

REGENERON PHARMACEUTICALS INC  
Form 424B1  
March 20, 2001

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Filed Pursuant to Rule 424(b)(1)  
Registration No. 333-54326

PROSPECTUS

7,000,000 SHARES

REGENERON PHARMACEUTICALS, INC.

COMMON STOCK

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Regeneron is selling 6,500,000 shares. The selling shareholder is selling 500,000 shares of our common stock.

The shares are quoted on the Nasdaq National Market under the symbol "REGN." On March 19, 2001, the last sale price of the shares as reported on the Nasdaq National Market was \$25.125 per share.

INVESTING IN THE COMMON STOCK INVOLVES RISKS THAT ARE DESCRIBED IN THE "RISK FACTORS" SECTION BEGINNING ON PAGE 5 OF THIS PROSPECTUS.

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	PER SHARE	TOTAL
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Public offering price.....	\$25.00	\$175,000,000
Underwriting discount.....	\$ 1.25	\$ 8,750,000
Proceeds, before expenses, to Regeneron.....	\$23.75	\$154,375,000
Proceeds, before expenses, to the selling shareholder.....	\$23.75	\$ 11,875,000

The underwriters may also purchase up to 1,050,000 additional shares from Regeneron at the public offering price, less the underwriting discount, within 30 days from the date of this prospectus to cover over-allotments.

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 shares will be ready for delivery on or about March 23, 2001.

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MERRILL LYNCH & CO.

JPMORGAN

ROBERTSON STEPHENS

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The date of this prospectus is March 19, 2001.

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In this prospectus, "Regeneron," "our company," "we," "us," "the issuer," "the registrant," and "our" refer to Regeneron Pharmaceuticals, Inc. You should rely only on the information contained or incorporated by reference in this prospectus. We have not, and the underwriters have not, authorized any other person to provide you with different information. If anyone provides you with different or inconsistent information, you should not rely on it. We are not, and the underwriters are not, making an offer to sell these securities in any jurisdiction where the offer or sale is not permitted. You should assume that the information appearing in this prospectus is accurate only as of the date on the front cover of this prospectus. Our business, financial condition, results of operations, and prospects may have changed since that date.

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## SUMMARY

The following summary highlights information contained in other parts of this prospectus or incorporated by reference in this prospectus. You should read this summary together with the more detailed information elsewhere in this prospectus and in our financial statements and accompanying notes and other information incorporated by reference in this prospectus. Unless otherwise indicated, all information in this prospectus assumes no exercise of the underwriters' over-allotment option, gives no effect to the exercise of outstanding options and warrants to purchase common stock, and assumes all share numbers set forth in this prospectus are as of March 16, 2001.

## REGENERON PHARMACEUTICALS, INC.

We are a biopharmaceutical company that discovers, develops and intends to commercialize therapeutic drugs for the treatment of serious medical conditions. Our product pipeline includes product candidates for the treatment of obesity, rheumatoid arthritis and other inflammatory conditions, cancer and related disorders, allergies, asthma, and other diseases and disorders. Since inception, we have not generated sales or any profits from the commercialization of any of

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our product candidates.

Our core business strategy is to combine our strong foundation in science and technology with state-of-the-art manufacturing and clinical development capabilities to build a successful, integrated biopharmaceutical company. Our efforts have yielded a diverse and growing pipeline of product candidates that have the potential to address a variety of unmet medical needs. Our ability to develop product candidates results from the application of our technology platforms. In contrast to basic genomics approaches which attempt to identify every gene in a cell or genome, our technology platforms are designed to discover specific genes of therapeutic interest for a particular disease or cell type. We will continue to invest in the development of enabling technologies to assist in our efforts to identify, develop, and commercialize new product candidates.

A key aspect of our strategy is to retain significant ownership and commercialization rights to our pipeline. Below is a summary of our leading clinical programs, as well as several product candidates that are expected to enter clinical trials over the next two years. We retain sole ownership and marketing rights for each of these programs and currently are developing them independent of any corporate partners.

- AXOKINE (R): Acts on the brain region regulating food intake and energy expenditure and is being developed for the treatment of obesity. In November 2000, we announced the preliminary results of a twelve-week Phase II dose-ranging trial of AXOKINE in 170 severely obese patients. In the trial, AXOKINE was generally well tolerated and patients treated with AXOKINE showed medically meaningful and statistically significant weight loss compared to those receiving placebo. Subject to discussions with the FDA, we intend to initiate Phase III testing of AXOKINE in severely obese patients in mid-2001.
- PEGYLATED AXOKINE: Chemically modified version of AXOKINE that is being developed as a more potent, longer-acting form of the protein. Pegylated AXOKINE currently is in late-stage preclinical development and we anticipate initiating a Phase I clinical trial in mid-2001.
- INTERLEUKIN-1 CYTOKINE TRAP (IL-1 TRAP): Protein-based antagonist for the interleukin-1 (called IL-1) cytokine. IL-1 is thought to play a major role in rheumatoid arthritis and other inflammatory diseases. In December 2000, we initiated a Phase I study to assess the safety and tolerability of the IL-1 Trap in patients with rheumatoid arthritis. We expect the study to be completed in the second half of 2001.
- INTERLEUKIN-4/INTERLEUKIN-13 CYTOKINE TRAP (IL-4/IL-13 TRAP): Protein-based antagonist for the interleukin-4 and interleukin-13 (called IL-4 and IL-13) cytokines which are thought to play a major role in diseases such as asthma, allergic disorders, and other inflammatory diseases. We expect to initiate a Phase I clinical trial of a dual IL-4/IL-13 Trap for asthma/allergy-related conditions in late 2001.

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- VEGF TRAP: Protein-based antagonist to Vascular Endothelial Growth Factor (called VEGF, also known as Vascular Permeability Factor or VPF). VEGF is required for the growth of blood vessels that are needed for tumors to grow and is a potent regulator of vascular permeability and leak. The VEGF Trap is expected to enter Phase I clinical trials in mid-2001.
- ANGIOPOIETINS: A new family of growth factors that act specifically on

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the endothelium cells that line blood vessels. Angiopoietins may be useful for growing blood vessels in diseased hearts and other tissues with decreased blood flow and for repairing blood vessel leaks that cause swelling and edema in many different diseases such as stroke, diabetic retinopathy, and inflammatory diseases. Selected Angiopoietins, including engineered forms of these growth factors, are in preclinical development.

In addition to the above programs which we are conducting independent of any corporate partners, we have formed collaborations to advance other research and development efforts. We are conducting research with The Procter & Gamble Company in muscle diseases and other fields. We are also collaborating with Medarex, Inc. to discover, develop, and commercialize certain human antibodies as therapeutics. In partnership with Amgen Inc., we are conducting clinical trials with Neurotrophin-3, or NT-3, for the treatment of constipating conditions. In all of these research collaborations, we retain 50% of the commercialization rights.

We have made a substantial investment in our manufacturing facilities in Tarrytown, New York and Rensselaer, New York in order to develop our own manufacturing capabilities to support our clinical and preclinical programs and better position us to commercialize our product candidates. Currently we dedicate approximately 200 people to these internal manufacturing activities, as well as the manufacture of a product for Merck & Co., Inc. We will continue to upgrade and expand our manufacturing facilities as we advance our product candidates toward commercialization.

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We are a New York corporation organized on January 8, 1988. Our executive offices are at 777 Old Saw Mill River Road, Tarrytown, NY 10591-6707 and our telephone number is (914) 347-7000.

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### THE OFFERING

Common stock offered.....	7,000,000 shares of our common stock. Of these shares, Regeneron will offer 6,500,000 shares and the selling shareholder will offer 500,000 shares.
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Shares outstanding after the offering:

Common stock.....	40,787,624 shares
Class A stock.....	2,575,165 shares
Total.....	43,362,789 shares

Holders of our Class A stock are entitled to ten votes per share and the holders of our common stock are entitled to one vote per share.

Use of proceeds.....	We will receive net proceeds from this offering of approximately \$153.6 million. We intend to use the net proceeds for preclinical and clinical development of our product candidates, basic research activities, development of novel technology platforms, and general corporate purposes, including
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capital expenditures and working capital. See "Use of Proceeds".

We will not receive any of the proceeds from the shares of common stock sold by the selling shareholder. See "Selling Shareholder".

Risk factors..... See "Risk Factors" and other information included in this prospectus for a discussion of factors you should carefully consider before deciding to invest in shares of our common stock.

Nasdaq National Market symbol..... REGN

The number of shares outstanding after the offering is as of March 16, 2001 and excludes (1) options to purchase 7,523,214 shares of our common stock under our 1990 Long-Term Incentive Plan and 2000 Long-Term Incentive Plan, of which 2,872,263 were exercisable at March 16, 2001 and (2) 107,400 warrants held by Medtronic, Inc. as of March 16, 2001.

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SUMMARY SELECTED FINANCIAL DATA

	YEAR ENDED DECEMBER 31,			
	2000	1999	1998	1997
	(IN THOUSANDS, EXCEPT PER SHARE DATA)			
STATEMENT OF OPERATIONS DATA:				
Revenues:				
Contract research and development.....	\$ 36,478	\$ 24,539	\$ 19,714	\$ 17,400
Research progress payments.....	6,200	--	9,500	5,000
Contract manufacturing.....	16,598	9,960	9,113	4,458
	59,276	34,499	38,327	26,858
Expenses:				
Research and development.....	56,256	44,940	37,047	27,770
Contract manufacturing.....	15,566	3,612	5,002	2,617
Other.....	12,730	9,781	8,857	10,154
	84,552	58,333	50,906	40,541
Loss from operations.....	(25,276)	(23,834)	(12,579)	(13,683)
Other income (expense):				
Loss in Amgen-Regeneron Partners.....	(4,575)	(4,159)	(2,484)	(3,403)
Other income, net.....	8,199	4,923	6,438	5,507
	3,624	764	3,954	2,104
Net loss before cumulative effect of a change in accounting principle.....	(21,652)	(23,070)	(8,625)	(11,579)
Cumulative effect of adopting Staff Accounting Bulletin 101.....	(1,563)	--	--	--

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Net loss.....	\$ (23,215)	\$ (23,070)	\$ (8,625)	\$ (11,579)
Weighted average number of Class A and common stock outstanding, basic and diluted.....	34,950	31,308	30,992	28,702
Net loss per share, basic and diluted.....	\$ (0.66)	\$ (0.74)	\$ (0.28)	\$ (0.40)

AS OF DECEMBER 31, 2000

ACTUAL	AS ADJUSTED (1)
(IN THOUSANDS)	

BALANCE SHEET DATA:

Cash, cash equivalents, and marketable securities.....	\$154,370	\$307,995
Total assets.....	208,274	361,899
Stockholders' equity.....	182,130	335,755

(1) Gives effect to the sale of 6,500,000 shares of common stock by Regeneron, at a public offering price of \$25.00 per share, and our receipt of the net proceeds after deducting the underwriting discount and estimated offering expenses. We will not receive any of the proceeds from the sale of 500,000 shares of our common stock by the selling shareholder. See "Capitalization."

RISK FACTORS

You should carefully consider the following risk factors before you decide to buy our common stock. If any of these risks actually occurs, our business, financial condition, operating results or cash flows could be materially adversely affected. This could cause the trading price of our common stock to decline and you may lose part or all of your investment.

RISKS RELATED TO OUR BUSINESS, INDUSTRY AND STRATEGY

OUR RESEARCH AND DEVELOPMENT PROGRAMS MAY BE UNSUCCESSFUL AND MAY NOT LEAD TO THE DEVELOPMENT OF ANY COMMERCIALY SUCCESSFUL PRODUCTS.

Only a small minority of all research and development programs ultimately result in commercially successful drugs. We are attempting to develop drugs for human therapeutic uses. In order to begin the development process, we need to identify potential product candidates. Although we currently have several product candidates, our research and development activities may not successfully identify new product candidates. Our ability to commercialize the product candidates we do identify depends on completing clinical trials which demonstrate their safety and efficacy to the satisfaction of the United States Food and Drug Administration (FDA) and applicable foreign regulatory authorities. Clinical trials are a multi-step process as the product candidate is tested in larger populations, and a product candidate could fail at any step. Each stage of clinical development is more costly than the prior stage and we may expend substantial resources on a product candidate and then determine it cannot be successfully commercialized. For example, following a review of the

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clinical trial data, we and Amgen discontinued the development of Brain-Derived Neurotrophic Factor (BDNF) for the treatment of amyotrophic lateral sclerosis in January 2001.

We may never obtain regulatory approval for any of our product candidates. Even if the safety and efficacy of our product candidates are demonstrated in clinical trials and the necessary regulatory approvals are obtained, the commercial success of any of our product candidates will depend on our ability to successfully develop, manufacture, and market our product candidates and upon their acceptance by patients, the medical community, and third-party payors. If our products are not successfully commercialized, we will not be able to recover the significant investment we have made in developing such products and our business would be severely harmed.

WE MAY BE REQUIRED TO SUSPEND, REPEAT, OR TERMINATE OUR CLINICAL TRIALS, WHICH COULD HAVE A MATERIAL ADVERSE EFFECT ON OUR BUSINESS.

In order to obtain regulatory approval for the commercialization of our product candidates, we will be required to complete extensive clinical trials in humans to demonstrate safety and efficacy of the product candidates. We have limited experience in conducting clinical trials. A clinical trial may be suspended or terminated by us or the FDA, or otherwise fail, for a number of reasons, including:

- the product candidate may cause unforeseen adverse side effects, including immune reactions;
- the time required to determine whether the product candidate is effective may be longer than expected;
- the product candidate may not appear to be more effective than current available therapies;
- the failure to enroll a sufficient number of patients meeting eligibility requirements;
- the clinical investigators, trial monitors, or trial subjects may fail to comply with the trial plan or protocol; or
- the failure to be able to supply sufficient quantities of the product candidate to complete the trial.

Success in preclinical and early clinical trials may not be predictive of the results in large-scale trials. Any failure or substantial delay in successfully completing clinical trials and obtaining regulatory approval for our product candidates could severely harm our business.

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WE MAY NOT BE SUCCESSFUL IN OUR ATTEMPT TO BROADEN OUR PRODUCT PIPELINE AS IT WILL REQUIRE EXPERTISE AND RESOURCES WE DO NOT CURRENTLY HAVE.

We have expanded from our initial focus on degenerative neurologic disease and broadened our product pipeline to include drug candidates for the treatment of other diseases. As our scientific efforts lead us in new directions into conditions or diseases outside of our areas of experience and expertise, we will require additional internal expertise or external collaborations in areas in which we currently do not have substantial resources and personnel. As we develop drug candidates independently, we will require additional resources that may be difficult to obtain. If we have to enter into collaboration arrangements with others, we may be required to relinquish rights to some of our

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technologies, product candidates, or products that we would otherwise pursue independently. We may not be able to acquire the necessary expertise internally or be able to enter into collaboration arrangements on acceptable terms to develop additional drug candidates.

WE HAVE NEVER GENERATED SALES OR PROFITS AND EXPECT TO INCUR LOSSES OVER THE NEXT SEVERAL YEARS.

We have not received revenue from the commercialization of our product candidates. We do not expect to receive any revenue from the commercialization of our product candidates for several years and we intend to continue to invest significantly in our product candidates. We have incurred losses in each year since inception of operations in 1988. As of December 31, 2000, we had an accumulated deficit of \$223.5 million. We may never have an approved or commercially successful product or achieve significant revenues or profitable operations. If we fail to gain approval from the FDA to commercialize a product candidate, we may not be able to earn sufficient revenue to continue as a going concern.

