

NUVELO INC
Form 424B3
January 24, 2006
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Filed Pursuant to Rule 424(b)(3)
Registration No. 333-126591

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

Subject to completion, dated January 24, 2006

Prospectus supplement

(to prospectus dated August 3, 2005)

5,500,000 shares

Common stock

We are selling 5,500,000 shares of our common stock.

Our common stock is quoted on The Nasdaq National Market under the symbol NUVO. On January 20, 2006, the last reported sale price for our common stock was \$15.57 per share.

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

We have granted the underwriters an option for a period of 30 days to purchase up to 825,000 shares to cover over-allotments, if any.

Investing in our common stock involves certain risks. See **Risk factors** beginning on page S-15 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.

JPMorgan

Deutsche Bank Securities

Lehman Brothers

, 2006

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Prospectus supplement

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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 our registered trade and service mark. All other trademarks, service marks and trade names referred to in this prospectus supplement or the accompanying prospectus are the property of their respective owners.

This prospectus supplement and the accompanying prospectus are part of a universal shelf registration statement on Form S-3 that we filed with the Securities and Exchange Commission, or the SEC. Under the shelf registration process, we may sell any combination of debt securities, preferred stock and common stock in one or more offerings from time to time up to a total dollar amount of \$100,000,000, of which this offering is a part. In the accompanying prospectus, we provide you a general description of the securities we may offer from time to time under our shelf registration statement. This prospectus supplement describes the specific details regarding this offering, including the price, the amount of common stock being offered and the risks of investing in our common stock.

This prospectus supplement, the accompanying prospectus and the documents incorporated by reference herein and therein include important information about us, our common stock being offered and other information you should know before investing. To the extent information in this prospectus supplement is inconsistent with the accompanying prospectus or any of the documents incorporated by reference herein and therein, you should rely on this prospectus supplement. You should read both this prospectus supplement and the accompanying prospectus, together with the additional information about us described in the sections entitled *Where you can find more information* and *Incorporation by reference*. In addition, you should carefully consider the facts set forth under *Risk factors* beginning on page S-15 of this prospectus supplement and in the reports incorporated by reference herein before making an investment decision to purchase shares of our common stock.

You should rely only on the information contained or incorporated by reference in this prospectus supplement and the accompanying prospectus or that is contained in any free writing prospectus we may authorize to be delivered to you. We have not, and the underwriters 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 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, regardless of the time of delivery of this prospectus supplement and the accompanying prospectus or of any sale of our common stock. Unless the context otherwise requires, references to *we* or *the company* in this prospectus supplement and the accompanying prospectus mean Nuvelo, Inc. and its subsidiaries.

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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 dedicated to improving the lives of patients through the discovery, development and commercialization of novel acute cardiovascular and cancer therapies.

Our development pipeline includes three acute cardiovascular programs focused on alfimeprase, rNAPc2 and a thrombin inhibiting aptamer, as well as an emerging oncology pipeline.

Our lead cardiovascular development program is for alfimeprase, a novel, direct-acting thrombolytic agent, or blood clot dissolver, that is currently in Phase 3 clinical trials for the treatment of acute peripheral arterial occlusion, or PAO, and for the treatment of catheter occlusion. We also intend to expand this development program by initiating a Phase 2 clinical trial in the second half of 2006 to evaluate the potential of alfimeprase for the treatment of ischemic stroke and another Phase 2 clinical trial in 2007 to evaluate the potential of alfimeprase to treat deep venous thrombosis, or DVT. As provided in the collaboration and license agreement that we entered into on January 4, 2006, we granted Bayer HealthCare AG the right to commercialize alfimeprase outside the United States, while retaining the right to commercialize alfimeprase in the United States.

Our second cardiovascular development program is for recombinant nematode anticoagulant protein c2, or rNAPc2, an anticoagulant that inhibits the factor VIIa and tissue factor protease complex, which is responsible for initiating the blood clotting process. We recently completed a Phase 2a clinical trial with rNAPc2 in acute coronary syndrome, or ACS, and are currently enrolling patients in a subsequent Phase 2 trial intended to evaluate its potential use as a replacement for heparin, an anticoagulant, in patients with ACS.

Our third cardiovascular development program is in the preclinical stage and is focused on identifying an optimized thrombin inhibiting aptamer for potential use as a rapid-on/rapid-off anticoagulant for patients undergoing acute cardiovascular procedures, such as coronary artery bypass graft, or CABG, surgery.

In addition to these programs, we have an emerging oncology development pipeline. We are progressing a potent gastrointestinal epithelial growth factor, NU206, as a preclinical development candidate for the potential treatment of mucositis, which is a side effect of chemotherapy and radiation therapies received by cancer patients. NU206 is targeted to enter Phase 1 clinical development in the second half of 2006. We are also investigating the potential of rNAPc2 as a cancer therapy based on its apparent role in the cellular signaling of both metastasis and angiogenesis in a variety of cancers.

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Finally, we have a drug discovery effort focused on two research programs: the first investigating secreted proteins and the second investigating antibodies against cell surface proteins as potential cancer targets. Through these programs, we plan to further expand our pipeline and create additional partnering and licensing opportunities.

As of December 31, 2005, our cash, cash equivalents and short-term investments totaled approximately \$70.3 million. In addition, in January 2006, following our entry into the alfimeprase collaboration and license agreement with Bayer, we received a \$50.0 million up-front cash payment from Bayer. We expect that our operating expenses will increase significantly in 2006 as we intensify our alfimeprase Phase 3 clinical trial activity, increase expenditures under our alfimeprase manufacturing agreement with Avecia Ltd. and incur additional general corporate expenses. We expect our alfimeprase-related expenses will be offset to a substantial extent by cost-sharing and milestone payments that we expect to receive from Bayer.

Product pipeline

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

Products in development

Alfimeprase

Our lead product candidate, alfimeprase, is a thrombolytic agent with a novel mechanism of action. It is a modified and recombinant version of fibrolyase, a naturally occurring enzyme that directly and rapidly degrades fibrin, the protein that provides the structural scaffold of blood clots. Thrombolytics currently on the market, such as alteplase (Activase), are plasminogen activators that work by activating plasminogen to form plasmin, which in turn degrades fibrin. In contrast, alfimeprase directly degrades fibrin, creating the potential for more rapid clot dissolution, or lysis. Alfimeprase is locally delivered at the site of the blood clot and is inactivated quickly by alpha-2 macroglobulin, a naturally occurring protein in the bloodstream. We believe

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this clearance mechanism limits the systemic activity of alteplase and implies that patients may experience fewer of the bleeding side effects associated with plasminogen activators.

Alteplase in acute peripheral arterial occlusion

The lead medical indication we are pursuing for alteplase is acute PAO. Acute PAO is a significant cause of morbidity in the United States, with estimates of over 100,000 cases reported annually. Acute PAO occurs when arterial blood flow is blocked to a distant part of the body, usually the leg, by a blood clot. Traditionally, surgical approaches have been used to treat acute PAO. However, thrombolytic agents such as Activase have been used as a less-invasive alternative, even though they have not been approved by the FDA to treat acute PAO. Studies have shown that current thrombolytic therapies can take 24 to 36 hours or more to restore flow to the blocked limb, with five to 16 percent of patients experiencing a major bleed and one to two percent of patients experiencing intracerebral hemorrhage. We believe alteplase has the potential to be a more effective agent than existing agents for use in treating acute PAO by reducing treatment time and the potential for bleeding side effects.

We completed our Phase 2 clinical trial in patients with acute PAO in the second quarter of 2004. This trial was an open label, dose-escalation study evaluating the safety and activity of alteplase. The trial enrolled 113 patients in multiple centers in the United States, Europe, Russia and other locations. The Phase 2 results indicate that alteplase has the potential to offer significant advances in the rapid resolution of a blood clot while minimizing potentially fatal side effects such as intracerebral hemorrhage and other bleeding complications. Analysis of the Phase 2 results showed that alteplase has the potential to partially or completely break up blood clots within four hours of initiation of dosing with rates of up to 76 percent and to restore arterial flow with rates of up to 60 percent. Up to 69 percent of study patients were able to avoid open vascular surgical intervention in the 30 days following treatment with alteplase. Among the 113 patients enrolled, there were no intracerebral hemorrhages or deaths at 30 days. There were seven major bleeding events reported, none of which were categorized as systemic bleeding events and only one of which was categorized by the investigator as possibly related to alteplase. Incidents of transient hypotension were also reported and were dose-related. Events associated with distal embolism were also noted. We do not believe that these events were more significant in number or severity than similar events associated with other therapies delivered by catheter to blood clots.

In April 2005, we commenced the first of two clinical trials in the alteplase Phase 3 acute PAO program, known as NAPA, or Novel Arterial Perfusion with Alteplase. This program consists of two overlapping trials that will include a total of 600 patients between the two trials. The first trial in this program, NAPA-2, is a randomized, double-blind study comparing 0.3 mg/kg of alteplase versus placebo in 300 patients. The trial is being conducted in over 100 centers worldwide. The study's primary endpoint is avoidance of open vascular surgery within 30 days of treatment. Open vascular surgery includes procedures such as surgical embolectomy, peripheral arterial bypass graft surgery and amputation, but does not include catheter-based procedures such as percutaneous angioplasty or stenting. A variety of secondary endpoints are also being evaluated, including safety endpoints such as the incidence of bleeding, as well as pharmacoeconomic endpoints such as length of hospital and intensive care unit stay. We expect to complete enrollment in the NAPA-2 trial in the second half of 2006.

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The second Phase 3 trial, NAPA-3, is the subject of a special protocol assessment, or SPA, agreement with the U.S. Food and Drug Administration, or FDA, and will essentially replicate the NAPA-2 trial. Under an SPA, the FDA provides guidance on the design of a trial prior to its initiation. We expect to begin enrollment in the NAPA-3 trial in early 2006.

We have been granted fast track designation by the FDA for alfimeprase in acute PAO. Fast track designation can potentially facilitate development and expedite review of biologics license applications. Fast track designation is reserved for new drugs that demonstrate the potential to address an unmet medical need and are intended for treatment of a serious or life-threatening condition. In addition, we have obtained orphan drug status for alfimeprase in the United States and Europe for the treatment of acute PAO, which may provide us with up to seven and ten years of market exclusivity in the United States and Europe, respectively, following market authorization.

Alfimeprase in catheter occlusion

We are also in late-stage clinical development for alfimeprase in catheter occlusion. Catheter occlusion is the obstruction of blood flow through a central venous catheter. It is estimated that about five million catheters are implanted in patients each year in the United States, and approximately 25 percent become occluded. Current treatment for catheter occlusion includes removal and replacement of the catheter, or treatment with alteplase (Cathflo Activase). Based on clinical trial evidence of alfimeprase's activity, we believe alfimeprase has the potential to restore flow to occluded catheters more rapidly than Cathflo Activase.

In the third quarter of 2004, we completed patient enrollment in a Phase 2 multi-center, double-blind, randomized study in 55 patients with occluded central venous catheters comparing three doses (0.3 mg, 1.0 mg and 3.0 mg) of alfimeprase against the approved dose of Cathflo Activase (2.0 mg). The alfimeprase 3.0 mg dose produced cumulative flow rates of 40 percent at five minutes after the first dose, 50 percent at 15 minutes after the first dose, 60 percent at 30 minutes and 120 minutes after the first dose, and 80 percent at 120 minutes after the second dose. This is compared to Cathflo Activase, which produced flow rates of zero percent at five minutes after the first dose, zero percent at 15 minutes after the first dose, 23 percent at 30 minutes after the first dose, 46 percent at 120 minutes after the first dose, and 62 percent at 120 minutes after the second dose. No major hemorrhagic events were reported in any treated patients and only one patient had a catheter-related infection.

In September 2005, we commenced the first of two multi-national trials in the alfimeprase Phase 3 catheter occlusion program, known as SONOMA, or Speedy Opening of Non-functional and Occluded catheters with Mini-dose Alfimeprase. The first trial is an efficacy study called SONOMA-2, which is a randomized, double-blind trial, comparing 3.0 mg of alfimeprase with placebo in 300 patients with occluded central venous catheters. Two-thirds of the patients will receive alfimeprase and the remainder will receive placebo. The study's primary endpoint is restoration of function to occluded central venous catheters at 15 minutes. We expect to complete enrollment in the SONOMA-2 trial in the second half of 2006.

The second study, known as SONOMA-3, will be an open label, single-arm trial evaluating alfimeprase in 800 patients. This study's primary endpoint is safety, although we will be evaluating efficacy in these patients as well. We expect to begin enrolling patients in this trial in the first half of 2006.

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Alfimeprase in stroke

In January 2006, we announced our intention to expand the alfimeprase development program and initiate a Phase 2 clinical trial in the second half of 2006 to study the potential of alfimeprase to treat patients with ischemic stroke. Each year, approximately 650,000 patients suffering from stroke are admitted into hospitals in the United States. Some of these patients have hemorrhagic strokes, which are characterized by the rupture of blood vessels in the brain and usually result in death. The large majority of stroke patients suffer from ischemic strokes, which are characterized by blood clots that prevent the flow of blood to the brain, thereby depriving the brain of oxygen. Depending on the location and severity of the blood clot, the most common consequence of ischemic stroke is loss of function, including paralysis.

Currently, the therapeutic options for patients with ischemic stroke are limited. Activase has been approved in the United States for treatment of ischemic stroke. Its use has been limited, however, by the requirement that patients receive it within three hours of onset of the stroke and by the increased bleeding risk associated with its use. We believe that alfimeprase has the potential to expand the treatment window for ischemic strokes due to its rapid and direct mechanism of action and its potential safety profile.

Alfimeprase in deep venous thrombosis

In January 2006, we also announced our intention to initiate a Phase 2 clinical program in 2007 to evaluate the potential of alfimeprase to treat patients suffering from DVT. Each year, approximately 300,000 patients are diagnosed with DVT in the United States. DVT is characterized by blood clots in the venous system of peripheral limbs, typically the legs. The consequences of DVT include pain and swelling of the affected limb and, in relatively rare circumstances, pulmonary embolism which can result in death.

Currently, very few DVT patients receive thrombolytics. DVT is rarely a life-threatening condition and, therefore, doctors are typically reluctant to administer thrombolytics, which expose DVT patients to significant bleeding risk. As a result, DVT patients generally receive anticoagulants intended to prevent further propagation of the blood clot and are told to limit activity until the blood clot resolves, often over a period of months. We believe alfimeprase has the potential to treat this patient population with a reduced bleeding risk because of its unique mechanism of action and its potential safety profile.

Alfimeprase license and collaboration agreements

In January 2006, we entered into a license and collaboration agreement with Bayer for the global development and commercialization of alfimeprase. Under this agreement, Bayer will commercialize alfimeprase in all territories outside the United States and will pay us tiered royalties ranging from a minimum of 15 percent to a maximum of 37.5 percent. We retain all commercialization rights and profits from alfimeprase sales in the United States. We are eligible to receive up to \$385.0 million in milestone payments from Bayer, including a \$50.0 million up-front cash payment that we have already received, up to \$165.0 million in development milestones and \$170.0 million in sales and commercialization milestones over the course of the agreement. In addition, Bayer will be responsible for 40 percent of the costs for global development programs. We will be responsible for 60 percent of the costs and will remain the lead for the design and conduct of the global development programs. Each party will bear its

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own expenses for any country-specific alfimeprase clinical trials it conducts, where the country-specific clinical trials are not part of the agreed global development program.

In October 2004, we obtained worldwide rights to develop and commercialize alfimeprase from Amgen, Inc. in exchange for the payment to Amgen of previously negotiated milestone payments and royalties. Future milestone payments under the license agreement could total as much as \$35.0 million, although we currently cannot predict if or when any of these additional milestones will be achieved. Under our agreement with Bayer, we will continue to bear sole responsibility for these milestone payments and royalties owed to Amgen.

In June 2005, we entered into a development and validation agreement with Avecia for the scaled-up manufacturing process of alfimeprase. Under this agreement, Avecia will conduct process development and process validation work for the manufacture of alfimeprase, in accordance with FDA regulations. We are obligated to pay Avecia fees totaling £10.0 million for completion of this work, payable upon completion by Avecia of pre-negotiated milestones, of which £7.5 million had yet to be paid as of September 30, 2005. In December 2005, we amended the work program under our agreement with Avecia to provide that Avecia will conduct additional process development and process validation work in exchange for our payment of an additional £2.9 million.

rNAPc2

Our second drug candidate, rNAPc2, is a recombinant version of a naturally occurring protein that has anticoagulant properties. Specifically, rNAPc2 has been shown to block the factor VIIa and tissue factor protease complex, which is responsible for the initiation of the process leading to blood clot formation and has also been shown to play a role in both metastasis, or the secondary growth of cancer cells, and angiogenesis, or the formation of new blood vessels, as they relate to tumor growth. 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 cascade. By blocking the coagulation cascade before amplification of the coagulation process, rNAPc2 could prove to be more effective in treating patients with conditions such as ACS, or as a prophylactic against clot formation in conditions such as DVT. In addition, the novel mechanism of action of rNAPc2 offers the potential to have therapeutic utility in cancer.

