# **Equity Research**

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#### **SPECULATIVE BUY**

AHX: TSX: \$0.38

## 12-MONTH TARGET PRICE: \$1.00

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## **Health Sciences and Biotechnology**

# Adherex Technologies Inc.

## Platform technology has multiple medical applications

Adherex is a biotechnology company with a platform technology consisting of compounds that target cadherins, a family of proteins that serve as "biological glues" to hold cells together. This anti-cell adhesion technology has many potential medical applications, including use as a novel therapy for cancer, and as an agent that assists in the transdermal delivery of drugs.

## Lead product, Exherin, destroys cancer blood vessels

Adherex has identified a lead compound, Exherin, which disrupts the blood vessels that feed cancer tumors. In so doing, Exherin causes the selective destruction of these blood vessels, which leads to the starvation and eventual death of the cancer. Following some promising pre-clinical data, Adherex plans to initiate Phase I clinical trials with Exherin later this year. The company has recently extended its research and development collaboration with AstraZeneca for anti-cancer applications of the cell adhesion technology, and may enter a licensing agreement at some point in the future.

## Technology enhances transdermal drug delivery

Adherex also has anti-cell adhesion compounds that may be used to increase the penetration of drugs through the skin when added to creams, gels or skin patches. The company aims to enter into a research and development collaboration agreement with a company specializing in transdermal drug delivery in order to help move this technology forward into clinical testing later this year.

# We are initiating coverage of Adherex Technologies with a SPECULATIVE BUY rating and a 12-month target price of \$1.00

Adherex has a promising anti-cell adhesion platform technology with diverse potential applications. The next 12 months are pivotal for Adherex as it transitions into clinical development. With success in upcoming human clinical trials, the company could be well positioned to capitalize on the significant potential of its novel technology.





## Figure 1: Company Statistics

## Figure 2: Price Chart

Adherex Technologies Inc. (AHX	– TSX)
Price	\$0.40 (\$1.45 - 0.28)
Shares	40M
FD Shares	44M
Mkt cap	\$16M
Cash	\$10M
Cash/share	\$0.25/share
Burn rate	\$500k/mo
Figure 3: Earnings Summary	
Year ending June 30	EPS
F2000	\$(0.11)
F2001	\$(0.15)
F2002E	\$(0.13)



Source: Canaccord Capital

# **EXECUTIVE SUMMARY**

Adherex is a biotechnology company developing a novel platform technology that targets cadherins, a family of proteins that function as "biological glues" to hold cells together. This platform technology consists of anti-cell adhesion compounds that have many potential medical applications. Adherex is moving its platform technology forward for two important applications: (i) a novel Vascular Targeting Agent for the treatment of cancer, and (ii) a transdermal drug delivery enhancer.

#### **Novel Vascular Targeting Agent for cancer treatment**

The company's primary focus is the development of anti-adhesion compounds to treat cancer. These compounds work by blocking the function of specific cadherins involved in holding the cells of blood vessels together. Adherex has identified a lead compound, Exherin, which disrupts the structure of blood vessels that feed cancer tumors. In so doing, Exherin causes the selective destruction of cancer blood vessels, which leads to the starvation and eventual death of the cancer. Adherex will be initiating a Phase I trial with Exherin for cancer treatment later this year.

#### Transdermal drug delivery enhancer

Adherex is also leveraging its platform technology to develop compounds that may be used to enhance the delivery of drugs through the skin, when added to creams, gels or patches. In the second half of the year, the company aims to enter into a research and development collaboration agreement with a company specializing in transdermal drug delivery in order to help move its technology forward into clinical testing.

#### Valuation and recommendation

We have conservatively valued Adherex based solely upon its lead project, Exherin for the treatment of cancer, and have compared it with other Canadian biotechnology companies with lead product(s) for cancer treatment. Although not included in our valuation, we believe Adherex's transdermal drug delivery application holds significant value and also serves to diversify the company's portfolio. Adherex's market cap is currently below the average of its peer group of pre-clinical cancer companies. Assuming that the company starts a Phase I trial later this year, and sees positive results, it should be in a position to enter Phase II in the second half of 2003. Over the next 12 months, we would expect Adherex's valuation to approach the average market cap (\$45 million) of Phase II cancer companies but at a slight discount, since it would not have yet started Phase II.

Adherex has a promising anti-cell adhesion platform technology with diverse potential applications. The next 12 months are pivotal for Adherex as it transitions into clinical development. With success in upcoming human clinical trials, the company could be well positioned to capitalize on the significant potential of its novel technology.

## We are initiating coverage of Adherex with a Speculative Buy rating and a 12-month target price of \$1.00.

# **COMPANY PROFILE**

Adherex Technologies, an Ottawa-based biotechnology company, develops novel drugs using its cell adhesion technology platform. While this technology platform has many potential medical applications, the company is currently focused on two main areas. The primary focus is on the clinical development of the company's lead product, a novel therapy that destroys cancer blood vessels. The secondary focus is the use of Adherex's cell adhesion technology for the enhancement of transdermal drug delivery.

#### **Brief history**

Adherex Technologies was incorporated in August, 1998 and subsequently acquired all the shares of Adherex Inc., a spin-off company from McGill University originally set up in 1996 to develop and commercialize cell adhesion research that was being conducted by Dr. Orest Blaschuk and Dr. Barbara Gour. Dr. Blaschuk, the main inventor of the technology, remains actively involved as Chief Scientist of Adherex, while Dr. Gour is now a consultant to the company.

Adherex Technologies went public on the Toronto Stock Exchange with a \$10 million IPO in May 2001 (6.7 million shares at \$1.50/share). The company has 28 employees, most of whom are involved in research and development. While the corporate head office and labs are located in Ottawa, Ontario, Adherex also has a network of international scientists conducting research in the cell adhesion field at leading universities around the world.

#### **Cell adhesion platform technology**

Adherex's platform technology targets cadherins, a family of proteins that act as "biological glue" and are responsible for cell adhesion. Targeting cell adhesion allows for diverse potential medical applications. In addition to the disruption of cancer blood vessels, and the enhancement of transdermal delivery, the company believes that its technology is capable of developing drugs that can be used in nerve regeneration, suppression of the immune system, wound healing, and facilitating the passage of drugs through the blood-brain barrier.