WE CURRENTLY RECEIVE REVENUE FROM THIRD PARTIES; IF WE DO NOT RECEIVE THESE REVENUES, WE MAY NEED TO FIND ALTERNATIVE SOURCES OF FUNDING FOR OUR RESEARCH AND DEVELOPMENT ACTIVITIES.

To date, we have received revenues from (1) our licensees and collaborators for research and development efforts, (2) Merck and Sumitomo Pharmaceuticals Co., Ltd. for contract manufacturing, and (3) investment income. We may not continue to receive these revenues or the amount of these revenues may be dramatically reduced. In the absence of these revenues, we will have to obtain other sources of funding to continue to conduct our research and development activities.

For example, in January 2001, Amgen-Regeneron Partners discontinued all clinical development of BDNF which is licensed to Sumitomo Pharmaceuticals for development in Japan. As a result, it is likely that Sumitomo Pharmaceuticals will exercise its discretionary right to terminate the license with us for BDNF and, other than amounts currently outstanding and any wind-down costs, we would not expect to receive further payments from Sumitomo Pharmaceuticals. We recognized revenue from Sumitomo Pharmaceuticals of \$7.6 million in 2000, \$0.1 million in 1999, and \$8.8 million in 1998.

WE MAY REQUIRE ADDITIONAL FINANCING, WHICH MAY BE DIFFICULT TO OBTAIN AND MAY DILUTE YOUR OWNERSHIP INTEREST.

We have had negative cash flow from operations in each year since our inception. We expect that the funding requirements for our activities will remain substantial and could increase significantly if our development or clinical trial programs are successful or our research is expanded. For example, if we are able to commence a Phase III study of AXOKINE, the costs of conducting such a study, or any potential further studies required by the FDA or foreign regulatory authorities, would likely exceed \$50 million or more.

In addition, we are required to provide capital from time to time to fund and remain equal partners with Amgen in Amgen-Regeneron Partners. Our aggregate capital contribution to Amgen-Regeneron Partners from the partnership's inception in June 1993 through December 31, 2000 was \$56.2 million. We expect that our capital contributions for 2001 will total at least \$2.2 million. These contributions could increase or decrease, depending upon, among other things, the nature and cost of ongoing and additional



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NT-3 studies that Amgen-Regeneron Partners may conduct, the outcomes of those studies, and costs associated with the discontinuation of the BDNF studies.

We anticipate that the net proceeds from this offering, together with our cash, cash equivalents, and marketable securities of \$154.4 million as of December 31, 2000, will be sufficient for our working capital needs for several years. However, we may need additional funding sooner due to a number of factors, including:

- the speed with which some of our earlier stage developmental products move into later stage clinical development;
- the identification of additional product candidates;
- the identification of new indications for a potential product in later stage clinical trials;
- the termination of any of our collaboration agreements;
- the acquisition of technologies or product candidates;
- the pursuit of new business opportunities;
- the cost of developing a marketing or sales force; and
- the cost of developing or defending our patents, patent applications, and other intellectual property rights.

We have no established banking arrangements through which we can obtain short-term financing or a line of credit. We may seek additional funding through collaborative arrangements and public or private financing. Additional financing may not be available to us on acceptable terms or at all. If we are unable to obtain additional funding when needed, we may have to delay or scale back some of our programs or grant to third parties rights to development or other product rights. If we raise additional funds by issuing equity securities, further dilution to our then existing shareholders may result.

UNDESIRABLE AND UNINTENDED SIDE EFFECTS OF AXOKINE MAY INTERRUPT OR DELAY CLINICAL STUDIES AND COULD ULTIMATELY PREVENT OR LIMIT ITS COMMERCIAL USE.

Various side-effects have been reported during the clinical trials of AXOKINE, our only product candidate that has completed Phase II trials. During the Phase I study that was conducted in 1999, incidents of nausea, vomiting, and recurrence of herpes simplex virus, or HSV, were reported by patients taking AXOKINE. Recurrence of HSV was also reported in previous clinical studies of CNTF, AXOKINE's parent molecule. In addition, in the Phase I study, one patient who was HSV positive prior to treatment and had been previously diagnosed with Bell's palsy, had a recurrence of Bell's palsy approximately two weeks after the patient's last administration of AXOKINE. In the recently completed Phase II study of AXOKINE, reported side effects included injection site reactions, nausea, cough, and vomiting.

Although AXOKINE was generally well tolerated in the recently completed Phase II trial, it is possible that as we test AXOKINE in a large and extended Phase III trial, these side effects as well as side effects that did not occur or went undetected in smaller clinical trials will become apparent. The FDA may not permit us to commence large-scale, Phase III testing of AXOKINE without first undertaking additional clinical or preclinical studies. This additional testing could substantially delay, or restrict, the further development of AXOKINE.

WE FACE SUBSTANTIAL COMPETITION WHICH MAY RESULT IN OTHERS DISCOVERING,

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DEVELOPING OR COMMERCIALIZING PRODUCTS BEFORE OR MORE SUCCESSFULLY THAN WE DO.

There is substantial competition in the biotechnology and pharmaceutical industries from pharmaceutical, biotechnology, and chemical companies. Our competition includes Hoffmann-La Roche, Inc., Merck, Amgen, and others. Each have products under development or currently available for sale that address the

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same or similar medical conditions as some of our product candidates. We discuss these and other competitors and their competing products in the "Business" section of this prospectus under the caption "Competition". Many of our competitors have substantially greater research, preclinical, and clinical product development and manufacturing capabilities, and financial, marketing and human resources than we do. Our smaller competitors may also obtain a significant competitive advantage if they acquire or discover patentable inventions, form collaborative arrangements, or merge with large pharmaceutical companies. Even if we achieve product commercialization, one or more of our competitors may achieve product commercialization earlier than we do or obtain patent protection that can exclude us from the market or adversely affect our activities. Our ability to compete will depend on how fast we can develop safe and effective product candidates, obtain patent protection, complete clinical testing, obtain regulatory approval to commercialize our product candidate, and supply commercial quantities of the product to the market.

If a competitor announces a successful clinical study involving a product that may be competitive with one of our product candidates or an approval by a regulatory agency to market a competing product, such announcement may have a material adverse effect on our operations, or future prospects, or the price of our common stock.

We also compete with academic institutions, governmental agencies, and other public or private research organizations, which conduct research, seek patent protection, and establish collaborative arrangements for the development and marketing of products that would provide royalties for use of their technology. These institutions are becoming more active in seeking patent protection and licensing arrangements to collect royalties for use of the technology that they have developed. Products developed in this manner may compete directly with products we develop. We also compete with others in acquiring technology from such institutions, agencies, and organizations.

COLLABORATIVE EFFORTS WITH OUR ACADEMIC AND CORPORATE PARTNERS MAY FAIL OR BE TERMINATED, RESULTING IN SIGNIFICANT DELAYS AND SUBSTANTIAL INCREASES IN OUR COSTS FOR RESEARCH, DEVELOPMENT, AND COMMERCIALIZATION OF SOME OF OUR PRODUCT CANDIDATES.

We are party to various arrangements with academic and corporate partners and others. Our collaborators may also be our competitors, such as Amgen. The successful development of product candidates covered by these arrangements depends upon these outside parties fully performing their contractual responsibilities. If any of our collaborators breaches or terminates its agreement with us or otherwise fails to conduct its collaborative activities in a timely manner consistent with the applicable contractual terms, the development or commercialization of the product candidate or research program under such collaborative arrangement may be delayed. If that is the case, we may be required to undertake unforeseen additional responsibilities or to devote unforeseen additional funds or other resources to such development or commercialization, or such development or commercialization could be terminated.

For example, our collaboration agreement with Procter & Gamble has an "opt-out" provision whereby a party may decline to participate further in a

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research or product development program. In such cases, the opting-out party will generally not have any further funding obligation and will not have any rights to the product or program in question (but may be entitled to a royalty on any product sales). If Procter & Gamble were to opt out of a product development program, and we were not to find a new partner, we would bear the full cost of the program which may be substantial. In addition, disagreements between collaborators and us could lead to delays in the collaborative research, development, or commercialization of certain products or could require or result in formal legal process or arbitration for resolution. These consequences could be time-consuming and expensive and could have material adverse effects on us.

We may seek additional collaborative arrangements to develop and commercialize our products in the future. We may not be able to negotiate collaborative arrangements on favorable terms and these collaborative arrangements may not be successful. In addition, our collaborative partners may pursue alternative technologies or develop alternative compounds independently or in collaboration with others as a means of developing treatments for the diseases targeted by their collaborative programs with us.

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IF WE CAN NOT SUCCESSFULLY MANUFACTURE OUR PRODUCT CANDIDATES IN AN EFFICIENT MANNER, OUR ABILITY TO CONDUCT CLINICAL TRIALS AND COMMERCIALIZE OUR PRODUCT CANDIDATES WOULD BE IMPAIRED.

Our ability to conduct timely preclinical and clinical research and development programs, obtain regulatory approval, commercialize our product candidates, and fulfill our contract manufacturing obligations to others will depend, in part, upon our ability to manufacture our products, either directly or through third parties, in accordance with FDA and other regulatory requirements.

We may not be able to manufacture products successfully or in a cost-effective manner at our facilities. We may also have difficulties obtaining the raw materials and supplies necessary to manufacture our product candidates or the products we manufacture for others. If we are unable to use our own manufacturing facilities or to contract with a third-party to manufacture our products on acceptable terms, we may not be able to conduct certain future preclinical and clinical testing or to supply commercial quantities of our product candidates. Our dependence upon third parties for the manufacture of some of our products and related therapies may adversely affect our profit margins and our ability to develop and deliver products on a timely and competitive basis. For example, we are aware of only one supplier of the reagent necessary to produce a pegylated formulation of AXOKINE, which is substantially longer acting than unmodified AXOKINE in preclinical studies. Any problems with the supply of reagent from this vendor could result in the delay or interruption in the development of any pegylated form of AXOKINE.

In addition, if our manufacturing facilities fail to comply with FDA and other regulatory requirements, we will be required to suspend manufacturing. This will have a material adverse effect on our financial condition, results of operations, and cash flow.

SINCE WE HAVE NO SALES AND MARKETING EXPERIENCE OR INFRASTRUCTURE, WE MAY HAVE TO ENGAGE THIRD PARTIES TO MARKET OUR PRODUCTS OR DEVELOP THIS EXPERIENCE AND INFRASTRUCTURE INTERNALLY WHICH WOULD BE TIME CONSUMING AND EXPENSIVE.

We have no internal sales, marketing, and distribution experience or infrastructure and may have to rely significantly on arrangements with third parties in order to perform these functions. If we choose to depend on third parties for the marketing and sale of our products, the cost of using such third

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parties may adversely affect our profit margins. If we decide to perform sales, marketing, and distribution functions ourselves, we would face a number of additional risks, including:

- we may not be able to attract and build a significant marketing or sales force;
- the significant cost of establishing a marketing or sales force may not be justifiable in light of any product revenues; and
- our direct sales and marketing efforts may not be successful.

WE MAY NOT BE ABLE TO ATTRACT OR RETAIN QUALIFIED SCIENTIFIC AND MANAGEMENT PERSONNEL, INCLUDING OUR KEY PERSONNEL, ON ACCEPTABLE TERMS.

We may not be able to retain our key personnel, in particular (1) our Chairman, P. Roy Vagelos, M.D., (2) our President and Chief Executive Officer, Leonard S. Schleifer, M.D., Ph.D., and (3) our Chief Scientific Officer, George D. Yancopoulos, M.D., Ph.D., on terms that are acceptable to us. In addition, our anticipated growth and expansion into new areas requiring additional expertise will place increased demands on our resources and require additional management personnel and the development of additional expertise by existing management personnel. Attracting and retaining qualified personnel is critical to our success. Many of our competitors are established pharmaceutical and biotechnology companies that may have greater success in recruiting skilled scientific workers from the limited pool of available talent. The failure to attract and retain management and scientific personnel could have a material adverse effect on our research and development work and on the operation of our business.

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WE COULD BE EXPOSED TO SIGNIFICANT LIABILITY CLAIMS AND OUR INSURANCE COVERAGE MAY NOT BE ADEQUATE TO COVER THESE CLAIMS.

The testing, manufacturing, and marketing of human pharmaceutical products entails significant inherent risks. Their use in clinical trials and their sale may expose us to substantial liability claims. These claims might be made directly by patients, consumers, pharmaceutical companies, or others selling the products. We are insured by health care product liability insurance policies, including a policy carried by Amgen-Regeneron Partners, the purpose of which is to cover certain claims that could arise during the clinical trials of AXOKINE, the IL-1 Trap, and NT-3. We may not be able to maintain or renew the insurance we have or obtain additional coverage. If our insurance coverage is insufficient, a significant product liability claim or recall would have a material adverse effect on us.

RISKS RELATED TO INTELLECTUAL PROPERTY

WE MAY NOT BE ABLE TO OBTAIN AND ADEQUATELY PROTECT OUR INTELLECTUAL PROPERTY RIGHTS OR AVOID INFRINGING THE RIGHTS OF OTHERS.

Our success depends to a large part upon our own, our licensors' and our collaborators' ability to obtain and defend patent rights and other intellectual property rights that are important to the commercialization of our product candidates. We or our licensors or collaborators have filed patent applications on products and processes relating to AXOKINE, Cytokine Traps, VEGF Trap, Angiopoietins, and NT-3, as well as other technologies and inventions in the United States and in certain foreign countries. Although we have obtained a number of U.S. patents, patent applications owned or licensed by us may not result in patents being issued. Moreover, these patents may not afford us

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protection against competitors with similar technology or products.

Parts of our technology, techniques, and product candidates may conflict with patents owned by or granted to others. Any patent holders could sue us for damages and seek to prevent us from selling or developing our product candidates.

In September 2000, Immunex Corporation filed a request with the European Patent Office seeking the declaration of an Opposition regarding the scope of our European patent relating to Cytokine Traps. This is a legal challenge to the validity and scope of our patent. Although we plan to defend the patent diligently, the scope of the patent may be adversely affected following the outcome of the Opposition.

Uncertainties resulting from the litigation and continuation of patent litigation or other proceedings could have a material adverse effect on our ability to compete in the marketplace. Any patent litigation or other proceeding even if resolved in our favor, absorbs significant financial resources and management time. Some of our competitors may be able to sustain these costs more effectively than we can because of their substantially greater financial and managerial resources. If a patent litigation or other intellectual property proceeding is resolved unfavorably to us, we may be enjoined from manufacturing or selling our products and services without a license from the other party and be held liable for significant damages. We may not be able to obtain any required license on commercially acceptable terms, if at all.

IF WE ARE NOT ABLE TO KEEP OUR TRADE SECRETS CONFIDENTIAL, OUR TECHNOLOGY AND INFORMATION MAY BE USED BY OTHERS TO COMPETE AGAINST US.

In addition to our reliance on patents, we attempt to protect our proprietary products and processes by relying on trade secret laws, nondisclosure and confidentiality agreements, and exclusive licensing arrangements with our employees and certain other persons who have access to our proprietary products or processes or have licensing or research arrangements exclusive to us. These agreements or arrangements may not provide meaningful protection for our proprietary products and processes in the event of unauthorized use or disclosure of such information. Others may independently develop substantially equivalent proprietary information and techniques or otherwise gain access to our trade secrets or technology which will adversely affect our competitive position.