ACS occurs when an atherosclerotic plaque ruptures in a coronary artery, which triggers the coagulation cascade and results 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, if severe, permanent heart muscle death. In the United States, ACS accounts for approximately 1.4 million hospital admissions annually. Patients with ACS are traditionally given aspirin and heparin, among other agents, to stabilize their medical condition. Recent guidelines also recommend the addition of the antiplatelet agent clopidogrel (Plavix) to the standard of 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 need for improved antithrombotic therapies.

rNAPc2, given alone or with standard therapy, may reduce the risk of subsequent heart attack or death in patients suffering from ACS. Unlike aspirin, heparin, and other 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,

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therefore, enable a multi-pronged attack at several points along the blood coagulation process. Alternatively, by stopping coagulation at the outset, rNAPc2 could also prove effective as a stand-alone therapy.

We licensed the worldwide rights for all indications of rNAPc2 and all of the rNAPc molecules owned by Dendreon Corporation in February 2004. The United States government may claim a non-exclusive right to use rNAPc2 with respect to the treatment of hemorrhagic fever. To date, rNAPc2 has been shown to be well tolerated in over 650 patients and healthy volunteers in several Phase 1 and 2 clinical studies.

In May 2005, we completed a Phase 2a double-blind, placebo-controlled clinical trial showing that rNAPc2 has an acceptable safety profile and is well tolerated in doses up to ten micrograms/kg in patients being treated for ACS, including unstable angina and non-ST segment elevation myocardial infarction. Results showed that treatment with rNAPc2, in addition to standard antithrombotic therapies in patients with ACS, resulted in a dose-related inhibition of thrombin generation without an increase in clinically significant bleeding. The difference in TIMI major or minor bleed rate was not statistically significant between the two treatment groups (4.3 percent in patients treated with rNAPc2 versus 2.5 percent in those treated with placebo). In addition, rNAPc2 suppressed prothrombin fragments one and two and prolonged the prothrombin time, both in a dose-related fashion.

Based on the encouraging safety results from the Phase 2a trial, we initiated a Phase 2 heparin-replacement trial with rNAPc2 in August 2005. The Phase 2 study is an open label study that is evaluating the efficacy and safety of rNAPc2 by reducing the dose of, and ultimately replacing, unfractionated heparin in patients being treated for ACS. The study will include 50 to 100 patients and is being conducted in approximately 25 centers across the United States and Canada. This trial is expected to complete enrollment in the first half of 2006.

In addition, we are planning to investigate the potential of rNAPc2 as a cancer therapy. The factor VIIa and tissue factor protease complex, which rNAPc2 inhibits, has been shown to play a role in the cellular signaling of both metastasis and angiogenesis in a variety of cancers. As an inhibitor of these processes, which are critical to the progression of a number of cancer types, rNAPc2 may have potential as a therapy for these cancers.

Thrombin inhibiting aptamer

We continue to pursue the development of a thrombin inhibiting aptamer under a collaboration agreement entered into with Archemix Corporation, a privately held biotechnology company located in Cambridge, Massachusetts, in January 2004. In September 2005, we concluded a Phase 1 clinical study for the first target molecule from this program, ARC183. This study evaluated the safety, tolerability, anticoagulation activity and titratability of ARC183 for potential use in acute cardiovascular settings such as CABG surgery. Preliminary results from the trial showed that administration of ARC183 resulted in a rapid onset of anticoagulation and demonstrated stable, dose-related anticoagulation activity and rapid self-reversal of drug effects after administration of the drug infusion ceased. However, the amount of drug needed to achieve the desired anticoagulation for use in CABG surgery resulted in a sub-optimal dosing profile. For that reason, we decided jointly with Archemix not to pursue further development of ARC183 and instead are pursuing an optimized thrombin inhibiting aptamer.

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Under the terms of our agreement, we paid Archemix an upfront fee of \$3.0 million and paid all of the first \$4.0 million of costs associated with development and commercialization. We and Archemix will equally share all such costs in excess of \$4.0 million. We incurred \$7.7 million in expenses for the upfront fee and related development costs in 2004 and \$2.3 million for related development costs in the first nine months of 2005. Archemix is initially responsible for leading development and for all clinical development activities through the dosing of the first patient in a Phase 2 study. Thereafter, we and Archemix will agree on leadership of clinical development and commercialization activities. We are required to pay Archemix total development milestone payments of up to \$11.0 million, including \$10.0 million upon dosing of the first patient in a Phase 2 trial and \$1.0 million upon the designation of any backup compound selected by both Archemix and us for IND-enabling studies. We currently cannot predict if or when any of these milestones will be achieved.

NU206

We expect to initiate a Phase 1 clinical program with NU206 in the second half of 2006. We plan to initially pursue NU206 as a supportive cancer therapy, specifically to treat radiation and chemotherapy-induced mucositis in the gastrointestinal tract. Research to date indicates that NU206 acts as a highly specific and potent stimulator of gastrointestinal epithelial cells. In addition, NU206 appears to be highly active in multiple animal models of gastrointestinal disease that could support clinical testing in additional indications.

In March 2005, we entered into a collaboration agreement with the Pharmaceutical Division of Kirin Brewery Company, Ltd., for the development and commercialization of NU206. Under this agreement, we received a \$2.0 million upfront cash payment from Kirin in April 2005, and we will lead worldwide development, manufacturing and commercialization of the compound. All operating expenses and profits related to the development and commercialization of NU206 will be shared 60 percent by us and 40 percent by Kirin. If this agreement is terminated, or Kirin or we elect under certain circumstances to no longer actively participate in the collaboration, the relationship with respect to NU206 will convert from an expense and profit-sharing structure to a royalty-based structure.

Research programs

In addition to our clinical and development stage drug candidates, we have two ongoing drug discovery programs focused on the identification of novel human genes that encode proteins with therapeutic potential: the first program is focused on secreted proteins and the second on cancer antibody targets. Over the long-term, we intend to develop additional product opportunities from our ongoing discovery efforts. In addition to the development of internal therapeutic candidates, we intend to leverage these discoveries to create revenue-generating licensing and partnering arrangements.

The secreted protein program included a research program with Kirin and includes our internal discovery program. Our 2001 collaboration agreement with Kirin for the research and development of secreted proteins expired December 31, 2005, in accordance with its terms. We and Kirin are currently discussing the possibility of extending the term of this collaborative program, as we have previously. We and Kirin have already advanced several secreted protein candidates to more extensive studies to better define their therapeutic utility based upon early

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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.

The cancer 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.

Our strategy

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

Successfully develop and commercialize our lead drug candidate, alfimeprase. We are seeking to develop and commercialize our lead drug candidate, alfimeprase, for the treatment of acute PAO, catheter occlusion, and a variety of other thrombotic conditions, including stroke and DVT. As part of this strategy, in 2005 we initiated two pivotal Phase 3 clinical programs in acute PAO and in catheter occlusion. We have exclusive rights to this compound in the United States and in 2006 we entered into a significant development and collaboration agreement with Bayer for the development and commercialization of alfimeprase outside the United States.

Commercialize our hospital-based products in the United States. Rather than license other companies to commercialize our products in the United States, we plan to sell them ourselves through our own hospital-based sales force. We believe that the resources required to develop a sales and marketing organization to sell products to hospitals is manageable for a company of our size, and will allow us to capture more value from our clinical development successes. In 2005, we began to hire a marketing organization, which we plan to expand in 2006. Our marketing organization is currently performing market research and planning for the anticipated launch of alfimeprase.

Leverage our expertise in cardiovascular disease and oncology to advance our clinical development programs. We are primarily focused on the development of acute, hospital-based, cardiovascular drug candidates and oncology drug candidates. We believe this portfolio leverages our expertise in cardiovascular and oncology drug development, enabling us to pursue a more rapid path toward drug commercialization.

Build a diversified pipeline of product candidates. We are pursuing several drug development candidates in various stages of clinical and preclinical development. In addition, we seek to identify drug development candidates that have the potential to receive regulatory approval to treat a number of different indications, thereby further diversifying our risk by providing each drug candidate with a number of potential commercialization paths. We believe this strategy reduces our exposure to the impact of any single product failure, maximizes our potential returns from successful compounds, and increases our flexibility to eliminate programs we deem less promising. By broadening our portfolio across indications and products, we intend to increase the probability of clinical and commercial success. In addition, we focus on molecules that we believe have a greater chance of success due to the predictability of preclinical models used in their development.

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

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. On March 25, 2004, we reincorporated from Nevada to Delaware. Our principal executive offices are located at 201 Industrial Road, Suite 310, San Carlos, California 94070 and our telephone number is (650) 517-8000. Our world wide web address is <http://www.nuvelo.com>. We have not incorporated by reference into this prospectus supplement or the accompanying prospectus the information contained on our website and you should not consider it to be part of this prospectus supplement or the accompanying prospectus.

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The offering

Common stock we are offering	5,500,000 shares
Common stock to be outstanding after this offering	47,763,782 shares
Use of proceeds	We estimate the net proceeds to us from this offering will be approximately \$80.0 million, based on an assumed public offering price of \$15.57, after payment of underwriting discounts and commissions and estimated expenses of this offering, or approximately \$92.1 million if the underwriters exercise their over-allotment option in full. We intend to use the net proceeds to us from this offering for general corporate purposes, including the advancement of our drug candidates in clinical trials, the development of a commercialization infrastructure, capital expenditures and to meet working capital needs. In addition, if we raise more than \$75.0 million in cash as a result of this offering, we must pay The Irvine Company the lesser of (i) ten percent of any amount raised in excess of \$75.0 million or (ii) any remaining deferred rent obligation that we have to The Irvine Company. See Use of proceeds.
Nasdaq National Market Symbol	NUVO
Risk factors	See Risk factors beginning on page S-15 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 immediately after the closing of this offering is based on 42,263,782 shares of our common stock outstanding as of September 30, 2005, but excludes:

an aggregate of 6,224,029 shares of our common stock issuable upon exercise of stock options outstanding as of September 30, 2005, granted under our 2004 Equity Incentive Plan, 2002 Equity Incentive Plan, 1995 Stock Option Plan, Non-Employee Director Stock Option Plan and Scientific Advisory Board/Consultants Stock Option Plan, and as of September 30, 2005, an aggregate of 823,539 shares of common stock issuable upon the exercise of stock options granted outside of any of our stock option plans, with exercise prices of all outstanding options ranging from \$2.34 to \$304.31 per share and a weighted average exercise price of \$15.17 per share;

an aggregate of 1,195,006 shares of common stock reserved for issuance pursuant to future award grants under our 2004 Equity Incentive Plan, based on options outstanding as of September 30, 2005;

an aggregate of 259,470 shares of common stock issuable under our Employee Stock Purchase Plan as of September 30, 2005;

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an aggregate of 1,797,273 shares of our common stock issuable upon the exercise of warrants, with exercise prices ranging from \$4.05 to \$24.87 per share and a weighted average exercise price of \$19.12 per share, outstanding as of September 30, 2005;

\$5.2 million of our common stock issuable at our option, to repay our convertible promissory note held by Affymetrix, Inc., including accrued interest as of September 30, 2005, at a conversion price based on 90 percent of the average price of our common stock over a ten-day period ending two days prior to conversion;

\$7.5 million of our common stock issuable upon mutual agreement, to convert the remaining amount due on the promissory note under our line of credit with Dr. George Rathmann, including accrued interest, as of September 30, 2005, at a conversion price equal to the average price of our common stock over a 20-day period, ending two days prior to conversion, or, if in connection with an equity financing, at the offering price; and

up to \$75.0 million of our common stock salable to Kingsbridge Capital Limited as of September 30, 2005, pursuant to the committed equity financing facility we entered into with Kingsbridge on August 4, 2005. Under this facility, we sold 653,103 shares for gross proceeds of \$5.0 million in November 2005 and 1,186,297 shares for gross proceeds of \$9.4 million in December 2005.

Unless otherwise stated, all information contained in this prospectus supplement assumes that the underwriters do not exercise their over-allotment option to purchase up to an additional 825,000 shares of common stock and all currency amounts are in United States 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, 2002 through December 31, 2004 are derived from our audited consolidated financial statements for those periods. The summary data for the nine-month periods ended September 30, 2004 and September 30, 2005 is derived from our unaudited condensed 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 filings, you should read the section of this prospectus supplement entitled "Incorporation by reference" beginning on page S-55. 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 5,500,000 shares of our common stock in this offering, at an assumed offering price of \$15.57 after deducting the underwriting discounts and commissions and estimated offering expenses payable by us.

Consolidated statement of operations data: (in thousands, except per share data)	Year ended December 31,			Nine months ended September 30,	
	2002	2003	2004	2004 (unaudited)	2005 (unaudited)
Contract revenues	\$ 25,554	\$ 1,024	\$ 195	\$ 152	\$ 362
Loss from continuing operations	(39,512)	(46,229)	(48,942)	(38,105)	(50,128)
Loss from discontinued operations, including loss on disposal	(5,466)	(3,958)	(3,547)	(1,402)	
Net loss	\$ (44,978)	\$ (50,187)	\$ (52,489)	\$ (39,507)	\$ (50,128)
Basic and diluted net loss per share:					
Continuing operations	(5.48)	(2.19)	(1.59)	(1.25)	(1.23)
Discontinued operations	(0.76)	(0.18)	(0.11)	(0.05)	
Total basic and diluted net loss per share	\$ (6.24)	\$ (2.37)	\$ (1.70)	\$ (1.30)	\$ (1.23)
Shares used in computation of basic and diluted net loss per share	7,220	21,054	30,874	30,427	40,727

Consolidated balance sheet data:	September 30, 2005	
	Actual	As adjusted(1)
Cash, cash equivalents and short-term investments	\$ 75,530	\$ 155,527
Working capital	51,480	131,477
Total assets	112,559	192,556
Current portion of debt obligations, excluding accrued interest	4,300	4,300
Non-current portion of debt obligations	8,871	8,871

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Accumulated deficit	(306,176)	(306,176)
Total stockholders' equity	64,047	144,044

- (1) A \$1.00 increase (decrease) in the assumed public offering price of \$15.57 per share would increase (decrease) each of cash, cash equivalents and short-term investments, working capital, total assets and total stockholders' equity by \$5.2 million,

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assuming that the number of shares offered by us, as set forth on the cover page of this prospectus supplement, remains the same, and after deducting the estimated underwriting discounts and commissions and estimated offering expenses payable by us. We may also increase or decrease the number of shares we are offering. An increase of 1.5 million shares in the number of shares offered by us, to a total of 7.0 million shares, together with a concomitant \$1.00 increase in the assumed offering price of \$15.57 per share, would increase each of cash, cash equivalents and short-term investments, working capital, total assets and total stockholders' equity by \$28.5 million. Similarly, a decrease of 1.5 million shares in the number of shares offered by us, to a total of 4.0 million shares, together with a concomitant \$1.00 decrease in the assumed offering price of \$15.57 per share, would decrease each of cash, cash equivalents and short-term investments, working capital, total assets and total stockholders' equity by \$25.7 million. The pro forma information discussed above is illustrative only and will be adjusted based on the actual public offering price and other terms of this offering determined at pricing.

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Risk factors

Investing 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 deciding to invest in our common stock. If any of the following risks actually occur, they may materially harm our business, financial condition, operating results and cash flow. As a result, the market price of our common stock could decline, and you could lose all or part of your investment. 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.

Risks related to our business

Our near-term success is dependent on the success of our lead product candidate, alfimeprase, and we cannot be certain that it will receive regulatory approval or be successfully commercialized.

Alfimeprase is currently being evaluated in two Phase 3 clinical trials for the treatment of acute PAO and catheter occlusion and will require the successful completion of these or other planned Phase 3 clinical trials before we are able to submit a biologics license application, or BLA, to the FDA for approval. If our Phase 3 or other clinical trials fail to demonstrate that alfimeprase is safe and effective, it will not receive regulatory approval. Even if alfimeprase receives FDA approval, it may never be successfully commercialized. We may also have inadequate financial or other resources to pursue this product candidate through the clinical trial process or through commercialization. In addition, prior to initiating our current Phase 3 trials for alfimeprase, we had never conducted a Phase 3 clinical trial, and we may be unable to successfully complete clinical trials involving the number of clinical sites and patients as planned for our alfimeprase Phase 3 clinical trials. If we are unable to successfully commercialize or obtain regulatory approval for alfimeprase, we may not be able to generate revenue, become profitable or continue our operations. Our second Phase 3 trial of alfimeprase, NAPA-3, is the subject of a special protocol assessment agreement with the FDA. Under this agreement, the FDA provides guidance on the design of a trial prior to its initiation. We have also been granted fast track designation by the FDA for alfimeprase in acute PAO. The special protocol assessment agreement and the fast track designation do not offer any assurance that alfimeprase will receive FDA approval, and the FDA is in no way constrained by the agreement or the designation in its ability to deny approval for alfimeprase.

