

NUVELO INC  
Form 424B3  
February 19, 2004  
Table of Contents

**The information in this preliminary prospectus supplement and the accompanying prospectus is not complete and may be changed. This preliminary prospectus supplement and the accompanying prospectus are not an offer to sell these securities and we are not soliciting an offer to buy these securities in any jurisdiction where the offer or sale is not permitted.**

Filed Pursuant to Rule 424(b)(3)

Registration No. 333-112209

PRELIMINARY PROSPECTUS SUPPLEMENT

Subject to Completion

February 19, 2004

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(To Prospectus dated February 5, 2004)

## 4,000,000 Shares

## Common Stock

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We are offering all of the 4,000,000 shares of common stock offered by this prospectus supplement.

Our common stock is quoted on the Nasdaq National Market under the symbol NUVO. On February 17, 2004, the last reported sale price for our common stock on the Nasdaq National Market was \$15.12 per share.

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*Unless otherwise indicated, all per share amounts in this prospectus supplement give effect to a one-for-three reverse split of our common stock that we anticipate will become effective on February 23, 2004.*  
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Investing in our common stock involves a high degree of risk. Before buying any shares you should carefully read the discussion of material risks of investing in our common stock under the heading Risk factors beginning on page S-9 of this prospectus supplement.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities, or determined if this prospectus supplement or the accompanying prospectus is truthful or complete. Any representation to the contrary is a criminal offense.

	Per share	Total
Public offering price	\$	\$
Underwriting discounts and commissions	\$	\$
Proceeds, before expenses, to us	\$	\$

The underwriters may also purchase up to an additional 600,000 shares of common stock from us at the public offering price, less the underwriting discounts and commissions, to cover over-allotments, if any, within 30 days from the date of this prospectus supplement. If the underwriters exercise the option in full, the total underwriting discounts and commissions will be \$ , and the total proceeds, before expenses, to us will be \$ .

The underwriters are offering the shares of common stock as set forth under Underwriting. Delivery of the shares will be made on or about , 2004.

*Sole Book-Running Manager*

**UBS Investment Bank**

**CIBC World Markets**

**Needham & Company, Inc.**

**JMP Securities**

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**Table of Contents**


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You should rely only on the information contained in or incorporated by reference in this prospectus supplement and the accompanying prospectus. We have not and the underwriters have not authorized anyone to provide you with information that is different from that contained or incorporated by reference in this prospectus supplement or the accompanying prospectus. We are not offering to sell or seeking offers to buy shares of common stock in jurisdictions where offers and sales are not permitted. The information contained in this prospectus supplement or the accompanying prospectus is accurate only as of the date of this prospectus, regardless of the time of delivery of this prospectus or of any sale of our common stock. Unless the context otherwise requires, references to we, us or the company in this prospectus supplement and the accompanying prospectus mean Nuvelo, Inc. and its subsidiaries.

**TABLE OF CONTENTS**


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**Prospectus supplement**

<u>Prospectus supplement summary</u>	S-1
<u>Risk factors</u>	S-9
<u>Forward-looking statements</u>	S-31
<u>Use of proceeds</u>	S-32
<u>Price range of common stock</u>	S-33
<u>Dividend policy</u>	S-33
<u>Capitalization</u>	S-34
<u>Dilution</u>	S-36
<u>Management</u>	S-37
<u>Underwriting</u>	S-40
<u>Legal matters</u>	S-43
<u>Experts</u>	S-43
<u>Incorporation by reference</u>	S-43

**Prospectus**

<u>About this prospectus</u>	1
<u>Risk factors</u>	1
<u>About Nuvelo</u>	1
<u>Cautionary note regarding forward-looking information</u>	2
<u>Use of proceeds</u>	2
<u>Ratio of earnings to fixed charges</u>	2
<u>Description of debt securities</u>	3
<u>Description of preferred stock</u>	12
<u>Description of common stock</u>	14
<u>Additional information concerning our capital stock</u>	16
<u>Plan of distribution</u>	18
<u>Legal matters</u>	18
<u>Experts</u>	19

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We own or have rights to use trademarks or trade names that we use in conjunction with the operation of our business. Nuvelo is a registered trade and service mark of ours. All other trademarks, service marks and trade names referred to in this prospectus supplement and the accompanying prospectus are the property of their respective owners.

## **CORPORATE INFORMATION**

We were incorporated as Hyseq, Inc. in Illinois in 1992 and reincorporated in Nevada in 1993. On January 31, 2003, we merged with Variagenics, Inc., a publicly traded Delaware corporation based in Massachusetts, and, in connection with the merger, changed our name to Nuvelo, Inc. Our principal executive offices are located at 675 Almanor Avenue, Sunnyvale, California 94085 and our telephone number is (408) 215-4000. Our World Wide Web address is <http://www.nuvelo.com>. Information contained on our web site should not be considered to be part of this prospectus supplement or the accompanying prospectus.

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**Table of Contents**

## Prospectus supplement summary

*This summary highlights information contained elsewhere or incorporated by reference in this prospectus supplement and the accompanying prospectus. This summary does not contain all of the information that you should consider before investing in our common stock. You should carefully read the entire prospectus supplement and the accompanying prospectus, including the Risk factors section, as well as the financial statements and the other information incorporated by reference herein before making an investment decision.*

### **BUSINESS OVERVIEW**

We are a biopharmaceutical company focused on the discovery, development and commercialization of novel products for acute cardiovascular indications and cancer. Our strategy is to focus on the clinical development of the drug candidates that we have partnered, in-licensed or discovered internally.

We currently have two drug candidates in clinical trials, and plan to have a third candidate enter clinical trials in the second half of 2004. Our lead drug candidate, alfimeprase, is a thrombolytic agent, or blood clot dissolver. Alfimeprase is currently in two separate Phase 2 clinical trials for the treatment of acute peripheral arterial occlusion (PAO) and catheter occlusion. Based on the current rate of enrollment, we project completing enrollment of the Phase 2 PAO trial in March or April of 2004 and, if the results of the Phase 2 trial are positive, we anticipate initiating a Phase 3 trial in this indication in the second half of 2004. We have obtained orphan drug status for alfimeprase in the United States for use in treating acute PAO. We are also currently conducting a Phase 2 multi-center, double-blind, randomized study in patients with occluded catheters. We project completing an interim analysis of the first 48 patients in March or April of 2004. We have a 50/50 cost/profit sharing collaboration in place with Amgen Inc. for the worldwide development and commercialization of alfimeprase.

Our second drug candidate is rNAPc2, which we recently in-licensed from Dendreon Corporation. rNAPc2 is a recombinant version of a naturally occurring protein that has anticoagulant properties resulting from its ability to block the Factor VIIa/Tissue Factor protease complex, which is responsible for the initiation of the process leading to blood clot formation. rNAPc2 is currently undergoing a Phase 2a double-blind, placebo controlled clinical trial for use in treating acute coronary syndromes (ACS), including unstable angina (UA) and non-ST segment elevation myocardial infarction (NSTEMI).

Our third drug candidate is ARC183, a novel thrombin inhibitor which we intend to develop for use in acute cardiac surgical procedures. We recently announced a collaboration agreement with Archemix Corporation for the development and commercialization of ARC183. We anticipate that an Investigational New Drug (IND) application for ARC183 will be filed in mid-2004. If an IND is accepted by the Food and Drug Administration (FDA), we expect that Phase 1 clinical trials will begin in the second half of 2004.

In addition to our clinical and development stage drug candidates, we have an ongoing discovery program that is focused on proprietary human genes encoding proteins that may have therapeutic applications. We intend to develop product opportunities from our ongoing discovery efforts by focusing on secreted proteins and antibody targets. The secreted protein program includes our collaboration with the pharmaceutical division of Kirin Brewery Company, Ltd. and our internal discovery program. Under our Kirin collaboration, we expect to complete the analysis of approximately 50 secreted protein genes in mouse models in the first half of 2004. We expect to leverage discoveries in these research programs to extend and expand our drug pipeline and to create revenue-generating licensing and partnering arrangements.



## **Table of Contents**

### **OUR LEAD DRUG CANDIDATES**

#### **ALFIMEPRASE**

Alfimeprase, our lead development candidate, is currently in two Phase 2 clinical trials in two distinct indications, acute PAO and catheter occlusion. Alfimeprase is a thrombolytic agent, or blood clot dissolver, with a novel mechanism of action. It is a modified and recombinant version of fibrolase, a naturally occurring enzyme that directly degrades fibrin, the protein which provides the structural scaffold of blood clots. Thrombolytics currently on the market such as urokinase (Abbokinase) or alteplase (Activase), are plasminogen activators that work by activating plasminogen to form plasmin which, in turn, degrades fibrin. In contrast, alfimeprase directly degrades fibrin, producing more rapid clot dissolution or lysis. Alfimeprase is locally delivered at the site of the blood clot and is inactivated quickly by a naturally occurring inhibitor in the bloodstream. This clearance mechanism limits the amount of drug in systemic circulation and associated side effects. Preclinical and early clinical data suggest that alfimeprase has the potential to lyse clots faster while also reducing the bleeding complications resulting from currently available agents.

Alfimeprase was identified through a research program at Amgen, who initiated the program with us in January 2002. The collaboration is a 50/50 cost/profit sharing arrangement with the parties sharing worldwide rights to alfimeprase. We are responsible for the clinical development activities and Amgen is responsible for manufacturing activities. Amgen will have the option to lead the commercialization in which both parties may participate.

#### **Alfimeprase in Acute Peripheral Arterial Occlusion (PAO)**

Our lead medical indication for alfimeprase is acute PAO. Acute PAO is a significant cause of morbidity in the United States with over 100,000 cases reported annually. We have obtained orphan drug status on alfimeprase in the United States for this indication, which may provide us with seven years of market exclusivity in the United States. Acute PAO occurs when arterial blood flow is blocked to a distant part of the body, usually the leg, by a blood clot. Traditionally, bypass surgery and angioplasty have been used to treat acute PAO. However, thrombolytic agents such as urokinase (Abbokinase) or alteplase (Activase) have been increasingly used as a less-invasive alternative. We believe alfimeprase has the potential to be a more effective agent than existing agents for use in treating acute PAO by reducing the treatment time and potential bleeding side effects. We completed our Phase 1 trial on alfimeprase in the first quarter of 2003. This trial was a multi-center, open label, dose-escalation study to evaluate the safety and pharmacokinetics of alfimeprase, and was completed in 20 patients across 7 centers in the United States. The Phase 1 results showed that alfimeprase was well-tolerated with no confirmed drug-related adverse events reported. We initiated a Phase 2 program with alfimeprase in June 2003 in acute PAO.

In September 2003, we announced completion of a planned interim analysis of our Phase 2 trial with alfimeprase for acute PAO. The interim analysis was conducted on data from the first 36 patients enrolled in the trial. Following review of the patient data, the Data Safety and Monitoring Board (DSMB) and the Trial Steering Committee recommended that we continue to move forward with the trial in three doses. At an investigator meeting following the interim analysis, it was recommended that we concentrate on the two highest doses of alfimeprase. This change will result in 115 patients being treated. Based on the current rate of enrollment, we project completing enrollment of the Phase 2 PAO trial in March or April of 2004. If we successfully complete the Phase 2 trial and discussions with the FDA regarding the design of our planned Phase 3 trial, we expect to begin a Phase 3 PAO trial in the second half of 2004.

## **Table of Contents**

### **Alfimeprase in catheter occlusion**

Our second medical indication for alfimeprase is catheter occlusion. Catheter occlusion is the obstruction of blood flow through a central venous catheter by a blood clot. It is estimated that about five million catheters are implanted in patients each year in the United States, and approximately 20-25% become occluded. Current treatment for catheter occlusion includes invasive surgery to remove and replace the catheter, or treatment with Cathflo Activase (alteplase). Based on clinical trial evidence of alfimeprase's rapid lysis activity, we believe alfimeprase has the potential to rapidly restore blood flow to these occluded catheters.

We are currently conducting a Phase 2 multi-center, double-blind, randomized study in patients with occluded catheters comparing three doses of alfimeprase against the approved dose of Cathflo Activase. We expect to treat approximately 100 patients in this trial. We have recently increased the number of sites participating in the trial and, as a result, we have seen increased enrollment over the past few months. We project completing an interim analysis on the first 48 patients in March or April of 2004.

### **rNAPc2 (recombinant Nematode Anticoagulant Protein c2)**

rNAPc2 is a recombinant version of a naturally occurring protein that has anticoagulant properties. Specifically, rNAPc2 has been shown to block the Factor VIIa/Tissue Factor protease complex, which is responsible for the initiation of the process leading to blood clot formation. Compared to other commercially available anticoagulants, which all exert their effects at later stages of the blood coagulation cascade, rNAPc2 is designed to block the first step in the clotting cascade, inhibiting coagulation before it starts. By blocking the coagulation cascade at such an early stage, rNAPc2 could prove to be safer and more effective in treating patients with conditions such as acute coronary syndrome or as a prophylactic against clot formation.

We recently licensed the worldwide rights for all indications of rNAPc2 and all of the rNAPc molecules owned by Dendreon. To date, rNAPc2 has been shown to be well-tolerated in over 500 patients and healthy volunteers in several Phase 1 and 2 studies. The indication that we are currently pursuing for rNAPc2 is acute coronary syndrome (ACS).

ACS, such as unstable angina (UA) and non-ST segment elevation myocardial infarction (NSTEMI), result when an atherosclerotic plaque ruptures in a coronary artery triggering the coagulation cascade and resulting in the formation of a blood clot. The clot blocks the flow of blood to the heart muscle depriving it of oxygen and causing chest pain and/or a heart attack. Worldwide, it is estimated that ACS accounts for more than 1.8 million hospital admissions annually. Patients with ACS are traditionally given aspirin and heparin to stabilize their medical condition. Recent guidelines also recommend the addition of the antiplatelet agent clopidogrel (Plavix) to standard care. However, based upon the significant number of patients with ACS who continue to experience poor outcomes such as recurrent angina, myocardial infarction or death, we believe there is a clear need for better antithrombotic therapy.

rNAPc2, given alone or with standard therapy, may significantly reduce the risk of subsequent heart attack or death in patients suffering from UA/NSTEMI. Unlike aspirin and heparin, or current antithrombotic agents, which all exert their effects at later stages of the blood coagulation cascade, rNAPc2 blocks the first step in the clotting cascade. A medical regimen that includes rNAPc2 could, therefore, enable a multi-pronged attack at several points along the blood coagulation process. Alternatively, by stopping coagulation before it starts, rNAPc2 could prove more effective even as a stand-alone therapy.





## **Table of Contents**

A Phase 2a double-blind, placebo controlled clinical trial to determine a safe and effective dose of rNAPc2 in moderate to high-risk patients with UA/NSTEMI has been initiated. The study was planned to be conducted in three parts, each of which would investigate rNAPc2 in combination with current anticoagulant and antiplatelet therapies. Currently, the study is being reinitiated with the TIMI Study Group led by Dr. Eugene Braunwald of Brigham and Women's Hospital and Harvard Medical School. We plan to complete the Phase 2a study and further evaluate future clinical development based on the data from this trial.

Another Phase 2 dose-ranging study of rNAPc2 was conducted in 293 subjects undergoing elective, unilateral total knee replacement. The study examined the drug's potential to reduce the incidence of deep vein thrombosis (DVT), a condition whereby a blood clot (thrombus) develops in a deep vein, usually in the leg following orthopedic surgery. This proof-of-principle study demonstrated that rNAPc2 could provide effective antithrombotic efficacy with minimal effects on surgical hemostasis in a clinical setting which is associated with a high risk of thrombosis. We are currently evaluating other potential indications of rNAPc2 such as DVT prophylaxis.

A recently published preclinical study suggests that rNAPc2 may also be effective in the treatment of the Ebola virus infection. In addition, preclinical studies have shown that blocking the protease complex Factor VIIa/Tissue Factor prevents the growth of primary and metastatic tumors in animal models.

## **ARC183**

ARC183 is a DNA aptamer, which is a single-stranded nucleic acid that forms well-defined three-dimensional shapes, allowing it to bind to thrombin with high affinity and specificity. The key advantage of ARC183 compared to other thrombin inhibitors is its rapid onset of action and short half-life, giving it the potential to be an ideal agent for medical procedures that require rapid resolution of anticoagulation or that require reversal of anticoagulation shortly after the procedure is completed.

We recently announced a collaboration agreement with Archemix, a privately held biotechnology company, located in Cambridge, Massachusetts, for the development and commercialization of ARC183. Our lead indication for ARC183 is as a thrombin inhibitor for use in coronary artery bypass graft (CABG) surgery.

According to the American Heart Association, more than 500,000 CABG procedures are performed in the United States annually. Currently, heparin is used to limit blood clotting in this indication, but is difficult to dose and can cause side effects such as bleeding and heparin-induced thrombocytopenia (HIT). Moreover, the effect of heparin must be reversed with the use of an antidote called protamine. Protamine is not approved by the FDA for reversal of heparin in CABG surgery and is associated with significant complications including hypotension, platelet dysfunction, complement activation and thrombus formation. We believe that there is a significant unmet medical need for a safe, fast-acting anticoagulant for use in CABG that is easier to administer, does not require a reversal agent and lacks the side effects such as bleeding and HIT.