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IF WE BREACH ANY OF THE AGREEMENTS UNDER WHICH WE LICENSE TECHNOLOGY FROM OTHERS, WE COULD LOSE LICENSE RIGHTS THAT ARE IMPORTANT TO OUR BUSINESS.

We are a party to technology licenses that are important to our business and expect to enter into additional licenses in the future. These licenses impose commercialization, sublicensing, royalty, insurance and other obligations on us. If we fail to comply with these requirements, our licensors may have the right to terminate our licenses which would have a negative impact on our business.

RISKS RELATING TO OUR COMMON STOCK

OUR STOCK PRICE COULD BE VOLATILE WHICH COULD CAUSE YOU TO LOSE PART OR ALL OF YOUR INVESTMENT.

There has been a history of significant volatility in the market price of shares of biotechnology companies, including our shares, and it is likely that the market price of our common stock will continue to be highly volatile. In

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1998, the bid price for our common stock fluctuated from a low of \$5.75 a share to a high of \$11.00 a share. In 1999, the bid price fluctuated from a low of \$5.38 per share to a high of \$13.00 per share. From January 1, 2000 to March 19, 2001, the bid price fluctuated from a low of \$10.95 per share to a high of \$57.38 per share. The following factors may have a significant effect on the market price of our common stock:

- fluctuations in our operating results;
- clinical trial results;
- announcements of technological innovations or new commercial therapeutic products introduced by us or our competitors;
- governmental regulation;
- regulatory delays;
- litigation;
- developments in patent or other proprietary rights;
- public concern as to the safety or other implications of the drugs sought to be developed by us or the genetic engineering involved in their production; and
- general market conditions.

Any clinical trial results that are below the expectations of financial analysts or investors would most likely cause our stock price to drop dramatically. Similarly, our stock is likely to drop dramatically if we are not permitted by the FDA to commence a Phase III trial for AXOKINE in 2001 or if the Phase II NT-3 trials expected to be completed in mid-2001 fail to achieve positive results.

OUR EXISTING SHAREHOLDERS MAY BE ABLE TO EXERT SIGNIFICANT INFLUENCE OVER MATTERS REQUIRING SHAREHOLDER APPROVAL.

Holders of Class A stock, who are the shareholders who purchased their stock from us before our initial public offering, are entitled to ten votes per share and holders of common stock are entitled to one vote per share. Upon completion of this offering, holders of Class A stock will hold 5.9% of the total of our outstanding shares of common stock and Class A stock, or collectively, our common shares, and have 38.7% of the combined voting power of the common shares. These shareholders, if acting together, will be in position to significantly influence the election of our directors and to effect or prevent certain corporate transactions which require majority or supermajority approval of the combined classes, including mergers and other business combinations. This may result in the company taking corporate actions that you may not consider to be in your best interest and may affect the price of our common stock. Specifically, upon the completion of this offering:

- our current officers and directors will own 8.9% of our outstanding common shares and 37.1% of the combined voting power of our common shares;

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- Procter & Gamble will hold 13.1% of our outstanding common shares and 8.5% of the combined voting power of our common shares; and
- Amgen will hold 10.2% of our outstanding common shares and 6.6% of the

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combined voting power of our common shares.

WE HAVE ANTITAKEOVER DEFENSES THAT COULD DELAY OR PREVENT AN ACQUISITION AND COULD ADVERSELY AFFECT THE PRICE OF OUR COMMON STOCK.

New York corporate law and our amended and restated certificate of incorporation and by-laws contain provisions that could have the effect of delaying or preventing a change in control of our company or our management that shareholders may consider favorable or beneficial. These provisions could discourage proxy contests and make it more difficult for you and other shareholders to elect directors and take other corporate actions. These provisions could also limit the price that investors might be willing to pay in the future for shares of our common stock. These provisions include:

- authorization to issue "blank check" preferred stock, which is preferred stock that can be created and issued by the board of directors without prior shareholder approval, with rights senior to our common stockholders; and
- a staggered board of directors, so that it would take three successive annual meetings to replace all directors.

In addition, we have a shareholders rights plan which will make it more difficult for a third party to acquire us without the support of our board of directors and principal shareholders.

A SIGNIFICANT NUMBER OF OUR SHARES ARE ELIGIBLE FOR RESALE. THIS COULD REDUCE OUR SHARE PRICE AND IMPAIR OUR ABILITY TO RAISE FUNDS IN NEW SHARE OFFERINGS.

Procter & Gamble and Amgen own 15.4% (or 5,662,505 shares) and 13.3% (or 4,916,808 shares), respectively, of our outstanding shares. Our agreements with both Procter & Gamble and Amgen grant them demand and piggyback registration rights with respect to their shares of common stock. Procter & Gamble and Amgen have each agreed not to sell shares of our common stock for 90 days following the date of this prospectus without the written consent of Merrill Lynch. In addition to this lock-up arrangement with Merrill Lynch, both Procter & Gamble and Amgen have agreed to separate lock-up arrangements with us. Procter & Gamble has agreed not to sell or transfer any of our common stock from March 12, 2001 until March 31, 2002. Amgen has agreed with us not to sell or transfer more than an additional 500,000 shares of our common stock from March 12, 2001 until March 31, 2002. If, for any reason, Amgen does not sell its full allotment of shares in this offering, the amount available for sale during this lock-up period would be increased by the number of shares not sold in this offering. After these lock-up periods expire, either one of these companies could cause a significant number of shares of our common stock to be registered and sold in the public market, particularly in light of the discontinuation of certain of our collaborative efforts with Procter & Gamble and Amgen, which could cause our stock price to decline.

Immediately after completion of this offering, we will have 43,362,789 common shares outstanding and available for resale beginning at various points of time in the future. In addition, we will have 7,523,214 outstanding stock options held by our directors, officers, and employees and 107,400 warrants held by Medtronic as of March 16, 2001. Sales of substantial amounts of shares of our common stock in the public market after this offering, or the perception that those sales will occur, could cause the market price of our common stock to decline. Those sales also might make it more difficult for us to sell equity and equity-related securities in the future at a time and at a price that we consider appropriate.

YOU WILL SUFFER IMMEDIATE AND SUBSTANTIAL DILUTION.

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The price you will pay for our common stock in this offering will be substantially higher than the \$7.75 pro forma net tangible book value per share of our outstanding common shares as of December 31, 2000. As a result, at the offering price of \$25.00, you will experience immediate dilution of \$17.25 in net tangible book value per share, and our current shareholders will experience an immediate increase in the net tangible book value per share of their common shares of \$2.80.

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### FORWARD-LOOKING STATEMENTS

This prospectus and the documents incorporated by reference include forward-looking statements. We have based these forward-looking statements on our current expectations and projections about future events. These forward-looking statements include, among other things, statements relating to:

- our anticipated business strategies;
- our anticipated clinical trials;
- our intention to introduce new products candidates;
- our relationships with collaborators;
- anticipated trends in our businesses;
- future capital expenditures; and
- our ability to conduct clinical trials and obtain regulatory approval.

The forward-looking statements included in this prospectus or in the documents incorporated by reference are subject to risks, uncertainties and assumptions about us. Our actual results of operations may differ materially from the forward-looking statements as a result of, among other things, the success or failure of our clinical trials, the speed at which our clinical trials progress, the success of our competitors in developing products equal or superior to ours, the success of our collaborative relationships and the other reasons described under "Risk Factors." We undertake no obligation to publicly update or revise any forward-looking statement, whether as a result of new information, future events or otherwise, except as required by law. In light of these risks, uncertainties and assumptions, the forward-looking events discussed in this prospectus might not occur.

For these statements, we claim the protection of the safe harbor for forward-looking statements contained in Section 21E of the Securities Act.

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### USE OF PROCEEDS

We will receive approximately \$153.6 million of net proceeds from the sale of 6,500,000 shares of our common stock, based on the public offering price of \$25.00 per share, after deducting underwriting discounts and commissions and the estimated expenses of this offering. We will not receive any of the proceeds from the sale of 500,000 shares of our common stock by Amgen, the selling shareholder. If the underwriters' over-allotment option is exercised in full, we estimate that such net proceeds will be approximately \$178.6 million.

We currently intend to use the net proceeds from this offering as follows:



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- approximately 50-70% for preclinical and clinical development of product candidates, including AXOKINE, pegylated AXOKINE, IL-1 Trap, IL-4/IL-13 Trap, VEGF Trap, and the Angiopoietins;
- approximately 10-30% for basic research activities;
- approximately 5-15% for the continued development of novel technology platforms, including potential efforts to commercialize these technologies; and
- the remainder for general corporate purposes, including capital expenditures and working capital.

Pending application of the net proceeds as described above, we intend to invest the net proceeds of this offering primarily in U.S. Government and other investment grade obligations, interest bearing money market funds and other financial instruments. See "Investment Company Act Considerations."

### DIVIDEND POLICY

We have never paid cash dividends and do not anticipate paying any in the foreseeable future. In addition, under the terms of our financing from the New York State Urban Development Corporation for the purchase and renovation of our Rensselaer facility, we are not permitted to declare or pay cash dividends.

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### CAPITALIZATION

The following table sets forth our capitalization as of December 31, 2000 as adjusted to give effect to our sale of 6,500,000 shares of our common stock in this offering, at the offering price of \$25.00, after deducting underwriting discounts and commissions and estimated expenses of this offering, and the application of the estimated net proceeds. See "Use of Proceeds."

	AT DECEMBER 31, 2000	
	ACTUAL	AS ADJUSTED
	(IN THOUSANDS, EXCEPT SHARE DATA)	
Cash, cash equivalents, and marketable securities.....	\$ 154,370	\$ 307,995
Capital lease obligations -- long-term portion.....	\$ 603	\$ 603
Note payable -- long-term portion.....	1,466	1,466
Stockholders' equity:		
Preferred stock, \$.01 par value; 30,000,000 shares authorized; issued and outstanding -- none.....	--	--
Class A stock, \$.001 par value, convertible into common stock; 40,000,000 shares authorized, 2,612,845 shares issued and outstanding -- actual and as adjusted.....	3	3
Common stock, \$.001 par value; 60,000,000 shares authorized; 34,197,104 shares issued and outstanding -- actual; 40,697,104 shares issued and outstanding -- as adjusted.....	34	41

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Additional paid-in capital.....	406,391	560,009
Unearned compensation.....	(1,314)	(1,314)
Accumulated deficit.....	(223,518)	(223,518)
Accumulated other comprehensive income.....	534	534
	-----	-----
Total stockholders' equity.....	182,130	335,755
	-----	-----
Total capitalization.....	\$ 184,199	\$ 337,824
	=====	=====

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DILUTION

As of December 31, 2000, our net tangible book value before the offering was \$182.1 million or \$4.95 per common share. "Net tangible book value per share" is determined by dividing our net tangible book value (total assets less total liabilities) by the number of common shares outstanding. After giving effect to the sale of the shares of our common stock in this offering at the offering price of \$25.00 and after deducting underwriting discounts and commissions and the estimated expenses of this offering, our pro forma net tangible book value as of December 31, 2000 would have been \$335.8 million in the aggregate, or \$7.75 per common share. This represents an immediate increase in net tangible book value of \$2.80 per common share to existing holders and immediate dilution of \$17.25 per common share to new investors purchasing shares of common stock in this offering. The following table illustrates this per share dilution:

Assumed public offering price.....		\$25.00
Net tangible book value per common share before this offering.....	\$4.95	
Increase attributable to new investors.....	2.80	
	-----	
Pro forma net tangible book value per common share after this offering.....		7.75
		-----
Dilution per common share to new investors.....		\$17.25
		=====

"Dilution per common share to new investors" means the difference between the public offering price per share of common stock and the pro forma net tangible book value per common share after giving effect to this offering.

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SELECTED FINANCIAL DATA

We have derived the selected financial data presented below for the years ended December 31, 2000, 1999 and 1998 and at December 31, 2000 and 1999 from our audited financial statements and notes thereto included in our Annual Report on Form 10-K for the year ended December 31, 2000 which is incorporated by reference in this prospectus. We have derived the selected financial data for the years ended December 31, 1997 and 1996 and at December 31, 1998, 1997 and 1996 from our audited financial statements and notes thereto not included in this prospectus. You should read the selected financial data together with the audited financial statements and the section entitled "Management's Discussion

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and Analysis of Financial Condition and Results of Operations" in our Annual Report on Form 10-K for the year ended December 31, 2000 which is incorporated by reference in this prospectus.

	YEAR ENDED DECEMBER 31,			
	2000	1999	1998	1997
	(IN THOUSANDS, EXCEPT PER SHARE DATA)			
<b>STATEMENT OF OPERATIONS DATA:</b>				
<b>Revenues:</b>				
Contract research and development.....	\$ 36,478	\$ 24,539	\$ 19,714	\$ 17,400
Research progress payments.....	6,200	--	9,500	5,000
Contract manufacturing.....	16,598	9,960	9,113	4,458
	-----	-----	-----	-----
	59,276	34,499	38,327	26,858
	-----	-----	-----	-----
<b>Expenses:</b>				
Research and development.....	56,256	44,940	37,047	27,770
General and administrative.....	8,309	6,355	5,838	5,765
Depreciation and amortization.....	4,421	3,426	3,019	4,389
Contract manufacturing.....	15,566	3,612	5,002	2,617
	-----	-----	-----	-----
	84,552	58,333	50,906	40,541
	-----	-----	-----	-----
Loss from operations.....	(25,276)	(23,834)	(12,579)	(13,683)
	-----	-----	-----	-----
<b>Other income (expense):</b>				
Investment income.....	8,480	5,207	6,866	6,242
Loss in Amgen-Regeneron Partners.....	(4,575)	(4,159)	(2,484)	(3,403)
Interest expense.....	(281)	(284)	(428)	(735)
	-----	-----	-----	-----
	3,624	764	3,954	2,104
	-----	-----	-----	-----
Net loss before cumulative effect of a change in accounting principle.....	(21,652)	(23,070)	(8,625)	(11,579)
Cumulative effect of adopting Staff Accounting Bulletin 101 ("SAB 101").....	(1,563)	--	--	--
	-----	-----	-----	-----
Net loss.....	\$ (23,215)	\$ (23,070)	\$ (8,625)	\$ (11,579)
	=====	=====	=====	=====
<b>Weighted average number of Class A and common stock outstanding, basic and diluted.....</b>				
	34,950	31,308	30,992	28,702
	=====	=====	=====	=====
<b>Net loss per share, basic and diluted:</b>				
Net loss before cumulative effect of a change in accounting principle.....	\$ (0.62)	\$ (0.74)	\$ (0.28)	\$ (0.40)
Cumulative effect of adopting SAB 101.....	(0.04)	--	--	--
	-----	-----	-----	-----
Net loss per share.....	\$ (0.66)	\$ (0.74)	\$ (0.28)	\$ (0.40)
	=====	=====	=====	=====

AT DECEMBER 31,

2000	1999	1998	1997
------	------	------	------

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(IN THOUSANDS)

BALANCE SHEET DATA:

Cash, cash equivalents, and marketable securities.....	\$154,370	\$ 93,599	\$113,530	\$128,04
Total assets.....	208,274	136,999	156,915	168,38
Capital lease obligations and note payable, long-term portion.....	2,069	2,731	3,066	3,75
Stockholders' equity.....	182,130	109,532	131,227	138,89

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BUSINESS

GENERAL

We are a biopharmaceutical company that discovers, develops and intends to commercialize therapeutic drugs for the treatment of serious medical conditions. Our product pipeline includes drug candidates for the treatment of obesity, rheumatoid arthritis and other inflammatory conditions, cancer and related disorders, allergies, asthma, and other diseases and disorders.

