

## CONFIDENTIAL OFFERING MEMORANDUM

*This Confidential Offering Memorandum (the "Memorandum") constitutes an offering (the "Offering") of these securities only in those jurisdictions and to those persons where and to whom they may be lawfully offered for sale and therein only by persons permitted to sell such securities. This Memorandum is not, and under no circumstances is it to be construed as, a prospectus, advertisement or public offering of the securities offered herein. No securities commission or similar regulatory authority has passed on the merits of the securities offered, nor has it reviewed this Memorandum, and any representation to the contrary is an offense.*

PRIVATE PLACEMENT

SEPTEMBER 6, 1996

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### ANGIOTECH PHARMACEUTICALS, INC.

Offering:	25,000 Class A Preference shares
Total Proceeds:	Cdn. \$68,750
Estimated Net Proceeds	Cdn. \$68,750
Price:	Cdn. \$2.75 per Class A Preference share
Minimum Subscription:	Cdn. \$25,000 for British Columbia residents.
Use of Proceeds:	The proceeds of the Offering will be used to pay for the continued research and development of the Company's technologies and products.

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There is no market for these securities and no market is anticipated to develop. As there is no market for these securities, it may be difficult or even impossible for the purchaser to sell them. Purchasers will be subject to the resale restrictions described under the section **RESALE RESTRICTIONS**.

Potential purchasers are advised to consult their own legal counsel and other professional advisers as to this investment. Consideration should be given to the merits of the investment. This Memorandum is confidential. By the receipt hereof, prospective investors agree that they will not transmit, reproduce or make available to anyone, other than their professional advisors, this Memorandum or any information contained herein. These securities are a speculative investment and are suitable only for long-term investors who can afford to lose all their investment. (See **RISK FACTORS**).

## CONFIDENTIAL OFFERING MEMORANDUM

This Confidential Offering Memorandum has been prepared by Angiotech Pharmaceuticals, Inc. ("Angiotech" or the "Company") solely for the purpose of assisting potential purchasers in making their own evaluation of the Company.

By accepting this Memorandum, the recipient acknowledges and agrees that:

1. all of the information contained herein is subject to confidentiality and will be used by the recipient solely for the purpose of evaluating this Memorandum;
2. the recipient will not make any copies of this Memorandum, in whole or in part or distribute this copy to any third party;
3. no contact may be made with non-officer employees or consultants of the Company without prior permission of Angiotech; and
4. any proposed actions by the recipient which are inconsistent in any manner with the foregoing agreements will require the prior written consent of Angiotech.

The Company reserves the right to negotiate with one or more prospective purchasers at any time and to enter into a definitive agreement for the sale of securities of the Company without prior notice to any prospective purchasers. Also, the Company reserves the right to terminate, at any time, further participation in the investigation and proposal process by any party and to modify the procedures without assigning any reason thereof, and the Company reserves the right to take any action, whether in or out of the ordinary course of business, which it deems necessary or prudent in the conduct of such business. Angiotech also reserves the right to close the subscription books at any time without notice.

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## EXECUTIVE SUMMARY

Angiotech Pharmaceuticals, Inc. ("Angiotech" or the "Company") is a privately owned British Columbia company engaged in the development and commercialization of innovative treatments for angiogenesis dependent diseases and conditions. These include arthritis, cancer, cardiovascular disease and neovascular disease of the eye.

Angiotech's core technologies were identified by the three founding scientists of the Company in 1992. In its first two years of operation, Angiotech focused on bringing together a nucleus of key scientific personnel, primarily through outside collaborations. Through these relationships, the Company completed the research and development necessary to both validate its technology and build its intellectual property position. As its technology has advanced, the Company has attracted additional research scientists, scientific advisors and collaborators, many of whom have extensive experience in taking products through the regulatory approval process. The company has 27 full time employees, including 13 Ph.D.'s and 2 M.D.'s involved in the development of the Company's lead products. An additional 12 Ph.D.'s and 12 M.D.'s currently work with the Company as consultants or advisors. The Company is currently bringing in-house many of these research and development activities.

Angiotech's core technology relates to:

- (1) Angiotech's knowledge of pathophysiology associated with the biological pathway (the "AP-1 pathway") involved in cell proliferation and the production of the enzymes (matrix metalloproteinases) that allow dividing cells to spread into other tissues. This unique understanding has led to the identification of two agents that disrupt the pathway in a manner that may have multiple pharmaceutical applications;
- (2) Angiotech's use of these two agents, paclitaxel (the active agent of "Taxol" ® Bristol-Myers Squibb) and vanadium compounds, and the Company's proprietary position with regard to certain of their uses; and
- (3) The use of polymeric delivery systems designed specifically to facilitate the use of the above agents for the particular pharmaceutical applications covered by the Company's intellectual property.

Angiotech's core technologies can potentially be applied to a broad range of diseases (there are at least 20 diseases recognized as angiogenesis dependent diseases). Angiotech has identified at least a dozen products for possible development. Of these, the Company is focusing its initial efforts on the following 4 candidates:

- **Paclitaxel Arthritis Program** - Angiotech has demonstrated *in vitro* and in animal models the potential of paclitaxel as a potent disease modifying agent in rheumatoid arthritis. Paclitaxel has been shown to be capable of favourably impacting upon five principle pathologies of the disease. Since systemic treatment with the drug (i.e., intravenous administration) might be associated with a higher risk of toxicity and therefore represents a greater development risk, the Company has chosen to first formulate paclitaxel into polymer compounds which release therapeutic amounts of drug over prolonged periods and which are designed to be injected locally into affected joints. The Company intends to file an Investigational New Drug ("IND") application to test this initial formulation in humans late in 1996. Additionally, the Company has also developed a systemic formulation which it expects to progress to human studies during the first half of 1997.
- **Stent Coating Program** - Stents are hollow cylindrical devices inserted into a bodily duct or tube to physically hold the tube open and to prevent compression or occlusion of the tube. Unfortunately, stents are often overgrown by inflammatory tissue or tumor cells, thereby limiting the duration and effectiveness of the treatment. Angiotech has created a drug-loaded coating for stents and other medical devices that will provide localized delivery of angiogenesis inhibitors ("AI's"), (particularly paclitaxel), and other compounds for extended periods of time, up to several months. Two patients with esophageal cancer have been treated on a compassionate basis at the University of British Columbia, during July and August, 1996. A formal clinical

study involving 20 patients is scheduled to commence during September, 1996 in London, England. A paclitaxel coated stent is also under development for coronary restenosis.

- ***Vanadium Compounds as Novel Chemotherapeutic Agents*** - Angiotech and its collaborators have demonstrated the ability of vanadium compounds to interrupt a key cellular "second messenger" in the AP-1 pathway that is the focus of the Company's efforts. Since this is potentially a novel mechanism of action for a cancer agent, these compounds represent a potentially new class of chemotherapeutic drugs. This is significant because anti-cancer drugs are traditionally given in combination according to different mechanisms of action, in an effort to block as many cellular pathways as possible to increase anti-tumor activity. The preclinical development work relating to these compounds is currently being performed by the British Columbia Cancer Agency and an IND filing is anticipated for late 1997 or early 1998.
- ***Surgical Paste Program*** - A paclitaxel-polymer compound has been formulated as a sterile composition that can be applied directly to cancer resection sites at the time of surgery to provide local, sustained release of the drug for the prevention of local tumor recurrence. At least 20% of all patients who have tumors surgically removed will suffer a recurrence of their disease at (or adjacent to) the site where the tumor was removed. Consequently, a paste treatment would be useful in, but not restricted to, breast cancer, prostate cancer, tumors of the central nervous system, colon cancer and head and neck cancer. Initiation of clinical studies has not yet been scheduled, but will likely be in 1997.

Angiotech's commercialization strategy involves identification of clinical applications for its two AP-1 inhibiting agents that have, in the Company's view, the highest likelihood of receiving approval for use in humans. Most of these applications also address large markets. Angiotech is not seeking at this point in time to become a fully integrated pharmaceutical company; rather, its focus is to develop its products and technologies quickly and efficiently to the stage where collaborations can be formed with strategic corporate partners. Angiotech is currently in discussions with several potential corporate partners for each of its initial product candidates.

Angiotech's management team has strong capabilities and experience in biotechnology, medical research and development, clinical medicine, regulatory affairs and corporate finance.

Angiotech has aggressively sought to protect its technologies by filing patent applications and in-licensing intellectual property rights where strategically important. Angiotech's original patent application, filed in 1993, has been split into 5 separate divisional applications covering multiple inventions. Subsequently, the Company has filed and licensed several additional patent applications, bringing the Company's total portfolio to 11. The Company is seeking patent protection on a worldwide basis, depending upon the commercial importance of each country as a market, and upon competition and enforcement issues.

The Company has raised approximately Cdn. \$9.0 million from founders, sophisticated investors and institutions since the commencement of operations in the fall of 1992.

## HIGHLIGHTS OF THE COMPANY

- **Angiotech Has A Strong Foundation of Proprietary Technologies And Products.** Angiotech's understanding of pathophysiology in the AP-1 Pathway has allowed it to identify paclitaxel and vanadium compounds as potential disease modifying agents in numerous diseases, and to establish a proprietary position for their use in these diseases.
- **Angiotech's Arthritis Products Are Potential Breakthroughs In The Treatment Of Arthritis.** In an animal model of rheumatoid arthritis, where few agents slow disease progression, Angiotech has demonstrated that paclitaxel (an approved chemotherapeutic) outperforms currently preferred drugs as a disease modifying agent. Paclitaxel is capable of positively impacting on 5 key pathological processes which characterize rheumatoid arthritis.
- **Angiotech's Vanadium Compounds Represent A Potentially New Class Of Chemotherapeutic Agents.** Much of cancer research is focused on identifying agents that have novel mechanisms of action. The vanadium compounds identified by Angiotech represent a potentially new class of chemotherapeutic, because of their unique mechanism of action in inhibiting the AP-1 pathway.
- **Angiotech Has Attracted An Experienced Management Team.** Angiotech's management team brings to bear over 100 years of experience in the pharmaceutical and biopharmaceutical industries. Their experience includes expertise in medical research, clinical medicine, product development and regulatory affairs.
- **Angiotech's Drug Delivery Vehicles and Expertise Represent A Commercial Asset.** While the Company's focus is on its own products, the drug delivery expertise and drug delivery systems developed by the Company have potential for broad applications. The Company's polymeric stent coating is currently being tested in human disease and could be utilized for a variety of clinical indications.
- **Angiotech's Products Are Subject To Fewer Development Risks.** The Company believes the regulatory approval process may be simplified, somewhat, because certain of Angiotech's products contain an already approved drug that the Company has reformulated into various polymers, and because the products are to be delivered to disease sites at lower doses than are presently being given to patients receiving the drug, thus reducing the risk of side effects.
- **Angiotech Has Brought Together A Distinguished Scientific And Clinical Team.** Angiotech has recruited a strong scientific team made up of its own scientists, scientific collaborators and members of the Company's Clinical Advisory Board. In all, Angiotech employs 27 employees, including 13 Ph.D.'s and 2 M.D.'s, and an additional 12 Ph.D.'s and 12 M.D.'s work with the company as collaborators, consultants or advisors.
- **Angiotech's Technology Has Been Validated By External Organizations.** The Company believes that its approach to disease has been validated through its 11 academic and institutional collaborations with leading research and development organizations, its Clinical Advisory Board (most of whom are either individually or through their institutions involved in the Company's development efforts) and its numerous peer-reviewed scientific papers, presentations and government grants.
- **Angiotech Has Identified Clinically Useful Products Targeted At Large, Expanding Markets.** All 4 products currently under development by Angiotech (arthritis microspheres, vanadium compounds for cancer treatment, a stent coating and a surgical paste) have significant market potential, competitive advantage and should be attractive to collaborators and corporate partners.
- **Angiotech Anticipates Near Term Clinical Development.** The Company has two clinical studies scheduled to commence by the fourth quarter of 1996. The first clinical study will be conducted in the Fall of 1996 by Dr. Andy Adam at Guy's Hospital in London, England using a paclitaxel-coated stent for the palliative treatment of esophageal cancer. The second clinical study will be a Phase I trial using the arthritis microsphere product and will be conducted by Dr. Ernest Brahn at the UCLA Medical Center.

## OFFERING SUMMARY

This summary is qualified by the more detailed information appearing elsewhere in this Memorandum, including certain risk factors (See RISK FACTORS). Certain terms used throughout this Memorandum are defined in Appendix A - DEFINITIONS.

Private Placement

September 6, 1996

### THE OFFERING

The Issuer: Angiotech Pharmaceuticals, Inc.

Issue: 25,000 Class A Preference shares

Price per Share: Cdn. \$2.75

Use of Proceeds: The proceeds of the Offering will be used to pay for the continued research and development of the Company's technologies and products.

Research and Development

After Offering

\$68,750  
\$68,750

Pro-forma  
Ownership:

Fully Diluted  
After Offering

Offering Subscribers  
Other Shareholders  
Management, Employees, and Founders

0.40%  
53.64%  
45.96%  
100.00%

Dividends: No dividends will accrue automatically on the Class A Preference shares.

Voting Rights: For voting purposes, each Class A Preference share shall rank equally with each issued Common share and Class A Preference share of the Company at any meeting of shareholders.

Conversion Right: The holders of the Class A Preference shares will have the right at any time to convert their Class A Preference shares into Class A Preference shares or Common shares. The conversion will be on a one to one basis.

Automatic Conversion: The Class A Preference shares will automatically be converted into Common shares:

Upon the issuance of a receipt or receipts by relevant regulatory authorities for a prospectus filed by or on behalf of the Company with such relevant regulatory authorities relating to an initial public offering of the Company's Common shares (which shall be deemed to have occurred upon the issuance by the directors on behalf of the Company of a certificate attesting to this fact), then all of the Class A Preference shares shall immediately and automatically be converted into fully paid Common shares on the basis of one (1) Class A Preference share for one (1) Common share. Effective as of the conversion date, the Company shall issue to each



holder of Class A Preference shares certificates representing fully paid and non-assessable Common shares in the number determined as set out above and shall cancel all share certificates representing the Class A Preference shares.

**Acceptance Date:** The closing will occur after subscriptions have been raised for the Offering. The final closing is herein referred to as the "Acceptance".

**Valuation:** The offering price per share was arbitrarily determined by the Company based on comparable valuations of similar bio-pharmaceutical companies at this stage of development and acknowledging current market conditions.

### **USE OF PROCEEDS**

The net proceeds to Angiotech are estimated to be \$68,750 in the case of the sale of 25,000 Class A Preference shares, assuming a price per Class A Preference share of Cdn \$2.75.

Angiotech anticipates that all of the net proceeds will be used to fund research and development activities.

Pending the use of proceeds outlined above, Angiotech intends to invest the net proceeds of the Offering in investment grade, interest-bearing securities primarily consisting of senior corporate and government securities.

### **DIVIDEND POLICY**

The Company has not paid dividends since its inception. Angiotech currently intends to retain all earnings, if any, for use in the expansion and development of its business and, therefore, does not anticipate paying any dividends in the foreseeable future.

### **CAPITALIZATION**

Outlined in the following table is the capitalization of the Company as at July 31, 1996, as adjusted to reflect the capital reorganization as approved by the shareholders on September 6, 1996, and the 25,000 Class A Preference shares offered hereby at a price of Cdn. \$2.75 per share:

	July 31, 1996 10 Months Unaudited	Adjusted for a Completed Offering
Long Term Debt	\$0	\$0
Shareholders' Equity		
Common shares:	\$0	\$0
50,000,000 Common shares with no par value authorized; of which 688,000 Common shares are currently allotted for Options granted. <sup>(1)</sup>		
Class A Preference shares:	\$5,927,629	\$5,996,379
50,000,000 Class A Preference shares without par value authorized, of which 5,269,687 are currently issued or outstanding <sup>(1,2)</sup>		
Accumulated Deficit	<u>\$4,223,741</u>	<u>\$4,223,741</u>
Total Shareholders Equity	<u>\$1,703,888</u>	<u>\$1,772,638</u>
Total Capitalization	<u>\$1,703,888</u>	<u>\$1,772,638</u>

<sup>(1)</sup> Reflects the restructuring of the Company's share structure as of September 6, 1996, where all Class A Common shares totaling 5,244,687 were converted to Class A Preference shares and the allotment of 688,000 options to purchase Common shares for issue to new senior executives and employees.

<sup>(2)</sup> On or about September 13, 1996, there will be a closing pursuant to which the Company will issue 1,084,500 Class B Preference shares - Series I to three investors. These shares may be issued prior to the completion of the Offering pursuant to this Confidential Offering Memorandum.

<sup>(3)</sup> See note 8 to the financial statements for information concerning the Company's various leases for its operating premises and other commitments.

# **BUSINESS OF ANGIOTECH PHARMACEUTICALS, INC.**

## **INTRODUCTION**

Angiotech's approach to the treatment of angiogenesis dependent diseases is to target not only the diseased tissue itself, but also a key body response to the disease, angiogenesis. The development of rheumatoid arthritis ("RA"), the growth and spread of cancer and the process of angiogenesis (i.e. the inappropriate blood vessel growth), which accompanies both of these diseases, rely on cell division and the production of cellular enzymes which allow dividing cells to invade other tissues.

The Company has exploited the commonality of these otherwise distinct processes to identify agents that inhibit a biological pathway shared by both the diseased tissue as well as the angiogenic response. These agents are expected to impact on several aspects of disease progression simultaneously, affecting both the pathological cells as well as inhibiting aspects of the body's inappropriate response to the disease (i.e., angiogenesis). By therapeutically targeting the two key cellular processes that are controlled by this pathway, cell division and enzyme production, the company believes it will be possible to more favourably impact diseases such as arthritis and cancer than by employing traditional therapeutic approaches that focus on a single aspect of disease.

## **HISTORY AND DEVELOPMENT**

Angiotech is a Canadian biopharmaceutical company incorporated in British Columbia, Canada on October 12, 1989. It began operations in October of 1992. The head office, principal place of business and registered and records office of the Company are located at 2120 - 1066 West Hastings Street, Vancouver, British Columbia, V6E 3X1. The Company has also established laboratory and pilot production facilities at the Multi-Tenant Facility adjacent to the University of British Columbia.

The founding of the Company came about as a result of a meeting between Drs. Hunter, Machan and Arsenault (principals of the Company) during which it became apparent that the treatment of so-called angiogenesis dependent diseases could be improved by applying a multi-disciplinary approach. They formed the Company to develop and commercialize innovative treatments for cancer, arthritis and other diseases which are characterized by both inappropriate cell proliferation and blood vessel growth.

Angiotech's technology platform consists of two agents, paclitaxel and vanadium compounds, as well as polymeric drug delivery vehicles designed to facilitate their use in clinical applications. The Company distinguishes itself by its understanding of the pathophysiology of the AP-1 biological pathway that leads to cell proliferation and the production of the enzymes (matrix metalloproteinases) that allow proliferating cells to invade other tissues. This AP-1 pathway can simultaneously impact on several aspects of disease progression in arthritis, cancer and other similar diseases. The Company has identified at least a dozen product applications based on this knowledge and its identification of these two pharmaceutical agents.

## **ACCOMPLISHMENTS**

Since commencing operations in the fall of 1992, Angiotech has steadily progressed in the development of its technologies and business. In particular, the following has been achieved:

- Establishment and verification of Angiotech's core technology, including:
  - identification and demonstration that paclitaxel acts as one of the most potent angiogenesis inhibitors ("AI") yet reported.
  - encapsulation of paclitaxel, vanadium compounds and other agents into various polymeric drug delivery systems such as microspheres, pastes, and medical device coatings.

- demonstration *in vitro* and in animal models that paclitaxel is effective in inhibiting angiogenesis, synovial proliferation, matrix metalloproteinase production and inflammation - 4 of the principle pathological processes in rheumatoid arthritis - while at the same time not interfering with the normal reparative functions of cartilage tissue.
- demonstration that the novel chemotherapeutic (i.e., vanadium compounds) under development by the Company has effectiveness *in vitro* and in animal models against established tumor cell lines and multi-drug resistant tumor cell lines.
- demonstration by Angiotech and collaborators at the NIH that paclitaxel is a potent inhibitor of restenosis at very low doses.
- Licensing of proprietary technology for the use of paclitaxel in the treatment of rheumatoid arthritis and similar conditions from UCLA (July 1995). The licensing of this technology compliments the Company's own intellectual property position as it relates to paclitaxel in the treatment of arthritis.
- Licensing of novel anti-proliferative agents (i.e., vanadium compounds) from the Samuel Lunenfeld Research Institute at Mount Sinai Hospital in Toronto (March 1995).
- 11 scientific collaborations with leading research institutions.
- Filing or in-licensing, of 11 patent applications.
- Publication of numerous peer-reviewed papers and presentation of results from the above research and development.
- Recruitment of a senior management team with successful experience in growing and managing biopharmaceutical companies.
- Private funding totaling Cdn. \$9.0 million.
- Government grants totaling Cdn. \$540,000 Cdn. received from National Research Council (Canada) - IRAP, Medical Research Council (Canada) - Industry Program, National Sciences and Engineering Research Council (NSERC Canada), the British Columbia Science Council and the Province of British Columbia.
- Preliminary human testing of polymeric paclitaxel-coated stents in patients with esophageal cancer (July 96).

## FUTURE FOCUS

Over the next year, Angiotech anticipates building on its early successes by:

- Entering into at least two corporate partnership agreements.
- Commencing a Phase 1 clinical study in the United Kingdom of paclitaxel coated esophageal stents in late 1996.
- Commencing a Phase 1 Clinical study of intra-articular paclitaxel microspheres for RA in early 1997.
- Completing preclinical work relating to the use of paclitaxel micelles for systemic treatment of RA in early 1997.
- Completing preclinical work relating to the use of vanadium compounds.
- Completing preclinical work relating to the use of paclitaxel in other disease indications.

Longer term, the Company will continue to capitalize on its core technologies by identifying novel compounds that can favourably impact on disease, developing and licensing out novel clinical products based on this core technology, and exploiting its drug delivery vehicles and expertise to improve the performance of other agents.

## INTRODUCTION TO MARKETS

Angiotech's initial product focus is in the area of arthritis, cancer and cardiovascular disease. In addition, polymeric drug delivery technology is being developed to increase the utility of existing pharmaceutical products. The following is a discussion of the primary markets being addressed by Angiotech products.

## Arthritis Market

The term "arthritis" means joint inflammation. Arthritis is an umbrella term covering a range of over 100 conditions of differing causes (most of which are unknown) and characteristics. Osteoarthritis results from wear and tear on joints and is tied to the aging process. It is the most prevalent form of arthritis and a future target product for the Company. Rheumatoid arthritis ("RA"), by contrast, is a systemic disease which causes fever, joint inflammation and pain. These symptoms are caused by the ingrowth of pannus tissue (synoviocytes, new blood vessels and inflammatory cells) which destroys the joint cartilage and behaves like a localized malignancy. Although the causes of osteoarthritis and RA are different, the mechanisms of action are thought to be the same.

The different forms of arthritis afflict 1 in 7 people (400 million people worldwide - 50 million people in Europe and 40 million people in the United States), and 2 in 100 people are diagnosed with RA. For RA, there are 150,000 new cases diagnosed each year in the United States. RA results in 3.5 million office visits and 100,000 hospital admissions annually, and 1 in 3 persons affected cease employment within five years of the initial diagnosis. In advanced stages of RA, the mortality rate over a five year time period is 40% to 60% (a mortality rate which rivals many forms of cancer).