ARC183 has shown potential in preclinical studies to be equally effective, with fewer side effects than heparin and protamine in combination. Due to its very short half-life, ARC183 is expected to lead to more predictable dosing as well as reduced incidence of bleeding side effects compared to heparin. We believe that ARC183 has the potential to replace current therapies and become the standard of care in cardiac surgical procedures. We are currently evaluating the potential for ARC183 for use in percutaneous intervention (PCI), such as angioplasty and stent placement, and non-coronary procedures, such as renal dialysis.



**Table of Contents**

We anticipate that an IND for ARC183 will be filed with the FDA in mid-2004. If our IND is accepted by the FDA, we expect to initiate Phase 1 clinical trials for use in CABG surgery in the second half of 2004.

**CLINICAL PRODUCT PIPELINE**

The following table summarizes key information about our current clinical product pipeline:

<b>Drug candidate (technology)</b>	<b>Indication</b>	<b>Development status</b>	<b>Commercialization rights</b>
alfimeprase (Fibrinolytic)	Acute Peripheral Arterial Occlusion	Phase 2	50/50 collaboration with Amgen
alfimeprase (Fibrinolytic)	Catheter Occlusion	Phase 2	50/50 collaboration with Amgen
rNAPc2 (Tissue Factor Inhibitor)	Acute Coronary Syndromes	Phase 2a	Nuvelo has exclusive commercialization rights
ARC183 (Thrombin-Inhibitor)	Coronary Artery Bypass Graft Surgery	IND anticipated to be filed mid-2004	50/50 collaboration with Archemix

**RESEARCH AND DEVELOPMENT PROGRAMS**

In addition to our clinical and development stage drug candidates, we have an ongoing discovery program focused on the identification of novel human genes that encode proteins with therapeutic potential. Over the long-term, we intend to develop additional product opportunities from our ongoing discovery efforts focused on secreted proteins and antibody targets.

The secreted protein program includes our collaboration with Kirin and our internal discovery program. Under our Kirin collaboration, we expect to complete the analysis of approximately 50 secreted protein genes in mouse models in the first half of 2004. We have already advanced several secreted protein candidates to more extensive studies to better define their therapeutic utility based upon early findings in initial mouse models. Within our internal secreted protein discovery program, we have developed a fast and efficient method of expressing human secreted proteins in mice. This program could significantly bolster our ability to identify which secreted proteins within our patent estate have the greatest potential for therapeutic use. We plan to test up to 55 secreted proteins with this internal program in 2004.

The antibody program is focused on screening our proprietary gene sequence collection to identify proteins located on the surface of tumor cells that could be targeted by therapeutic monoclonal antibodies. We are currently evaluating 18 targets in blood cancers and solid cancers. Of these 18, we have advanced 7 into in-vivo testing.

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We expect to move the most promising internal drug candidates forward and potentially advance at least one of these into IND-enabling studies in 2004. In addition to the development of internal therapeutic candidates, we intend to leverage these discoveries to create revenue-generating licensing and partnering arrangements.

S-5

## **Table of Contents**

### **OUR STRATEGY**

We are focused on building a successful biopharmaceutical business and committed to creating a valuable product-focused company that leverages our drug discovery and development expertise. Key elements of our strategy are to:

#### **Develop and successfully commercialize alfimeprase**

We are seeking to develop and commercialize alfimeprase for the treatment of acute PAO and catheter occlusion. Alfimeprase is in Phase 2 clinical trials in these two indications, and we have an established collaboration with Amgen to facilitate its worldwide commercialization.

#### **Progress our portfolio of cardiovascular clinical and development stage products**

We have developed a portfolio of acute, hospital-based, cardiovascular drug candidates. We believe this portfolio leverages our established expertise in cardiovascular drug development, provides synergy with alfimeprase during both development and commercialization and enables us to pursue a more rapid path toward drug development.

#### **Increase probability of commercial success**

We are pursuing several drug development candidates simultaneously in order to reduce the impact of any single product failure. By broadening our product portfolio, we intend to increase the probability of clinical and commercial success. In addition, we focus on molecules that have a greater chance of success due to the predictability of preclinical models used in their development.

#### **Opportunistically seek to license or acquire complementary products and technologies**

We intend to supplement our internal drug discovery efforts through the acquisition of products and technologies that complement our development strategy. We continue to identify, evaluate and pursue the acquisition or licensing of strategically valuable product opportunities.

### **RECENT DEVELOPMENTS**

On January 12, 2004, we entered into a worldwide collaboration agreement with Archemix to develop and commercialize thrombin inhibitor ARC183 for potential use in CABG surgery, PCI and other acute anticoagulant applications. We paid Archemix an upfront payment of \$3.0 million and we will also pay a milestone payment upon initiation of the Phase 2 trial and a reimbursement of \$1.0 million upon the designation of any backup compound. Under the terms of the agreement, Archemix will initially lead development and be responsible for all clinical development activities. As part of the transaction, we and Archemix will equally share all revenues and costs associated with the development and commercialization of ARC183 after we fund the first \$4.0 million in research and development costs. We will have the option to lead commercialization efforts in which both companies may participate.

On February 4, 2004, we entered into a worldwide licensing agreement with Dendreon for Dendreon's novel anticoagulant, rNAPc2, and all other rNAPc molecules owned by Dendreon. Under the terms of the agreement, we paid Dendreon an upfront payment of \$4.0 million (\$500,000 in

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cash and \$3.5 million worth of Nuvelo common stock). In addition, we will pay to Dendreon milestone payments prior to and upon any commercialization, as well as royalties if and when we reach commercialization. Our license from Dendreon grants us exclusive worldwide rights to all indications for rNAPc products.

On February 4, 2004, we announced the appointment of Barry L. Zubrow, a former senior executive of The Goldman Sachs Group, Inc., to our board of directors. Mr. Zubrow replaced Thomas McCarter, who stepped down as a member of our board of directors effective February 3, 2004. Mr. Zubrow also replaced Mr. McCarter on our audit committee.

**S-6**

**Table of Contents**

**The offering**

Common stock we are offering	4,000,000 shares
Common stock to be outstanding after this offering	29,637,981 shares
NASDAQ National Market Symbol	NUVO
Use of proceeds	We are raising funds in this offering primarily for general corporate purposes, including current and future clinical trials of our lead drug candidate, alfimeprase, as well as other research and product development activities. See Use of proceeds.
Risk factors	See Risk factors beginning on page S-9 for a discussion of factors you should carefully consider before deciding to invest in shares of our common stock.

The number of shares of our common stock to be outstanding after this offering in the summary above is based on 25,637,981 shares outstanding as of January 31, 2004, and does not include, as of that date:

- Ø an aggregate of 1,561,212 shares of our common stock reserved for issuance upon exercise of outstanding stock options granted under our 2002 Equity Incentive Plan, 1995 Stock Option Plan, Non-Employee Director Stock Option Plan, Scientific Advisory Board/Consultants Stock Option Plan and the Variagenics, Inc. Amended 1997 Employee, Director and Consultant Stock Option Plan;
- Ø an aggregate of 1,494,804 shares of common stock reserved for issuance pursuant to future option grants under these plans;
- Ø an aggregate of 88,307 shares of common stock reserved for issuance under our Employee Stock Purchase Plan;
- Ø an aggregate of 987,242 shares of common stock reserved for issuance upon the exercise of outstanding stock options granted outside of any of our stock option plans;
- Ø warrants to purchase an aggregate of 1,887,325 shares of our common stock, with exercise prices ranging from \$4.05 to \$25.53 per share, and a weighted average exercise price of \$17.76 per share;
- Ø 519,181 shares of common stock issuable upon repayment of our note held by Affymetrix and 1,098,286 shares of common stock issuable upon mutual agreement to convert the promissory note under the Rathmann line of credit; and
- Ø 263,296 shares issued on February 4, 2004 to Dendreon.

Unless otherwise stated, all information contained in this prospectus supplement assumes that our one-for-three reverse stock split has become effective and that the underwriters do not exercise their over-allotment option to purchase up to an additional 600,000 shares of common stock, and all currency amounts in this prospectus supplement are stated in US dollars.





Table of Contents

## Summary consolidated financial data

The tables below present summary consolidated statement of operations and balance sheet data. The summary financial data for the years ended December 31, 2001 through December 31, 2003 are derived from our audited consolidated financial statements for those periods. This information is only a summary and should be read in conjunction with our historical consolidated financial statements and related notes contained in our annual reports, quarterly reports and recent current reports on file with the SEC incorporated by reference in this prospectus supplement and the accompanying prospectus. For more details on how you can obtain our SEC reports, you should read the section of this prospectus supplement entitled "Incorporation by reference" beginning on page S-43. Our consolidated statement of operations data includes the results of operations of Variagenics, Inc. from February 1, 2003. The as adjusted consolidated balance sheet data gives effect to the sale by us of 4,000,000 shares of our common stock in this offering, assuming a public offering price of \$15.12 per share and after deducting the underwriting discounts and commissions and estimated offering expenses payable by us.

Consolidated statement of operations data:	Year ended December 31,		
	2001	2002	2003
	(in thousands, except per share data)		
Revenue	\$ 24,590	\$ 26,433	\$ 2,290
Research and development expenses	\$ 46,506	\$ 50,157	\$ 33,084
General and administrative expenses	\$ 13,452	\$ 18,108	\$ 17,223
Total operating expenses	60,783	70,368	51,532
Interest and other income	319	87	747
Net loss	\$ (36,472)	\$ (44,978)	\$ (50,187)
Net loss per common share, basic and diluted	\$ (6.77)	\$ (6.23)	\$ (2.38)
Shares used in computation of basic and diluted net loss per share	5,386	7,220	21,054

Consolidated balance sheet data:	December 31, 2003	
	Actual	As adjusted
	(in thousands)	
Cash, cash equivalents and short-term investments	\$ 34,189	\$ 90,465
Working capital	25,772	82,048
Total assets	57,809	114,085
Current portion of capital lease and line of credit obligations	4,741	4,741
Non-current portion of capital lease and line of credit obligations	8,871	8,871
Accumulated deficit	(203,559)	(203,559)
Total stockholders' equity	22,701	78,977

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**Table of Contents**

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## Risk factors

*An investment in our common stock involves a high degree of risk. You should consider carefully the risk factors described below and all other information contained in or incorporated by reference in this prospectus supplement and the accompanying prospectus before making an investment decision. If any of the following risks actually occurs, our business, financial condition, operating results or cash flow could be harmed. As a result, the trading price of our common stock could decline, and you could lose all or part of your investment.*

### **RISK RELATED TO OUR BUSINESS**

#### **We have not achieved profitability, have recent and anticipated continuing losses and may never become profitable.**

For the years ended December 31, 2001, 2002 and 2003, we had net losses of \$36.5 million, \$45.0 million and \$50.2 million, respectively. As of December 31, 2003, we had an accumulated deficit of \$203.6 million.

All of our product candidates are in various stages of product development, and some are still in research or in early development. None of them are approved for sale. The process of developing biotherapeutics and related products will require significant additional research and development, preclinical testing, clinical trials and regulatory approvals. These activities, together with general administrative and other expenses, are expected to result in operating losses for the foreseeable future. To date, we have not generated any revenues from product sales. We do not expect to achieve significant product sales or royalty revenue for several years, and we may never do so. We expect to incur additional operating losses in the future, and these losses may increase significantly as we continue preclinical research and clinical trials, apply for regulatory approvals, develop our drug candidates, expand our operations and develop systems that support commercialization of our potential products. These losses, among other things, have caused and may cause our stockholders' equity and working capital to decrease. We may not be successful in developing our drug candidates, obtaining regulatory approvals and commercializing our products, and our operations may not be profitable even if any of our drug candidates are commercialized. We may never generate profits and, as a result, the trading price of our common stock could decline. Moreover, utilization of our net operating loss carryforwards and credits may be subject to an annual limitation due to the change in ownership provisions of the Internal Revenue Code of 1986 and similar state law provisions. It is possible that certain transactions that we have entered into, including our merger with Variagenics that occurred in January 2003, when considered in connection with other transactions, may result in a change in ownership for purposes of these provisions.

#### **Our relatively short operating history may affect our ability to execute our business strategy.**

We have a short operating history. We commenced operations in the fourth quarter of 1994 with an initial business focused on gene discovery using our signature-by-hybridization platform and applications of our sequencing-by-hybridization technology, including the HyChip system. In 1998, we began to transition our business strategy from gene discovery to research and development of potential therapeutic protein candidates. As a company with a relatively short operating history, we face risks and uncertainties frequently encountered by companies in new and rapidly evolving markets, including:

Ø the implementation and successful execution of our business strategy and our sales and marketing initiatives;

Ø retention of current customers and collaborators and attraction of new customers and collaborators;

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**Table of Contents**

**Risk factors**

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- Ø our ability to respond effectively to competitive and technological developments related to our technologies, products and services;
- Ø our ability to attract, retain and motivate qualified personnel; and
- Ø our ability to effectively manage our anticipated growth.

If we fail to address these risks and uncertainties successfully, our business, results of operations, financial condition and prospects will be materially adversely affected.

**We may face fluctuations in operating results.**

Our operating results may rise or fall significantly as a result of many factors, including:

- Ø the amount of research and development we engage in;
- Ø the number of product candidates we have and their progress in research and preclinical studies;
- Ø our ability to expand our facilities to support our operations;
- Ø our ability to enter into new strategic relationships;
- Ø the scope, duration and effectiveness of our collaborative arrangements;
- Ø the costs involved in prosecuting, maintaining and enforcing patent claims;
- Ø the possibility that others may have or obtain patent rights that are superior to ours;
- Ø changes in government regulation; and
- Ø release of successful products into the market by our competitors.

Excluding our three clinical and development stage drug candidates, our potential products currently are in research or preclinical development, and revenues from the sales of any products resulting from these efforts may not occur for several years, if at all. We also have a high percentage

of fixed costs such as lease obligations. As a result, we may experience fluctuations in our operating results from quarter to quarter and continue to generate losses. Quarterly comparisons of our financial results may not necessarily be meaningful, and investors should not rely upon such results as an indication of our future performance. In addition, investors may react adversely if our reported operating results are less favorable than in a prior period or are less favorable than those anticipated by investors or the financial community, which may result in a drop of our stock price.

**We will need to raise additional capital, and such capital may be unavailable to us when we need it or not available on acceptable terms.**

We will need to raise significant additional capital before we can become profitable. Financing may be unavailable when we need it or may not be available on acceptable terms. The unavailability of financing may require us to delay, scale back or eliminate expenditures for our research, development and marketing activities necessary to commercialize our potential biopharmaceutical products. We may also be required to grant rights to third parties to develop and market drug candidates that we would prefer to develop and market on our own, potentially reducing the ultimate value of these drug candidates that we could realize.

If we are unable to obtain additional financing when we need it, the capital markets may perceive that we may not be able to raise the amount of financing we desire, or on terms favorable to us, which may negatively affect the trading price of our common stock. Additional equity financings could result in

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**Table of Contents**

**Risk factors**

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significant dilution of current stockholders' equity interests. If sufficient capital is not available, we will delay, reduce the scope of, eliminate or divest one or more of our subsidiaries or our discovery, research or development programs. Any such action could significantly harm our business, financial condition and results of operations.

Our future capital requirements and the adequacy of our currently available funds will depend on many factors, including, among others, the following:

- ∅ continued scientific progress in our research and development programs, including progress in our research and preclinical studies;
- ∅ the cost involved in any facilities expansion to support research and development of our product candidates;
- ∅ our ability to attract additional financing on favorable terms;
- ∅ the magnitude and scope of our research and development programs, including development of product candidates;
- ∅ our ability to maintain, and the financial commitments involved in our existing collaborative and licensing arrangements;
- ∅ our ability to establish new collaborative relationships with other companies to share costs and expertise of identifying and developing drug candidates;
- ∅ the cost of prosecuting and enforcing our intellectual property rights;
- ∅ the cost of manufacturing our material for preclinical, clinical and commercial purposes;
- ∅ progress in our clinical studies of alfimeprase;
- ∅ the time and cost involved in obtaining regulatory approvals;
- ∅ our need to develop, acquire or license new technologies or products;
- ∅ competing technological and market developments;
- ∅ future funding commitments to our subsidiary, Callida, and our ability to borrow funds from Affymetrix to fund our commitment, under the terms of the Affymetrix settlement;

- Ø our ability to use our common stock to repay the outstanding note to Affymetrix and our line of credit from our Chairman, Dr. George B. Rathmann;
- Ø legal and Nasdaq restrictions that impede our ability to raise funds from private placements of our common stock;
- Ø future funding commitments to our collaborators;
- Ø general conditions in the financial markets and in the biotech sector;
- Ø the uncertain condition of the capital markets; and
- Ø other factors not within our control.

**Development of our products will take years, and our products require regulatory approval before they can be sold.**

Excluding our three clinical and development stage drug candidates, our potential products currently are in research or preclinical development and revenues from the sales of any products resulting from these efforts may not occur for several years, if at all. We cannot be certain that any of our products will be



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**Table of Contents**

**Risk factors**

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demonstrated to be safe and effective or that we will obtain regulatory approvals. In addition, any products that we develop may not be economical to manufacture on a commercial scale. Even if we develop a product that becomes available for commercial sale, we cannot be certain that consumers will accept the product. We cannot predict whether we will be able to develop and commercialize any of our drug candidates successfully. If we are unable to do so, our business, results of operations and financial condition will be affected in a materially adverse manner.

