid Tumors [Projects 3,4,5]

There is significant market potential in treatment of the major solid tumors in dogs and horses as well as extremely valuable clinical experience pertinent to human disease. Development of successful treatments for these animal tumors in 1-2 years has a high probability of success based on lesional chemotherapy and BCG-type cell wall immunotherapy studies to date. An estimated 16,000 small animal and 1,000 equine vets would be expected to see an average of 10 cases each per year or 170,000 cases/yr. Assuming a treatment cost of \$40/case, a market potential of \$6.8m/yr. is available.

	Six Year Estimate (\$ in thousands)					
	<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>6</u>
Product Sales:	0	70	700	1,400	2,450	3,500
Development Costs:	130	130	130	400	400	500
Total Profit (loss):	(130)	(190)	380	1,380	3,430	6,430

- Year-2: Introduction of lesional chemo-Immunotherapy drugs  
1% of market
- Year-3: 10% mkt
- Year-4: 20%
- Year-5: 35%
- Year-6: 50%

Targeted Pharmaceuticals Program

Chlamydia Immunodiagnostic Assay  
[Project 7]

Chlamydial trachomatis infections have become the major type of venereal infection. Pregnant woman (3 million) and 10-20 million patients tested for gonorrhoeae represent a minimum test population. A market potential of 30 million assays would be available if a simple, reliable and low cost (~\$1.50/test) immunoassay is developed (market of \$45m/yr.). Research to date suggests an excellent short-term (1-2 years) prospect for successful development of a suitable antibody assay.

	Six Year Estimate (\$ in thousands)					
	<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>6</u>
Product Sales:	0	0	450	4,500	9,000	14,850
Development Costs:	260	260	260	2,000	4,000	4,000
Total Profit (loss)	(260)	(520)	(330)	2,170	7,170	18,020

- Year-3: Introduction of antibody immunoassay-1% market
- Year-4: 10%
- Year-5: 20%
- Year-6: 33%

## Targeted Pharmaceuticals Program

### Antibody Targeted Antibiotics for Ophthalmic *Pseudomonas* Infections [Project 6]

*Pseudomonas* infections of the cornea epithelium are the most common type of damaging ophthalmic bacterial infection and are especially difficult to treat because of rapid dilution of drugs in the eye. Other bacterial and fungal ENT infections are also resistant to treatment. Using antibodies to the bacteria, drug-antibody preparations offer the promise of far more effective therapy at lower doses of such antibiotics as gentamycin. An estimated market of 3 million drug doses at \$5/dose (\$15m/yr. market) exists for treatment of only ophthalmic *Pseudomonas* infections. Research conducted to date indicates a good prospect for successful short-term development (in 1-2 years).

	Six Year Estimate (\$ in thousands)					
	<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>6</u>
Product Sales:	0	0	150	1,500	3,750	6,000
Development Costs:	130	130	130	500	750	750
Total Profit (loss):	(130)	(260)	(390)	610	3,610	8,860

Year-3: Introduction of Antibody-Gentamycin preparation: 1% of market

Year-4: 10%

Year-5: 25%

Year-6: 40%

Cancer Detection and Monitoring Using Tumor-Specific Antibody Immunoassays  
[Project 8]

This project will utilize the unique antigen and antibody preparations from satellite research groups for the major human solid tumors: breast, colon/rectal, lung. Immunoassay development will utilize conventional as well as polymer-bound and microsphere reagents. The 1981 incidence of the solid tumors for which assays will be developed are: breast-110,000, colon/rectal-120,000 and lung-120,000. These three constitute 43% of all cancers and about 50% of all cancer deaths. For diagnostic and patient monitoring assays, it is reasonable to estimate about 1 million cancer patients under medical care per year (who would average 5 tests/yr. each) and a potential screening population of 25 million people (1 test/yr.) Assuming a reliable immunoassay cost of \$5/test, a conservative market of 30 million tests (\$150 million) exists. This market will also become increasingly competitive and majority penetration will be difficult for any single company.

	Six Year Estimate (\$ in thousands)					
	<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>6</u>
Product Sales:	0	0	0	1,500	7,500	22,500
Development Costs:	700	700	700	2,000	3,000	4,000
Total Profit (loss):	(700)	(1,400)	(2,100)	(2,600)	1,900	20,400

Year-4: Introduction of Immunoassays-1% of market

Year-5: Development of market-5%

Year-6: 15% of market

## COMPANY MANAGEMENT

Dr. Eugene P. Goldberg, Chairman, Board of Directors, will remain on the faculty at the University of Florida and will devote at least 50% of his time to Company activities directing contracted research at Florida and working with Company management on all aspects of operations. He will spend 3 months (June-August) full time at the Company's headquarters and laboratories and will interact closely with Company staff and contract groups throughout the year. He will assist and advise the President on a regular basis in all matters concerning technical and business operations and he will preside at the Scientific Advisory Council Meetings.

