NEOSE TECHNOLOGIES INC
Form 424B5
February 18, 2005

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Filed pursuant to Rule 424(b)(5)
Registration Number 333-121112

PROSPECTUS SUPPLEMENT

(To Prospectus dated January 10, 2005)

7,000,000 Shares

Common Stock

We are offering all of the 7,000,000 shares of common stock offered by this prospectus supplement.

Our common stock is listed on The NASDAQ National Market under the symbol NTEC. On February 17, 2005, the last reported sale price of our common stock on The NASDAQ National Market was $4.76 per share.

Investing in our common stock involves a high degree of risk. Before buying any shares, you should carefully read the discussion of material risks of investing in our common stock under the heading Risk factors beginning on page S-9 of this prospectus supplement.

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

	Per share	Total
Public offering price	$4.00	$28,000,000
Underwriting discounts and commissions	$0.24	$ 1,680,000
Proceeds, before expenses, to us	$3.76	$26,320,000

The underwriters may also purchase up to an additional 1,050,000 shares of our common stock at the public offering price, less underwriting discounts and commissions payable by us, to cover over-allotments, if any, within 30 days of the date of this prospectus supplement. If the underwriters exercise the option in full, the total underwriting discounts and commissions will be $1,932,000, and the total proceeds, before expenses, to us will be $30,268,000.

The underwriters are offering the shares of our common stock as set forth under Underwriting. Delivery of the shares of common stock will be made on or about February 24, 2005.

Sole Book-Running Manager

UBS Investment Bank **JPMorgan**

Jefferies & Company, Inc.

The date of this prospectus supplement is February 18, 2005.

You should rely only on the information contained or incorporated by reference in this prospectus supplement and the accompanying prospectus. We have not, and the underwriters have not, authorized anyone to provide you with 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 this 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.

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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 in this prospectus supplement, as well as the financial statements and the other information incorporated by reference herein before making an investment decision.

Unless the context requires otherwise, the words Neose, we, company, us and our refer to Neose Technologies, Inc.

BUSINESS OVERVIEW

We are a biopharmaceutical company using our enzymatic technologies to develop proprietary drugs, focusing primarily on therapeutic proteins. We believe that our core enzymatic technologies, GlycoAdvance™ and GlycoPEGylation™, improve the drug properties of therapeutic proteins by building out, and attaching polyethylene glycol (PEG) to, carbohydrate structures on the proteins. We are using our technologies to develop proprietary versions of protein drugs with proven safety and efficacy and to improve the therapeutic profiles of proteins being developed by our partners. We expect these modified proteins to offer significant advantages, including less frequent dosing and possibly improved efficacy, over the original versions of the drugs now on the market, as well as to meet or exceed the pharmacokinetic profile of next-generation versions of the drugs now on the market. We believe this strategy of targeting drugs with proven safety and efficacy allows us to lower the risk profile of our proprietary development portfolio as compared to *de novo* protein drug development.

Our proprietary drug development portfolio currently consists of two therapeutic protein candidates. GlycoPEG-EPO (NE-180) is a long-acting version of erythropoietin (EPO) produced in insect cells. EPO is prescribed to stimulate production of red blood cells, and is approved for sale in major markets around the world for treatment of chemotherapy-induced anemia and anemia associated with chronic renal failure. During the second quarter of 2005, we plan to have a pre-Investigational New Drug application (IND) meeting with the U.S. Food and Drug Administration (FDA) and submit an IND to the FDA for NE-180. Our second proprietary protein, GlycoPEG-GCSF, is a long-acting version of granulocyte colony stimulating factor (G-CSF) that we are co-developing with BioGeneriX AG, a company of the ratiopharm Group. G-CSF is prescribed to stimulate production of neutrophils (a type of white blood cell) and is approved for sale in major markets around the world for treatment of neutropenia associated with myelosuppressive chemotherapy. Prior to the end of 2005, in collaboration with our partner, BioGeneriX, we plan to request scientific advice from regulatory authorities in the European Union (EU) and submit the equivalent of an IND in an EU country for GlycoPEG-GCSF. In 2003, the EPO and G-CSF drug categories had aggregate worldwide sales of approximately $9.7 billion and $3.0 billion, respectively.

Market opportunity

Worldwide sales of protein drugs in 2003 have been reported at approximately $40 billion, and by some estimates are expected to grow to over $70 billion by 2008. We believe that many of the proteins now on the market will lose the protection of certain patent claims over the next 15 years. In addition, many marketed proteins are facing increased competition from next-generation versions or from other drugs approved for the same disease indications. Although not every protein drug is a candidate for the use of our technologies, we believe our technologies can be applied to many of these marketed drugs to create products with improved clinical profiles. We are pursuing opportunities in this field through our own proprietary drug development portfolio, our exploratory research program and our partnering and licensing program.

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OUR TECHNOLOGY

Our GlycoAdvance and GlycoPEGylation technologies involve the use of enzymes to modify or initiate, and attach PEG to, carbohydrate structures on glycoproteins (proteins with carbohydrate structures attached). We have developed a special expertise and extensive intellectual property position in this area. Our technologies may permit the development of therapeutic proteins with improved clinical profiles. In some cases, these improvements to therapeutic proteins may also allow us to create new intellectual property relating to our core technologies as well as new compositions of matter. We continue to make significant investments in research and development and legal services to protect and expand our intellectual property position. We believe our core technologies have broad application to protein drug development and can be extended to provide an opportunity for sustainable growth. We are using our GlycoAdvance and GlycoPEGylation technologies in our proprietary drug development portfolio, in our exploratory research program and in our partnering and licensing program.