We do not yet have products in the commercial markets. We must demonstrate that our product candidates satisfy rigorous standards of safety and efficiency before the FDA and comparable agencies in foreign markets. We cannot apply for regulatory approval of our potential products until we have performed significant additional research and development and testing. We cannot be certain that we, or our strategic partners, will be permitted to undertake clinical testing of our potential products or continue clinical testing of alfimeprase or rNAPc2. If we are successful in initiating clinical trials, we may experience delays in conducting them. Our clinical trials may not demonstrate the safety and efficacy of our potential products, and we may encounter unacceptable side effects or other problems in the clinical trials. Should this occur, we may have to delay or discontinue development of the potential product that causes the problem. After a successful clinical trial, we cannot market products in the United States until we receive regulatory approval. Even if we are able to gain regulatory approval of our products after successful clinical trials and then commercialize and sell those products, we may be unable to manufacture enough products to maintain our business, which could have a negative impact on our financial condition.

**We face heavy government regulation, and FDA regulatory approval of our products is uncertain.**

The research, testing, manufacturing and marketing of drug products such as those proposed to be developed by us or our collaboration partners are subject to extensive regulation by federal, state and local governmental authorities, including the FDA, and comparable agencies in other countries. In order to obtain regulatory approval of a drug product, we or our collaboration partners must demonstrate to the satisfaction of the applicable regulatory agency, among other things, that such product is safe and effective for its intended uses. In addition, we must show that the manufacturing facilities used to produce the products are in compliance with current Good Manufacturing Practices, or cGMP, requirements.

The process of obtaining FDA and other required regulatory approvals and clearances typically takes several years and will require us to expend substantial capital and resources. Despite the time and expense exerted, regulatory approval is never guaranteed. The number of preclinical and clinical tests that will be required for FDA approval varies depending on the drug candidate, the disease or condition that the drug candidate is in development for, and the regulations applicable to that particular drug candidate. The FDA can delay, limit or deny approval of a drug candidate for many reasons, including:

- ∅ a drug candidate may not be safe or effective;
- ∅ FDA officials may interpret data from preclinical and clinical testing in different ways than we and our collaboration partners interpret it;
- ∅ the FDA may not approve our manufacturing processes or facilities or the processes or facilities of our collaboration partners; or
- ∅ the FDA may change its approval policies or adopt new regulations.

S-12

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**Table of Contents**

**Risk factors**

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Moreover, if and when our products do obtain such approval or clearances, the marketing, distribution and manufacture of such products would remain subject to extensive ongoing regulatory requirements. Failure to comply with applicable regulatory requirements could result in:

Ø warning letters;

Ø fines;

Ø civil penalties;

Ø injunctions;

Ø recall or seizure of products;

Ø total or partial suspension of production;

Ø refusal of the government to grant approvals; or

Ø withdrawal of approvals and criminal prosecution.

Any delay or failure by us or our collaboration partners to obtain regulatory approvals for our products:

Ø would adversely affect our ability to generate product and royalty revenues;

Ø could impose significant additional costs on us or our collaboration partners;

Ø could diminish competitive advantages that we may attain; and

Ø would adversely affect the marketing of our products.

Even if we do receive regulatory approval for our drug candidates, the FDA or international regulatory authorities may impose limitations on the indicated uses for which our products may be marketed, subsequently withdraw approval or take other actions against us or our products adverse to our business. The FDA and international regulatory authorities generally approve products for particular indications. If an approval is for a limited indication, this limitation reduces the size of the potential market for the product. Product approvals, once granted, may be withdrawn if

problems occur after initial marketing.

We also are subject to numerous federal, state and local laws, regulations and recommendations relating to safe working conditions, laboratory and manufacturing practices, the experimental use of animals, the environment and the use and disposal of hazardous substances used in connection with our discovery, research and development work, including radioactive compounds and infectious disease agents. In addition, we cannot predict the extent of government regulations or the impact of new governmental regulations that might significantly harm the discovery, development, production and marketing of our products. We may be required to incur significant costs to comply with current or future laws or regulations, and we may be adversely affected by the cost of such compliance.

**Our clinical trials may not yield results that will enable us to obtain regulatory approval for our products.**

We will only receive regulatory approval for a drug candidate if we can demonstrate in carefully designed and conducted clinical trials that the drug candidate is safe and effective. We do not know whether our pending or any future clinical trials will demonstrate sufficient safety and efficacy to obtain the requisite regulatory approvals or will result in marketable products. Clinical trials are lengthy, complex, expensive and uncertain processes. It will take us several years to complete our testing, and failure can occur at any stage of testing. Results attained in preclinical testing and early clinical studies, or trials, may not be predictive of results that are obtained in later studies. We may suffer significant setbacks in advanced clinical trials, even after promising results in earlier studies.

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**Table of Contents**

**Risk factors**

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Based on results at any stage of clinical trials, we may decide to repeat or redesign a trial or discontinue development of one or more of our drug candidates. If we fail to adequately demonstrate the safety and efficacy of our products under development, we will not be able to obtain the required regulatory approvals to commercialize our drug candidates.

Clinical trials are subject to continuing oversight by governmental regulatory authorities and institutional review boards, or IRBs, and must meet the requirements of these authorities in the United States, including those for informed consent and good clinical practices. We may not be able to comply with these requirements and the FDA, an IRB or we may suspend or terminate clinical trials at any time.

Administering any drug candidates we develop to humans may produce undesirable side effects. These side effects could interrupt, delay or halt clinical trials of our drug candidates and could result in the FDA or other regulatory authorities denying approval of our drug candidates for any or all targeted indications.

We rely on third parties, including contract research organizations and outside consultants, to assist us in managing and monitoring clinical trials. Our reliance on these third parties may result in delays in completing, or in failing to complete, these trials if they fail to perform with the speed and competency we expect.

If clinical trials for a drug candidate are unsuccessful, we will be unable to commercialize the drug candidate. If one or more of our clinical trials are delayed, we will be unable to meet our anticipated development or commercialization timelines. Either circumstance could cause the price of our shares to decline.

**If we encounter difficulties enrolling patients in our clinical trials, our trials could be delayed or otherwise adversely affected.**

Clinical trials for our drug candidates require that we identify and enroll a large number of patients with the disorder under investigation. We may not be able to enroll a sufficient number of patients to complete our clinical trials in a timely manner. Patient enrollment is affected by factors including:

- Ø design of the protocol;
- Ø the size of the patient population;
- Ø eligibility criteria for the study in question;
- Ø perceived risks and benefits of the drug under study;

- ∅ availability of competing therapies;
- ∅ efforts to facilitate timely enrollment in clinical trials;
- ∅ patient referral practices of physicians; and
- ∅ availability of clinical trial sites.

If we have difficulty enrolling a sufficient number of patients to conduct our clinical trials as planned, we may need to delay or terminate ongoing clinical trials.

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**S-14**

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**Table of Contents**

**Risk factors**

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**If we fail to maintain existing third-party arrangements and collaborative agreements or fail to develop new collaborative arrangements, our business will be harmed.**

The success of our business is dependent, in significant part, upon our ability to enter into multiple collaboration agreements and to manage effectively the numerous issues that arise from such arrangements. Management of our relationships with these third parties have required and will require:

- ∅ our management team to devote a significant amount of time and effort to the management of these relationships;
- ∅ effective allocation of our and third-party resources to multiple projects;
- ∅ agreement with third parties as to ownership of proprietary rights and development plans, including clinical trials or regulatory approval strategy; and
- ∅ an ability to obtain and retain management, scientific and other personnel.

Our collaboration with Amgen is a 50/50 cost/profit sharing arrangement with certain additional payment obligations by us prior to commercialization and upon regulatory approval. Both parties share worldwide rights to alfimeprase, and Amgen has the option to lead the commercialization in which both parties may participate. If Amgen decides not to pursue this option, we would be responsible for the commercialization and manufacturing activities in addition to clinical development activities, which may cause us to reduce or delay further development of some of our drug candidates and/or increase our capital expenditures.

In our collaboration with Archemix, we share equally all research and developments costs and revenues after we fund the first \$4.0 million in research and development costs and make a milestone payment of \$10.0 million upon commencement of Phase 2 trials and a reimbursement of \$1.0 million upon the designation of any backup compound. We are obligated to make this Phase 2 milestone payment to Archemix even if the collaboration is terminated by Archemix or Archemix does not meet its obligations under the agreement and we terminate the collaboration for its default. We have the option to lead commercialization in which both parties may participate if we establish commercialization capabilities, however, if we do not establish such commercialization capabilities, Archemix or a third party selected by the parties' joint steering committee will have the option to lead commercialization. We do not currently have established commercialization experience or an internal trained sales force and we may not successfully develop such capabilities without incurring additional expenses while competing with other companies who have such operations. If we do not lead the commercialization efforts, we are dependent on Archemix or a third party's experience in commercialization and ability to perform and we may also incur additional expenses for a third party to undertake commercialization efforts.

We are subject to a number of additional risks associated with our collaboration with Archemix for ARC183, including the following: the right of Archemix to terminate its collaboration with us on limited notice and for reasons outside our control and loss of significant rights if the collaboration is terminated because we fail to meet our obligations under it or we elect to terminate for our convenience. In particular, if we terminate the collaboration or if Archemix terminates for our breach, all of our rights to ARC183 and other collaboration products will become the property of Archemix, and we may not practice certain activities related to anti-thrombin compounds in the field of modifying blood-clotting times in therapeutic applications through the use of aptamers such as ARC183, including research and development, manufacture and commercialization activities.

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In our licensing arrangement with Dendreon, we are obligated to make milestone payments prior to and upon commercialization, including \$2.0 million upon the first dosing of the first patient in a Phase 3 clinical trial for the first indication, although there is no guarantee that we will reach commercialization

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S-15



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**Table of Contents**

**Risk factors**

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or that our product will be accepted by the market. We may not generate any revenue from this licensing arrangement.

Our efforts, including the efforts of our direct and indirect subsidiaries, to manage simultaneously a number of collaboration arrangements may not be successful, and the failure to manage effectively such collaborations would significantly harm our business, financial condition and results of operations.

Due to these factors and other possible disagreements with Amgen, Archemix and Dendreon, we may be delayed or prevented from developing or commercializing alimeprase, ARC183 and rNAPc2 or we may become involved in litigation or arbitration, which would be time-consuming or expensive and could have a material adverse effect on our stock price.

In addition to our existing collaborations, we will focus on effecting new collaborative arrangements where we would share costs of identifying, developing and marketing drug candidates. We cannot assure you that we will be able to negotiate new collaboration arrangements of this type on acceptable terms, or at all.

**We are currently dependent on third parties for a variety of functions and may enter into future collaborations for the manufacture of our products. Our arrangements with these third parties may not provide us with the benefits we expect.**

We currently rely upon third parties to perform functions related to the research, development, preclinical testing and clinical trials of our drug candidates. In addition, because we do not have the resources, facilities or experience to manufacture our drug candidates on our own, we currently rely, and will continue to rely, on third parties to manufacture our drug candidates for clinical trials, and, if our products are approved, in quantities for commercial sales. We currently rely on a number of sole-source suppliers and do not have long-term supply agreements with our third-party manufacturers. Our reliance on these relationships poses a number of risks, including:

- ∅ disagreements with third parties could delay or terminate the research, development or manufacturing of drug candidates, or result in litigation or arbitration;
- ∅ our inability to effectively control the resources devoted by our partners to our programs or products;
- ∅ inadequate contractual protection or difficulty in enforcing the contracts if one of our partners fails to perform;
- ∅ failure of these third parties to comply with regulatory requirements;
- ∅ conflicts of interest between their work for us and their work for another entity, and the loss of their services;
- ∅ failure to locate acceptable manufacturers or other suppliers or enter into favorable long-term agreements with them;

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- Ø inability of third parties to manufacture our drug candidates in a cost-effective or timely manner or in quantities needed for clinical trials or commercial sales;
  
- Ø delays in, or failures to achieve, scale-up to commercial quantities, or changes to current raw material suppliers or product manufacturers (whether the change is attributable to us or the supplier or manufacturer), resulting in delayed clinical studies, regulatory submissions and commercialization of our drug candidates; and
  
- Ø lack of all necessary intellectual property rights to manufacture our drug candidates.

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S-16

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**Table of Contents**

**Risk factors**

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Given these risks, our current and future collaborative efforts with third parties may not be successful. If these efforts fail, we would be required to devote additional internal resources to the activities currently performed, or to be performed, by third parties, to seek alternative third-party collaborators, or to delay our product development or commercialization.

**We lack manufacturing experience and intend to rely initially on contract manufacturers.**

We do not currently have significant manufacturing facilities for clinical or commercial production of our drug candidates and depend on contract research and manufacturing organizations. We may not be able to finalize contractual arrangements, transfer technology or maintain relationships with such organizations in order to file an Investigational New Drug application, or IND, with the Food and Drug Administration, or FDA, and proceed with clinical trials for any of our drug candidates. We currently rely on Amgen to manufacture our clinical drug product, alfimeprase. We also rely on other third parties to manufacture rNAPc2 and ARC183. The cost of manufacturing our drug product by Amgen is based upon a standard cost which has not been determined. This cost may be more than we are anticipating and may make it difficult or impossible to profitably market alfimeprase.

We are dependent on third-party contract research organizations to conduct certain research, including good laboratory practices toxicology studies, in order to gather the data necessary to file INDs with the FDA for ARC183 or any of our drug candidates. ARC183 and our other drug candidates have never been manufactured on a commercial scale. Third-party manufacturers may not be able to manufacture these drug candidates at a cost or in quantities necessary to make them commercially viable. In addition, if ARC183 or any of our other drug protein candidates enter the clinical trial phase, we will initially depend on third-party contract manufacturers to produce the volume of current good manufacturing practices materials needed to complete such trials. We will need to enter into contractual relationships with these or other organizations in order to (1) complete the Good Laboratory Practices, or GLP, toxicology and other studies necessary to file an IND with the FDA, and (2) produce a sufficient volume of current Good Manufacturing Practices (cGMP) grade material in order to conduct clinical trials of ARC183 and our other drug candidates. We cannot be certain that we will be able to do so on a timely basis or that we will be able to obtain sufficient quantities of material on commercially reasonable terms. In addition, the failure of any of these relationships with third-party contract organizations may delay our filing for an IND or impede our progress through the clinical trial phase. Any significant delay or interruption would have a material adverse effect on our ability to file an IND with the FDA and/or proceed with the clinical trial phase for ARC183 or any of our drug candidates.

Moreover, contract manufacturers that we may use must continually adhere to current cGMP regulations enforced by the FDA through a facilities inspection program. If one of our contract manufacturers fails to maintain compliance, the production of our product candidates could be interrupted, resulting in delays, additional costs and potentially lost revenues. In addition, if the facilities of such manufacturers do not pass a pre-approval plant inspection, the FDA will not grant premarket approval of our products.

**The commercial success of our products will be dependent upon our ability to protect the intellectual property rights associated with our products and drug candidates.**

Our competitive success will depend in part on our ability to obtain and maintain patent protection for our inventions, technologies and discoveries, including intellectual property that we license. The patent positions of biotechnology companies involve complex legal and factual questions, and we cannot assure you that our patents and licenses will successfully preclude others from using our technology. We could incur substantial costs in seeking enforcement of our proprietary rights against infringement. In addition, to obtain a patent on a novel gene, we need to identify a utility for the novel gene or the encoded protein we



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## Table of Contents

### **Risk factors**

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seek to protect under patent law. Identifying a utility may require significant research and development with respect to which we may incur a substantial expense and invest a significant amount of time.

We currently have, or have in-licensed, patents and patent applications that cover portions of our in-licensed clinical products. ARC183 is covered both by a US patent specifically claiming ARC183 and by US patents covering aptamers generically. However, there are no equivalent international applications pending specifically claiming ARC183. International patent applications generically covering aptamers are pending but we cannot assure you that such patents will issue. We also currently have patents that cover some of our technological discoveries and patent applications that we expect to protect some of our gene, protein and technological discoveries. We have approximately 25 issued patents relating to our gene and protein discoveries. We cannot assure you that any of our applications will issue as patents, or that any patent issued to us will not be challenged, invalidated, circumvented or held unenforceable by way of an interference proceeding or litigation.

The timing of the grant of a patent cannot be predicted. Patent applications describing and seeking patent protection of methods, compositions, or processes relating to proprietary inventions involving human therapeutics could require us to generate data, which may involve substantial costs. Our pending patent applications may lack priority over others' applications or may not result in the issuance of patents. Even if issued, our patents may not be sufficiently broad to provide protection against competitors with similar technologies and may be challenged, invalidated or circumvented.

In addition to patents, we rely on a combination of trade secrets, copyright and trademark laws, nondisclosure agreements, licenses and other contractual provisions and technical measures to maintain and develop our competitive position with respect to intellectual property. Nevertheless, these measures may not be adequate to safeguard the technology underlying our products. For example, employees, consultants and others who participate in the development of our products may breach their agreements with us regarding our intellectual property and we may not have adequate remedies for the breach. Our trade secrets could become known through other unforeseen means.