Dr. Charles A. McLaughlin, President, Director, will be the chief operating executive and will devote full time to directing the activities of the Company. He will coordinate research projects within the central research facility and among the contracting institutions, and will supervise certain specific research projects conducted within the central research facility. As one of the three scientists on the Board of Directors, Dr. McLaughlin will make recommendations regarding the general goals and directions to be assumed by the Company as well as managerial and specific scientific operations. Dr. McLaughlin will act as the principal scientific liaison, in addition to his management functions with the contracting scientists. This responsibility will require considerable travel. An administrative assistant will be employed to assist Dr. McLaughlin and Mr. Cobain in the daily operations of the Company.

The specific research activities to be conducted by Dr. McLaughlin will be (1) development of a single, widely applicable endotoxin immunoassay and (2) investigation of microspheres as carrier systems for immunization with antigens and adjuvants. The second project will be done in collaboration with Dr. Goldberg and his group.

Dr. McLaughlin is a veterinarian and will also establish and maintain contacts with veterinarians in communities and universities near the central research facility. In many instances products developed primarily for treatment of human cancers, will be tested first in the treatment of animal tumors. This testing will be done by veterinarians within the state to simplify and expedite regulatory approval of such testing. Dr. McLaughlin also will provide support for other research activities conducted within the central research facility, such as assisting in animal experimentation and establishing suitable animal models for use by scientists within the facility.

## BIOGRAPHICAL SKETCHES FOR KEY SCIENTIFIC STAFF

Dr. Eugene P. Goldberg has MS (1951 Ohio U.) and PhD (1953 Brown U.) degrees in Organic Chemistry and is currently a professor at the University of Florida holding appointments in the Departments of Materials Science and Engineering, Surgery, and Chemistry. He is also Director of the Biomedical Engineering Center at the University. Since 1975, his research program at the University has pioneered two new areas of biopolymer science; macromolecular drugs for targeted or localized therapy and use of hydrophilic polymers to control tissue damage in surgery.

Prior to his University appointment, he worked for 22 years in industrial research principally in the field of polymer science. At General Electric, he was the coinventor of polycarbonate engineering thermoplastics commercialized under the trade name of Lexan. This was probably the most important thermoplastic polymer development after Nylon and today represents a business well in excess of one half billion dollars/yr. in sales. At GE, he was also responsible for research and development which led to new high voltage dielectric capacitors and new methods of polymerizing thin dielectric films which have also become important commercially.

As Associate Director of the Borg Warner Research Center, he was responsible for initiating and directing programs in diverse areas of research which led to a new oil well chemicals business, air conditioning refrigerants, and new polyesters and hydrocarbon block copolymers which are in use today. At the Xerox Corp., during the period of 1966-1975, Dr. Goldberg was responsible for creating and developing one of the outstanding chemistry research laboratories in U.S. industry. This laboratory produced many advances of scientific and commercial significance in the fields of materials science, imaging and information science, photoconductors, and liquid crystals, as well as in enzyme chemistry and diagnostic medical analyses.

Dr. Goldberg holds more than 100 U.S. and foreign patents and has published or presented more than 100 scientific papers in the fields of polymer and biopolymer science. He has edited two books, Polymer Grafts in Biochemistry (Dekker) and Biomedical Polymers (Academic Press) and is currently completing work on a third book, Targeted Drugs (Wiley). He is an industrial consultant to a number of medical device companies and has consulted for several institutes of the



Jon E. Cobain (title to be established) will function as director of business operations of the Company. He will provide guidance for implementation of the business mechanisms required to achieve the goals of the Company. He will participate in negotiations with contracting institutions and companies interested in the scientific technology of the Company. He will provide guidance and recommendations for commercialization of rights of the Company. It is anticipated that he will devote approximately 25% of his professional efforts and time toward meeting his responsibilities to the Company. He will be assisted by a full time administrative assistant and work closely with Dr. McLaughlin and Dr. Goldberg.

Dr. Harlan D. Caldwell's principal responsibilities will be as a senior scientist directing microbiological research activities. He will conduct research on immuno-diagnostic assays e.g. for chlamydial infections. In addition, he will provide assistance in directing and in supporting other research activities conducted in the central research facility. The general areas of immunoassays, bacterial product isolation, and cell culture research are specific activities for which Dr. Caldwell will provide assistance and direction.