#### **Business strategy**

The goal of Adherex is to become a world leader in the field of cell adhesion technology by establishing a network of specialists in this field, and by developing and maintaining a comprehensive patent portfolio. The company has developed a number of compounds that target cell adhesion, and some of these will be progressing into human clinical development. Other drug candidates in new therapeutic areas will be selected based upon market potential and opportunity for partnership. At the appropriate time in development, the company intends to partner and/or license certain applications of its technology to healthcare companies for further development and eventual commercialization.

# **CELL ADHESION PLATFORM TECHNOLOGY**

The science of cadherins and cell adhesion is quite complex. For this report, we have simplified the science down to a few points needed to understand how the technology works, and how Adherex is leveraging this technology in its lead applications.

#### **Technology overview**

Cadherins are "biological glues" that hold cells together

Cell adhesion refers to the mechanisms by which cells are bound together to make up the tissues and organs of the body. One of the instrumental players in cell adhesion is a family of proteins called cadherins. Cadherins are one type of "biological glue" that holds cells together, and function by linking with each other between cells (see simplified diagram below). The linking of cadherins between cells is made possible through a "recognition sequence" made up of three amino acids, Histidine, Alanine and Valine, and goes by the acronym HAV. This recognition sequence was identified at McGill University by Dr. Orest Blaschuk and his team.



#### Source: Adapted from Adherex Technologies Inc.

Adherex's technology is based on cyclic peptides that inhibit cadherin binding Subsequently, Dr. Blaschuk and Dr. Barbara Gour (co-founders of Adherex) discovered that cyclic peptides containing the HAV recognition sequence inhibited and disrupted the binding of cadherins between cells, and hence prevented/disrupted cell adhesion. These cyclic peptides form the basis of Adherex's platform technology. They inhibit the binding of cadherins to each other by blocking the active site that is essential to the binding process.





Adherex compounds disrupt/prevent cell to cell binding

Source: Adapted from Adherex Technologies Inc.

#### **Broad potential applications**

The role of cadherins in cancer growth is well recognized Over the last decade, medical researchers have increasingly recognized the significant involvement of cadherins in many biological processes. Their activity as regulators of cancer growth is now almost universally recognized. Modulation of cadherins in skin tissue is now being targeted as a way of enhancing delivery of drugs through the skin.

There are many other areas of medicine that are now being seen as influenced by cadherins. Some of these additional applications of Adherex's platform technology include the following:

- Tissue repair Cadherins are involved in reattaching cells after tissue injury.
- Neural regeneration Research is being conducted into the role of cadherins in neural repair.
- **Blood-brain barrier** The blood-brain barrier is a series of tightly bound cells in the brain's blood vessels that prevents potentially dangerous compounds from entering the brain. Modulation of the cadherins involved in the cell adhesion of this barrier could facilitate the crossing of important drugs into the brain.
- Immune system Cadherins are also produced by immune system cells. Regulating this production could have potential use in autoimmune diseases or in areas requiring immune suppression.

#### Strong intellectual property position

At the foundation of Adherex's future success is the strong and effective patent protection that surrounds its technology and applications. To fulfill this objective, Adherex has retained a prominent US patent law firm called the Seed Intellectual Property Law Group based in Seattle, Washington, to assist the company in developing and maintaining a comprehensive patent portfolio. Adherex currently has a portfolio of 13 composition-of-matter and use patents to date, with many more in process.

The lead Adherex patent, "Compounds and Methods for Modulating Cell Adhesion", was filed in July 1996 in the US and worldwide through the Patent Cooperation Treaty (PCT) process. Subsequently, the company was awarded this US patent in February 2000 for the protection of Exherin and related compounds.

Certain cell adhesion patents have been licensed exclusively to Adherex by McGill University in return for an equity interest of 2.5 million (6%) Adherex shares and a 2% royalty on gross income derived from the application of these patents.

# **EXHERIN - LEAD PRODUCT FOR CANCER**

#### Exherin exploits the weaknesses of cancer blood vessels

Exherin is a compound that targets and exploits one of the key weaknesses of tumors, their flawed and fragile blood vessels. The blood vessels that feed tumors are very unique in that their structure tends to be twisted and irregular. Blood vessels are made up of endothelial cells and then supported by a basement membrane and muscle cells. The basement membrane and certain muscle layers are either missing or incomplete in places along the length of tumor blood vessels. Also, tumor blood vessels have fewer pericyctes (supporting cells), further weakening their structure.

Normal blood vessels have multiple types of adhesions systems working together to keep the cells together. In cancer blood vessels, cadherins are the primary adhesion molecules that are in effect at the weak spots of the blood vessels' walls. These weaknesses in tumor vasculature allow Exherin to cause ruptures in these specific areas.

While Exherin affects the cancer blood vessels, it has no direct activity against the cancer cells themselves, like most anti-cancer agents. This is thought to be an advantage since there is not likely to be a resistance problem like that seen for some chemotherapeutic drugs.

#### **Proposed mechanism of action of Exherin**

N-cadherin is important in cell to cell binding in blood vessels Exherin inhibits N-cadherin

exnerin initions in-cauterin activity A cell adhesion protein called N-cadherin is primarily responsible for cell to cell binding in normal blood vessels. Other cell adhesion molecules also play a role in stabilizing the initial binding by N-cadherin. As previously discussed, cancer blood vessels lack the full support structure that normal vessels have, and hence are vulnerable to destruction if the N-cadherin binding is disrupted.

*Cancer blood vessels are structurally unstable and vulnerable to Exherin activity* 



Adherex research suggests that Exherin inhibits the binding of N-cadherin by mimicking its activity at the N-cadherin active site. This prevention of N-cadherin binding results in a fatal weakening of cancer blood vessels and their ultimate destruction.