Our core business strategy is to combine our strong foundation in science and technology with state-of-the-art manufacturing and clinical development capabilities to build a successful, integrated biopharmaceutical company. Our efforts have yielded a diverse and growing pipeline of product candidates that have the potential to address a variety of unmet medical needs. A key aspect of our strategy is to retain significant ownership and commercialization rights to our pipeline. The ability to participate in the commercialization of our products will enable us to retain the majority of the potential economic rewards from discovering and developing our pipeline. Longer-term, we will continue to invest in the development of additional enabling technologies to assist in our efforts to identify, develop, and commercialize new product candidates.

OUR INDEPENDENT PROGRAMS

The following table lists the programs and product candidates for which we retain sole ownership and marketing rights.

PROGRAM AND PRODUCT CANDIDATE -----	TARGETED INDICATION -----	STAGE -----
AXOKINE (R)	Obesity	Clinical
PEGYLATED AXOKINE	Obesity	Preclinical
IL-1 TRAP	Rheumatoid arthritis	Clinical
IL-4/13 TRAP	Asthma and allergic disorders	Preclinical
TRAPS FOR IL-2, IL-3, IL-4, IL-5, IL-6, IL-15, GAMMA-INTERFERON, TGF-BETA AND OTHERS	Multiple diseases	Research
VEGF TRAP	Cancer and related conditions	Preclinical
ANGIOPOIETIN-1	Vascular leak and edema	Preclinical
EPHRINS, ANGIOPOIETIN-2	Cancer and ischemia	Research
REGENERON ORPHAN RECEPTORS (RORS)	Osteoarthritis and other cartilage diseases	Research

AXOKINE. AXOKINE is our patented second generation ciliary neurotrophic factor, called CNTF. We are developing AXOKINE for the treatment of obesity.

Obesity is a major health problem in all developed countries. The

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prevalence of obesity in the United States has increased substantially during the past decade. A 1999 Congressional Report funded by the National Institutes of Health confirmed that obesity significantly increases a number of health risks, including Type II diabetes. Obesity-related conditions, such as stroke and myocardial infarct are estimated to contribute to about 300,000 deaths yearly, ranking second only to smoking as a cause of preventable death. Current treatment of obesity consists of diet, exercise and other lifestyle changes, and a limited number of drugs. There are two approved drugs currently indicated for the treatment of obesity -- sibutramine (Meridia(R), a registered trademark of Knoll Pharmaceutical Company), and orlistat (Xenical(R), a registered trademark of Hoffmann-La Roche, Inc.). According to their approved product labels, over a twelve month treatment period, these drugs, at their approved starting doses, have produced weight loss of between approximately five and nine pounds as compared to patients taking placebo.

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In November 2000, we announced the preliminary results of a Phase II clinical trial, which tested the safety and efficacy of AXOKINE in severely obese patients. This Phase II trial was a randomized, double-blind, placebo-controlled, out-patient study conducted at seven sites in the United States. Following an initial two week "run-in period," all subjects received twelve weeks of daily treatment, administered under the skin by patient self-injection. A total of 170 patients were divided into five patient groups. The first four patient groups comprised the pre-specified population for the primary analyses and received placebo, a daily dose of 0.3 micrograms (mcg) of AXOKINE per kilogram (kg), a daily dose of 1.0 mcg/kg, or a daily dose of 2.0 mcg/kg, in each case, over the twelve week treatment period. A fifth group received a daily dose of 1.0 mcg/kg for eight weeks, followed by a blinded withdrawal period in which they received placebo for four weeks. The pre-specified end points of the study were change in weight for the patients who completed the full twelve weeks of treatment ("Completer Analysis"), and change in weight for all patients, whether or not they completed the full twelve weeks of treatment ("Last Observed Value Analysis"). All AXOKINE-treated groups showed medically meaningful and statistically significant weight loss compared to placebo. Summarized below are the results of the four groups comprising the primary analyses.

### COMPLETER ANALYSIS

	MEAN WEIGHT CHANGE FROM BASELINE (POUNDS)	p VALUE (RELATIVE TO PLACEBO)
	-----	-----
Placebo (n=19)	+1.3	--
0.3 mcg/kg (n=23)	-3.4	p = 0.01
1.0 mcg/kg (n=26)	-8.9	p <0.0001
2.0 mcg/kg (n=19)	-7.5	p <0.0001

### LAST OBSERVED VALUE ANALYSIS

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	MEAN WEIGHT CHANGE FROM BASELINE (POUNDS)	p VALUE (RELATIVE TO PLACEBO)
	-----	-----
Placebo (n=31)	+0.6	--
0.3 mcg/kg (n=31)	-2.4	p = 0.04
1.0 mcg/kg (n=37)	-7.5	p <0.0001
2.0 mcg/kg (n=33)	-5.8	p <0.0001

As used in the table above, "n" refers to the number of patients in each patient group. The reference to "p" value (relative to placebo) means the probability of being wrong when asserting that a true difference exists between the results for the patient group in question and the placebo group. For example, a p-value of less than 0.0001 indicates that there is a less than one in ten thousand chance that the mean weight loss observed in the group treated with drug and the mean weight loss observed in the group treated with placebo are the same.

The trial established the optimal dose of AXOKINE to be 1.0 mcg/kg daily. Patients who received the optimal dose of AXOKINE over the twelve week treatment period averaged 10 pounds more weight loss than patients on placebo. Moreover, 46% of these patients in the optimal dose group lost at least 10 pounds, compared to just 5% of the patients who received placebo. Nausea was shown not to be a factor that determined average weight loss in this Phase II study.

The 38 patients in the fifth group who received 1.0 mcg/kg of AXOKINE daily for eight weeks followed by a four week blinded withdrawal period lost weight during the treatment period and did not regain weight while taking placebo during the withdrawal period.

On February 28, 2001, we announced that based on a preliminary analysis of interim data, patients who received AXOKINE therapy during the Phase II study maintained their average weight loss during the three months following their last AXOKINE treatment, relative to patients who received placebo. Moreover, patients in the fifth group who were treated with AXOKINE for only eight weeks continued to maintain their average weight loss for an additional four months following their last treatment. This preliminary analysis is based on a total of 87 patients, comprised of patients from all five groups, who completed the full twelve weeks of treatment (drug or placebo) in the study and the twelve week follow-up.

No serious adverse events associated with the drug were reported during the trial and the drug was generally well tolerated, as reflected by the following ratio of patients in each treatment group completing the full twelve weeks of treatment according to the protocol: placebo, 61%; 0.3 mcg/kg, 74%; 1.0 mcg/kg, 70%, and 2.0 mcg/kg, 58%. The most common side effect was dose-dependent injection site reactions (skin redness), which occurred in all patient groups, including placebo, and were generally mild. Other side effects associated with the drug included cough and vomiting, which were notable only in the 2.0 mcg/kg dose group, and nausea, which occurred most frequently in the 2.0 mcg/kg dose group. There was no increase compared to placebo in the incidence of herpes simplex infections in patients taking AXOKINE. Neutralizing antibodies, based on a laboratory test, were not dose-related and occurred in less than 10% of all

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patients receiving AXOKINE.

Subject to discussions with the FDA, we intend to initiate Phase III testing of AXOKINE in severely obese patients in mid-2001. This Phase III program likely will involve the enrollment of several thousand severely obese patients with a primary double-blind treatment period of approximately one year and an additional one year follow-up treatment period.

In March 2000, we established a research and development collaboration with Emisphere Technologies, Inc. to utilize Emisphere's oral drug delivery technology for AXOKINE. In preliminary preclinical pharmacokinetic studies, the Emisphere technology was able to achieve measurable blood levels of AXOKINE.

PEGYLATED AXOKINE. We are developing a pegylated version of AXOKINE (pegAXOKINE) as a more potent, longer-acting form of the protein. PegAXOKINE may allow for less frequent and/or lower dosing in patients. PegAXOKINE currently is in late-stage preclinical development and we anticipate initiating a Phase I clinical trial in mid-2001. Shearwater Corporation has contracted with us to develop and supply the pegylated reagent for this product candidate.

CYTOKINE TRAPS. Our research on the CNTF class of neurotrophic factors led to the discovery that CNTF, although it is a neurotrophic factor, belongs to the "superfamily" of signaling molecules referred to as cytokines. Cytokines are soluble proteins secreted by the cells of the body. In many cases, cytokines act as messengers to help regulate immune and inflammatory responses. In excess, cytokines can be harmful and have been linked to a variety of diseases. Blocking cytokines and growth factors is a proven therapeutic approach with a number of drugs already approved or in clinical development. The cytokine superfamily includes factors such as erythropoietin, thrombopoietin, granulocyte-colony stimulating factor and the interleukins (or ILs).

In the early 1990's, our scientists made a breakthrough in understanding how receptors work for an entire class of interleukins in the human body. Based on this finding, we developed a family of antagonists referred to as "Cytokine Traps." This includes Cytokine Traps for IL-1, IL-4, and IL-6, and a single Trap that blocks both IL-4 and IL-13. Because these Traps mimic the body's natural receptors, they are effective at catching and holding the cytokines. With cytokines trapped, the immune system responds as if the perceived threat is under control.

In preclinical studies, these Cytokine Traps are more potent than other antagonists, potentially allowing lower levels of the drug to be used. Moreover, because these Cytokine Traps are comprised entirely of natural human-derived protein sequences they may be less likely to induce an immune reaction in humans. Because pathological levels of IL-1, IL-4, IL-6, and IL-13 seem to contribute to a variety of disease states, these Cytokine Traps have the potential to be important therapeutic agents.

IL-1 Trap. In December 2000, we initiated a Phase I study of the IL-1 Trap to assess its safety and tolerability in patients with rheumatoid arthritis. The placebo-controlled, double-blind, dose-escalation study is being conducted at several centers in the United States and includes a single dose phase and a multiple dose phase. We expect the study to be completed in the second half of 2001. The IL-1 Trap is also being evaluated for potential uses in treating other inflammatory diseases.

Rheumatoid arthritis is a chronic disease in which the immune system attacks the tissue that lines and cushions joints. Over time, the cartilage, bone, and ligaments of the joint erode, leading to progressive

joint deformity and joint destruction, generally in the hand, wrist, knee, and foot. Joints become painful and swollen and motion is limited. Over time, the cartilage erodes, resulting in structural damage to the joint. Over two million people, 1% of the U.S. population, are estimated to have rheumatoid arthritis, and 10% of those eventually become disabled. Women account for roughly two-thirds of these patients.

Rheumatoid arthritis involves an excess of certain cytokines, including IL-1 and tumor necrosis factor (TNF). Drugs that block TNF have already been approved for the treatment of rheumatoid arthritis, while animal studies indicate that IL-1 is also an attractive target for drug development in this disease. In animal models, our IL-1 Trap is a potent blocker of IL-1 activity, has a long half-life in the blood, penetrates into the inflamed joint, and blocks cartilage erosion.

While both TNF and IL-1 can induce arthritis, IL-1 more potently induces cartilage destruction in animal models. In addition, the arthritis caused by TNF in some animals can be prevented by blocking the action of IL-1, indicating that the arthritogenic action of TNF may be mediated, in part, through IL-1. Even stronger evidence for the role of IL-1 in rheumatoid arthritis is that mice that are deficient in the interleukin-1 receptor antagonist (IL-1-ra), a naturally occurring blocker of IL-1 action, develop spontaneously occurring arthritis. The validation of IL-1 blockade as a target for drugs to treat rheumatoid arthritis also appears to have been demonstrated by the positive results reported by another company with administration of IL-1-ra in clinical trials in patients with rheumatoid arthritis.

IL-4/IL-13 Trap. Antagonists for IL-4 and IL-13 may be therapeutically useful in a number of allergy and asthma-related conditions, including as adjuncts to vaccines where blocking IL-4 and IL-13 may help to elicit more of the desired type of immune response to the vaccine. We have developed both an IL-4 Trap and an IL-4/IL-13 Trap, which is a single molecule that can block both interleukin-4 and interleukin-13. We expect to initiate a clinical trial of a dual IL-4/IL-13 Trap to assess its safety and tolerability for the treatment of asthma/allergy-related conditions late in 2001.

One in 13 Americans suffers from allergies and one in 18 suffers from asthma. The number of people afflicted with these diseases has been growing at an alarming rate. It is believed that IL-4 and IL-13 play a role in these diseases. These two cytokines are essential to the normal functioning of the immune system, creating a vital communication link between white blood cells. In the case of asthma and allergies, however, there are too many interleukins present, causing the immune system to overact. Our IL-4/IL-13 Trap may offer unique advantages over other products and product candidates for asthma and allergy-related conditions because of its ability to block both of the cytokines thought to be at the root of these disorders.

Other Cytokine Traps. We have a late stage research program underway for an IL-6 Cytokine Trap. IL-6 has been implicated in the pathology and progression of multiple myeloma, certain solid tumors, AIDS, lymphomas (both AIDS-related and non-AIDS-related), osteoporosis, and other conditions. We also have patents covering additional Cytokine Traps for IL-2, IL-3, IL-5, IL-15, gamma-interferon, transforming growth factor beta, and others, which are being pursued at the research level. Our research regarding protein-based cytokine antagonists currently includes molecular and cellular research to improve or modify Cytokine Trap technology, process development efforts to produce experimental and clinical research supplies, and in vivo and in vitro studies to further understand and demonstrate the efficacy of the Cytokine Traps.

VEGF TRAP AND ANGIOPOIETINS. A plentiful blood supply is required to nourish every tissue and organ of the body. Diseases such as diabetes and



atherosclerosis wreak their havoc, in part, by destroying blood vessels (arteries, veins, and capillaries) and compromising blood flow. Decreases in blood flow (known as ischemia) can result in non-healing skin ulcers and gangrene, painful limbs that cannot tolerate exercise, loss of vision, and heart attacks. In other cases, disease processes can damage blood vessels by breaking down vessel walls, resulting in defective and leaky vessels. Leaking vessels can lead to swelling and edema, as occurs in brain tumors following ischemic stroke, in diabetic retinopathy, and in arthritis and other inflammatory diseases. Finally, some disease processes such as tumor growth depend on the induction of new blood vessels.

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Depending on the clinical situation, positively or negatively regulating blood vessel growth could have important therapeutic benefits, as could the repair of damaged and leaky vessels. Thus, building new vessels, by a process known as angiogenesis, can improve circulation to ischemic limbs and heart, aid in healing of skin ulcers or other chronic wounds, and in establishing tissue grafts. Reciprocally, blocking tumor-induced angiogenesis can blunt tumor growth. In addition, repairing leaky vessels can reverse swelling and edema.

Vascular endothelial growth factor (VEGF) was the first growth factor shown to be specific for blood vessels, by virtue of having its receptor specifically expressed on blood vessel cells. Our scientists discovered a second family of angiogenic growth factors, termed the Angiopoietins, and we have received patents for the members of this family. The Angiopoietins include naturally occurring positive and negative regulators of angiogenesis, as described in numerous scientific manuscripts published by our scientists and their collaborators.

Our studies have revealed that VEGF and the Angiopoietins normally function in a coordinated and collaborative manner during blood vessel growth. Thus, the growth of new blood vessels to nourish ischemic tissue appears to require use of both these agents. In addition, Angiopoietin-1 seems to play a critical role in stabilizing the vessel wall, and the use of this growth factor can prevent or repair leaky vessels in animal models. In terms of blocking vessel growth, manipulation of both VEGF and Angiopoietin seems to be of value.