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

We currently have two clinical stage drug candidates. All of our other potential products currently are in research or pre-clinical development, and revenues from the sales of any products may not occur for several years, if at all. We cannot be certain that any of our products will be demonstrated to be safe and effective or that we will obtain regulatory approvals for any indication. We cannot predict whether we will be able to develop and commercialize any of our drug candidates successfully. If we are unable to obtain regulatory approval and successfully commercialize our potential products, our business, results of operations and financial condition will be affected in a materially adverse manner.

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

We, and our collaborators, 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 current 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 and expensive processes with uncertain results. It will take us several years to complete our testing, and failure can occur at any stage of testing. To date, we have not successfully completed any Phase 3 clinical trials, and we have not completed all planned pre-clinical and Phase 1 clinical trials for each of our product candidates. The results we obtain in pre-clinical testing and early clinical 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. 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, and our business, results of operations and financial condition will be materially adversely affected.

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 and in foreign countries, including those for informed consent and good clinical practices. We may not be able to comply with these requirements and the FDA, a similar foreign authority, an IRB, or we may suspend or terminate clinical trials at any time.

Administering our drug candidates 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 market price of our common stock 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 or condition under investigation. We, or our collaborators, 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:

design of the protocol;

the size of the patient population;

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eligibility criteria for the study in question;

perceived risks and benefits of the drug under study;

availability of competing therapies;

efforts to facilitate timely enrollment in clinical trials;

the success of our personnel in making the arrangements with potential clinical trial sites necessary for those sites to begin enrolling patients;

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 or planned clinical trials, either of which would have a negative effect on our business. Delays in enrolling patients in our clinical trials would also adversely affect our ability to generate product, milestone and royalty revenues and could impose significant additional costs on us or on our collaborators.

We face heavy government regulation, and FDA and international 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. 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 the 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, regulations, and that the process for manufacturing the product has been validated in accordance with the requirements of the FDA and comparable agencies in other countries.

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 expended, regulatory approval is never guaranteed. The number of pre-clinical and clinical tests that will be required for FDA and international regulatory 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 or comparable international regulatory authorities can delay, limit or deny approval of a drug candidate for many reasons, including:

a drug candidate may not be safe or effective;

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the FDA or comparable international regulatory authorities may interpret data from pre-clinical and clinical testing in different ways than we and our collaboration partners interpret them;

the FDA or comparable international regulatory authorities may not approve our manufacturing processes or facilities or the processes or facilities of our collaboration partners; or

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the FDA or comparable international regulatory officials may change their approval policies or adopt new regulations.

In addition, in order to market any products outside of the United States, we and our collaborators must establish and comply with numerous and varying regulatory requirements of other jurisdictions, including the European Agency for the Evaluation of Medicinal Products, or the EMEA, regarding safety and efficacy. Approval procedures vary among countries and can involve additional product testing and additional administrative review periods. The time required to obtain approval in other countries differs from that required to obtain FDA approval. The regulatory approval process in other countries can include all of the risks detailed above regarding FDA approval in the United States as well as other risks. Regulatory approval in one country does not ensure regulatory approval in another, but a failure or delay in obtaining regulatory approval in one country may have a negative effect on the regulatory process in others. Failure to obtain regulatory approval in other countries or any delay or setback in obtaining such approval could have the same adverse effects detailed above regarding FDA approval in the United States.

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:

warning letters;

fines;

civil penalties;

injunctions;

recall or seizure of products;

total or partial suspension of production;

refusal of the government to grant approvals; or

withdrawal of approvals and criminal prosecution.

Any delay or failure by us, or our collaboration partners, to obtain regulatory approvals for our product candidates:

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

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

could diminish competitive advantages that we may attain;

would adversely affect the marketing of our products; and

could cause the price of our shares to decline.

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, that are adverse to our business. The FDA and comparable international regulatory authorities generally approve products for particular indications. An approval for a limited indication reduces the size of the potential market for the product. Product approvals, once granted, may be withdrawn if problems occur after initial marketing.

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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.

If we fail to maintain existing licenses and collaborations, or fail to develop new collaborations, our business will be harmed.

The success of our business is dependent, in significant part, upon our ability to maintain current licensing and collaborative relationships and enter into multiple new licenses and collaboration agreements. We also must manage effectively the numerous issues that arise from such arrangements and agreements. Management of our relationships with these third parties has required and will require:

a significant amount of our management team's time and effort;

effective allocation of our and third-party resources to multiple projects;

agreements with third parties as to ownership of proprietary rights and development plans, including clinical trials or regulatory approval strategy; and

the recruitment and retention of management, scientific and other personnel.

In January 2006, we entered into a license and collaboration agreement with Bayer for the development and commercialization of alfimeprase internationally. Under the agreement, Bayer will commercialize alfimeprase in all territories outside the United States and will pay us tiered royalties ranging from a minimum of 15 percent to a maximum of 37.5 percent. We will retain all commercialization rights and profits from alfimeprase sales in the United States. We received an up-front cash payment from Bayer of \$50.0 million upon entry into the agreement, and are eligible to receive up to an additional \$335.0 million in milestone payments, including \$165.0 million in development milestones and \$170.0 million in sales and commercialization milestones, over the course of the agreement. In addition, Bayer will be responsible for 40 percent of the costs for global development programs. We will be responsible for 60 percent of the costs and will remain the lead for the design and conduct of the global development programs. Each party will solely bear the expense of any country-specific alfimeprase clinical trials conducted by it, where the country-specific clinical trials are not part of the agreed global development program.

In October 2004, we obtained worldwide rights to develop and commercialize alfimeprase from Amgen in exchange for payment to Amgen of development milestones and royalties. Future milestone payments under the license agreement could total as much as \$35.0 million. Under our agreement with Bayer, we retain sole responsibility for making these payments to Amgen. In accordance with the terms of the license agreement, Amgen has transferred the technology necessary for the manufacture of alfimeprase to our designated manufacturer, Avecia. In June 2005, we entered into a definitive agreement with Avecia for the scale up and validation of the manufacturing process for alfimeprase, in anticipation of the potential commencement of the manufacture of commercial quantities. While we currently believe we have enough supplies of alfimeprase for phase 3 trials for the treatment of acute PAO and catheter occlusion, additional

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supplies may be necessary for these trials and for anticipated trials in other indications, and we are not yet certain that Avecia will succeed in manufacturing additional supplies of alfimeprase for such trials. We may need to conduct comparative studies or utilize other means to determine bioequivalence between alfimeprase manufactured by Avecia and that previously manufactured by Amgen. If Avecia is unable to produce alfimeprase in the quantities and with the quality we need, when we need it, we may incur significant additional expenses, and our and Bayer's efforts to complete our clinical trials and obtain approval to market alfimeprase could be significantly delayed.

Pursuant to our licensing arrangement with Dendreon relating to rNAPc2, we are obligated to make milestone payments, ranging from \$2.0 million to \$6.0 million, upon dosing of the first patient in a Phase 3 clinical trial, upon submission of an NDA and upon first commercial sale, for both the first and second indications of rNAPc2. If these and other milestones are all achieved, total milestone payments to Dendreon may reach as much as \$23.5 million.

In March 2005, we entered into a collaboration agreement with the Pharmaceutical Division of Kirin for the development and commercialization of NU206. All operating expenses and profits related to the development and commercialization of NU206 will be shared 60 percent by us and 40 percent by Kirin. If this agreement is terminated, or we or Kirin elects under certain circumstances to no longer actively participate in the collaboration, the relationship with respect to NU206 will convert from an expense and profit sharing structure to a royalty-based structure. Our 2001 collaboration agreement with Kirin for research and development of secreted proteins expired on December 31, 2005 in accordance with its terms. We and Kirin are currently discussing the possibility of extending the term of this collaborative program, as we have previously. If we cannot reach agreement on a continuation of the research program with Kirin, we may need to find another partner to research and develop the compounds previously being researched in collaboration with Kirin, or we may have to delay or abandon further research and development of these compounds.

In our collaboration with Archemix for the research and development of a thrombin inhibiting aptamer, we share equally all research and development costs and revenues subsequent to our initial funding of these costs reaching \$4.0 million in the third quarter of 2004. We are obligated to make milestone payments of \$10.0 million upon dosing of the first patient in a Phase 2 trial and \$1.0 million upon the designation of any backup compound selected by both us and Archemix for pre-clinical studies. During the collaboration, we are limited in our ability to influence Archemix's conduct of clinical trials prior to the dosing of the first patient in a Phase 2 trial. The payment of \$10.0 million upon reaching the Phase 2 milestone is payable even if Archemix voluntarily terminates the collaboration, or does not meet its obligations under the agreement and we terminate the collaboration for Archemix's default, provided that in any of those cases we have rights to the compound when the Phase 2 trial is initiated. Archemix can terminate its collaboration with us on limited notice and for reasons outside our control. We lose significant rights if the collaboration is terminated because we fail to meet our obligations under it. In particular, if Archemix terminates the collaboration for our breach, all of our rights to collaboration products will become the property of Archemix, and we may not practice certain activities, including research and development, manufacturing and commercialization activities, in the field of modifying blood-clotting times in therapeutic applications through the use of aptamers.

Under our collaboration with Archemix, we have the option to lead commercialization in which both parties may participate if we establish certain commercialization capabilities; however, if we do not establish such commercialization capabilities, Archemix, or a third party selected by the

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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. If we cannot develop an internal sales force, we will not be able to lead commercialization activities on our own. 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.

Our efforts to manage simultaneously a number of collaboration arrangements may not be successful, and our 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 current or potential collaborative partners, we may be delayed or prevented from developing or commercializing alfimeprase, rNAPc2, NU206, a thrombin inhibiting aptamer or other pre-clinical product candidates, 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 arrangements for the manufacture and sale 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 administrative functions and functions related to the research, development, pre-clinical 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, which includes manufacturing bulk compound, filling and finishing, and labeling and packaging, 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 service providers and suppliers and do not have long-term supply agreements with our third-party manufacturers.

We do not currently have 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 FDA, and proceed with clinical trials for any of our drug candidates. Until recently, we have relied on Amgen to manufacture our clinical drug product, alfimeprase. We have entered into a definitive Development and Validation Agreement with Avecia for the scale up and validation of the alfimeprase manufacturing process and have transitioned the process of manufacture of alfimeprase from Amgen to Avecia, but do not yet have a definitive agreement with Avecia for the manufacture of commercial quantities of alfimeprase. We may need to conduct comparative studies or utilize other means to determine bioequivalence between alfimeprase manufactured by Avecia and that previously manufactured by Amgen. If Avecia is unable to manufacture clinical or commercial grade alfimeprase for us, or we are unable to complete commercial arrangements with Avecia, we may not have adequate supplies of alfimeprase to complete our

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clinical trials or to obtain regulatory approvals for alfimeprase on our anticipated schedule. Our drug candidates have never been manufactured on a commercial scale. We received a supply of rNAPc2 from Dendreon, which we have used in our research and development activities. When we deplete this existing supply, we will need to contract with a third party manufacturer to produce additional rNAPc2. 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 and when any of our other drug candidates, such as NU206, enter the clinical trial phase, we will initially depend on third-party contract manufacturers to develop the necessary production processes, and produce the volume of cGMP-grade material needed to complete such trials. We will need to enter into contractual relationships with these or other organizations in order to (i) complete the Good Laboratory Practices, or GLP, toxicology and other studies necessary to file an IND with the FDA, (ii) produce a sufficient volume of cGMP-grade material in order to conduct clinical trials of these other drug candidates, and (iii) fill and finish, and label and package our material. We cannot be certain that we will be able to complete these tasks on a timely basis or that we will be able to obtain sufficient quantities of material or other manufacturing services 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 any of our drug candidates.

Moreover, contract manufacturers that we may use must continually adhere to 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 pre-market approval of our products.

We are dependent on third-party contract research organizations to conduct certain research, including GLP toxicology studies, in order to gather the data necessary to file INDs with the FDA for any of our drug candidates. These third parties may not conduct their research properly, or they may fail to complete their contract research on the anticipated schedule. In either case, the progress of our clinical programs may be delayed and our research and development costs may increase, which may in turn have a material adverse affect on our business.

Our reliance on these relationships poses a number of risks, including:

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;

inability of third parties to manufacture, including filing and finishing, and labeling and packaging, our drug candidates in a cost-effective or timely manner or in quantities needed for clinical trials or commercial sales;

our inability to effectively control the resources devoted by our partners to our programs or products;

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disagreements with third parties that could disrupt our operation or delay or terminate the research, development or manufacturing of drug candidates, or result in litigation or arbitration;

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 third parties work for us and their work for another entity, and the resulting loss of their services;

failure to identify acceptable manufacturers or other suppliers or enter into favorable long-term agreements with them; and

lack of all necessary intellectual property rights to manufacture and sell our drug candidates.

Given these risks, our current and future arrangements 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 sources, or to delay our product development or commercialization.

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, disagreements with current or future clinical development collaborative partners, the uncertainties inherent in the regulatory approval process and manufacturing scale-up 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, our business will be materially adversely affected and the price of our shares could decline.

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

The success of our business is highly dependent on the principal members of our scientific and management staff, including our 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 clinical development. Retaining and training personnel with the requisite skills is challenging and extremely competitive, particularly in Northern California, where we are located.

Our success will depend on our ability to attract and retain qualified employees to help develop our potential products and execute our research, development and commercialization strategy. We have programs in place to retain personnel, including programs to

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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. Our success also depends on the continued availability of outside scientific

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collaborators, including collaborators at research institutions, to perform research and develop processes to advance and augment our internal research efforts. Competition for collaborators is intense. We also rely on services provided by outside consultants. Attracting and retaining qualified outside consultants is competitive, and, generally, outside consultants can terminate their relationship with us at will. If we do not attract and retain qualified personnel, outside consultants and scientific collaborators, or if we experience turnover or difficulties recruiting new employees or outside consultants, our research, development and commercialization programs could be delayed and we could experience difficulties in generating sufficient revenue to maintain our business.

In addition, we do not currently have a marketing and sales organization. As the potential commercialization of our products approaches, we intend to hire marketing and sales personnel to enable us to participate in the commercialization of our products in the United States. If we are unsuccessful in hiring and retaining sales and marketing personnel with appropriate qualifications and talent, our ability to generate product revenues will be adversely affected.

Finally, in September 2005, we relocated our corporate headquarters from Sunnyvale, California to San Carlos, California. This relocation has caused and could cause some of our employees to seek new employment with employers located closer to their homes. The loss of key employees could have a serious adverse effect on our operations.

The success of our potential products in pre-clinical studies does not guarantee that these results will be replicated in humans.

Although our clinical development-stage drug candidates have shown results in pre-clinical studies, these results may not be replicated in our clinical trials with humans. Consequently, there is no assurance that the results in our pre-clinical 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.

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

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

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

the possibility that a product is toxic, ineffective or unreliable;

failure to obtain regulatory approval for the product;

difficulties in manufacturing the product on a large scale;

difficulties in planning, coordinating and executing the commercial launch of the product;

difficulties in marketing, distribution or sale of the product;

competition from superior products; or

third-party patents that preclude us from marketing a product.

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

Under our license and collaboration agreement with Bayer, we share the costs of global development of alfineprase, with Nuvelo responsible for 60 percent of these costs and Bayer responsible for 40 percent. We and Bayer will manage the design and conduct of the global development program jointly, but in the event of a disagreement, we retain the right to make any final decision.

Under our collaboration with Archemix, Archemix leads development until the first dosing of a patient in a Phase 2 clinical trial, and thereafter, a joint steering committee will designate one party to lead development until commercialization. With respect to these arrangements, we run the risk that Bayer or Archemix may not pursue clinical development in a timely or effective manner.

Any regulatory approvals that we or our collaboration partners receive for our product candidates may 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 approves 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.

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

Finally, even if a product candidate such as alfimeprase or rNAPc2 were approved for commercial sale, significant strategic planning and resources will be necessary to effectively coordinate commercial launch of the product in the approved indication or indications, and to effectively market, distribute and sell the product for use in the approved indication or indications. In addition, the marketing, distribution, sale and reimbursement of pharmaceutical products is heavily regulated, and we must comply with all such applicable laws and regulations, or incur

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costs, fees and other liabilities associated with non-compliance. If our or a collaboration partner's commercial launch of a product approved for commercial sale were to be unsuccessful, or if we or a collaboration partner were to fail in our or their efforts to properly market, distribute or sell any product approved for sale, our business, financial condition and operating results would suffer significant harm.

We lack marketing and commercialization experience for biopharmaceutical products and we may have to rely on third parties for these capabilities.