GlycoAdvance

Our GlycoAdvance technology employs enzymes to modify or initiate carbohydrate structures on proteins. Currently, recombinant glycoprotein drugs are often produced in mammalian cell culture expression systems, primarily Chinese hamster ovary (CHO) cells. Generally, carbohydrates are added to proteins during the process of expression. CHO cells, and many other expression systems used for commercial manufacturing of proteins, tend to produce protein molecules with incomplete or inconsistent carbohydrate structures. In the human body, these incompletely glycosylated proteins may be cleared too rapidly and thus compromise the half-life and effectiveness of these proteins. Conventional approaches to improving the glycosylation of recombinant protein drugs, such as changing the cell line used for expression, re-engineering the protein, and modifying cell culture conditions or media, are time consuming and frequently provide only partial solutions. In addition, when a protein is inconsistently glycosylated, additional purification may be required to remove incompletely glycosylated drug molecules from the desired drug product, resulting in lower manufacturing yields and increased expense.

Our GlycoAdvance technology addresses these problems by employing enzymes to modify the carbohydrate structures on proteins that have inadequate carbohydrate structures and to initiate carbohydrate structures on proteins that have none. Proteins may have inadequate carbohydrate structures as a result of the cell expression systems used, or may have no carbohydrate structures in their native state or as a result of the cell expression system used. Our GlycoAdvance technology enables the use of multiple expression systems to produce protein drugs, including not only CHO and *E. coli*, but also insect cells. By modifying or initiating carbohydrate structures on proteins, GlycoAdvance also enables the application of our GlycoPEGylation technology to these proteins.

GlycoPEGylation

Our GlycoPEGylation technology employs enzymes to attach PEG selectively to the carbohydrate structures on glycoprotein drugs, rather than attaching PEG directly to the protein backbone.

Common protein drug delivery problems include poor solubility and stability, proteolysis (rapid degradation), rapid clearance, and immunogenicity. For some proteins, one approach to these problems has been conventional chemical pegylation the attachment of the large, water-soluble polymer, PEG, directly to the amino acid backbone of the protein. Pegylation has been used in marketed drugs, such as PEG-INTRON®, PEGASYS® and Neulasta®. Pegylation increases the effective size of the drug and in some cases improves its solubility, stability, half-life and immunogenicity profile.

For some protein drugs, it has been difficult to achieve the benefits of pegylation by the conventional approach of attaching PEG directly to the protein backbone. A possible explanation is that the sites for the attachment of PEG occur at positions where the bulky PEG molecules block access to the active site on the protein or alter the conformation of the protein. This may diminish or eliminate drug activity.

By employing GlycoAdvance and GlycoPEGylation, we are able to attach PEG efficiently and selectively. By linking PEG to carbohydrate structures that are remote from the protein s active site,

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GlycoPEGylation may preserve the bioactivity of the drug and extend its half-life. We believe that significant clinical benefits may be achieved through the application of our GlycoPEGylation technology to proteins. By using our GlycoPEGylation technology, we have been able to demonstrate with several drug candidates a prolonged drug effect in animals.

PROPRIETARY DRUG DEVELOPMENT PORTFOLIO

Our proprietary drug development portfolio currently consists of two next-generation therapeutic protein candidates: a long-acting version of EPO (NE-180) and a long-acting version of G-CSF (GlycoPEG-GCSF).

NE-180

We are developing NE-180, a long-acting version of EPO that is produced in insect cells. We expect to complete various preclinical activities for NE-180, including having a pre-IND meeting with the FDA and submitting an IND to the FDA, during the second quarter of 2005. Our goal is to initiate clinical trials during the third quarter of 2005. We expect that data from these trials will be included in data submitted to the appropriate government agencies for regulatory approval.

EPO is prescribed to stimulate production of red blood cells, and is approved for sale in major markets around the world for the treatment of chemotherapy-induced anemia and anemia associated with chronic renal failure. EPO accounts for more sales worldwide than any other glycoprotein drug. Worldwide sales in the EPO category in 2003 were approximately $9.7 billion. Of these sales, approximately $6.2 billion were in the U.S., approximately $2.7 billion were in Europe, and approximately $0.8 billion were in Japan.

Based on early preclinical studies, we believe it is feasible to develop a long-acting EPO through GlycoPEGylation. These studies suggest that the pharmacokinetic profile of EPO can be adjusted by manipulating the number of carbohydrate attachment sites and the molecular weight of the PEG that we attach to the compound. In these early animal studies, multiple constructs of GlycoPEGylated EPO, including NE-180, had improved pharmacokinetic and pharmacodynamic profiles as compared with unmodified EPO, and pharmacokinetic and pharmacodynamic profiles comparable to Aranesp®, Amgen s long-acting EPO analog. Based on our preliminary market research, we believe that clinicians, particularly oncologists, would respond favorably to a long-acting EPO. This is supported by reported sales data for Aranesp, indicating cumulative sales of approximately $4.5 billion during the period from its launch in 2001 through the fourth quarter of 2004.

We believe that the expiration of key patents covering EPO will provide commercial opportunities in time frames consistent with our development timeline. While we expect to pursue early entry opportunities in the U.S., we plan to pursue regulatory and marketing approval first in Europe, where we believe the key blocking patents expire sooner. We believe that the key patents in Europe and Japan will expire by the end of 2005.

In the U.S., we believe that the key patents surrounding EPO will expire by the end of 2015. However, many of the applicable patent claims in the U.S. apply to EPO expressed in vertebrate or mammalian cells, and we believe that our use of an insect cell expression system may allow us to enter the U.S. market prior to the expiration of these patents. Some of the issues relevant to the analysis of our freedom to operate in the U.S. are the subject of ongoing litigation between other parties. We continue to monitor these matters, as well as evaluate whether the applicable patent claims would block our entry into the U.S. market prior to expiration. In the meantime, we expect to continue development in the U.S. of NE-180 under the protection of a statutory safe harbor.