Currently, we have a highly potent VEGF antagonist, termed the VEGF Trap, in preclinical development as an anti-angiogenic agent for cancer. We expect to begin a clinical trial of the VEGF Trap as a potential treatment for harmful angiogenesis or vascular leak in settings of cancer and/or other conditions in mid-2001. In addition, we are evaluating Angiopoietin-1 and engineered designer versions of Angiopoietins in preclinical studies to determine their utility for repairing blood vessel leak and for growing blood vessels in ischemia.

We and others have identified a family of growth factors termed the Ephrins and their receptors termed the Ephs. Members of this family have specific roles in angiogenesis and hemopoiesis, which are being pursued in preclinical studies.

CARTILAGE GROWTH FACTOR SYSTEM AND OSTEOARTHRITIS. Osteoarthritis results from the wearing down of the articular cartilage surfaces that cover joints. Thus, growth factors that specifically act on cartilage cells could have utility in osteoarthritis. Our scientists have discovered a growth factor receptor system selectively expressed by cartilage cells, termed Regeneron Orphan Receptor 2 (ROR2). Furthermore, our scientists have demonstrated that this growth factor receptor system is required for normal cartilage development in mice. In addition, together with collaborators, our scientists have proven that mutations in this growth factor receptor system cause inherited defects in cartilage development in humans. Thus, this growth factor receptor system is a promising new target for cartilage diseases such as osteoarthritis.

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### OUR COLLABORATIVE PROGRAMS

**MUSCLE ATROPHY AND RELATED DISORDERS.** Muscle atrophy occurs in many neuromuscular diseases and also when muscle is unused, as often occurs during prolonged hospital stays and during convalescence. Currently, physicians have few options to prescribe for patients with muscle atrophy or other muscle conditions which afflict millions of patients globally. Thus, a factor that might have beneficial effects on skeletal muscle could have significant clinical benefit. Our muscle program is currently focused on conducting in vivo and in vitro experiments with the objective of demonstrating and further understanding the molecular mechanisms involved in muscle atrophy and hypertrophy. This work is being conducted in collaboration with scientists at Procter & Gamble as part of our collaboration.

NT-3. Amgen-Regeneron Partners' clinical development of NT-3 is currently focused on the treatment of constipating conditions. In 1998, we, on behalf of Amgen-Regeneron Partners, completed a small clinical study that included healthy volunteers and patients suffering from severe idiopathic constipation. We also conducted additional small studies in patients who suffer from constipation

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associated with conditions such as spinal cord injury and the use of narcotic analgesics. In 2000, we initiated double-blind, placebo-controlled Phase II studies of NT-3 in patients with functional constipation and in spinal cord injury patients with bowel dysfunction. These studies currently are underway and we expect them to be completed in mid-2001. Amgen-Regeneron Partners is developing NT-3 in the United States under a license from Takeda Chemical Industries, Ltd.

**OTHER EARLY STAGE PROGRAMS: FIBROSIS AND G-PROTEIN COUPLED RECEPTORS.** Fibrotic diseases, such as cirrhosis, result from the excess production of fibrous extracellular matrix by certain cell types that are inappropriately activated in these diseases. We and our collaborators identified orphan receptors, termed Discoidin Domain Receptors 1 and 2 (DDR1 and DDR2), that are expressed by the activated cell types in fibrotic disease. We have further shown that these receptors bind and are activated by the fibrous matrix they produce. Thus, these receptors are important new targets in fibrotic disease.

Our work in this area is currently focused on determining whether selective inhibition or activation of DDR1 and DDR2 would be beneficial in the setting of fibrotic disease. Further, we are studying key signaling pathways which allow particular fibrosis-inducing cells to multiply. Inhibition of such pathways may be useful in preventing the development of fibrosis. These research activities are being conducted in collaboration with scientists at Procter & Gamble.

We also have a research program focused on the discovery and characterization of G-Protein Coupled Receptors, which have historically been among the most useful targets for pharmaceuticals. We use a genomics approach to discover new receptors and then we characterize these receptors in our disease models by examining their expression. Early stage research work on selected G-Protein Coupled Receptors is being conducted in collaboration with scientists at Procter & Gamble.

### OUR TECHNOLOGY PLATFORMS

Our ability to discover and develop product candidates for a wide variety of serious medical conditions results from the leveraging of our powerful technology platforms, many of which were developed or enhanced by us. Although

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the primary use of these technology platforms is for our own research and development programs, we are also exploring the possibilities of exploiting these technologies commercially through, for example, direct licensing or sale of technology, or the establishment of research collaborations to discover and develop drug targets.

**TARGETED GENOMICS(TM):** In contrast to basic genomics approaches, which attempt to identify every gene in a cell or genome, we use Targeted Genomics approaches to identify specific genes likely to be of therapeutic interest. These approaches do not depend on random gene sequencing, but rather on function-based approaches to specifically target the discovery of genes for growth factors, peptides, and their receptors that are most likely to have use for developing drug candidates. This technology has already led to our discovery of the Angiopoietin and Ephrin growth factor families for angiogenesis and vascular disorders, the MuSK growth factor receptor system for muscle disorders, and the Regeneron Orphan Receptor (ROR) growth factor receptor system that regulates cartilage formation.

**HIGH THROUGHPUT FUNCTIONOMICS(TM):** A major challenge facing the biopharmaceutical industry in the post-genomic era involves the efficient assignment of function to random gene sequences to enable the identification of validated drug targets. One way to help determine the function of a gene is to generate mice in which the gene is removed (referred to as "knockout mice"), or is over-produced (referred to as "transgenic mice"), or in which a color-producing gene is substituted for the gene of interest (referred to as "reporter knockin mice") to identify which cells in the body are expressing the gene. Until recently, technical hurdles involved in the generation of mouse models restricted the ability to produce multiple models quickly and efficiently. We have developed proprietary technology that we believe will allow for the rapid and efficient production of genetically modified mice on a high throughput scale enabling rapid assignment of function to gene sequences.

**DESIGNER PROTEIN THERAPEUTICS(TM):** In cases in which the natural gene product is itself not a product candidate, we utilize our Designer Protein Therapeutics platform to genetically engineer product candidates

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with the desired properties. We use these technologies to develop derivatives of growth factors and their receptors, which can allow for modified agonistic or antagonistic properties that may prove to be therapeutically useful. Examples include the generation of AXOKINE and the development of Cytokine Traps and the VEGF Trap. This technology platform has already produced more than 10 patented proteins, including the IL-1 Trap currently in Phase I clinical testing, and several others in preclinical development.

### COLLABORATIVE RELATIONSHIPS

In addition to our independent programs, we currently conduct programs in collaboration with academic and corporate partners. We have entered into research collaboration and licensing agreements with various corporate partners, including Procter & Gamble, Medarex, Amgen, and Sumitomo Pharmaceuticals.

**PROCTER & GAMBLE.** In May 1997, we entered into a long-term collaboration agreement with Procter & Gamble to discover, develop, and commercialize pharmaceutical products. Procter & Gamble agreed over the first five years of the 1997 collaboration to purchase up to \$60.0 million of our equity, of which \$42.9 million was purchased in June 1997 and \$17.1 million was purchased in August 2000. These equity purchases were in addition to a purchase by Procter & Gamble of \$10.0 million of our common stock that was completed in March 1997. Procter & Gamble also agreed over the first five years of the 1997 collaboration

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to provide funding in support of our research efforts related to the collaboration. In September 1997, we and Procter & Gamble amended the 1997 collaboration agreement to include AXOKINE and related molecules. Procter & Gamble paid us research progress payments of \$5.0 million in 1997 and \$5.0 million in 1998 upon the achievement of defined milestones related to AXOKINE. During the third quarter of 1999, Procter & Gamble returned the product rights to AXOKINE to us and ended related research support for our AXOKINE program. However, Procter & Gamble will be entitled to receive a small royalty on any sales of AXOKINE.

In August 2000, Procter & Gamble made two non-recurring research progress payments to us totaling \$3.5 million. In addition, in August 2000, we and Procter & Gamble agreed through a binding memorandum of understanding to enter into a new collaboration agreement, replacing the companies' 1997 collaboration agreement. The new agreement extends Procter & Gamble's obligation to fund our research under the new collaboration through December 2005, with no further research obligations by either party thereafter, and focuses the companies' collaborative research on therapeutic areas that are of particular interest to Procter & Gamble, including muscle atrophy and muscle diseases, fibrotic diseases, and selected G-Protein Coupled Receptors. For each of these program areas, the parties contribute research activities and necessary intellectual property rights pursuant to mutually agreed upon plans and budgets established by operating committees. Neither party may independently perform research on targets subject to research or development activities under the collaboration. In addition, during the research term and for five years thereafter, neither party may develop or commercialize a product that competes with a product developed as part of the collaboration.

Pursuant to the August 2000 binding memorandum of understanding, we and Procter & Gamble have divided rights to the programs from the 1997 collaboration agreement that are no longer part of the companies' collaboration. Procter & Gamble has obtained rights to certain early stage programs. We have rights to all other research programs including exclusive rights to the VEGF Trap, the Angiopoietins and Regeneron's Orphan Receptors (RORs). Any drugs that result from the new collaboration will continue to be jointly developed and marketed worldwide, with the companies equally sharing development costs and profits. Under the new agreement, beginning in the first quarter of 2001 and continuing through December 2005, research support from Procter & Gamble will be \$2.5 million per quarter, or \$50.0 million in the aggregate (before adjustments for future inflation). From the inception of our collaboration with Procter & Gamble through February 28, 2001, we have received research funding and research progress payments, including payments related to AXOKINE, totaling \$81.3 million.

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The new collaboration agreement will expire on the later of December 31, 2005 or the termination of research, development, or commercial activities relating to compounds that meet predefined success criteria before that date. In addition, if either party successfully develops a compound covered under the agreement to a predefined development stage during the two-year period following December 31, 2005, the parties shall meet to determine whether to reconvene joint development of the compound under the agreement. The agreement is also subject to termination if either party enters bankruptcy, breaches its material obligations, or undergoes a change of control.

In addition to these termination rights, the agreement with Procter & Gamble has an "opt-out" provision, whereby a party may decline to participate further in a research or product development program. In such cases, the opting-out party will generally not have any further funding obligation and will not have any rights to the product or program in question (but may be entitled

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to a royalty on any product sales). If Procter & Gamble opts out of a product development program, and we do not find a new partner, we would bear the full cost of the program.

MEDAREX. In March 2000, we entered into a collaboration under a binding memorandum of understanding with Medarex to discover, develop, and commercialize human antibodies as therapeutics. We will contribute our expertise in discovering and characterizing proteins as drug targets, and Medarex will contribute its HuMAB-Mouse(TM) technology to create fully human antibody products for those targets. Together we have selected more than twenty initial targets, including growth factors, cytokines, and receptors, and plan to add additional targets in the future. We and Medarex intend to prioritize targets based upon a variety of criteria, including target validation, reagent availability, market opportunity, competitive factors, intellectual property position, and the expected feasibility of obtaining antibodies that have the desired properties. The HuMAB-Mouse is a transgenic mouse whose genes for creating mouse antibodies have been inactivated and replaced by human antibody genes. This makes it possible to rapidly create and develop fully human antibodies as drug candidates.

Under the agreement, Medarex and we will share equally all development, manufacturing, and clinical costs of jointly developed products and all net profits and losses. Each of us has the right to opt out of the joint development of an antigen target and receive instead milestones and royalty payments on net sales as may be negotiated by the parties. The agreement terminates upon the later of three years or the date on which neither party is exploiting any jointly developed products. During the term of the agreement, neither party may independently develop any antibody-based products against any of the targets included within the collaboration. In addition, we and Medarex have agreed not to purchase more than twenty percent of each other's stock.

EMISPHERE. In March 2000, we signed an agreement with Emisphere to establish a research and development collaboration to utilize Emisphere's oral drug delivery technology for AXOKINE. In preliminary preclinical pharmacokinetic studies, the Emisphere technology was able to achieve measurable blood levels of AXOKINE. Under the terms of the agreement, we will support research at Emisphere and make payments, including license and milestone payments, based on the satisfaction of pre-determined criteria during the development of orally delivered AXOKINE. The parties have established a steering committee to determine these milestones, which trigger either payment obligations or termination rights for us. The first of these milestones is based on the status of the program as of March 31, 2001. The steering committee shall meet on at least a quarterly basis to review the results of the program. In addition, the agreement is also subject to termination if either party breaches its material obligations thereunder. During the term of the agreement, we will receive exclusive worldwide commercialization rights to oral products that result from the collaboration and pay Emisphere a royalty on sales of any such products.

SHEARWATER. In December 2000, we entered into a license and supply agreement with Shearwater Corporation under which Shearwater will develop and supply a pegylated reagent that could be used to formulate a modified form of AXOKINE. In preclinical studies, a pegylated AXOKINE was substantially longer lasting than unmodified AXOKINE. This may allow less frequent and/or lower dosing in patients. Under the terms of the agreement, Shearwater will develop and supply the reagent and we will manufacture and have exclusive rights to pegylated AXOKINE. Shearwater is entitled to receive

milestone payments based on the development of the modified AXOKINE and will be the exclusive supplier of the reagent. We will pay Shearwater a royalty not to

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exceed 2.5% on sales of any pegylated AXOKINE. The agreement remains in force until the later of ten years from the grant of the first marketing approval for a pegylated AXOKINE or the last-to-expire patent covering Shearwater's pegylated reagent. In addition, each party has the right to terminate the agreement upon bankruptcy of the other party or the other party's breach of a material obligation under the agreement. We have additional termination rights if market or other conditions, including regulatory restrictions, seriously inhibit the ability to develop or market pegylated AXOKINE.

AMGEN. In August 1990, we entered into a collaboration agreement with Amgen to develop and attempt to commercialize two proprietary product candidates, BDNF and NT-3, in the United States. Pursuant to the agreement with Amgen, we formed a partnership with Amgen (Amgen-Regeneron Partners) to complete the development and commercialization of these product candidates. We are required to fund 50% of the development costs of Amgen-Regeneron Partners in order to maintain 50% of the commercialization rights. Assuming equal capital contributions to Amgen-Regeneron Partners, we and Amgen share any profits or losses of Amgen-Regeneron Partners equally. Amgen-Regeneron Partners has been conducting clinical trials of BDNF for the treatment of amyotrophic lateral sclerosis (or ALS). Following notification that BDNF did not provide any therapeutic advantage to ALS patients in the clinical trials, we and Amgen discontinued the development of BDNF for ALS in January 2001. We conduct clinical trials of NT-3 on behalf of Amgen-Regeneron Partners. Under our agreement with Amgen, we are attempting to develop NT-3 with Amgen and, if such effort is successful, commercialize, market and distribute NT-3 in the United States through Amgen-Regeneron Partners.

Our agreement with Amgen will continue for the longer of the life of the patents covering NT-3 or BDNF or fifteen years from the date on which either product candidate is approved for commercial marketing in any country. The agreement is also subject to termination if either party enters into bankruptcy or breaches its material obligations thereunder. During the term of the agreement, there are restrictions on the ability of either party to independently conduct research or development of NT-3 or BDNF without the other party. Our aggregate capital contribution to Amgen-Regeneron Partners from the partnership's inception in June 1993 through December 31, 2000 was \$56.2 million. We expect that our capital contributions for 2001 will total at least \$2.2 million. These contributions could increase or decrease, depending upon, among other things, the nature and cost of ongoing and additional NT-3 studies that Amgen-Regeneron Partners may conduct, the outcomes of those studies, and costs associated with the discontinuation of the BDNF studies. From the inception of our collaboration agreement with Amgen through February 28, 2001, we have received payments from Amgen or Amgen-Regeneron Partners for product development funding, research progress payments, and services rendered totaling \$55.1 million. We do not expect to receive any further payments for BDNF under this agreement. Future payments that we receive related to NT-3 will depend on the success of this product candidate's development, which we cannot predict at this time.