Dr. George F. Rowland will function as a senior scientist directing research activities for antibody-drug targeting for treatment of neoplastic diseases. He will be responsible for production, characterization, and use of antibodies prepared in animals and by hybridoma techniques. He and Dr. Caldwell will share overlapping responsibilities in this work. Dr. Rowland will provide expertise in the production of antibody-drug conjugates and monitoring antitumor activity in cell cultures as well as in animal tumor models. He will work closely with Dr. Goldberg and with appropriate contract research groups. In addition to his primary research responsibilities, he will support other immunology and biochemistry research activities conducted in the central research facility.

Administrative Assistant (to be selected). An administrative assistant will provide accounting, business and laboratory operational services for the Company having responsibility for such tasks as: (1) maintaining records of obligations and expenditures, (2) requisition of supplies, services, and equipment (3) collating reports from contracting scientists and assisting in monitoring contracted research activities, (4) supervising support personnel, such as part-time employees (students) and (5) assuring normal day to day laboratory maintenance and services.

National Institutes of Health (including Heart, Lung and Blood; Arthritis and Infectious Disease; and the National Eye Institute). He is a consultant for the Veterans Administration and the National Science Foundation and serves as a member of the Materials Science Advisory Committee of the National Science Foundation. For many years he has been a member of the Solid State Science Advisory Panel to the National Academy of Sciences and National Research Council and has served on various sub-committees of that body including chairmanship of the Polymer Science Sub-committee and member of a National Research Council Ad Hoc Study Panel which recently produced a comprehensive report on Polymer Science and Engineering for the National Academy of Sciences.

His extensive management, research and academic experience afford a balance of experience uniquely suited to the proposed venture. An attached CV and reprint from the 1980 University of Florida Engineering College review provide additional information.

Dr. Charles A. McLaughlin, holds a BSc degree (Montana State University, 1962) and a Doctorate in Veterinary Medicine (Washington State University, 1966). He was an honor student and graduated in the top quarter of his class. He was selected to receive a full scholarship as an officer in the U.S. Army Veterinary Corps and following graduation served as an officer in charge of a veterinary unit responsible for quality control of large industrial food processing operations. He was responsible for an inspection program which led to major modernization of facilities and operations in the salmon canning industry. He was awarded the U.S. Army Commendation Medal, an unusual achievement for a junior veterinary officer. In 1970, he began graduate training in Oncology at the McArdle Laboratories for Cancer Research, School of Medicine, University of Wisconsin; one of the most prestigious basic research facilities for cancer research in the world. He was awarded a National Institutes of Health individual fellowship as a graduate student and a research grant for a four year period. He was awarded a Doctorate in Oncology (with a minor in pathology) in 1975 and, is probably the only veterinarian in the United States with a Ph.D. in Oncology.

Dr. McLaughlin joined the National Institutes of Health in 1974 as a research scientist. His research at the NIH Rocky Mountain Laboratory has led to the publication of one book chapter and over 27 technical papers. In collaboration with other scientists he has formulated and developed immunotherapeutic preparations which regress tumors in laboratory animals, horses, cattle, and dogs. He

supervised the successful completion of laboratory studies accepted by the FDA for use of such preparations in human clinical trials designed by physicians at the M.D. Anderson Tumor Institute.

Dr. McLaughlin's areas of expertise include immunotherapy for treatment of neoplastic diseases, isolation and characterization of bacterial products, development of vaccines with natural and synthetic products serving as adjuvants, and the biochemistry of the shock-producing substance, endotoxin, isolated from gram negative bacteria. He is a member of the American Association for Cancer Research and two honorary scholastic societies.

Dr. Harland D. Caldwell received his Bachelor of Science degree with honors from the University of Wyoming in 1970. He obtained a Masters degree in Micro-biology and Immunology from the University of Wyoming in 1972 and a Doctorate in Pathobiology from the University of Washington in 1976. Dr. Caldwell was the recipient of the Heisir Research Foundation Fellowship in the Department of Microbiology and Immunology at the University of California Medical Center, San Francisco. During this period, Dr. Caldwell was the principle investigator of a NIH research grant on "Immunochemistry of Chlamydial Surface Antigens". In 1980 he was employed as an Expert at the NIH, National Institute of Allergy and Infectious Diseases, where he has continued his research on the immunology and biochemistry of chlamydial biology.

Dr. Caldwell has a total of nine years research experience related to the immunochemistry of chlamydial antigens and holds two patents concerning antigenic preparations. He is internationally recognized as a leading authority in this field. He has published numerous articles in medical journals relating to the immunology and antigenic structure of chlamydia. Dr. Caldwell is a member of the American Association of Immunologists, American Society of Microbiology and Sigma Xi.

Dr. George F. Rowland holds degrees from London University in Chemistry (BS 1957), Physiology (BS 1958) and Biochemistry (Ph.D. 1961). He was a Beit Memorial Research Fellow at U.C.H. Medical School, a Research Lecturer in Surgery and Biochemistry at St. Bartholomew's Hospital Medical School and a Visiting Fellow of the Hall Institute of Medical Research in Melbourne. From 1972 to 1978 he was Deputy Head of Immunopathology at the R & D Center of the G.D. Searle Co. He is currently a Senior Research Scientist and Project Coordinator for Immunology at the Lilly Research Centre in Surrey, England.