We also may not be able to effectively protect our intellectual property rights in some foreign countries, as many countries do not offer the same level of legal protection for intellectual property as the United States. Furthermore, certain of the patent applications describing our proprietary methods are filed only in the United States. Even where we have filed our patent applications internationally, for some cases and in certain countries, we have chosen not to maintain foreign patent protection by opting not to enter national phase or opting not to pay maintenance annuities.

Notwithstanding our efforts to protect our intellectual property, our competitors may independently develop similar or alternative technologies or products that are equal or superior to our technology. Our competitors may also develop similar products without infringing on any of our intellectual property rights or design around our proprietary technologies.

**If our products infringe on the intellectual property rights of others, we could face costly litigation, which could cause us to pay substantial damages and limit our ability to sell some or all of our products.**

Our market success depends in part on us neither infringing valid, enforceable patents or proprietary rights of third parties, nor breaching any licenses that may relate to our technologies and products. We are aware of third-party patents that may relate to our technology. We may be required to obtain licenses to patents or other proprietary rights of others in order to conduct research, development, or commercialization of some or all our programs. We plan to seek licenses, as we deem appropriate, but it



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**Table of Contents**

**Risk factors**

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is possible that we may unintentionally infringe upon these patents or proprietary rights of third parties. If we do not obtain these licenses, we may encounter delays in product market introductions, incur substantial costs while we attempt to design around existing patents or not be able to develop, manufacture or sell products. In response, third parties may assert infringement or other intellectual property claims against us. We may consequently be subjected to substantial damages for past infringement or be required to modify our products if it is ultimately determined that our products infringe a third party's proprietary rights. Further, we may be prohibited from selling our products before we obtain a license, which, if available at all, may require us to pay substantial royalties, which could adversely impact our product costs and have an impact on our business. Further, if we do obtain these licenses, the agreed terms may necessitate reevaluation of the potential commercialization of any one of our programs. Failing to obtain a license could result in litigation. Even if these claims are without merit, defending a lawsuit takes significant time, may be expensive and may divert management attention from other business concerns. Any public announcements related to litigation or interference proceedings initiated or threatened against us could cause our stock price to decline.

**We may be subject to litigation and infringement claims that may be costly, divert management's attention, and materially harm our business.**

Extensive litigation regarding patents and other intellectual property rights has been common in the genomics and biopharmaceutical industries. Litigation may be necessary to assert infringement claims, enforce patent rights, protect trade secrets or know-how and determine the enforceability, scope and validity of certain proprietary rights. The defense and prosecution of intellectual property lawsuits, United States Patent and Trademark Office interference proceedings, and related legal and administrative proceedings in the United States and internationally involve complex legal and factual questions. As a result, such proceedings are costly and time-consuming to pursue and their outcome is uncertain.

Regardless of merit or outcome, our involvement in any litigation, interference or other administrative proceedings could cause us to incur substantial expense and could significantly divert the efforts of our technical and management personnel. An adverse determination may subject us to the loss of our proprietary position or to significant liabilities, or require us to seek licenses that may include substantial cost and ongoing royalties. Licenses may not be available from third parties, or may not be obtainable on satisfactory terms. An adverse determination or a failure to obtain necessary licenses may restrict or prevent us from manufacturing and selling our products, if any. These outcomes could materially harm our business, financial condition and results of operations.

**We face intense competition.**

The biopharmaceutical industry is intensely competitive and is accentuated by the rapid pace of technological development. We expect to face increased competition in the future as new companies enter our markets. Research and discoveries by others may result in breakthroughs that render our potential products obsolete even before they begin to generate any revenue. Our competitors include major pharmaceutical, biotechnology and diagnostic firms, not-for-profit entities and US and foreign government-financed programs, many of which have substantially greater research and product development capabilities and financial, scientific, marketing and human resources than we have. They may succeed in developing products or identifying genes and determining their functions earlier than we or our collaboration partners. They also may obtain patents and regulatory approvals for such products more rapidly than we or our collaboration partners, or develop products that are more effective than those developed by us or our collaboration partners. Any potential products based on genes we identify ultimately will face competition from other companies developing gene-based products as well as from companies developing other forms of treatment for diseases which may be caused by, or related to, the

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**Table of Contents**

**Risk factors**

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genes we identify. Similarly, our products will face competition from other companies developing similar products as well as from companies developing other forms of treatment for the same conditions.

In addition, our technologies have undergone and are expected to continue to undergo rapid and significant change. Our competitors may make rapid technological developments which may result in products or technologies becoming obsolete, before we can recover the expenses incurred. The introduction of less expensive or more effective drug discovery and development technologies may also make our products and services obsolete. We may not be able to make the necessary enhancements to our technology to compete successfully with newly emerging technologies.

Many of the companies developing competing products have significantly greater financial resources than we have. Many such companies also have greater expertise than we or our collaboration partners have in discovery, research and development, manufacturing, preclinical and clinical testing, obtaining regulatory approvals and marketing. Other smaller companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. Academic institutions, government agencies and other public and private research organizations may also conduct research, seek patent protection and establish collaborative arrangements for discovery, research, clinical development and marketing of products similar to our products. These companies and institutions compete with us in recruiting and retaining qualified scientific and management personnel as well as in acquiring technologies complementary to our programs. We will face competition with respect to:

- ∅ product efficacy and safety;
- ∅ the timing and scope of regulatory approvals;
- ∅ availability of resources;
- ∅ reimbursement coverage; and
- ∅ price and patent position, including potentially dominant patent positions of others.

There can be no assurance that research and development by others will not render the products that we may develop obsolete or uneconomical, or result in treatments or cures superior to any therapy or diagnostic developed by us or that any therapy we develop will be preferred to any existing or newly developed technologies.

**We lack marketing experience for biopharmaceutical products.**

We have no sales, marketing or distribution capability. For the foreseeable future, we intend to rely primarily on collaboration partners or licensees, if any, to market our products. These collaboration partners or other third parties may not have effective sales forces and distribution systems. If we are unable to maintain or establish such relationships, we will be required to market our products directly and we will have to develop our own marketing and sales force with the appropriate technical expertise and with supporting distribution capabilities. We may not be



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able to maintain or establish such relationships with third parties or develop in-house sales and distribution capabilities. To the extent that we may depend on our collaboration partners or other third parties for marketing and distribution, any revenues we receive will depend upon the efforts of our collaboration partners or other third parties. Such efforts may not be successful, and we will not be able to control the amount and timing of resources that our collaboration partners or other third parties devote to our products.

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S-20

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**Table of Contents**

**Risk factors**

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**The success of our potential products in preclinical studies does not guarantee that these results will be replicated in humans.**

Although ARC183 and some of our other drug candidates have shown results in preclinical studies, these results may not be replicated in our clinical trials with humans. Human clinical results could be different from our expectations following our preclinical studies. Consequently, there is no assurance that the results in our preclinical studies are predictive of the results that we will see in our clinical trials with humans or that they are predictive of whether the resulting products will be safe and effective in humans. ARC183 and our other drug candidates may have undesirable and unintended side effects or other characteristics that may prevent or limit their use.

**Our products may not be accepted in the marketplace, and we may not be able to generate significant revenue, if any.**

Even if they are approved for marketing, our products may never achieve market acceptance among physicians, patients and the medical community. Our products, if successfully developed, will compete with a number of traditional drugs and therapies manufactured and marketed by major pharmaceutical and other biotechnology companies. Our products will also compete with new products currently under development by such companies and others. The degree of market acceptance of any products developed by us, alone, or in conjunction with our collaboration partners, will depend on a number of factors, including:

- ∅ the establishment and demonstration of the clinical efficacy and safety of the products;
- ∅ convenience and ease of administration;
- ∅ cost-effectiveness;
- ∅ our products' potential advantage over alternative treatment methods;
- ∅ marketing and distribution support of our products; and
- ∅ reimbursement policies of government and third-party payors.

Physicians, patients or the medical community in general may not accept and utilize any of the products that we alone, or in conjunction with our collaboration partners, develop. In practice, competitors may be more effective in marketing their drugs. The lack of such market acceptance would significantly harm our business, financial condition and results of operations.

**We face uncertainty with respect to coverage, pricing, third-party reimbursements and health care reform.**

Our ability to collect significant royalties from our products may depend on our ability, and the ability of our collaboration partners or customers, to obtain adequate levels of coverage for our products and reimbursement from third-party payors such as:

Ø government health administration authorities;

Ø private health insurers;

Ø health maintenance organizations;

Ø pharmacy benefit management companies; and

Ø other health care related organizations.

Third-party payors may deny coverage or offer inadequate levels of reimbursement if they determine that a prescribed product or device has not received appropriate clearances from the FDA or other

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**Table of Contents**

**Risk factors**

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government regulators, is not used in accordance with cost-effective treatment methods as determined by the third-party payor, or is experimental, unnecessary or inappropriate. If third-party payors deny coverage or offer inadequate levels of reimbursement, we may not be able to market our products effectively. We also face the risk that we will have to offer our products at prices lower than anticipated as a result of the current trend in the United States towards managed health care through health maintenance organizations. Currently, third-party payors are increasingly challenging the prices charged for medical products and services. Prices could be driven down by health maintenance organizations that control or significantly influence purchases of health care services and products. Legislative proposals to reform health care or reduce government insurance programs could also adversely affect prices of our products. The cost containment measures that health care providers are instituting and the results of potential health care reforms may prevent us from maintaining prices for our products that are sufficient for us to realize profits and may otherwise significantly harm our business, financial condition and operating results.

**Because we have not yet commercialized any of our drug candidates, our ability to commercialize products is unproven.**

We have not yet commercialized any of our in-licensed therapeutic products. We have not developed any therapeutic products using proteins produced by the genes we have discovered in our internal research programs. Before we make any products available to the public, we or our collaboration partners will need to conduct further research and development and complete laboratory testing and animal and human studies. Moreover, with respect to biopharmaceutical products, we or our collaboration partners will need to obtain regulatory approval before releasing any such products. We have spent, and expect to continue to spend, significant amounts of time and money in determining the function of genes and the proteins they produce, using our own capabilities and those of our collaboration partners. Such determination process constitutes the first step in developing commercial products. We also have spent and will continue to spend significant amounts of time and money in developing processes for manufacturing of our recombinant proteins under preclinical development, yet we may not be able to produce sufficient proteins for preclinical studies. A commercially viable product may never be developed from our gene discoveries.

Our development of products is subject to several risks, including but not limited to:

- Ø the possibility that a product is toxic, ineffective or unreliable;
  
- Ø failure to obtain regulatory approval for the product;
  
- Ø the product may be difficult to manufacture on a large scale, or may not be economically feasible to market;
  
- Ø competitors may have or develop a superior product; or
  
- Ø third-party patents may preclude us from marketing a product.

Our internally developed biopharmaceutical development programs are currently in the research stage or in preclinical development. None of our potential therapeutic protein candidates from our own portfolio have advanced to Phase 1 clinical trials. Our programs may not move beyond their current stages of development. Even if our research does advance, we will need to engage in certain additional preclinical development efforts to determine whether a product is sufficiently safe and effective to enter clinical trials. We have little experience with these activities and may not be successful in developing or commercializing products.

Under our Kirin collaboration arrangement, Kirin has primary responsibility for clinical development in its territory and we have primary responsibility in our territory. Under our collaboration arrangement

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S-22

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## **Table of Contents**

### **Risk factors**

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with Deltagen, we share responsibility for development of a product. Under our collaboration with Archemix, Archemix leads development until Phase 2 clinical trials are reached, and thereafter, a joint steering committee will designate one party to lead development until commercialization. Deltagen has filed a petition for Chapter 11 bankruptcy protection and we will not be continuing our collaboration arrangement. With respect to these arrangements, we run the risk that Kirin or Archemix may not pursue clinical development in a timely or effective manner.

If a product receives approval from the FDA to enter clinical trials, Phases 1, 2 and 3 of those trials typically include multi-phase, multi-center clinical studies to determine the product's safety and efficacy prior to marketing. We cannot predict the number or extent of clinical trials that will be required to obtain regulatory approval or the length of the period of mandatory patient follow-up that will be imposed. Assuming clinical trials of any product are successful and other data appear satisfactory to us, we or our applicable collaboration partner will submit an application to the FDA and appropriate regulatory bodies in other countries to seek permission to market the product. Typically, the review process at the FDA is not predictable and can take up to several years. Any regulatory approvals that we or our collaboration partners receive for our product candidates may also be subject to limitations on the intended uses for which the product candidates may be marketed or contain requirements for potentially costly post-marketing follow-up studies. In addition, if the FDA approved of our or our collaboration partners' product candidates, the labeling, packaging, adverse event reporting, storage, advertising, promotion and record-keeping for the products will be subject to extensive regulatory requirements.

In addition, we may not be able to produce any products in commercial quantities at a reasonable cost or may not be able to market successfully such products. If we do not develop a commercially viable product, then we would suffer significant harm to our business, financial condition and operating results.

#### **Our subsidiary Callida may not be able to raise third-party financing.**

In October 2001, we formed Callida to develop and commercialize our sequencing-by-hybridization, or SBH, technology. We recognized 90% of Callida's operating losses in our consolidated results of operations up to the point where Affymetrix's initial minority interest investment was depleted in the first quarter of 2002. Beyond that point, we absorb 100% of the net losses until Callida generates net income. There is no guarantee, however, that Callida will meet its technical milestone and other requirements to obtain additional funding through Affymetrix and us. There is also no assurance that Callida will be able to obtain any third-party financing or that any such financing that Callida obtains will be on favorable terms or that the funding from outside sources will be sufficient to fund Callida's operations. We cannot assure the success of Callida, and if Callida is unable to obtain sufficient funding from outside sources, we may reduce projects and/or bear the costs of financing Callida ourselves, which will divert our resources from biopharmaceutical projects. In March 2003, Callida reduced its number of employees from 25 to 7 in order to preserve cash. As of December 31, 2003, Callida and its subsidiary, N-Mer, Inc., had approximately \$135,000 in cash and investments balances available for future operations.

#### **Our officers and directors will control many corporate actions, regardless of the opposition of other stockholders or the desire of other stockholders to pursue an alternative course of action.**

Our executive officers and directors beneficially own, in the aggregate, approximately 18.80% of our common stock outstanding as of December 31, 2003. For purposes of this paragraph, beneficial ownership is determined in accordance with Rule 13d-3 under the Securities Exchange Act of 1934, as amended. If they act together, our directors and officers will be able to exercise substantial influence and control over all matters requiring approval by our stockholders, including the election of directors and



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**Table of Contents**

**Risk factors**

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approval of significant corporate transactions. This concentration of ownership may also have the effect of delaying or preventing a change in our control.

**We face product liability exposure and potential unavailability of insurance.**

We risk financial exposure to product liability claims in the event that the use of products developed by us or our collaboration partners, if any, result in personal injury. We may experience losses due to product liability claims in the future. We have obtained limited product liability insurance coverage. Such coverage, however, may not be adequate or may not continue to be available to us in sufficient amounts or at an acceptable cost, or at all. We may not be able to obtain commercially reasonable product liability insurance for any product approved for marketing. A product liability claim or other claim, product recalls, as well as any claims for uninsured liabilities or in excess of insured liabilities, may significantly harm our business, financial condition and results of operations.

**We use hazardous materials, chemicals and patient samples in our business and any disputes relating to improper handling, storage or disposal of these materials could be time consuming and costly.**

Our research and development, production and service activities involve the controlled use of hazardous or radioactive materials, chemicals, including oxidizing and reducing reagents, patient tissue and blood samples. We, our collaborators and service providers are subject to federal, state and local laws and regulations governing the use, storage, handling and disposal of these materials and certain waste products. We could be liable for accidental contamination or discharge or any resultant injury from hazardous materials, and conveyance, processing, and storage of and data on patient samples. If we, our collaborators or service providers fail to comply with applicable laws or regulations, we could be required to pay penalties or be held liable for any damages that result and this liability could exceed our financial resources. Further, future changes to environmental health and safety laws could cause us to incur additional expense or restrict our operations.

In addition, our collaborators and service providers may be working with these types of hazardous materials, including viruses and hazardous chemicals, in connection with our collaborations. In the event of a lawsuit or investigation, we could be held responsible for any injury caused to persons or property by exposure to, or release of, these patient samples that may contain viruses and hazardous materials. The cost of this liability could exceed our resources.

**We are dependent on key personnel and we must attract and retain qualified employees and collaborators.**

The success of our business is highly dependent on the principal members of our scientific and management staff, including our chairman and senior management team. The loss of the services of any such individual might seriously harm our product development and commercialization efforts. In addition, we will require additional skilled personnel in areas such as business development and clinical development. Retaining and training personnel with the requisite skills is challenging, and, if general economic conditions improve, is likely to become extremely competitive, particularly in the Silicon Valley area of California where our main office is located.

Our success will depend on our ability to attract and retain qualified employees to help develop our potential products and execute our research and development strategy. We have programs in place to retain personnel, including programs to create a positive work environment and competitive compensation packages. Because competition for employees in our field is intense, however, we may be unable to retain our existing personnel or attract additional qualified employees.