The development and commercialization of NT-3 outside of the United States, Japan, China, and certain other Pacific Rim countries, if any, will be conducted solely by Amgen through a license from us and from Takeda Chemical Industries, Ltd. In return, we will receive royalty payments based on Amgen's net sales of any products in the licensed territory. In the licensed territory, Amgen is solely responsible for funding clinical development and related costs of the licensed products, as well as costs of their commercial exploitation, and has sole discretion with respect to all such development, manufacturing, and marketing of the products and sole responsibility for filing applications for regulatory approvals.

During October 2000, we and Amgen entered into an agreement whereby we acquired Amgen's patents and patent applications relating to CNTF and related

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molecules for \$1.0 million. As part of this agreement, we granted back to Amgen exclusive, royalty free rights under these patents and patent applications solely for human ophthalmic uses. In addition, we agreed not to sue Amgen under our patents and patent applications relating to CNTF and related molecules solely for human ophthalmic uses.

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SUMITOMO. In March 1989, Sumitomo Chemical Company, Ltd. entered into a Technology Development Agreement with us and paid us \$5.6 million. In addition, Sumitomo Chemical purchased \$4.4 million of our equity. In connection with this agreement, we granted Sumitomo Chemical a limited right of first negotiation, over a fifteen year period, to license up to three of our product candidates to commercialize in Japan on financial and commercial terms as we may offer. If Sumitomo Chemical decides it does not wish to enter into a license agreement with us on the terms we propose, we are free to license the product candidate to any other third party for Japan on terms and conditions no more favorable than those offered to Sumitomo Chemical. We are obligated periodically to inform and, if requested, to meet with Sumitomo Chemical management about our progress in research and development. This agreement shall expire on the earlier of March 20, 2004 or the date that Sumitomo Chemical licenses three product candidates from us, provided that the parties may extend the agreement for an additional five-year term.

BDNF is licensed to Sumitomo Pharmaceuticals (a subsidiary of Sumitomo Chemical) for development in Japan. Under our agreement, we supply Sumitomo Pharmaceuticals with BDNF for clinical and preclinical testing and receive payments for manufacturing costs and research progress payments based on the development of BDNF. From the inception of our agreement through February 28, 2001, Sumitomo Pharmaceuticals has paid us \$60.9 million in connection with supplying BDNF for preclinical and clinical use, research funding, and research progress payments. In addition, we will receive a royalty based on any potential BDNF sales in Japan. The agreement expires at the later of fifteen years from the date of the first commercial sale of BDNF in Japan and the last-to-expire patent covering BDNF in Japan. In addition, Sumitomo Pharmaceuticals has the unilateral right to terminate the agreement at any time. In light of the recent Amgen-Regeneron Partners' unfavorable clinical trial results for BDNF, it is likely that Sumitomo Pharmaceuticals will exercise its discretionary right to terminate the license with us for BDNF. Other than amounts currently outstanding and any wind-down costs, we do not expect to receive further payments from Sumitomo Pharmaceuticals for research progress payments, contract research and development, or contract manufacturing. We recognized revenue from Sumitomo Pharmaceuticals of \$7.6 million in 2000, \$0.1 million in 1999, and \$8.8 million in 1998.

### MANUFACTURING

We maintain an 8,000 square foot manufacturing facility in Tarrytown, New York. This facility, which was designed to comply with FDA current good manufacturing practices (called GMP), produces preclinical and clinical supplies of our product candidates.

In 1993, we purchased our 100,000 square foot Rensselaer, New York manufacturing facility, which is being used to manufacture drugs for our own preclinical and clinical studies. We also use the facility to manufacture a product for Merck under a long-term contract.

Currently we dedicate approximately 200 people to our manufacturing operations at these facilities.

### PATENTS, TRADEMARKS AND TRADE SECRETS

Our success depends, in part, on our ability to obtain patents, maintain trade secret protection and operate without infringing on the proprietary rights of third parties. Our policy is to file patent applications to protect technology, inventions, and improvements that are considered important to the development of our business. We have been granted 55 U.S. patents and we have more than 100 pending applications. We are the exclusive or nonexclusive licensee of a number of additional U.S. patents and patent applications. We also rely upon trade secrets, know-how, and continuing technological innovation to develop and maintain our competitive position. We or our licensors or collaborators have filed patent applications on products and processes relating to neurotrophic factors and other technologies and inventions in the United States and in certain foreign countries. We intend to file additional patent applications, when appropriate, relating to improvements in these technologies and other specific products and processes. We plan to aggressively prosecute, enforce, and defend our patents and other proprietary technology.

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In September 2000, Immunex filed a request with the European Patent Office seeking the declaration of an Opposition regarding our European patent relating to Cytokine Traps. This is a legal challenge to the validity and scope of our patent. Although we plan to defend the patent diligently, the scope of the patent may be adversely affected following the outcome of the Opposition.

#### COMPETITION

There is substantial competition in the biotechnology and pharmaceutical industries from pharmaceutical, biotechnology, and chemical companies. Many of our competitors have substantially greater research, preclinical, and clinical product development and manufacturing capabilities, and financial, marketing, and human resources than we do. Our smaller competitors may also be significant if they acquire or discover patentable inventions, form collaborative arrangements, or merge with large pharmaceutical companies. Even if we are ultimately successful in our efforts to commercialize our product candidates, one or more of our competitors may achieve product commercialization earlier than we do or obtain patent protection that dominates or adversely affects our activities. Our ability to compete will depend on how fast we can develop safe and effective product candidates, complete clinical testing and the approval processes, and supply commercial quantities of the product to the market. Competition among product candidates approved for sale will also be based on efficacy, safety, reliability, availability, price, patent position, and other factors.

**AXOKINE:** There is substantial competition in the discovery and development of treatments for obesity. In addition, there are well-established and cost-effective prescription and over-the-counter treatments for this condition. For example, Hoffmann-La Roche and Knoll Pharmaceuticals already market well-established drugs for the treatment of obesity and Amgen and a number of other pharmaceutical companies are developing leptin and related molecules. Clinical trials of leptin are under way. Some of these drugs may offer competitive advantages over AXOKINE. For example, AXOKINE currently is available only in injectable form, while the currently available marketed drugs for the treatment of obesity are delivered in oral dosage forms, which generally are favored by patients over injectable drugs. Therefore, even if AXOKINE is approved for sale, the fact that it must be delivered by injection may severely limit its market acceptance among patients and physicians.

**CYTOKINE TRAPS:** Similarly, marketed products for the treatment of rheumatoid arthritis and asthma are available as either oral or inhaled drugs, whereas our Cytokine Traps currently are only planned for clinical trials as



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injectables. The markets for both rheumatoid arthritis and asthma are very competitive. Several new, highly successful drugs recently became available for these disease states. Examples include the TNF-antagonists Enbrel(R) (a registered trademark of Immunex Corporation) and Remicade(R) (a registered trademark of Centocor, Inc.) for rheumatoid arthritis and the leukotriene-modifier Singulair(R) (a registered trademark of Merck & Co., Inc.) as well as various inexpensive corticosteroid drugs for asthma.

**VEGF TRAP:** Many companies are developing drugs designed to block the actions of VEGF specifically and angiogenesis in general. A variety of approaches have been employed, including antibodies to VEGF, antibodies to the VEGF receptor, small molecule antagonists to the VEGF receptor tyrosine kinase, as well as multiple other anti-angiogenesis strategies. Many of these alternative approaches may offer competitive advantages to our VEGF Trap in efficacy, side-effect profile, cost, or form of delivery. Additionally, many of these developmental drugs may be at a more advanced stage of development than our product candidate.

**NT-3:** The treatment of constipating conditions is highly competitive, with a number of companies providing over-the-counter remedies and other competitors attempting to discover and develop improved over-the-counter or prescription treatments. These products may offer competitive advantages over our NT-3 product candidate in efficacy, side-effect profile, cost, or form of delivery.

**OTHER AREAS:** Many pharmaceutical and biotechnology companies are attempting to discover and develop small-molecule based therapeutics, similar in at least certain respects to our program with Procter & Gamble. In these and related areas, intellectual property rights have been sought and certain rights have been granted to competitors and potential competitors of ours and we may be at a substantial competitive

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disadvantage in such areas as a result of, among other things, our lack of experience, trained personnel, and expertise. A number of corporate and academic competitors are involved in the discovery and development of novel therapeutics using tyrosine kinase receptors, orphan receptors, and compounds that are the focus of other research or development programs we are now conducting. These competitors include Amgen and Genentech, Inc., as well as many others. Many firms and entities are engaged in research and development in the areas of cytokines, interleukins, angiogenesis, and muscle conditions. Some of these competitors are currently conducting advanced preclinical and clinical research programs in these areas. These and other competitors may have established substantial intellectual property and other competitive advantages.

If a competitor announces a successful clinical study involving a product that may be competitive with one of our product candidates or an approval by a regulatory agency of the marketing of a competitive product, such announcement may have a material adverse effect on our operations, or future prospects, or the price of our common stock.

We also compete with academic institutions, governmental agencies, and other public or private research organizations, which conduct research, seek patent protection, and establish collaborative arrangements for the development and marketing of products that would provide royalties for use of their technology. These institutions are becoming more active in seeking patent protection and licensing arrangements to collect royalties for use of the technology that they have developed. Products developed in this manner may compete directly with products we develop. We also compete with others in acquiring technology from such institutions, agencies, and organizations.

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### GOVERNMENT REGULATION

Producing and marketing our product candidates and our research and development activities are subject to regulations relating to product safety and efficacy by numerous governmental authorities in the United States and other countries. In the United States, drugs are subject to rigorous FDA regulation. The Federal Food, Drug and Cosmetic Act and other federal and state statutes and regulations govern, among other things, the testing, manufacture, safety, effectiveness, labeling, storage, record keeping, approval, advertising, and promotion of our products.

Before we may market a pharmaceutical product in the United States, the FDA requires us to complete the following steps:

- preclinical laboratory and animal tests;
- submission to the FDA of an investigational new drug application, or IND, which must become effective before human clinical trials may commence;
- adequate and well controlled human clinical trials conforming with good laboratory and clinical practices to establish the safety and efficacy of the product;
- submission to the FDA of a New Drug Application, or NDA, with respect to drugs, and a Biological License Application, or BLA, with respect to biological products; and
- FDA approval of the NDA or BLA before any commercial sale or shipment of the product.

In addition, the FDA requires the registration of each drug and approval of each manufacturing establishment. Domestic manufacturing establishments are subject to FDA inspection and must comply with current good manufacturing practices, or cGMP, for pharmaceutical products.

Preclinical tests include laboratory evaluation and animal studies to assess the potential safety and efficacy of the product and its formulation. To comply with FDA regulations, laboratories must conduct these preclinical safety tests according to Good Laboratory Practices. The results of the preclinical tests are submitted to the FDA as part of an IND, and the FDA reviews the results before the commencement of human clinical trials. Unless the FDA objects, the IND will become effective 30 days following its receipt. There is no certainty that submission of an IND will result in FDA authorization to commence

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clinical trials. Similarly, once we have completed early stage clinical testing of product candidates, there is no assurance that we will be able to commence large scale clinical trials.

Human clinical trials involve the administration of the investigational compound to patients or other volunteers under the supervision of a qualified principal investigator. Clinical trials are conducted in accordance with protocols that detail the objectives of the study, the parameters to be used to monitor safety and the efficacy criteria to be evaluated. Each protocol must be submitted to the FDA as part of the IND. Further, each clinical study must be conducted under the auspices of an independent institutional review board, or IRB, at the institution where the study will be conducted. The IRB will consider, among other things, ethical factors, the safety of human subjects and the possible liability of the institution.

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Clinical trials are typically conducted in four sequential phases, which may overlap. In Phase I, the initial introduction of the product into human subjects, the product is tested for safety (adverse effects), dosage tolerance, metabolism, distribution, excretion and clinical pharmacology. Phase II involves studies in a limited patient population:

- to determine the efficacy of the product for specific, targeted indications;
- to determine dosage tolerance and optimal dosage; and
- to identify possible adverse effects and safety risks.

When a product is found to be effective and to have an acceptable safety profile in Phase II evaluations, Phase III trials are undertaken:

- to continue to evaluate clinical efficacy; and
- to test further for safety within an expanded patient population at geographically dispersed clinical study sites.

We may not successfully complete clinical testing of our products candidates within any specified time period, if at all. Furthermore, we or the FDA may suspend clinical trials at any time if it is felt that the subjects or patients are being exposed to an unacceptable health risk. Phase IV studies may be performed after FDA approval to address safety issues that were not examined in earlier trials.

The results of the pharmaceutical development, preclinical studies and clinical studies are submitted to the FDA in the form of an NDA or BLA to approve marketing and commercial shipment of the product. The testing and approval process frequently requires substantial time and effort and approval may not be granted on a timely basis, if at all. The FDA may deny an NDA or BLA if applicable regulatory criteria are not satisfied, require additional testing or information or require postmarketing testing and surveillance to monitor the safety and efficacy of the product. Notwithstanding the submission of this data, the FDA may ultimately decide that the application does not satisfy its regulatory criteria for approval. Finally, product approvals may be withdrawn if compliance with regulatory standards is not maintained or if problems including adverse side effects occur following initial marketing.

Among the conditions for NDA or BLA approval is that the prospective manufacturer's quality control and manufacturing procedures conform to current Good Manufacturing Practices. In complying with standards set forth in these regulations, manufacturers must continue to expend time, monies and effort in the area of production and quality control to ensure full compliance.

In addition to FDA regulations, we are subject to regulation under the United States Atomic Energy Act, the Clean Air Act, the Clean Water Act, the Comprehensive Environmental Response, Compensation and Liability Act, the National Environmental Policy Act, the Toxic Substances Control Act, the Resource Conservation and Recovery Act and other federal, state or local regulations.

For marketing outside the United States, we also are subject to foreign regulatory requirements governing human clinical trials and marketing approval for pharmaceutical products. The requirements governing the conduct of clinical trials, product licensing, pricing and reimbursement vary widely from

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country to country. Whether or not we obtain FDA approval, we must obtain approval of a product by the comparable regulatory authorities of foreign countries before manufacturing or marketing the product in those countries. The approval process varies from country to country and the time required for these approvals may differ substantially from that required for FDA approval. The clinical trials conducted in one country may not be accepted by other countries and approval in one country may not result in approval in any other country.

### EMPLOYEES

As of February 28, 2001, we had 494 full-time employees, 96 of whom hold a Ph.D. or M.D. degree or both. We believe that we have been successful in attracting skilled and experienced personnel in a highly competitive environment.