We currently have limited sales, marketing and distribution capability. As the potential commercialization of our products approaches, we intend to hire additional marketing and sales personnel to enable us to participate in the commercialization of our products in the United States. If we are unsuccessful in hiring and retaining sales and marketing personnel with appropriate technical and sales expertise or in developing an adequate distribution capability to support them, our ability to generate product revenues will be adversely affected. To the extent we cannot or choose not to use internal resources for the marketing, sales or distribution of any potential products in the United States or elsewhere, we intend to rely on collaboration partners or licensees. We may not be able to establish or maintain such relationships. To the extent that we depend on collaboration partners or other third parties for marketing, sales and distribution, any revenues we receive will depend upon their efforts. Such efforts may not be successful, and we will not be able to control the amount and timing of resources that collaboration partners or other third parties devote to our products.

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, if any, 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, medical device and 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 advantages over alternative treatment methods;

marketing, sales and distribution support of our products; and

reimbursement policies of government and third-party payers.

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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.

Even if our product candidates are approved for marketing and are accepted by physicians, patients and the medical community, the size of the market for these products may be insufficient to sustain our business, or may not provide an acceptable return on our investment in the development of these

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products. For example, our lead product candidate, alfimeprase, is undergoing clinical trials for the treatment of acute PAO. There are currently no thrombolytic agents specifically approved for the treatment of acute PAO in the United States or overseas, and as a result there is currently limited market data available for us to use in judging the market size for a therapeutic product of this nature. The number of incidents of acute PAO that are treatable with an approved thrombolytic agent may not be sufficient to create a sustainable market for alfimeprase, if approved. As a result, the commercialization of alfimeprase for the treatment of acute PAO, or any of our other product candidates, could fail even if we receive marketing approval from the FDA or similar foreign authority, and acceptance by the medical and patient communities.

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, medical device and biotechnology firms, many of which have substantially greater research and product development capabilities and financial, scientific, marketing and human resources than we have. Our lead product candidate alfimeprase, if approved, will face competition in the catheter occlusion indication from alteplase, an approved Genentech, Inc. product, and will potentially face competition in the acute PAO indication from product candidates being developed and/or marketed by PDL BioPharma, Inc. and Genentech.

Our competitors may obtain patents and regulatory approvals for their competing 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. All of our products will face competition from companies developing similar products as well as from companies developing other forms of treatment for the same conditions.

Many of the companies developing competing products have significantly greater financial resources than we have. Many such companies also have greater expertise than we have, and may have greater expertise than our collaboration partners have, in discovery, research and development, manufacturing, pre-clinical 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. 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 the 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 developed by us or that any therapy we develop will be preferred to any existing or newly-developed alternative products.

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

Our ability to collect significant revenues 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 payers such as:

government health administration authorities;

private health insurers;

health maintenance organizations;

pharmacy benefit management companies; and

other healthcare-related organizations.

Third-party payers may deny coverage or offer inadequate levels of reimbursement if they determine that a prescribed product has not received appropriate clearances from the FDA or other government regulators, is not used in accordance with cost-effective treatment methods as determined by the third-party payer, or is experimental, unnecessary or inappropriate. If third-party payers 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 healthcare through health maintenance organizations. Currently, third-party payers 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 healthcare services and products. Existing U.S. laws, such as the Medicare Prescription Drug and Modernization Act of 2003, or future legislation to reform healthcare or reduce government insurance programs could also adversely affect prices of our approved products, if any. The cost-containment measures that healthcare providers are instituting and the results of potential healthcare 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. In addition, to the extent that our products are marketed outside of the United States, foreign government pricing controls and other regulations may prevent us and our collaboration partners 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.

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 we 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 and/or our subsidiary include, among others:

consolidating research and development operations;

retaining key employees;

consolidating corporate and administrative infrastructures;

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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 and other 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.

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.

We are subject to the risk of natural disasters.

Our facilities are located in Northern California. If a fire, earthquake, or other natural disaster disrupts our research or development efforts, our business, financial condition and operating results could be materially adversely affected. Some of our landlords may 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.

Risks related to our capital structure and financial results

We have not been profitable, anticipate continuing losses and may never become profitable.

We had net losses of \$50.2 million in 2003, \$52.5 million in 2004 and \$50.1 million in the nine months ended September 30, 2005. As of September 30, 2005, we had an accumulated deficit of \$306.2 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 our drug products will require significant additional research and development, pre-clinical 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

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product sales or royalty revenue from product sales 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 pre-clinical 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 market price of our common stock could decline.

Moreover, utilization of our net operating loss carry forwards and credits may be subject to an annual limitation due to the change in ownership provisions of the Internal Revenue Code of

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1986 and similar state law provisions. It is possible that certain transactions that we have entered into, including our merger with Variagenics in January 2003, when considered in connection with other transactions, may result in a change in ownership for purposes of these provisions.

In January 2005, we entered into a lease agreement for 61,826 square feet of industrial space in San Carlos, California. In connection with our lease of this new facility, we are examining the potential to sublease or otherwise exit our existing facility at 985 Almanor Avenue in Sunnyvale, California, which is currently primarily being used for storage and for which we have a lease through May 30, 2011. In accordance with Statement of Financial Accounting Standards No. 146, *Accounting for Costs Associated with Exit or Disposal Activities*, if we sublease or otherwise exit this facility, we could incur a significant charge to our earnings based on the remaining lease rental expense for this facility, reduced by the estimated income from sublease rental, if any. As of September 30, 2005, the remaining lease rental expense for this facility was \$31.9 million. Similarly, in accordance with Statement of Financial Accounting Standards No. 144, *Accounting for the Impairment or Disposal of Long-Lived Assets*, if we sublease or otherwise exit this facility, we could also incur a significant charge to our earnings for the impairment of leasehold improvements related to this facility, based on the difference between their carrying value and fair value at the time of the sublease or exit. As of September 30, 2005, this difference was estimated to be \$3.9 million.

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 to finance the research and clinical development of our drug products. If future securities offerings are successful, they could dilute our current shareholders' equity interests and reduce the market price of our common stock. 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 raise capital by granting 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 that we could realize from these drug candidates.

If we are unable to obtain additional financing when we need it, the capital markets may perceive that we are not able to raise the amount of financing we desire, or on the terms that we desire. This perception, if it occurs, may negatively affect the market price of our common stock. If sufficient capital is not available, we may be forced to delay, reduce the scope of, eliminate or divest one or more of our 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:

our ability to maintain, and the financial commitments involved in, our existing collaborative and licensing arrangements;

the success of our collaborative relationship with Bayer, in accordance with the alfineprase license and collaboration agreement we entered into in January 2006;

progress in current and anticipated clinical studies of our products, including alfineprase, rNAPc2 and a thrombin inhibiting aptamer;

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the cost of manufacturing our material for pre-clinical, clinical and commercial purposes;

our ability to establish new collaborative relationships with other companies to share costs and expertise of identifying and developing drug candidates;

the magnitude and scope of our research and development programs, including development of product candidates;

continued scientific progress in our research and development programs, including progress in our research and pre-clinical studies;

the cost involved in any facilities expansion to support research and development of our product candidates;

the cost of prosecuting and enforcing our intellectual property rights;

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;

our ability to use our common stock to repay an outstanding convertible promissory note to Affymetrix and our line of credit with Dr. George Rathmann;

future funding commitments to our collaborators;

general conditions in the financial markets and in the biotech sector;

the uncertain condition of the capital markets and in the biotech sector; and

other factors not within our control.

We may face fluctuations in operating results.

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

the amount of research and development we engage in;

the number of product candidates we have and their progress in research, pre-clinical and clinical studies;

our ability to expand our facilities to support our operations;

our ability to maintain existing and enter into new strategic relationships;

the scope, duration and effectiveness of our licensing and collaborative arrangements;

the costs involved in prosecuting, maintaining and enforcing patent claims;

the possibility that others may have or obtain patent rights that are superior to ours;

changes in government regulation;

changes in accounting policies or principles; and

release of successful products into the market by our competitors.

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Excluding our two clinical stage drug candidates, our potential products currently are in research or pre-clinical development, and revenues from the sales of any products resulting from this research and development may not occur for several years, if at all. A high percentage of our expenses are 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 in the market price of our common stock.

We face exposure to currency fluctuations for transactions denominated in foreign currencies, which may adversely affect our results of operations.

To mitigate the impact of currency exchange rate fluctuations on our cash outflows for certain foreign currency-denominated purchases, we have developed and implemented a foreign exchange risk management policy utilizing forward contracts to hedge against this exposure. For example, in the third quarter of 2005, we entered into \$16.7 million of foreign exchange hedge contracts with Silicon Valley Bank in relation to our Development and Validation Agreement with Avecia, pursuant to which we are required to make payments to Avecia in British pounds. Although we use forward contracts to reduce the impact of foreign currency fluctuations on our future results, these efforts may not be successful, and any such fluctuations could adversely affect our results of operations.

Recent accounting pronouncements may impact our future financial position and results of operations.

There may be potential new accounting pronouncements or regulatory rulings, which may have an impact on our future financial position and results of operations. On December 16, 2004, the Financial Accounting Standards Board, or FASB, issued Statement of Financial Accounting Standards No. 123 (revised 2004), *Share-Based Payment*, also known as SFAS 123(R), an amendment of Statements of Financial Accounting Standards No. 123 and 95, that addresses the accounting for share-based awards to employees. The standard requires companies to recognize the fair value of employee stock options and other stock-based compensation as an expense. The statement eliminates the ability to account for share-based employee compensation transactions using APB Opinion No. 25, *Accounting for Stock Issued to Employees*, also known as APB 25, and generally requires instead that such transactions be accounted for using a fair value-based method, such as Black-Scholes, to fairly value stock options and recognize that value as an expense over the requisite service period. The standard will be effective for public companies as of the beginning of the first fiscal year after June 15, 2005. We currently account for our stock-based employee compensation plans in accordance with APB 25. We will be required to implement SFAS 123(R) effective from the beginning of our 2006 fiscal year, and we expect that its adoption will have a material adverse impact to our results of operations.

The committed equity financing facility with Kingsbridge may not be available to us when we desire to draw upon it, may require us to make additional blackout payments to Kingsbridge, and may result in dilution to our stockholders.

In August 2005, in connection with a committed equity financing facility, or CEFF, we entered into a stock purchase agreement and related registration rights agreement with Kingsbridge Capital Ltd. The CEFF entitles us to sell and obligates Kingsbridge to purchase, from time to time

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over a period of three years, shares of our common stock for cash consideration up to an aggregate of \$75.0 million, subject to certain conditions and restrictions. In November 2005, under this stock purchase agreement, we sold 653,103 shares for gross proceeds of \$5.0 million, and in December 2005 sold 1,186,297 shares for gross proceeds of \$9.4 million. The balance of \$60.6 million remains available for use by us over the remainder of the three-year period. Kingsbridge will not be obligated to purchase shares under the CEFF unless certain conditions are met, which include a minimum price for our common stock; the accuracy of representations and warranties made to Kingsbridge; compliance with laws; effectiveness of a registration statement to register such shares for resale by Kingsbridge; and the continued listing of our stock on the Nasdaq National Stock Market. In addition, Kingsbridge is permitted to terminate the CEFF if it determines that a material and adverse event has occurred affecting our business, operations, properties or financial condition. If we are unable to access funds through the CEFF, or if the CEFF is terminated by Kingsbridge, we may be unable to access capital on favorable terms or at all.

We are entitled in certain circumstances, to deliver a blackout notice to Kingsbridge to suspend the use of the registration statement under which shares sold under the CEFF are registered for resale, thereby prohibiting Kingsbridge from selling shares. If we deliver a blackout notice in the 15 trading days following the settlement of a sale of shares under the CEFF, or if the registration statement is not effective in circumstances not permitted by our agreement with Kingsbridge, then we must make a payment to Kingsbridge, or issue Kingsbridge additional shares in lieu of this payment, calculated on the basis of the number of shares held by Kingsbridge and the change in the market price of our common stock during the period in which the use of the registration statement is suspended. If the market price of our common stock declines during a suspension of the registration statement, the blackout payment could be significant.

Should we sell additional shares to Kingsbridge under the CEFF, or issue shares in lieu of any blackout payment, it will have a dilutive effect on the holdings of our current stockholders, and may result in downward pressure on the market price of our common stock. If we draw down under the CEFF, we will issue shares to Kingsbridge at a discount of up to ten percent from the volume weighted average price of our common stock. If we draw down amounts under the CEFF when our share price is decreasing, we will need to issue more shares to raise the same amount than if our share price was higher. Issuances in the face of a declining share price will have an even greater dilutive effect than if our share price were stable or increasing, and may further decrease our share price.

We have implemented anti-takeover provisions that could discourage, prevent or delay a takeover, even if the acquisition would be beneficial to our stockholders.

The existence of our stockholder rights plan and provisions of our certificate of incorporation and bylaws, as well as provisions of Delaware law, could make it more difficult for a third party to acquire us, even if doing so would benefit our stockholders. These provisions:

establish a classified board of directors so that not all members of our board may be elected at one time;

authorize the issuance of up to 5,000,000 shares of preferred stock that could be issued by our board of directors to increase the number of outstanding shares and hinder a takeover attempt;

limit who may call a special meeting of stockholders;

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prohibit stockholder action by written consent, thereby requiring all stockholder actions to be taken at a meeting of our stockholders; and

establish advance notice requirements for nominations for election to our board of directors or for proposing matters that can be acted upon at a stockholder meeting.

Specifically, our certificate of incorporation provides that all stockholder action must be effected at a duly called meeting, and not by a written consent. 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 percent of our common stock. These provisions of our certificate of incorporation and our by-laws could discourage potential acquisition proposals and could delay or prevent a change in 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.

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 A junior participating preferred stock at a purchase price that is 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 percent (27.5 percent 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. This rights agreement was amended on March 19, 2004, to reflect our reincorporation under Delaware law.

We are subject to the Delaware anti-takeover laws regulating corporate takeovers. These anti-takeover laws prevent a Delaware corporation from engaging in a merger or sale of more than ten percent of its assets with any stockholder, including all affiliates and associates of the stockholder, who owns 15 percent or more of the corporation's outstanding voting stock, for three years following the date that the stockholder acquired 15 percent or more of the corporation's stock unless:

the board of directors approved the transaction where the stockholder acquired 15 percent or more of the corporation's stock;

after the transaction in which the stockholder acquired 15 percent or more of the corporation's stock, the stockholder owned at least 85 percent of the corporation's outstanding voting stock, excluding shares owned by directors, officers and employee stock plans in which employee participants do not have the right to determine confidentially whether shares held under the plan will be tendered in a tender or exchange offer; or

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on or after this date, the merger or sale is approved by the board of directors and the holders of at least two-thirds of the outstanding voting stock that is not owned by the stockholder.

The provisions of our governing documents, stockholder rights plan and current Delaware law may, collectively:

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;

discourage bids for our common stock at a premium over market price; and

generally deter efforts to obtain control of us.

We have adopted an Executive Change in Control and Severance Benefit Plan that could discourage, prevent or delay a takeover, even if the acquisition would be beneficial to our stockholders.

On December 14, 2004, our board of directors approved an Executive Change in Control and Severance Benefit Plan for our executive officers and other eligible employees. The purpose of the plan is to provide for the payment of severance benefits and/or change in control benefits to certain of our eligible employees, and the plan supersedes and replaces any change in control and/or severance plans adopted by us previously. All of our executive employees at the level of Vice President or above have been designated as participants in the plan and our board of directors may designate other eligible individuals as participants. The plan provides that, upon a change in control of the company as defined under the plan, all Nuvelo stock options and stock awards held by a plan participant will become fully vested. Such shares held by a plan participant will also become fully vested if the participant is terminated without cause, or constructively terminated, within one month preceding our change in control. If a participant is terminated without cause or constructively terminated one month before or one year after our change in control, he or she will also be entitled to certain cash severance and continued medical benefits. The change in control and severance benefits for certain of our employees provided for under this plan could make it more difficult and expensive, or less desirable, for a third party to acquire us, even if doing so would benefit our stockholders.

Risks related to intellectual property and other legal matters

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.

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We currently have, or have in-licensed, issued patents and pending patent applications that include claims to our in-licensed clinical products. We obtained exclusive worldwide rights to alfimeprase from Amgen in October 2004. We obtained exclusive worldwide rights for all indications of rNAPc2 and all of the rNAPc molecules owned by Dendreon in February 2004. The United States government may claim a non-exclusive right to use rNAPc2 with respect to the treatment of hemorrhagic fever. We also currently have patents that cover some of our

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technological discoveries and patent applications that we expect to protect some of our gene, protein and technological discoveries. We will continue to apply for patents for our discoveries. We cannot assure you that any of our applications, or our licensors' applications, will issue as patents, or that any patent issued or licensed 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 depend on our collaborators and other third parties that license intellectual property to us to protect our licensed intellectual property. These collaborators and other third parties could fail to take a necessary step to protect our licensed intellectual property, which could seriously harm our intellectual property position.