#### Summary of Exherin preclinical data

# Very promising pre-clinical results for Exherin in cancer

To date, Exherin has only been tested on animal models of cancer. Its first testing in humans, Phase I, is expected to begin later this year. Pre-clinical efficacy studies have all been carried out in mice cancer xenograft models (human tumors implanted into mice for the purposes of testing new therapies). Exherin has demonstrated activity in rupturing cancer blood vessels in models of colon cancer, breast cancer, ovarian cancer, lung cancer and, most recently, glioblastoma (a form of brain cancer). The following features of Exherin have been demonstrated in pre-clinical studies:

- Destruction of cancer blood vessels Exherin causes the rupture of cancer blood vessels (angiolysis), thereby destroying the existing tumor blood supply. Exherin has demonstrated angiolytic activity in a wide variety of tumor types. Pathological analysis has provided clear evidence that Exherin is destroying tumorspecific blood vessels and in some cases causing a reduction in tumor volume.
- **Rapid onset of action** Rupture of cancer blood vessels is apparent within approximately 30 minutes of dosing.
- **Relatively short half-life** Half-life refers to the time it takes to metabolize one half of a given dose of drug. Exherin's half-life is approximately 15 minutes. The drug is rapidly broken down by serum proteases (enzymes in the blood) and excreted through the kidneys. Exherin has a number of metabolites and there is at least one metabolite that has activity similar to the parent compound.
- Safety profile Exherin has no apparent side effects and toxicities to date. Exherin has been administered at doses as high as 1000mg/kg IV to healthy rats over a 2 to 24 hour period with no drug-related toxicity.



Exherin treatment causes a decrease in tumor volume

Source: Adherex Technologies Inc.

#### Physical properties and manufacturing of Exherin

Exherin is a five amino acid cyclic peptide. Because it is a peptide (protein), it is rapidly degraded by enzymes in the stomach, and therefore cannot be administered orally. Exherin will be given intravenously (i.v.) when studies begin in humans.

Adherex has contracted a bulk drug manufacturer, UCB (Belgium), to manufacture Exherin for its clinical trials. UCB has been able to manufacture Exherin synthetically, and has shown that the manufacturing process is scalable. UCB has already been successful in making small batches of the product, and has also completed a clinical trial batch for the upcoming Phase I clinical trial.

Exherin's formulation requires that it undergo lyophilization (a form of freeze-drying) to enhance its stability; in lyophilized form, the product is stable for two years. Lyophilization and final formulation is being done by ProPharma of Glasgow, Scotland. Formulation of the product takes about one month, after which the drug must pass a GLP (Good Lab Practices) animal safety study, which takes about two months. The company will then be in a position to use the manufactured product in human trials.



# COMPETITION IN VASCULAR TARGETING OF CANCER

Vascular targeting as a strategy to treat cancer has become an area of intense focus in cancer research. This therapeutic strategy has evolved from the notion, first proposed by Dr. Judah Folkman, that interrupting the blood flow to a tumor should result in the inhibition of its growth and its eventual death.

Vascular targeting is now a key<br/>area of cancer researchMany biotech and pharmaceutical companies are conducting research into finding<br/>agents that achieve this effect. Vascular targeting agents (VTAs) generally fall into two<br/>categories: (i) Angiogenesis Inhibitors - Compounds that inhibit the growth of new<br/>tumor blood vessels, and (ii) Angiolytic Agents – Compounds that disrupt and destroy<br/>existing tumor blood vessels.

The table below summarizes only some of the VTAs in development, split by category. Adherex's product, Exherin, falls into the angiolytic category.

Droduct	Compony	Status	Notos
	Company	Status	Notes
Angiogenesis Innibi	tors		
Neovastat	Aeterna (AEL:T)	Phase III	Inhibits angiogenesis through multiple mechanisms. Phase III in renal cell carcinoma
Panzem	Entremed (ENMD:Q)	Phase II	Has both antiangiogenic activity and anti-tumor activity
Endostatin	Entremed (ENMD:Q)	Phase II	Has both antiangiogenic activity and anti-tumor activity. Orphan drug status for malignant metastatic melanoma and neuroendocrine tumors
ABT-510	Abbott	Phase I	Mimics naturally ocurring antiangiogenic protein called thrombospondin
IMC-1C11	ImClone (IMCL:Q)	Phase I	Monoclonal antibody that blocks the ability of VEGF to initiate receptor activation and induce angiogenesis
Angioarrestin	Curagen (CRGN:Q)	Pre-clinical	Has shown very early potential as an angiogenesis inhibitor and protein therapeutic to treat cancer
Angiolytic Agents			
ZD6126	AstraZeneca	Post-Phase I	Tubulin inhibitor. Has shown some toxicities in Phase I. Licensed from Angiogene Pharmaceuticals in 1999
VCAM-1 inhibitor	Peregrine (PPHM:Q)	Pre-clinical	Monoclonal antibody with attached coagulation factor targets endothelial cells and effectively blocks the tumor blood vessels
Combretastatin	Oxigene (OXGN:Q)	Post-Phase I	Tubulin inhibitor. Originally licensed to BMS, but was returned due to toxicity in Phase I
Exherin	Adherex (AHX:T)	Pre-Phase I	Inhibits cadherin function - No toxicities observed in pre-clinical studies. Collaboration agreement with AstraZeneca

### Figure 7: Vascular Targeting Agents (VTAs) in cancer

Source: Company reports

## **ANGIOGENESIS INHIBITORS**

Angiogenesis is the process by which new blood vessels form. Cancers require a constantly expanding blood supply in order to grow. Prevention of new blood vessel growth by angiogenesis inhibitors aims to slow growth and to eventually kill the tumor through starvation. While experts view the development of angiogenesis inhibitors to be very promising, they also feel that these drugs have less of a chance of completely destroying the tumor since the existing blood vessel system is still intact. However, there are now compounds that have a dual action on both the blood vessel growth as well as a direct effect on the cancer cells. Currently, angiogenesis inhibitors are slightly further along in development that the angiolytic agents.

## ANGIOLYTIC AGENTS

Angiolytic agents not only inhibit the growth of new blood vessels, but also disrupt and destroy existing tumor blood vessels. By nature of their activity, angiolytics may be viewed as being more effective than angiogenesis inhibitors because they do not leave existing blood vessels intact. As can be seen in the previous table, there are a number of mechanisms by which one can destroy cancer blood vessels. Exherin is the only one of the list that works by inhibiting cadherin function. Furthermore, some of the other agents in this category, ZD6126 and combretastatin, have experienced toxicity problems in clinical trials. The current status of these products is currently unknown.

# TRANSDERMAL DRUG DELIVERY APPLICATION

Delivery of drugs through the skin has a great deal of appeal in many therapeutic areas, especially where the alternative is regular injections. Unfortunately, the skin has proven to be a very difficult barrier for most drugs to penetrate, and companies are constantly searching for means by which to enhance this penetration.