GlycoPEG-GCSF

We are developing GlycoPEG-GCSF, a long-acting version of G-CSF, in collaboration with our partner BioGeneriX. We and BioGeneriX plan to complete preclinical development activities for GlycoPEG-GCSF prior to the end of 2005, including requesting scientific advice from regulatory authorities in the EU and submitting the equivalent of an IND in an EU country.

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G-CSF is prescribed to stimulate production of neutrophils (a type of white blood cell), and is approved for sale in major markets around the world for treatment of neutropenia associated with myelosuppressive chemotherapy. Worldwide sales in the G-CSF category in 2003 were approximately $3.0 billion. Of these sales, approximately $2.0 billion were in the U.S., approximately $0.6 billion were in Europe, and approximately $0.4 billion were in Japan.

Based on proof-of-concept data and preclinical development activities, we believe it is feasible to develop a long-acting G-CSF through GlycoPEGylation. These studies suggest that the pharmacokinetic profile of G-CSF can be adjusted by manipulating the number of carbohydrate attachment sites and the molecular weight of the PEG that we attach to the compound. In these early animal studies, multiple constructs of GlycoPEGylated G-CSF, including GlycoPEG-GCSF, had improved pharmacokinetic and pharmacodynamic profiles as compared with unmodified G-CSF (Neupogen®), and pharmacokinetic and pharmacodynamic profiles comparable to Neulasta, Amgen s long-acting G-CSF analog. We believe that clinicians would respond favorably to a long-acting G-CSF as supported by reported sales data for Neulasta, indicating cumulative sales of approximately $3.5 billion during the period from its launch in 2002 through the fourth quarter of 2004.

We believe that the expiration of key patents covering G-CSF will provide commercial opportunities in a time frame consistent with our development timeline. We expect that regulatory approval for GlycoPEG-GCSF will be sought both in and outside the U.S. We believe that key patents covering G-CSF will expire in Europe in 2006, in the U.S. in late 2013 and in other jurisdictions between these times. We expect to pursue regulatory and marketing approval for GlycoPEG-GCSF first in the EU.

EXPLORATORY RESEARCH PROGRAM

We conduct exploratory research, both independently and with collaborators, on therapeutic candidates, primarily proteins, using our enzymatic technologies. Successful therapeutic candidates may be advanced for development through our own proprietary drug development program, our partnering and licensing program, or a combination of the two. Although our primary focus is the development of long-acting proteins, we are also conducting research to assess opportunities to use our enzymatic technologies in other areas, such as glycopeptides and glycolipids.

PARTNERING AND LICENSING PROGRAM

Currently we have the following collaborations:

BioGeneriX GlycoPEG-GCSF

In April 2004, we entered into an agreement with BioGeneriX to use our proprietary GlycoAdvance and GlycoPEGylation technologies to develop a long-acting version of G-CSF. Under the agreement, we and BioGeneriX share the expenses of preclinical development and BioGeneriX is responsible for supplying the protein and funding the entire clinical development program. If we and BioGeneriX proceed to commercialization, we will have commercial rights in the U.S., Canada, Mexico and Japan, and BioGeneriX will have commercial rights in Europe and the rest of the world. Each company will receive significant royalties on product sales in the other company s territory. In connection with the agreement, we received an upfront fee from BioGeneriX. BioGeneriX has the right to terminate the agreement without cause following the completion of preclinical development. Each party has the right, in various circumstances, to terminate the agreement by giving the required notice to the other party, subject to the other party s right to continue working on the development and commercialization of a long-acting version of G-CSF, as provided in the agreement.

BioGeneriX Additional GlycoPEGylated Protein

In January 2005, we entered into a supply and option agreement with BioGeneriX that provides for BioGeneriX to make a non-refundable payment to Neose and to supply to Neose a marketed therapeutic protein (target protein) for research purposes. During a three-month research period, BioGeneriX has an exclusive option to enter into a pre-negotiated research, license and option agreement (license agreement) for the use of our proprietary GlycoAdvance and GlycoPEGylation

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technologies to develop a long-acting version of the target protein. If BioGeneriX exercises the option to enter into the license agreement, Neose would receive an additional non-refundable payment as well as research payments, and could receive milestone payments totaling up to $61.5 million, as well as significant royalties on product sales. The license agreement contemplates that Neose would conduct research on behalf of BioGeneriX for approximately 12 months and grant BioGeneriX the right to obtain an exclusive, worldwide license to use our enzymatic technologies to develop and commercialize a long-acting version of the target protein. If BioGeneriX exercises its right to obtain the license, they will be responsible for the further development and commercialization of the target protein. If requested by BioGeneriX, Neose will provide, and be fully reimbursed for, any required technical assistance. BioGeneriX would have the right to terminate the license agreement any time after the research period. Neose would have the right to terminate the license agreement if specific development milestones were not met within certain periods of time.

Novo Nordisk

In 2003, we entered into agreements with Novo Nordisk A/S to use our GlycoAdvance and GlycoPEGylation technologies to develop and commercialize three next-generation versions of currently marketed proteins, one of which is marketed by Novo Nordisk. Under these agreements, we received a $4.3 million upfront fee, and Novo Nordisk funds our research and development activities for these three proteins. We may also receive up to $51.3 million in development milestones, as well as significant royalties on sales of the licensed products. Under these agreements, Novo Nordisk s license with respect to each protein continues until the expiration of the last Neose patent covering a licensed product, or until the earlier termination of the applicable agreement. Novo Nordisk has the right to terminate each of the agreements without cause. We have the right to terminate the agreement with respect to two of the proteins if there are no commercial sales of licensed products within a specified period, subject to Novo Nordisk s ability to extend by paying minimum royalties.