The estimated cost of arthritis to the United States economy is \$54.6 billion per annum (comprised of medical care and lost wages) and 14% of all prescriptions are for arthritis. The 1996 world market for arthritis treatments is estimated to be U.S. \$15.9 billion, with approximately \$0.9 billion being attributable to disease modifying RA agents. Although the majority of current arthritis treatment sales are in nonsteroidal anti-inflammatory drugs ("NSAID's"), the major market opportunity in arthritis is in disease modifying agents, a market which is projected to expand at an annual rate of 14.5% to the year 2000. The reasons for this anticipated shift are:

- (1) NSAID's and over the counter medications ("OTC's") only alleviate the symptoms without altering the progression of the disease;
- (2) some studies have suggested that certain NSAID's may actually hasten the progression of some forms of arthritis; and
- (3) the treatment philosophy of rheumatologists has shifted as physicians attempt to intervene earlier with disease modifying agents in the attempt to prevent irreparable joint damage. The American College of Rheumatology (in its Guidelines for the Management of Rheumatoid Arthritis) recommend that optimal management of rheumatoid arthritis "requires....timely introductions of agents that reduce the probability of irreversible joint damage", usually within 3 months of diagnosis.

Angiotech, together with Dr. Ernest Brahn of the UCLA Medical Center, has shown that paclitaxel has significant potential as a disease modifying agent in RA and is developing various paclitaxel formulations to address this disease.

(Sources - Dr. Ernest Brahn and Dr. Stephen Oliver, "National Institutes of Health Core Curriculum on Women's Health: Rheumatoid Arthritis"; Frost and Sullivan, Inc., "Report on the World Arthritis Treatment Product Markets", 1993; The Arthritis Foundation; Arthritis & Rheumatism, Vol.39, No.5, May 1996, pp. 713-722)

## Cancer Market

Cancer is not a single disease, nor is it a simple one; rather, it is a family of at least 100 diseases with similar origins, progression and treatment strategies. Cancer results from an abnormal, rapid growth of cells. These cells divide and multiply unchecked, invading healthy tissue. They also quickly adapt to changes in their environment and are capable of developing resistance to chemotherapeutic or radiation treatments. For these reasons, the focus of much current research is on new treatment approaches and agents that work along new biological pathways (i.e., pathways different from those affected by existing anti-cancer drugs).

Cancer is also a serious disease. One in three people will be diagnosed with cancer in their lifetime (an estimated 1.2 million in the United States in 1995) and of these people 50% to 60% will ultimately die from the disease. Every minute there is another death from cancer in the United States. It is not surprising that in North America cancer is the second leading cause of death (1 in 5 deaths) next to cardiovascular diseases and is projected to be the leading cause of death by the year 2000.

The market for anti-cancer drugs in the United States is approximately \$1.65 billion (85% of this amount is accounted for by traditional cytotoxic agents) and is growing by 10% per annum. The factors contributing to this growth are the need for more effective treatments, an increasing understanding of the disease and the positive climate at the FDA and other regulatory agencies (promising cancer treatments can be expedited through the regulatory review process). The cancer market is dominated by a few companies - Bristol Myers Squibb ("BMS") being the largest - and the typical cancer drug has a market of less than \$100 million annually. Paclitaxel, the active component in Taxol®, is an exception to the general rule. Sales in the first half of 1996 were reported by BMS to be approximately U.S. \$400 million and Taxol® is expected to be the first U.S. \$1 billion per annum cancer drug.

In the coming years, two therapeutic areas where growth in the cancer market is anticipated to be the greatest include anti-angiogenesis treatments and cytotoxic agents (agents that kill cancer cells) that work along new pathways. Angiotech is developing promising technologies in each of these areas, including novel uses of paclitaxel in cancer and its cytotoxic vanadium compounds. Angiotech is also using its drug delivery expertise to reformulate paclitaxel and other agents for specific applications.

(Sources - American Association of Cancer Research, "Recent Progress and Future Opportunities in Cancer Research", 1995; Find/SVP, Inc., "The Market for Cancer Therapeutics and Diagnostics - A Market Intelligence Report", 1992; Bristol-Myers Squibb press releases)

## **Cardiovascular Disease Market**

Vascular diseases often result in the narrowing, weakening and/or obstruction of blood vessels and arteries, conditions that can lead to heart attack (myocardial infarction), heart failure and other complications. The primary cause of this disease is the development of atherosclerosis (the formation of fatty "plaques" in arteries) which is associated with several risk factors such as smoking, high blood pressure, increased blood cholesterol levels, diabetes, and heredity. According to 1993 estimates, over 60 million Americans have one or more forms of cardiovascular disease; these diseases claimed approximately 1 million lives in 1993 (42% of all deaths in the United States).

Balloon angioplasty (with or without stenting) is one of the most widely used treatments for vascular disease. In this procedure, a catheter with a balloon is advanced via the bloodstream to the site of arterial narrowing or obstruction and the balloon is inflated to force open the blood vessel. While this is the treatment of choice for patients with severe narrowing of the vasculature, between 30 and 50% of patients undergoing the procedure have renewed narrowing of the treated arteries (a process called "restenosis"), within 6 months from the initial procedure and require further interventions. Restenosis is characterized by a thickening of the blood vessel lining due to migration and proliferation of vascular smooth muscle cells and extra-cellular matrix deposition. In an effort to overcome the limitation of balloon angioplasty, physicians often insert metallic stents to physically maintain opening of the vessel in addition to balloon angioplasty, thereby reducing the incidence of restenosis in uncomplicated cases by approximately 10 to 15%.

In a large part due to the above advances in the treatment of cardiovascular disease, there has been an explosion in the market for devices for the treatment of heart disease and restenosis in the last two years. The worldwide market has grown from an estimated U.S. \$200 million in 1994 to U.S. \$1 billion in 1996. This growth has been fueled by the acceptance of stenting as a treatment for cardiovascular disease. Some leading interventional

cardiologists are reporting that more than half of the procedures they perform now involve insertion of coronary stents, up from 20% a year ago, and analysts project compounded annual growth of 30% through to 1999.

Notwithstanding the phenomenal growth in this market segment, even with stenting, restenosis rates continue to be high (between 20 and 30%) and there is keen interest in the development of treatments to further reduce the incidence of this recurrence. The major manufacturers of stents are all interested in identifying agents and developing stent coatings to prevent restenosis after stent insertion. Other companies are working on other approaches to the same problem. Angiotech is developing a paclitaxel stent coating and related treatments to prevent the occurrence of restenosis. The Company believes that paclitaxel is one of the most promising agents for the prevention of restenosis in development today.

(Source: Heart and Stroke Foundation; "Coronary Stents: Breaking J&J's Lock on the Market", Start-Up, Windhover's Review of Emerging Medical Ventures, Vol. 1, No. 1, May 1996, pp. 20-26)

### **Polymeric Drug Delivery Market**

A limiting factor in the clinical utility of many pharmaceuticals is drug delivery. Many agents that show promising biological activity often do not progress to commercialization because of problems of unwanted toxicity, bioavailability, solubility, and the necessity for local, sustained drug concentrations. Many of these factors are tied to drug delivery. The activity of already approved agents can often be enhanced by effective drug delivery vehicles designed to address these problems. For these reasons, and also because some agents that are coming off-patent can have their useful life extended through innovations in formulation, interest in drug delivery within the pharmaceutical industry has been growing steadily.

The drug delivery market includes oral formulations, transdermal techniques, implants, liposomes and other novel systemic treatments. Each of these different technologies will have applicability for different agents and product applications.

Another reason for increased interest in drug delivery is that innovations in drug delivery technologies are often less expensive and less time consuming to develop than new chemical entities. An original pharmaceutical product can cost as much as U.S. \$360 million and 7 to 12 years to develop, while in comparison a new formulation for an existing drug might be developed for as little as U.S. \$10 million over a period of only 3 to 5 years.

In a recent article on drug delivery, MedAd News (August 1994, Vol. 13, No. 10) estimated the 1994 worldwide drug delivery market at approximately U.S. \$4 billion and predicted that the market would expand at an annual rate of 20% to between U.S. \$10 and U.S. \$15 billion by the turn of the century. Of this market, parenteral drug delivery (e.g. liposomes and related technologies) represents approximately 20% of the present market and is expected to expand to between 30 and 35% of the total market by 1998. This projected growth is fueled by the need to increase efficacy (by increasing local drug concentrations) and decrease toxicity (by decreasing systemic drug levels), while at the same time using sustained release to reduce the need for repeated interventions.

Angiotech uses polymeric drug delivery to enhance the performance of its agents. Polymers are repeating units of the same "building block" which are extremely useful for sustained delivery of different types of drugs either quickly or slowly (days or months). Polymers can be biodegradable or not (depending on the requirements of the application) and can be made into various shapes or consistencies (e.g. nanospheres, microspheres, pastes, sprays, meshes, coatings, etc.). Angiotech has successfully incorporated paclitaxel, vanadium compounds and other agents into a variety of polymeric carriers and demonstrated the sustained release of these drugs from the polymeric matrix for periods ranging from days to months. The Company is developing a number of different clinical products based on these formulations.

## TECHNOLOGY AND PRODUCT DEVELOPMENT

### ANGIOTECH'S TECHNOLOGY PLATFORM

#### Background

Diseases such as cancer and arthritis are characterized by two general pathological processes:

- (1) the alteration and transformation of normal cells into abnormal tissues which grow uncontrollably and no longer respond to the body's regulatory signals; and
- (2) the induction of a response from normal cells to the diseased cells located in their immediate environment.

In many pathological conditions, the disease tissue "tricks" the normal surrounding tissue into performing important supporting functions which facilitate disease progression to the detriment of the body as a whole. For example, in both cancer and arthritis, the tumor cells and the pannus tissue (the pathological tissue in rheumatoid arthritis) produce factors that induce normal blood vessels to grow into the tumor/pannus from the surrounding environment (a process called "angiogenesis"). The new blood vessels provide the pathological cells with the nutrients they require to grow and expand; as an example, a tumor cannot grow to a size greater than 2 mm without a corresponding development of blood vessels.

The traditional approach to the treatment of arthritis and malignancy is to focus on eliminating the pathological cells themselves. Tumors are almost always removed surgically, if possible, and then the patient is given chemotherapy and/or radiation to kill any remaining cancer cells. Similarly, rheumatologists have for years sought to cure rheumatoid arthritis (commonly regarded as an immunological disease) through down regulation of the immune system. While this approach has yielded important advances in the treatment of these conditions, a cure based solely on this premise has remained an elusive goal.

Recently, another therapeutic approach has centered on agents which block the inappropriate blood vessel growth found in response to arthritic or malignant changes. Unfortunately, inhibition of angiogenesis alone does not appear to be sufficient to completely reverse or control disease progression, although these agents have shown promise as adjuncts to traditional therapies. To date, no anti-angiogenic treatments have enjoyed a significant commercial impact, largely because the agents developed have been unable to shut down both the upregulated blood vessel growth and the uncontrolled cell proliferation present in diseases such as cancer and arthritis.

The Company's research and development efforts have revolved around agents with the potential to impact on both of these disease parameters.

Although different in many respects, the progression of rheumatoid arthritis ("RA") in affected joints and the growth and spread of cancerous tumors share many common features. The Company's scientists have developed technologies based upon an in-depth understanding of an important biological pathway involved in both cell division and the production of cellular enzymes associated with tissue degradation. The process by which cells divide to increase in number (mitosis) is a critical component of tumor growth, the development of RA and the progression of numerous other chronic inflammatory diseases. Also, in a number of pathological conditions, cells produce enzymes (called proteinases) that digest or break down the components of the tissue (the extracellular matrix) which normally tightly surrounds them. The enzymatic digestion of its surrounding environment allows a growing tumor to spread to adjacent and distant sites (metastasis). In RA and osteoarthritis, one of the proteinase enzymes (called collagenase) is responsible for the digestion of collagen and ultimate destruction of the joint cartilage.



In addition to this, both arthritis and cancer are dependent upon blood vessel growth and are considered to be "angiogenesis dependent" diseases. The process of angiogenesis is itself dependent upon proliferation of its component cells (endothelial cells) and digestion of the surrounding tissue through which the blood vessels must move to reach their target (which, in this case, is an inappropriate one). The Company has exploited the commonality of these otherwise distinct processes to identify agents that target the pathway (the AP-1 pathway) that controls cell proliferation and matrix metalloproteinases ("MMP") production.

## AP-1 Pathway

Angiotech's technology platform consists of intellectual property and expertise in the AP-1 pathway, a biological pathway involved in a variety of cellular responses including cell division and the production of specific proteases involved in the degradation of tissues. Initially, the Company is focusing its efforts on the development of two agents, paclitaxel and vanadium. Where it has been necessary to target these agents for particular indications, polymeric drug delivery vehicles have been designed to facilitate their use in clinical applications.

The AP-1 pathway is illustrated in Figure 1. To summarize, a growth factor or cytokine (such as FGF, IL-1; TNF, a hormone, etc.) binds to a receptor on the cell surface that directs the cell (ultimately) to divide and produce proteinases. The growth factor-receptor binding initiates a cascade of events resulting in the formation of so called "second messengers" (i.e., couriers which relay the signal received at the cell surface to the location in the cell where the message will be processed). In response to these messengers, the cell produces and activates a number of transcription factors.

Two key transcription factors produced are named *c-fos* and *c-jun*, which combine to form a transcription complex, AP-1. Transcription is the process of synthesizing RNA from a DNA template, an essential part of the production of proteins from the genetic code (the end result of the activation of any gene being the synthesis of a protein). Transcription factors are proteins which regulate (usually to promote, but occasionally to inhibit) the transcription of another gene. Many of the messengers that instruct the cell to produce transcription factors have been identified, but those produced downstream closer to the primary gene response (the production of *c-fos* and *c-jun*) are largely unknown. Theoretically, the closer a blockage is prior to the primary gene response, the greater the likelihood that this obstruction will be complete; i.e., the probability that there will be an alternate route to circumvent the blockade decreases as the signal progresses down the pathway.

Angiotech scientists and others have shown that the transcription factors *c-fos* and *c-jun* are required, but not sufficient, for the processes of cell division and the production of digestive enzymes (e.g. collagenase). To phrase this differently, activation of *c-fos* and *c-jun* alone will not produce cell division and enzyme synthesis (i.e., in isolation, they are insufficient to produce this); however, if *c-fos* and *c-jun* are not present, cell proliferation and collagenase production does not occur (i.e., they are required).

A given transcription factor often regulates the transcription of numerous genes and therefore can impact on several cellular responses simultaneously (these subsequent cellular genetic responses to transcription factor activity are called secondary gene responses). It is this type of mechanism which allows the cell to respond to a single stimulus with a variety of different activities. If the signal can be interrupted before it spreads to cause diverse cellular responses (such as cell division and collagenase production), it is possible to obtain multiple effects from a single intervention. Conversely, if one sought to obtain the same results through interruption of the pathway at a later stage (after transcription factor activation), multiple interventions would be required (i.e., cell division and collagenase production would have to be therapeutically targeted independently).

The AP-1 complex is formed when *c-fos* and *c-jun* transcription factor proteins combine (as *jun-jun* or *fos-jun* complexes) to form a molecule which functions to promote one of the final steps in the pathway - transcription of the required genes and initiation of the actual cellular activity which the growth factor instructed the cell to perform (i.e., collagenase production and cell proliferation). Company scientists have discovered a heretofore

unknown property of paclitaxel, the ability to disrupt AP-1 function and thus block collagenase transcription and cell division at the genetic level (Note: paclitaxel has long been known to block cell division as part of its chemotherapeutic activity, but this was thought to be due exclusively to its effect on part of the cell's skeleton called microtubules).

This finding by Angiotech allowed it to be the first to recognize that paclitaxel should be an effective agent in the treatment of other diseases in addition to malignancy, for example RA - a finding which was later confirmed experimentally in animals. It was also demonstrated that paclitaxel was a potent inhibitor of angiogenesis.

## Second Messengers

Angiotech also demonstrated that reactive oxygen species such as hydrogen peroxide are essential second messengers in the pathway prior to the production of *c-fos* and *c-jun* (Figure 1). This permitted the Company and its collaborators to synthesize novel vanadium compounds that interact with hydrogen peroxide and other reactive oxygen species and break them down (into oxyvanadium compounds and hydroxyl free radicals which cannot function as signal molecules); this not only destroys the signal but also produces compounds which are themselves toxic to malignant or diseased cells. Thus, by destroying the message, vanadium can inhibit both cell proliferation and collagenase production and generate cytotoxic effects. The Company's vanadium compounds have demonstrated efficacy in animal models of malignancy and arthritis, with acceptable toxicity to normal tissues and functions.

Angiotech's understanding of the AP-1 pathway is valuable in the Company's anti-cancer indications. In the treatment of malignancy, there is presently a great need to identify agents that work along entirely different biological pathways than traditional drugs. Malignant cells quickly adapt to changes in their environment and are frequently able to develop a mechanism of resistance to a particular chemotherapeutic drug. Agents which have similar activity to the parent drug (so called "me too" drugs) are frequently subject to the same limitations. To counter this, chemotherapeutic agents are often used together in combination, such that each compound targets a different biological pathway. The mechanisms of action of numerous common anti-cancer drugs, in comparison to the Company's agents (vanadium and paclitaxel), are illustrated in Figure 2.

Many chemotherapeutic agents act to disrupt DNA replication via a variety of different mechanisms, others impair the process of cell division and several recently devised therapies alter cell surface events. Angiotech's compounds act to interrupt one of the pathways interspersed between these cellular activities (i.e., they block transmission of an important cell surface message which directs the cell to copy its DNA and divide) in addition to being cytotoxic to the diseased tissue. Used by themselves, Angiotech's compounds might be efficacious in treating certain cancer tumors. Also, because of their unique mechanism of action, Angiotech's compounds also may be complimentary when used in combination with other chemotherapeutic agents.

## Polymer Formulations

The final aspect of Angiotech's technology platform involves the use of polymeric carriers as drug delivery vehicles for the compounds under investigation. The systemic administration of chemotherapeutic agents and their associated toxicity is acceptable in the treatment of malignancy. However, the use of these drugs in nonmalignant disease such as arthritis and restenosis requires that their side effects be minimized. To accomplish this, Company scientists chose polymeric carriers to provide sustained local delivery of its agents in order to increase drug levels at the disease site, while at the same time decreasing unwanted distribution of the drug to other parts of the body. Angiotech's polymeric formulations also eliminate solubilizing agents, such as Cremophor® E.L. (BASF Aktiengesellschaft) (polyethoxylated castor oil), which have significant toxic side effects.

Using the same core technology, the polymer-drug complexes can be formulated into a variety of clinical end products including; (1) intra-articular microspheres, (2) systemic formulations, (i.e., intravenous administration), (3) stent coatings, (4) a surgical paste and (5) ophthalmic preparations. Some of these formulations could be suitable for use with other pharmacologic agents.

## **TAXANES IN ARTHRITIS**

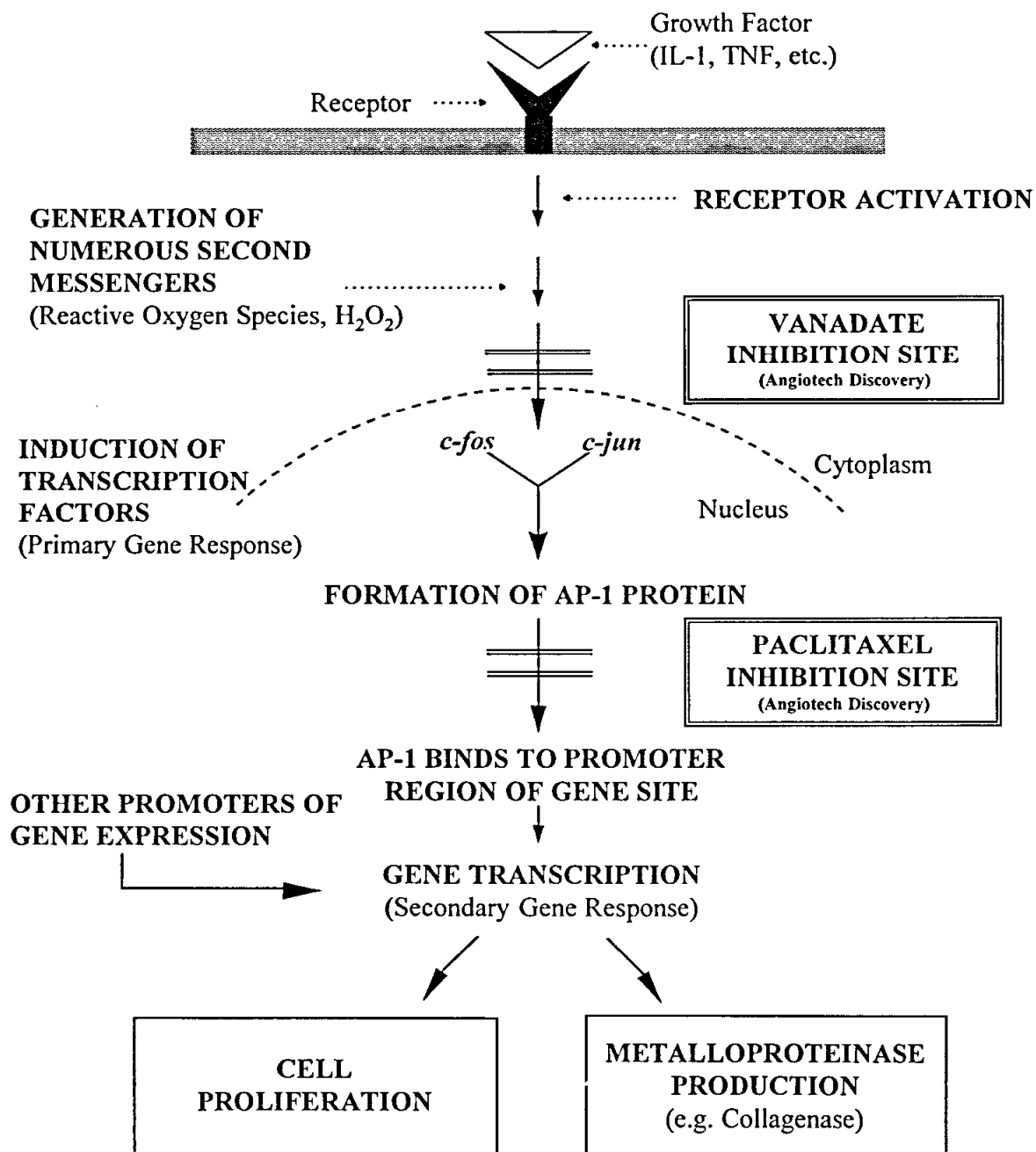
Angiotech and its collaborator Dr. Ernest Brahn (Department of Rheumatology, UCLA, Los Angeles, California) have conducted a series of cell culture and animal studies that have demonstrated the potential of taxanes (paclitaxel and similar compounds) as therapeutic agents in the treatment of RA. These agents are capable of influencing many of the pathological changes considered important to the progression of the disease, including inflammation, proliferation of the cells lining the joint (synoviocytes), collagenase expression and angiogenesis, while at the same time not impairing the normal ability of cartilage to repair itself.

RA is a multisystem, chronic, relapsing, inflammatory disease of unknown cause. During the development of RA, the cells which line the joint capsule (synoviocytes) act like a small tumor within the joint, i.e., they grow uncontrollably, invade surrounding tissues and destroy the joint cartilage they come into contact with. Pathologically, the disease is characterized by a marked thickening and layering of the synovial membrane that extends into the joint space (synovocyte proliferation) and infiltration of this synovial membrane with white blood cells (inflammatory synovitis).

The tissue formed as a result of this process is called pannus and eventually it grows to fill the joint space. The pannus develops an extensive network of new blood vessels (composed of endothelial cells) through the process of angiogenesis, which is essential to the evolution of the joint destruction. The cells of the pannus release digestive enzymes (matrix metalloproteinases such as collagenase and stromelysin) and these enzymes, together with other mediators of the inflammatory process produced by the white blood cells, lead to the progressive destruction of the articular cartilage tissue. The pannus then invades the articular cartilage, leading to erosions and fragmentation of the joint surface. Once the cartilage has been destroyed, the joint damage is considered to be largely irreversible. Eventually, there is erosion of the subchondral bone with fibrous ankylosis and ultimately bony ankylosis of the involved joint (i.e., the joint becomes fused together with little or no capacity for movement).