#### Proposed activity of Adherex compounds in transdermal applications

Similar to the way in which Exherin mimics the activity of N-cadherin in the cells of blood vessels, Adherex has other anti-cell adhesion compounds that mimic other types of cadherins. The maintenance of skin cell binding and the regulation of skin permeability are due, in large part, to the protein E-cadherin. Adherex has developed compounds that are capable of interfering with E-cadherin, thus increasing the permeability of the skin.

#### **Proof of concept data**

Adherex believes that the addition of its compounds to current topical formulations (creams, gels, etc.) or skin patches may improve the transdermal penetration of drugs. The company has data demonstrating that its compounds increase the penetration of both charged and uncharged dyes through human skin in a laboratory setting (please see chart on the next page).

E-cadherin helps to maintain skin cell binding – Adherex has compounds that inhibit this

Exherin is an angiolytic agent



#### Figure 8: Penetration of dye through human cadaver skin



Source: Adherex Technologies Inc.

# **PRODUCT DEVELOPMENT STRATEGY**

Positive Phase I data may lead to a licensing agreement with AstraZeneca for Exherin Adherex continues to focus on the steps required to take its lead product, Exherin, into human clinical trials later this year. Depending on the success in Phase I human trials, Adherex may conclude a full licensing agreement with AstraZeneca for further clinical development and commercialization. In addition, it also intends to accelerate the development of its drug delivery enhancer technology through a research and development collaboration with a transdermal drug delivery company.

## **EXHERIN FOR CANCER**

#### **Next steps**

The clinical trial supply of Exherin has been manufactured by the Belgian manufacturer and has been delivered to the formulation company, ProPharma. After formulation, samples of the clinical trial batch will undergo a GLP (Good Laboratory Practices) safety study in animals. Once the safety testing is complete, the company will file an IND (Investigational New Drug application) to seek approval to start a Phase I clinical trial. The IND filing is expected in late Q3, or early Q4 of this year, with the Phase I trial starting enrollment late in the year.

#### **Phase I clinical trial**

The Exherin Phase I clinical trial protocol is currently being developed and will be finalized after input from Health Canada in a meeting on July 9, 2002. This trial is expected to be a single center study with about 30 cancer patients. Patients recruited for the study will have solid tumours, with or without secondary deposits, and are likely to have resistant and advancing disease.



The primary focus in the Phase I trial will be on safety and pharmacokinetics. Pharmacokinetic data will give a clearer picture as to the optimal required dosing in humans. The trial will investigate a range of four or five doses, constantly checking for toxicity. The Phase I study will likely take about six months to complete, and is expected to cost approximately \$300,000.

### **Phase II clinical trials**

While it is still too early to be discussing Phase II clinical trials when the company has not even started Phase I trials, there are a number of points about a future Phase II trial that are worth mentioning. Please note these are only preliminary indications of what a Phase II trial may entail based on very general discussions with Adherex management.

Phase II may focus on renal cell carcinoma as the likely indication for a number of key reasons:

- High mortality rate five year mortality rate is 90%
- High unmet need difficult to treat surgically or with chemotherapy
- Highly vascularized tumor (extensive blood supply)
- Adherex expects good results for this tumor type
- Potential for fast track designation

#### **Combination therapy for cancer**

Adherex does not intend for Exherin to be used as monotherapy for the treatment of cancer, and will not be seeking approval on this basis. It is likely that Exherin will eventually be used in combination with other anticancer agents, and thus the selection of an anticancer agent for future clinical trials will be important. It would be best to select chemotherapeutic agents that can be effective in the hypoxic (low oxygen) environment that will result from the destruction of cancer blood vessels by Exherin.

## TRANSDERMAL DRUG DELIVERY APPLICATION

In order to move forward with the transdermal delivery application (creams, gels, skin patches, etc.) of its cell adhesion technology, Adherex will require the assistance of a specialist in this field. To this end, Adherex is in discussions to strike a research and development collaboration with a company with key expertise in the transdermal drug delivery field. Dr. Robin Norris, Adherex's COO, has extensive previous experience with Noven and Powderject Inc., two well-known drug delivery companies. Dr. Norris will be using his expertise and contacts to consummate this collaboration, the timing of which is expected in the second half of the year.

Adherex will likely enter into a transdermal drug delivery collaboration in H2/02

# **ANTICIPATED MILESTONES**

Adherex has an eventful 12 months ahead Adherex has clearly stated that its focus for this year will be on the initiation of Phase I clinical trials for Exherin in cancer patients, and on the ongoing development of the transdermal drug delivery application of its cell adhesion platform technology.

#### Exherin for the treatment of cancer

- File Investigational New Drug (IND) application in Q3/2002
- Start Phase I trial of Exherin in cancer patients in Q4/2002
- Report results from Phase I trial of Exherin in cancer patients in mid-2003
- Potential licensing agreement with AstraZeneca, assuming positive Phase I results, in H2/2003.

#### Transdermal drug delivery enhancer

- Complete ongoing pre-clinical testing in H2/2002
- Enter into research and development agreement with established transdermal drug delivery company in H2/2002
- File IND for Phase I clinical testing in healthy volunteers in late 2002
- Commence a Phase I human clinical trial for transdermal drug delivery enhancer by the end of the year

# **CORPORATE COLLABORATIONS**

#### **Past collaborations**

In August 2000, Adherex had entered into a co-development deal with Biochem Pharma for the joint development of Adherex's anti-cancer compound, Exherin. Subsequently in May 2001, Biochem Pharma was acquired by Shire Pharmaceuticals of the UK. In July 2001, Shire and Adherex mutually decided to dissolve the collaboration without penalties to either party. Adherex regained all rights to Exherin and then began discussions with other potential partners.