MacroGenics

In 2004, we entered into a research collaboration agreement with MacroGenics to use our GlycoAdvance and GlycoPEGylation technologies on multiple monoclonal antibodies of MacroGenics, with the goal of improving the therapeutic profiles of these proteins. Under this agreement, MacroGenics has the right to take a limited number of remodeled compounds into development. During the research phase, we and MacroGenics each fund our own expenses. If MacroGenics decides to proceed with any of the remodeled compounds beyond the initial research phase, MacroGenics will be responsible for all further development of the licensed compounds and we will receive royalties on any product sales.

BUSINESS STRATEGY

Our primary focus is to develop proprietary protein drugs with proven safety and efficacy, and improve the therapeutic profiles of glycoproteins being developed by our partners. We also plan to develop other therapeutic drugs by applying our enzymatic technologies in other areas, such as glycopeptides and glycolipids. Key elements of our strategy are to:

- **Continue to develop our two long-acting therapeutic protein candidates.** We continue to develop our two long-acting proprietary therapeutic protein candidates: NE-180 and GlycoPEG-GCSF. We expect to complete preclinical activities for NE-180, including having a pre-IND meeting with the FDA and submitting an IND to the FDA, in the second quarter of 2005. We expect to complete preclinical activities for GlycoPEG-GCSF, including requesting scientific advice from the regulatory authorities in a country in the EU and submitting the equivalent of an IND in an EU country, by the end of 2005 in collaboration with our partner, BioGeneriX.

- **Target drugs with proven safety and efficacy.** We are developing improved therapeutics with a current focus on therapeutic proteins using our proprietary enzymatic technologies, GlycoAdvance and GlycoPEGylation. We expect these modified proteins to offer significant advantages, including less frequent dosing and possibly improved efficacy, over the original versions of the drugs now on the market, as well as to meet or exceed the pharmacokinetic and pharmacodynamic profile of

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next-generation versions of the drugs now on the market. We believe this strategy of targeting the many commercially attractive protein drugs with proven safety and efficacy allows us to lower the risk profile of our proprietary drug development portfolio as compared to *de novo* protein drug development. We intend to continue to focus our research and development resources on several therapeutic proteins that we believe have the highest probability of clinically meaningful therapeutic profile improvements from our technology and are in commercially attractive categories.

- **Leverage our core competencies.** We believe that our core enzymatic technologies improve the drug properties of therapeutic proteins. We will continue to use our technologies to research and develop improved versions of protein drugs with proven safety and efficacy and to improve the therapeutic profiles of glycoproteins being developed by our partners. In addition, we intend to explore the application of our technology and our development capabilities to glycopeptides and antibodies. We will also continue to conduct exploratory drug development research in novel therapeutic categories, such as glycolipids, where our proprietary enzymatic technology, intellectual property and internal expertise provide us with opportunities.

- **Continue to seek attractive partnership opportunities.** We will continue our efforts to build a portfolio of commercially attractive partnerships in a blend of co-developments and licenses. Where possible, we will seek partnerships that allow us to significantly participate in the commercial success of each of the compounds. This will be accomplished by not only securing upfront payments, research funding and milestone payments, but by continuing to seek agreements that retain meaningful commercial rights in certain territories and securing significant royalty rates on product sales in other territories.

OUR CORPORATE INFORMATION

We were incorporated in Delaware in May 1991. Our principal executive offices are located at 102 Witmer Road, Horsham, PA 19044, and our telephone number is 215-315-9000. We maintain an Internet website at *http://www.neose.com.* We have not incorporated by reference into this prospectus supplement or the accompanying prospectus the information in, or that can be accessed through, our website, and you should not consider it to be a part of this prospectus supplement or the accompanying prospectus.

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The offering

Common stock we are offering	7,000,000 shares
Common stock to be outstanding after this offering	31,732,372 shares
Use of proceeds	We estimate that the net proceeds to us from this offering after deducting underwriting discounts and commissions and the estimated offering expenses will be approximately $25.8 million, or approximately $29.8 million if the underwriters exercise their over-allotment option in full. We intend to use the net proceeds from this offering to fund ongoing research and development activities, general and administrative expenses, capital expenditures, and general working capital. See Use of proceeds.
NASDAQ National Market symbol	NTEC

The number of shares of our common stock outstanding after this offering is based on approximately 24,732,372 shares outstanding as of February 17, 2005 and excludes:

- 4,966,329 shares of our common stock issuable upon exercise of options outstanding as of February 17, 2005, at a weighted average exercise price of $17.11 per share, of which options to purchase 3,322,014 shares were exercisable as of that date at a weighted average exercise price of $18.25 per share; and

- 1,591,794 shares of our common stock available for future grant under our 2004 Equity Incentive Plan as of February 17, 2005.

Unless we specifically state otherwise, the information in this prospectus supplement assumes that the underwriters do not exercise their option to purchase up to 1,050,000 shares of our common stock to cover over-allotments, if any.

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Summary financial data

The following summary financial data for the years ended December 31, 2001 through 2003 is derived from our audited financial statements. The following summary financial data as of September 30, 2004 and for the nine-month periods ended September 30, 2003 and 2004 is derived from our unaudited interim condensed financial statements. The unaudited financial statement data include, in our opinion, all adjustments (consisting only of normal recurring adjustments) that are necessary for a fair presentation of our financial position and results of operations for these periods. Operating results for the nine months ended September 30, 2004 are not necessarily indicative of the results that may be expected for the year ended December 31, 2004.

This information is only a summary and should be read together with the financial statements, the related notes and other financial information incorporated by reference into this prospectus supplement and the accompanying prospectus and on file with the SEC. For more details on how you can obtain our SEC reports incorporated by reference into this prospectus supplement and the accompanying prospectus, see Additional information in the accompanying prospectus.