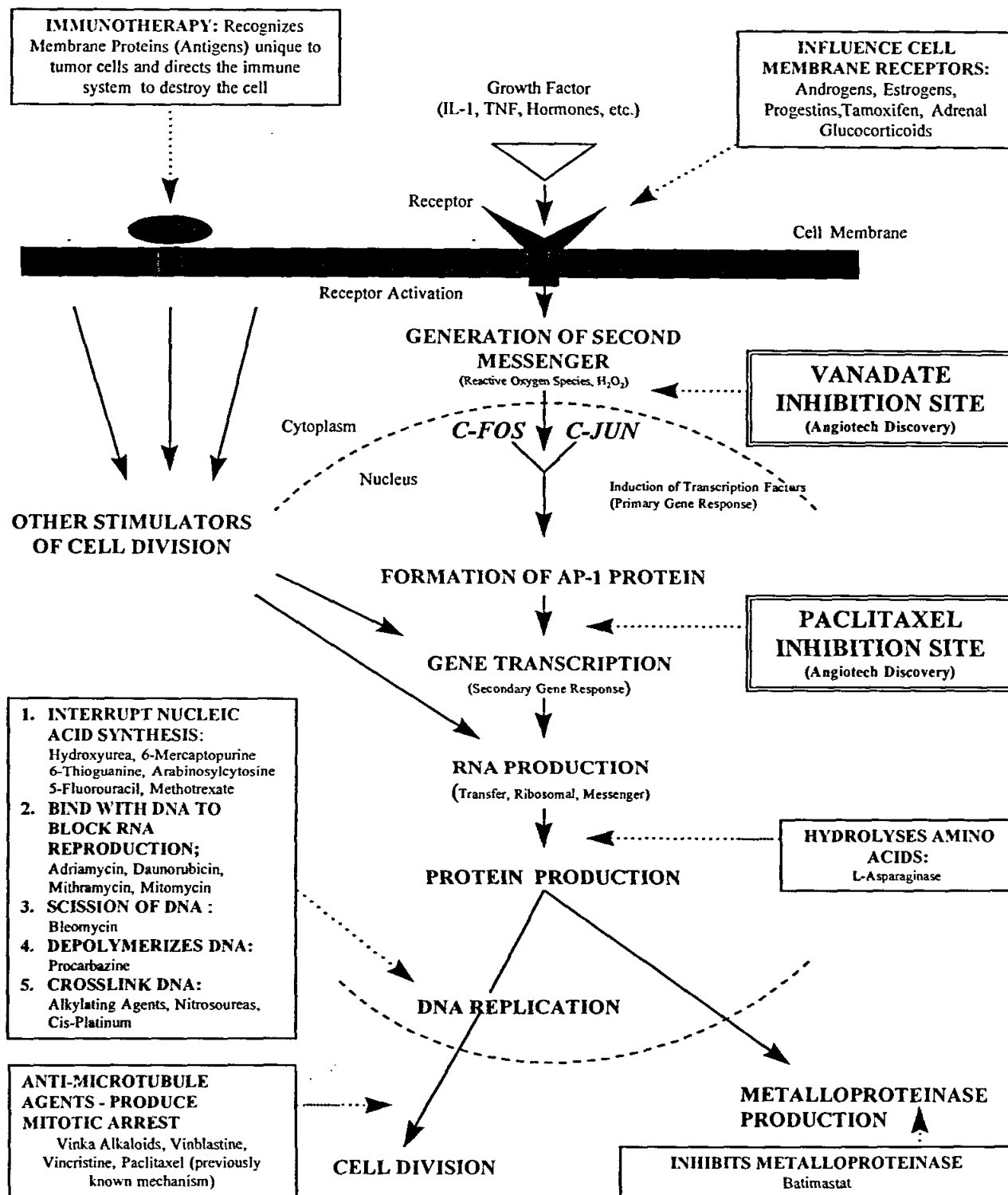
Figure 1

## INHIBITION OF CELL PROLIFERATION AND COLLAGENASE EXPRESSION BY PACLITAXEL AND VANADATE



**Figure 2**

## SITES OF ACTION OF COMMON ANTICANCER DRUGS



Therapies designed for the management of RA generally possess one or more (but not all) of the following activities:

- (1) downregulation of the white blood cell ("WBC") response that initiates the inflammatory cascade and results in synovitis, swelling, pain and tissue destruction (i.e., act as "anti-inflammatory" agents);
- (2) inhibition of the "tumor-like" proliferation of synoviocytes that leads to the development of a locally invasive and destructive pannus tissue;
- (3) blocking the process of angiogenesis which provides the framework and supplies the nutrients necessary for the growth and development of the pannus tissue;
- (4) decreasing the production/activity of matrix metalloproteinases (e.g. collagenase) produced by WBC's, synoviocytes, chondrocytes and endothelial cells which degrade the cartilage matrix and result in irreversible destruction of the articular cartilage; and
- (5) obtaining desired pharmacological activity without toxicity to existing chondrocytes (cartilage cells) or impairing the normal production of cartilage matrix components (which form the bulk of the cartilage tissue).

Angiotech's original premise for developing a treatment for RA was to screen anti-cancer agents (which are designed to inhibit cell proliferation and frequently disrupt WBC function) for anti-angiogenesis activity; i.e., a drug with these properties would already possess 3 of the 5 disease modifying activities described above. A vast array of drugs were screened. Paclitaxel, surprisingly, was by far the most potent. In fact, the Company discovered that paclitaxel is a more potent inhibitor of angiogenesis than any previously reported compound, an activity which had not been recognized previously.

By conducting a series of *in vitro* and *in vivo* studies, the Company then discovered that paclitaxel was effective in altering all 5 of the above disease parameters. The Company discovered that:

- (1) **Paclitaxel Has Anti-Inflammatory Activity.** Paclitaxel is recognized to be an effective functional inhibitor of cellular structures known as microtubules. Microtubules act as a supporting "skeleton" for the cell and as such, are required for a variety of cellular activities, including cell movement, cell division and the transport and secretion of a variety of cell products (including proteinases). Since many of these activities are important to the normal functioning of WBC, it was hypothesized that the drug could have some anti-inflammatory properties. Paclitaxel has been demonstrated *in vitro* to be an inhibitor of several important aspects of neutrophil (a type of WBC) function, including the disruption of signal transduction, cell structure and cell function, all of which involve microtubule control and play a role in the generation of reactive oxygen species and proteinases. It also suppresses lymphocyte (another WBC involved in the pathology of arthritis) cytotoxic function without being directly lethal to the lymphocytes themselves. Furthermore, it acts to decrease these WBC activities regardless of the stimulus which is responsible for triggering the inflammatory response. The data resulting from these studies support the concept that paclitaxel may offer anti-arthritic properties via its inhibitory action on WBC function and inflammation.
- (2) **Paclitaxel Inhibits Synoviocyte Proliferation.** Paclitaxel is capable of inhibiting proliferation of synoviocytes *in vitro* and inducing apoptosis (programmed cell death) at concentrations as low as  $10^{-7}$  M, and is cytotoxic lethal to the synoviocytes at slightly higher concentrations of  $10^{-6}$  to  $10^{-5}$  M. Similar concentrations do not produce any effect in chondrocyte cultures, i.e., non-proliferating cartilage cells. Given the role of synoviocytes in the development of pannus tissue and their malignant behavior during the pathogenesis of RA, blocking synoviocyte proliferation and inducing apoptosis could be expected to favorably affect the outcome of the disease *in vivo*.
- (3) **Paclitaxel Is A Potent Angiogenesis Inhibitor.** Paclitaxel has shown strong anti-angiogenic activity when tested in the chorioallantoic membrane ("CAM") of the developing chick embryo (a model assay for studying the stimulation and inhibition of angiogenesis). Paclitaxel produced a dose-dependent inhibition of angiogenesis at doses as low as 0.5  $\mu$ g, which is significantly lower than other well documented anti-

angiogenic agents. Many approved anti-arthritis agents have anti-angiogenic properties (e.g., methotrexate, penicillamine, steroids) and comparison of these agents to paclitaxel in CAM studies has indicated that paclitaxel is a more potent inhibitor of angiogenesis.

- (4) **Paclitaxel Inhibits Collagenase Production By Chondrocytes *In Vitro*.** Concentrations of  $10^{-7}$  M of paclitaxel reduced collagenase expression by over 50% in cultured chondrocytes. This inhibition occurs downstream from the transcription factor activity of *c-fos* and *c-jun*, apparently by disrupting the normal functioning of the AP-1 molecule, resulting in inhibition of transcription of the collagenase gene (Figure 1). As such, inhibition of collagenase secretion by paclitaxel is not strictly due to interruption of the protein secretory pathway which is dependent upon microtubule function for the movement of secretory granules. Paclitaxel also appears to act at the level of the genetic response to stimuli directing the cell to produce collagenase. Regardless of the mechanism of action, paclitaxel is capable of inhibiting collagenase production by at least one cell type known to produce this enzyme *in vivo*, and given the importance of collagenase in the destruction of articular cartilage, this effect could be expected to improve disease outcome. Tumor necrosis factor ("TNF") and interleukin-1 ("IL-1") are important to the progression of both RA and osteoarthritis; the ability to block their influence on cellular function and collagenase production is considered to be important in altering disease progression.
- (5) **Paclitaxel Is Not Toxic To Normal Chondrocytes.** It is critical that agents that possess anti-arthritis properties (i.e., are toxic to the pannus tissue) are not detrimental to the normal cartilage chondrocytes, as this would hasten the destruction of the articular cartilage and lead to progression of the disease. When chondrocytes were incubated in the presence or absence (control) of paclitaxel for 72 hours, it was observed that even at concentrations greater than those required to block the pathological processes described above ( $10^{-5}$ M), paclitaxel was not toxic to chondrocytes *in vitro*. In addition, examination of paclitaxel-treated chondrocytes by DAPI staining and DNA fragmentation studies did not show evidence of apoptosis in these cells. The Company's data have also shown that paclitaxel is capable of partially reversing IL-1 induced inhibition of aggrecan production by chondrocytes. Aggrecan is an important structural molecule in cartilage tissue. As part of the arthritic process, production of this molecule by chondrocytes is significantly decreased in response to IL-1. This weakens the cartilage tissue and makes it more susceptible to destruction by the cells of the pannus tissue. Paclitaxel does not enhance the inhibition of cartilage matrix synthesis (as seen with many anti-arthritis agents) and is effective in protecting the cartilage tissue from the destructive effects of cytokines produced during the inflammatory cascade.

### **Paclitaxel Significantly Reduces RA in an Animal Model of the Disease**

Dr. Ernest Brahn of the Department of Rheumatology at UCLA has demonstrated the ability of a polymeric paclitaxel formulation administered systemically to substantially reduce the development and progression of inflammatory arthritis in a rat model of RA (known as collagen-induced arthritis or "CIA"). Paclitaxel reduced swelling, redness and warmth of arthritic joints, all clinical indicators of the degree of joint inflammation. Paclitaxel treatment also significantly reduced joint destruction as measured by radiographic evaluation of treated and untreated arthritic animals at doses significantly lower than are required to treat malignancy. In fact, the majority of paclitaxel treated animals were judged to have radiographically normal joints by experts blinded to treatment groups. Using a standard scoring system designed to evaluate the severity of the disease, untreated animals were scored as a "6", while paclitaxel treated animals were an almost normal "2". The Company believes this is a very significant response in this disease model as the results significantly exceed those obtained with methotrexate, the most widely prescribed disease-modifying drug for RA.

### **Proposed Use of Paclitaxel in the Treatment of Human Arthritis**

One major drawback to the systemic (intravenous) administration of the currently marketed formulations of paclitaxel is that it is frequently associated with several important side effects and severe allergic reactions.

Paclitaxel administration is associated diarrhea, neutropenia (leading to an increased susceptibility to infection), hair loss, weight loss and peripheral neuropathy, while the agent Cremophor used to solubilize the drug for intravenous use often causes severe allergic reactions and requires pre-medication.

To avoid these complications, the Company has developed and is first evaluating a polymeric paclitaxel formulation to be injected directly into affected joints (intra-articular administration). The advantage of using polymeric drug delivery is that it can be used to attain relatively high drug levels at a specific disease site through local administration of a total dose lower than that required to achieve similar levels via systemic administration. A second advantage of polymeric drug delivery is that the therapeutic agent is released gradually over a period of time (ranging from days to weeks depending on formulation) covering the active phase of the disease. As many of the side effects of paclitaxel are due to effects on tissues which are not a therapeutic target in arthritis (gut, skin, bone marrow), local administration has definite advantages. Also, intra-articular injection is a commonly practiced office procedure used to effectively deliver therapeutic agents to a variety of joints. Systemic uptake of drugs from the joint space (i.e., the amount of drug which will find its way into the bloodstream and be distributed to the rest of the body) after intra-articular injection is often only a fraction of the total dose administered; this should further reduce the potential toxicity of paclitaxel on other body organs.

The Company has successfully incorporated paclitaxel into polymeric microspheres (ranging in size from 0.1 to 100  $\mu\text{m}$ ), which release the drug for a prolonged period of time (weeks to months *in vitro*). Biodegradable polymers have significant potential as drug carriers for this application *in vivo*, since these polymers undergo hydrolytic or enzymatic degradation leading to erosion and complete degradation of the polymer. Presently, pre-clinical animal studies are underway at Mount Sinai Hospital in Toronto using a recognized small animal model of RA. Additional work is being conducted at UCLA using a second model of the disease.

By utilizing a potential disease-modifying agent like paclitaxel in combination with a sustained-release polymer, the Company believes it is possible to produce a formulation which is:

- (1) fully biodegradable;
- (2) contains an effective therapeutic agent(s) at the appropriate drug dose;
- (3) features release kinetics that reduce the need for repeated interventions; and
- (4) has minimal side effects.

The Company hopes to advance this formulation into human studies by the end of 1996. The Company is also developing a systemic paclitaxel formulation as a second generation mode of therapy and hopes to advance it into human clinical studies during 1997.

## STENT COATING

### Scientific Overview

Stents are hollow cylindrical devices inserted into a bodily duct or tube to prevent compression or occlusion of that tube. Stents are produced in a collapsible form which can be inserted through catheters. The catheters are advanced across the blockage and then expanded in place to provide an unobstructed passage (a "tube-within-a-tube"). Unfortunately, stents are often overgrown by inflammatory tissue or tumor cells and this limits the duration and effectiveness of the treatment. Stent overgrowth results in an incorporation of the stent within the vessel wall, thereby causing a narrowing of the stent lumen and a shortening of the effective lifespan of the device. Coating endoluminal stents with a paclitaxel-polymer compound could prevent overgrowth (either benign or malignant) and increase its efficacy and duration of clinical effectiveness.



In malignant overgrowth, paclitaxel should have a direct cytotoxic effect on the tumor cells themselves, while inhibiting vascularization of the tumor (which often requires lower paclitaxel levels), limiting any mass capable of growing on the stent surface to a thickness of less than 2 mm.

In benign overgrowth, the ability of paclitaxel to inhibit angiogenesis, inflammation, cell division and cell migration will restrict the development of restenosis. As such, a coated stent would be useful in diseases that obstruct bodily ducts and vessels, such as cancer of the bile duct, esophageal cancer, pancreatic cancer and arteriosclerosis.

Paclitaxel has been successfully incorporated into a polymeric coating suitable for stents and other medical devices. Unlike the arthritis formulations and the surgical paste, which use a biodegradable polymer, the stent coating is composed of a non-biodegradable polymer plastic (EVA - ethylene vinyl acetate) which is designed to provide localized, sustained delivery of the drug over an extended period of time (months). For some applications, a non-degradable stent coating can provide an additional physical barrier to malignant cell ingrowth of a stent. The elastic nature of the EVA polymer is ideal because it binds to the stent surface and ensures the stability of the coating during stent deployment and during subsequent movements *in situ* (in the patient).

The stents are coated with a polymer-drug combination consisting of 66% EVA and 33% paclitaxel by weight. Although the amount of paclitaxel loaded on to a stent can vary, the total amount of drug contained in the device, even if released completely at one time, would not begin to approach the amount of drug given to a patient as a single intravenous dose in a traditional chemotherapeutic regimen. The standard chemotherapeutic dose of paclitaxel given as a three-hour infusion in the treatment of patients with advanced breast cancer is approximately 175 mg/M<sup>2</sup> (about 200-250 mg in an average patient) repeated every three weeks. By way of comparison, only 100 mg of paclitaxel (and no Cremophor) is loaded onto a typical esophageal stent and less than 1 mg is loaded onto a vascular stent. Therefore, the total amount of paclitaxel administered should be much lower than doses presently used in patients.

*In vitro* testing of the paclitaxel stent coating revealed a slight burst phase of drug release in the first few hours followed by a very steady and slow release of paclitaxel thereafter. Approximately 10% of the total amount of paclitaxel incorporated into the coating is released within the first six days.

To assess the anti-angiogenic properties of the paclitaxel-loaded stent coating, the formulation was tested on the CAM assay as described previously. A stent coating suspension containing paclitaxel at concentrations of 2.5%, 10% and 33% was sprayed onto stent tines and placed onto the developing capillaries of the CAM. In each instance, an avascular zone was induced in the vicinity of the paclitaxel stent tines.

The formulation was also assessed for *in vivo* efficacy in the porcine bile duct model of benign epithelial overgrowth. In this study, paclitaxel-coated stents were assessed for their ability to prevent reactive epithelial tissue from growing within the stent and obstructing the lumen. Stainless steel stents coated with 33% paclitaxel-loaded EVA polymer were placed into the biliary duct of microswine and the animals were sacrificed and examined at different time intervals post-insertion. The paclitaxel-loaded stent coating prevented benign epithelial overgrowth in the microswine biliary duct when compared to control stents.

### **Proposed Human Use of Paclitaxel-Coated Stents**

The Company's first clinical study employing paclitaxel-coated stents will be for the palliative treatment of esophageal cancer. During the summer of 1996, two patients were treated on a compassionate use basis at the University of British Columbia Hospital. No adverse reactions have been noted.

A formal study has been organized and is scheduled to begin in late 1996 at Guy's Hospital in London, England under the direction of Dr. Andy Adam, a leading European interventional radiologist.

## VANADIUM COMPOUNDS IN CANCER

### Scientific Overview

As described previously, the Company has investigated the importance of a particular pathway leading to cell division and the production of proteinases. The transcription factors *c-fos* and *c-jun* are involved in, and required for, the induction of genes involved in cellular proliferation and collagenase production. These two cellular functions are considered to be essential for both tumor growth and distant spread of malignant disease. Company scientists noted that hydrogen peroxide and reactive oxygen species were essential second messengers in the AP-1 pathway prior to the production of *c-fos* and *c-jun* (Figure 1). They recognized that vanadium compounds would interact with hydrogen peroxide and reactive oxygen species to break them down into oxyvanadium compounds and hydroxyl free radicals, which cannot function as signal molecules, thus destroying the signal and producing compounds which are themselves toxic to malignant or diseased cells. As a result of destroying the message, vanadium can inhibit both cell proliferation and collagenase production.

Angiotech's researchers and collaborators have created novel vanadium complexes that are cytotoxic to tumor cells at micromolar concentrations *in vitro* and can produce significant anti-tumor activity in animal models of malignancy. Orthovanadate and several other vanadium complexes are highly toxic to proliferating cell lines (both tumor cells and normal cells) but not to non-proliferating cells *in vitro*. Vanadium compounds at micromolar concentrations are cytotoxic *in vitro* to a variety of human tumor cell lines including cancer cells which are resistant to other chemotherapeutic agents. This suggests that orthovanadate is acting through a mechanism which is distinct from some other anticancer drugs (Figure 2).

In an animal model of malignancy, Angiotech researchers have demonstrated that vanadium complexes can provide effective anti-tumor activity. Subcutaneous administration of orthovanadate (500µg daily) to mice bearing solid tumors resulted in tumor growth inhibition (80-95% reduction in growth), complete elimination of detectable tumor in some animals (20-30% of those treated) and evidence of decreased metastatic spread of disease. Other vanadium compounds, including some proprietary agents have shown even greater anti-tumor activity and less toxicity.

There is a positive association between tumor aggressiveness and the ability of the cells to produce matrix metalloproteinases (such as collagenase) which contribute to the invasive process. Inhibition of these proteinases has been shown to prevent or reduce invasion and metastases. As described previously, vanadate compounds can reduce collagenase production through inhibition of *c-fos/c-jun* production. This suggests that vanadate might be capable of reducing the metastatic potential of some cancer cells via inhibition of collagenase and other matrix metalloproteinase.

In the Company's opinion, studies conducted to this point suggest that vanadium complexes may represent a new class of anti-cancer agents with novel mechanisms of action. Several features of these compounds indicate potential clinical usefulness in the treatment of malignancy, including:

- (1) Vanadium compounds appear to have a different mode of action that involves the suppression of *c-fos* and *c-jun*, the two transcription factors which are required for cell proliferation and tumor growth (a comparison to traditional chemotherapeutic agents is provided in Figure 2).
- (2) Vanadium compounds act on some cell lines which are resistant to conventional chemotherapeutic drugs such as colchicine, vinblastine and doxorubicin, indicating that these agents may be useful for the treatment of drug resistant tumors. Further, these data appear to indicate that certain mechanisms which normally expel chemotherapeutic agents from cancer cells may not recognize vanadium compounds.
- (3) Vanadium compounds are potent inhibitors of matrix metalloproteinases which are involved in tumor metastases. Thus, these compounds are not only cytotoxic to cancer cells, but may be able to prevent cellular invasion and colony formation.

- (4) Vanadium complexes not only inhibited tumor growth *in vivo*, but also eradicated tumor in some treated animals.

The Company expects to identify a specific vanadium drug candidate by early 1997 and to complete preclinical studies by the end of 1997. Commencement of human studies could begin in early 1998.

## **POLYMERIC DRUG DELIVERY FOR THE TREATMENT OF DISEASE**

### **Scientific Overview**

Currently, paclitaxel has demonstrated significant activity in clinical studies against a variety of human tumors, including ovarian carcinoma, breast carcinoma, esophageal adenocarcinoma, malignant melanoma and leukemia's. Although paclitaxel has shown activity against many human tumors, like most chemotherapeutic agents, clinical use of the agent is associated with several toxic side effects. Because of paclitaxel's poor water solubility, systemic administration of this drug depends upon concomitant use of Cremophor to produce an adequately soluble formulation. Unfortunately, Cremophor use is also associated with patient toxicity, is not well tolerated and leads to hypersensitivity reactions in some individuals. To overcome these difficulties, clinicians have attempted to prolong infusion schedules or use corticosteroids and antihistamines as a part of a premedication regimen. However, to improve the efficacy of paclitaxel in anti-cancer therapy, reformulation of the drug into better tolerated drug delivery vehicles appears advisable.

Additionally, in order to use paclitaxel as an agent for the treatment of nonmalignant disease, formulations must be created which deliver sufficient drug levels to the disease site without causing unwanted toxicity in both surrounding and distant normal tissues. While a certain degree of toxicity is acceptable for use in the cancer patient, it would be intolerable to a patient with arthritis, cardiovascular disease or macular degeneration. To prevent these potential problems, Angiotech has focused on the use of polymeric drug delivery to produce sustained, site-specific targeting of paclitaxel. In angiogenesis-dependent diseases, localized delivery of paclitaxel leads to inhibition of unwanted blood vessel growth, inhibition of cellular proliferation and disease modification using lower drug doses .

Dr. Helen Burt (Department of Pharmaceutical Sciences, University of British Columbia), in collaboration with the Company, has spent several years encapsulating paclitaxel, vanadium compounds and other agents into polymeric carriers for a variety of applications. These formulations offer several potential advantages, including:

- (1) increased solubility of paclitaxel;
- (2) sustained release of therapeutically effective amounts of drug for periods extending from days to months beyond the administration time;
- (3) elimination of the use of Cremophor as a solubilizing agent for paclitaxel and its associated toxicity;
- (4) localized drug delivery to the disease site through minimally invasive interventions; and
- (5) reduced non-target organ toxicity by decreasing the total amount of drug administered and limiting its distribution.