#### **Current collaboration with AstraZeneca**

In October 2001, Adherex signed a collaboration and option agreement for the development of Adherex's proprietary cancer compounds, including its lead compound, Exherin. The financial terms of the collaboration agreement are not being disclosed. The preliminary agreement had an initial term of six months, at which time the agreement could be extended. In April 2002, AstraZeneca chose to extend the collaboration agreement indefinitely. AstraZeneca also has the right of first negotiation on a licensing deal. The two parties will continue to work together on Adherex's proprietary compounds and, with positive progress, will work towards a comprehensive

AstraZeneca is a leader in the anti-cancer field

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licensing agreement. Adherex's working relationship with AstraZeneca has been very collaborative, and both parties are excited by the potential of Exherin. In June, Adherex will actively participate in a joint Vascular Targeting Symposium with AstraZeneca at BIO 2002. This will be co-chaired by two pre-eminent researchers in the field of cancer, Phil Thorpe of University of Texas and Robert Kerbel, Head of Oncology at Sunnybrook Hospital.

#### **Collaboration with Fujisawa**

In January 2000, Fujisawa made a \$300,000 equity investment in Adherex. Fujisawa is interested in working with Adherex's technology for immunosuppressant applications. This project will move forward at a time agreed upon by both parties.

#### Future collaboration In transdermal drug delivery

In order to move its transdermal drug delivery application forward, Adherex recognizes the need to partner with a company having expertise in this area. With this in mind, Adherex anticipates signing a research and development collaboration agreement with a key player in the transdermal drug delivery field within the next few months. The two parties will then select a lead compound, and start clinical testing later this year.

# **INVESTMENT RISKS**

**Clinical Development Risk** – Adherex has not tested its compounds in humans. There is no guarantee that the positive pre-clinical results will be duplicated in Phase I, or that there will not be any adverse effects.

**Competitive Risk** – Adherex is entering into therapeutic areas with significant current competition. It is not possible to accurately predict its future competitive position relative to other companies and other products in development.

**Financing Risk** – As a research and development company, Adherex is still in relatively early stages of development. It will require further funding in order to progress its compounds through clinical testing. Success in financing will be subject to the company's ability to meet its milestones, and to the prevailing state of the capital markets.

**Partnership Risk** – Much of Adherex's future success will be determined by its ability to negotiate and execute partnership agreements with pharmaceutical companies for the development and commercialization of its compounds.



# **FINANCIAL ANALYSIS & VALUATION**

#### **Capital structure and major shareholders**

As at January 31, 2002 Adherex had 40 basic shares outstanding and 44 million fully diluted shares outstanding.

Figure 9: Adherex capital structure	
Basic shares	40,163,985
Warrants (Price = $$1.25$ )	346,000
Options (Weighted average price = \$0.74)	3,757,500
FD shares	44,267,485

Source: Company reports

Management owns approximately 7%, non-management directors own approximately 7.5%, and the founders own 18% of the basic shares outstanding. In addition, McGill University owns approximately 2.5 million (6%) of the shares outstanding.

Figure 10: Insider holdings		
Management	2,964,972	7%
Non-Management Directors	3,023,984	8%
Founders	7,400,000	18%
Total Insiders	13,388,956	33%

Source: Company reports

#### **Financials**

Adherex has a current cash position of approximately \$10 million, and has no material debt at this time. With a burn rate of about \$500,000 per month (includes cost of Phase I trial), the company has enough cash to last approximately 18 months. As part of its collaboration with AstraZeneca, Adherex has received some financial support for the development of Exherin. The amount of this funding from AstraZeneca has not been disclosed. However management does not expect this funding to continue in the future until such time as a full licensing agreement is in place.

Although Adherex has sufficient cash to fund this trial, we would expect the company to seek additional financing within the next 12 months, especially if it intends to begin a Phase I clinical trial for the transdermal delivery application.

#### Valuation

While Adherex's platform technology targeting cell adhesion has many potential medical applications, the company is still at a relatively early stage of development. Therefore, we have taken a conservative approach and valued the company based solely upon its lead project, Exherin for the treatment of cancer. Although not included in our valuation, we believe Adherex's transdermal drug delivery application holds significant

value and also serves to diversify the company's portfolio. With this in mind, we have compared Adherex with other Canadian biotechnology companies with lead product(s) for the treatment of cancer.

Fig	Figure 11: Canadian companies having a lead product in cancer						
	Company	Symbol	Price S (C\$)	hares O/S	Cash (\$M)	Market Cap (\$M)	Lead Cancer Indication
	Aeterna Laboratories	AEL	7.50	33	54	246	kidney
a	Axcan Pharma	AXP	23.00	44	204	1017	esophageal
20 N	Biomira	BRA	4.21	53	85	221	breast
dde	Bioniche Life Sciences	BNC	3.45	28	11	96	refractory bladder
1/	Inex Pharmaceuticals	IEX	6.90	33	75	227	relapsed lymphoma
H	Lorus Therapeutics	LOR	0.73	144	49	105	melanoma
lase	Oncolytics	ONC	2.36	19	15	45	prostate
노	Stressgen	SSB	4.15	58	63	239	cervical
	Mean					275	
	Altarex	AXO	0.50	37	9	18	ovarian
=	Anormed	AOM	3.80	26	79	97	prostate
se ]	Genetronics Biomedical	GEB	0.77	40	7	31	head and neck
ha	Glycodesign	GD	1.99	12	37	24	renal
-	Viventia Biotech	VBI	0.27	195	7	53	breast/prostate
	Mean					45	
No F	hase I companies in univers	e					
	Adherex	AHX	0.38	40	17	16	all solid tumors
ical	Arius Research	YAR	2.30	5	4	11	lung
clin	Procyon Biopharma	PBP	1.00	51	10	51	prostate
Pre	SignalGene	SGI	0.25	122	23	30	breast
	Mean					27	

Source: Company reports, Starquote

Adherex's market cap is currently below the average of its peer group of pre-clinical cancer companies. Assuming that the company starts a Phase I trial later this year, and sees positive results, it should be in a position to enter Phase II in the second half of 2003. Over the next 12 months, we would expect Adherex's valuation to approach the average market cap (\$45 million) of Phase II cancer companies but at a slight discount, since it would not have yet started Phase II. Predicated on Adherex meeting its set milestones, we estimate a future market cap of approximately \$40 million and a 12-month target price of \$1.00.

#### Recommendation

Adherex has a promising anti-cell adhesion platform technology with diverse medical applications. The next 12 months are pivotal for Adherex as it transitions into a clinical development company. With success in the upcoming human clinical trials, Adherex could be well positioned to capitalize on the potential of its novel technology.