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 or licensing fees and limit our ability to sell some or all of our products.

Extensive litigation regarding patents and other intellectual property rights has been common in the biopharmaceutical industry. 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.

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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.

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 of our programs. We plan to seek licenses, as we deem appropriate, but it is possible that we may 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 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 and production activities involve the controlled use of hazardous or radioactive materials, chemicals, including oxidizing and reducing reagents, patient tissue and

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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, or 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 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, patient samples that may contain viruses and hazardous materials. The cost of this liability could exceed our resources.

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 who are also named defendants in the lawsuit. Plaintiffs in the suit allege that underwriters took these commissions and in exchange allocated shares of Variagenics stock to their preferred customers through alleged agreements with these preferred customers that tied the allocation of initial public offering shares to agreements by the customers 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. Failure to finalize a settlement could require us to pay substantial damages.

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 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.

Historically, our stock price has been extremely volatile. Between January 1, 2005 and December 31, 2005, the price ranged between a high of \$10.35 per share and a low of \$5.75 per share. The significant market price fluctuations of our common stock can be due to a variety of factors, including:

the depth of the market for the common stock;

the experimental nature of our potential products;

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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 convertible promissory note to Affymetrix, or upon repayment of our line of credit with Dr. George 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; and

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 or the possibility of 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 September 30, 2005, we had 42,263,782 shares of our common stock outstanding. All of these shares are freely transferable without restriction or further registration under the Securities Act, except for shares held by our directors, officers and greater than five percent stockholders and unregistered shares held by non-affiliates. As of September 30, 2005, our directors, officers and greater than five percent stockholders held approximately 8.5 percent of the shares of our outstanding common stock. Although we do not believe that our directors, officers and greater than five percent stockholders have any present intentions to dispose of large amounts of any shares of common stock owned by them, there can be no assurance that such intentions will not change in the future. The sale of these additional shares could depress the market price of our common stock.

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Under registration statements on Form S-8 under the Securities Act, as of September 30, 2005, we have also registered approximately 8,502,044 shares of our common stock which may be issued under our 2004 Equity Incentive Plan, 2002 Equity Incentive Plan, 1995 Stock Option Plan, Non-Employee Director Stock Option Plan, Scientific Advisory Board/Consultants Stock Option

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Plan, stock option agreements entered into outside of any of our stock option plans, and our Employee Stock Purchase Plan. Included in the 8,502,044 shares, as of September 30, 2005, are (i) 6,224,029 shares of our common stock issuable under outstanding options to purchase our common stock under the specified plans, (ii) 823,539 shares of our common stock issuable under stock option agreements entered into outside of any of our stock option plans, (iii) 1,195,006 shares of our common stock reserved for future option grants under our 2004 Equity Incentive Plan, and (iv) 259,470 shares of our common stock reserved for future issuance under our Employee Stock Purchase Plan. As of September 30, 2005, 2,580,169 of the shares issuable upon exercise of our outstanding options were exercisable. Once these shares are exercised, such shares are available for sale in the open market without further registration under the Securities Act. The existence of these outstanding options and share reserves may negatively affect our ability to complete future equity financings at acceptable prices and on acceptable terms. The exercise of those options, and the prompt resale of shares of our common stock received, may also result in downward pressure on the price of our common stock.

As of September 30, 2005, 1,797,273 shares of our common stock were issuable upon the exercise of outstanding warrants. As of that same date, warrants to purchase 1,447,273 of these shares were exercisable. Once a warrant is exercised, the holder can arrange for the resale of shares either by invoking any applicable registration rights, causing the shares to be registered under the Securities Act and thus freely transferable, or by relying an exemption to the Securities Act. If these registration rights, or similar registration rights that may apply to securities we may issue in the future, are exercised, it could result in additional sales of our common stock in the market, which may have an adverse effect on our stock price.

As of September 30, 2005, \$5.2 million of our common stock was issuable, at our option, to repay our convertible promissory note held by Affymetrix, Inc., including accrued interest, at a conversion price based on 90 percent of the average price of our common stock over a ten-day period ending two days prior to conversion. 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 \$50.0 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 ten percent of our market capitalization. Pursuant to registration rights we granted to Affymetrix, we have registered for resale a portion of these shares on a registration statement that has been declared effective by the SEC. If we decide to repay this note with our common stock, whether pursuant to acceleration of the note or otherwise, the resale of shares of our common stock by Affymetrix may also result in significant downward pressure on the market price of our common stock.

As of September 30, 2005, \$7.5 million of our common stock was issuable, upon mutual agreement, to convert the remaining amount due on the promissory note under our line of credit with Dr. George Rathmann, including accrued interest, at a conversion price equal to the average price of our common stock over a 20-day period, ending two days prior to conversion, or, if in connection with an equity financing, at the offering price. If we agree to repay this note with our common stock, whether pursuant to acceleration of the note or otherwise, the resale of shares of our common stock received by Dr. Rathmann may also result in significant downward pressure on the market price of our common stock.

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Under the August 2005 CEFF with Kingsbridge and related stock purchase and registration rights agreements, we may periodically sell up to \$75.0 million in shares of our common stock to Kingsbridge over a three-year period, subject to certain conditions and restrictions. In November 2005, under this CEFF, we sold 653,103 shares for gross proceeds of \$5.0 million, and in December 2005 sold 1,186,297 shares for gross proceeds of \$9.4 million. We may sell the balance of \$60.6 million of shares of our common stock over the remainder of the three-year term of the CEFF. Should we sell further securities under the CEFF, it could have a dilutive effect on the holdings of our current stockholders, and may result in downward pressure on the market price of our common stock.

We will need to raise significant additional capital to finance the research and clinical development of our drug products. If future securities offerings are successful, they could dilute our current stockholders' equity interests and reduce the market price of our common stock.

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. See "Use of proceeds."

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 our board of directors. Under our August 31, 2004 Loan and Security Agreement with Silicon Valley Bank, as amended, we cannot pay dividends without Silicon Valley Bank's prior written consent, except for dividends paid in shares of our capital stock. Furthermore, we may incur additional indebtedness that may severely restrict or prohibit the payment of dividends.

You will experience immediate dilution in the book value per share of the common stock you purchase.

Since the price per share of our common stock being offered is substantially higher than the book value per share of our common stock, you will suffer substantial dilution in the net tangible book value of the common stock you purchase in this offering. Based on an assumed offering price to the public of \$15.57 per share, if you purchase shares of common stock in this offering, you will suffer immediate and substantial dilution of \$12.66 per share in the net tangible book value of the common stock. See the section entitled "Dilution" below for a more detailed discussion of the dilution you will incur if you purchase common stock in this offering.

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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 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 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, 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 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 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.

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Use of proceeds

We estimate the net proceeds to us from this offering will be approximately \$80.0 million, based on an assumed public offering price of \$15.57 per share and after payment of underwriting discounts and commissions and estimated expenses of this offering, or approximately \$92.1 million if the underwriters exercise their over-allotment option in full. A \$1.00 increase (decrease) in the assumed public offering price of \$15.57 per share would increase (decrease) the net proceeds to us from this offering by approximately \$5.2 million, assuming the number of shares offered by us, as set forth on the cover page of this prospectus supplement, remains the same. We may also increase or decrease the number of shares we are offering. An increase of 1.5 million shares in the number of shares offered by us, to a total of 7.0 million shares, together with a concomitant \$1.00 increase in the assumed offering price of \$15.57 per share, would increase the net proceeds to us from this offering by approximately \$28.5 million. Similarly, a decrease of 1.5 million shares in the number of shares offered by us, to a total of 4.0 million shares, together with a concomitant \$1.00 decrease in the assumed offering price of \$15.57 per share, would decrease the net proceeds to us from this offering by approximately \$25.7 million. We do not expect that a change in the offering price or the number of shares by these amounts would have a material effect on our uses of the proceeds from this offering, although it may impact the amount of time prior to which we will need to seek additional capital.

We intend to use the net proceeds to us from this offering for general corporate purposes, including the advancement of our drug candidates in clinical trials, the development of a commercialization infrastructure, capital expenditures, and to meet working capital needs. 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. 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. In addition, under our lease agreement, as amended, with The Irvine Company for our facilities at 985 Almanor Avenue, Sunnyvale, California, if we raise more than \$75.0 million in cash as a result of this offering or any other single offering, we must pay The Irvine Company the lesser of (i) ten percent of any amount raised in excess of \$75.0 million or (ii) any remaining deferred rent obligation which, as of September 30, 2005, was approximately \$7.2 million. 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 the offering. Accordingly, we will retain broad discretion over the use of these proceeds.

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. Under our August 31, 2004 Loan and Security Agreement with Silicon Valley Bank, we cannot pay dividends without Silicon Valley Bank's prior written consent, except for dividends paid in shares of our capital stock.

Table of Contents**Capitalization**

The following table shows our cash, cash equivalents and short-term investments and capitalization as of September 30, 2005:

on an actual basis; and

on an as adjusted basis to give effect to our sale of 5,500,000 shares of common stock offered by us, 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 September 30, 2005	
	Actual	As Adjusted(1)
	(unaudited)	
Cash, cash equivalents and short-term investments	\$ 75,530	\$ 155,527
Non-current portion of debt obligations	8,871	8,871
Stockholders' equity:		
Preferred stock, \$0.001 par value; 5,000,000 shares authorized; no shares issued or outstanding, actual and as adjusted		
Common stock, \$0.001 par value; 100,000,000 shares authorized; 42,263,782 shares issued and outstanding, actual; 47,763,782 shares issued and outstanding, as adjusted	42	48
Additional paid-in capital	370,180	450,171
Accumulated other comprehensive loss	1	1
Accumulated deficit	(306,176)	(306,176)
Total stockholders' equity(2)	64,047	144,044
Total capitalization(2)	\$ 72,918	\$ 152,915

- (1) A \$1.00 increase (decrease) in the assumed public offering price of \$15.57 per share would increase (decrease) each of cash, cash equivalents and short-term investments, additional paid-in capital, total stockholders' equity and total capitalization by \$5.2 million, assuming that the number of shares offered by us, as set forth on the cover page of this prospectus supplement, remains the same, and after deducting the estimated underwriting discounts and commissions and estimated offering expenses payable by us. We may also increase or decrease the number of shares we are offering. An increase of 1.5 million shares in the number of shares offered by us, to a total of 7.0 million shares, together with a concomitant \$1.00 increase in the assumed offering price of \$15.57 per share, would increase each of cash, cash equivalents and short-term investments, additional paid-in capital, total stockholders' equity and total capitalization by \$28.5 million. Similarly, a decrease of 1.5 million shares in the number of shares offered by us, to a total of 4.0 million shares, together with a concomitant \$1.00 decrease in the

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assumed offering price of \$15.57 per share, would decrease each of cash, cash equivalents and short-term investments, additional paid-in capital, total stockholders' equity and total capitalization by \$25.7 million. The pro forma information discussed above is illustrative only and will be adjusted based on the actual public offering price and other terms of this offering determined at pricing.

- (2) The number of shares of common stock outstanding is based on the actual number of shares outstanding as of September 30, 2005, but excludes:

an aggregate of 6,224,029 shares of our common stock issuable upon exercise of stock options outstanding as of September 30, 2005, granted under our 2004 Equity Incentive Plan, 2002 Equity Incentive Plan, 1995 Stock Option Plan, Non-Employee Director Stock Option Plan and Scientific Advisory Board/Consultants Stock Option Plan, and as of September 30, 2005, an aggregate of 823,539 shares of common stock issuable upon the exercise of stock options granted outside of any of our stock option plans, with exercise prices of all outstanding options ranging from \$2.34 to \$304.31 per share and a weighted average exercise price of \$15.17 per share;

an aggregate of 1,195,006 shares of common stock reserved for issuance pursuant to future award grants under our 2004 Equity Incentive Plan, based on options outstanding as of September 30, 2005;

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an aggregate of 259,470 shares of common stock issuable under our Employee Stock Purchase Plan as of September 30, 2005;

an aggregate of 1,797,273 shares of our common stock issuable upon the exercise of warrants, with exercise prices ranging from \$4.05 to \$24.87 per share and a weighted average exercise price of \$19.12 per share, outstanding as of September 30, 2005;

\$5.2 million of our common stock issuable at our option, to repay our convertible promissory note held by Affymetrix, Inc., including accrued interest as of September 30, 2005, at a conversion price based on 90 percent of the average price of our common stock over a ten-day period ending two days prior to conversion;

\$7.5 million of our common stock issuable upon mutual agreement, to convert the remaining amount due on the promissory note under our line of credit with Dr. George Rathmann, including accrued interest, as of September 30, 2005, at a conversion price equal to the average price of our common stock over a 20-day period, ending two days prior to conversion, or, if in connection with an equity financing, at the offering price; and

up to \$75.0 million of our common stock salable to Kingsbridge Capital Limited as of September 30, 2005, pursuant to the committed equity financing facility we entered into with Kingsbridge on August 4, 2005. Under this facility, we sold 653,103 shares for gross proceeds of \$5.0 million in November 2005 and 1,186,297 shares for gross proceeds of \$9.4 million in December 2005.

Unless otherwise stated, all information contained in this prospectus supplement assumes that the underwriters do not exercise their over-allotment option to purchase up to an additional 825,000 shares of common stock and all currency amounts are in United States dollars.

Table of Contents**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 September 30, 2005 was approximately \$59.1 million, or \$1.40 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 September 30, 2005. After giving effect to the sale by us of the 5,500,000 shares of common stock we are offering, assuming an offering price of \$15.57 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 \$139.1 million, or \$2.91 per share of common stock. This represents an immediate increase in net tangible book value of \$1.51 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:

Public offering price per share	\$ 15.57
Net tangible book value per share as of September 30, 2005	\$ 1.40
Increase per share attributable to the offering	1.51
	<hr/>
As adjusted net tangible book value per share after this offering	2.91
	<hr/>
Dilution per share to new investors	\$ 12.66
	<hr/>

A \$1.00 increase (decrease) in the assumed public offering price of \$15.57 per share would increase (decrease) our pro forma net tangible book value by \$5.2 million, or \$0.11 per share, and the dilution in pro forma net tangible book value per share to investors in this offering by \$0.89 per share, assuming that the number of shares offered by us, as set forth on the cover page of this prospectus supplement, remains the same and after deducting the estimated underwriting discounts and commissions and estimated offering expenses payable by us. We may also increase or decrease the number of shares we are offering. An increase of 1.5 million shares in the number of shares offered by us, to a total of 7.0 million shares, together with a concomitant \$1.00 increase in the assumed offering price of \$15.57 per share, would result in an as adjusted net tangible book value of approximately \$167.7 million, or \$3.40 per share, and the dilution in as adjusted net tangible book value per share to investors in this offering would be \$13.17 per share. Similarly, a decrease of 1.5 million shares in the number of shares offered by us, to a total of 4.0 million shares, together with a concomitant \$1.00 decrease in the assumed offering price of \$15.57 per share, would result in an as adjusted net tangible book value of approximately \$113.4 million, or \$2.45 per share, and the dilution in as adjusted net tangible book value per share to investors in this offering would be \$12.12 per share. The pro forma information discussed above is illustrative only and will be adjusted based on the actual public offering price and other terms of this offering determined at pricing.

If the underwriters exercise their over-allotment option in full, at an assumed offering price of \$15.57 per share, the as adjusted net tangible book value as of September 30, 2005 would have been \$3.11 per share, representing an increase to existing stockholders of \$1.71 per share, and there will be an immediate dilution of \$12.46 per share to new investors.

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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 September 30, 2005, there were:

an aggregate of 6,224,029 shares of our common stock issuable upon exercise of stock options outstanding as of September 30, 2005, granted under our 2004 Equity Incentive Plan, 2002 Equity Incentive Plan, 1995 Stock Option Plan, Non-Employee Director Stock Option Plan and Scientific Advisory Board/Consultants Stock Option Plan, and as of September 30, 2005, an aggregate of 823,539 shares of common stock issuable upon the exercise of stock options granted outside of any of our stock option plans, with exercise prices of all outstanding options ranging from \$2.34 to \$304.31 per share and a weighted average exercise price of \$15.17 per share;

an aggregate of 1,195,006 shares of common stock reserved for issuance pursuant to future award grants under our 2004 Equity Incentive Plan, based on options outstanding as of September 30, 2005;

an aggregate of 259,470 shares of common stock issuable under our Employee Stock Purchase Plan as of September 30, 2005;

an aggregate of 1,797,273 shares of our common stock issuable upon the exercise of warrants, with exercise prices ranging from \$4.05 to \$24.87 per share and a weighted average exercise price of \$19.12 per share, outstanding as of September 30, 2005;

\$5.2 million of our common stock issuable at our option, to repay our convertible promissory note held by Affymetrix, Inc., including accrued interest as of September 30, 2005, at a conversion price based on 90 percent of the average price of our common stock over a ten-day period ending two days prior to conversion;

\$7.5 million of our common stock issuable upon mutual agreement, to convert the remaining amount due on the promissory note under our line of credit with Dr. George Rathmann, including accrued interest as of September 30, 2005, at a conversion price equal to the average price of our common stock over a 20-day period, ending two days prior to conversion, or, if in connection with an equity financing, at the offering price; and

up to \$75.0 million of our common stock salable to Kingsbridge Capital Limited as of September 30, 2005, pursuant to the committed equity financing facility we entered into with Kingsbridge on August 4, 2005. Under this facility, we sold 653,103 shares for gross proceeds of \$5.0 million in November 2005 and 1,186,297 shares for gross proceeds of \$9.4 million in December 2005.