The main principle behind this delivery approach is to increase efficacy (by increasing local drug levels) and decrease toxicity (by decreasing systemic drug levels), while at the same time reducing the need for repetitive interventions through sustained drug release. The formulations can be manipulated to encapsulate a variety of drugs, release them quickly or slowly, be biodegradable or non-degradable and be made into various shapes or consistencies (i.e., micelles, microspheres, pastes, sprays, meshes, coatings, etc.) - all utilizing the same basic core polymer technology.

The polymeric formulations developed by Angiotech include:

- (1) polymeric microspheres for use in inflammatory arthritis;
- (2) highly soluble polymeric micelles for systemic administration in arthritis and other diseases;
- (3) stent coatings, to prevent overgrowth by tumors and neointimal hyperplasia; and
- (4) a surgical paste, initially for use in superficially accessible disease and eventually for intralesional application at tumor resection sites.

In each formulation, paclitaxel (an approved chemotherapeutic drug with known toxicity and efficacy profiles) is encapsulated in polymers currently being used in human applications and the total drug dosage given is lower than that currently given to patients in a single intravenous administration for chemotherapy.

## **SURGICAL PASTE**

### **Scientific Overview**

Local recurrence of malignancy at or near surgical excision sites poses a significant clinical problem in cancer patients. Of those patients who present with localized disease (no evidence of metastatic spread), the primary treatment for the vast majority is to remove the tumor mass surgically. Of those patients whose disease is potentially "curable" by surgery, it is estimated that 32% will suffer a recurrence of their malignancy; of these patients, 66% will relapse due to local recurrence of the tumor (or 21% of "curable" patients) versus only 34% (or 11% of "curable" patients) who will relapse due to distant metastatic spread of the disease.

Local recurrence generally occurs at or near the previous surgical excision site, with 90% of all local recurrences located within a 2 cm margin of the primary tumor. A chemotherapeutic paste applied locally during tumor resection surgery could potentially have a wide range of applications in malignancies where local recurrence is a prominent clinical problem.

Angiotech has developed a paclitaxel-loaded polymeric surgical paste designed to provide a sustained release of the drug at the tumor site in an effort to reduce local recurrence and to decrease the need for adjuvant cancer therapy (local radiation and systemic chemotherapy). This treatment could potentially be useful for treating breast cancer, head and neck cancer, tumors of the central nervous system, colon cancer, hepatic malignancy and others.

Surgical paste utilizes a biocompatible, biodegradable polymer. This polymer has been previously investigated for a variety of medical applications and is characterized by its low melting point (50°C). The surgical paste is melted by heating it to slightly above body temperature and delivering it by injection or topical application directly to the tumor resection site. The paste solidifies at 37°C to form a solid implant conforming to the surgical wound or injection site. The polymer-paclitaxel implant then gives a sustained release of drug over a period of time until the polymer degrades completely. Increased paclitaxel levels are maintained in the region of the implant and nonspecific drug targeting to distant sites is reduced. Since Cremophor is not required for this formulation, the toxic side effects attributable to this agent are eliminated.

In addition to the uses outlined above, the surgical paste may also be useful for the treatment of superficial predominant disease, such as superficial chest wall disease in breast cancer patients, recurrent head and neck carcinoma, Kaposi's sarcoma, malignant melanoma and peripheral vascular disease. In these applications, the surgical paste could be applied externally to the lesions (or injected intralesionally) to release paclitaxel locally and induce disease regression.

## **COMPETITIVE ADVANTAGES**

Angiotech's unique approach to the treatment of cancer, arthritis and other diseases characterized by unwanted cell proliferation and inappropriate blood vessel growth is described in detail in the previous section titled "TECHNOLOGY AND PRODUCT DEVELOPMENT". Angiotech management believes that this approach to

disease and the core technology used by Angiotech to develop its clinical products represent significant advantages over competing companies.

While the traditional approach to these diseases has been to therapeutically target the pathological tissue and, more recently, block inappropriate body responses to disease (such as angiogenesis), Angiotech's research and development programs have focused on agents with the potential to impact both of these processes. It is Angiotech's belief that this approach will allow for the development of products which will favourably impact on diseases such as cancer and arthritis to a greater extent than traditional approaches have done to date. Angiotech is presently unaware of any other companies that take this approach to these diseases.

Angiotech's detailed knowledge of the biological pathway that leads to cell proliferation and the production of proteinase enzymes has already led to the identification of previously unknown properties of paclitaxel. Angiotech has also identified vanadium compounds as a potential new class of anti-proliferative agents. Angiotech will continue to exploit this knowledge to identify and develop agents that function along this pathway and to identify new uses for the agents it has been working with to date.

The ability to screen a large number of agents in a cost effective manner for activity along this pathway represents a significant opportunity for the Company. The knowledge of the pathway and the mechanisms of action of its agents will also be an advantage when the Company's products enter the regulatory environment. Once agents are identified as having this biological activity, there is a potential for applying these agents to multiple diseases due to the fact that the pathway is of key importance in cancer, arthritis and a number of other conditions.

With respect to paclitaxel, the identification, by the Company, of the potential of this agent in the treatment of diseases other than malignancy, (in particular in arthritis, a U.S. \$16 billion worldwide market; the disease modifying sector being approximately U.S. \$500 million) represents potential market extension for an agent in which a large number of companies already have a vested interest. These include Bristol-Myers Squibb Co., Rhône Poulenc Rorer Inc., American Home Products (and their development partner Hauser), NaPro Biotherapeutics Inc. (and their development partners Ivax and F.H. Faulding), Phytogen Life Sciences Inc. (and their marketing partner Mylan Laboratories Inc.) and others. Because the Company has discovered and developed the field of paclitaxel (and analogues thereof) in the treatment of conditions other than malignancy, it is the Company's belief that any company planning to extend the use of paclitaxel to arthritis and other angiogenesis dependent diseases will be required to enter into negotiations with Angiotech.

Vanadate's unique activity in blocking cell proliferation and the production of proteinase enzymes (such as collagenase) at a unique point in their biological pathway means that vanadium compounds represent a potential new weapon against cancer (Figure 2). As this pathway is also common to other proliferative disorders, vanadium compounds also have potential in a broad range of other diseases, including arthritis.

Paclitaxel and vanadium compounds exert their effects prior to the transcription of the genes that lead to cell proliferation and the production of digestive enzymes such as collagenase. As a result, Angiotech's agents act to inhibit the production of enzymes such as collagenase. This is a distinct advantage over those companies that seek to favourably impact disease by developing agents known as "TIMP's", or tissue inhibitors of matrix metalloproteinases (collagenase is a matrix metalloproteinase), which seek to inactivate these destructive enzymes after they have been produced and released from the cell.

By way of example, every hour during a rheumatoid arthritis flare, upwards of 2 million inflammatory cells enter each affected joint. These cells produce many of the digestive enzymes that break down the cartilage in the joint. TIMP's act to chemically bind one to one to the matrix metalloproteinase enzymes that are produced by these cells to neutralize their activity. Unfortunately, this does not stop the continued infiltration of inflammatory cells into the joint, or decrease the number of synoviocytes or endothelial cells (the cells which compose the angiogenic blood vessels) which also produce the enzymes. By contrast, Angiotech's agents downregulate the inflammatory

response and eliminate proliferating cells, so there are both fewer cells present to produce enzymes and those cells remaining are inhibited from producing the digestive enzymes.

The drug delivery systems and expertise developed by Angiotech and its collaborators allow the Company to be innovative and expand uses for its proprietary agents and other agents. Drug delivery is a major challenge for many compounds, particularly compounds such as paclitaxel which are highly water insoluble. Polymeric delivery is a new field and there are relatively few companies working in this area. The Company believes that the drug delivery expertise and the drug delivery systems developed represent additional commercial opportunities for Angiotech as its business progresses.

## **COMMERCIALIZATION AND LICENSING STRATEGY**

The current environment in the health care industry is one in which there is an increased reliance and interaction between large pharmaceutical companies and research and development companies such as Angiotech. Large pharmaceutical companies must feed their product pipelines and more and more are looking to the biotech industry as a source of innovative new product opportunities. Biotech companies have shown their ability to innovate and complete initial product development quicker and more cost effectively than large pharmaceuticals. On the other hand, large pharmaceutical companies have the financial capability and infrastructure to advance promising products through the regulatory environment and to market the products once approved.

Recognizing these realities, Angiotech's focus is on its strength in research and development and it will rely on partnerships and collaborations to support its efforts once they have reached an appropriate stage. Just as Angiotech believes it sources the best possible scientists and facilities to complete development and clinical trials for its products, it will also seek out industry leaders at appropriate times to expedite regulatory approvals and the commercialization of its products. As indicated above, these companies have the infrastructure in place to complete late stage clinical trials, seek regulatory approval and market Angiotech's products effectively and quickly. Indeed, these companies have a need for products to support their large marketing infrastructure.

Angiotech has structured its company with this strategy in mind. The Company has chosen products and technologies that will be attractive to potential partners (these products address indications that are greatly underserved or for which there are few effective treatments, they represent a new approach to disease and, in the case of the paclitaxel applications, they represent an opportunity for product expansion). Angiotech believes that its products and organization will be attractive to potential partners for these reasons.

## **MANAGEMENT AND SCIENTIFIC PERSONNEL**

### **ORGANIZATION**

People and relationships are in many respects as important to a company as is its technology. Effective management provides direction, leadership, organization, financing opportunities, strategic partnering and commercialization strategies. A well designed scientific and development team takes good science and commercializes it. Relationships with business, financial and scientific personnel and institutions allow management and scientists to leverage existing expertise and provide additional opportunities and direction.

Angiotech is fortunate to have assembled experienced management and scientific teams (which very much includes the members of the Clinical Advisory Board and other collaborators). Management of Angiotech recognizes the need for swift commercialization of its technologies and has expertise in medical research and development, clinical medicine, business and corporate finance, as well as exceptional relationships and contacts in the health care and securities industries. Management knows the course to commercialization of its technologies and products and is directing the Company toward its goal of being a leader in the treatment of angiogenesis dependent diseases.

## MANAGEMENT

Management views itself as stewards of the business and technologies being developed by Angiotech, and actively looks for ways to accelerate development and commercialization while at the same time building value for its shareholders.

The following people comprise Angiotech's management team:

***Robert T. Abbott, PH.D., MBA., President and CEO, and Director***

Dr. Abbott became the President and CEO of the Company effective January 1, 1996. He has held numerous senior positions with biotech companies in the United States, including President and CEO of Viagene Inc. of San Diego, California and Director, President and CEO of NeoRx Corporation of Seattle, Washington. Dr. Abbott was also a founder of NeoRx. Dr. Abbott received his B.Sc. in biochemistry and genetics (McGill University), a Ph.D. in pathology (McGill University) and an M.B.A. in marketing (University of Missouri). Dr. Abbott is a resident of Surrey, B.C.

***William L. Hunter, M.D., Chief Scientific Officer, Director and Chairman of the Board***

Dr. Hunter is a founder of Angiotech and has been a member of the scientific and management teams of the Company since its formation in the fall of 1992. Dr. Hunter earned his B.Sc. degree from McGill University, a M.Sc. degree (focus on angiogenesis) and a M.D. from the University of British Columbia. Dr. Hunter continues to practice medicine. Dr. Hunter is responsible for directing the scientific efforts of the Company. He is also a principal inventor and author of the Company's patent applications. Dr. Hunter is a resident of Vancouver, B.C.

***Donald E. Longenecker, Ph.D., Chief Operating Officer***

Dr. Longenecker has over 25 years of experience with large and mid-sized drug companies, biotechnology companies and the FDA, including Senior Vice President of Viagene Inc. of San Diego, California and Vice President, Operations and Director, Regulatory Affairs of NeoRx Corporation of Seattle, Washington. Dr. Longenecker received his M.Sc. and Ph.D. in Reproductive Physiology from the University of Missouri and his B.Sc. in Animal Science from Iowa State University. Dr. Longenecker is responsible for overseeing internal operations. Dr. Longenecker is presently a resident of San Diego, California, however, he will be relocating to Vancouver around October 1, 1996.

***Jefferson Works, M.B.A., consulting Chief Financial Officer***

Mr. Works has extensive experience in the finance and biotech industries, most recently as Vice President and Chief Financial Officer of Viagene Inc. from 1991 to 1995 and Senior Vice President and Chief Financial Officer of Cetus Corporation from 1990 to 1991. Mr. Works received his B.A. and M.B.A. from the University of California at Berkeley and is a Certified Public Accountant. Mr. Works acts as a consultant to the Company on all of its financial affairs. Mr. Works is a resident of Medford, Oregon.

***Kennith A. Mellquist, LL.B., Vice President***

Mr. Mellquist has been an executive with Angiotech since the Company's formation in the fall of 1992 and was named President in the summer of 1993 (a position he vacated with the hiring of Dr. Abbott). Mr. Mellquist is a lawyer by training whose expertise is in the establishment and organization of new enterprises, including business structure, intellectual property protection and negotiation of collaboration, licensing, joint venture and technology transfer agreements. Mr. Mellquist practiced law prior to becoming the Corporate

Counsel and part of the management team of ID Biomedical Corporation. Mr. Mellquist is a resident of Lion's Bay, B.C.

***Anthony Cruz, Ph.D., Vice President - Science and Director***

Dr. Tony Cruz is an Associate Professor at the University of Toronto and a Senior Staff Scientist at the Samuel Lunenfeld Research Institute at Mount Sinai Hospital in Toronto, and one of the Principal Scientists of the Company. Dr. Cruz leads the Company's work in cell biology and cancer therapeutics. Dr. Cruz is resident in Toronto, Canada.

***David M. Hall, B.A., B.Comm., Vice President - Finance***

Mr. Hall is Vice President - Finance, Secretary and Treasurer of Angiotech. He has been an officer of the Company since the spring of 1994. Mr. Hall was previously the Corporate Development Officer for IDB. He has worked as an institutional research analyst and corporate financier for a national institutional brokerage company and as an equity portfolio manager for a large Canadian insurance company. Mr. Hall is responsible for the financial and securities regulatory affairs of the Company, communicating with the brokerage industry, financial partners and shareholders and raising capital on behalf of the Company. Mr. Hall is a resident of Vancouver, B.C.

***Sheryl Osborne, Vice President - Regulatory Affairs and Clinical Development***

Ms. Osborne became the Vice President, Regulatory Affairs and Clinical Development of the Company effective January, 1996. Ms. Osborne has held numerous senior positions with biotech companies in the United States, including Director, Regulatory and Clinical Affairs at Chiron-Viagene Inc. (1995 to January 1996), Director, Regulatory Affairs and Project Management at Viagene Inc. (1991 to 1995) and Director Clinical/Regulatory Affairs at Synbiotics Corp. (1988 to 1991). Ms. Osborne is responsible for the Company's regulatory and clinical studies programs and is a resident of Vancouver, B.C.

***David Hartnett M.Sc., M.B.A., Vice President - Operations***

Mr. Hartnett became the Vice President, Operations of the Company effective January, 1996. Mr. Hartnett has held numerous senior positions with biotech companies in the United States, including Vice President of Quality Assurance and Quality Control at Viagene Inc. (1991 to 1995), Director of Quality Assurance at NeoRx (1985 to 1991) and Vice President of Manufacturing at Benedict Nuclear Pharmaceuticals Inc. (1983 to 1985). Mr. Hartnett is responsible for the Company's operations including all laboratory facilities, quality control, quality assurance and manufacturing. Mr. Hartnett is a resident of Vancouver, B.C.

## **SCIENTIFIC AND PRODUCT DEVELOPMENT TEAM**

The scientific and development efforts of Angiotech require a diverse group of scientists and clinicians. This is particularly the case because the products under development by Angiotech are for the most part comprised of active agents plus drug delivery systems. Currently the Company's research and development program is divided into (i) the isolation and characterization of angiogenesis stimulators and inhibitors (and related compounds that also work as chemotherapeutics), (ii) the development of inexpensive and efficient methods of assaying the effectiveness of the compounds at all stages of production, (iii) the identification of mechanisms of action of these agents/products, (iv) the development of drug delivery systems, (v) the testing and optimization of the delivery systems and angiogenesis inhibitors in widely accepted animal models and (vi) the completion of pre-clinical studies and clinical trials. To accomplish the above, the Company has built a scientific team comprised of in-house specialists and outside collaborators as follows:



***William L. Hunter, M.D. Chief Scientific Officer, Director and Chairman of the Board***

Dr. Hunter is responsible for the coordination of the scientific efforts of Angiotech, intellectual property matters and business/science interactions. With such a diverse group of scientists it is crucial that all scientists have a focal point from which all efforts are directed. Dr. Hunter is the focal point for the scientific efforts of the Company.

***Anthony Cruz, Ph.D., Vice President - Science and Director, - Mechanisms of Action, Animal and Clinical Testing (Surgical Paste and Arthritis Applications) and Novel Chemotherapeutics***

Dr. Tony Cruz is an Associate Professor at the University of Toronto and a Senior Staff Scientist at the Samuel Lunenfeld Research Institute at Mount Sinai Hospital in Toronto, one of the leading research institutes in Canada. Dr. Cruz specializes in the molecular biology of cartilage tissue and cell signaling and has worked extensively in the field of protein biochemistry and the structural composition of cartilage, which has enabled him to understand the key mechanisms of action of the compounds being developed by the Company, including Angiotech's novel vanadium compounds (which were first identified by Dr. Cruz) and arthritis treatments. Dr. Cruz conducts *in vitro* and *in vivo* testing in these two areas pursuant to a research agreement between Mount Sinai Hospital and Angiotech. Dr. Cruz leads the Company's work in cell biology and cancer therapeutics.

***Helen M. Burt, B.Pharm., Ph.D., - Development of Drug Delivery Systems***

Dr. Burt is a Professor in the Faculty of Pharmaceutical Sciences at UBC. Dr. Burt's polymeric drug delivery group is one of the largest academic groups of this nature in Canada and is responsible for the development of Angiotech's proprietary drug delivery systems. Dr. Burt's work is being conducted pursuant to a collaborative research agreement between the University of British Columbia and Angiotech. Dr. Burt is taking a 1 year sabbatical from her teaching duties to work full time on Angiotech related research.

***Vincent Lee, Ph.D., - Development of Drug Delivery Systems - Collaboration***

Dr. Vincent Lee, a member of the Clinical Advisory Board, is a leader in the field of polymeric drug delivery. He is an important support person to Dr. Burt's group on the design and formulation of drug delivery systems.

***Larry Arsenault, Ph.D., - Biological Assay of Angiogenesis and Electron Microscopy - Collaboration***

Dr. Arsenault, a scientific founder of the Company, is a Professor in the Department of Pathology at McMaster University. He has worked in the field of cartilage biology and electron microscopy for many years and has published numerous papers dealing with the structural composition of cartilage tissue. Dr. Arsenault uses the CAM assay to compare the inhibitory activity of numerous compounds, both on their own and in combination with drug carriers, and to test and optimize the drug delivery systems being developed by the Company. Dr. Arsenault's expertise with the electron microscope also enables the direct visualization of the activity and effects of the Company's agents and drug delivery systems. Dr. Arsenault's research is being completed pursuant to a cooperative research agreement between McMaster University and Angiotech.

***Chris Orvig, Ph.D., - Synthesis of Novel Vanadium Compounds - Collaboration***

Dr. Orvig is a Professor in the Department of Chemistry at the University of British Columbia. Dr. Orvig has extensive experience in vanadate chemistry through his research relating to the potential use of vanadium compounds in the treatment of diabetes. The Company is currently testing novel vanadium compositions developed by Dr. Orvig to determine their potential as anti-proliferative agents. Dr. Orvig will also be

collaborating with the Company to develop additional novel vanadium compounds for the Company. Dr. Orvig's work is being completed pursuant to a research agreement between the UBC and Angiotech.

***Dr. Lindsay Machan, - M.D., F.R.C.P.(C), Animal and Clinical Testing (Interventional Radiology Applications) - Collaboration***

Dr. Machan, a scientific founder of Angiotech, is a practicing clinical interventional radiologist at University Hospital - UBC Site. He has an international reputation in the field of interventional radiology and minimally invasive therapy - his field of expertise being angiography, embolization, stent insertion and balloon angioplasty. Dr. Machan is responsible for the *in vivo* and clinical testing of Angiotech's products based on interventional radiology techniques. Dr. Machan's work is being conducted pursuant to a collaborative research agreement between the University Hospital - UBC Site and the Company. Dr. Machan's contacts in the medical device and minimally invasive therapy fields have also been extremely helpful to the Company.

***Ernest Brahn, M.D. F.A.C.R., - Animal and Clinical Testing (Arthritis Formulations) - Collaboration***

Dr. Ernest Brahn, a Member of the Clinical Advisory Board, is a tenured Associate Professor of Medicine, Division of Rheumatology at the UCLA School of Medicine. Dr. Brahn assists with the design of arthritis applications, screens Angiotech's agents and products using his assay systems and will be responsible for pre-clinical and clinical trials of arthritis treatments. Dr. Brahn's extensive clinical trial experience in his field is a key part of the arthritis product development program. Dr. Brahn's work on this project is being funded in part by a research gift donated to his lab by Angiotech.

***Peter McDonnell, M.D., and Vincent Lee, Ph.D., - Animal and Clinical Testing (Ophthalmic Applications) - Collaboration***

Dr. McDonnell is a Professor of Ophthalmology at the University of California School of Medicine. He is an experienced clinician and ophthalmic surgeon with active laboratory investigations in the area of corneal inflammation and corneal wound healing. Dr. McDonnell will oversee the animal studies to test Angiotech's products in diseases of the eye. Dr. Lee will also participate in the development work on this project, and in particular he will oversee the formulation of drug/polymer compounds for testing in the eye. This project is being completed pursuant to a collaborative research agreement between the Doheny Eye Institute and the Company.

***Lawrence D. Mayer, Ph.D., - Investigational Drug Program, BC Cancer Agency, - Pre-Clinical Development of Novel Chemotherapeutic - Collaboration***

Dr. Mayer is Research Scientist, Drug Development Program Manager, at the British Columbia Cancer Agency, division of Oncology. The Investigational Drug Program ("IDP") at the BCCA in Vancouver, Canada specializes in all aspects of pre-clinical work leading up to the filing of an IND submission. Once a submission is filed, the BCCA (the largest cancer agency in Canada) is available to complete clinical trials. The IDP has agreed to participate in pre-clinical work relating to the novel chemotherapeutic agent identified by Dr. Cruz and to assist in the preparation and filing of the IND for this agent. The IDP only takes on two to three projects per year. Work under this agreement commenced in February 1995.

***CTRC Research Foundation, - Preclinical and Clinical Testing (Cancer Treatments) - Collaboration***

Angiotech engaged the Foundation in February 1995 to complete certain studies of the polymeric micelles and surgical paste using preclinical models and assays available at the Cancer Therapy and Research Center, San Antonio, Texas. These studies include the use of these products in indications identified by the Company and the testing of the products in an indication that the Foundation has identified as a potential candidate for

localized delivery of chemotherapeutic agents. Once these studies are completed, the CTRC is available to complete pre-clinical studies, design clinical trials and complete clinical trials. Dr. Von Hoff and Dr. Dan Dexter are supervising the work conducted at the CTRC.

***Andy Adam, M.D., Bob Mason, M.D., - Clinical Testing of the Stent Coating - Collaboration***

Dr. Adam is at Guy's Hospital in London, England and is one of the leading interventional radiologists in Europe. Dr. Adam, Dr. Mason and their group at Guy's Hospital have agreed to conduct the Company's first clinical trial testing the polymer-paclitaxel stent coating in esophageal stents which is scheduled to begin in September, 1996.

***Edward Lakatta, Ph.D., - Cardiovascular Stent Coatings - Collaboration***

Dr. Lakatta is Head, Laboratory of Cardiovascular Science, Gerontology Research Center, National Institute on Aging, in Baltimore, Maryland. Dr. Lakatta and his research team are collaborating with the Company on paclitaxel coated cardiovascular stents for the prevention of restenosis.