# We are initiating coverage of Adherex with a Speculative Buy rating and a 12-month target price of \$1.00.



# APPENDIX 1: MANAGEMENT TEAM & BOARD OF DIRECTORS

#### MANAGEMENT TEAM

#### John Brooks, CFA, President and CEO

John Brooks has been President and CEO of Adherex since 1998. In 2001, he won the NRC/OCRI award as the Ottawa Innovator of the Year for his work at Adherex. Mr. Brooks sits on the Board of Directors of BIOTECanada, Canada's biotechnology industry trade organization. Previously, Mr. Brooks was Vice-President at CIBC Wood Gundy Private Client Investments. He also served as the CEO/Director General of the Canadian Gymnastics Federation, Director of the Canadian Olympic Association and was a Canadian Track and Field Champion. He holds a Master of Science degree in Physiology from the University of Toronto, is a Fellow of the Canadian Securities Industry and is a Chartered Financial Analyst.

#### **Robin Norris, MD, Chief Operating Officer**

Dr. Robin Norris received his medical education and degree in the UK with postgraduate qualifications in obstetrics, general medicine and pharmaceutical medicine. Following eight years of clinical practice, Dr. Norris spent 23 years in the pharmaceutical industry, predominantly in the USA but with global, drug development responsibilities. During his career, Dr. Norris has been responsible for the successful development of a wide range of pharmaceutical products and devices, moving and transitioning them from fundamental "bench-level" research and development, through the regulatory process and into the global marketplace. The earlier part of Dr. Norris's career was spent with major multinational pharmaceutical companies such as Schering-Plough, where he was Medical Director with international responsibilities. Subsequently, he spent six years with Rhone-Poulenc Rorer (now Aventis, NYSE:AVE) with international medical, regulatory, pharmaceutical development, new product planning, business development, new product and strategic marketing responsibilities. Since 1993, Dr. Norris has held senior positions with small to mid-cap, high-tech and biotech companies, including as COO with Noven Pharmaceuticals (NASDAQ:NOVN) and COO of PowderJect Pharmaceuticals (LSE: PJP).

## **Orest Blaschuk, Ph D., Chief Scientist**

Dr. Orest Blaschuk, Chief Scientist (and co-founder) of Adherex and Associate Professor, McGill University, is a cell biologist with particular expertise in cell adhesion molecules. Dr. Blaschuk completed his Ph.D. at the University of Toronto in Biochemistry in 1984, where he characterized a novel cell adhesion molecule, clusterin. Dr. Blaschuk completed postdoctoral training at Princeton University and accepted a position at McGill University in 1987. Dr. Blaschuk discovered the classical cadherin cell adhesion recognition sequence. In 1995, the Canadian Association of Anatomists honored Dr. Blaschuk for his work with the Murray L. Barr Award. He is advisory editor of Anatomy and Embryology. Dr. Blaschuk has been a member of several granting agency panels including the Medical Research Council of Canada panel on Pathology and Morphology, the California Breast Cancer Research Program panel on Tumor Biology, and the National Cancer Institute of Canada panel on Metastasis, Tumor Biology and Growth Factors. Dr. Blaschuk has authored over 50 articles in peer-reviewed journals. His body of scientific research has led to him being named in "American Men and Women of Science".

#### **Robert Browne, C.A., Chief Financial Officer**

Robert Browne has been CFO of Adherex since February 7, 2001. He served as Vice President Finance and Chief Financial Officer for Bioniche Life Science Inc., a TSX-listed biotechnology company, from July 1996 to July 2000. From August 2000 to February 2001, he worked as a consultant to Viron Therapeutics Inc. He received his Chartered Accountancy designation in 1984.

## **BOARD OF DIRECTORS**

#### Peter Morand, Ph D., Chairman of the Board

Dr. Peter Morand is the President and CEO of the Canadian Science and Technology Growth Fund Inc., a mutual fund investing in early stage research in Canada's science and engineering sectors, and past chair of the Ottawa Life Sciences Council. Dr. Morand is past president of the Natural Sciences and Engineering Research Council of Canada (NSERC). Prior to his NSERC appointment, he spent many years at the University of Ottawa as a professor of chemistry and occupied the positions of Dean of Science and Engineering and Vice Rector.

#### Francesco Bellini, Ph D.

Dr. Francesco Bellini co-founded BioChem Pharma Inc. and served as the Chairman and CEO of the company prior to its acquisition by Shire Pharmaceuticals Group PLC. Prior to co-founding BioChem, Dr. Bellini headed the Biochemicals Division of the Institut Armand-Frappier at the Université du Québec. From 1968 to 1984, he was engaged in research at the Canadian subsidiary of Ayerst Laboratories (now Wyeth-Ayerst), a multinational pharmaceutical company.

#### John Brooks (President & CEO)

See "Management Team"

#### Hon. Judith Erola

The Hon. Judith Erola is the past president of the Pharmaceutical Manufacturers Association of Canada, retiring from that post in December 1998 after 12 years of service. She has served in various cabinet positions in the Canadian federal government, including as Minister of Consumer and Commercial Services. Currently she is a member of the Board of Directors of Inco, Imasco, the Loeb Research Institute and the University of Ottawa.



#### **Raymond Hession**

Raymond Hession is president of HNA Management Services Inc., a management consulting firm. He has served as President of Canada Mortgage and Housing, Deputy Ministry of Industry for the Canadian government and President of Kinburn Corporation. He is the Chairman of the Adherex Audit Committee of the Board.

#### Edwin Levy, Ph D.

Dr. Edward Levy is Vice-President, Business Affairs at QLT Inc. His focus is in the areas of strategic alliances, intellectual property and the commercialization of devices. Dr. Levy's efforts have resulted in the formation of a number of strategic partnerships including alliances with CIBA Vision, Sanofi Pharmaceuticals and Medtronic. Previously, he was a professor at the University of British Columbia.

#### Julia G. Levy, Ph D.

Dr. Levy is past President and CEO of QLT Inc. Under Dr. Levy's direction, QLT achieved a number of significant milestones including European and FDA approvals for its age-related macular degeneration therapy, and corresponding market launches. She sits on the National Advisory Board of Science and Technology in Canada, chairs the Premier's Advisory Council for Science and Technology in British Columbia and holds an industrial professorship at the University of British Columbia.