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### MANAGEMENT

#### DIRECTORS AND EXECUTIVE OFFICERS

The following table provides information with respect to our directors and executive officers as of February 28, 2001:

NAME ----	AGE ---	POSITION -----
P. Roy Vagelos, M.D.....	71	Chairman of the Board of Directors (Class II)
Leonard S. Schleifer, M.D., Ph.D. ....	48	Director (Class I), President, Chief Executive Officer and Founder
George D. Yancopoulos, M.D., Ph.D. ....	41	Executive Vice President and Chief Scientific Officer and President, Regeneron Research Laboratories
Murray A. Goldberg.....	56	Senior Vice President, Finance & Administration, Chief Financial Officer, Treasurer, and Assistant Secretary
Randall G. Rupp, Ph.D. ....	53	Senior Vice President, Manufacturing and Process Sciences
Neil Stahl, Ph.D. ....	44	Senior Vice President, Preclinical Development Biomolecular Science
Charles A. Baker.....	68	Director (Class III)
Michael S. Brown, M.D. ....	59	Director (Class III) and Member of Scientific Advisory Board
Alfred G. Gilman, M.D., Ph.D. ....	59	Director (Class II), Member of Scientific Advisory Board and Co-Founder
Joseph L. Goldstein, M.D. ....	60	Director (Class II) and Member of Scientific Advisory Board
Fred A. Middleton.....	51	Director (Class I)
Eric M. Shooter, Ph.D. ....	76	Director (Class I), Member of Scientific Advisory Board and Co-Founder
George L. Sing.....	51	Director (Class III)

Each member of our senior management team has significant experience in the biopharmaceutical industry. In addition, our Board of Directors consists of noted business and scientific leaders, including three Nobel Laureates. Our Scientific Advisory Board consists of individuals with recognized expertise in neurobiology, clinical neurology, molecular biology and related fields who

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advise us about present and long-term scientific planning, research and development. The Board of Directors is divided into three classes, denominated Class I, Class II and Class III, with members of each class holding office for staggered three-year terms. Our Class I Directors will stand for election in 2001.

P. ROY VAGELOS, M.D., 71, has been chairman of the board of our company and a member of the Scientific Advisory Board since January 1995. He became a part-time employee of Regeneron in January 1999. Prior to joining Regeneron, Dr. Vagelos was Chairman of the Board and Chief Executive Officer of Merck & Co., Inc. He joined Merck in 1975, became a director in 1984, President and Chief Executive Officer in 1985 and Chairman in 1986. Dr. Vagelos retired from all positions with Merck in 1994. Dr. Vagelos is the President and Chief Executive Officer and a Trustee of the American School of Classical Studies at Athens. He is also currently a member of the Board of Directors of The Prudential Insurance Company.

LEONARD S. SCHLEIFER, M.D., Ph.D., 48, founded our company in 1988 and has been its President and Chief Executive Officer since its inception and served as Chairman of the Board from 1990 through 1994. In 1992, Dr. Schleifer was appointed Clinical Professor of Neurology at the Cornell University Medical School and from 1984 to 1988 he was Assistant Professor at the Cornell University Medical School in the Departments of Neurology and Neurobiology. Dr. Schleifer received his M.D. and Ph.D. in Pharmacology

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from the University of Virginia. Dr. Schleifer is a licensed physician and is certified in Neurology by the American Board of Psychiatry and Neurology.

GEORGE D. YANCOPOULOS, M.D., PH.D., 41, Executive Vice President and Chief Scientific Officer and President, Regeneron Research Laboratories, was until December 2000 our Senior Vice President, Research, a position he held since June 1997 and Chief Scientific Officer, a position he held since January 1998. Dr. Yancopoulos was Vice President, Discovery from January 1992 until June 1997, Head of Discovery from January 1991 to January 1992 and Senior Staff Scientist from March 1989 to January 1991. He received his Ph.D. in Biochemistry and Molecular Biophysics and his M.D. from Columbia University. In a 1997 survey by the Institute for Scientific Information, he was listed among the 11 most highly cited scientists and was the only non-academic scientist in that group.

MURRAY A. GOLDBERG, 56, Senior Vice President, Finance and Administration, Chief Financial Officer, Treasurer, and Assistant Secretary, was until December 2000 our Vice President, Finance and Administration, Chief Financial Officer and Treasurer, a position he held since March 1995, and Assistant Secretary, a position he held since January 2000. Prior to joining us, Mr. Goldberg was Vice President, Finance, Treasurer and Chief Financial Officer of PharmaGenics, Inc. from February 1991 and a Director of that company from May 1991. From 1987 to 1990, Mr. Goldberg was Managing Director, Structured Finance Group at the Chase Manhattan Bank, N.A. and from 1973 to 1987 he served in various managerial positions in finance and corporate development at American Cyanamid Company.

RANDALL G. RUPP, PH.D., 53, Senior Vice President, Manufacturing and Process Sciences, was until December 2000 our Vice President, Manufacturing and Process Science, a position he held since January 1992. Dr. Rupp was our director of manufacturing from July 1991 until December 1992. He received his Ph.D. in Biomedical Sciences from the University of Texas, M.D. Anderson Hospital and Tumor Institution, Houston.

NEIL STAHL, PH.D., 44, Senior Vice President, Preclinical Development and Biomolecular Science, was until December 2000 our Vice President, Preclinical

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Development and Biomolecular Sciences, a position he held since January 2000. He joined us in 1991. Before becoming Vice President, Biomolecular Sciences in July 1997, Dr. Stahl was Director, Cytokines and Signal Transduction. Dr. Stahl received his Ph.D. in Biochemistry from Brandeis University.

CHARLES A. BAKER, 68, has been a director of our company since February of 1989. In September of 2000, Mr. Baker retired as Chairman, President, and Chief Executive Officer of The Liposome Company, Inc., a position he had held since December of 1989. During his career, Mr. Baker served in a senior management capacity in various pharmaceutical companies, including his tenures as Group Vice President, Squibb Corporation (now Bristol-Myers Squibb) and President, Squibb International. He also held various senior executive positions at Abbott Laboratories and Pfizer, Inc. Mr. Baker currently is a member of the Board of Directors of Progenics Pharmaceuticals, Inc. and a member of the Council of Visitors of the Marine Biological Laboratories at Woods Hole, Massachusetts (a not-for-profit organization). He is also a special limited partner in Sanderling Ventures, which is a shareholder of Regeneron.

MICHAEL S. BROWN, M.D., 59, has been a director of our company since June 1991 and a member of our Scientific Advisory Board since January 1988. Dr. Brown is Professor of Medicine and Genetics and the Director of the Center for Genetic Diseases at The University of Texas Southwestern Medical Center at Dallas. He is a member of the National Academy of Sciences. He is a Director of Pfizer, Inc. His scientific contributions in cholesterol and lipid metabolism were made in collaboration with Dr. Joseph L. Goldstein. Dr. Brown and Dr. Goldstein jointly received the Nobel Prize for Physiology or Medicine in 1985.

ALFRED G. GILMAN, M.D., PH.D., 59, a co-founder of our company, has been a director of our company since July 1990 and a member of our Scientific Advisory Board since 1988. Dr. Gilman has been the Raymond and Ellen Willie Professor of Molecular Neuropharmacology and Chairman of the Department of Pharmacology at The University of Texas Southwestern Medical Center at Dallas since 1981 and was named a Regental Professor in 1995. Dr. Gilman is a member of the National Academy of

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Sciences. He is the Consulting Editor of "Goodman and Gilman's The Pharmacological Basis of Therapeutics," the leading medical pharmacology textbook. Dr. Gilman received the Nobel Prize for Physiology or Medicine in 1994. Dr. Gilman is a member of the Board of Directors of Eli Lilly & Company.

JOSEPH L. GOLDSTEIN, M.D., 60, has been a director of our company since June 1991 and a member of our Scientific Advisory Board since January 1988. Dr. Goldstein has been the Professor of Medicine and Genetics and Chairman of the Department of Molecular Genetics at The University of Texas Southwestern Medical Center at Dallas for more than five years. Dr. Goldstein is a member of the National Academy of Sciences. Dr. Goldstein and Dr. Brown jointly received the Nobel Prize for Physiology or Medicine in 1985.

FRED A. MIDDLETON, 51, has been a director of our company since July 1990. Mr. Middleton is a General Partner of Sanderling Ventures, a venture capital firm he co-founded with Dr. Robert McNeil in December 1987 specializing in early stage biomedical companies. Sanderling Ventures is a shareholder of the Company. Between 1984 and 1987, he was Managing General Partner of Morgan Stanley Ventures and, from 1978 through 1984, was Vice President and Chief Financial Officer of Genentech, Inc. and President, Genentech Development Corporation.

ERIC M. SHOOTER, PH.D., 76, a co-founder of our company, has been a director of our company and member of the Scientific Advisory Board since 1988. Dr. Shooter has been a professor at Stanford University School of Medicine since

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1968. He was the founding Chairman of the Department of Neurobiology at Stanford University School of Medicine in 1975 and served as its Chairman until 1987. He is a Fellow of the Royal Society of England and a member of the National Academy of Sciences.

GEORGE L. SING, 51, has been a director of our company since January 1988. Since 1998, he has been a Managing Director of Caduceus Capital Partners, a venture capital investment firm in the health care field. From 1993 to 1998 Mr. Sing was a general partner of Zitan Capital Partners, an investment and advisory firm. From February 1990 until February 14, 1991, Mr. Sing served as a consultant to Merrill Lynch Venture Capital Inc. From 1982 to February 1990, Mr. Sing was a Vice President and member of the Board of Directors of Merrill Lynch Venture Capital Inc., a venture capital firm.

### INVESTMENT COMPANY ACT CONSIDERATIONS

The Investment Company Act of 1940, as amended, requires the registration of, and imposes various substantive restrictions on, certain companies that engage primarily, or propose to engage primarily, in the business of investing, reinvesting or trading in securities, or fail certain statistical tests regarding the composition of assets and sources of income and are not primarily engaged in businesses other than investing, holding, owning, or trading securities. We presently satisfy these statistical tests and intend to remain primarily engaged in businesses other than investing, reinvesting, owning, holding, or trading securities. In addition, we are relying on an SEC position that biotechnology companies such as our company are not investment companies required to register under the 1940 Act. We will seek temporarily to invest the proceeds of this offering, pending their use as described under the caption "Use of Proceeds." We expect to continue to be able to avoid registration requirements of the 1940 Act. If we were required to register as an investment company under the 1940 Act, we would become subject to substantial regulations with respect to our capital structure, management, operations, transactions with affiliates described in the 1940 Act and other matters. Application of the provisions of this Act would have a material adverse effect on our business.

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### DESCRIPTION OF CAPITAL STOCK

Our authorized capital stock consists of 60,000,000 shares of common stock, par value \$.001 per share, 40,000,000 shares of Class A stock, par value \$.001 per share, and 30,000,000 shares of preferred stock, par value \$.01 per share. As of March 16, 2001, 34,287,624 shares of our common stock were outstanding and held by 608 shareholders of record and 2,575,165 shares of our Class A stock were outstanding and held by 65 shareholders of record. The following is a summary description of our capital stock. For more information, see our Restated Certificate of Incorporation, a copy of which is incorporated by reference as an exhibit to the registration statement of which this prospectus forms a part.

#### COMMON STOCK AND CLASS A STOCK

**General.** The rights of holders of common stock and holders of Class A stock are identical except for voting and conversion rights and restrictions on transferability.

**Voting Rights.** The holders of Class A stock are entitled to ten votes per share and the holders of common stock are entitled to one vote per share. Except as otherwise required by law or as described below, holders of Class A stock will vote together as a single class on all matters presented to the shareholders for their vote or approval, including the election of directors. Shareholders are not entitled to vote cumulatively for the election of directors

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and no class of outstanding common stock acting alone is entitled to elect any directors.

**Transfer Restrictions.** Class A stock is subject to certain limitations on transfer that do not apply to the common stock.

**Dividends and Liquidation.** Holders of Class A stock and holders of our common stock have an equal right to receive dividends when and if declared by our Board of Directors out of funds legally available therefor. If a dividend or distribution payable in Class A stock is made on the Class A stock, we must also make a pro rata and simultaneous dividend or distribution on the common stock payable in shares of common stock. Conversely, if a dividend or distribution payable in common stock is made on the common stock, we must also make a pro rata and simultaneous dividend or distribution on the Class A stock payable in shares of Class A stock. In the event of our liquidation, dissolution, or winding up, holders of the shares of Class A stock and common stock are entitled to share equally, share-for-share, in the assets available for distribution after payment of all creditors and the liquidation preferences of our preferred stock.

**Optional Conversion Rights.** Each share of Class A stock may, at any time and at the option of the holder, be converted into one fully paid and nonassessable share of common stock. Upon conversion, such shares of common stock would not be subject to restrictions on transfer that applied to the shares of Class A stock prior to conversion except to the extent such restrictions are imposed under applicable securities laws.

The shares of common stock are not convertible into or exchangeable for shares of Class A stock or any other of our shares or securities.

**Other Provisions.** Holders of Class A stock and common stock have no preemptive rights to subscribe to any additional securities of any class which we may issue and there are no redemption provisions or sinking fund provisions applicable to either such class, nor is the Class A stock or the common stock subject to calls or assessments.

**Nasdaq National Market Listing.** Our common stock is quoted on the Nasdaq National Market. The current rules of the National Association of Securities Dealers, Inc. (the "NASD") effectively preclude the trading or quotation through the Nasdaq National Market of any securities of an issuer which has issued securities or taken other corporate action that would have the effect of nullifying, restricting, or disparately reducing the per share voting of an outstanding class or classes of equity securities registered under section 12 of the Exchange Act. Certain national securities exchanges have adopted similar rules or policies. We do not intend to issue any additional shares of any stock that would make it ineligible for

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inclusion on the Nasdaq National Market or any national securities exchange. However, if we issue additional stock that causes us to become ineligible for continued inclusion on the Nasdaq National Market, then the ineligibility would be likely to materially reduce the liquidity of an investment in our common stock and would likely depress its market value below that which would otherwise prevail.

**Transfer Agent and Registrar.** The Transfer Agent and Registrar for the common stock is American Stock Transfer & Trust Company.

PREFERRED STOCK



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Our Restated Certificate of Incorporation allows us to issue up to 30,000,000 shares of preferred stock in one or more series and as may be determined by our Board of Directors who may establish from time to time the number of shares to be included in each such series, to fix the designation, powers, preference and rights of the shares of each such series and any qualifications, limitations, or restrictions thereof and to increase or decrease the number of shares of any such series without any further vote or action by the shareholders. Our Board of Directors may authorize, without shareholder approval, the issuance of preferred stock with voting and conversion rights that could adversely affect the voting power and other rights of holders of our common stock. Preferred stock could thus be issued quickly with terms designed to delay or prevent a change in control or to make the removal of management more difficult. In certain circumstances, this could have the effect of decreasing the market price of our common stock.

### REGISTRATION RIGHTS OF CERTAIN HOLDERS

Certain of our shareholders have registration rights. Under the agreements between us and the holders of registration rights, certain holders may under certain circumstances request that we file a registration statement under the Securities Act and, upon such request and subject to certain minimum size conditions, we will generally be required to use our best efforts to effect any such registration. We are not generally required to effect more than two such registrations. However, we are required under certain circumstances to effect an unlimited number of Form S-3 or similar short form registrations for such holders. We are generally obligated to bear the expenses, other than underwriting discounts and sales commissions, of all of these registrations.

In addition, if we propose to register any of our securities, either for our own account or for the account of other shareholders, with certain exceptions, we are required to notify the holders noted above and to include in such registration all of the shares of our common stock requested to be included by such holders. In connection with this offering, we have notified each of the holders who have registration rights and each holder, other than the selling shareholder, has waived its rights to exercise its respective registration rights.