	Year ended December 31,			Nine months ended September 30,	
Statement of operations data:	**2001**	**2002**	**2003**	**2003**	**2004**
(In thousands, except per share amounts)				**(unaudited)**	
Revenue from collaborative agreements	$ 1,266	$ 4,813	$ 1,435	$ 871	$ 3,592
Operating expenses:					
Research and development	14,857	21,481	26,821	19,031	24,971
Marketing, general and administrative	9,374	12,510	11,148	8,657	9,047
Total operating expenses	24,231	33,991	37,969	27,688	34,018
Operating loss	(22,965)	(29,178)	(36,534)	(26,817)	(30,426)
Other income	6,120	1,653			
Impairment of equity securities			(1,250)	(1,250)	
Interest income	3,704	1,108	564	420	431
Interest expense	(188)		(461)	(338)	(658)
Net loss	$(13,329)	$(26,417)	$(37,681)	$(27,985)	$(30,653)
Basic and diluted net loss per share	$ (0.95)	$ (1.85)	$ (2.14)	$ (1.66)	$ (1.38)
Weighted average shares outstanding used in computing basic and diluted net loss per share	14,032	14,259	17,611	16,828	22,284

	September 30, 2004	
Balance sheet data:	**Actual**	**As adjusted[1]**
(In thousands)	**(unaudited)**	

Cash and cash equivalents	$ 55,016	$ 80,836
Total assets	101,080	126,900
Total debt and capital lease obligations	17,725	17,725
Deficit accumulated during development stage	(176,392)	(176,392)
Total stockholders equity	71,829	97,649

(1) As adjusted to give effect to the sale of 7,000,000 shares of common stock we are offering pursuant to this prospectus supplement, after deducting underwriting discounts and commissions and estimated offering expenses to be paid by us.

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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 occurs, it 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.

FINANCIAL RISKS

If we fail to obtain necessary funds for our operations, we will be unable to maintain and improve our technology position and we will be unable to develop and commercialize our therapeutic proteins.

To date, we have funded our operations primarily through proceeds from the public and private placements of equity securities. We have also funded our operations to a lesser extent from proceeds from property and equipment financing, interest earned on investments, revenues from corporate collaborations and gains from the sale of investments. We believe that our existing cash and cash equivalents, expected revenue from our existing collaborations and license arrangements, and interest income should be sufficient to meet our operating and capital requirements through 2005, although changes in our collaborative relationships or our business, whether or not initiated by us, may affect the rate at which we deplete our cash and cash equivalents. Our present and future capital requirements depend on many factors, including:

- level of research and development investment required to develop our therapeutic proteins, and maintain and improve our technology position;
- the costs of obtaining or manufacturing proteins and reagents for research and development and at commercial scale;
- the results of preclinical and clinical testing, which can be unpredictable in drug development;
- changes in product candidate development plans needed to address any difficulties that may arise in manufacturing, preclinical activities, clinical studies or commercialization;
- our ability and willingness to enter into new agreements with collaborators and to extend or maintain our existing collaborations, and the terms of these agreements;
- our success rate and that of our collaborators in preclinical and clinical efforts associated with milestones and royalties;
- the costs of investigating patents that might block us from developing potential drug candidates;
- the costs of recruiting and retaining qualified personnel;
- the time and costs involved in obtaining regulatory approvals;
- the timing, willingness, and ability of our collaborators to commercialize products incorporating our technologies;
- the costs of filing, prosecuting, defending, and enforcing patent claims and other intellectual property rights; and
- our need or decision to acquire or license complementary technologies or new drug targets.

We will require significant amounts of additional capital in the future, and we do not have any assurance that funding will be available when we need it on terms that we find favorable, if at all. We may seek to raise these funds through public or private equity offerings, debt financings, credit facilities, or corporate collaborations and licensing arrangements.

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If we raise additional capital by issuing equity securities, our existing stockholders percentage ownership will be reduced and they may experience substantial dilution. We may also issue equity securities that provide for rights, preference and privileges senior to those of our common stock. If we raise additional funds by issuing debt securities, these debt securities would have rights, preferences, and privileges senior to those of our common stock, and the terms of the debt securities issued could impose significant restrictions on our operations. If we raise additional funds through collaborations and licensing arrangements, we may be required to relinquish some rights to our technologies or drug candidates, or to grant licenses on terms that are not favorable to us. If adequate funds are not available or are not available on acceptable terms, our ability to fund our operations, take advantage of opportunities, develop products and technologies, and otherwise respond to competitive pressures could be significantly delayed or limited, and we may need to downsize or halt our operations.

Our debt obligations include restrictive covenants which may restrict our operations or otherwise adversely affect us.

We entered into a credit agreement with a bank, dated as of January 30, 2004, under which the outstanding balance, as of September 30, 2004, was $9.0 million. Under the credit agreement, we agreed to limit our total outstanding debt to $22.0 million; therefore, we cannot exceed this limit without the bank s consent. As of September 30, 2004, our total outstanding debt was $17.7 million. The limit on our total debt under the credit agreement could adversely affect us by reducing our flexibility in planning for, or reacting to, changes in our business and our industry.

Under our credit agreement, if the bank determines a material adverse change has occurred in our business, financial condition, results of operations, or business prospects, the bank, in its sole discretion, may declare at any time an event of default, of which one potential outcome could be the accelerated repayment of the then outstanding loan balance under the credit agreement. Under the credit agreement, if we fail at any time to maintain a minimum required cash and short-term investments balance of at least $22.0 million, or at any time after January 30, 2008, the bank has the option to require additional collateral from us in the form of a security interest in certain cash and short-term investments, or in the form of a letter of credit, which may have the effect of requiring us to repay the then outstanding loan balance under the credit agreement. As of September 30, 2004, we maintained a cash and cash equivalents balance of $55.0 million.