#### **Douglas Tam**

Douglas Tam is an independent businessman with interests in several companies and an investor in Adherex.

#### Kevin O'Brien Fehr, Ph D.

Since 1992, Kevin has managed basic research and genetics studies conducted in Canadian companies and universities on behalf of GlaxoSmithKline (GSK). She has extensive contacts in the academic and biotechnology communities throughout the country, and is actively working to attract funding from GSK's international sources for the support of Canadian researchers. Her previous experiences include ten years at the Addiction Research Foundation of Ontario as a scientist and educator, and five years with the Medical Liaison Service of Sandoz Canada, acting as an interface between the company and the Canadian medical research community.

# **APPENDIX 2: SCIENTIFIC ADVISORY BOARD**

## Stephen Byers, Ph D., Professor, Georgetown University

Dr. Stephen Byers is a cell biologist with expertise in cell adhesion and cancer. Currently, he is Professor of Human Oncology and Cell Biology at Georgetown University and the Lombardi Cancer Center. He is noted for the characterization of the epithelial barriers of the male reproductive system, as well as his studies on the role of cadherins and catenins in tumorigenesis. Dr. Byers has authored over 70 journal articles, and is a named inventor on several patents.

## Patrick Doherty, Ph D., Professor and Chair, Guy's Hospital

Dr. Patrick Doherty, Chair in Cell Biology at the United Medical and Dental Schools of Guy's and St. Thomas' Hospitals, London UK, is an expert in neural cell adhesion molecules. He is noted for developing bioassays to measure the growth promoting activity of cell adhesion molecules. Dr. Doherty sits on the editorial board of the journal Molecular and Cellular Neuroscience and has published over 100 articles in peer-reviewed journals.

#### Riaz Farookhi, MD, Associate Professor, McGill University

Dr. Riaz Farookhi is an experienced endocrinologist and expert in reproductive endocrinology and ovarian biology. He is currently an Associate Professor of McGill University in the Departments of Obstetrics & Gynecology, Physiology, and Experimental Medicine. In 1989, he was named Director of the McGill Centre for the Study of Reproduction. Dr. Farookhi is noted for his discovery of the regulation of cadherins by estrogen.

## Benjamin Geiger, Ph D., Chairman, Dept. Molecular Cell Biology, Weizmann Institute of Science

Dr. Benjamin Geiger, Chairman of the Department of Molecular Cell Biology at the Weizmann Institute of Science, is considered one of Israel's top scientists and an expert on cadherins. Dr. Geiger is the former Dean of the Feinberg Graduate School at the Weizmann Institute of Science. Dr. Geiger is the Chairman of the National Steering Committee for Science and Technology Education, and the Curriculum Planning Committee for the Israeli Ministry of Education. He is a member of the editorial board of seven journals, and has published over 200 scientific articles.

## Robert Kerbel, Ph D., Director, Cancer Biology Research, Sunnybrook Health Science Center

Dr. Robert Kerbel, Director of Cancer Biology Research at Sunnybrook Health Science Center and the John and Elizabeth Tory Chair in Experimental Oncology at the University of Toronto, is an expert in the fields of angiogenesis, cancer metastasis and drug resistance in cancer. Dr. Kerbel is the Editor-in-Chief of Cancer and Metastasis Reviews, and has been on the Editorial Board of eleven journals. He has chaired the



National Cancer Institute of Canada's Grants Panel on Molecular and Cellular Biology, and for his achievements, Dr. Kerbel has received the Terry Fox Senior Cancer Research Scientist Award from the National Cancer Institute of Canada.

#### Hartley Stern, MD, Chairman, Dept. Surgery, University of Ottawa

Dr. Hartley Stern is an expert on colorectal surgery and colorectal cancer. Dr. Stern holds the positions of Chairman of the Department of Surgery at the University of Ottawa and CEO of the Ottawa Regional Cancer Centre. Dr. Stern is President of Canadian Oncology Society and Steering Committee Member for the Canadian Strategy for Cancer Control.

#### Shaomeng Wang, Ph D., Associate Professor, University of Michigan

Dr. Shaomeng Wang is currently Associate Professor at the University of Michigan. He is an expert in the areas of molecular modeling and computer-aided drug design, and his work led to discoveries of both anti-cancer and anti-AIDS drugs and four US and international patents. He has published more than 60 scientific articles in the last eight years.

# **APPENDIX 3: INCOME STATEMENT**

## Figure 12: Income statement

	Years ended June 30					
	F1999	F2000	F2001	F2002E	F2003E	F2004E
Expenses						
General and administration (\$)	243,662	528,659	1,118,051	1,371,751	1,454,056	1,541,300
Research and development (\$)	1,207,928	1,847,657	2,890,950	4,298,156	4,835,426	5,439,854
	1,451,590	2,376,316	4,009,001	5,669,907	6,289,482	6,981,154
Licensing Payment (\$)						(4,900,000)
Investment income (\$)	(4,123)	(12,297)	(293,876)	(315,244)	(110,838)	(181,239)
Net loss (\$)	1,447,467	2,364,019	3,715,125	5,354,663	6,178,644	1,899,915
Accumulated deficit						
Beginning of period (\$)	639,651	2,087,118	4,451,137	8,166,262	13,520,925	19,699,568
End of period (\$)	2,087,118	4,451,137	8,166,262	13,520,925	19,699,568	21,599,483
Net earnings per common share						
Basic (\$)	(0.09)	(0.11)	(0.15)	(0.13)	(0.13)	(0.03)
Fully diluted (\$)	(0.09)	(0.11)	(0.15)	(0.12)	(0.12)	(0.03)
Weighted avg. common shares						
Basic	16,002,715	22,392,300	25,458,417	40,163,985	48,547,485	57,117,485
Fully Diluted	16,002,715	22,392,300	25,458,417	44,267,485	49,617,485	57,467,485