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**Table of Contents**

**Risk factors**

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Our success also depends on the continued availability of outside scientific collaborators to perform research and develop processes to advance and augment our internal research efforts. Competition for collaborators is intense. If we do not attract and retain qualified personnel and scientific collaborators, or if we experience turnover or difficulties recruiting new employees, our research and development programs could be delayed and we could experience difficulties in generating sufficient revenue to maintain our business.

**We are subject to the risk of natural disasters and power blackouts.**

Our facilities are located in Sunnyvale, California. In the event that a fire or other natural disaster (such as an earthquake) disrupts our research or development efforts, our business, financial condition and operating results could be materially, adversely affected. Some of our landlords maintain earthquake coverage for our facilities. Although we maintain personal property and business interruption coverage, we do not maintain earthquake coverage for personal property or resulting business interruption.

**We may merge with or acquire other companies and our failure to receive the anticipated benefits in these transactions could harm our business.**

In January 2003, we merged with Variagenics, and may merge with or acquire other companies in the future. The success of any merger or acquisition depends, in part, on our ability to realize the anticipated synergies, cost savings and growth opportunities from integrating the business of the merged or acquired company with our business. The integration of two independent companies is a complex, costly and time-consuming process. The difficulties of combining the operations of the companies include, among others:

- ∅ consolidating research and development operations;
- ∅ retaining key employees;
- ∅ consolidating corporate and administrative infrastructures;
- ∅ preserving the research and development and other important relationships of the companies;
- ∅ integrating and managing the technology of two companies;
- ∅ using the merged or acquired company's liquid capital assets efficiently to develop the business of the combined company;
- ∅ minimizing the diversion of management's attention from ongoing business concerns; and
- ∅ coordinating geographically separate organizations.

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Moreover, we have assumed the costs of defending against litigation claims asserted against Variagenics, and anytime we merge with or acquire another company, we will be exposed to similar costs. In addition, we may be exposed to a number of other risks in connection with future transactions, including:

- ∅ we may experience unbudgeted expenses in attempting to complete the transaction and integration process and exposure to unknown liabilities of the merged or acquired business; and
- ∅ our stock price may suffer if the former stockholders of the merged or acquired entity dispose of significant numbers of shares of our common stock that they receive in the transaction within a short period of time.

We cannot assure you that we will receive all of the anticipated benefits of any mergers or acquisitions, or that any of the risks described above will not occur. Our failure to receive anticipated benefits of, and our exposure to inherent risks in, any such merger or acquisition transaction could significantly harm our business, financial condition and operating results.

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S-25

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**Table of Contents**

**Risk factors**

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**Variagenics has been named as a defendant in a class action suit and defending this litigation could hurt our business.**

Variagenics has been named as a defendant in a securities class action lawsuit alleging the failure to disclose additional and excessive commissions purportedly solicited by and paid to underwriters also named in the lawsuit in exchange for allocating shares of Variagenics stock to preferred customers and alleged agreements among the underwriters named in the lawsuit and preferred customers tying the allocation of initial public offering shares to agreements to make additional aftermarket purchases at pre-determined prices. As a result of our merger with Variagenics, we are obligated to continue to defend against this litigation. Currently we are in the process of approving a settlement by and between the issuers that are defendants in the lawsuit, the insurers of those issuers, and the plaintiffs. We believe that any loss or settlement amount will not be material to our financial position or results of operation, and that any settlement payment and attorneys' fees accrued with respect to the suit will be paid by our insurance provider. However, we cannot assure you that this will be the case until a final settlement is executed and a failure to finalize a settlement could require us to pay substantial damages.

**We may not achieve our projected development goals in the time frames we announce and expect.**

We set goals for and make public statements regarding the timing of certain accomplishments, such as the commencement and completion of clinical trials, anticipated regulatory approval dates and time of product launch, which we sometimes refer to as milestones. The actual timing of these events can vary dramatically due to a number of factors such as delays or failures in our clinical trials, the uncertainties inherent in the regulatory approval process and delays in achieving manufacturing or marketing arrangements sufficient to commercialize our products. There can be no assurance that our clinical trials will be completed, that we will make regulatory submissions or receive regulatory approvals as planned or that we will be able to adhere to our current schedule for the launch of any of our products. If we fail to achieve one or more of these milestones as planned, the price of our shares could decline.

**We have implemented anti-takeover provisions that may reduce the market price of our common stock.**

Our by-laws provide that members of our board of directors serve staggered three-year terms. Our articles of incorporation provide that all stockholder action must be effected at a duly called meeting and not by a consent in writing. The by-laws provide, however, that our stockholders may call a special meeting of stockholders only upon a request of stockholders owning at least 50% of our common stock. These provisions of our articles of incorporation and our by-laws could discourage potential acquisition proposals and could delay or prevent a change in control. These provisions are intended to enhance the likelihood of continuity and stability in the composition of our board of directors and in the policies formulated by our board of directors. These provisions may also discourage certain types of transactions that may involve an actual or threatened change of control. We designed these provisions to reduce our vulnerability to unsolicited acquisition proposals and to discourage certain tactics that may be used in proxy fights. These provisions, however, could also have the effect of discouraging others from making tender offers for our shares. As a consequence, they also may inhibit fluctuations in the market price of our shares that could result from actual or rumored takeover attempts. Such provisions also may have the effect of preventing changes in our management.

We are permitted to issue shares of our preferred stock without stockholder approval upon such terms as our board of directors determines. Therefore, the rights of the holders of our common stock are subject to, and may be adversely affected by, the rights of the holders of our preferred stock that may be issued in the future. In addition, the issuance of preferred stock could have a dilutive effect on the holdings of our current stockholders.

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## Table of Contents

### **Risk factors**

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On June 5, 1998, our board of directors adopted a rights plan and declared a dividend with respect to each share of our common stock then outstanding. This dividend took the form of a right, which entitles the holders to purchase one-one thousandth of a share of our Series B junior participating preferred stock at a purchase price of \$175, subject to adjustment from time to time. These rights have also been issued in connection with each share of our common stock issued after June 15, 1998. The rights are exercisable only if a person or entity or affiliated group of persons or entities acquires, or has announced its intention to acquire, 15% (27.5% in the case of certain approved stockholders) or more of our outstanding common stock. The adoption of the rights plan makes it more difficult for a third party to acquire control of us without the approval of our board of directors.

Nevada Revised Statutes Sections 78.411 through 78.444 prohibit an interested stockholder, under certain circumstances, from entering into specified combination transactions with a Nevada corporation, unless certain conditions are met. Under the statute, an interested stockholder is a person who beneficially owns, directly or indirectly, 10% or more of a corporation's voting stock or an affiliate or associate of a corporation who at any time within the prior three years beneficially owned, directly or indirectly, 10% or more of a corporation's voting stock. According to the statute, we may not engage in a combination within three years after an interested stockholder acquires our shares, unless (1) our board of directors approves the combination prior to the interested stockholder becoming an interested stockholder or (2) holders of a majority of voting power not beneficially owned by the interested stockholder approve the combination at a meeting called no earlier than three years after the date the interested stockholder became an interested stockholder.

Nevada Revised Statutes Sections 78.378 through 78.3793 further prohibit an acquirer, under certain circumstances, from voting shares of a target corporation's stock after crossing certain threshold ownership percentages, unless the acquirer obtains the approval of the target corporation's stockholders. This statute only applies to Nevada corporations that do business directly or indirectly in Nevada. We do not intend to do business in Nevada within the meaning of the statute. Therefore, it is unlikely that the statute will apply to us.

The provisions of our governing documents, our existing agreements and current Nevada law may, collectively:

- Ø lengthen the time required for a person or entity to acquire control of us through a proxy contest for the election of a majority of our board of directors;
- Ø discourage bids for our common stock at a premium over market price; and
- Ø generally deter efforts to obtain control of us.

### **RISKS RELATED TO THIS OFFERING**

**Our stock price has historically been and is likely to remain highly volatile, and an investment in our stock could suffer a decline in value.**

Stock prices and trading volumes for many biopharmaceutical companies fluctuate widely for a number of reasons, including factors which may be unrelated to their businesses or results of operations such as media coverage, legislative and regulatory measures and the activities of various

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interest groups or organizations. This market volatility, as well as general domestic or international economic, market and political conditions, could materially and adversely affect the market price of our common stock and the return on your investment.

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S-27

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**Table of Contents**

**Risk factors**

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Historically, our stock price has been extremely volatile. Between January 1, 2003 and February 17, 2004, the price has ranged between a high of \$16.50 per share and a low of \$1.92 per share. The significant market price fluctuations of our common stock are due to a variety of factors, including:

- ∅ the depth of the market for the common stock;
- ∅ the experimental nature of our potential products;
- ∅ actual or anticipated fluctuations in our operating results;
- ∅ sales of our common stock by existing holders, or sales of shares issuable upon exercise of outstanding options and warrants, upon repayment of our outstanding note to Affymetrix, or upon repayment of our line of credit with Dr. Rathmann;
- ∅ market conditions relating to the biopharmaceutical and pharmaceutical industries;
- ∅ any announcements of technological innovations, new commercial products, or clinical progress or lack thereof by us, our collaborative partners or our competitors;
- ∅ announcements concerning regulatory developments, developments with respect to proprietary rights and our collaborations;
- ∅ changes in or our failure to meet market or, to the extent securities analysts follow our common stock, securities analysts' expectations;
- ∅ loss of key personnel;
- ∅ changes in accounting principles;
- ∅ general market conditions; or
- ∅ public concern with respect to our products.

In addition, the stock market in general, and the market for biotechnology and other life science stocks in particular, has historically been subject to extreme price and volume fluctuations. This volatility has had a significant effect on the market prices of securities issued by many companies for reasons unrelated to the operating performance of these companies. In the past, following periods of volatility in the market price of a company's securities, class action securities litigation has often been instituted against such a company. Any such litigation instigated against us could result in substantial costs and a diversion of management's attention and resources, which could significantly harm our business, financial condition and operating results.

**Future sales of our common stock may depress the market price of our common stock.**

Sales in the public market of substantial amounts of our common stock could depress prevailing market prices of our common stock. As of December 31, 2003, we had 25,621,235 shares of our common stock outstanding. All of these shares are freely transferable without restriction or further registration under the Securities Act of 1933, as amended, or the Securities Act, except for shares held by our affiliates and unregistered shares held by non-affiliates. As of December 31, 2003, our affiliates held 3,802,296 shares of our common stock, which are transferable pursuant to Rule 144 or in some cases Rule 145, each as promulgated under the Securities Act, or pursuant to effective registration statements. Although we do not believe that our affiliates have any present intentions to dispose of any shares of common stock owned by them, there can be no assurance that such intentions will not change in the future.

As of December 31, 2003, warrants to purchase approximately 1,887,325 shares of our common stock were outstanding. In addition, under registration statements on Form S-8 under the Securities Act, we



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**Table of Contents**

**Risk factors**

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have registered approximately 4,248,229 shares of our common stock for sale upon the exercise of outstanding options under our 2002 Equity Incentive Plan, 1995 Stock Option Plan, Non-Employee Director Stock Option Plan, Scientific Advisory Board/Consultants Stock Option Plan, and stock option agreements entered into outside of any of our stock option plans and under our Employee Stock Purchase Plan and the Variagenics, Inc. Amended 1997 Employee Director and Consultant Stock Option Plan. Shares of our common stock acquired pursuant to these plans and agreements are available for sale in the open market. Included in this 4,248,229 shares, we have reserved approximately 1,085,852 shares of our common stock for issuance upon the exercise of outstanding options under stock option agreements entered into outside of any of our stock option plans. As of December 31, 2003, 799,145 of the 1,085,852 shares of these options were exercisable. The exercise of those options or warrants, and the prompt resale of shares of our common stock received, may result in downward pressure on the price of our common stock. The existence of the currently outstanding warrants and options to purchase our common stock may negatively affect our ability to complete future equity financings at acceptable prices and on acceptable terms.

As of December 31, 2003, 519,181 shares of our common stock were issuable upon repayment of a note held by Affymetrix. Affymetrix has the ability to declare all outstanding principal and interest under the note immediately due and payable in the event that our market capitalization is under \$50 million and Affymetrix reasonably determines that the loan evidenced by the note is impaired, and we have an obligation to prepay amounts owing under the note to the extent that the amounts outstanding exceed 10% of our market capitalization. Moreover, we have registered for resale a portion of these shares on a registration statement that has been declared effective by the Securities and Exchange Commission. If we decide to repay this note with our common stock, whether pursuant to acceleration of the note or otherwise, the prompt resale of shares of our common stock received by Affymetrix may also result in significant downward pressure on the price of our common.

Upon completion of this offering, based on information as of December 31, 2003 we will have outstanding an aggregate of 29,621,235 shares of common stock, assuming no issuance of shares under our Employee Stock Purchase Plan, no exercise of outstanding options or warrants and excluding 519,181 shares of common stock issuable upon repayment of our note held by Affymetrix, 1,098,286 shares of common stock issuable upon mutual agreement to convert the promissory note under the Rathmann line of credit and 263,296 shares issued to Dendreon on February 4, 2004. All of the shares sold in this offering will be freely tradable without restriction or further registration under the Securities Act unless these shares are purchased by affiliates.

**Our management will have broad discretion with respect to the use of proceeds of this offering, and may not apply the proceeds to uses that will benefit stockholders.**

Our management will have broad discretion as to how to use the proceeds of this offering. You will be relying on the judgment of our management regarding the application of the proceeds of this offering. The results and effectiveness of the use of proceeds are uncertain.

**If registration rights that we have previously granted are exercised, then our stock price may be negatively affected.**

We have granted registration rights in connection with the issuance of our securities to a number of our stockholders and warrant holders. In the aggregate, as of January 31, 2004, these registration rights covered approximately 1,887,325 shares of our common stock which were then outstanding or which may become outstanding upon the exercise of warrants that were then outstanding. If these registration rights, or similar registration rights that may apply to securities we may issue in the future, are exercised

**Table of Contents**

**Risk factors**

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by the holders, it could result in additional sales of our common stock in the market, which may have an adverse effect on our stock price.

**New investors in our common stock will experience immediate and substantial dilution.**

The purchase price of the common stock offered by this prospectus supplement will be substantially higher than the net tangible book value per share of our outstanding shares of common stock. As a result, purchasers of our common stock in this offering will incur immediate and substantial dilution in net tangible book value per share of common stock and will experience additional dilution upon the exercise of outstanding stock options and warrants. See [Dilution](#) on page S-36 for a more detailed discussion of the dilution new investors will incur in this offering.

**We do not intend to pay cash dividends on our common stock in the foreseeable future.**

We do not anticipate paying cash dividends on our common stock in the foreseeable future. Any payment of cash dividends will depend upon our financial condition, results of operations, capital requirements and other factors and will be at the discretion of the Board of Directors. Furthermore, we may incur additional indebtedness that may severely restrict or prohibit the payment of dividends.

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S-30

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**Table of Contents**

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## Forward-looking statements

All statements included or incorporated by reference in this prospectus supplement and the accompanying prospectus, other than statements of historical fact, that address activities, events or developments that we intend, expect, project, believe or anticipate will or may occur in the future are forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. Such statements are typically characterized by terminology such as believe, anticipate, should, intend, plan, will, expect, estimate, project, positioned, strategic, and other similar expressions. These statements are based on assumptions and assessments made by our management in light of its experience and its perception of historical trends, current conditions, expected future developments and other factors our management believes to be appropriate.

These forward-looking statements are subject to a number of risks and uncertainties, including those risks described or incorporated by reference in this prospectus supplement under **Risk factors**, as well as other factors that our management has not yet identified. Any such forward-looking statements are not guarantees of future performance. Actual results, performance, developments and business decisions may differ materially from those contemplated by such forward-looking statements as a result of many factors, including, without limitation, uncertainties related to drug discovery, clinical development processes and the development and commercialization of our molecular diagnostics technology; changes in relationships with strategic partners and dependence upon strategic partners for the performance of critical activities under collaborative agreements; the impact of competitive products and technological changes, uncertainties relating to patent protection and regulatory approval uncertainties relating to our ability to obtain substantial additional funds required for progress in drug discovery and development and those factors described in **Risk factors** beginning on page S-9 of this prospectus supplement. We disclaim any duty to update any forward-looking statements.

**We encourage you to read this prospectus supplement and the accompanying prospectus, as well as the information that is incorporated by reference in this prospectus supplement and the accompanying prospectus, in their entireties. You should carefully consider the facts set forth under **Risk factors** beginning on page S-9 in this prospectus supplement and in the other reports incorporated by reference herein before making an investment decision to purchase shares of our common stock.**

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**Table of Contents**

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## Use of proceeds

We estimate the net proceeds to us from this offering will be approximately \$56.3 million, assuming a public offering price of \$15.12 per share and after payment of underwriting discounts and commissions and estimated expenses of this offering. If the underwriters' over-allotment option is exercised in full, we anticipate that the net proceeds will be approximately \$64.8 million.

We intend to use the net proceeds to us from this offering for general corporate purposes, including current and future clinical trials of our lead drug candidate, alfimeprase, as well as other research and drug development activities. The amounts and timing of the expenditures will depend on numerous factors, such as the timing and progress of our clinical trials and research and development efforts, technological advances and the competitive environment for our drug candidates. As of the date of this prospectus supplement, we cannot specify with certainty all of the particular uses for the net proceeds to us from this offering. Accordingly, we will retain broad discretion over the use of these proceeds.