## **CLINICAL ADVISORY BOARD**

Angiotech has established a Clinical Advisory Board comprised of scientific and clinical experts in the areas of oncology, interventional radiology, drug delivery and arthritis. The members of the Clinical Advisory Board take an active role in the development efforts of Angiotech, providing direction and contacts to the Company and collaborating with the Company in their respective areas of expertise (see previous section). Several members of the Clinical Advisory Board have the facilities and expertise to take the Company's products through to Phase I and II Clinical Trials and have taken products to the approval stage. They are also an important source of new product ideas and technologies for Angiotech. The current members of the Clinical Advisory Board are:

***Daniel Von Hoff, M.D., F.A.C.P.***

Dr. Von Hoff is the Director of the Institute for Drug Development at the Cancer Therapy and Research Center, San Antonio, Texas. His group at the Institute is the one of the largest clinical trial organizations (approximately 100 professionals) in the United States focused on Phase I/II oncological trials. Dr. Von Hoff is one of only seventeen scientists in the United States authorized by the National Cancer Institute to treat patients with new compounds identified at the NCI. During the past ten years, Dr. Von Hoff's Phase I/II clinical research team has been instrumental in the approval of several commercial drugs, including fludara, paclitaxel and novantrone. The Institute is collaborating with Angiotech on the development of drug-loaded polymeric micelles and surgical paste for the treatment of cancer. Dr. Von Hoff assists the Company with product design and clinical trial design, and his group at the CTRC will complete pre-clinical studies and clinical trials in oncology on behalf of the Company.

***Ernest Brahn, M.D., F.A.C.R.***

Dr. Brahn, a tenured Associate Professor of Medicine in the Division of Rheumatology at the UCLA School of Medicine, is a rheumatologist in the United States. Dr. Brahn's animal models of arthritis are accepted by the FDA for the evaluation of anti-arthritis compounds, and he has screened numerous compounds using this assay. Dr. Brahn will be extremely helpful in the verification and testing of Angiotech's products and compounds against arthritis and in the design and completion of clinical trials for these products. In addition, Dr. Brahn has shown that paclitaxel can completely shut down arthritis when given systemically in his animal model. Dr. Brahn's work is partially funded by a research gift from Angiotech.

*Sidney Wallace, M.D., F.A.C.P.*

Dr. Wallace is a Professor and Deputy Division Head for Research, Division of Diagnostic Imaging at the University of Texas, MD Anderson Cancer Center, Houston, Texas. Dr. Wallace is one of the founding fathers of interventional radiology (one of the methods of minimally invasive therapy used by Angiotech to deliver its compounds) and is a well respected researcher in the area of oncology. Dr. Wallace participates in product design with Angiotech and is interested in working with the Company on the stent coating. He has also initiated discussions regarding joint venture opportunities for Angiotech with some of the compounds and devices currently under development at MD Anderson.

*Lionel Israels, M.D., F.R.C.P.(C)*

Dr. Israels is a well respected hematologist who has held the positions of Director of Research at the Manitoba Institute of Cell Biology and Executive Director of the Manitoba Cancer Treatment and Research Foundation spanning a period between 1964 and 1992. Dr. Israels stepped down as Executive Director of the Foundation in 1992 to concentrate on both laboratory and clinical research. Dr. Israels assists with the design of cancer treatments and the development plans for the Company. Through Dr. Israel's contacts at the National Cancer Institute in the United States, Angiotech presented data relating to its novel chemotherapeutic to the NCI which led to a collaborative agreement to screen agents and products under development by the Company.

*Vincent Lee, Ph.D.*

Dr. Lee is the Gavin S. Herbert Professor and Chairman, Department of Pharmaceutical Sciences at the School of Pharmacy and Professor of Ophthalmology, School of Medicine, University of Southern California, Los Angeles, and is a leader in the area of controlled drug delivery. Dr. Lee has numerous executive positions with periodicals and drug delivery organizations, and is the author of many scientific publications and presentations. Dr. Lee is currently working with the scientists at the Doheny Eye Institute on the ophthalmic applications of Angiotech's technologies. He is also an important resource for Dr. Burt and her polymeric drug delivery group at UBC.

*Edward Keystone M.D., F.R.C.P.(C)*

Dr. Keystone is a Professor, Department of Medicine, University of Toronto, and the Director - Division of Rheumatology, Director of Research of the Department of Medicine, Director of the Division of Advanced Therapeutics in Rheumatic Disease in the Arthritis and Autoimmunity Research Centre at The Wellesley Hospital, Toronto, Ontario. Dr. Keystone is also a member of the Editorial Board for the Journal of Rheumatology and a grant reviewer for numerous Canadian medical research funding organizations. Dr. Keystone acts as an advisor to a number of major pharmaceutical companies nationally and internationally. Dr. Keystone will provide important scientific and clinical trial direction for the Company in addition to overseeing clinical trials in rheumatic diseases.

## **OTHER ADVISORS**

To protect and develop its intellectual property position, Angiotech has retained Seed and Berry, Attorneys at Law, of Seattle, Washington as patent counsel.

## ANGIOTECH'S COLLABORATIONS AND COLLABORATION STRATEGY

Angiotech's scientific and development team includes research groups, development groups and clinical groups, which will allow the Company to quickly and efficiently develop and move its products into and through clinical trials. Each of these scientists is a leader in his or her respective field of expertise. Angiotech sources the best possible scientists and facilities to complete pre-clinical studies, design the clinical protocols and complete the clinical studies. As a result, Angiotech has entered into no less than eleven collaborations with leading researchers, clinicians and institutions in North America. These include the following collaborations:

<u>Name</u>	<u>Type &amp; Content of Agreement</u>	<u>Date</u>
McMaster University <i>Larry Arsenault, Ph.D.</i> (Company Principal)	Cooperative research agreement - Biological assay of angiogenesis factors and drug delivery systems	Oct. 92
University of British Columbia <i>Helen Burt, Ph.D.</i>	Cooperative research agreement - Development of drug delivery systems	Jan. 93
University Hospital - UBC Site <i>Lindsay Machan, M.D.,</i> <i>F.R.C.P.(C)</i> (Company Principal)	Cooperative research agreement - Animal testing of angiogenesis inhibitors and drug delivery systems	Oct. 92
Samuel Lunenfeld Institute - Mount Sinai Hospital <i>Tony Cruz, Ph.D.</i> (Company Principal)	Cooperative research agreement - Animal testing of angiogenesis inhibitors and drug delivery systems and development of novel chemotherapeutic	Jan. 94
Doheny Eye Institute - University of Southern California <i>Peter McDonnell, M.D. and</i> <i>Vincent Lee, Ph.D.</i>	Cooperative research agreement - Testing of polymeric-drug formulations in animal models of disease	Oct. 94
UCLA Medical Center, Los Angeles <i>Ernest Brahn M.D., F.A.C.R.</i>	Research Gift to Dr. Ernest Brahn's laboratory - Paclitaxel in arthritis and arthritis microspheres. Animal testing of angiogenesis inhibitors and drug delivery systems.	Jan 95
CTRC Research Foundation, Univ. of Texas at San Antonio <i>Daniel D. Von Hoff, M.D.,</i> <i>F.A.C.P.</i>	Cooperative research agreement - surgical paste and other formulations for local delivery of paclitaxel and other compounds in malignancy.	Feb. 95
B.C. Cancer Agency	Cooperative research agreement - Animal testing, IND and Phase I Clinical testing of vanadium compounds.	June 95
University of British Columbia <i>Chris Orvig, Ph.D.</i>	Cooperative research agreement and option - Synthesis of novel vanadium compounds	October 95
Guy's Hospital <i>Andy Adam, M.D., F.R.C.P.</i>	Clinical trial agreement - clinical trials for the stent coating	October 95
NIH - NIA <i>Ed Lakatta, Ph.D.</i>	CRADA - preclinical and clinical program for a stent coating for restenosis.	April 96

## INTELLECTUAL PROPERTY

Intellectual property is the cornerstone upon which Angiotech is built. The Company has and will aggressively file for patent protection on its inventions and will seek opportunities to license technologies from other targeted corporations or institutions. Patents are typically filed in the United States, Canada, Japan, Western European countries and other selective jurisdictions to provide the Company with the widest international protection possible. The Company also plans to augment its proprietary position with orphan drug designations for some of its products where appropriate.

Angiotech's intellectual property strategy is designed to give it the broadest patent protection possible to allow the Company to exploit its novel approach to the treatment of diseases such as cancer, arthritis and other angiogenesis dependent diseases. In simple terms, Angiotech's core technology relates to (1) The Company's knowledge of a biological pathway and its effects on several disease states and Angiotech's ability to identify agents which have therapeutic potential for different clinical indications, (2) Angiotech's use of two primary therapeutic agents - paclitaxel and vanadate (and their derivatives) - to impact on several diseases through this biological pathway and (3) proprietary drug delivery systems used to deliver the two agents in a variety of disease indications. Usage claims have been utilized to protect paclitaxel and vanadium for certain disease states, while composition of matter claims have been constructed to protect novel vanadium compounds and polymeric drug delivery vehicles. In addition, Angiotech is constantly in the process of identifying other agents and delivery systems to broaden its patent position.

## TAXANE PATENT POSITION

### History of Taxol Development

Paclitaxel (commonly referred to as "Taxol" ® of Bristol-Myers Squibb Co.) was discovered in the early 1960's by the Natural Products Branch ("NPB") of the National Cancer Institute ("NCI") in the United States. The NPB evaluated thousands of natural and plant products for anti-cancer activity between 1950 and 1980. In 1963, Wani et. al. of the Research Triangle Institute ("RTI"), an affiliate of the NCI, first isolated a crude paclitaxel extract from the bark of the Pacific yew *TAXUS brevifolia*. This extract was cytotoxic against a broad range of murine tumors. In 1969, the RTI group identified paclitaxel as the active constituent of the extract and, in 1971, reported on its structure. Despite promising anti-tumor activities, development of paclitaxel as an anti-neoplastic agent progressed slowly because of paclitaxel's scarcity and the difficulty of large-scale isolation, extraction and preparation.

Interest in paclitaxel was rekindled in the late 1970's because (1) paclitaxel's unique mechanism of anti-tumor action as a promoter of microtubule assembly was discovered and (2) adequate supplies of paclitaxel were obtained for conventional preclinical screening, toxicological studies and preliminary clinical trials (largely as a result of the effort on the part of the NCI).

In January, 1991, after an open competition initiated by the NCI in 1989, Bristol-Myers Squibb Co. ("BMS") was selected and given exclusive rights to develop and market paclitaxel pursuant to a cooperative research and development agreement ("CRADA") with the Institute. The CRADA required BMS to organize research and rapid development of alternate sources of the drug.

Since the execution of the CRADA between the NCI and BMS, paclitaxel has been the number one cancer research and development priority at BMS. BMS's unprecedented commitment to the development of paclitaxel has led to its initial approval for marketing in more than 50 countries around the globe (for late stage ovarian and metastatic breast cancer). Recently, the Food and Drug Administration ("FDA") determined that semi-synthetic paclitaxel (derived from the branches and needles of the Pacific Yew tree and therefore obtainable without destroying the

tree) developed by BMS is bioequivalent to that produced from the Pacific yew tree bark and gave its marketing approval.

There is no patent on the composition of paclitaxel and BMS does not hold orphan drug status on the drug. As a result, BMS has no monopoly other than that afforded by its existing approvals in various jurisdictions and some patent protection provided by claims covering methods of administration in the treatment of cancer. This situation has created an opportunity for a number of other companies to pursue approval of paclitaxel equivalents or generics for the treatment of malignancy, including Hauser Pharmaceuticals Inc., NaPro Biotherapeutics Inc. (which has received approval to market their form of paclitaxel in Australia) and Phytogen Life Sciences Inc. Several pharmaceutical companies (including BMS) have developed analogues of paclitaxel which have been patented for the treatment of malignancy. The most advanced project of this nature is the development of docitaxel (Taxotere®) by Rhône-Poulenc Rorer and the NCI; this drug is currently marketed for breast cancer in Europe. Any new paclitaxel analogue (i.e., any chemical compound which is not identical to paclitaxel) must undergo the pharmacological, toxicological, and efficacy testing required of new chemical entities; a process which often takes many years.

In order for a new taxane compound with an identical mechanism of action to gain approval and widespread use in the treatment of malignancy, the agent will often be required to demonstrate superior activity or safety as compared to paclitaxel in head-to-head clinical studies. This can be a difficult and expensive task as is evidenced by the FDA's refusal to approve docitaxel in 1994 (following Phase 3 studies) due to concerns regarding the drug's toxicity as compared to paclitaxel.

Notwithstanding the above, BMS reported first half 1996 sales of Taxol to be approximately U.S. \$400 million which points to Taxol becoming the first billion dollar chemotherapeutic agent. BMS has stated that its extraordinary investment in the development of paclitaxel continues with the search for additional indications for the drug. Approval for the treatment of lung cancer and other malignancies is expected to be granted in the near future.

### **Status of Intellectual Property in the Industry**

Patents relating to paclitaxel focus on method claims for the treatment of malignancy. As described above, there is no protection for the composition of paclitaxel itself. Composition of matter claims have been granted for a large number of paclitaxel analogues or derivatives.

At the present time, none of these analogues have shown a clear clinical superiority to paclitaxel and method claims contained in these patents focus on methods for the treatment of malignancy (i.e., patent applications written prior to Angiotech's discovery of several nonmalignant uses of paclitaxel and its analogues cover use of the drugs in cancer; applications written after the Company's discovery are not applicable to this invention).

### **Angiotech's Patent Strategy Relating to Paclitaxel and Paclitaxel Analogues**

Angiotech was the first to identify the activity of paclitaxel as a potent inhibitor of angiogenesis, describe new molecular mechanisms of action of the drug(s), and demonstrate its effectiveness as a potential therapeutic agent in the treatment of nonmalignant angiogenesis-dependent diseases. The Company's molecular understanding of how paclitaxel functions in these different, but related disease states allows the determination of which paclitaxel analogues might have utility for a variety of nonmalignant indications. Based on this knowledge, the Company has focused on obtaining the broadest protection possible for the use of paclitaxel in the treatment of a wide range of clinical indications.

In diseases other than malignancy, Angiotech is in a unique position in that it believes it was the first to invent and file for patent protection on the discovery that paclitaxel and analogues thereof can be used in the treatment of angiogenesis dependent diseases such as arthritis, restenosis, psoriasis, and vascular adhesions.

The Company believes the above method claims, should they issue, have significant value as no other company could market and sell a paclitaxel-containing product for the treatment of these diseases without infringing Angiotech's claims. For example, a company marketing paclitaxel for use in malignancy is able to rely on method claims such as "administering a 3 hour infusion of paclitaxel;" although difficult to enforce, the company is able to make this economically viable as it provides some protection. By comparison, Angiotech has sought broad usage and method coverage in the form of "Paclitaxel in the Treatment of Arthritis and Other Angiogenesis Dependent Conditions;" this coverage is not dependent upon route of administration, dosage, duration of treatment, formulation, or analogue type and protects the use of paclitaxel (in any form) for these indications. Getting regulatory approval for these indications will further augment this position.

The Company has received notification of allowance of claims from the European Patent Office covering the use of paclitaxel and analogues in the treatment of angiogenesis dependent conditions, including arthritis and restenosis. It should be noted that under European conventions, these claims will not issue (be finalized) until after a review period; the United States application is presently still under review.

To further enhance its intellectual property position for paclitaxel in the treatment of arthritis and similar conditions, Angiotech has acquired a worldwide exclusive license from the UCLA Board of Regents for all rights in and to a patent application filed by UCLA and Dr. Ernest Brahn (Dr. Brahn is the inventor, a Company collaborator and Clinical Advisor). This application, which recently received a notice of allowance from the United States Patent Office, covers the use of paclitaxel alone, and in combination with other anti-arthritic drugs, for the treatment of rheumatoid arthritis and other similar conditions.

Angiotech's drug delivery group, in collaboration with the University of British Columbia, continues to develop novel drug delivery vehicles for paclitaxel in the treatment of malignancy and other conditions, including arthritis. For example, formulating paclitaxel into microspheres for intra-articular administration provides potential method ("treatment of arthritis") and composition ("paclitaxel-polymeric microspheres") coverage. These may lead to further patent applications in the future. As far as synthesis of novel paclitaxel analogues is concerned, this is not a business that Angiotech is currently involved in. However, Angiotech is currently seeking collaborations with companies interested in taxanes to develop the Company's paclitaxel products clinically and to screen novel agents (analogues and derivatives of paclitaxel) to determine those with the best potential in arthritis and other angiogenesis dependent diseases.

With respect to paclitaxel cancer products, Angiotech's intellectual property position is no different than that of other companies in the field, since composition of matter protection is not available for paclitaxel itself. The Company's patent protection is directed towards novel methods of administration of the drug and novel paclitaxel formulation compositions. To obtain as broad patent coverage as possible, the Company has applied for method claims for the treatment of a number of different specific clinical conditions (for example, paclitaxel surgical paste for the treatment of cancer resection sites and paclitaxel stent coatings) as well as composition claims for its own paclitaxel-polymer formulations.

The composition claims of the Company may be significant in that one of the major problems of paclitaxel and other water insoluble drugs has been an inability to deliver the drugs effectively (in the case of paclitaxel, some of the toxicity associated with the administration of the drug can be attributed to the use of Cremophor as a solubilizing agent). Polymeric delivery offers a new approach to the delivery of paclitaxel that may be more efficacious than the traditional administration methods and allows formulation of the drug without the use of Cremophor. The composition claims of the Company may also be extended to other water-insoluble compounds that face similar delivery problems.



The Company has received notification of allowance of claims from the European Patent Office covering the use of anticancer drugs including paclitaxel (and analogues) in stent coatings. As mentioned previously, these claims will not issue (be finalized) until after a review period; the United States application is presently still in prosecution.

## **VANADATE PATENT POSITION**

### **History of Vanadate Development and Status of Intellectual Property in the Industry**

The anti-proliferative and anti-arthritic properties of vanadium (a natural element) and vanadium compounds were discovered by Dr. Tony Cruz (a principal scientist of the Company) while working at Mount Sinai Hospital in Toronto. Dr. Cruz, a molecular biologist, was conducting research on a pathway (the AP-1 pathway) which leads to cell proliferation, cellular enzyme production (metalloproteinases) and metastasis. He discovered a key intracellular second messenger in this pathway and determined that vanadate and vanadium compounds were effective agents in blocking this pathway leading to potent anti-tumor and anti-arthritic effects in animal models of disease. Dr. Cruz and Mt. Sinai Hospital filed U.S. and international patent applications on the invention shortly after this discovery; a divisional application was filed earlier this year.

Other groups have reported anti-neoplastic effects of vanadate and related compounds, but the method of administration differs from the Cruz application. The majority of the interest in vanadium over the last few years has resulted from the insulin mimetic effects of the agent and therefore its potential use in the treatment of diabetes. Dr. John McNeil (Department of Pharmaceutical Sciences, UBC) and Dr. Chris Orvig (Department of Chemistry, UBC) are recognized as world leaders in the field of vanadate chemistry and have worked extensively on its potential use in the treatment of diabetes. Angiotech is now collaborating with these individuals to identify and license additional novel vanadium compositions for use in cancer and arthritis.

### **Angiotech's Patent Strategy Relating to Vanadate**

Mount Sinai Hospital and Dr. Cruz filed patent applications disclosing methods of use of numerous vanadium compounds in the treatment of proliferative diseases such as cancer and arthritis. Angiotech was granted a worldwide exclusive license to the intellectual property represented by the above patent applications in the spring of 1995. Several claims of the international (PCT) application have received notice of allowance in Europe, but as with the paclitaxel application, these claims will not be finalized for several months. The U.S. application is under prosecution as of the time of writing.

The Company has also taken steps to obtain composition of matter claims for effective novel vanadium compounds. Internally, Angiotech chemist Dr. Zaihui Zhang (a former post doctoral fellow of Dr. Orvig) is working in collaboration with the BC Cancer Agency to develop novel vanadium compounds for the treatment of malignancy. Externally, Angiotech has established a research collaboration and option agreement with UBC relating to the work of Drs. McNeil and Orvig. The focus of this collaborative effort is to test novel vanadium compounds already developed and patented by Drs. McNeil and Orvig and to synthesize novel vanadium compounds for indications related to the Company's business. Other compounds that impact on the biological pathway that is the focus of the Company will also be examined.

## **COMPETITION**

### **OVERVIEW**

Due to the broad application of the core technologies of Angiotech, many groups and companies will be considered to be competing either closely or generally with the Company. However, Angiotech's novel approach to the treatment of diseases such as cancer and arthritis (which focuses on impacting both on the diseases themselves and

the body's inappropriate responses to these diseases) distinguishes it from other companies and researchers who take a more traditional approach to disease by either targeting the disease process or the body's response.

Angiotech believes that the majority of its products and technologies will actually be synergistic, not competitive with the products and technologies of others. Diseases such as cancer and arthritis are extremely complicated diseases and must be attacked from a number of different directions. This means that new approaches to disease, such as the approach taken by Angiotech, in the opinion of management, should be complementary to most existing treatments.

There are many companies focused on paclitaxel, arthritis, cancer (including angiogenesis companies) and drug delivery. Some of the companies which could be considered to be competitors with Angiotech have substantially more financial and technical resources, more extensive research and development capabilities and greater marketing, distribution and human resources.

## **PACLITAXEL COMPANIES**

Bristol-Myers Squibb Co. ("BMS") is perhaps the best known of the paclitaxel companies. The other major players in this area known to the Company are Rhône-Poulenc Rorer Inc., Hauser Chemical Research Inc. (partnered with American Home Products), NaPro Biotherapeutics Inc. (partnered with IVAX and F.H. Faulding) and Phytogen Life Sciences Inc. (partnered with Mylan Laboratories Inc.). The main focus of these companies is cancer.

Angiotech does not view itself as a competitor with these companies as it has no current plans to commercialize systemic paclitaxel or any derivative thereof for treating malignancy. Rather, the paclitaxel-polymer formulations developed by Angiotech represent a very real opportunity for companies such as BMS to expand their markets for paclitaxel in and beyond the field of oncology.

Angiotech's identification of novel mechanisms of action of paclitaxel and its potential for use in other also provides the above companies with an opportunity for product extension. Angiotech and Dr. Brahn (a member of the Company's Clinical Advisory Board) have shown that paclitaxel has strong potential as a disease modifying agent in RA and other forms of arthritis. As the major market opportunity in arthritis over the next few years will be in disease modifying agents, the use of paclitaxel in arthritis represents a major new market for the drug. Similar opportunities may be available in cardiovascular disease (for the prevention of restenosis) and other applications.

## **ARTHRITIS**

Paclitaxel has shown potential as a disease modifying agent in arthritis. There are existing products on the market (such as methotrexate and gold) that are used as disease modifying agents in the treatment of arthritis. These agents are not overly efficacious. The advantage of paclitaxel is that it appears to be able to stop the progression of the disease at drug levels that are not damaging to normal cartilage tissue. Arthritis is not unlike cancer and other diseases in that it is a very complicated disease. This means that the likelihood is that paclitaxel and one or more compounds would be used in combination to treat patients. The market for disease modifying drugs such as paclitaxel should also expand as physicians shift to the early use of these agents at the onset of the disease in order to prevent joint damage.

There also several arthritis disease modifying drugs presently in clinical trials. These drugs may or may not show significant improvement on existing treatments. They include companies developing new forms of NSAID's, treatments based on monoclonal antibodies and new forms of disease modifiers. However, to the Company's knowledge, none of those drugs seek to positively affect all aspects of the arthritis biological pathway.

## **CANCER COMPANIES**

In addition to the companies identified above, there are many companies developing treatments for cancers based on various technologies. These will be competitors for the novel chemotherapeutic agent licensed from Mount Sinai Hospital. The advantage of the novel chemotherapeutic agent identified by Dr. Cruz is that it represents a potential new class of anti-proliferative drugs working along a different biological pathway. When searching for new chemotherapeutic agents, investigators focus on agents that will work along entirely new biological pathways, as opposed to "me too" agents which are subject to the same limitations as the agents upon which they are modeled. The vanadium compounds under development by the Company represent a potentially new class of chemotherapeutic agent.