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Set forth below is information regarding each of our executive officers and directors as of December 31, 2005.

Name	Age	Position
Ted W. Love, M.D.	46	Chairman of the Board and Chief Executive Officer
Michael D. Levy, M.D., F.F.P.M.	44	Senior Vice President of Research and Development
Lee Bendekgey, J.D.	48	Senior Vice President and General Counsel
Gary S. Titus, C.P.A.	46	Vice President of Finance, Chief Accounting Officer and acting Chief Financial Officer
Barry L. Zubrow, J.D., M.B.A.(2)(3)	52	Vice Chairman of the Board
Mary K. Pendergast, J.D., L.L.M.(1)	55	Director
Mark L. Perry, J.D.(2)(3)	50	Director
Kimberly Popovits(1)(2)	47	Director
George B. Rathmann, Ph.D.	78	Director and Chairman Emeritus
Burton E. Sobel, M.D.(1)(3)	68	Director

(1) Member of the Nominating and Governance Committee of the Board of Directors.

(2) Member of the Compensation Committee of the Board of Directors.

(3) Member of the Audit Committee of the Board of Directors.

Ted W. Love, M.D., has served as our president since January 2001, as our chief executive officer since March 2001, as a member of our Board of Directors since February 2001 and as chairman of our Board of Directors since September 2005. 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., a biopharmaceutical company formerly known as Advanced Medicine, Inc., from 1998 to 2001 and as a research physician and vice president of product development at Genentech, Inc., a biotechnology company, from 1992 to 1998. Dr. Love serves as a member of the board of directors for Predix Pharmaceuticals, Inc. and Santarus, Inc., both pharmaceutical companies, and serves on the 29 member California Independent Citizens Oversight Committee, which oversees the \$3.0 billion allocated to stem cell research authorized by California Proposition 71. Dr. Love holds a B.A. in molecular biology from Haverford College and a M.D. from Yale Medical School.

Michael D. Levy, M.D., F.F.P.M., has served as our senior vice president, research and development since November 2004. In addition to his responsibilities directing our research and development efforts, Dr. Levy oversees our manufacturing operations and the development of our commercial infrastructure. Prior to joining us, Dr. Levy served as vice president of development and chief medical officer of Tularik Inc., a biotechnology company that was acquired by Amgen, Inc. in August 2004. While at Tularik, Dr. Levy created and built a new development organization and directed the clinical development of seven novel drugs across three therapeutic areas: oncology, metabolic disease and inflammation/immunology. Prior to joining Tularik, Dr. Levy spent 12 years at GlaxoSmithKline Inc. in Canada, a pharmaceutical company, where he held several positions, including senior vice president of

research and development and chief medical officer. While at

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GSK, he had dual responsibilities for supporting global drug development and the Canadian commercial business. Dr. Levy holds a B.A., M.A. and M.D. from Cambridge University, U.K., completed his surgical residency at the Mayo Clinic and is a Fellow of the Faculty of Pharmaceutical Medicine of the Royal College of Physicians.

Lee Bendekgey, J.D., has served as our senior vice president and general counsel since July 2004. Mr. Bendekgey served as our chief financial officer from July 2004 until November 2005. Mr. Bendekgey brings over 20 years of legal experience to Nuvelo. Prior to joining us, Mr. Bendekgey spent approximately six years at Incyte Corporation, a pharmaceutical company, where he held several executive positions, including executive vice president, general counsel, acting chief financial officer and acting general manager of information business. From 1993 to 1997, Mr. Bendekgey worked for Silicon Graphics, Inc., a computer technology company, where he held a variety of positions in their legal group, including director of legal services, products and technology and director of strategic relations, and helped the company negotiate strategic relationships and providing legal support to all product divisions. Prior to his time at Silicon Graphics, he served as a partner at Graham & James LLP, now known as Squire Sanders & Dempsey LLP, where he specialized in intellectual property law, corporate and commercial law and founded the firm's Palo Alto office. Mr. Bendekgey holds a B.A., magna cum laude, from Kalamazoo College and a J.D. from Stanford University.

Gary S. Titus, C.P.A., has served as our vice president finance and chief accounting officer since July 2004 and as our acting chief financial officer since November 2005. Mr. Titus served as our senior director of finance from January 2003 until July 2004. Mr. Titus brings 18 years of financial management experience to Nuvelo. Prior to joining us, he served as a senior director of finance at Metabolex, Inc. and IntraBiotics Pharmaceuticals, Inc., both biopharmaceutical companies, from January 2002 until January 2003 and from January 2000 until January 2002, respectively. In addition, Mr. Titus held a variety of financial management positions at Johnson & Johnson, a diversified pharmaceutical and biotechnology company, from August 1997 to January 2000. Mr. Titus is a certified public accountant and holds a B.A. in finance from the University of Florida and a B.A. in accounting from University of South Florida.

Barry L. Zubrow, J.D., M.B.A., has served as a member of our Board of Directors since February 2004, as vice chairman of our Board of Directors since March 2005 and as our lead independent director since September 2005. 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, an investment banking firm, including chief administrative officer and head of the operations and administration divisions. As Goldman Sachs'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 serving as Goldman Sachs's chief administrative officer, Mr. Zubrow was elected the firm's first chief credit officer, with responsibility for overseeing the entire firm's global credit exposures. Mr. Zubrow serves as an advisory director of Promontory Financial Group LLC, a financial consulting firm, as Co-Chairman of the board of Haverford College and as a member of the board of directors of a number of other non-profit organizations. Mr. Zubrow holds a J.D. and M.B.A. from University of Chicago.

Mary K. Pendergast, J.D., LL.M., has served as a member of our Board of Directors since May 2002. Ms. Pendergast is president of Pendergast Consulting, which provides regulatory advice to biotechnology companies, federal agencies, trade organizations and related groups. Ms. Pendergast previously served as executive vice president, government affairs for Elan

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Corporation, a biotechnology company, from January 1998 to June 2003. Ms. Pendergast was deputy commissioner/senior advisor to the Commissioner, Food and Drug Administration, Department of Health and Human Services from November 1990 to January 1998 and was an attorney in various positions at the Department of Health and Human Services from 1977 to 1990.

Ms. Pendergast serves as a member of the board of directors of two non-profit organizations. Ms. Pendergast holds a LL.M. from Yale Law School and a J.D. from University of Iowa College of Law.

Mark L. Perry, J.D., has served as a member of our Board of Directors since October 2003. Mr. Perry currently serves as the senior business advisor for Gilead Sciences, Inc., a biopharmaceutical company. Mr. Perry was an executive officer of Gilead from 1994 to 2004, serving in a variety of capacities, including general counsel, chief financial officer and executive vice president of operations. As Gilead's executive vice president of operations, Mr. Perry was responsible for worldwide sales & marketing, legal, manufacturing and facilities. From 1981 to 1994, Mr. Perry served as a partner at Cooley Godward LLP. Mr. Perry serves on the board of directors of Nvidia Corporation, a technology company, and Aerovance, Inc., biopharmaceutical company. Mr. Perry holds a J.D. degree from University of California, Davis.

Kimberly Popovits has served as a member of our Board of Directors since July 2005. Ms. Popovits brings more than 20 years of pharmaceutical and biopharmaceutical experience as well as extensive expertise in marketing commercialization to Nuvelo. She currently serves as president, chief operating officer and director of Genomic Health, Inc, a life science company. Prior to joining Genomic Health in February 2002, Ms. Popovits served in various roles at Genentech, Inc., a biotechnology company, as senior vice president, marketing and sales from February 2001 to February 2002 and as vice president, sales from October 1994 to February 2001. While at Genentech, she led the launch of its oncology business and was vital to the development of its cardiovascular, endocrine and respiratory markets. She has extensive experience in building new markets and has consistently achieved market leadership through the development of innovative strategies focused on patient needs. Prior to joining Genentech in 1987, she served as division manager for American Critical Care, a division of American Hospital Supply, a medical supply company. She also brings extensive operational experience in the areas of managed care, reimbursement and organization development. Ms. Popovits serves on the board of directors for BayBio and holds a B.A. in business from Michigan State University.

George B. Rathmann, Ph.D., has served as a member of our Board of Directors since February 2000 and as our chairman emeritus since September 2005. Dr. Rathmann served as chairman of our Board of Directors from February 2000 until September 2005 and as our chief executive officer from May 2000 until March 2001. Dr. Rathmann was a founder of ICOS Corporation, a biopharmaceutical company, and served as its chairman until January 2000. While at ICOS, he served as chief executive officer and president from September 1991 until June 1999. In 1980, he co-founded Amgen Inc., a biotechnology company. He was a director of Amgen until 1993 and served as its chairman of the board, president and chief executive officer. From 1975 to 1977, Dr. Rathmann served as the director of research and development and divisional vice president for Abbott Laboratories, Inc., a healthcare products manufacturer. Dr. Rathmann serves on the board of directors of ZymoGenetics, Inc., a biopharmaceutical company, Cellerant Therapeutics, Inc., a biotechnology company, and Warren Pharmaceuticals, Inc., also a biotechnology company. Dr. Rathmann holds a Ph.D. in physical chemistry from Princeton University.

Burton E. Sobel, M.D., has served as a member of our Board of Directors since September 2004. Dr. Sobel has served as the E.L. Amidon professor in the department of medicine and professor of

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biochemistry of the University of Vermont and Fletcher Allen Health Care since 1994 and as the director of the Cardiovascular Research Institute since 2002. Dr. Sobel has served as Chair of Medicine at the University of Vermont, as the Director of Cardiology at Washington University in St. Louis, Missouri, as senior counsel to both the executive dean of the University of Vermont College of Medicine and the executive vice president of Fletcher Allen Health Care, and as an adjunct professor of medicine at Washington University in St. Louis, Missouri. Dr. Sobel is currently the President-elect for the Society for Experimental Biology and Medicine and serves on the board of directors of Ariad Pharmaceuticals, Inc., and New River Pharmaceuticals, Inc., both pharmaceutical companies. Dr. Sobel holds an A.B. from Cornell University and a M.D., magna cum laude, from Harvard Medical School.

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Underwriting

We are offering the shares of common stock described in this prospectus supplement through a number of underwriters for which J.P. Morgan Securities Inc., Deutsche Bank Securities Inc. and Lehman Brothers Inc. are acting as representatives. J.P. Morgan Securities Inc. and Deutsche Bank Securities Inc. are acting as joint book-running managers of the offering. We have entered into an underwriting agreement with the underwriters. Subject to the terms and conditions of the underwriting agreement, we have agreed to sell to the underwriters, and each underwriter has severally agreed to purchase, at the public offering price less the underwriting discounts and commissions set forth on the cover page of this prospectus, the number of shares of common stock listed next to its name in the following table:

Name	Number of Shares
J.P. Morgan Securities Inc.	
Deutsche Bank Securities Inc.	
Lehman Brothers Inc.	
Total	

The underwriters are committed to purchase all the common shares offered by us if they purchase any shares. The underwriting agreement also provides that if an underwriter defaults, the purchase commitments of non-defaulting underwriters may also be increased or the offering may be terminated. The underwriters propose to offer the common shares directly to the public at the initial public offering price set forth on the cover page of this prospectus supplement and to certain dealers at that price less a concession not in excess of \$ _____ per share. Any such dealers may resell shares to certain other brokers or dealers at a discount of up to \$ _____ per share from the initial public offering price. After the initial public offering of the shares, the offering price and other selling terms may be changed by the underwriters.

The underwriters have an option to buy up to 825,000 additional shares of common stock from us to cover sales of shares by the underwriters which exceed the number of shares specified in the table above. The underwriters have 30 days from the date of this prospectus supplement to exercise this over-allotment option. If any shares are purchased with this over-allotment option, the underwriters will purchase shares in approximately the same proportion as shown in the table above. If any additional shares of common stock are purchased, the underwriters will offer the additional shares on the same terms as those on which the shares are being offered.

The underwriting fee is equal to the public offering price per share of common stock less the amount paid by the underwriters to us per share of common stock. The underwriting fee is \$ _____ per share. The following table shows the per share and total underwriting discounts and commissions to be paid to the underwriters assuming both no exercise and full exercise of the underwriters' option to purchase additional shares.

	Without over-allotment exercise	With full over-allotment exercise

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Per Share	\$	\$
Total	\$	\$
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We estimate that the total expenses of this offering, including registration, filing and listing fees, printing fees and legal and accounting expenses, but excluding the underwriting discounts and commissions, will be approximately \$500,000.

A prospectus in electronic format may be made available on the web sites maintained by one or more underwriters, or selling group members, if any, participating in the offering. The underwriters may agree to allocate a number of shares to underwriters and selling group members for sale to their online brokerage account holders. Internet distributions will be allocated by the representatives to underwriters and selling group members that may make Internet distributions on the same basis as other allocations.

We and our directors and executive officers have entered into lock-up agreements with the underwriters prior to the commencement of this offering pursuant to which we and each of these persons, with limited exceptions, for a period of 90 days after the date of this prospectus supplement, may not, without the prior written consent of J.P. Morgan Securities Inc., (1) offer, pledge, announce the intention to sell, grant any option, right or warrant to purchase, or otherwise transfer or dispose of, directly or indirectly, any shares of our common stock (including, without limitation, common stock which may be deemed to be beneficially owned by such directors, executive officers, managers and members in accordance with the rules and regulations of the SEC and securities which may be issued upon exercise of a stock option or warrant) or (2) enter into any swap or other agreement that transfers, in whole or in part, any of the economic consequences of ownership of the common stock, whether any such transaction described in clause (1) or (2) above is to be settled by delivery of common stock or such other securities, in cash or otherwise. Notwithstanding the foregoing, if (1) during the last 17 days of the 90-day restricted period, we issue an earnings release or material news or a material event relating to our company occurs, or (2) prior to the expiration of the 90-day restricted period, we announce that we will release earnings results during the 16-day period beginning on the last day of the 90-day period, the restrictions described above shall continue to apply until the expiration of the 18-day period beginning on the issuance of the earnings release or the occurrence of the material news or material event.

We have agreed to indemnify the underwriters against certain liabilities, including liabilities under the Securities Act of 1933.

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

In connection with this offering, the underwriters may engage in stabilizing transactions, which involves making bids for, purchasing and selling shares of common stock in the open market for the purpose of preventing or retarding a decline in the market price of the common stock while this offering is in progress. These stabilizing transactions may include making short sales of the common stock, which involves the sale by the underwriters of a greater number of shares of common stock than they are required to purchase in this offering, and purchasing shares of common stock on the open market to cover positions created by short sales. Short sales may be covered shorts, which are short positions in an amount not greater than the underwriters' over-allotment option referred to above, or may be naked shorts, which are short positions in excess of that amount. The underwriters may close out any covered short position either by 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 compared to the price at which the underwriters may purchase shares through the over-allotment option. A naked short position is

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more likely to be created if the underwriters are concerned that there may be downward pressure on the price of the common stock in the open market that could adversely affect investors who purchase in this offering. To the extent that the underwriters create a naked short position, they will purchase shares in the open market to cover the position.

The underwriters have advised us that, pursuant to Regulation M of the Securities Act of 1933, they may also engage in other activities that stabilize, maintain or otherwise affect the price of the common stock, including the imposition of penalty bids. This means that if the representatives of the underwriters purchase common stock in the open market in stabilizing transactions or to cover short sales, the representatives can require the underwriters that sold those shares as part of this offering to repay the underwriting discount received by them.

These activities may have the effect of raising or maintaining the market price of the common stock or preventing or retarding a decline in the market price of the common stock, and, as a result, the price of the common stock may be higher than the price that otherwise might exist in the open market. If the underwriters commence these activities, they may discontinue them at any time. The underwriters may carry out these transactions on the The Nasdaq National Market, in the over-the-counter market or otherwise.

Certain of the underwriters and their affiliates have provided in the past to us and our affiliates and may provide from time to time in the future certain commercial banking, financial advisory, investment banking and other services for us and such affiliates in the ordinary course of their business, for which they have received and may continue to receive customary fees and commissions. In addition, from time to time, certain of the underwriters and their affiliates may effect transactions for their own account or the account of customers, and hold on behalf of themselves or their customers, long or short positions in our debt or equity securities or loans, and may do so in the future.