Pending such uses, we may invest the net proceeds in interest-bearing securities of investment grade.

**Table of Contents**

## Price range of common stock

Our common stock is quoted on the Nasdaq National Market under the symbol NUVO. The following table sets forth, for the periods indicated, the high and low reported sales prices of our common stock as reported on the Nasdaq National Market, both before and after giving effect to a one-for-three reverse split of our common stock that we anticipate will become effective on February 23, 2004:

	Post-split		Pre-split	
	High	Low	High	Low
<b>Year ended December 31, 2001</b>				
First quarter	\$ 49.32	\$ 22.50	\$ 16.44	\$ 7.50
Second quarter	54.00	22.50	18.00	7.50
Third quarter	34.05	15.60	11.35	5.20
Fourth quarter	30.66	17.82	10.22	5.94
<b>Year ended December 31, 2002</b>				
First quarter	\$ 27.00	\$ 15.96	\$ 9.00	\$ 5.32
Second quarter	15.99	5.10	5.33	1.70
Third quarter	8.52	4.50	2.84	1.35
Fourth quarter	5.70	2.55	1.90	0.85
<b>Year ended December 31, 2003</b>				
First quarter	\$ 4.47	\$ 1.92	\$ 1.49	\$ 0.64
Second quarter	8.16	2.58	2.72	0.86
Third quarter	12.03	5.28	4.01	1.76
Fourth quarter	12.66	7.47	4.22	2.49
<b>Year ended December 31, 2004</b>				
First quarter (through February 17)	\$ 16.50	\$ 10.53	\$ 5.50	\$ 3.51

As of January 31, 2004, we estimate there were approximately 275 holders of record of our common stock. On February 17, 2004, the last sale price reported on the Nasdaq National Market for our common stock, after giving effect to the reverse split, was \$15.12 per share.

## Dividend policy

The holders of our common stock are entitled to dividends in such amounts and at such times, if any, as may be declared by our board of directors out of legally available funds. We have not paid any dividends on our common stock and do not anticipate paying any cash dividends on our common stock in the foreseeable future.



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**Table of Contents**


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## Capitalization

The following table shows our cash, cash equivalents and investments and capitalization as of December 31, 2003:

Ø on an actual basis; and

Ø on an as adjusted basis to give effect to our sale of 4,000,000 shares of common stock offered by us, assuming a public offering price of \$15.12 per share and after deducting underwriting discounts and commissions and estimated offering expenses payable by us.

This table should be read with Management's discussion and analysis of financial condition and results of operations and our financial statements and the related notes incorporated by reference in this prospectus supplement and the accompanying prospectus.

	As of December 31, 2003	
	Actual	As adjusted
	(in thousands, except share and per share data)	
Cash, cash equivalents and short- and long-term investments	\$ 34,189	\$ 90,465
Current portion of capital lease and line of credit obligations	4,741	4,741
Non-current portion of capital lease and line of credit obligations	8,871	8,871
Stockholders' equity:		
Preferred stock, \$0.001 par value; 8,000,000 shares authorized; no shares issued or outstanding, actual and as adjusted		
Common stock \$0.001 par value; 100,000,000 shares authorized; 25,621,235 shares issued and outstanding, actual; 29,621,235 shares issued and outstanding, as adjusted	\$ 26	\$ 30
Additional paid-in capital	226,279	282,551
Deferred stock-based compensation	(30)	(30)
Accumulated other comprehensive loss	(15)	(15)
Accumulated deficit	(203,559)	(203,559)
Total stockholders' equity	22,701	78,977
Total capitalization	\$ 36,313	\$ 92,589

The number of shares of common stock outstanding is based on the actual number of shares outstanding as of December 31, 2003 and excludes, as of that date:

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- Ø an aggregate of 1,594,318 shares of common stock reserved for issuance upon exercise of outstanding stock options granted under our 2002 Equity Incentive Plan, 1995 Stock Option Plan, Non-Employee Director Stock Option Plan, Scientific Advisory Board/Consultants Stock Option Plan and the Variagenics, Inc. Amended 1997 Employee, Director and Consultant Stock Option Plan;
  
- Ø an aggregate of 1,479,752 shares of common stock reserved for issuance pursuant to future option grants under these plans;
  
- Ø an aggregate of 88,307 shares of common stock reserved for issuance under our Employee Stock Purchase Plan;

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S-34



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**Table of Contents**

**Capitalization**

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- Ø an aggregate of 1,085,852 shares of common stock reserved for issuance upon the exercise of outstanding stock options granted outside of any of our stock option plans;
- Ø warrants to purchase an aggregate of 1,887,325 shares of our common stock with exercise prices ranging from \$4.05 to \$25.53 per share, and a weighted average exercise price of \$17.76 per share;
- Ø 519,181 shares of common stock issuable upon repayment of our note held by Affymetrix and 1,098,286 shares of common stock issuable upon mutual agreement to convert the promissory note under the Rathmann line of credit; and
- Ø 263,296 shares issued on February 4, 2004 to Dendreon.

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**Table of Contents**


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## Dilution

If you invest in our common stock, your interest will be diluted to the extent of the difference between the public offering price per share you pay in this offering and the net tangible book value per share of our common stock immediately after this offering. Our net tangible book value as of December 31, 2003 was approximately \$16.8 million, or \$0.65 per share of common stock. Net tangible book value per share is equal to our total tangible assets minus total liabilities, all divided by the number of shares of common stock outstanding as of December 31, 2003. After giving effect to the sale by us of the 4,000,000 shares of common stock we are offering, assuming a public offering price of \$15.12 per share and after deducting underwriting discounts and commissions and our estimated offering expenses, our as adjusted net tangible book value would have been approximately \$73.0 million, or \$2.46 per share of common stock. This represents an immediate increase in net tangible book value of \$1.81 per share to our existing stockholders and an immediate dilution of \$12.66 per share to new investors. The following table illustrates this calculation on a per share basis:

Assumed offering price per share	\$ 15.12
Net tangible book value per share as of December 31, 2003	\$ 0.65
Increase per share attributable to the offering	1.81
	<hr/>
As adjusted net tangible book value per share after this offering	2.46
	<hr/>
Dilution per share to new investors	\$ 12.66
	<hr/>

If the underwriters exercise their over-allotment option in full, the as adjusted net tangible book value as of December 31, 2003 would have been \$2.70 per share, representing an increase to existing stockholders of \$2.04 per share, and there will be an immediate dilution of \$12.42 per share to new investors.

The foregoing table does not take into effect further dilution to new investors that could occur upon the exercise of outstanding options and warrants having a per share exercise price less than the offering price per share in this offering. As of December 31, 2003, there were:

- ∅ an aggregate of 1,594,318 shares of common stock reserved for issuance upon exercise of outstanding stock options granted under our 2002 Equity Incentive Plan, 1995 Stock Option Plan, Non-Employee Director Stock Option Plan, Scientific Advisory Board/ Consultants Stock Option Plan and the Variagenics, Inc. Amended 1997 Employee, Director and Consultant Stock Option Plan;
- ∅ an aggregate of 1,479,752 shares of common stock reserved for issuance pursuant to future option grants under these plans;
- ∅ an aggregate of 88,307 shares of common stock reserved for issuance under our Employee Stock Purchase Plan;
- ∅ an aggregate of 1,085,852 shares of common stock reserved for issuance upon the exercise of outstanding stock options granted outside of any of our stock option plans;

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- Ø warrants to purchase an aggregate of 1,887,325 shares of our common stock with exercise prices ranging from \$4.05 to \$25.53 per share, and a weighted average exercise price of \$17.76 per share;
  
- Ø 519,181 shares of common stock issuable upon repayment of our note held by Affymetrix and 1,098,286 shares of common stock issuable upon mutual agreement to convert the promissory note under the Rathmann line of credit; and
  
- Ø 263,296 shares issued on February 4, 2004 to Dendreon.

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S-36

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**Table of Contents**


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## Management

Set forth below is information regarding each of our executive officers and directors as of February 17, 2004.

<b>Name</b>	<b>Age</b>	<b>Position</b>
George B. Rathmann	76	Chairman of the Board of Directors
Ted W. Love	44	President, Chief Executive Officer and Director
Peter S. Garcia	42	Senior Vice President, Chief Financial Officer and Secretary
Linda A. Fitzpatrick	46	Senior Vice President of Human Resources
Walter D. Funk	43	Vice President of Research
Luis C. Peña	41	Vice President of Development
Susan L. Meyer	34	Associate General Counsel and Assistant Secretary
Philippe O. Chambon	45	Director
Mary K. Pendergast	53	Director
Mark Perry	48	Director
Martin A. Vogelbaum	40	Director
Barry L. Zubrow	51	Director

*George B. Rathmann, Ph.D.* has served as chairman and a member of our board of directors since February 2000. Dr. Rathmann served as our chief executive officer from May 2000 to March 2001, and also served as our president from May 2000 to January 2001. Dr. Rathmann was a founder of ICOS Corporation, a publicly held biopharmaceutical company, in 1990 and served as its chairman until January 2000. While at ICOS, he also served as chief executive officer and president from September 1991 until June 1999. In 1980, he co-founded Amgen Inc., a publicly held biotechnology company. He was a director of Amgen until 1993 and at various times also served as its chairman of the board, president and chief executive officer. Dr. Rathmann was also associated with Abbott Laboratories, Inc., a healthcare products manufacturer, where from 1975 to 1977 he was director of research and development and from 1977 to 1980 he was divisional vice president. Dr. Rathmann received his Ph.D. in physical chemistry from Princeton University.

*Ted W. Love, M.D.* has served as our president since January 2001, our chief executive officer since March 2001, and as a director since February 2001. Dr. Love served as our president and chief operating officer from January 2001 until March 2001. Prior to joining us, Dr. Love served as senior vice president of development at Theravance Inc. (formerly Advanced Medicine, Inc.) and as a research physician and vice president of product development at Genentech from 1992 to 1998. Dr. Love holds a B.A. in molecular biology from Haverford College and a M.D. from Yale Medical School.

*Peter S. Garcia, M.B.A.* joined us in May 2001 as our senior vice president and chief financial officer. In January 2003, Mr. Garcia began to serve as our secretary. Prior to joining us, Mr. Garcia served as chief financial officer at Novacept, Inc., from May 2000 to April 2001, chief financial officer and consultant at IntraBiotics Pharmaceuticals, Inc. from January 1999 to April 2000 and chief financial officer at Dendreon Corporation from July 1996 to December 1998. Prior to this experience, Mr. Garcia worked at Amgen Inc. from 1990 to 1996 in a variety of financial executive positions, including assistant corporate controller. Mr. Garcia graduated with honors with a Bachelor of Arts degree in economics and sociology from Stanford University, and earned his M.B.A. from the University of California at Los Angeles.



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**Table of Contents**

**Management**

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*Linda A. Fitzpatrick* joined us in April 2001 as our senior vice president of human resources. Prior to joining us, Ms. Fitzpatrick served as senior advisor at Theravance, Inc. (formerly Advanced Medicine, Inc.) from April 1999 to January 2001 and vice president, human resources, corporate communications and operations at Gilead Sciences, Inc. from 1992 to 1998. Prior to her tenure at Gilead Sciences, Ms. Fitzpatrick served eight years at Genentech, Inc. where her positions included director, investor relations and director, compensation, benefits and systems. Ms. Fitzpatrick graduated with honors with a Bachelor of Science degree in sociology and psychology from San Francisco State University.

*Walter D. Funk, Ph.D.* joined us in August 2000 and currently holds the position of vice president of research. Prior to joining us, Dr. Funk was a founding scientist at Geron Corp. from 1993 to 2000 where he was project leader on molecular biology projects focused on telomerase biology, cell immortalization and senescence. He later led the company's genomics efforts in human stem cell biology. Dr. Funk did post-doctoral work at the University of Texas Southwestern Medical Center at Dallas in the labs of Woodring Wright and Jerry Shay and received his Ph.D. and B.Sc.(Hon) degrees in biochemistry from the University of British Columbia. He has published over thirty journal papers and is an assignee on seven US patents.

*Luis C. Peña* joined Nuvelo in March 2001, bringing over 16 years of experience in drug development. Mr. Peña joined Nuvelo from Theravance, Inc. (formerly Advanced Medicine, Inc.), where he served as senior director of product development and helped build their development organization. Prior to Theravance, Mr. Peña held various positions in manufacturing, research and development during his 12 years at Genentech, Inc. There he participated in the discovery of TNKase, a thrombolytic approved for the treatment of acute myocardial infarction, and managed their cardiovascular development portfolio, which included tPA, TNK-tPA, VEGF and oral IIbIIIa inhibitors. Mr. Peña attended San Francisco State University and the University of California, Berkeley and majored in biochemistry.

*Susan L. Meyer, J.D.* joined Nuvelo in April 2003 and currently holds the position of associate general counsel and assistant secretary, bringing extensive experience in biotechnology licensing, portfolio management, corporate due diligence and general contract law. She comes to Nuvelo from Entelos, Inc., a predictive biosimulation company located in Foster City, California, where she served as director of licensing and corporate counsel from May 2000 to April 2003. Prior to her tenure at Entelos, Ms. Meyer was an associate at Cooley Godward LLP from 1997 to 2000. She has a bachelor's degree from Stanford University and a law degree from Northwestern University School of Law.

*Philippe O. Chambon, M.D., Ph.D.* has served as a member of our board of directors since our merger with Variagenics, Inc., in January 2003. Dr. Chambon served as a member of the board of directors of Variagenics from July 1999 until January 2003. Since January 1997, Dr. Chambon has been a general partner of the Sprout Group. Dr. Chambon joined the Sprout Group in May 1995. From May 1993 to April 1995, Dr. Chambon served as manager in the healthcare practice of The Boston Consulting Group, a leading management consulting firm. From September 1987 to April 1993, he was an executive with Sandoz Pharmaceutical (Novartis), where he had late-stage product development and pre-marketing responsibilities. Dr. Chambon currently serves as a member of the board of directors of Deltagen, Inc., Pharsight Corp. and several privately funded biotechnology companies. Dr. Chambon holds an M.D. and a Ph.D. from the University of Paris and an M.B.A. from Columbia University.

*Mary K. Pendergast, J.D., LL.M.* has served as a member of our board of directors since May 2002. Ms. Pendergast served as executive vice president, government affairs for Elan Corporation since January 1998. Ms. Pendergast was deputy commissioner/senior advisor to the Food and Drug Administration, Department of Health and Human Services from November 1990 to January 1998. Ms. Pendergast



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**Table of Contents**

**Management**

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received her L.L.M. from Yale Law School in 1977, her J.D. from the University of Iowa College of Law in 1976 and her B.A. from Northwestern University in 1972.

*Mark Perry, J.D.* has served as a member of our board of directors since October 2003. Mr. Perry currently serves as the executive vice president of operations for Gilead Sciences, Inc., a biopharmaceutical company located in Foster City, California. Mr. Perry joined Gilead in 1994 as vice president, general counsel and secretary and later assumed the additional responsibilities of chief financial officer in 1996. At Gilead, Mr. Perry is responsible for worldwide commercial operations and the legal, intellectual property, manufacturing and facilities functions. Prior to joining Gilead, Mr. Perry served as a partner at the law firm Cooley Godward LLP, based in San Francisco and Palo Alto, California. Mr. Perry also sits on the board of directors of IntraBiotics Pharmaceuticals, Inc. and DNA Sciences, Inc. Mr. Perry received his J.D. from the University of California, Davis and is a member of the California bar.

*Martin A. Vogelbaum* has served as a member of our board of directors since our merger with Variagenics in January 2003. Mr. Vogelbaum served as a member of the board of directors of Variagenics from June 1997 until January 2003. Since June 2000, Mr. Vogelbaum has been a general partner of Apple Tree Partners. Previously, Mr. Vogelbaum was a general partner of Oxford Bioscience Partners. Prior to joining Oxford in 1993, he held senior executive positions at the public and investor relations firms of Burns McClellan, Inc. and Hill & Knowlton, where he implemented marketing and investor initiatives for biotechnology and pharmaceutical companies. Previously, he was a research associate in the Bone Marrow Transplant Unit at Memorial Sloan-Kettering Cancer Center. Mr. Vogelbaum received his A.B. in biology and history from Columbia University.

*Barry L. Zubrow, J.D., M.B.A.* has served as a member of our board of directors since February 3, 2004. Mr. Zubrow brings over 26 years of corporate finance experience to our board of directors. From 1977 to 2003, Mr. Zubrow held a variety of positions at The Goldman Sachs Group including chief administrative officer and head of the operations and the administration division. As the firm's first chief administrative officer, he was responsible for overseeing a 4,500 plus person group of departments in charge of financial reporting, credit and risk functions, operations and trade processing, facilities, security and corporate services. Prior to that, Mr. Zubrow was elected the firm's first chief credit officer, with responsibility for overseeing the entire firm's global credit exposures. He received his J.D. and M.B.A. for the University of Chicago and is an active board member for a number of non-profit organizations.