The credit agreement also contains covenants that, among other things, require us to obtain consent from the bank prior to paying dividends, making certain investments, changing the nature of our business, assuming or guaranteeing the indebtedness of another entity or individual, selling or otherwise disposing of a substantial portion of our assets, or merging or consolidating with another entity.

A breach of any of the financial tests or other covenants in the credit agreement could result in a default under our credit agreement. Upon the occurrence of such an event of default, the bank could elect to declare all amounts outstanding thereunder to be immediately due and payable, and terminate all commitments to extend further credit.

We have a history of losses, and we may incur continued losses for some time.

We have incurred losses each year of our existence, including net losses of $13.3 million for the year ended December 31, 2001, $26.4 million for the year ended December 31, 2002, $37.7 million for the year ended December 31, 2003, and $30.7 million for the nine months ended September 30, 2004.

Given our planned level of operating expenses, we expect to continue incurring losses for some time. As of September 30, 2004, we had an accumulated deficit of approximately $176.4 million. To date, we have derived substantially all of our revenue from corporate collaborations, license agreements and investments. We expect that substantially all of our revenue for the foreseeable future will result from these sources and from the licensing of our technologies. We also expect to spend significant amounts to expand our research and development on our proprietary drug candidates and technologies, maintain and expand our intellectual property position, expand our manufacturing scale-up activities and expand our business development and commercialization efforts. Our level of operating

expenditures will vary depending upon the stage of development of our proprietary proteins and the number and nature of our collaborations. We may continue to incur substantial losses even if our revenues increase.

We have not yet commercialized any products or technologies, and we may never become profitable.

We have not yet commercialized any products or technologies, and we may never be able to do so. Since we began operations in 1990, we have not generated any revenues, except from corporate collaborations, license agreements, and investments. We do not know when or if we will complete any of our product development efforts, obtain regulatory approval for any product candidates incorporating our technologies, or successfully commercialize any approved products. Even if we are successful in developing products that are approved for marketing, we will not be successful unless these products gain market acceptance. The degree of market acceptance of these products will depend on a number of factors, including:

- the timing of regulatory approvals in the countries, and for the uses, we seek;
- the competitive environment;
- the establishment and demonstration in the medical community of the safety and clinical efficacy of our products and their potential advantages over existing therapeutic products;
- the adequacy and success of distribution, sales and marketing efforts; and
- the pricing and reimbursement policies of government and third-party payors, such as insurance companies, health maintenance organizations and other plan administrators.

Physicians, patients, payors or the medical community in general may be unwilling to accept, utilize or recommend any of our products or products incorporating our technologies. As a result, we are unable to predict the extent of future losses or the time required to achieve profitability, if at all. Even if we or our collaborators successfully develop one or more products that incorporate our technologies, we may not become profitable.

Failure to comply with the new SEC rules regarding internal controls over financial reporting by the deadline for compliance could have a material adverse effect on our stock price.

Beginning with our annual report for the year ended December 31, 2004, Section 404 of the Sarbanes-Oxley Act of 2002 will require us to include a report by our management on our internal controls over financial reporting. This report must contain an assessment by management of the effectiveness of our internal controls over financial reporting as of the end of our fiscal year and a statement as to whether or not our internal controls are effective. The report must also contain a statement that our independent auditors have issued an attestation report on management s assessment of such internal controls. Because this is the first annual report to be filed by us requiring this additional information pursuant to Section 404 of the Sarbanes-Oxley Act of 2002, neither we nor our independent auditors have previously performed an evaluation of our internal controls over financial reporting under these new rules. If we are unable to assert that our internal controls over financial reporting are effective, or if our independent auditors are unable to attest that our management s report is fairly stated or they are unable to express an opinion on our management s evaluation or on the effectiveness of our internal controls, the market price of our common stock could be adversely affected.

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RISKS RELATED TO DEVELOPMENT OF PRODUCTS AND TECHNOLOGIES

We may be unable to develop next-generation therapeutic proteins.

We are seeking to use our enzymatic technologies to develop proprietary next-generation proteins, generally in collaboration with a partner. The development of protein drugs involves a range of special challenges at various stages of the process.

In the preclinical phase of product development, we and our partners will face several potential problems, including producing or obtaining supplies of the protein on commercially reasonable terms, successfully remodeling the protein using our enzymatic technologies, and achieving adequate yields of the next-generation protein. Even if a protein development program appears to be proceeding well in the early phases, a product candidate may fail in clinical trials for several reasons, such as results indicating that the product candidate is less effective than desired (e.g., the trial failed to meet its primary objectives) or that it has harmful or problematic side effects. If clinical trials are successful, it is possible that problems may arise later during commercialization. For example, we are aware that one marketed EPO product of a competitor was associated with pure red cell aplasia in post-marketing surveillance studies. This highlights the fact that even after a product is approved for marketing, problems may arise which can negatively affect sales and increase costs.

Our failure to solve any of these problems could delay or prevent the commercialization of products incorporating our technologies and could negatively impact our business.

Proteins are uniquely susceptible to neutralizing antibodies that could result in diminished efficacy of our products.

Proteins that are foreign to a living body often provoke an immune response. Protein drugs produced by recombinant technology, even though they have the same primary amino acid sequence as a native human protein, sometimes provoke formation of antibodies that bind to the protein drug. Some such antibodies bind so as to prevent the protein drug from engaging its receptor, and thus neutralize the drug activity of the protein. Furthermore, neutralizing antibodies provoked by administration of a protein drug may react with endogenous proteins whose natural activity the drug was intended to supplement, thereby inducing a total lack of the intended activity in the patient. Such a condition can prove fatal. We will not know if the proteins we develop as product candidates will provoke neutralizing antibody responses in humans until the commencement of clinical trials. It is possible that our product candidates may be rendered ineffective for the therapeutic purpose for which they are intended or could induce harm to patients because of the neutralizing effect of antibodies created in humans in response to our proteins.