As explained in the section on COMPETITIVE ADVANTAGES, it is the Company's belief that while treatments based solely on inhibition of angiogenesis (as opposed to the Company's dual approach) could one day be useful as an adjunct to other treatments, it will not form the basis of a first line treatment for disease.

## **DRUG DELIVERY COMPANIES**

There are a number of drug delivery companies that are focusing on similar products to those under development by the Company, in particular the paste. Angiotech uses polymeric carriers for the delivery of compounds generally. In some instances, Angiotech's polymeric systems will be more advantageous to use than the delivery systems being used by other companies and in other situations the delivery vehicles used by these companies will be more advantageous. One key advantage that the Company has is that it has established its own polymeric delivery group which focuses on solving problems as they arise. The Company has also worked extensively on the delivery of paclitaxel, which will be an advantage as the indications for this drug are expanded.

## **GOVERNMENT REGULATIONS**

### **REGULATORY AFFAIRS**

The development, manufacturing and ultimate marketing of the Company's products are subject to the regulations relating to the demonstration of safety and efficacy established by the government authorities in those jurisdictions where these products are to be marketed.

In Canada, these activities are regulated under the Food and Drug Act and are enforced by the Health Protection Branch ("HPB") of the Government of Canada's Department of Health and Welfare. In the United States, all drugs and medical devices are regulated by the Food and Drug Administration ("FDA"), including oversight of the manufacturing process, and evaluation of all non-clinical and clinical studies used in support of approval for marketing of therapeutic products. In addition, good manufacturing practices ("GMP") must be adhered to during production of all products intended for human use, including during the clinical evaluation. In its initial stages of development, Angiotech will source all possible components from suppliers who manufacture according to GMPs.

In general, the regulatory pathway to product approval in Canada and the U.S. includes conducting preclinical studies in animals, filing and review of an Investigational New Drug application ("IND") prior to clinical testing in humans. Results of these controlled clinical studies are detailed in the filing of a New Drug Submission ("NDS") in Canada and a New Drug Application ("NDA") in the United States, together with detailed information related to the drug product and the manufacturing process.

In summary, the following steps must be completed prior to obtaining approval for marketing in Canada and the U.S.:

- (1) *Preclinical Animal Studies* - These studies evaluate the safety and potential efficacy of a therapeutic product and form part of an IND for which review under HPB and FDA regulations is necessary prior to initiation of human clinical studies.
- (2) *Phase 1 Clinical Studies* - These studies test the product in a small number of patients to determine toxicity (safety), maximum dose tolerance ("MTD") and pharmacokinetics properties. In the proposed products, these will be conducted in the intended patient population.
- (3) *Phase 2 Clinical Studies* - These studies include a larger patient population than in Phase 1 and determine the safety in a larger patient base as well as the potential effectiveness of a product.
- (4) *Phase 3 Clinical Studies* - These studies are for the controlled evaluation in an expanded patient population at multiple sites to determine longer term clinical safety and efficacy. It is from the data of these studies that the benefit/risk relationship is established and the final drug labeling claims are defined.

Results from each clinical step must be reviewed before the Company can progress to the next phase. In certain circumstances in the U.S., the approval process can be accelerated. In 1991, the FDA announced plans to significantly increase resources in processing new drug applications for serious and life threatening diseases. Therefore, in cancer applications or applications for late stage arthritis where mortality rates approach those of cancer, the Company may be in a position to expedite the approval process of its products. The Orphan Drug Act in the U.S. also offers an opportunity to accelerate the clinical process. The Act requires that the FDA give higher priority to compounds which qualify for orphan drug status (i.e., agents used in the treatment of diseases which have a prevalence of less than 200,000 people). The most important aspect of the orphan drug designation, however, is the seven year period of marketing exclusivity granted to compounds receiving regulatory approval as an Orphan Drug.

For the purposes of this document, only the jurisdictions of the United States and Canada will be discussed. However, the Company does intend to seek regulatory approval in other jurisdictions and may initiate clinical studies in Europe in certain instances where disease prevalence dictates, before North America. Nevertheless, the Company would in most instances follow the steps required in the United States, to support subsequent U.S. filings. The development, manufacturing and ultimate marketing of the Company's products are subject to the regulations relating to the demonstration of safety and efficacy established by the government authorities in those jurisdictions where these products are to be marketed.

## REGULATORY STRATEGY

Angiotech has begun to communicate in advance of IND filings with regulatory agencies in Canada, the United States and Europe to ensure that its pre-clinical and clinical protocols are designed to capture adequate data in support for filing of regulatory approval. The venue for clinical studies will be determined on a project by project basis based on the availability of the best possible clinicians to complete the clinical studies. While certain clinical studies may be pursued first in jurisdictions other than the United States and Canada, all clinical studies will be completed with the requirements of the FDA and the United States market in mind.

Wherever possible, Angiotech will seek the designation of Orphan status in the United States. The significance of this Act has been explained above. Most cancers meet this criteria, as do certain categories of arthritic disease.

Angiotech's initial products have not only been selected with respect to commercial end, they have also been targeted with regulatory pathways in mind. The paclitaxel products make use of an approved chemotherapeutic drug combined with polymers which also are used in marketed products. The approval of new formulations for existing drugs is often shorter and less costly than the approval of a new chemical entity. In addition, the paclitaxel arthritis microspheres are not conceptually blazing a new trail with respect to the use of a chemotherapeutic in arthritis, as the fastest growing arthritis disease modifying drug is an agent previously approved as a chemotherapeutic. In the case of the Company's paclitaxel paste formulation, the initial indication chosen by the Company is one for which there is no effective treatment.

It is also the stated goal of the Company in its early years of development to collaborate with large pharmaceutical companies once its products have been developed to a certain stage. These companies already have the corporate infrastructure in place to effectively and efficiently advance the Company's products into clinical studies and through the regulatory environment. The Company neither has the financial nor human resources to undertake the large and expensive studies associated with most Phase 2 and 3 clinical studies. Even as the Company grows, commercial licensing and collaborations will be the main pathway through the clinic. This strategy is designed to be both capital and risk efficient.

The respective regulatory plans for each of the products currently under development by Angiotech are discussed under the respective subsections of the TECHNOLOGY AND PRODUCT DEVELOPMENT Section.

## FINANCE

### CURRENT FINANCIAL POSITION

Audited financial statements for the fiscal years ended September 30, 1994 and 1995 are included in Appendix A. Unaudited financial statements for the 10 months ended July 31, 1996 are included in Appendix A. Presented below is selected financial information derived from those statements.

	Summary Financial Information		
	Unaudited	Audited	
	July 31, 1996 (10 months) Cdn \$	September 30, 1995 Cdn \$	September 30, 1994 Cdn \$
<u>Operations:</u>			
Expenses			
Research and Development	\$2,095,961	\$1,035,216	\$428,987
Less Grants and Investment Tax Credits	(16,635)	367,224	190,247
	2,079,326	667,992	238,740
General and Administrative	671,222	230,440	34,417
Net Loss	2,750,548	898,432	273,157
Deficit, beginning of period	1,473,193	574,761	197,604
Premium paid on cancellation of share subscriptions			104,000
Deficit, end of period	4,223,741	1,473,193	574,761
<u>Balance Sheet</u>			
Current Assets	1,332,548	737,089	269,639
Working Capital	815,084	572,108	183,597
Total Assets	2,221,352	1,016,677	351,858
Shareholders' Equity			
Common shares	5,927,629	2,053,114	840,577
Less Deficit	4,233,741	574,761	197,604
	\$1,703,888	\$265,816	\$131,713

## CAPITAL STRUCTURE

The Company has raised approximately \$6.0 million from founders, close associates of the Company principals, via an Offering Memorandum dated November 27, 1995 and via an exemption, since the Company's inception in 1992. The following table outlines the current ownership as of September 6, 1996 as adjusted to reflect the capital reorganization as approved by the shareholders on September 6, 1996 and as adjusted for this Offering:

	Fully Diluted shares Pre-Private Placement	%	Fully Diluted shares Post-Private Placement	%
Scientists, Management and Employees	2,864,713	46.15	2,864,713	45.96
Other shareholders	3,342,974	53.85	3,342,974	53.64
Private Placees	0	0.00	25,000	0.40
	6,207,687	100.00	6,232,687	100.00

Note: (1) There are 250,000 Class A Preference shares have been reserved for issuance on exercise of an incentive stock options at an exercise price of \$2.75 per share, expiring January 31, 2006. Another 25,000 Class A Preference shares have been reserved for issuance on exercise of an option related to a previous private placement at an exercise price of \$2.75, expiring on the earlier of the day prior to the receipt of a prospectus qualifying the Company's shares to be listed on a recognized stock exchange or, January 30, 1998. A further 688,000 options to acquire Common shares at a strike price of \$0.25 have been authorized for issuance under a shareholder approved stock option plan, to certain officers, employees and consultants of the Company. All of the shares available for issuance under the stock option plan are subject to vesting over a three year period. The fully diluted calculation above include all options.

(2) In addition, on or about September ????, 1996 there will be a closing pursuant to which the Company will be issuing 1,084,500 Class B Preference Shares - Series I at \$3.00 per share, for total gross proceeds of Cdn \$3,253,500.

Shown in the following table are the full name, municipality of residence, position with the Company, pre-Offering fully diluted share positions and principal occupations of each of the directors and senior officers of the Company:

Name and Municipality of Residence	Position with Company	Principal Occupation	F.D. Beneficial shares Owned	Related Ownership	Current F.D. Ownership	Post-Offering F.D. Ownership
Dr. Robert Abbott Surrey, B.C.	CEO, President & Director	CEO and President of the Company	250,000	0	4.03%	4.01%
Dr. William L. Hunter, Vancouver, B.C.	CSO & Director	CSO of the Company	273,734	150,000 <sup>(1)</sup>	6.83%	6.80%
Dr. Don Longenecker, Vancouver, B.C.	COO	COO of the Company	200,000	0	3.22%	3.21%
Kennith A. Mellquist, Lions Bay, B.C.	Vice President & Director	Vice President of the Company	193,353	80,000 <sup>(2)</sup>	4.40%	4.38%
Mr. Mark Godsy, West Vancouver, B.C.	Director	Business Consultant	227,020	0	3.66%	3.64%

Frank A. Holler, W. Vancouver, B.C.	Director	President and CEO of ID Biomedical	197,520	0	3.18%	3.17%
Judith Donaldson; Chicago, Illinois	Director	Investment Counselor <sup>(3)</sup>	0	0	0%	0%
Dr. Anthony Cruz, Etobicoke, Ontario	Director and Vice President - Science	Associate Professor, U. of Toronto, Senior Staff Scientist, Samuel Lunenfeld Research Institute, Toronto	356,233		5.74%	5.72%
David M. Hall, Vancouver, B.C.	Vice President Finance	Vice President, Finance of the Company <sup>(4)</sup>	148,854	80,000 <sup>(4)</sup>	3.69%	3.67%
Sheryl Osborne	Vice President Regulatory Affairs and Clinical Development	V.P., Regulatory Affairs and Clinical Development of the Company	60,000	0	0.97%	0.96%
David Hartnett	Vice President Operations	V.P., Operations of the Company	50,000	0	0.81%	0.80%

(1) - Shares owned by Dr. Hunter's spouse. (2) - Shares owned by Ken Mellquist's spouse. (3) - Ms. Donaldson exercises fiduciary voting control over 180,000 Class A Preference shares. (4) - Shares owned by David Hall's spouse.

Note: 250,000 options to acquire Class A Preference shares at a strike price of \$2.75 have been authorized and reserved for issuance to directors, officers and employees of the Company. A further 25,000 options to acquire Class A Preference shares at a strike price of \$2.75 have been authorized and reserved for First Marathon Securities Limited pursuant to a previous Offering. A further 688,000 options to acquire Common shares at a strike price of \$0.25 have been authorized and issued under a shareholder approved stock option plan, to certain officers, employees, members of the Clinical Advisory Board and consultants of the Company. All of the shares available for issuance under the stock option plan are subject to vesting over a three year period.

Prior to becoming CEO and President of the Company, Dr. Abbott was CEO, President and a Director of Viagene Inc. of San Diego, California and previous to that held the same position with NeoRx Corporation of Seattle, Washington. Prior to becoming the Chief Scientific Officer of the Company, Dr. Hunter was the CEO of the Company until Dr. Abbott's appointment on January 1, 1996. Prior to that Dr. Hunter was the Director of Research of the Company from its inception in the fall of 1992. Dr. Hunter is still an active medical clinician. Prior to becoming COO of the Company, Dr. Longenecker was Senior Vice President of Viagene Inc. of San Diego, California and previous to that he was Vice President, Operations and director, Regulatory Affairs of NeoRx Corporation of Seattle, Washington. Mr. Mellquist was the President of the Company from the summer of 1993 until Dr. Abbott's appointment whereupon he became a Senior Vice President of the Company. Prior to joining the Company, Mr. Mellquist was the Corporate Counsel for ID Biomedical and a practising corporate lawyer. Mr. Godsy was a co-founder and officer of ID Biomedical from 1991 until the summer of 1995 and prior to that, a self-employed business consultant. Mr. Godsy is presently a self-employed business consultant. Mr. Holler has been President and CEO of ID Biomedical since 1991. Prior to joining ID Biomedical, Mr. Holler was an investment banker for an international investment bank. Dr. Cruz has been a principal scientist of the Company since 1993. Dr. Cruz is also an Associate Professor at the University of Toronto and staff scientist at Samuel Lunenfeld Research Institute. Dr. Arsenault, a founder of the Company, is a Professor in the Department of Pathology at McMaster University. Mr. Hall has been an officer of the Company since the spring of 1994. Prior to that he was the Corporate Development Officer for ID Biomedical beginning in 1993. Mr. Hall was previously an institutional research analyst and corporate financier with a national institutional brokerage company, and an equity portfolio manager for a Canadian insurance company. Prior to becoming the Vice President, Regulatory Affairs and Clinical Development of the Company, Ms. Osborne was Director, Regulatory and Clinical Affairs at Chiron Viagene Inc., Director, Regulatory Affairs and Project Management at Viagene Inc. and Director, Clinical/Regulatory Affairs at Synbiotics Corp.. Prior to becoming the Vice President, Operations of the Company, Mr. Hartnett was Vice-President of Quality Assurance and Quality Control at Viagene Inc., Director of Quality Assurance at NeoRx and Vice President of Manufacturing at Benedict Nuclear Pharmaceuticals Inc.

## FINANCING STRATEGY

Angiotech's financing strategy is based on raising sufficient capital in advance to meet its budgeted research and development and administrative expenses. The Company anticipates that, subject to market conditions generally, it will be able to complete larger equity offerings as the Company's value appreciates in concert with the achievement of its development milestones.

In budgeting, the Company will acknowledge any planned licensing revenues during the forecasted period. As well, the business strategy of the Company dictates that the Company's equity be leveraged by outsourcing and collaborating on certain research and clinical development programs with strategic partners. Angiotech will also

continue to access government research grants and to recover scientific research expenditures through available Scientific Research and Experimental tax credit refunds.

## AFFILIATIONS

### AUDITORS:

Ernst & Young  
P.O. Box 10101, Pacific Centre  
700 West Georgia Street  
Vancouver, B.C., V7Y 1C7

### LEGAL COUNSEL:

DuMoulin Black  
10<sup>th</sup> Floor, 595 Howe Street  
Vancouver, B.C., V6C 2T5

### BANK:

Royal Bank of Canada  
Pender & Butte Branch  
1205 West Pender Street  
Vancouver, B.C., V6E 2V5

### PATENT COUNSEL

Seed and Berry  
6300 Columbia Center  
701 Fifth Avenue  
Seattle, Wash, 98104-7092

## DETAILS OF OFFERING AND SHARE CAPITAL

The authorized capital of Angiotech consists of 160,000,000 shares without par value divided into 50,000,000 Common shares without par value, 50,000,000 Class A Preference shares, 10,000,000 Class B Preference shares and 50,000,000 Class C Preference shares. All classes of shares rank equally in their voting rights.

Common shares - The common shares rank equally with all other classes of shares except as set out in the special rights and restrictions attaching to the Preference shares (see below).

Class A Preference shares - The Class A Preference shares shall have the rights and shall be subject to restrictions, conditions and limitations as follows:

- (a) Conversion Right - Each of the registered holders of the Class A Preference shares may at any time, by written notice to the Company and upon surrender of the share certificate(s) representing such Class A Preference shares, convert all of his, her or its issued and outstanding Class A Preference shares into Common shares, on the basis of one (1) Class A Preference share for one (1) Common share. Upon receipt of written notice from any holder of the Class A Preference shares and the share certificate(s) representing such Class A Preference shares to be converted, the Company shall cancel the share certificate(s) representing such Class A Preference shares (and such shares shall be canceled and returned to the status of authorized but unissued shares in the capital of the Company), issue new share certificates for the Common shares resulting from the conversion and make the necessary entries in and alterations to the registers of members and allotments of the Company. Any Common share issued on the conversion of a Class A Preference share is deemed to be fully paid.
- (b) Automatic Conversion - Upon the issuance of a receipt or receipts by relevant regulatory authorities for a prospectus filed by or on behalf of the Company with such relevant regulatory authorities relating to an initial public offering of the Company's Common shares (which shall be deemed to have occurred upon the issuance by the directors on behalf of the Company of a certificate attesting to this fact), then all of the Class A Preference shares shall immediately and automatically be converted into fully paid Common shares on the basis of one (1) Class A Preference share for one (1) Common share. Effective as of the conversion date, the Company shall issue to each holder of Class A Preference shares certificates representing fully paid and non-assessable Common shares in the number determined as set out above and shall cancel all share certificates representing the Class A Preference shares.
- (c) Rights on Dissolution - In the event of the liquidation, dissolution or winding up of the Company or other distribution of the property or assets of the Company among its members for the purpose of winding up its



affairs, whether voluntary or involuntary, and subject to the special rights and restrictions attaching to the Class B Preference shares, the Class C Preference shares and any shares of any series of the Class B Preference shares and the Class C Preference shares, the distributions to the holders of the Class A Preference shares and the Common shares shall be in the following order:

- i) firstly, the holders of the Class A Preference shares shall be entitled to receive, prior to any distribution to the holders of the Common shares, an amount equal to \$2.75 per Class A Preference share held, plus any declared but unpaid dividends on the Class A Preference shares; and
- ii) thereafter, the holders of the Class A Preference shares and the Common shares shall be entitled to receive an equal amount with respect to each Class A Preference share and Common share held.

Class B Preference shares - There are no Class B preference shares outstanding.

Class C Preference shares - There are no Class C preference shares outstanding.

Dilution Rights - The Company shall not subdivide, consolidate, reclassify or otherwise change the Common shares or any other class or series of Preference shares unless the Common shares and the other classes or series of Preference shares shall be contemporaneously subdivided, consolidated, reclassified or otherwise changed in the same proportion and in the same manner.

Details of Offering - As at September 6, 1996, there were 5,244,687 Class A Preference shares, 275,000 Options convertible into Class A Preference shares, and 688,000 Options convertible into Common shares issued and outstanding. There are no Common shares, Class B Preference shares or Class C Preference shares issued and outstanding.

The Offering consists of 25,000 Class A Preference shares. Angiotech plans to accept ("Acceptance" or "Acceptances") subscriptions pursuant to this Offering in one closing. The Acceptance is planned to occur upon Angiotech receiving subscriptions for shares sufficient to fill the Offering. At a price of \$2.75 per Class A Preference share, the gross proceeds of the Offering will be \$68,750.

The minimum subscription to purchase Class A Preference shares pursuant to the Offering is Cdn. \$25,000 or 9,901 Class A Preference shares for residents of British Columbia. Subscriptions will be received, subject to prior sale and subject to rejection or allotment, in whole or in part, by Angiotech prior to the Acceptance. (See SUBSCRIPTION PROCEDURE)

The Offering price of \$2.75 per Class A Preference share was established arbitrarily by the Company.

## **DILUTION**

The net tangible fully diluted (as if all shares were converted to Common shares) book value of the Company's shares as per the July 31, 1996 unaudited financial statements as adjusted to reflect the capital reorganization as approved by the shareholders on September 6, 1996 was \$1,218,629 or \$0.20 per share. "Net tangible book value per share" represents the total tangible assets of the Company less total liabilities, divided by the total number of fully diluted (as if all shares were converted to Common shares) shares of the Company outstanding.

After taking into the estimated proceeds from the sale of 25,000 Class A Preference shares in the Offering at a price of \$2.75 per share, the pro-forma net tangible book value of the Company estimated as at July 31, 1996 would have been \$1,287,379 or \$0.21 per share, representing an immediate increase in the net tangible book value of \$0.01 per fully diluted (as if all shares were converted to Common shares) share to existing shareholders and an immediate dilution of \$2.54 per share or 92.49% to new investors purchasing shares at the current Offering price. "Dilution to new investors" represents the difference between the price of the Class A Preference shares issued

pursuant to the Offering and the pro-forma net tangible book value per fully diluted (as if all shares were converted to Common shares) share as at July 31, 1996, as adjusted to give effect to this Offering. Illustrated in the following table is the dilution described on the previous page:

	Maximum Offering
Offering Price of Class A Preference shares	\$2.75
Net tangible book value per share before Offering	\$0.20
Increase per share attributable to new investors <sup>(1)</sup>	\$0.01
Pro-forma net tangible book value per share after Offering	\$0.21
Dilution to new investors	\$2.54

## SUBSCRIPTION PROCEDURE

Pursuant to this Offering, 25,000 Class A Preference shares are available for subscription by investors in accordance with the terms of this Offering and a Subscription Agreement available from the Company. An investor wishing to subscribe for Class A Preference shares must deliver a fully executed Subscription Agreement and a cheque or bank draft in the amount of the subscription price. All documentation referred to above is available upon request. Certificates evidencing the purchase of Class A Preference shares will be issued to Subscribers by Angiotech at the time of Acceptance and delivered to the Agent on behalf of Subscribers. If a subscription is not accepted by Angiotech or if the Offering is not completed, the Company will return all funds it has received pursuant to that subscription, without interest or deduction.

Provided that all of the conditions precedent to Acceptance (see PLAN OF DISTRIBUTION) have been satisfied and an Acceptance occurs, including completion of the Minimum Offering, the subscribers shall become Class A Preference shares shareholder. Any subscription received thereafter will, upon acceptance by Angiotech, be processed and the proceeds of subscription will be released to Angiotech to be applied as described under USE OF PROCEEDS.

The Offering is made pursuant to the prospectus exemptions contained in section 128(b) of the Rules to the British Columbia *Securities Act*.

## RESALE RESTRICTIONS

Applicable securities legislation provides that a trade in the Class A Preference shares acquired pursuant to this Offering is deemed to be a distribution and is subject to the prospectus requirements of the respective legislation, unless *inter alia*:

- (a) the Class A Preference shares have been held for at least 12 months for British Columbia from the later of the date of issue of the shares and the date the Company becomes a reporting issuer in the province;
- (b) no unusual effort is made to prepare the market or create a demand for the Class A Preference shares;
- (c) no extraordinary commission or other consideration is paid in respect of the trade; and
- (d) the seller is not a control person of Angiotech.

## PLAN OF DISTRIBUTION

The Class A Preference shares will be offered for sale in British Columbia. No director, officer or employee of the Company will receive any commission.

The Subscription Agreements and proceeds received in connection with this Offering will be released to Angiotech upon receiving subscriptions totalling the Offering.

This Offering shall be completed on the Acceptance Date.

If all conditions precedent to the completion of this Offering have not been satisfied before the Acceptance Date, the Company shall promptly return to the applicable Subscribers all Subscription Agreements together with the Subscription Price without interest or deduction. If all conditions precedent to the completion of this Offering have been satisfied before the Acceptance Date, an Acceptance will occur and the proceeds of subscriptions will be released to be applied as described under the Use of Proceeds.

Subscriptions will be received subject to rejection or allotment in whole or in part and the right is reserved to close the subscription books at any time without notice. If Angiotech rejects any Subscription Agreements, such Subscription Agreement together with the Subscription Price, without interest or deduction, will be returned to the applicable Subscribers.