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Legal matters

The validity of the securities being offered by this prospectus supplement will be passed upon for us by Cooley Godward LLP, Palo Alto, California. Davis Polk & Wardwell, Menlo Park, California is counsel for the underwriters in connection with this offering.

Experts

The consolidated financial statements of Nuvelo, Inc. and its subsidiaries as of December 31, 2004 and 2003, and for each of the years in the three-year period ended December 31, 2004, and management's assessment of the effectiveness of internal control over financial reporting as of December 31, 2004 have been incorporated by reference herein and in the registration statement in reliance upon the reports of KPMG LLP, independent registered public accounting firm, incorporated by reference herein, and upon the authority of said firm as experts in accounting and auditing.

Where you can find more information

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 100 F Street, N.E., 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. In addition, you can read and copy our SEC filings at the office of the National Association of Securities Dealers, Inc. at 1735 K Street, Washington, D.C. 20006. Our SEC filings are also available at the SEC's web site at www.sec.gov and our website at www.nuvelo.com. We have not incorporated by reference into this prospectus the information contained on our website and you should not consider it to be part of this prospectus.

Incorporation by reference

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 this prospectus supplement but before the end of any offering made under this prospectus supplement and accompanying prospectus (other than current reports or portions thereof furnished under Item 2.02 or Item 7.01 of Form 8-K):

our annual report on Form 10-K for the fiscal year ended December 31, 2004, filed with the SEC on March 16, 2005;

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our quarterly report on Form 10-Q for the quarter ended March 31, 2005, filed with the SEC on May 10, 2005;

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our quarterly report on Form 10-Q for the quarter ended June 30, 2005, filed with the SEC on August 8, 2005;

our quarterly report on Form 10-Q for the quarter ended September 30, 2005, filed with the SEC on November 8, 2005;

our proxy statement for our stockholders meeting on May 24, 2005, filed on April 15, 2005;

our current report on Form 8-K, filed with the SEC on January 14, 2005;

our current reports on Form 8-K, filed with the SEC on January 24, 2005;

our current report on Form 8-K, filed with the SEC on January 31, 2005;

our current report on Form 8-K, filed with the SEC on February 2, 2005;

our current report on Form 8-K, filed with the SEC on February 14, 2005;

our current report on Form 8-K, filed with the SEC on February 16, 2005;

our current report on Form 8-K, filed with the SEC on March 29, 2005;

our current report on Form 8-K, filed with the SEC on April 5, 2005;

our current report on Form 8-K, filed with the SEC on May 13, 2005;

our current report on Form 8-K, filed with the SEC on May 26, 2005;

our current report on Form 8-K, filed with the SEC on July 5, 2005;

our current report on Form 8-K, filed with the SEC on July 21, 2005;

our current report on Form 8-K, filed with the SEC on August 5, 2005;

our current report on Form 8-K, filed with the SEC on September 20, 2005;

our current reports on Form 8-K and Form 8-K/A, filed with the SEC on September 22, 2005;

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our current report on Form 8-K, filed with the SEC on September 29, 2005;

our current report on Form 8-K, filed with the SEC on November 17, 2005;

our current reports on Form 8-K and Form 8-K/A, filed with the SEC on December 19, 2005; and

our current report on Form 8-K, filed with the SEC on January 6, 2006.

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: Gary Titus
201 Industrial Road, Suite 310
San Carlos, California 94070
(650) 517-8000

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Prospectus

\$100,000,000

Nuvelo, Inc.

Debt securities

Preferred stock

Common stock

We may sell from time to time in one or more offerings up to \$100,000,000 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. **This prospectus may not be used to offer or sell any securities unless accompanied by a prospectus supplement.**

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

Our common stock is quoted on the Nasdaq National Market under the symbol NUVO. On July 13, 2005, the last reported sale price for our common stock on the Nasdaq National Market was \$8.70 per share. The applicable prospectus supplement will contain information, where applicable, as to any other listing on the Nasdaq National Market or any securities exchange of the securities covered by the 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 is truthful or complete. Any representation to the contrary is a criminal offense.

The date of this prospectus is August 3, 2005

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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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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 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. **This prospectus may not be used to consummate a sale of securities unless it is accompanied by a prospectus supplement.**

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 Annual Report on Form 10-K, and in our most recent Quarterly Report on Form 10-Q, both as filed with the Securities and Exchange Commission, or SEC, and both of which are incorporated herein by reference. You should also consider 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 a biopharmaceutical company focused on the discovery, development and commercialization of therapeutics for the treatment of acute cardiovascular indications and cancer. We currently have three drug candidates in clinical trials. Our lead drug candidate, alfineprase, is a direct acting thrombolytic agent, or blood clot dissolver. Our second drug candidate, recombinant nematode anticoagulant protein c2, or rNAPc2, is an anticoagulant that inhibits the interaction of factor VIIa and tissue factor. Our third drug candidate, ARC183, is a direct thrombin inhibiting aptamer that is being developed for use in acute anticoagulant applications. In addition, we recently identified NU206 as a preclinical development candidate from our proprietary research programs and expect to leverage expertise in secreted proteins and antibody discovery to expand our pipeline and create partnering and licensing opportunities.

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. On March 25, 2004, we reincorporated in the State of Delaware. 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>. We have not incorporated by reference into this prospectus the information contained on our website and you should not consider it to be part of this prospectus.

Table of Contents**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, project, positioned, 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, the advancement of our drug candidates in clinical trials, 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.

Ratio of earnings to fixed charges

Our earnings were insufficient to cover fixed charges in each of the years in the five-year period ended December 31, 2004 and in the three-month period ended March 31, 2005. Earnings consist of loss from continuing operations before income taxes, extraordinary items, cumulative effect of accounting changes, equity in net losses of affiliates and fixed charges, adjusted for capitalized interest. Fixed charges consist of interest expense, including the interest component of rent expense, capitalized and amortized premiums and discounts, and capitalized expenses related to indebtedness. The extent to which earnings were insufficient to cover fixed charges is as follows:

	Fiscal year ended December 31,					Three months ended March 31, 2005
	2000	2001	2002	2003	2004	
(in thousands)						
Ratio of earnings to fixed charges(1)						
Coverage deficiency	\$ (22,253)	\$ (36,472)	\$ (44,978)	\$ (50,187)	\$ (52,489)	\$ (14,662)

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- (1) Adjusted earnings, as described above, were insufficient to cover fixed charges in each period. 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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Description of debt securities

The following description, together with the additional information we include in any applicable prospectus supplements, summarizes the material terms and provisions of the debt securities that we may offer under this prospectus. While the terms we have summarized below will apply generally to any future debt securities we may offer under this prospectus, we will describe the particular terms of any debt securities that we may offer in more detail in the applicable prospectus supplement. The terms of any debt securities we offer under a prospectus supplement may differ from the terms we describe below. However, no prospectus supplement shall fundamentally change the terms that are set forth in this prospectus or offer a security that is not registered and described in this prospectus at the time of its effectiveness. 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. As of March 31, 2005, we have \$17.9 million in outstanding indebtedness including accrued interest.

We will issue the senior debt securities under the senior indenture that we will enter into with the trustee named in the senior indenture. We will issue the subordinated debt securities under the subordinated indenture that we will enter into with the trustee named in the subordinated indenture. We have filed forms of these documents as exhibits to the registration statement which includes this prospectus. We use the term indentures in this prospectus to refer to both the senior indenture and the subordinated indenture.

The indentures will be qualified under the Trust Indenture Act of 1939. We use the term trustee to refer to either the senior trustee or the subordinated trustee, as applicable.

The following summaries of material provisions of the senior debt securities, the subordinated debt securities and the indentures are subject to, and qualified in their entirety by reference to, all the provisions of the indenture applicable to a particular series of debt securities. Except as we may otherwise indicate, the terms of the senior indenture and the subordinated indenture are identical.

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:

whether the debt securities will be senior or subordinated;

the offering price;

the title;

any limit on the aggregate principal amount;

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

the date the principal will be payable;

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

the place where payments may be made;

any mandatory or optional redemption provisions;

if applicable, the method for determining how the principal, premium, if any, or interest will be calculated by reference to an index or formula;

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;

the portion of the principal amount that will be payable upon acceleration of stated maturity, if other than the entire principal amount;

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;

any defeasance provisions if different from those described below under Satisfaction and Discharge; Defeasance;

any conversion or exchange provisions;

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

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

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

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

any other specific terms of such debt securities.

Unless otherwise specified in the prospectus supplement:

the debt securities will be registered debt securities; and

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.

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

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

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:

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

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

the depository has notified us that it is unwilling or unable to continue as depository or has ceased to be qualified to act as depository;

an event of default is continuing; or

any other circumstances described in a prospectus supplement.

As long as the depository, or its nominee, is the registered owner of a global security, the depository 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:

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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.

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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.

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 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.

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.

If the debt securities are convertible for our other securities or securities of other entities, the person with whom we consolidate or merge or to whom we sell all of our property must make provisions for the conversion of the debt securities into securities which the holders of the debt securities would have received if they had converted the debt securities before the consolidation, merger or sale.

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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 90 days when due;
- (3) failure to deposit any sinking fund payment when due;
- (4) failure to perform any other covenant in the indenture continued for 90 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.

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 90 days after the original request.

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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:

change the stated maturity of any debt security;

reduce the principal, premium, if any, or interest on any debt security;

reduce the principal of an original issue discount security or any other debt security payable on acceleration of maturity;

reduce the rate of interest on any debt security;

change the currency in which any debt security is payable;

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 in any material respect; 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 will contain 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 a subordinated indenture; and

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(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.

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 indentures will limit the right of the trustee, should it become a creditor of us, to obtain payment of claims or secure its claims.

The trustee will be 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 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. Subordinated debt securities also are effectively subordinated to all debt and other liabilities, including trade payables and lease obligations, if any, of our subsidiaries.

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Upon any distribution of our assets upon any dissolution, winding up, liquidation or reorganization, the payment of the principal of and interest on 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 subordinated debt securities are entitled to receive any payment or distribution. The indentures will require us or the trustee to promptly notify holders of designated senior indebtedness if payment of subordinated debt securities is accelerated because of an event of default.

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

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, which is called a payment default ; or

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, which is called a payment blockage notice from us or any other person permitted to give such notice under the indenture, which is called a non-payment default .

We may resume payments and distributions on subordinated debt securities:

in the case of a payment default, upon the date on which such default is cured or waived or ceases to exist; and

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.

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.

If the trustee or any holder of the notes receives any payment or distribution of our assets in contravention of the subordination provisions on 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 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 March 31, 2005, \$17.9 million in senior indebtedness was outstanding. Unless we inform you otherwise in the prospectus supplement, we will not be prohibited from incurring debt, including senior indebtedness, under any indenture relating to subordinated debt securities. We may from time to time incur additional debt, including senior indebtedness.

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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 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.

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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 liabilities, contingent or otherwise, as lessee under leases for facility equipment (and related assets leased together with such equipment) and under any lease or related document (including a purchase agreement, conditional sale or other title retention or synthetic lease agreement) in connection with the lease of real property or improvement thereon (or any personal property included as part of any such lease) which provides that such Person is contractually obligated to purchase or cause a third party to purchase the leased property or pay an agreed upon residual value of the leased property, including the obligations under such lease or related document to purchase or cause a third party to purchase such leased property (whether or not such lease transaction is characterized as an operating lease or a capitalized lease in accordance with GAAP) or pay an agreed upon residual value of the leased property to the lessor;
- (5) all obligations with respect to an interest rate or other swap, cap or collar agreement or other similar instrument or agreement or foreign currency hedge, exchange, purchase agreement or other similar instrument or agreement;
- (6) all direct or indirect guaranties or similar agreements in respect of, and our obligations or liabilities to purchase, acquire or otherwise assure a creditor against loss in respect of, indebtedness, obligations or liabilities of others of the type described in (1) through (5) above;
- (7) any indebtedness or other obligations described in (1) through (6) above secured by any mortgage, pledge, lien or other encumbrance existing on property which is owned or held by us; and
- (8) any and all refinancings, replacements, deferrals, renewals, extensions and refundings of, or amendments, modifications or supplements to, any indebtedness, obligation or liability of the kind described in clauses (1) through (7) above.

senior indebtedness means the principal, premium, if any, interest, including any interest accruing after bankruptcy, and rent or termination payment on or other amounts due on our current or future indebtedness, whether created, incurred, assumed, guaranteed or in effect

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guaranteed by us, including any deferrals, renewals, extensions, refundings, amendments, modifications or supplements to the above. However, senior indebtedness does not include:

indebtedness that expressly provides that it shall not be senior in right of payment to subordinated debt securities or expressly provides that it is on the same basis or junior to subordinated debt securities;

our indebtedness to any of our majority-owned subsidiaries; and

subordinated debt securities.

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Description of preferred stock

We currently have authorized 5,000,000 shares of preferred stock, of which 100,000 shares have been designated Series A Junior Participating Preferred Stock, or Series A Preferred. Shares of Series A Preferred are issuable under certain circumstances in connection with our stockholder rights agreement, which, together with the rights preferences and privileges of the Series A Preferred, is described below under the heading Description of common stock Stockholder rights agreement. As of July 14, 2005, we do not have any shares of preferred stock outstanding.

General

Prior to issuance of shares of each series of our undesignated preferred stock, our Board of Directors is required by the Delaware General Corporate Law, or DGCL, and our Amended and Restated Certificate of Incorporation, or certificate of incorporation, to adopt resolutions and file a Certificate of Designation with the Secretary of State of the State of Delaware, fixing for each such series the designations, powers, preferences, rights, qualifications, limitations and restrictions of the shares of such series. Our Board of Directors could authorize the issuance of shares of preferred stock with terms and conditions which could have the effect of discouraging a takeover or other transaction which holders of some, or a majority, of such shares might believe to be in their best interests or in which holders of some, or a majority, of such shares might receive a premium for their shares over the then-market price of such shares.

Subject to limitations prescribed by the DGCL, our certificate of incorporation and our Amended and Restated Bylaws, or bylaws, our Board of Directors is authorized to fix the number of shares constituting each series of preferred stock and the designations, powers, preferences, rights, qualifications, limitations and restrictions of the shares of such series, including such provisions as may be desired concerning voting, redemption, dividends, dissolution or the distribution of assets, conversion or exchange, and such other subjects or matters as may be fixed by resolution of the Board of Directors. Each series of preferred stock that we offer under this prospectus will, when issued, be fully paid and nonassessable and will not have, or be subject to, any preemptive or similar rights.

The applicable prospectus supplement(s) will describe the following terms of the series of preferred stock in respect of which this prospectus is being delivered:

the title and stated value of the preferred stock;

the number of shares of the preferred stock offered, the liquidation preference per share and the purchase price of the preferred stock;

the dividend rate(s), period(s) and/or payment date(s) or the method(s) of calculation for dividends;

whether dividends shall be cumulative or non-cumulative and, if cumulative, the date from which dividends on the preferred stock shall accumulate;

the procedures for any auction and remarketing, if any, for the preferred stock;

the provisions for a sinking fund, if any, for the preferred stock;

the provisions for redemption, if applicable, of the preferred stock;

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any listing of the preferred stock on any securities exchange or market;

the terms and conditions, if applicable, upon which the preferred stock will be convertible into common stock or another series of our preferred stock, including the conversion price (or its manner of calculation) and conversion period;

the terms and conditions, if applicable, upon which preferred stock will be exchangeable into our debt securities, including the exchange price, or its manner of calculation, and exchange period;

voting rights, if any, of the preferred stock;

a discussion of any material and/or special United States federal income tax considerations applicable to the preferred stock;

whether interests in the preferred stock will be represented by depositary shares;

the relative ranking and preferences of the preferred stock as to dividend rights and rights upon liquidation, dissolution or winding up of our affairs;

any limitations on issuance of any series of preferred stock ranking senior to or on a parity with the preferred stock as to dividend rights and rights upon liquidation, dissolution or winding up of our affairs; and

any other specific terms, preferences, rights, limitations or restrictions on the preferred stock.

Unless otherwise specified in the prospectus supplement, the preferred stock will, with respect to dividend rights and rights upon liquidation, dissolution or winding up of Nuvelo rank:

senior to all classes or series of our common stock, and to all equity securities issued by us the terms of which specifically provide that such equity securities rank junior to the preferred stock with respect to dividend rights or rights upon the liquidation, dissolution or winding up of us;

on a parity with all equity securities issued by us that do not rank senior or junior to the preferred stock with respect to dividend rights or rights upon the liquidation, dissolution or winding up of us; and

junior to all equity securities issued by us the terms of which do not specifically provide that such equity securities rank on a parity with or junior to the preferred stock with respect to dividend rights or rights upon the liquidation, dissolution or winding up of us (including any entity with which we may be merged or consolidated or to which all or substantially all of our assets may be transferred or which transfers all or substantially all of our assets).