Source: Adherex Technologies Inc. and Canaccord Capital estimates

# **APPENDIX 4: BALANCE SHEET**

## Figure 13: Balance sheet

	Years ended June 30					
	F1999	F2000	F2001	F2002E	F2003E	F2004E
Current assets						
Cash and cash equivalents	128,449	164,452	14,152,528	9,450,951	8,178,113	20,278,197
Amounts receivable	59,764	44,204	204,366	15,000	10,000	10,000
Prepaid expense	16,158	36,434	77,429	100,000	102,500	105,063
Investment tax credits recoverable	575,224	400,000	602,605	20,242	-	-
	779,595	645,090	15,036,928	9,586,193	8,290,613	20,393,259
Capital assets	337,513	306,836	787,005	929,346	904,346	879,346
	1,117,108	951,926	15,823,933	10,515,539	9,194,959	21,272,605
Current liabilities						
Accounts payable and accrued liabilities	283,159	626,785	667,867	736,013	772,814	811,454
Portion of deferred lease inducements	44,975	44,975	89,817	89,817	86,080	-
Portion of capital lease obligation	1,615	4,583	3,954	4,583	1,615	1,615
Portion of long-term debt	-	33,333	33,333	33,333	-	-
	329,749	709,676	794,971	863,746	860,509	813,069
Deferred lease inducements	168,657	123,682	153,442	86,080	-	-
Capital lease obligation	5,058	4,961	2,166	-	-	-
Long-term debt	-	44,444	11,111	-	-	-
Other Advances	258,116	-	-	-	-	
	761,580	882,763	961,690	949,826	860,509	813,069
Shareholders' equity						
Capital stock	2,442,646	4,520,300	23,028,505	23,086,638	28,034,019	42,059,019
Retained earnings	(2,087,118)	(4,451,137)	(8,166,262)	(13,520,925)	(19,699,568)	(21,599,483)
	355,528	69,163	14,862,243	9,565,713	8,334,451	20,459,536
	1 117 100	051 020	15 000 000	10 515 520	0 104 050	21 272 605
	1,117,108	921,920	12,023,933	10,515,539	3,134,323	21,272,005

Source: Adherex Technologies Inc. and Canaccord Capital estimates

# **APPENDIX 5: CASH FLOW STATEMENT**

## Figure 14: Cash flow statement

	Years ended June 30					
	F1999	F2000	F2001	F2002E	F2003E	F2004E
Cash flows from (used in)						
Operating activities						
Net loss	(1,447,467)	(2,364,019)	(3,715,125)	(5,354,663)	(6,178,644)	(1,899,915)
Adjustments for non-cash items;						
Amortization of capital assets	27,863	76,974	150,994	300,000	300,000	300,000
Unrealized foreign exchange loss	12,999	-	-	-	-	-
Leasehold inducement (amortization)	(11,243)	(44,975)	(67,398)	-	(3,737)	(86,080)
Changes in non-cash working capital;						
Amounts receivable	(53,350)	15,560	(160,162)	189,366	5,000	-
Prepaid expense	(16,158)	(20,276)	(40,995)	(22,571)	(2,500)	(2,562)
Investment tax credits recoverable	(420,945)	181,824	(202,605)	582,363	20,242	-
Accounts payable and accrued liabilities	(284,633)	343,626	(33,702)	68,146	36,801	38,641
	(2,192,934)	(1,811,286)	(4,068,993)	(4,237,359)	(5,822,838)	(1,649,916)
Investing activities						
Purchase of capital assets	(123,075)	(47,827)	(501,883)	(413,654)	(50,000)	(50,000)
Disposal of capital assets	-	-	12,720	-	-	-
	(123,075)	(47,827)	(489,163)	(413,654)	(50,000)	(50,000)
Financing activities						
Other advances	-	-		-	-	-
Proceeds of long-term debt	-	100,000		-	-	-
Long-term debt repayments	-	(22,222)	(33,333)	(44,444)	-	-
Capital lease repayments	(232)	(2,200)	(3,424)	(6,120)	-	-
Proceeds from issuance of capital stock	2,442,546	1,819,538	18,582,989	-	4,600,000	13,800,000
	2,442,314	1,895,116	18,546,232	(50,564)	4,600,000	13,800,000
Net change in cash and equivalents	126,305	36,003	13,988,076	(4,701,577)	(1,272,838)	12,100,084
Cash and cash equivalents						
Beginning of period	2,144	128,449	164,452	14,152,528	9,450,951	8,178,113
End of period	128,449	164,452	14,152,528	9,450,951	8,178,113	20,278,197

Source: Adherex Technologies Inc. and Canaccord Capital estimates

# **APPENDIX 6: GLOSSARY**

Angiogenesis - A physiological process by which new blood vessels are formed

**Angiolytic -** Any drug or agent that is capable of disrupting or breaking up newly formed blood vessels

**Angiostatic or Anti-Angiogenic -** Any drug or agent that is capable of stopping the growth of new blood vessels

**Basement Membrane** - Material produced by cells and secreted into the surrounding medium, characteristically found under a layer of cells

**Blood-Brain Barrier** - A protective barrier formed by the blood vessels of the brain. It prevents some substances in the blood from entering brain tissue

**Cadherin** - A family of proteins located at the surface of cells that bind identical molecules on neighboring cells resulting in the process known as cell adhesion

Cadherin Antagonist - A substance that inhibits the action of cadherin molecules

Catenins - A class of proteins found inside the cell associated with cadherins

**Cell Adhesion** - The physiological process whereby similar cells adhere to one another to form tissues, also called Cell-to-Cell Adhesion.

**Endocrinology** - The study of the glands and hormones of the body and their related disorders

**Epithelial -** Referring to the tissue that forms the outer lining of the body. The epithelial tissues form a complete barrier to the external environment and include the tissues that line the gut or other hollow structure

**GMP** - **G**ood **M**anufacturing **P**ractice, the standard required by regulatory authorities for the manufacture of drugs

**Investigational New Drug Submission (or IND) -** Documentation filed with government agencies responsible for evaluating and licensing pharmaceutical drugs. This documentation is necessary for the initiation of clinical trials

**Metastasis** - The process whereby a tumor cell is able to leave the original tumor mass and spread to secondary sites in the body forming additional tumor sites

**Occludin** - A cell adhesion protein involved in the formation of tight junctions, specialized cellular contacts that prevent fluid moving between cells

**Patent Cooperation Treaty (PCT)** - An international patent treaty, of which Canada is a member, whereby a single patent application can be filed in the applicant's or inventor's home country for possible protection in over 100 member countries

Pharmacokinetics - The action of drugs in the body over a period of time



NOTES

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