There are substantial resale restrictions on the Common shares under Canadian and U.S. law. (See RESALE RESTRICTIONS).

## **MATERIAL CONTRACTS**

The following is a list of the material contracts entered into by Angiotech since inception:

### **General Agreements**

- (1) the offer to lease dated August 17, 1995 with Discovery Parks Inc. (for research facilities in the Multi-Tenant Facility at University of British Columbia);
- (2) the rental agreements dated November 3, 1994 and July 24, 1995 respectively with University of British Columbia ("UBC") relating to the use of space in the lab of Dr. Burt at UBC;
- (3) the offering memorandum dated November 27, 1995 and amendments thereto dated January 5 and 31, 1996;
- (4) the agency agreement dated January 26, 1996 with First Marathon Securities Limited ("First Marathon") relating to the January 1996 private placement;
- (5) the shareholders agreement dated February 27, 1996 with certain shareholders of the Company; and
- (6) the share purchase warrant dated February 28, 1996 with First Marathon.
- (7) the stock option agreements dated September 6, 1996 with various current and former employees, officers, directors and consultants.

### **Intellectual Property Agreements**

- (1) the asset purchase agreement dated September 30, 1992, and subsequently amended, with Drs. Hunter, Machan and Arsenault;
- (2) the research collaboration and technology transfer agreement dated November 19, 1993, and subsequently amended, with H.D.M. Research Inc. and Dr. Cruz;
- (3) the assignment agreement dated July 11, 1994 with McMaster University;
- (4) the exclusive, worldwide, royalty bearing license dated April 25, 1995 with Mount Sinai Hospital Corporation (granting Angiotech rights to the Mount Sinai intellectual property relating to the use of vanadium compounds in the treatment of anti-proliferative diseases);

- (5) the exclusive, worldwide, royalty bearing license dated August 1, 1995 with UCLA (granting Angiotech rights to the UCLA intellectual property relating to the use of taxanes in the treatment of arthritis); and
- (6) the option agreement dated February 15, 1996 with the UBC.

#### **Research Agreements**

- (1) the collaborative research agreement dated October 23, 1992 with Dr. Larry Arsenault;
- (2) the research agreement dated January 22, 1993 with UBC (Dr. Burt);
- (3) the collaborative research agreement dated February 1, 1994 with UBC (Dr. Machan);
- (4) the collaborative research agreement dated October 21, 1993, and subsequently amended, with UBC (Dr. Burt);
- (5) the collaborative research agreement dated July 11, 1994 with McMaster University (relating to the research of Dr. Arsenault);
- (6) the collaborative research agreement commencing fall 1994 with the Dohenny Eye Institute, University of California;
- (7) the service agreement dated December 13, 1994 with the British Columbia Cancer Agency Investigational Drug Section (the "BCCA");
- (8) the gift dated January 24, 1995 to support the research of Dr. Brahn at the University of California at Los Angeles ("UCLA");
- (9) the research license and confidentiality agreement dated January 24, 1995 with Dr. Ernest Brahn (granting a license to Dr. Brahn to allow him to conduct research on the Company's technologies);
- (10) the service agreements dated February 13, February 28 and April 12, 1995 with the CTRC Research Foundation (University of Texas at San Antonio);
- (11) the material transfer agreement dated March 20, 1995 with UCLA;
- (12) the collaborative research agreement dated April 25, 1995 with Mount Sinai Hospital Corporation;
- (13) the agreements for submitting products to the Division of Cancer Treatment, National Cancer Institute dated June 16, 1995;
- (14) the grant in aid agreement dated September 27, 1995 with the University of British Columbia;
- (15) the cooperative research agreement dated February 15, 1996 with the UBC
- (16) the service agreement dated February 16, 1996 with the BCCA;
- (17) the cooperative research agreement dated February 16, 1996 with the BCCA;
- (18) the CRADA letter of intent dated April 4, 1996 with the National Institute of Aging, of the U.S. National Institutes of Health; and
- (19) the cooperative research agreement dated April 17, 1996 with Ribozyme Pharmaceuticals, Inc.

#### **Employment and Advisor Agreements**

- (1) the employment agreements and principal scientist agreements with Dr. Hunter, Ken Mellquist, David Hall, Dr. Arsenault, Dr. Cruz, Dr. Machan, Dr. Zhang, Dr. Min and Ann Marie Oktaba;
- (2) the scientific advisory board agreements with Drs. Brahn, Von Hoff, Wallace, Israels, Lee and Keystone;
- (3) the employment agreements with Dr. Robert Abbott, Sheryl Osborne and David Hartnett; and
- (4) the consulting agreements with Don Longenecker, Ph.D. and Jefferson Works.

## **Government Grant Agreements**

- (1) the technology enhancement grant agreements dated January 11, July 23, and October 25, 1993, May 16, 1994 and June 1996 with the National Research Council (Canada)/Industrial Research Assistance Program;
- (2) the University Industry Operating Grant dated May 31, 1993 with the Medical Research Council of Canada and Dr. Burt (supporting research conducted in Dr. Burt's lab);
- (3) the letter agreement dated January 6, 1994 with the National Research Council (Canada)/Industrial Research Assistance Program;
- (4) the letter agreement dated May 2, 1994 with the Science Council of British Columbia relating to Technology BC Application #129 (T-6) (Clinical Uses of Inhibitors of Angiogenesis in the Treatment of Cancer);
- (5) the letter agreement dated November 1994 with the Science Council of British Columbia relating to MART Grant #94/95 - 11; and
- (6) the research fellowship agreement dated August 1, 1995 with the National Sciences and Engineering Research Council.

Copies of the above agreements (or in the case of confidential agreements, summaries) may be inspected by prospective investors qualified by Angiotech at the Company's offices at 2120 - 1066 West Hastings Street, Vancouver, British Columbia, Canada, V6E 3X1, during normal business hours at any time during the period of distribution of the Class A Preference shares pursuant to this Memorandum.

## **LEGAL MATTERS**

Angiotech is not engaged in any legal proceedings and is not aware of any proceedings whether contemplated by or against the Company.

## **RISK FACTORS**

AN INVESTMENT IN THE CLASS A PREFERENCE SHARES - SERIES I INVOLVES VARIOUS RISKS. PROSPECTIVE INVESTORS SHOULD REVIEW THESE RISKS WITH THEIR PROFESSIONAL ADVISORS AND SHOULD CONSIDER, IN ADDITION TO THE MATTERS DISCUSSED ELSEWHERE IN THIS MEMORANDUM, THE FOLLOWING:

### **TECHNOLOGICAL CHANGE**

The ability of Angiotech to compete is dependent in large part on its ability to commercialize its products and technologies or to enter into strategic relationships to accomplish these goals. In order to do so, Angiotech must effectively utilize and expand its research and development activities and, once developed, be able to attract large commercial health care companies to license and market its products. Angiotech's competitors may succeed in developing technologies and products which render Angiotech's technologies and products obsolete. Many companies and research institutions are researching and developing technologies and products which may supersede Angiotech's own products presently under development. Because clinical trials are not complete, no assurances can be made that Angiotech's products will pass clinical trials. For the same reason, no assurances can be made as to the extent of Angiotech's products ultimate uses.

## PATENTS AND PROPRIETARY RIGHTS

There can be no assurance that either Angiotech's or its academic partners existing patent applications will mature into issued patents, that Angiotech will obtain any necessary or desired additional licenses to patents or technologies of others or that Angiotech will be able to develop its own additional patentable technologies. Angiotech believes that the patent position of biotechnology and pharmaceutical companies generally is highly uncertain and involves complex legal and factual questions all of which are expensive to deal with. There can be no assurance that any future patent applications or patents issued to Angiotech will provide it with competitive advantages or will not be challenged as infringing upon patents or proprietary rights of others which could result in damages or the requirement to obtain licenses, or that the patents, proprietary rights or other developments of others will not have an adverse effect on the ability of Angiotech to do business. The Company may be required to obtain licenses from third parties to avoid infringing patents or other proprietary rights. No assurance can be given that any licenses required under any such patents or proprietary rights would be made available, if at all, on terms acceptable to the Company. If the Company does not obtain such licenses, it could encounter delays in the introduction of products, or could find that development, manufacture or sale of products requiring such licenses could be prohibited. In addition, the Company could incur substantial costs in defending itself in suits brought against the Company on patents it might infringe or in filing suits against others to have such patents declared invalid. Patent litigation is becoming more widespread in the biotechnology industry and it is not possible to predict how any such litigation will affect the Company's efforts to form strategic alliances, to conduct clinical testing or to manufacture and market any products under development. Further, there can be no assurance that the Company's patents, if issued, would be held valid by a court of competent jurisdiction. The Company may also become involved in interference proceedings in connection with one or more of its patents or patent applications to determine priority of invention, which could result in substantial cost to the Company, as well as a possible adverse decision as to priority of invention of the patent or patent application involved. The Company also relies upon unpatented proprietary technology, and no assurance can be given that third parties will not independently develop proprietary information and techniques substantially equivalent or gain access to the Company's trade secrets or disclose such technology to the public. In addition, the obligation to maintain the confidentiality of such proprietary technology could be breached wrongfully by employees, consultants, advisors or others, or the Company could be unable to maintain and protect unpatented proprietary technology.

## CONFIDENTIAL INFORMATION

Much of the Company's know-how and technology may not be patentable. To protect its rights, Angiotech requires employees, consultants, advisors and collaborators to enter into confidentiality agreements. There can be no assurance, however, that these agreements will provide meaningful protection for the Company's trade secrets, know-how or other proprietary information in the event of any unauthorized use or disclosure. Further, the Company's business may be adversely affected by competitors who independently develop competing technologies, especially if Angiotech obtains no, or only narrow, patent protection. (See INTELLECTUAL PROPERTY section.)

## GOVERNMENT REGULATION

The development, manufacture, testing and marketing of Angiotech's products are subject to extensive regulation by numerous authorities in Canada, the United States and other countries. In Canada and the United States, before pharmaceutical products are permitted to be marketed commercially, they must be approved by the Health Protection Branch of the Government of Canada and the Food and Drug Administration of the United States respectively. Additionally, approval by analogous regulatory authorities in other countries must be obtained prior to commencing marketing of pharmaceutical products in those countries. The approval process varies from country to country and approval of a drug for sale in one country does not ensure approval in other countries. Such an approval process can be costly and an estimate of those costs cannot be accurately determined at the present time. Delays in obtaining regulatory approvals may adversely affect the development, testing and marketing of

Angiotech's products and the ability of Angiotech to generate revenues from the sale of such products. There can be no assurance that Angiotech will obtain regulatory approval for its products in a timely manner, or at all.

## **LIMITED MARKETABILITY**

The Class A Preference shares offered by this Offering are speculative securities. **THERE IS NO PUBLIC MARKET FOR THE CLASS A PREFERENCE SHARES AND NONE IS EXPECTED TO DEVELOP IN THE NEAR TERM.** It may be difficult or impossible to resell the Class A Preference shares. This Offering is not qualified by way of prospectus and consequently the resale of the Class A Preference shares is subject to restrictions under applicable securities legislation. An investment in the Class A Preference shares should only be considered by those investors who are able to take and bear the economic risk of a long-term investment, and the possible loss of their investment. (See **RESALE RESTRICTIONS**)

## **RELIANCE ON MANAGEMENT**

In assessing the risks and rewards of an investment in the Class A Preference shares, potential investors should appreciate that they are relying on the good faith, experience and judgement of Angiotech and its ability to make appropriate decisions in respect of the management and operation of the Company. It would be inappropriate for investors to purchase Class A Preference shares if they are unwilling to rely upon and entrust Angiotech with all aspects of the management of the Company. The success of the Company is dependent in part on the expertise of management of Angiotech. The loss of one or more of those individuals could have a material adverse effect on the Company.

## **RISK OF INVESTMENT IN THE BUSINESS**

There is no assurance that the business of Angiotech will be operated successfully. Further, since a significant aspect of the potential return to the subscribers will be based on the revenue generated by the products which are to be developed by Angiotech, there can be no assurance that such business activities will generate revenues sufficient to meet the operational or financial needs of Angiotech.

## **RELIANCE ON KEY PERSONNEL**

Angiotech's success is largely dependent on the continued services of a limited number of skilled managers and scientists. While the loss of any one person would not have a significant adverse effect on the Company, the loss of several of these individuals could. Likewise, a key success factor will be the ability of the Company to recruit and retain additional highly skilled managers, technical staff and similar individuals. There is also no assurance that Angiotech will be able to retain existing employees or to attract and retain the necessary additional skilled staff required given the competitive climate for such personnel and the geographic location of Angiotech.

## **PRODUCT LIABILITY**

The testing, marketing and sale of human healthcare products entail an inherent risk of allegations of product liability and there can be no assurance that substantial product liability claims will not be brought against the Company. Angiotech does not currently have any product liability insurance coverage. However, the Company will seek to obtain product liability insurance if and when its products are commercialized. Yet there can be no assurances that adequate insurance coverage will be available at acceptable costs, if at all, or that a product liability claim would not materially affect the business or financial condition of the Company.

## **DILUTION**

Angiotech contemplates a public offering of its Common shares in the future which will give those future investors an interest in Angiotech. Accordingly, the investor's fully diluted interest in Angiotech will be diluted.

## FINANCIAL PERFORMANCE

The Company has not generated any sales revenue and is in the early stage of development. The Company has suffered losses in each year and may continue to have losses for the several years until a commercial licensing agreement is secured. No formal contracts have been entered into, nor orders taken, in respect of the sale of the Company's products. The Company has yet to establish a direct sales force or distribution network. The Company may require extensive additional financing for further research, development and marketing. Such financing may or may not be available and, if available, may result in substantial dilution to existing shareholders.

## COMPETITION

The industry within which the Company proposes to operate is subject to significant competition. Other medical companies which have greater financial and technical resources and larger marketing organizations than the Company pose a potential threat if they commence an effort to compete with the Company in its market segments.

## RIGHTS FOR PURCHASERS IN BRITISH COLUMBIA

A purchaser resident in British Columbia to whom this Memorandum, together with any amendments thereto, has been delivered shall have a contractual right of action against the Company on the following basis. If this Memorandum, together with any amendments thereto, contains an untrue statement of a material fact or omits to state a material fact that is required to be stated or that is necessary in order to make any statement in it not false or misleading in the light of the circumstances in which it was made (a "BC Misrepresentation") and it was a BC Misrepresentation at the time of purchase of the Class A Preference shares, the purchaser will be deemed to have relied upon the BC Misrepresentation and will, as provided below, have a right of action against Angiotech, every person who signed the Memorandum or any amendments thereto, and every director of Angiotech at such time for damages or, alternately, while still the owner of any of the Class A Preference shares purchased by that purchaser, for rescission, in which case, if the purchaser elects to exercise the right of rescission, the purchaser will have no right of action for damages against Angiotech, provided that:

- i) the right of action for rescission or damages will be exercisable by a purchaser resident in British Columbia only if the purchaser gives written notice, not later than 90 days after the date on which the payment is made for the Class A Preference shares, that the purchaser is exercising this right of action for rescission or damages and an action is commenced to enforce this right,
  - a) in the case of an action for rescission, within 180 days after the date of purchase, or
  - b) in the case of an action other than for rescission, within the earlier of 180 days following the date the purchaser had knowledge of the BC Misrepresentation or three (3) years following the date of purchase;
- ii) The persons identified above will not be liable if it proves that the purchaser purchased the Class A Preference shares with knowledge of the BC Misrepresentation;
- iii) in the case of an action for damages, the persons identified above will not be liable for all or any portion of the damages that it proves does not represent a depreciation in value of the Class A Preference shares as a result of the BC Misrepresentation relied upon; and
- iv) in no case will the amount recoverable in any action exceed the price at which the Class A Preference shares were sold to the purchaser.

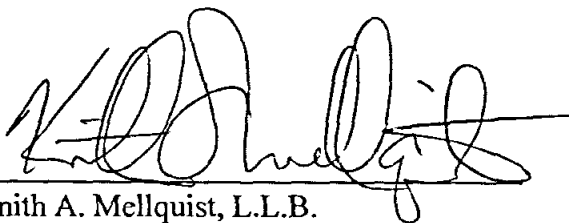


## CERTIFICATE

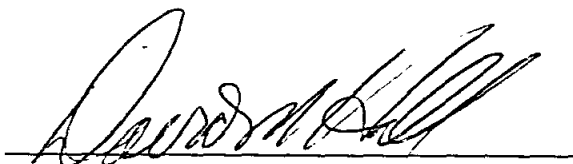
The foregoing contains no untrue statement of a material fact and does not omit to state a material fact that is required to be stated or that is necessary to prevent a statement that is made from being false or misleading in the circumstances in which it was made.

DATED: September 6, 1996

### ANGIOGENESIS TECHNOLOGIES INC.



Kennith A. Mellquist, L.L.B.  
Vice President and Director



David M. Hall  
Vice President, Finance

## **APPENDICES**

### **APPENDIX A - AUDITED FINANCIAL STATEMENTS**

September 30, 1995, 1994 and 1993

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FINANCIAL STATEMENTS

ANGIOGENESIS TECHNOLOGIES, INC.

September 30, 1995

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## AUDITORS' REPORT

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To the Shareholders of  
**Angiogenesis Technologies, Inc.**

We have audited the balance sheet of **Angiogenesis Technologies, Inc.** as at September 30, 1995 and the statements of loss and deficit and changes in financial position for the year then ended. These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on these financial statements based on our audit.

We conducted our audit in accordance with generally accepted auditing standards. Those standards require that we plan and perform an audit to obtain reasonable assurance whether the financial statements are free of material misstatement. An audit includes examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements. An audit also includes assessing the accounting principles used and significant estimates made by management, as well as evaluating the overall financial statement presentation.

In our opinion, these financial statements present fairly, in all material respects, the financial position of the Company as at September 30, 1995 and the results of its operations and the changes in its financial position for the year then ended in accordance with generally accepted accounting principles. As required by the British Columbia Company Act, we report that, in our opinion, these principles have been applied on a basis consistent with that of the preceding year.

Vancouver, Canada,  
November 8, 1995.

*Ernst & Young*

Chartered Accountants

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**Angiogenesis Technologies, Inc.**  
Incorporated under the laws of British Columbia

**BALANCE SHEET**

As at September 30

	1995 \$	1994 \$
<b>ASSETS</b>		
Current		
Cash	328,585	69,977
Investment tax credits receivable	352,220	179,283
Grants receivable	35,134	—
Prepaid expenses and other	21,150	20,379
<b>Total current assets</b>	<b>737,089</b>	<b>269,639</b>
Fixed assets <i>[note 3]</i>	27,969	22,674
Patents and medical technology <i>[note 4]</i>	251,619	59,545
	<b>1,016,677</b>	<b>351,858</b>
<b>LIABILITIES AND SHAREHOLDERS' EQUITY</b>		
Current		
Accounts payable and accrued liabilities	164,981	86,042
<b>Total current liabilities</b>	<b>164,981</b>	<b>86,042</b>
Share subscriptions received in advance <i>[note 5]</i>	271,777	—
<b>Total liabilities</b>	<b>436,758</b>	<b>86,042</b>
Shareholders' equity		
Common shares <i>[note 6]</i>	2,053,114	840,577
Deficit	(1,473,195)	(574,761)
<b>Total shareholders' equity</b>	<b>579,919</b>	<b>265,816</b>
	<b>1,016,677</b>	<b>351,858</b>

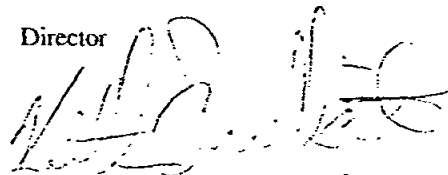
See accompanying notes

On behalf of the Board:

Director



Director



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Angiogenesis Technologies, Inc.

STATEMENT OF LOSS AND DEFICIT

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Year ended September 30

	1995 \$	1994 \$
<b>EXPENSES</b>		
<b>Research and development</b>		
Contract services	725,481	210,075
Consumable supplies	344	1,569
Depreciation	12,834	3,305
Office and rent	33,929	15,669
Other	9,918	3,539
Salaries and benefits	223,676	159,050
Travel	29,034	35,780
	1,035,216	428,987
Less: Investment tax credits	(260,000)	(92,220)
Government grants	(107,224)	(98,027)
	667,992	238,740
<b>General and administration</b>		
Accounting and legal	37,987	6,582
Consulting	33,327	—
Bank charges	58	103
Interest income	(4,918)	(4,573)
Office and rent	32,336	6,595
Other	18,853	1,297
Salaries and benefits	112,799	24,413
	230,442	34,417
<b>Loss for the year</b>	898,434	273,157
<b>Deficit, beginning of year</b>	574,761	197,604
Premium paid on cancellation of share subscriptions	—	104,000
<b>Deficit, end of year</b>	1,473,195	574,761

*See accompanying notes*

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Angiogenesis Technologies, Inc.

STATEMENT OF CHANGES IN FINANCIAL POSITION

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Year ended September 30

	1995 \$	1994 \$
<b>OPERATING ACTIVITIES</b>		
Loss for the year	(898,434)	(273,157)
Add items not involving cash:		
Depreciation	12,834	3,305
Net change in non-cash working capital balances related to operations	(202,279)	(76,109)
<b>Cash used in operating activities</b>	<b>(1,087,879)</b>	<b>(345,961)</b>
<b>INVESTING ACTIVITIES</b>		
Purchase of fixed assets	(18,129)	(21,373)
Cost of patents and medical technology	(119,698)	(42,422)
<b>Cash used in investing activities</b>	<b>(137,827)</b>	<b>(63,795)</b>
<b>FINANCING ACTIVITIES</b>		
Share subscriptions - net	—	(57,183)
Issue of shares for cash	1,143,787	511,260
Issue of shares for medical technology	68,750	—
Share subscriptions received in advance	271,777	—
Cancellation of share subscriptions	—	(104,000)
<b>Cash provided by financing activities</b>	<b>1,484,314</b>	<b>350,077</b>
<b>Net increase (decrease) in cash during the year</b>	<b>258,608</b>	<b>(59,679)</b>
Cash, beginning of year	69,977	129,656
<b>Cash, end of year</b>	<b>328,585</b>	<b>69,977</b>

*See accompanying notes*

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**Angiogenesis Technologies, Inc.**

**NOTES TO FINANCIAL STATEMENTS**

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September 30, 1995

**1. NATURE OF BUSINESS**

Angiogenesis Technologies Inc. (the "Company"), was incorporated under the British Columbia Company Act on October 12, 1989. The Company changed its name to Angiogenesis Technologies, Inc. on January 6, 1993. The primary business purpose of the Company is to research and develop medical products and technologies relating to angiogenesis or blood vessel growth.

No revenues have been earned to date from technology under development and the Company has financed its cash requirements primarily from share issuances and government grants and investment tax credits. The Company's ability to realize the carrying value of its assets is dependent on successfully bringing its new technologies to the market and achieving future profitable operations, the outcome of which cannot be predicted at this time. It will be necessary for the Company to raise additional funds in the coming year for the continuing development of its technologies.

**2. SUMMARY OF SIGNIFICANT ACCOUNTING POLICIES**

The following is a summary of the significant accounting policies used in the preparation of these financial statements.

**Fixed assets**

Fixed assets are stated at cost. Office furniture and equipment is depreciated over three years and research equipment over two years on the straight-line method.

**Research and development costs**

Research costs are expensed in the year incurred. Development costs are expensed in the year incurred unless the Company believes a development project meets generally accepted accounting criteria for deferral and amortization.

No development costs have been deferred to date. Research-related government assistance, grant and research contract revenue received is credited against research and development expenditures.



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Angiogenesis Technologies, Inc.

NOTES TO FINANCIAL STATEMENTS

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September 30, 1995

2. ACCOUNTING POLICIES (cont'd.)

Investment tax credits

The benefits of income tax credits for scientific research and development expenditures are recognized in the year the qualifying expenditure is made. The investment tax credit reduces the carrying cost of expenditures for capital assets and research and development.