Dr. Rowland is internationally known for his pioneering work on antibody targeted anti-tumor drugs beginning in the early 1970s. He has conducted research and published extensively (more than 40 papers and several reviews) on immunology and antibody preparation, drug coupling biochemistry, cell biology of tumors and drug pharmacology. He has also worked in parasitic disease therapy and graft rejection in transplantation surgery. He has numerous collaborative clinical studies in progress and is one of the leading scientists today in the field of antibody targeted therapy. He has had both academic and industrial pharmaceutical research and management experience.

Mr. Jon E. Cobain is a marketing and finance oriented business generalist who brings a wide range of outstanding line, staff, and management skills to the Company. He received Bachelor of Science and Bachelor of Arts degrees in economics (1964) from the University of Nevada where he was an honor roll student and senior class president. He received a M.B.A. in marketing as a Dean's List student from Northwestern University in 1965.

Mr. Cobain's multifaceted career spans an array of successful experiences in product development and marketing. He has a productive track record as a salesman, salesmanager, market manager, manager of new product development and market research, vice president of marketing, and director of marketing. He has recently served as senior vice president and associate for two corporations providing management consultation for national and international marketing and financial corporations.

His skills include financial analysis, venture capitalization, market research, product and market development, foreign marketing, advertisement, mergers and acquisitions, trade and industry association interfacing, patent and license agreement, and general marketing and business planning.

A detailed summary of his professional experiences and consulting activities is attached herein.

PARTNERSHIP INCOME

Date	Principal Payment Per Limited Part- nership Unit	Interest Due on L.P.'s Notes (Backed by letter of Credit) at 10%	Total Payment Per Partnership Unit	Total Payment by All L.P.'s (66 Units)
4/30/82	20,000	--	20,000	1,320,000
4/30/83	40,000	13,000	53,000	3,498,000
10/31/83	--	--	--	--
4/30/84	45,000	9,000	54,000	3,564,000
10/31/84	45,000	2,250	47,250	3,118,500
TOTAL	150,000	24,250	174,250	11,500,500

PARTNERSHIP EXPENSES

Date	Total R&D Contract Paid To TPI	1) Syndication Fee Due to Sales Agent (10%) 2) Start-up Costs 3) G.P.'s Organizational Fee <u>Total</u>	Partnership Operating Expenses	Payment of Interest on Partnership Loan	Payment of Principal on Partnership Loan	Total Partnership Expenses
4/30/82	3,850,000	1) 300,000 2) 175,000 3) 150,000 <u>625,000</u>	75,000	--	--	4,550,000
4/30/83	--	1) 180,000 2) -- 3) 150,000 <u>330,000</u>	100,000	646,000	2,422,000	1,076,000
10/31/83	4,000,000	1) 170,000 2) -- 3) 100,000 <u>270,000</u>	--	--	--	4,270,000
4/30/84	--	1) 170,000 2) -- 3) 150,000 <u>320,000</u>	150,000	588,600	2,505,400	1,058,600
10/31/84	--	1) 170,000 2) -- 3) 50,000 <u>220,000</u>	68,640	257,260	2,572,600	545,900
TOTAL	7,850,000	1,765,000	393,640	1,491,860	7,500,000	11,500,500

PARTNERSHIP BORROWING

Date	Required Partnership "Borrowing" Amount (Loan)	Previous Partnership Loan Amount	Interest Due On Previous Loan at 20%	New Total Loan Required by Partnership	Payment on Principal of Total Loan
4/30/82	3,230,000	--	--	3,230,000	--
4/30/83	--	3,230,000	646,000	808,000	2,422,000
10/31/83	4,270,000	808,000	80,800	5,078,000	--
4/30/84	--	5,078,000	507,800	2,572,600	2,505,400
10/31/84	--	2,572,600	257,260	--	2,572,600
TOTAL	7,500,000		1,491,860		7,500,000

PARTNERSHIP DEDUC

Year	R&D Con- tract To TPI	Start-up Costs (Amortized)	G.P.'s Ad- ministrat- ion Fee (Amortized)	Partnership Operational Expenses	Interest Paid on Partnership Borrowing	Total "Gross ducta Losse Partn ship
1982	3,850,000	23,333	80,000	75,000	--	4,028
1983	4,000,000	35,000	120,000	100,000	726,800	4,98
1984	--	35,000	120,000	150,000	765,060	1,07
TOTAL	7,850,000	93,333	320,000	325,000	1,491,860	10,0