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**Table of Contents**


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## Underwriting

We are offering the shares of our common stock described in this prospectus supplement through the underwriters named below. UBS Securities LLC, CIBC World Markets Corp., Needham & Company, Inc. and JMP Securities LLC are the representatives of the underwriters. UBS Securities LLC is the sole book-running manager of this offering.

We have entered into an underwriting agreement with the representatives. Subject to the terms and conditions of the underwriting agreement, each of the underwriters has severally agreed to purchase the number of shares of common stock listed next to its name in the following table:

<b>Underwriters</b>	<b>Number of shares</b>
UBS Securities LLC	
CIBC World Markets Corp.	
Needham & Company, Inc.	
JMP Securities LLC.	
<b>Total</b>	<b>4,000,000</b>

The underwriting agreement provides that the underwriters must buy all of the shares if they buy any of them. However, the underwriters are not required to take or pay for the shares covered by the underwriters' over-allotment option described below.

Our common stock is offered subject to a number of conditions, including:

Ø receipt and acceptance of our common stock by the underwriters; and

Ø the underwriters' right to reject orders in whole or in part.

In connection with this offering, certain of the underwriters or securities dealers may distribute prospectus supplements and prospectuses electronically.

Sales of shares made outside of the United States may be made by affiliates of the underwriters.

## **OVER-ALLOTMENT OPTION**

We have granted the underwriters an option to buy up to an aggregate of 600,000 additional shares of our common stock. The underwriters may exercise this option solely for the purpose of covering over-allotments, if any, made in connection with this offering. The underwriters have 30 days from the date of this prospectus supplement to exercise this option. If the underwriters exercise this option, they will each purchase additional shares approximately in proportion to the amounts specified in the table above.

## **COMMISSIONS AND DISCOUNTS**

Shares sold by the underwriters to the public will initially be offered at the public offering price set forth on the cover of this prospectus supplement. Any shares sold by the underwriters to securities dealers may be sold at a discount of up to \$        per share from the public offering price. Any of these securities dealers may resell any shares purchased from the underwriters to other brokers or dealers at a discount of up to \$        per share from the public offering price. If all the shares are not sold at the public offering price, the representatives may change the offering price and the other selling terms.

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S-40

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**Table of Contents**

**Underwriting**

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The following table shows the per share and total underwriting discounts and commissions we will pay to the underwriters. These amounts are shown assuming both no exercise and full exercise of the underwriters' option to purchase up to an additional 600,000 shares.

<b>Paid by the Company</b>	<b>No exercise</b>	<b>Full exercise</b>
Per share	\$	\$
Total	\$	\$

We estimate that the total expenses of this offering payable by us, not including underwriting discounts and commissions, will be approximately \$575,000.

**NO SALES OF SIMILAR SECURITIES**

We and our executive officers, directors and certain of our stockholders have entered into lock-up agreements with the underwriters. Under these agreements, we and each of these persons generally may not, without the prior written approval of UBS Securities LLC, subject to certain permitted exceptions, offer, sell, contract to sell or otherwise dispose of or hedge our common stock or securities convertible into or exercisable or exchangeable for our common stock. These restrictions will be in effect for a period of 90 days after the date of this prospectus supplement. At any time and without public notice, UBS Securities LLC may in its sole discretion, release all or some of the securities from these lock-up agreements.

**INDEMNIFICATION AND CONTRIBUTION**

We have agreed to indemnify the underwriters against certain liabilities, including liabilities under the Securities Act, and to contribute to payments the underwriters may be required to make in respect thereof.

**NASDAQ NATIONAL MARKET QUOTATION**

Our common stock is quoted on the Nasdaq National Market under the symbol NUVO.

**PRICE STABILIZATION, SHORT POSITIONS, PASSIVE MARKET MAKING**

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In connection with this offering, the underwriters may engage in activities that stabilize, maintain or otherwise affect the price of our common stock, including:

- Ø stabilizing transactions;
- Ø short sales;
- Ø purchases to cover positions created by short sales;
- Ø imposition of penalty bids;
- Ø syndicate covering transactions; and
- Ø passive market making.

Stabilizing transactions consist of bids or purchases made for the purpose of preventing or retarding a decline in the market price of our common stock while this offering is in progress. Short sales involve the sale by the underwriters of a greater number of shares of common stock than they are required to purchase in this offering. Short sales may be covered short sales, which are short positions in an amount not greater than the underwriters' over-allotment option referred to above, or may be naked short sales, which are short positions in excess of that amount.

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**Table of Contents**

**Underwriting**

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The underwriters may close out any covered short position by either exercising their over-allotment option, in whole or in part, or by purchasing shares in the open market. In making this determination, the underwriters will consider, among other things, the price of shares available for purchase in the open market as compared to the price at which they may purchase shares through the over-allotment option. The underwriters must close out any naked short position by purchasing shares in the open market. A naked short position is more likely to be created if the underwriters are concerned that there may be downward pressure on the price of the shares in the open market after pricing that could adversely affect investors who purchased in this offering.

The underwriters also may impose a penalty bid. This occurs when a particular underwriter repays to the underwriters a portion of the underwriting discount received by it because the representatives have repurchased shares sold by or for the account of that underwriter in stabilizing or short covering transactions.

As a result of these activities, the price of our common stock may be higher than the price that otherwise might exist in the open market. If the activities are commenced, they may be discontinued by the underwriters at any time. The underwriters may carry out these transactions on the Nasdaq National Market, in the over-the-counter market or otherwise.

In addition, in connection with this offering, certain of the underwriters (and selling group members) may engage in passive market making transactions in our common stock on the Nasdaq National Market prior to the pricing and completion of this offering. Passive market making consists of displaying bids on the Nasdaq National Market no higher than the bid prices of independent market makers and making purchases at prices no higher than these independent bids and effected in response to order flow. Net purchases by a passive market maker on each day are limited to a specified percentage of the passive market maker's average daily trading volume in the common stock during a specified period and must be discontinued when such limit is reached. Passive market making may cause the price of our common stock to be higher than the price that otherwise would exist in the open market in the absence of these transactions. If passive market making is commenced, it may be discontinued at any time.

**AFFILIATIONS**

JMP Securities LLC has in the past provided, and certain of the underwriters may in the future provide, financial advisory services to us. For these services, we have paid, or will pay, them customary compensation. The underwriters and their affiliates may from time to time in the future engage in transactions with us and perform services for us in the ordinary course of their business.

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**Table of Contents**

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## Legal matters

The validity of the shares being offered by this prospectus supplement will be passed upon for us by Kummer Kaempfer Bonner & Renshaw of Las Vegas, Nevada. Certain legal matters will be passed upon for us by Latham & Watkins LLP, Menlo Park, California. Dewey Ballantine LLP, New York, New York, is counsel for the underwriters in connection with this offering.

## Experts

The consolidated financial statements of Nuvelo, Inc. as of December 31, 2003 and 2002 and for each of the years in the three year period ended December 31, 2003 have been incorporated by reference herein and in the registration statement in reliance upon the report of KPMG LLP, independent accountants, incorporated by reference herein, and upon the authority of said firm as experts in accounting and auditing.

The consolidated financial statements of Variagenics, Inc. as of December 31, 2002 and 2001, and for each of the three years in the period ended December 31, 2002 incorporated by reference in this prospectus by reference to the Current Report on Form 8-K/A, dated July 3, 2003 of Nuvelo, Inc., have been so incorporated in reliance on the reports of PricewaterhouseCoopers LLP, independent accountants, given on the authority of said firm as experts in auditing and accounting.

## Incorporation by reference

We are a reporting company and file annual, quarterly and current reports, proxy statements and other information with the Securities and Exchange Commission, or the SEC. You may read and copy these reports, proxy statements and other information at the SEC's public reference rooms at 450 Fifth Street, N.W., Washington, D.C. 20549. You can request copies of these documents by writing to the SEC and paying a fee for the copying cost. Please call the SEC at 1-800-SEC-0330 for more information about the operation of the public reference rooms. Our SEC filings are also available on the SEC's web site at <http://www.sec.gov>.

The SEC allows us to incorporate by reference information that we file with them, which means that we can disclose important information to you by referring you to those documents. The information incorporated by reference is an important part of this prospectus supplement, and information that we file later with the SEC will automatically update and supersede this information. We incorporate by reference the documents listed below and any future filings we will make with the SEC under Section 13(a), 13(c), 14 or 15(d) of the Securities Exchange Act of 1934, after the date of the prospectus but before the end of any offering made under this prospectus supplement and accompanying prospectus:

Ø our annual report on Form 10-K for the fiscal year ended December 31, 2002, filed with the SEC on March 31, 2003, as amended on Form 10-K/A filed with the SEC on April 30, 2003;

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Ø our quarterly report on Form 10-Q for the quarter ended March 31, 2003, filed with the SEC on May 14, 2003;

Ø our quarterly report on Form 10-Q for the quarter ended June 30, 2003, filed with the SEC on August 14, 2003;

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S-43

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**Table of Contents**

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- Ø our quarterly report on Form 10-Q for the quarter ended September 30, 2003, filed with the SEC on November 14, 2003;
- Ø our current report on Form 8-K, filed with the SEC on January 21, 2003;
- Ø our current report on Form 8-K, filed with the SEC on January 28, 2003;
- Ø our current report on Form 8-K, filed with the SEC on February 4, 2003, as amended on Form 8-K/A filed with the SEC on February 14, 2003, and as further amended on Form 8-K/A filed with the SEC on July 3, 2003;
- Ø our current report on Form 8-K, filed with the SEC on October 2, 2003;
- Ø our current report on Form 8-K, filed with the SEC on October 22, 2003;
- Ø our current report on Form 8-K, filed with the SEC on October 30, 2003 (incorporated by reference solely with respect to Item 5);
- Ø our current report on Form 8-K, filed with the SEC on January 14, 2004;
- Ø our current report on Form 8-K, filed with the SEC on February 5, 2004 (incorporated by reference solely with respect to Item 5);
- Ø our current report on Form 8-K, filed with the SEC on February 19, 2004; and
- Ø the description of our common stock set forth in our Registration Statement on Form 8-A, filed with the SEC on July 23, 1997, which is therein incorporated by reference from Description of Capital Stock at page 54 of our preliminary prospectus included in our Registration Statement on Form S-1, File No. 333-29091, filed with the SEC on June 12, 1997, as amended on July 2, 1997, July 17, 1997 and July 18, 1997.

We will provide to you at no cost a copy of any and all of the information incorporated by reference into this prospectus supplement and the accompanying prospectus. You may make a request for copies of this information in writing or by telephone. Requests should be directed to:

**Nuvelo, Inc.**

**Attention: Peter S. Garcia**

**675 Almanor Avenue**

**Sunnyvale, CA 94085**

**(408) 215-4000**



S-44

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**Table of Contents**

PROSPECTUS

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# Nuvelo, Inc.

**\$75,000,000**

**Debt Securities**

**Preferred Stock**

**Common Stock**

We may offer from time to time in one or more offerings sell up to \$75,000,000 in the aggregate of:

- ∅ our secured or unsecured debt securities, in one or more series, which may be either senior, senior subordinated or subordinated debt securities;
- ∅ shares of our preferred stock in one or more series;
- ∅ shares of our common stock; and
- ∅ any combination of the foregoing.

We will provide the specific terms of these securities in supplements to this prospectus. You should read this prospectus and any prospectus supplement carefully before you invest.

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**Investing in our securities involves risks. See Risk factors on page 1.**

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Our common stock is quoted on the Nasdaq National Market under the symbol NUVO. On January 23, 2004, the last reported sale price for our common stock on the Nasdaq National Market was \$4.40 per share.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or determined if this prospectus is truthful or complete. Any representation to the contrary is a criminal offense.

February 5, 2004

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**Table of Contents**

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**TABLE OF CONTENTS**

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<u>About this prospectus</u>	1
<u>Risk factors</u>	1
<u>About Nuvelo</u>	1
<u>Cautionary note regarding forward-looking information</u>	2
<u>Use of proceeds</u>	2
<u>Ratio of earnings to fixed charges</u>	2
<u>Description of debt securities</u>	3
<u>Description of preferred stock</u>	12
<u>Description of common stock</u>	14
<u>Additional information concerning our capital stock</u>	16
<u>Plan of distribution</u>	18
<u>Legal matters</u>	18
<u>Experts</u>	19
<u>Where you can find more information</u>	19

This prospectus is part of a registration statement we filed with the Securities and Exchange Commission. You should rely only on the information we have provided or incorporated by reference in this prospectus or any prospectus supplement. We have not authorized anyone to provide you with additional or different information. We are not making an offer of these securities in any jurisdiction where the offer is not permitted. You should assume that the information in this prospectus or any prospectus supplement is accurate only as of the date on the front of the document and that any information we have incorporated by reference is accurate only as of the date of the document incorporated by reference.

We own or have rights to use trademarks or trade names that we use in conjunction with the operation of our business. Nuvelo is a registered trade and service mark of ours. All other trademarks, service marks and trade names referred to in this prospectus are the property of their respective owners.

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**Table of Contents**

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## About this prospectus

This prospectus is part of a Registration Statement on Form S-3 that we filed with the Securities and Exchange Commission utilizing a shelf registration process. Under this shelf process, we may, over the next two years, offer any combination of securities described in this prospectus in one or more offerings. This prospectus provides you with a general description of the securities we may offer. Each time we use this prospectus to offer securities, we will provide a prospectus supplement that will contain specific information about the terms of that offering. The prospectus supplement may also add, update or change information contained in this prospectus. You should read both this prospectus and any prospectus supplement together with additional information described below under the heading **Where You Can Find More Information**.

## Risk factors

An investment in our debt securities, preferred stock or common stock involves a high degree of risk. You should consider carefully the risk factors contained in our most recent filing on Form 10-K, as amended, or Form 10-Q, and all other information contained in and incorporated by reference in this prospectus before making an investment decision. Additional risks and uncertainties that are not yet identified or that we think are immaterial may also materially harm our business, operating results and financial condition and could result in a complete loss of your investment.

## About Nuvelo

We are strategically focused on the discovery and development of novel biotherapeutics. This strategy resulted from a careful review of all assets and programs at both Hyseq, Inc. and Variagenics, Inc. following the close of our merger between the two companies on January 31, 2003.

As part of our strategic focus, we will dedicate our resources to advancing our most promising biopharmaceutical discovery and development programs, including alfineprase, which entered Phase II trials in the first half of 2003.

We will leverage our proprietary gene collection and opportunistic in-licensing and partnering strategy to build upon our pipeline of attractive therapeutic candidates. We also intend to out-license or partner our immunotherapeutics portfolio and monetize non-core assets including our microarray business, pharmacogenomic technology and molecular diagnostic programs, to further support our biopharmaceutical development programs. Our focus is on building a successful biopharmaceutical business. This strategic initiative reflects our commitment to creating a valuable product-focused company that leverages our drug discovery and development expertise. To execute on this strategy, we will align our assets and resources and efficiently manage our finances to provide our key development programs with the greatest chance of success.

We were incorporated as Hyseq, Inc. in Illinois in 1992 and reincorporated in Nevada in 1993. On January 31, 2003, we merged with Variagenics, Inc., a publicly traded Delaware corporation based in Massachusetts, and, in connection with the merger, changed our name to

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Nuvelo, Inc. Our principal executive offices are located at 675 Almanor Avenue, Sunnyvale, California 94085 and our telephone number is (408) 215-4000. Our World Wide Web address is <http://www.nuvelo.com>. Information contained on our web site should not be considered to be part of this prospectus.

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**Table of Contents**


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## Cautionary note regarding forward-looking information

All statements included or incorporated by reference in this prospectus, other than statements of historical facts, that address activities, events or developments that we intend, expect, project, believe or anticipate will or may occur in the future are forward-looking statements. Such statements are typically characterized by terminology such as believe, anticipate, should, intend, plan, will, expect, estimate, strategy, and similar expressions. These statements are based on assumptions and assessments made by our management in light of its experience and its perception of historical trends, current conditions, expected future developments and other factors our management believes to be appropriate. These forward-looking statements are subject to a number of risks and uncertainties, including those risks described or incorporated by reference in this prospectus under Risk factors above, as well as other factors that our management has not yet identified. Any such forward-looking statements are not guarantees of future performance and actual results, developments and business decisions may differ from those contemplated by such forward-looking statements. We disclaim any duty to update any forward-looking statements.

## Use of proceeds

Unless otherwise indicated in the prospectus supplement, the net proceeds from the sale of securities offered by this prospectus will be used for general corporate purposes, including capital expenditures and to meet working capital needs. We expect from time to time to evaluate the acquisition of businesses, products and technologies for which a portion of the net proceeds may be used, although we currently are not planning or negotiating any such transactions.

Pending such uses, we may invest the net proceeds in interest bearing securities.

## Ratio of earnings to fixed charges

Our earnings are inadequate to cover fixed charges. The following table sets forth the dollar amount of the coverage deficiency:

	Fiscal Year Ended December 31,					Nine Months Ended
	1998	1999	2000	2001	2002	September 30, 2003
	(in thousands)					
Ratio of earnings to fixed charges <sup>(1)</sup>						
Coverage deficiency	\$ (16,369)	\$ (18,547)	\$ (22,253)	\$ (36,472)	\$ (44,978)	\$ (40,797)

(1) We have not included a ratio of earnings to combined fixed charges and preferred stock dividends because we do not have any preferred stock outstanding.