Patents and medical technology

Patents consist of the consideration paid for the patents and related legal costs and will be amortized over the lesser of the estimated useful life of the related technology and the life of the patent commencing with commercial production.

The costs of acquiring medical technology are capitalized and will be amortized over the life of the technology once commercial production of the related product commences or once the Company enters into a licensing agreement.

If management determines that successful development of products to which patent and medical technology costs relate is not reasonably certain, or that deferred patent and medical technology costs exceed recoverable value, such costs are charged to operations.

3. FIXED ASSETS

	Cost \$	Accumulated depreciation \$	Net book value \$
<b>1995</b>			
Research equipment	9,719	5,560	4,159
Office furniture and equipment	35,979	12,169	23,810
	45,698	17,729	27,969
<b>1994</b>			
Research equipment	9,719	700	9,019
Office furniture and equipment	17,850	4,195	13,655
	27,569	4,895	22,674

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Angiogenesis Technologies, Inc.

NOTES TO FINANCIAL STATEMENTS

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September 30, 1995

4. PATENTS AND MEDICAL TECHNOLOGY

	1995 \$	1994 \$
Patents	121,655	48,745
Medical technology	129,964	10,800
	251,619	59,545

The Company and Dr. B. Hunter, Dr. L. Machan and Dr. L. Arsenault (the "Scientists") entered into an asset purchase agreement dated September 30, 1992, and subsequently amended, (the "Scientist Agreement") that provides for the transfer of all right, title and interest in and to certain assets, proprietary technology and intellectual property associated with anti-angiogenic therapy, (the "Core Technology"). Pursuant to the Scientist Agreement, the Company made available to the Scientists 400,000 common shares at a price of \$0.01 per share and 525,700 common shares at a price of \$0.25 per share. The Company also entered into a collaborative research agreement with the Scientists to fund the costs associated with the further research and development of the Core Technology, such costs not to exceed \$500,000 in aggregate by March 31, 1993.

The Company and H.D.M. Research Inc. ("HDM") and Dr. T. Cruz entered into an asset purchase agreement dated November 19, 1993, and subsequently amended, (the "HDM Agreement") that provides for the transfer of HDM and Dr. T. Cruz's right, title and interest in and to certain assets, proprietary technology and intellectual property associated with Vanadium compounds in the treatment of proliferation disorders (the "Vanadate Technology"). Pursuant to the HDM Agreement, the Company made available to Dr. T. Cruz 133,333 common shares at a price of \$0.01 per share and 175,233 common shares at a price of \$0.25 per share.

The Company and McMaster University ("McMaster") entered into an assignment agreement dated July 11, 1994 for certain data ("Data") and all right, title and interest in intellectual property in anti-angiogenic compositions and methods of use. The Company paid an assignment fee of \$10,800 upon execution of the agreement.

The Company and Mount Sinai Hospital Corporation (the "Hospital") entered into a licensing agreement (the "Hospital Agreement") dated April 25, 1995, pursuant to which the Company was granted an exclusive, world-wide, royalty-bearing license to vanadate compounds and derivatives or analogues thereof for the treatment of proliferative disorders, metastases and drug resistant tumors (the "Hospital Technology"). The Hospital also granted the Company the right to issue exclusive or non-exclusive sub-licenses to third parties for the use of the Hospital Technology. The Hospital has agreed to collaborate with the Company in further research, development and testing of the licensed technology.

## NOTES TO FINANCIAL STATEMENTS

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September 30, 1995

### 4. PATENTS AND MEDICAL TECHNOLOGY (cont'd.)

Under the Hospital Agreement, the Company paid the Hospital a license issue fee of \$10,000 and issued 25,000 common shares to the Hospital at a deemed value of \$2.75 per share [see note 6]. In addition, the Company may be required to make further payments of cash and/or shares (shares to be issued at the option of the Company) to the Hospital upon the attainment of certain milestones relating to the commercial development of the Hospital Technology. The aggregate costs to the Company to obtain the exclusive, world-wide license to the Hospital Technology, including the license issue fee, shares and all development milestones, will not exceed \$300,000. Milestones payments will only be required to the extent that the consideration paid to the date of the milestone (including any increased value of any shares issued to the Hospital) is less than the total consideration required to be provided to the Hospital as of the attainment of the milestone.

The Company and the Regents of the University of California ("The Regents") entered into a licensing agreement (the "UCLA Agreement") dated August 1, 1995, pursuant to which the Company was granted an exclusive, world-wide royalty-bearing license to use certain technologies of the Regents (the "UCLA Technology") for the use of paclitaxel and derivatives or analogues thereof in the treatment of rheumatoid arthritis. The Regents also granted the Company the right to issue exclusive or non-exclusive sub-licenses to third parties for the use of the UCLA Technology.

Under the UCLA Agreement, the Company acquired a license for \$30,000 U.S. to be paid in cash or shares, at The Regents option. Upon signing of the agreement, the Company paid an initial instalment of \$10,000 U.S. towards the license issue fee. The final payment of \$20,000 U.S. is included in accounts payable and accrued liabilities and is payable no sooner than February, 1996. In addition, the Company must make further payments of cash and/or shares (shares to be issued at the option of The Regents) to The Regents upon the attainment of certain milestones relating to the commercial development of the UCLA Technology. The aggregate costs to the Company to obtain the exclusive, world-wide license to the UCLA Technology, including the license issue fee and all development milestones, will not exceed \$230,000 U.S.

### 5. SHARE SUBSCRIPTIONS RECEIVED IN ADVANCE

This represents funds received in advance of common shares issued.

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Angiogenesis Technologies, Inc.

NOTES TO FINANCIAL STATEMENTS

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September 30, 1995

6. SHARE CAPITAL

(a) Authorized

100,000,000 Class A common shares without par value  
100,000,000 Class B common shares without par value  
100,000,000 Class A preference shares with a par value of \$1.00  
100,000,000 Class B preference shares with a par value of \$10.00

(b) Issued and outstanding - Class A common shares

	No. of shares #	Amount \$
Issued and outstanding		
Issued for cash on incorporation	100	100
Issued for cash pursuant to a private placement	2,476,866	329,217
Balance, September 30, 1993	2,476,966	329,317
Issued for cash pursuant to a private placement	737,200	511,260
Balance, September 30, 1994	3,214,166	840,577
Issued for cash pursuant to a private placement	515,558	1,143,787
Issued for the acquisition of certain medical technology [note 4]	25,000	68,750
Balance, September 30, 1995	3,754,724	2,053,114

(c) Performance shares

The Company has issued 1,338,433 common performance shares to be released as determined by the Board of Directors.

(d) Incentive and other stock options

At September 30, 1995 the Company has 20,000 common shares reserved for issuance on exercise of incentive stock options at a price of \$2.00 per share and expiring on September 30, 1996. In addition, options to acquire 250,000 common shares at \$2.75 per share have been authorized to directors, officers, employees and consultants of the Company. At September 30, 1995, these options have not been allocated.

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Angiogenesis Technologies, Inc.

NOTES TO FINANCIAL STATEMENTS

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September 30, 1995

7. INCOME TAXES

The Company has non-capital loss carryforwards for income tax purposes available to reduce taxable income for future years. These losses expire as follows:

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	\$
2000	277,000
2001	167,000
2002	497,000
	<hr/> 941,000

In addition, the Company has timing differences relating primarily to fixed assets and scientific research and experimental development expenditures of approximately \$680,000 which may be used to reduce future taxable income. The potential income tax benefits relating to these losses, timing differences and tax balances have not been recognized in the accounts as their realization is not reasonably assured.

8. COMMITMENTS

Lease commitments

The Company has entered into an operating lease agreement for office and laboratory space. Future minimum annual lease payments under this lease are as follows:

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	\$
1996	48,700
1997	19,500
1998	19,500
1999	19,500
2000	19,500
Thereafter	3,300
	<hr/> 130,000

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Angiogenesis Technologies, Inc.

NOTES TO FINANCIAL STATEMENTS

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September 30, 1995

8. COMMITMENTS (cont'd.)

Research contracts

Under the terms of various research contracts, the Company is committed to making the following annual payments:

	\$
1996	446,435
1997	90,000
	<u>536,435</u>

9. SUBSEQUENT EVENTS

- a) Subsequent to the year end the Company issued 98,828 common shares for total consideration of \$271,777.
- b) Subsequent to September 30, 1995 the Company anticipates completing an agency agreement for a private placement of up to 1,818,200 Class A common shares at \$2.75 per share on a "best efforts" basis.

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FINANCIAL STATEMENTS

ANGIOGENESIS TECHNOLOGIES, INC.

September 30, 1994

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## AUDITORS' REPORT

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To the Shareholders of  
**Angiogenesis Technologies, Inc.**

We have audited the balance sheet of **Angiogenesis Technologies, Inc.** as at September 30, 1994 and the statements of loss and deficit and changes in financial position for the year then ended. These financial statements are the responsibility of the company's management. Our responsibility is to express an opinion on these financial statements based on our audit.

We conducted our audit in accordance with generally accepted auditing standards. Those standards require that we plan and perform an audit to obtain reasonable assurance whether the financial statements are free of material misstatement. An audit includes examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements. An audit also includes assessing the accounting principles used and significant estimates made by management, as well as evaluating the overall financial statement presentation.

In our opinion, these financial statements present fairly, in all material respects, the financial position of the company as at September 30, 1994 and the results of its operations and the changes in its financial position for the year then ended in accordance with generally accepted accounting principles. As required by the British Columbia Company Act, we report that, in our opinion, these principles have been applied on a basis consistent with that of the preceding year.

Vancouver, Canada,  
July 21, 1995.

*Ernst & Young*

Chartered Accountants



**Angiogenesis Technologies, Inc.**  
Incorporated under the laws of British Columbia

**BALANCE SHEET**

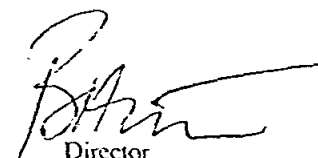
As at September 30

	1994 \$	1993 \$
<b>ASSETS</b>		
<b>Current</b>		
Cash	69,977	129,656
Investment tax credits receivable	179,283	82,490
Prepaid expenses and other	20,379	2,915
Share subscriptions receivable	—	254,817
	269,639	469,878
Fixed assets <i>[note 3]</i>	22,674	4,606
Patents and medical technology <i>[note 4]</i>	59,545	17,123
	351,858	491,607
<b>LIABILITIES AND SHAREHOLDERS' EQUITY</b>		
<b>Current</b>		
Accounts payable and accrued liabilities	86,042	47,894
Total current liabilities	86,042	47,894
Share subscriptions received in advance <i>[note 5]</i>	—	312,000
Total liabilities	86,042	359,894
<b>Shareholders' equity</b>		
Common shares <i>[note 6]</i>	840,577	329,317
Deficit	(574,761)	(197,604)
Total shareholders' equity	265,816	131,713
	351,858	491,607

See accompanying notes

On behalf of the Board:

  
Director

  
Director

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Angiogenesis Technologies, Inc.

STATEMENT OF LOSS AND DEFICIT

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Year ended September 30

	1994 \$	1993 \$
<b>EXPENSES</b>		
Research and development		
Contract services	210,075	244,031
Consumable supplies	1,569	2,969
Depreciation	3,305	1,590
Office and rent	15,669	12,423
Other	3,539	522
Salaries and benefits	159,050	23,021
Travel	35,780	3,771
	428,987	288,327
Less: Investment tax credits	(92,220)	(82,490)
Grants	(98,027)	(15,000)
	238,740	190,837
<b>General and administration</b>		
Accounting and legal	6,582	3,505
Bank charges	103	36
Interest income	(4,573)	(2,347)
Office and rent	6,595	4,000
Other	1,297	484
Salaries and benefits	24,413	—
	34,417	5,678
Loss for the year	273,157	196,515
Deficit, beginning of year	197,604	1,089
Premium paid on cancellation of share subscriptions [note 5]	104,000	—
Deficit, end of year	574,761	197,604

See accompanying notes

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Angiogenesis Technologies, Inc.

STATEMENT OF CHANGES IN FINANCIAL POSITION

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	1994 \$	1993 \$
<b>OPERATING ACTIVITIES</b>		
Loss for the year	(273,157)	(196,515)
Add items not involving cash:		
Depreciation	3,305	1,590
Net change in non-cash working capital balances related to operations	(76,109)	(37,811)
Cash used in operating activities	(345,961)	(232,736)
<b>INVESTING ACTIVITIES</b>		
Purchase of fixed assets	(21,373)	(6,196)
Cost of patents and medical technology	(42,422)	(17,123)
Cash used in investing activities	(63,795)	(23,319)
<b>FINANCING ACTIVITIES</b>		
Repayment of shareholder's loan	—	(737)
Share subscriptions - net	(57,183)	57,183
Issue of shares for cash	511,260	329,217
Cancellation of share subscriptions	(104,000)	—
Cash provided by financing activities	350,077	385,663
Net increase (decrease) in cash during the year	(59,679)	129,608
Cash, beginning of year	129,656	48
Cash, end of year	69,977	129,656

*See accompanying notes*

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Angiogenesis Technologies, Inc.

NOTES TO FINANCIAL STATEMENTS

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September 30, 1994

**1. NATURE OF BUSINESS**

Angiogenesis Technologies Inc. (the "Company"), was incorporated under the British Columbia Company Act on October 12, 1989. The Company changed its name to Angiogenesis Technologies, Inc. on January 6, 1993. The primary business purpose of the Company is to research and develop medical products and technologies relating to angiogenesis or blood vessel growth.

No revenues have been earned to date from technology under development and the Company has financed its cash requirements primarily from share issuances and government grants and investment tax credits. The Company's ability to realize the carrying value of its assets is dependent on successfully bringing its new technologies to the market and achieving future profitable operations, the outcome of which cannot be predicted at this time. It will be necessary for the company to raise additional funds in the coming year for the continuing development of its technologies.

**2. ACCOUNTING POLICIES**

The following is a summary of the significant accounting used in the preparation of these financial statements.

**Fixed assets**

Fixed assets are stated at cost. Office furniture and equipment is depreciated over three years and research equipment over two years on the straight-line method.

**Research and development costs**

Research costs are expensed in the year incurred. Development costs are expensed in the year incurred unless the Company believes a development project meets generally accepted accounting criteria for deferral and amortization.

No development costs have been deferred to date. Research-related government assistance, grant and research contract revenue received is credited against research and development expenditures.

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Angiogenesis Technologies, Inc.

NOTES TO FINANCIAL STATEMENTS

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September 30, 1994

2. ACCOUNTING POLICIES (cont'd.)

Investment tax credits

The benefits of income tax credits for scientific research and development expenditures are recognized in the year the qualifying expenditure is incurred when there is reasonable assurance the tax credits will be realized. The investment tax credit reduces the carrying cost of expenditures for capital assets and research and development.

Patents and medical technology

Patents consist of the consideration paid for the patents and related legal costs and will be amortized over the lesser of the estimated useful life of the related technology and the life of the patent commencing with commercial production.

The costs of acquiring medical technology are capitalized and will be amortized over the life of the technology once commercial production of the related product commences or once the Company enters into a licensing agreement.

If management determines that development of products to which patent and medical technology costs relate is not reasonably certain, or that deferred patent and medical technology costs exceed recoverable value, such costs are charged to operations.

3. FIXED ASSETS

	Cost \$	Accumulated depreciation \$	Net book value \$
1994			
Research equipment	9,719	700	9,019
Office furniture and equipment	17,850	4,195	13,655
	27,569	4,895	22,674
1993			
Research equipment	6,196	1,590	4,606
Office furniture and equipment	—	—	—
	6,196	1,590	4,606

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Angiogenesis Technologies, Inc.

NOTES TO FINANCIAL STATEMENTS

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September 30, 1994

4. PATENTS AND MEDICAL TECHNOLOGY

	1994	1993
	\$	\$
Patents	48,745	17,123
Medical technology	10,800	—
	59,545	17,123

The Company and Dr. B. Hunter, Dr. L. Machan and Dr. L. Arsenault (the "Scientists") entered into an asset purchase agreement dated September 30, 1992, and subsequently amended, (the "Scientist Agreement") that provides for the transfer of all right, title and interest in and to certain assets, proprietary technology and intellectual property associated with anti-angiogenic therapy, (the "Core Technology"). Pursuant to the Scientist Agreement, the Company made available to the Scientists 400,000 common shares at a price of \$0.01 per share and 525,700 common shares at a price of \$0.25 per share. The Company also entered into a collaborative research agreement with the Scientists to fund the costs associated with the further research and development of the Core Technology, such costs not to exceed \$500,000 in aggregate by March 31, 1993.

The Company and H.D.M. Research Inc. ("HDM") and Dr. T. Cruz entered into an asset purchase agreement dated November 19, 1993, and subsequently amended, (the "HDM Agreement") that provides for the transfer of HDM's right, title and interest in and to certain assets, proprietary technology and intellectual property associated with Vanadium compounds in the treatment of proliferation disorders (the "Vanadate Technology"). Pursuant to the HDM Agreement, the Company made available to HDM 133,333 common shares at a price of \$0.01 per share and 175,233 common shares at a price of \$0.25 per share.

The Company and McMaster University ("McMaster") entered into an assignment agreement dated July 11, 1994 for certain data ("Data") and all right, title and interest in intellectual property in anti-angiogenic compositions and methods of use. The Company paid an assignment fee of \$10,800 upon execution of the agreement.

5. SHARE SUBSCRIPTIONS RECEIVED IN ADVANCE

This represents funds received in advance of common shares issued. The share subscriptions were cancelled during 1994 and the premium paid on the cancellation has been charged to the deficit.

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Angiogenesis Technologies, Inc.

NOTES TO FINANCIAL STATEMENTS

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September 30, 1994

6. SHARE CAPITAL

(a) Authorized

100,000,000 Class A common shares without par value  
100,000,000 Class B common shares without par value  
100,000,000 Class A preference shares with a par value of \$1.00  
100,000,000 Class B preference shares with a par value of \$10.00

(b) Issued and outstanding - Class A common shares

	No. of shares #	Amount \$
Issued and outstanding		
Issued for cash on incorporation	100	100
Issued for cash pursuant to a private placement	2,476,866	329,217
Balance, September 30, 1993	2,476,966	329,317
Issued for cash pursuant to a private placement	737,200	511,260
Balance, September 30, 1994	3,214,166	\$840,577

(c) Escrowed shares

The Company has issued 1,238,433 common performance shares to be released as determined by the Board of Directors.

(d) Incentive stock options

At September 30, 1994 the Company has 20,000 common shares reserved for issuance on exercise of incentive stock options at a price of \$2.00 per share and expiring on September 30, 1996.

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Angiogenesis Technologies, Inc.

NOTES TO FINANCIAL STATEMENTS

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September 30, 1994

7. INCOME TAXES

The Company has non-capital loss carryforwards for income tax purposes available to reduce taxable income for future years. These losses expire as follows:

	\$
2000	277,000
2001	167,000
	<u>444,000</u>

In addition, the Company has timing differences of approximately \$6,600 relating primarily to fixed assets and scientific research and experimental development expenditures of \$125,000 which may be used to reduce future taxable income. The potential income tax benefits relating to these losses, timing differences and tax balances have not been recognized in the accounts as their realization is not virtually certain.

8. COMMITMENTS

Lease commitments

The Company entered into an operating lease agreement for office and laboratory space. Future minimum annual lease payments under this lease are as follows:

	\$
1995	8,600
1996	<u>7,200</u>

Research contracts

Under the terms of various research contracts, the company is committed to making the following annual payments:

	\$
1995	437,400
1996	<u>18,800</u>
	<u>456,200</u>



## NOTES TO FINANCIAL STATEMENTS

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September 30, 1994

### 9. SUBSEQUENT EVENTS

- [a] The Company and Mount Sinai Hospital Corporation (the "Hospital") entered into a licensing agreement (the "Hospital Agreement") dated April 25, 1995, pursuant to which the Company was granted an exclusive, world-wide royalty-bearing license to use certain technologies of the Hospital (the "Hospital technology") for the treatment of proliferative disorders, metastases and drug resistant tumors with vanadate compounds and derivatives or analogues thereof. The Hospital also granted the Company the right to issue exclusive or non-exclusive sub-licenses to third parties for the use of the Hospital technology. The Hospital has agreed to collaborate with the Company in further research, development and testing of the licensed technology.

Under the Hospital Agreement, the Company paid the Hospital a license issue fee of \$10,000 and issued 25,000 common shares to the Hospital at a deemed value of \$2.75 per share. In addition, the Company may be required to make further payments of cash and/or shares (shares to be issued at the option of the Company) to the Hospital upon the attainment of certain milestones relating to the commercial development of the Hospital technology. The aggregate costs to the Company to obtain the exclusive, world-wide license to the Hospital technology, including the license issue fee, shares and all development milestones, will not exceed \$300,000. Milestones payments will only be required to the extent that the consideration paid to the date of the milestone (including any increased value of any shares issued to the Hospital) is less than the total consideration required to be provided to the Hospital as of the attainment of the milestone.

- [b] The Company has issued 440,558 common shares at a price of \$2.75 per share for a total consideration of \$1,142,785, pursuant to a private financing plan.
- [c] The Company has entered into various research contracts and is committed to making future payments of approximately \$380,000.

## **APPENDIX B - UNAUDITED FINANCIAL STATEMENTS**

10 months ended July 31, 1996

**ANGIOGENESIS TECHNOLOGIES INC.**  
**BALANCE SHEET**  
**JULY 31, 1996**  
 (unaudited)

	<u>1996</u>
<b>ASSETS</b>	
Current Assets:	
Cash and Term Deposits	1,215,534
Investment tax credits receivable	-
Other	117,014
	<u>1,332,548</u>
Fixed assets, net	403,545
Licences and Patents	355,295
Medical technology	129,964
	<u>2,221,352</u>
<b>LIABILITIES AND SHAREHOLDERS' EQUITY</b>	
Current liabilities:	
Accounts payable & accrued liabilities	517,464
Shareholders' equity:	
Common shares	5,927,629
Deficit	(4,223,741)
	<u>1,703,888</u>
	<u>2,221,352</u>

**ANGIOGENESIS TECHNOLOGIES INC.**  
**STATEMENT OF OPERATIONS AND DEFICIT**  
For the ten months ending July 31, 1996  
(Unaudited)

	July 1996	Y-T-D 1996
Research and development expenses:		
Contract services	106,526	\$ 1,021,121
Depreciation	4,657	21,324
Laboratory supplies	7,667	91,154
Office and rent	13,957	96,411
Other	(3,875)	27,646
Salaries and benefits	159,034	730,469
Stationary and supplies	1,302	15,167
Travel	17,797	92,669
	307,065	2,095,961
Less: Grants	-	(16,635)
	307,065	2,079,326
General and administration expenses:		
Accounting and legal	22,692	72,721
Consulting	10,462	111,412
Depreciation	8,795	27,025
Office and rent	10,385	64,787
Other	525	16,044
Salaries and benefits	71,452	360,815
Stationary and supplies	1,537	15,408
Travel	(906)	55,325
	124,942	723,537
Less: Interest income	(13,044)	(52,315)
	111,898	671,222
Loss for the period	418,963	2,750,548
Deficit, beginning of period	3,804,778	1,473,193
Deficit, end of period	\$ 4,223,741	\$4,223,741

**ANGIOGENESIS TECHNOLOGIES INC.**  
**STATEMENT OF CHANGES IN FINANCIAL POSTION**  
For the ten months ending July 31, 1996  
(Unaudited)

	<u>1996</u>
Cash provided by (used in):	
Operations:	
Loss for the period	(2,750,548)
Items not affecting cash:	
Depreciation	48,349
Net change in non-cash working capital balances relating to operations	643,975
	<u>(2,058,224)</u>
Financing:	
Share subscriptions received in advance	(271,777)
Proceeds from issuance of common shares for cash	3,874,515
	<u>3,602,738</u>
Investments:	
Fixtures and laboratory equipment	(423,925)
Cost of patent rights and licences	(233,640)
	<u>(657,565)</u>
Increase (decrease) in cash and term deposits	886,949
Cash, beginning of period	328,585
Cash, end of period	<u>1,215,534</u>