Additionally, all protein drugs expressed by recombinant technology retain some trace of contaminating proteins from the host cells used to express the protein drug. These host cell proteins may increase the chances of an immunogenic response that could diminish the therapeutic efficacy of the protein. Our GlycoAdvance technology enables the use of protein drugs produced in insect cells, an expression system which has certain technical advantages in enabling the application of our technology to this protein, but for which no product to date has received marketing authorization in the U.S. or EU. It is possible that our product candidates may be rendered ineffective for the therapeutic purpose for which they are intended because of the neutralizing effects of antibodies provoked by the presence of trace amounts of insect cell proteins in our drug preparations.

We have limited product development and commercial manufacturing experience, and face manufacturing challenges unique to proteins.

To date, we have not manufactured, at commercial scale, any pharmaceutically active proteins nor the enzymes, sugar nucleotides or other reagents we use to modify proteins.

We face the significant, normal scale-up risks associated with protein manufacturing: proteins are difficult to produce; it is difficult to scale up protein manufacturing processes; and it is expensive to produce proteins. We also face special risks in connection with the EPO protein that we are currently manufacturing to support preclinical and early clinical development of NE-180. Our success with this program will depend on our ability to manufacture this protein, at commercial scale, in the insect cell

expression system (the production source of NE-180), either independently or with a collaborator or supplier. We do not know if we will be able to locate a contract manufacturer outside of the U.S. that will be able to manufacture this protein at commercial scale and on economically feasible terms. To date, no product produced in this expression system has received marketing authorization in the U.S. or the EU, which means that we may face previously unidentified problems resulting from the use of this expression system and related regulatory challenges.

We are also manufacturing, directly or through suppliers, the enzymes, sugar nucleotides and other reagents we need to apply our technologies. We have sought and continue to have collaborators, licensees or contract manufacturers manufacture at least some of the compounds necessary to commercialize our technologies. We may not be able to find parties willing and able to manufacture these compounds at acceptable prices, and we may become dependent on suppliers that could discontinue our supply arrangements or change supply terms to our disadvantage. Our success depends on our ability to manufacture these compounds on a commercial scale or to obtain commercial quantities, in either case, at reasonable cost. Our manufacturing processes also must comply with current Good Manufacturing Practices, or cGMP, prescribed by the FDA. We may not be able to manufacture or obtain sufficient quantities of the products we develop to meet our needs for pre-clinical or clinical development, and we may have problems complying, or maintaining compliance, with cGMP.

Any manufacturing facility must adhere to the FDA s evolving regulations on cGMP, which are enforced by the FDA through its facilities inspection program. The manufacture of products at any facility will be subject to strict quality control, testing, and record keeping requirements, and continuing obligations regarding the submission of safety reports and other post-market information. Ultimately, we or our contract manufacturers may not meet these requirements.

If we encounter delays or difficulties in connection with manufacturing, commercialization of our products and technologies could be delayed, and we could breach our obligations under our collaborative agreements and we may have difficulty obtaining necessary financing.

Our success depends on the success of our collaborative relationships and the success of our collaborators.

We plan to rely to a large extent on collaborative partners to co-develop our products and to commercialize products made using our technologies. We currently have collaborative agreements with Novo Nordisk, BioGeneriX and MacroGenics. We anticipate that substantially all of our revenues during the next several years will continue to be generated from collaboration or license agreements. Our partnering strategy entails many risks, including:

- we may be unsuccessful in entering into or maintaining collaborative agreements for the co-development of our products or the commercialization of products incorporating our technologies;
- we may not be successful in applying our technologies to the needs of our collaborative partners;
- our collaborators may not be successful in, or may not remain committed to, co-developing our products or commercializing products incorporating our technologies;
- our collaborators may seek to develop other proprietary alternatives to our products or technologies;
- our collaborators may not commit sufficient resources to incorporating our technologies into their products;
- our collaborators are not obligated to market or commercialize our products or products incorporating our technologies, and they are not required to achieve any specific commercialization schedule;
- our collaborative agreements may be terminated by our partners on short notice; and

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- continued consolidation in our target markets may limit our ability to enter into collaboration agreements, or may result in terminations of existing collaborations.

Given these risks, there is a great deal of uncertainty regarding the success of our current and future collaborative efforts.

Any of our present or future collaborators may breach or terminate their agreements with us or otherwise fail to conduct their collaborative activities successfully and in a timely manner. In addition, we may dispute the application of payment provisions under any of our collaborative agreements. If any of these events occurs or if we fail to enter into or maintain collaborative agreements, we may not be able to commercialize our products and technologies, and our prospects would be significantly harmed.

We may be exposed to product liability and related risks.

The use in humans of compounds developed by us or incorporating our technologies may result in product liability claims. Product liability claims can be expensive to defend, and may result in large settlements of claims or judgments against us. Even if a product liability claim is not successful, the adverse publicity, time, and expense involved in defending such a claim may interfere with our business. We may not be able to obtain insurance coverage at a reasonable cost or in sufficient amounts to protect us against losses.

RISKS RELATED TO INTELLECTUAL PROPERTY

Blocking patents or claims of infringement may stop or delay our development of our proprietary products.

Our commercial success depends in part on avoiding claims of infringement of the patents or proprietary rights of third parties. As we seek to develop next-generation proprietary products, we devote significant resources to investigating the patent protection surrounding our target proteins. Patent protection for therapeutic proteins often comprises numerous claims for composition of matter, methods of use, and methods of making. The numerous patents may be difficult to uncover and interpret, leading to uncertainty about our freedom to operate. It is possible that we will not be aware of issued patents or pending patent applications that are relevant to our product candidates because our searches do not find them, or pending patent applications because they are not yet publicly available. Our interpretation of patents could be challenged, leading to litigation, and we could face claims of infringement of rights of which we are unaware.