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**Table of Contents**

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## Description of debt securities

The debt securities covered by this prospectus will be our convertible senior or subordinated debt securities issued under one or more separate senior or subordinated indentures to be entered into between us and a trustee to be identified in the applicable prospectus supplement. This prospectus, together with its prospectus supplement, will describe all the material terms of a particular series of debt securities.

The following is a summary of the most important provisions and definitions of the indentures. For additional information, you should look at the applicable indenture that is filed as an exhibit to the registration statement which includes the prospectus. The indentures are substantially identical except for the subordination provisions described below under Subordinated Debt Securities. In this description of the debt securities, the words Nuvelo, we, us or our refer only to Nuvelo and not to any of our subsidiaries.

### **GENERAL**

Debt securities may be issued in separate series without limitation as to aggregate principal amount. We may specify a maximum aggregate principal amount for the debt securities of any series.

We are not limited as to the amount of debt securities we may issue under the indentures. The prospectus supplement will set forth:

Ø whether the debt securities will be senior or subordinated;

Ø the offering price;

Ø the title;

Ø any limit on the aggregate principal amount;

Ø the person who shall be entitled to receive interest, if other than the record holder on the record date;

Ø the date the principal will be payable;

Ø the interest rate, if any, the date interest will accrue, the interest payment dates and the regular record dates;

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- Ø the place where payments may be made;
  - Ø any mandatory or optional redemption provisions;
  - Ø if applicable, the method for determining how the principal, premium, if any, or interest will be calculated by reference to an index or formula;
  - Ø if other than U.S. currency, the currency or currency units in which principal, premium, if any, or interest will be payable and whether we or the holder may elect payment to be made in a different currency;
  - Ø the portion of the principal amount that will be payable upon acceleration of stated maturity, if other than the entire principal amount;
  - Ø if the principal amount payable at stated maturity will not be determinable as of any date prior to stated maturity, the amount which will be deemed to be the principal amount;
  - Ø any defeasance provisions if different from those described below under Satisfaction and Discharge; Defeasance;
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**Table of Contents**

**Description of debt securities**

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Ø any conversion or exchange provisions;

Ø any obligation to redeem or purchase the debt securities pursuant to a sinking fund;

Ø whether the debt securities will be issuable in the form of a global security;

Ø any subordination provisions, if different from those described below under Subordinated Debt Securities;

Ø any deletions of, or changes or additions to, the events of default or covenants; and

Ø any other specific terms of such debt securities.

Unless otherwise specified in the prospectus supplement:

Ø the debt securities will be registered debt securities; and

Ø registered debt securities denominated in U.S. dollars will be issued in denominations of \$1,000 or an integral multiple of \$1,000.

Debt securities may be sold at a substantial discount below their stated principal amount, bearing no interest or interest at a rate which at the time of issuance is below market rates.

**EXCHANGE AND TRANSFER**

Debt securities may be transferred or exchanged at the office of the security registrar or at the office of any transfer agent designated by us.

We will not impose a service charge for any transfer or exchange, but we may require holders to pay any tax or other governmental charges associated with any transfer or exchange.

In the event of any potential redemption of debt securities of any series, we will not be required to:

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- Ø issue, register the transfer of, or exchange, any debt security of that series during a period beginning at the opening of business 15 days before the day of mailing of a notice of redemption and ending at the close of business on the day of the mailing; or
- Ø register the transfer of or exchange any debt security of that series selected for redemption, in whole or in part, except the unredeemed portion being redeemed in part.

We may initially appoint the trustee as the security registrar. Any transfer agent, in addition to the security registrar, initially designated by us will be named in the prospectus supplement. We may designate additional transfer agents or change transfer agents or change the office of the transfer agent. However, we will be required to maintain a transfer agent in each place of payment for the debt securities of each series.

### **GLOBAL SECURITIES**

The debt securities of any series may be represented, in whole or in part, by one or more global securities. Each global security will:

- Ø be registered in the name of a depositary that we will identify in a prospectus supplement;
- Ø be deposited with the depositary or nominee or custodian; and
- Ø bear any required legends.

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**Table of Contents**

**Description of debt securities**

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No global security may be exchanged in whole or in part for debt securities registered in the name of any person other than the depositary or any nominee unless:

- ∅ the depositary has notified us that it is unwilling or unable to continue as depositary or has ceased to be qualified to act as depositary;
- ∅ an event of default is continuing; or
- ∅ any other circumstances described in a prospectus supplement.

As long as the depositary, or its nominee, is the registered owner of a global security, the depositary or nominee will be considered the sole owner and holder of the debt securities represented by the global security for all purposes under the indenture. Except in the above limited circumstances, owners of beneficial interests in a global security:

- ∅ will not be entitled to have the debt securities registered in their names;
- ∅ will not be entitled to physical delivery of certificated debt securities; and
- ∅ will not be considered to be holders of those debt securities under the indentures.

Payments on a global security will be made to the depositary or its nominee as the holder of the global security. Some jurisdictions have laws that require that certain purchasers of securities take physical delivery of such securities in definitive form. These laws may impair the ability to transfer beneficial interests in a global security.

Institutions that have accounts with the depositary or its nominee are referred to as participants. Ownership of beneficial interests in a global security will be limited to participants and to persons that may hold beneficial interests through participants. The depositary will credit, on its book-entry registration and transfer system, the respective principal amounts of debt securities represented by the global security to the accounts of its participants.

Ownership of beneficial interests in a global security will be shown on and effected through records maintained by the depositary, with respect to participants' interests, or any participant, with respect to interests of persons held by participants on their behalf.

Payments, transfers and exchanges relating to beneficial interests in a global security will be subject to policies and procedures of the depositary.

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The depositary policies and procedures may change from time to time. Neither we nor the trustee will have any responsibility or liability for the depositary's or any participant's records with respect to beneficial interests in a global security.

### **PAYMENT AND PAYING AGENT**

The provisions of this paragraph will apply to the debt securities unless otherwise indicated in the prospectus supplement. Payment of interest on a debt security on any interest payment date will be made to the person in whose name the debt security is registered at the close of business on the regular record date. Payment on debt securities of a particular series will be payable at the office of a paying agent or paying agents designated by us. However, at our option, we may pay interest by mailing a check to the record holder. The corporate trust office will be designated as our sole paying agent.

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**Table of Contents**

**Description of debt securities**

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We may also name any other paying agents in the prospectus supplement. We may designate additional paying agents, change paying agents or change the office of any paying agent. However, we will be required to maintain a paying agent in each place of payment for the debt securities of a particular series.

All moneys paid by us to a paying agent for payment on any debt security which remain unclaimed at the end of two years after such payment was due will be repaid to us. Thereafter, the holder may look only to us for such payment.

**CONSOLIDATION, MERGER AND SALE OF ASSETS**

We may not consolidate with or merge into any other person, in a transaction in which we are not the surviving corporation, or convey, transfer or lease our properties and assets substantially as an entirety to, any person, unless:

- ∅ the successor, if any, is a U.S. corporation, limited liability company, partnership, trust or other entity;
- ∅ the successor assumes our obligations on the debt securities and under the indenture;
- ∅ immediately after giving effect to the transaction, no default or event of default shall have occurred and be continuing; and
- ∅ certain other conditions are met.

**EVENTS OF DEFAULT**

Unless we inform you otherwise in the prospectus supplement, the indenture will define an event of default with respect to any series of debt securities as one or more of the following events:

- (1) failure to pay principal of or any premium on any debt security of that series when due;
- (2) failure to pay any interest on any debt security of that series for 30 days when due;
- (3) failure to deposit any sinking fund payment when due;

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- (4) failure to perform any other covenant in the indenture continued for 60 days after being given the notice required in the indenture;
- (5) our bankruptcy, insolvency or reorganization; and
- (6) any other event of default specified in the prospectus supplement.

An event of default of one series of debt securities is not necessarily an event of default for any other series of debt securities.

If an event of default, other than an event of default described in clause (5) above, shall occur and be continuing, either the trustee or the holders of at least 25% in aggregate principal amount of the outstanding securities of that series may declare the principal amount of the debt securities of that series to be due and payable immediately.

If an event of default described in clause (5) above shall occur, the principal amount of all the debt securities of that series will automatically become immediately due and payable. Any payment by us on the subordinated debt securities following any such acceleration will be subject to the subordination provisions described below under Subordinated Debt Securities.



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**Table of Contents**

**Description of debt securities**

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After acceleration the holders of a majority in aggregate principal amount of the outstanding securities of that series may, under certain circumstances, rescind and annul such acceleration if all events of default, other than the non-payment of accelerated principal, or other specified amount, have been cured or waived.

Other than the duty to act with the required care during an event of default, the trustee will not be obligated to exercise any of its rights or powers at the request of the holders unless the holders shall have offered to the trustee reasonable indemnity. Generally, the holders of a majority in aggregate principal amount of the outstanding debt securities of any series will have the right to direct the time, method and place of conducting any proceeding for any remedy available to the trustee or exercising any trust or power conferred on the trustee.

A holder will not have any right to institute any proceeding under the indentures, or for the appointment of a receiver or a trustee, or for any other remedy under the indentures, unless:

- (1) the holder has previously given to the trustee written notice of a continuing event of default with respect to the debt securities of that series;
- (2) the holders of at least 25% in aggregate principal amount of the outstanding debt securities of that series have made a written request and have offered reasonable indemnity to the trustee to institute the proceeding; and
- (3) the trustee has failed to institute the proceeding and has not received direction inconsistent with the original request from the holders of a majority in aggregate principal amount of the outstanding debt securities of that series within 60 days after the original request.

Holders may, however, sue to enforce the payment of principal, premium or interest on any debt security on or after the due date or to enforce the right, if any, to convert any debt security without following the procedures listed in (1) through (3) above.

We will furnish the trustee an annual statement by our officers as to whether or not we are in default in the performance of the indenture and, if so, specifying all known defaults.

**MODIFICATION AND WAIVER**

Nuvelo and the trustee may make modifications and amendments to the indentures with the consent of the holders of a majority in aggregate principal amount of the outstanding securities of each series affected by the modification or amendment.

However, neither we nor the trustee may make any modification or amendment without the consent of the holder of each outstanding security of that series affected by the modification or amendment if such modification or amendment would:

- Ø change the stated maturity of any debt security;
  - Ø reduce the principal, premium, if any, or interest on any debt security;
  - Ø reduce the principal of an original issue discount security or any other debt security payable on acceleration of maturity;
  - Ø reduce the rate of interest on any debt security;
  - Ø change the currency in which any debt security is payable;
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**Table of Contents**

**Description of debt securities**

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- ∅ impair the right to enforce any payment after the stated maturity or redemption date;
- ∅ waive any default or event of default in payment of the principal of, premium or interest on any debt security;
- ∅ waive a redemption payment or modify any of the redemption provisions of any debt security;
- ∅ adversely affect the right to convert any debt security; or
- ∅ change the provisions in the indenture that relate to modifying or amending the indenture.

**SATISFACTION AND DISCHARGE; DEFEASANCE**

We may be discharged from our obligations on the debt securities of any series that have matured or will mature or be redeemed within one year if we deposit with the trustee enough cash to pay all the principal, interest and any premium due to the stated maturity date or redemption date of the debt securities.

Each indenture contains a provision that permits us to elect:

- ∅ to be discharged from all of our obligations, subject to limited exceptions, with respect to any series of debt securities then outstanding; and/or
- ∅ to be released from our obligations under the following covenants and from the consequences of an event of default resulting from a breach of these covenants:
  - (1) the subordination provisions under the subordinated indenture; and
  - (2) covenants as to payment of taxes and maintenance of corporate existence.

To make either of the above elections, we must deposit in trust with the trustee enough money to pay in full the principal, interest and premium on the debt securities. This amount may be made in cash and/or U.S. government obligations. As a condition to either of the above elections, we must deliver to the trustee an opinion of counsel that the holders of the debt securities will not recognize income, gain or loss for Federal income tax purposes as a result of the action.

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If any of the above events occurs, the holders of the debt securities of the series will not be entitled to the benefits of the indenture, except for the rights of holders to receive payments on debt securities or the registration of transfer and exchange of debt securities and replacement of lost, stolen or mutilated debt securities.

### **NOTICES**

Notices to holders will be given by mail to the addresses of the holders in the security register.

### **GOVERNING LAW**

The indentures and the debt securities will be governed by, and construed under, the law of the State of New York.

### **REGARDING THE TRUSTEE**

The indenture limits the right of the trustee, should it become a creditor of us, to obtain payment of claims or secure its claims.

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**Table of Contents**

**Description of debt securities**

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The trustee is permitted to engage in certain other transactions. However, if the trustee, acquires any conflicting interest, and there is a default under the debt securities of any series for which they are trustee, the trustee must eliminate the conflict or resign.

**SUBORDINATED DEBT SECURITIES**

Payment on the subordinated debt securities will, to the extent provided in the indenture, be subordinated in right of payment to the prior payment in full of all of our senior indebtedness. The subordinated debt securities also are effectively subordinated to all debt and other liabilities, including trade payables and lease obligations, if any, of our subsidiaries.

Upon any distribution of our assets upon any dissolution, winding up, liquidation or reorganization, the payment of the principal of and interest on the subordinated debt securities will be subordinated in right of payment to the prior payment in full in cash or other payment satisfactory to the holders of senior indebtedness of all senior indebtedness. In the event of any acceleration of the subordinated debt securities because of an event of default, the holders of any senior indebtedness would be entitled to payment in full in cash or other payment satisfactory to such holders of all senior indebtedness obligations before the holders of the subordinated debt securities are entitled to receive any payment or distribution. The indenture requires us or the trustee to promptly notify holders of designated senior indebtedness if payment of the subordinated debt securities is accelerated because of an event of default.

We may not make any payment on the subordinated debt securities, including upon redemption at the option of the holder of any subordinated debt securities or at our option, if:

- Ø a default in the payment of the principal, premium, if any, interest, rent or other obligations in respect of designated senior indebtedness occurs and is continuing beyond any applicable period of grace (called a **payment default**); or
- Ø a default other than a payment default on any designated senior indebtedness occurs and is continuing that permits holders of designated senior indebtedness to accelerate its maturity, and the trustee receives notice of such default (called a **payment blockage notice**) from us or any other person permitted to give such notice under the indenture (called a **non-payment default**).

We may resume payments and distributions on the subordinated debt securities:

- Ø in the case of a payment default, upon the date on which such default is cured or waived or ceases to exist; and
- Ø in the case of a non-payment default, the earlier of the date on which such nonpayment default is cured or waived or ceases to exist and 179 days after the date on which the payment blockage notice is received by the trustee, if the maturity of the designated senior indebtedness has not been accelerated.

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No new period of payment blockage may be commenced pursuant to a payment blockage notice unless 365 days have elapsed since the initial effectiveness of the immediately prior payment blockage notice and all scheduled payments of principal, premium and interest, including any liquidated damages, on the notes that have come due have been paid in full in cash. No non-payment default that existed or was continuing on the date of delivery of any payment blockage notice shall be the basis for any later payment blockage notice unless the non-payment default is based upon facts or events arising after the date of delivery of such payment blockage notice.

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**Table of Contents**

**Description of debt securities**

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If the trustee or any holder of the notes receives any payment or distribution of our assets in contravention of the subordination provisions on the subordinated debt securities before all senior indebtedness is paid in full in cash, property or securities, including by way of set-off, or other payment satisfactory to holders of senior indebtedness, then such payment or distribution will be held in trust for the benefit of holders of senior indebtedness or their representatives to the extent necessary to make payment in full in cash or payment satisfactory to the holders of senior indebtedness of all unpaid senior indebtedness.

In the event of our bankruptcy, dissolution or reorganization, holders of senior indebtedness may receive more, ratably, and holders of the subordinated debt securities may receive less, ratably, than our other creditors (including our trade creditors). This subordination will not prevent the occurrence of any event of default under the indenture.

As of September 30, 2003, \$8.2 million senior indebtedness was outstanding. We are not prohibited from incurring debt, including senior indebtedness, under the indenture. We may from time to time incur additional debt, including senior indebtedness.

We are obligated to pay reasonable compensation to the trustee and to indemnify the trustee against certain losses, liabilities or expenses incurred by the trustee in connection with its duties relating to the subordinated debt securities. The trustee's claims for these payments will generally be senior to those of noteholders in respect of all funds collected or held by the trustee.

**CERTAIN DEFINITIONS**

indebtedness means:

- (1) all indebtedness, obligations and other liabilities for borrowed money, including overdrafts, foreign exchange contracts, currency exchange agreements, interest rate protection agreements, and any loans or advances from banks, or evidenced by bonds, debentures, notes or similar instruments, other than any account payable or other accrued current liability or obligation incurred in the ordinary course of business in connection with the obtaining of materials or services;
- (2) all reimbursement obligations and other liabilities with respect to letters of credit, bank guarantees or bankers' acceptances;
- (3) all obligations and liabilities in respect of leases required in conformity with generally accepted accounting principles to be accounted for as capitalized lease obligations on our balance sheet;
- (4) all obligations and other liabilities under any lease or related document in connection with the lease of real property which provides that we are contractually obligated to purchase or cause a third party to purchase the leased pr