As used for these purposes, the term equity securities does not include convertible debt securities.

Transfer agent and registrar

The transfer agent and registrar for any series of preferred stock will be set forth in the applicable prospectus supplement.

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Description of common stock

The following is only a summary of the material terms of our common stock and our stockholder rights agreement. Because it is only a summary, it does not contain all the information that may be important to you. Accordingly, you should read carefully the more detailed provisions of our amended and restated certificate of incorporation, bylaws and rights agreement, each of which has been filed with the SEC, as well as applicable Delaware law.

We currently have authorized 100,000,000 shares of common stock, par value \$0.001, and, as of June 30, 2005, we had 42,049,297 shares of common stock outstanding. As of June 30, 2005, we had an aggregate of 4,648,120 shares of common stock reserved for issuance upon exercise of outstanding stock options granted under our 2004 Equity Incentive Plan, 2002 Equity Incentive Plan, 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, and an aggregate of 2,967,410 shares of common stock reserved for issuance pursuant to future grants under our 2004 Equity Incentive Plan. As of June 30, 2005, we also had 277,461 shares of common stock reserved for issuance under our Employee Stock Purchase Plan. As of June 30, 2005, we had an aggregate of 872,719 shares of common stock reserved for issuance upon the exercise of stock options granted outside of any of our stock option plans. As of June 30, 2005, we had warrants to purchase an aggregate of 1,516,792 shares of our common stock outstanding, with exercise prices ranging from \$4.05 to \$25.53 per share, and a weighted average exercise price of \$20.88 per share.

As of June 30, 2005, 735,800 shares of our common stock were issuable, at our option, to repay a note in the principal amount of \$4.0 million 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 \$50.0 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. In addition, as of June 30, 2005, 1,095,319 shares of common stock were issuable, upon mutual agreement, to convert the promissory note that we have issued under a line of credit with Dr. George Rathmann.

Common stock

Holders of our common stock are entitled to one vote per share for the election of directors and all other matters submitted for stockholder vote, except matters submitted to the vote of another class or series of shares. Holders of common stock are not entitled to cumulative voting rights. The approval of 66 2/3% of the voting rights of the common stock is required to make certain amendments to our certificate of incorporation, amend our by-laws, and to remove a director from our board of directors.

The holders of 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. Under our August 31, 2004 Loan and Security Agreement with Silicon Valley Bank, we cannot pay dividends without Silicon Valley Bank's prior written consent,

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except for dividends paid in shares of our capital stock. Upon liquidation, dissolution or winding up of us, the holders of our common stock are entitled to share ratably in all net assets available for distribution to stockholders after payments to creditors and holders of senior securities. The common stock is not redeemable and has no preemptive, conversion or sinking fund rights. The rights of the holders of our common stock are subject to the rights of the holders of any preferred stock which may, in the future, be issued. All outstanding shares of our common stock are, and any shares of common stock issued pursuant to this prospectus when issued will be, duly authorized, validly issued, fully paid and non-assessable.

As of June 30, 2005, we had 42,049,297 shares of common stock issued and outstanding.

Transfer agent

The transfer agent and registrar for our common stock is U.S. Stock Transfer Corporation. Its offices are located at 1745 Gardena Ave., Glendale, California 91204, and its telephone number is (818) 502-1404.

Stockholder rights agreement

On June 5, 1998, our board of directors adopted a stockholder rights agreement, or rights agreement, which was subsequently amended on November 9, 2002 and March 19, 2004. Pursuant to the rights agreement, one whole right attaches to each outstanding share of our common stock. Each right entitles the registered holder to purchase from us one one-thousandth (1/1000) of a share of our Series A Junior Participating Preferred Stock at an initial purchase price of \$175.00 per one-thousandth of a share of our Series A Preferred, subject to customary antidilution adjustments. The rights do not become exercisable until the earlier to occur of:

10 business days following a public announcement that a person or group has acquired beneficial ownership of 15% (or 27.5% in the case of an approved stockholder) or more of our outstanding common stock (any such person or group is referred to as an acquiring person); or

10 business days (or a later date as determined by our board of directors) following the commencement or announcement of an intention to make a tender offer or exchange offer, that would result in a person or entity becoming an acquiring person.

The rights will expire on June 5, 2008, unless they are redeemed or exchanged by us before that time. Until a right is exercised, the rights do not convey the right to vote, receive dividends or otherwise provide the holder with any rights as a stockholder.

Each whole share of Series A Preferred purchasable upon exercise of the rights will be entitled to a minimum preferential quarterly dividend payment of \$1.00 per share but will be entitled to an aggregate dividend of 1,000 times the dividend, if any, declared per common share. In the event of liquidation, the holders of the Series A Preferred will be entitled to a minimum preferential liquidation payment of \$1,000 per share but will be entitled to an aggregate payment of 1,000 times the payment made per common share (if more than \$1,000 per share of Series A Preferred). Each share of Series A Preferred will have 1,000 votes and will vote together with the common shares. In the event of any merger, consolidation or other transaction in which common shares are exchanged,

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each share of Series A Preferred will be entitled to receive 1,000 times the amount received per common share. These rights are protected by customary antidilution provisions.

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When a person or group becomes an acquiring person (or at such later time as determined by independent directors of our board of directors) then each registered holder of a right, except for such person or group, will be entitled to purchase, for the purchase price, shares of our common stock having a then current market value equal to two times the purchase price of the right. Subject to specified exemptions, in the event that we are involved in a merger, or we sell more than 50% of our assets or earning power to an acquiring company, each right will entitle the holder, other than an acquiring person, to purchase, upon exercise, a number of shares of common stock of the acquiring company having a then current market value of two times the purchase price of the right.

We may, at our option, at any time prior to the close of business on the tenth day following the day a person or group becomes an acquiring person, redeem all of the then-outstanding rights at a redemption price of \$0.001 per right, subject to certain adjustments. At any time after a person or group becomes an acquiring person and prior to the acquisition by that person or group of 50% or more of the outstanding shares of our common stock, our board of directors may cause us to acquire the rights (other than rights owned by the acquiring person), in whole or in part, in exchange for one share of common stock per right.

While the rights are redeemable, we may supplement or amend any provision of the rights agreement in any respect without the approval of any holders of rights or shares of common stock. When the rights are no longer redeemable, we may supplement or amend the rights agreement without the approval of any holders of rights certificates as long as the supplement or amendment does not adversely affect the interests of the holders of rights (other than an acquiring person). Any supplement or amendment to the rights agreement shall require the affirmative vote of a majority of our independent directors. Any extension of the final expiration date of the rights shall require the affirmative vote of three-quarters of the independent directors.

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Additional information concerning our capital stock

Anti-takeover effects of our certificate of incorporation and bylaws

Our certificate of incorporation and by-laws include a number of provisions that may have the effect of encouraging persons considering unsolicited tender offers or other unilateral takeover proposals to negotiate with our board of directors rather than pursue non-negotiated takeover attempts. These provisions:

establish a classified board of directors so that not all members of our board may be elected at one time;

establish that the holders of 66 2/3% of the voting rights of all classes of stock entitled to vote are required to remove our directors or to amend the by-laws and certain provisions of our certificate of incorporation;

authorize the issuance of up to 5,000,000 shares of preferred stock that could be issued by our board of directors to increase the number of outstanding shares and hinder a takeover attempt;

limit who may call a special meeting of stockholders;

prohibit stockholder action by written consent, thereby requiring all stockholder actions to be taken at a meeting of our stockholders; and

establish advance notice requirements for nominations for election to our board of directors or for proposing matters that can be acted upon at a stockholder meeting.

These provisions could discourage, delay or prevent certain types of transactions involving an actual or potential change in control of us, including transactions in which stockholders might otherwise receive a premium for their shares over current market prices.

Business combination statute under Delaware law

We are also subject to provisions of Delaware law that could discourage, delay or prevent an actual or potential change in control of us. These anti-takeover laws prevent a Delaware corporation from engaging in a merger or sale of more than 10 percent of its assets with any stockholder, including all affiliates and associates of the stockholder, who owns 15 percent or more of the corporation's outstanding voting stock, for three years following the date that the stockholder acquired 15 percent or more of the corporation's stock unless:

the board of directors approved the transaction where the stockholder acquired 15 percent or more of the corporation's stock;

after the transaction in which the stockholder acquired 15 percent or more of the corporation's stock, the stockholder owned at least 85 percent of the corporation's outstanding voting stock, excluding shares owned by directors, officers and employee stock plans in which employee participants do not have the right to determine confidentially whether shares held under the plan will be tendered in a tender or exchange offer; or

on or after this date, the merger or sale is approved by the board of directors and the holders of at least two-thirds of the outstanding voting stock that is not owned by the stockholder.

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Limitation of liability and indemnification

To the fullest extent permitted by the Delaware law, our certificate of incorporation provides that directors shall not be personally liable to us or any of our stockholders for monetary damages for breach of fiduciary duty as a director. However, this provision does not eliminate the duty of care, and in appropriate circumstances, equitable remedies such as injunctive or other forms of nonmonetary relief that will remain available under Delaware law. In addition, each director will continue to be subject to liability for (i) breach of the directors duty of loyalty to us or our stockholders, (ii) acts or omissions not in good faith or which involve intentional misconduct or a knowing violation of law, (iii) violating Section 174 of the Delaware General Corporation Law, or (iv) any transaction from which the director derived an improper personal benefit. The provision also does not affect a director's responsibilities under any other law, such as the federal securities laws or state or federal environmental laws.

In accordance with Delaware law, our by-laws provide that we shall indemnify any person who was or is a party or is threatened to be made a party to, or otherwise becomes involved in, any proceeding (other than an action by or in the right of Nuvelo) by reason of the fact that he is an officer, director or agent of Nuvelo against losses actually and reasonably incurred by that person if the person acted in good faith and in a manner the person reasonably believed to be in or not opposed to our best interests. Losses are the total amount that the officer, director or agent becomes legally obligated to pay, including judgments, fines, amounts paid in settlement, attorneys' fees, expenses of establishing a right to indemnification and other expenses. If the proceeding is a criminal proceeding, the person to be indemnified must have had no reasonable cause to believe his or her conduct was unlawful.

Our bylaws provide for similar indemnification for expenses resulting from an action by or in the right of Nuvelo, except that no indemnification will be made if the person is adjudged by a court of competent jurisdiction after exhaustion of all appeals to be liable to us or for amounts paid in settlement to us unless the court determines that the person is fairly and reasonably entitled to indemnity for expenses. Expenses of officers, directors and agents include attorneys' fees, any expenses of establishing a right to indemnification and amounts paid in settlement. Our bylaws also provide for advancement of expenses.

We also maintain liability insurance for our officers and directors and have entered into indemnification agreements with them.

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Plan of distribution

We may sell the securities separately or together:

through one or more underwriters or dealers in a public offering and sale by them;
directly to investors; or
through agents.

We may sell the securities from time to time in one or more transactions at a fixed price or prices, which may be changed from time to time:

at market prices prevailing at the times of sale;
at prices related to such prevailing market prices; or
at negotiated prices.

We will describe the method of distribution of the securities in the prospectus supplement.

Underwriters, dealers or agents may receive compensation in the form of discounts, concessions or commissions from us or our purchasers (as their agents in connection with the sale of securities). These underwriters, dealers or agents may be considered to be underwriters under the Securities Act. As a result, discounts, commissions, or profits on resale received by the underwriters, dealers or agents may be treated as underwriting discounts and commissions. The prospectus supplement will identify any such underwriter, dealer or agent, and describe any compensation received by them from us. Only underwriters named in the prospectus supplement are underwriters of the securities offered by the prospectus supplement. Any initial public offering price and any discounts or concessions allowed or reallocated or paid to dealers may be changed from time to time.

We may sell securities directly or through agents we designate from time to time. We will name any agent involved in the offering and sale of securities and we will describe any commissions we will pay the agent in the prospectus supplement. Unless the prospectus supplement states otherwise, our agent will act on a best-efforts basis for the period of its appointment.

We may authorize agents or underwriters to solicit offers by certain types of institutional investors to purchase securities from us at the public offering price set forth in the prospectus supplement pursuant to delayed delivery contracts providing for payment and delivery on a specified date in the future. We will describe the conditions to these contracts and the commissions we must pay for solicitation of these contracts in the prospectus supplement.

Underwriters, dealers and agents may be entitled to indemnification by us against certain civil liabilities, including liabilities under the Securities Act, or to contribution with respect to payments made by the underwriters, dealers or agents, under agreements between us and the underwriters, dealers and agents.

We may grant underwriters who participate in the distribution of securities an option to purchase additional securities to cover over-allotments, if any, in connection with the distribution. Any underwriter may engage in overallotment, stabilizing transactions, short covering transactions and penalty bids in accordance with Regulation M under the Securities Exchange Act of 1934, as amended, or the Exchange Act. Overallotment involves sales in excess of

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the offering size, which create a short position. Stabilizing transactions permit bids to purchase the underlying security so long as the stabilizing bids do not exceed a specified maximum. Short covering transactions involve purchases of the common stock in the open market after the distribution is completed to cover short positions. Penalty bids permit the underwriters to reclaim a selling concession from a dealer when the common stock originally sold by the dealer is purchased in a covering transaction to cover short positions. Those activities may cause the price of the common stock to be higher than it would otherwise be. If commenced, the underwriters may discontinue any of the activities at any time.

Any underwriters who are qualified market makers on the Nasdaq National Market may engage in passive market making transactions in the common stock on the Nasdaq National Market in accordance with Rule 103 of Regulation M, during the business day prior to the pricing of the offering, before the commencement of offers or sales of the common stock. Passive market makers must comply with applicable volume and price limitations and must be identified as passive market makers. In general, a passive market maker must display its bid at a price not in excess of the highest independent bid for such security; if all independent bids are lowered below the passive market maker's bid, however, the passive market maker's bid must then be lowered when certain purchase limits are exceeded.

In compliance with guidelines of the National Association of Securities Dealers, or NASD, the maximum consideration or discount to be received by any NASD member or independent broker dealer may not exceed 8% of the aggregate amount of the securities offered pursuant to this prospectus and any applicable prospectus supplement.

All securities we offer, other than common stock, will be new issues of securities with no established trading market. Underwriters involved in the public offering and sale of these securities may make a market in these securities. However, they are not obligated to make a market and may discontinue market making activity at any time. No assurance can be given as to the liquidity of the trading market for any of these securities.

Underwriters or agents and their associates may be customers of, engage in transactions with or perform services for us in the ordinary course of business.

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Legal matters

The validity of the securities being offered by this prospectus will be passed upon for us by Cooley Godward LLP of Palo Alto, California.

Experts

The consolidated financial statements of Nuvelo, Inc. as of December 31, 2004 and 2003, and for each of the years in the three-year period ended December 31, 2004, and management's assessment of the effectiveness of internal control over financial reporting as of December 31, 2004, have been incorporated by reference herein in reliance upon the reports of KPMG LLP, independent registered public accounting firm, incorporated by reference herein, and upon the authority of said firm as experts in accounting and auditing.

Where you can find more information

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 100 F Street, N.E., 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 at the SEC's web site at www.sec.gov and our website at www.nuvelo.com. We have not incorporated by reference into this prospectus the information contained on our website and you should not consider it to be part of this prospectus. In addition, you can read and copy our SEC filings at the office of the National Association of Securities Dealers, Inc. at 1735 K Street, Washington, D.C. 20006.

Incorporation by reference

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, and information that we file later with the SEC will automatically update and supersede this information. Further, all filings we make under the Securities Exchange Act after the date of the initial registration statement and prior to effectiveness of the registration statement shall be deemed to be incorporated by reference into this prospectus. 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:

our annual report on Form 10-K for the fiscal year ended December 31, 2004, filed with the SEC on March 16, 2005;

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our quarterly report on Form 10-Q for the quarter ended March 31, 2005, filed with the SEC on May 10, 2005;

our proxy statement for our stockholders meeting on May 24, 2005, filed on April 15, 2005;

our current report on Form 8-K, filed with the SEC on January 14, 2005;

our current reports on Form 8-K, filed with the SEC on January 24, 2005;

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our current report on Form 8-K, filed with the SEC on January 31, 2005;

our current report on Form 8-K, filed with the SEC on February 2, 2005;

our current report on Form 8-K, filed with the SEC on February 14, 2005;

our current report on Form 8-K, filed with the SEC on February 16, 2005;

our current report on Form 8-K, filed with the SEC on March 29, 2005;

our current report on Form 8-K, filed with the SEC on April 5, 2005;

our current report on Form 8-K, filed with the SEC on May 13, 2005;

our current report on Form 8-K, filed with the SEC on May 26, 2005; and

our current report on Form 8-K, filed with the SEC on July 5, 2005.

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

Nuvelo, Inc.

Attention: Lee Bendekgey

675 Almanor Avenue

Sunnyvale, CA 94085

(408) 215-4000

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