### RIGHTS PLAN

In September 1996, we adopted a Shareholder Rights Plan. Our rights agreement provides that each of our common shares will have one right to purchase a unit consisting of one-thousandth of a preferred share at a purchase price of \$120 per unit.

Initially, the rights under our rights agreement are attached to outstanding certificates representing our common shares and no separate certificates representing the rights will be distributed. The rights will separate from our common shares and be represented by separate certificates approximately 10 days after someone acquires or commences a tender offer for 20% of our outstanding common shares.

After the rights separate from our common shares, certificates representing the rights will be mailed to record holders of our common stock. Once distributed, the rights certificates alone will represent the rights.

All of our common shares issued prior to the date the rights separate from the common shares will be issued with the rights attached. The rights are not exercisable until the date the rights separate from the common shares. We may redeem the rights by action of the Board of Directors, at which time the rights

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will terminate and the holder of the rights will have only the right to receive \$0.01 per right. The rights will expire automatically on October 18, 2006 unless earlier redeemed or exchanged by us.

If an acquiror obtains or has the right to obtain 20% or more of our common shares, then each right will entitle the holder to purchase a number of our common shares initially equal to two times the purchase price of each right, unless the acquisition is made pursuant to a tender or exchange offer for all of our outstanding shares at a price determined by a majority of our independent directors. In this event, rights held by the acquiring person shall become null and void.

In certain circumstances, a right will entitle the holder to purchase a number of shares of common stock of the acquiror having a then current market value of twice the right's purchase price.

Holders of rights will have no rights as our shareholders, including the right to vote or receive dividends, simply by virtue of holding the rights.

Our rights agreement may have anti-takeover effects. The rights may cause substantial dilution to a person or group that attempts to acquire us. Accordingly, the existence of the rights may deter acquirors from making takeover proposals or tender offers. However, the rights are not intended to prevent a takeover, but rather are designed to enhance the ability of our board to negotiate with an acquiror on behalf of all the shareholders. In addition, the rights should not interfere with a proxy contest.

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SELLING SHAREHOLDER

Amgen is an equal partner with us in Amgen-Regeneron Partners. The following table sets forth certain information with respect to the beneficial ownership of our common stock by Amgen as of March 16, 2001 (before and after giving effect to the issuance and sale of shares pursuant to this prospectus).

NAME AND ADDRESS -----	SHARES BENEFICIALLY OWNED PRIOR TO THE OFFERING		SHARES BEING OFFERED	SHARES BENEFICIALLY OWNED AFTER THE
	NUMBER	PERCENT		NUMBER
Amgen Inc. .... One Amgen Center Drive Thousand Oaks, CA 91320	4,916,808	14.3%	500,000	4,416,808

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UNDERWRITING

Merrill Lynch, Pierce, Fenner & Smith Incorporated, J.P. Morgan Securities Inc. and Robertson Stephens, Inc. are acting as representatives of each of the underwriters named below. Subject to the terms and conditions described in a purchase agreement among us, the selling shareholder and the underwriters, we and the selling shareholder have agreed to sell to the underwriters and the

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underwriters severally have agreed to purchase from us and the selling shareholder the number of shares of common stock listed opposite their names below.

UNDERWRITER	NUMBER OF SHARES
Merrill Lynch, Pierce, Fenner & Smith Incorporated.....	4,200,000
J.P. Morgan Securities Inc.....	1,400,000
Robertson Stephens, Inc.....	1,400,000
	-----
Total.....	7,000,000
	=====

The underwriters have agreed to purchase all of the shares sold under the purchase agreement if any of these shares are purchased. If an underwriter defaults, the purchase agreement provides that the purchase commitments of the nondefaulting underwriters may be increased or the purchase agreement may be terminated.

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

The underwriters are offering the shares, subject to prior sale, when, as and if issued to and accepted by them, subject to approval of legal matters by their counsel, including the validity of the shares, and other conditions contained in the purchase agreement, such as the receipt by the underwriters of officers' certificates and legal opinions. The underwriters reserve the right to withdraw, cancel or modify offers to the public and to reject orders in whole or in part. Out of the 7,000,000 shares offered for sale by this prospectus, 4,000,000 shares will be acquired by a single investor.

### COMMISSIONS AND DISCOUNTS

The underwriters have advised us and the selling shareholder that they propose initially to offer the shares to the public at the public offering price on the cover page of this prospectus and to dealers at that price less a concession not in excess of \$.75 per share. The underwriters may allow, and the dealers may reallow, a discount not in excess of \$.10 per share to other dealers. After the initial public offering, the public offering price, concession and discount may be changed.

The following table shows the public offering price, underwriting discount, and proceeds before expenses to us and the selling shareholder. The information assumes either no exercise or full exercise by the underwriters of their over-allotment options.

	PER SHARE	WITHOUT OPTION	WITH OPTION
Public offering price.....	\$25.00	\$175,000,000	\$201,250,000
Underwriting discount.....	\$ 1.25	\$ 8,750,000	\$ 10,062,500
Proceeds, before expenses, to Regeneron.....	\$23.75	\$154,375,000	\$179,312,500

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Proceeds, before expenses, to the selling shareholder.....	\$23.75	\$ 11,875,000	\$ 11,875,000
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The expenses of the offering, including those of the selling shareholder, but not including the underwriting discount, are estimated at \$750,000 and are payable by us.

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### OVER-ALLOTMENT OPTION

We have granted an option to the underwriters to purchase up to 1,050,000 additional shares at the public offering price less the underwriting discount. The underwriters may exercise this option for 30 days from the date of this prospectus solely to cover any over-allotments. If the underwriters exercise this option, each will be obligated, subject to conditions contained in the purchase agreement, to purchase a number of additional shares proportionate to that underwriter's initial amount reflected in the above table.

### NO SALES OF SIMILAR SECURITIES

We and our executive officers and directors and certain existing shareholders, including Amgen and Procter & Gamble, have agreed, with exceptions (including an exception for the shares offered by the selling shareholder), not to sell or transfer any common stock for 90 days after the date of this prospectus without first obtaining the written consent of Merrill Lynch. Specifically, we and these other individuals or entities have agreed not to directly or indirectly:

- offer, pledge, sell or contract to sell any common stock;
- sell any option or contract to purchase any common stock;
- purchase any option or contract to sell any common stock;
- grant any option, right or warrant for the sale of any common stock;
- lend or otherwise dispose of or transfer any common stock;
- file a registration statement related to the common stock; or
- enter into any swap or other agreement that transfers, in whole or in part, the economic consequence of ownership of any common stock whether any such swap or transaction is to be settled by delivery of shares or other securities, in cash or otherwise.

This lockup provision applies to common stock and to securities convertible into or exchangeable or exercisable for or repayable with common stock. It also applies to common stock owned now or acquired later by the person executing the agreement or for which the person executing the agreement later acquires the power of disposition.

We, however, may issue (1) shares upon the exercise of an option or warrant or the conversion of a security outstanding on the date of this prospectus, (2) shares or options to purchase shares granted pursuant to our existing and future employee benefit plans and (3) shares pursuant to any non-employee director stock plan or dividend reinvestment plan.

In addition to the lock-up described above, both Procter & Gamble and Amgen have agreed to separate lock-up arrangements with us. Procter & Gamble has

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agreed not to sell or transfer any of our common stock from March 12, 2001 until March 31, 2002. Amgen has agreed with us not to sell or transfer more than an additional 500,000 shares of our common stock from March 12, 2001 until March 31, 2002. If, for any reason, Amgen does not sell its full allotment of shares in this offering, the amount available for sale during this lock-up period would be increased by the number of shares not sold in this offering.

The shares are quoted on the Nasdaq National Market under the symbol "REGN."

### UK SELLING RESTRICTIONS

Each underwriter has agreed that

- it has not offered or sold and will not offer or sell any shares of common stock to persons in the United Kingdom, except to persons whose ordinary activities involve them in acquiring, holding, managing or disposing of investments (as principal or agent) for the purposes of their businesses or otherwise in circumstances which do not constitute an offer to the public in the United Kingdom within the meaning of the Public Offers of Securities Regulations 1995;
- it has complied and will comply with all applicable provisions of the Financial Services Act 1986 with respect to anything done by it in relation to the common stock in, from or otherwise involving the United Kingdom; and

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- it has only issued or passed on and will only issue or pass on in the United Kingdom any document received by it in connection with the issuance of common stock to a person who is of a kind described in Article 11(3) of the Financial Services Act 1986 (Investment Advertisements) (Exemptions) Order 1996 as amended by the Financial Services Act 1986 (Investment Advertisements) (Exemptions) Order 1997 or is a person to whom such document may otherwise lawfully be issued or passed on.

### NO PUBLIC OFFERING OUTSIDE THE UNITED STATES

No action has been or will be taken in any jurisdiction (except in the United States) that would permit a public offering of the shares of common stock, or the possession, circulation or distribution of this prospectus or any other material relating to our company, the selling shareholder or shares of our common stock in any jurisdiction where action for that purpose is required. Accordingly, the shares of our common stock may not be offered or sold, directly or indirectly, and neither this prospectus nor any other offering material or advertisements in connection with the shares of common stock may be distributed or published, in or from any country or jurisdiction except in compliance with any applicable rules and regulations of any such country or jurisdiction.

Purchasers of the shares offered by this prospectus may be required to pay stamp taxes and other charges in accordance with the laws and practices of the country of purchase in addition to the offering price on the cover page of this prospectus.

### PRICE STABILIZATION, SHORT POSITIONS AND PENALTY BIDS

Until the distribution of the shares of common stock is completed, the SEC rules may limit the underwriters from bidding for or purchasing our common stock. However, the representatives may engage in transactions that stabilize

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the price of the common stock, such as bids or purchases that peg, fix or maintain that price.

The underwriters may purchase and sell the common stock in the open market. These transactions may include short sales, stabilizing transactions, and purchases to cover positions created by short sales. Short sales involve the sale by the underwriters of a greater number of shares than they are required to purchase in the offering. "Covered" short sales are sales made in an amount not greater than the underwriters' option to purchase additional shares from the issuer in the offering. The underwriters may close out any covered short position by either exercising their option to purchase additional shares or purchasing shares in the open market. In determining the source of share to close out the covered short position, the underwriters will consider, among other things, the price of shares available for purchase in the open market as compared to the price at which they may purchase shares through the over-allotment option. "Naked" short sales are any sales in excess of such option. The underwriters must close out any naked short position by purchasing shares in the open market. A naked short position is more likely to be created if the underwriters are concerned that there may be downward pressure on the price of the common shares in the open market after pricing that could adversely affect investors who purchase in the offering. Stabilizing transactions consist of various bids for or purchases of shares of common stock made by the underwriters in the open market prior to the completion of the offering.

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

Similar to other purchase transactions, the underwriters' purchases to cover the syndicate short sales 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 shares of common stock. As a result, the price of the shares of common stock may be higher than the price that might otherwise exist in the open market.

Neither we nor any of the underwriters make any representation or prediction as to the direction or magnitude of any effect that the transactions described above may have on the price of the common stock.

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In addition, neither we nor any of the representatives make any representation that the representatives will engage in these transactions or that these transactions, once commenced, will not be discontinued without notice.

### ELECTRONIC PROSPECTUS

Merrill Lynch, Pierce, Fenner & Smith Incorporated will be facilitating Internet distribution for this offering to certain of its Internet subscription customers. Merrill Lynch intends to allocate a limited number of shares for sale to its online brokerage customers. An electronic prospectus is available on the Internet website maintained by Merrill Lynch. Other than the prospectus in electronic format, the information on the Merrill Lynch website is not part of this prospectus.

### PASSIVE MARKET MAKING

In connection with this offering, underwriters and selling group members may engage in passive market making transactions in the common stock on the

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Nasdaq National Market in accordance with Rule 103 of Regulation M under the Exchange Act during a period before the commencement of offers or sales of common stock and extending through the completion of distribution. A passive market maker must display its bid at a price not in excess of the highest independent bid of that security. However, if all independent bids are lowered below the passive market maker's bid, that bid must then be lowered when specified purchase limits are exceeded.

### OTHER RELATIONSHIPS

Some of the underwriters and their affiliates have engaged in, and may in the future engage in, investment banking and other commercial dealings in the ordinary course of business with us. They have received customary fees and commissions for these transactions.

### LEGAL MATTERS

Skadden, Arps, Slate, Meagher & Flom LLP, New York, New York will pass upon the validity of our common stock offered by this prospectus. Shearman & Sterling, New York, New York will pass upon certain legal matters in connection with this offering for the underwriters.

### EXPERTS

The financial statements of Regeneron Pharmaceuticals, Inc. incorporated in this prospectus by reference to the Annual Report on Form 10-K of Regeneron Pharmaceuticals, Inc. for the year ended December 31, 2000, except as they relate to Amgen-Regeneron Partners, have been audited by PricewaterhouseCoopers LLP, independent accountants, and, insofar as they relate to Amgen-Regeneron Partners, by Ernst & Young LLP, independent auditors, whose report thereon is incorporated by reference herein. Such financial statements have been so incorporated in this prospectus by reference in reliance on the report of such independent accountants given on the authority of such firm as experts in auditing and accounting.

Ernst & Young LLP, independent auditors, have audited the financial statements of Amgen-Regeneron Partners included in our Annual Report on Form 10-K for the year ended December 31, 2000, as set forth in their report, which is incorporated by reference in this prospectus and elsewhere in the registration statement. The Amgen-Regeneron Partners' financial statements are incorporated by reference in reliance on Ernst & Young LLP's report, given on their authority as experts in accounting and auditing.

### WHERE YOU CAN FIND ADDITIONAL INFORMATION

We file annual, quarterly and special reports, proxy statements and other information with the SEC. You may read and copy any documents we file at the SEC's Public Reference Room at 450 Fifth Street,

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N.W., Washington, D.C. 20549 and at the Regional Offices of the SEC at 7 World Trade Center, 13th Floor, New York, New York 10048 and Citicorp Center, 500 West Madison Street, Suite 1400, Chicago, Illinois 60601. Please call the SEC at 1-800-SEC-0330 for further information on the public reference rooms. The SEC maintains a site on the World Wide Web at <http://www.sec.gov> that contains our SEC filings and reports, proxy and information statements and other information regarding registrants.

The SEC allows us to "incorporate by reference" the information we file with them, which means that we can disclose important information to you by

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referring you to those documents. The information incorporated by reference is considered to be part of this prospectus 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 all future filings we make with the SEC after the date of the initial registration statement and prior to effectiveness of the registration statement and any filings thereafter and prior to the termination of this offering with the SEC under Section 13(a), 13(c), 14, or 15(d) of the Securities Exchange Act of 1934:

(1) our Annual Report on Form 10-K for the year ended December 31, 2000;

(2) our definitive proxy statement filed on May 5, 2000; and

(3) the description of our common stock contained in Item 1 of our Registration Statement on Form 8-A filed on February 20, 1991, as amended by a Form 8 filed on March 27, 1991.

You may request a copy of these filings, at no cost, by writing or telephoning us at the following address:

Regeneron Pharmaceuticals, Inc.  
777 Old Saw Mill River Road  
Tarrytown, New York 10591-6707  
(914) 347-7000  
Attention: Murray A. Goldberg  
Chief Financial Officer

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7,000,000 SHARES  
REGENERON PHARMACEUTICALS, INC.  
COMMON STOCK

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PROSPECTUS  
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MERRILL LYNCH & CO.

JPMORGAN  
ROBERTSON STEPHENS

MARCH 19, 2001  
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