We rely on certain exemptions and safe harbors in order to conduct the necessary research and development to support our regulatory filings. The Supreme Court of the United States has recently agreed to hear a case related to a particular safe harbor upon which we rely in the U.S. The elements of this safe harbor could be modified by the Supreme Court in a manner that is adverse to us, causing an increase in challenges or claims of infringement against us in relation to the patents of third parties and the possibility of our products being blocked from development in the U.S.

There have been significant litigation and interference proceedings regarding patent rights, and the patent situation regarding particular products is often complex and uncertain. For example, with respect to EPO, the target of our first development program, the status of issued patents is currently being litigated by others and these patents could delay our ability to market a long-acting EPO in the U.S. As we proceed with this program and other targets, we may face uncertainty and litigation could result, which could lead to liability for damages, prevent our development and commercialization efforts, and divert resources from our business strategy.

The cost of any litigation challenging our right to pursue our target proteins or technologies could be substantial. Others seeking to develop next-generation versions of proteins, or the holders of patents on our target proteins, may have greater financial resources, making them better able to bear the cost of litigation. In particular, one company that produces products that will likely be in direct competition with our current product candidates has aggressively defended the patents related to its products and this could increase the likelihood of litigation or the cost of litigation. Uncertainties

resulting from the initiation and continuation of patent litigation or other proceedings could have a material adverse effect on our ability to develop, manufacture, and market products, form strategic alliances, and compete in the marketplace.

Third parties from time to time may assert that we are infringing their patents, trade secrets or know-how, although we believe our product candidates do not infringe the products, trade secrets or know-how of third parties. In addition, patents may issue in the future to third parties that our technology may infringe. We could incur substantial costs in defending ourselves and our partners against any such claims. Furthermore, parties making such claims may be able to obtain injunctive or other equitable relief, which could effectively block our ability or our partners ability to further develop or commercialize some or all of our products or technologies in the U.S. and abroad, and could result in the award of substantial damages. If we are found to infringe, we may be required to obtain one or more licenses from third parties or be unable to proceed. There can be no assurance that we will be able to obtain such licenses at a reasonable cost, if at all. Defense of any lawsuit or failure to obtain any such required license could have a material adverse effect on us.

The failure to obtain, maintain or protect patents and other intellectual property could impact our ability to compete effectively.

To compete effectively, we need to develop and maintain a proprietary position with regard to our own technologies, products and business. Legal standards relating to the validity and scope of claims in our technology field are still evolving. Therefore, the degree of future protection for our proprietary rights in our core technologies and products made using these technologies is also uncertain. The risks and uncertainties that we face with respect to our patents and other proprietary rights include the following:

- the pending patent applications we have filed or to which we have exclusive rights may not result in issued patents or may take longer than we expect to result in issued patents;
- we may be subject to interference proceedings;
- we may be subject to opposition proceedings in foreign countries;
- the claims of any patents that are issued may not provide meaningful protection;
- we may not be able to develop additional proprietary technologies that are patentable;
- the patents licensed or issued to us or our customers may not provide a competitive advantage;
- other companies may challenge patents licensed or issued to us or our customers;
- other companies may independently develop similar or alternative technologies, or duplicate our technologies;
- other companies may design around technologies we have licensed or developed; and
- enforcement of patents is complex, uncertain and expensive.

We cannot be certain that patents will be issued as a result of any of our pending applications, and we cannot be certain that any of our issued patents will give us adequate protection from competing products. For example, issued patents may be circumvented or challenged, declared invalid or unenforceable, or narrowed in scope. In addition, since publication of discoveries in the scientific or patent literature often lags behind actual discoveries, we cannot be certain that we were the first to make our inventions or to file patent applications covering those inventions. In the event that another party has also filed a patent application relating to an invention claimed by us, we may be required to participate in an interference proceeding declared by the U.S. Patent and Trademark Office to determine priority of invention, which could result in substantial uncertainties and costs for us, even if the eventual outcome were favorable to us. It is also possible that others may obtain issued patents that could prevent us from commercializing our products or require us to obtain licenses requiring the payment of significant fees or royalties in order to enable us to conduct our business. As to those

patents that we have licensed, our rights depend on maintaining our obligations to the licensor under the applicable license agreement, and we may be unable to do so.

The cost to us of any patent litigation or other proceeding relating to our patents or applications, even if resolved in our favor, could be substantial. Our ability to enforce our patent protection could be limited by our financial resources, and may be subject to lengthy delays. If we are unable to effectively enforce our proprietary rights, or if we are found to infringe the rights of others, we may be in breach of our license agreements with our partners.

In addition to patents and patent applications, we depend upon trade secrets and proprietary know-how to protect our proprietary technology. We require our employees, consultants, advisors, and collaborators to enter into confidentiality agreements that prohibit the disclosure of confidential information to any other parties. We require our employees and consultants to disclose and assign to us their ideas, developments, discoveries, and inventions. These agreements may not, however, provide adequate protection for our trade secrets, know-how, or other proprietary information in the event of any unauthorized use or disclosure.

International patent protection is uncertain.

In addition to the issues discussed under the two preceding risks, patent law outside the U.S. differs from country to country. The laws of some foreign countries may not protect our intellectual property rights to the same extent as U.S. laws. We may participate in opposition proceedings to determine the validity of foreign patents belonging to us or our competitors, which proceedings could result in substantial costs and diversion of our efforts. Finally, some of our patent protection in the U.S. is not available to us in fore