

[QuickLinks](#) -- Click here to rapidly navigate through this document

The information in this preliminary prospectus supplement is not complete and may be changed. This preliminary prospectus supplement and the accompanying prospectus are not an offer to sell nor do they seek an offer to buy these securities in any jurisdiction where the offer or sale is not permitted.

Filed Pursuant to Rule 424(b)(5)
Registration No. 333-66134

Subject to Completion. Dated June 12, 2003.

Prospectus Supplement to Prospectus dated August 7, 2001.

10,000,000 Shares



Common Stock

Exelixis, Inc. is selling 10,000,000 shares of its common stock in this offering.

The common stock is quoted on the Nasdaq National Market under the symbol "EXEL". The last reported sale price of the common stock on June 11, 2003 was \$8.78 per share.

See "Risk Factors" beginning on page S-6 and "Cautionary Note Regarding Forward-Looking Statements" on page S-17 to read about factors you should consider before buying shares of the common stock.

Neither the Securities and Exchange Commission nor any other regulatory body has approved or disapproved of these securities or passed upon the accuracy or adequacy of this prospectus supplement or the accompanying prospectus. Any representation to the contrary is a criminal offense.

	Per Share	Total
Initial price to public	\$	\$
Underwriting discount	\$	\$
Proceeds, before expenses, to Exelixis	\$	\$

To the extent that the underwriters sell more than 10,000,000 shares of common stock, the underwriters have the option to purchase up to an additional 1,500,000 shares from Exelixis at the initial price to public less the underwriting discount.

The underwriters expect to deliver the shares against payment in New York, New York on June , 2003.

Goldman, Sachs & Co.

SG Cowen

Prospectus Supplement dated June , 2003.

ABOUT THIS PROSPECTUS SUPPLEMENT

You should read this prospectus supplement along with the accompanying prospectus carefully before you invest in our common stock. Both documents contain important information you should consider when making your investment decision. This prospectus supplement may add, update or change information in the accompanying prospectus. You should rely only on the information provided in this prospectus supplement and the accompanying prospectus or incorporated by reference in the accompanying prospectus. We have not authorized anyone to provide you with different information.

S-i

PROSPECTUS SUPPLEMENT SUMMARY

This is a summary of the information contained elsewhere in this prospectus supplement and the accompanying prospectus or incorporated by reference into the accompanying prospectus. Investors should carefully consider the information set forth under "Risk Factors" in this prospectus supplement and in the accompanying prospectus. Unless otherwise indicated, all information in this prospectus supplement assumes that the underwriters will not exercise their option to purchase additional shares of our common stock.

Exelixis, Inc.

We believe that we are a leader in the discovery of potential new drug therapies, specifically for cancer and other proliferative diseases. By combining our expertise in the identification and validation of high-quality novel targets with our powerful, integrated gene-to-drug discovery and development platform, we believe that we will be able to generate and advance a sustainable pipeline of novel compounds and, over time, build an integrated pharmaceutical business. These compounds have potential as assets in our proprietary programs as well as for corporate partnering.

We believe that among our key competitive advantages are the breadth and critical mass of our platform and our ability to apply the tools of modern biology and chemistry to address commercially relevant questions. In particular, we believe the following are our most significant competitive strengths:

- Our broad biology-based research platform leverages our expertise in model systems genetics and comparative genomics, informatics, cell biology and protein production for high throughput target identification and validation;
- Our discovery platform integrates capabilities in combinatorial chemistry, high throughput screening and new lead discovery, structural biology, medicinal chemistry, pharmacology and drug metabolism and drug properties, or pharmacokinetics, in order to rapidly identify and advance the most promising candidates into development; and
- Our development group is comprised of experienced professionals with the expertise to move our candidate compounds from preclinical testing to investigational new drug application, or IND, status and through clinical development.

In the last few years, we have focused on leveraging our gene-to-drug platform and building our clinical development pipeline.

XL119: Rebeccamycin Analogue

XL119, a rebeccamycin analogue, is an anticancer compound that we in-licensed from Bristol-Myers Squibb in July 2001 as part of a broad cancer research collaboration. Data presented in June 2003 at the American Society of Clinical Oncology, or ASCO, from a Phase 2 clinical trial in 33 patients with bile duct tumors treated with XL119 showed encouraging early results relative to overall survival and progression free survival. The Phase 2 clinical trial was sponsored by the U.S. National Cancer Institute, or the NCI. Following discussions with the U.S. Food and Drug Administration, or FDA, we intend to initiate a Phase 3 clinical trial of XL119 in patients with bile duct tumors. We anticipate that this trial will begin in late 2003 or early 2004. Our market research estimates that the annual incidence of bile duct tumors is approximately 7,500 to 10,000 cases in each of the United States and Europe. The drug substance to be used in company-sponsored clinical trials has been manufactured in bulk supply by third-party suppliers, and we expect that the available supply of XL119 will be sufficient to support our clinical needs as well as any trials that may be initiated by the NCI. We have exclusive worldwide rights to XL119.

S-1

XL784

We submitted our IND to the FDA for a proprietary small molecule anticancer compound, XL784, in March 2003. XL784 targets a cell surface protease, the inhibition of which has shown effects that are both anti-angiogenic (inhibiting blood vessel formation) and anti-proliferative (inhibiting unregulated cell growth). In preclinical studies, XL784 is orally active, and it has shown good potency, pharmacologic activity and a safety profile appropriate to support a Phase 1 clinical trial. We plan to initiate a Phase 1 clinical trial in the second quarter of 2003, to be conducted in healthy volunteers, while we continue to explore the therapeutic utility of the compound in various animal models of disease, including renal and cardiovascular diseases. The trial is expected to be conducted at a single center and to be designed as a dose escalation study to measure the safety, pharmacokinetics and biological activity of XL784 following oral administration.

Preclinical Pipeline

We believe that there are several compounds within our discovery programs that represent potential future clinical candidates.

We have discovered novel inhibitors to a class of targets called receptor tyrosine kinases, or RTKs, that are involved in both angiogenesis and tumor growth. While some of these compounds target specific RTKs, we have focused our efforts toward engineering inhibitory activity against a wide spectrum of RTKs implicated in cancer progression. Lead compounds from these projects, including XL647 and XL999, are orally active in preclinical cancer models and are moving into preclinical toxicology studies. Recent high throughput screening efforts have also provided a variety of structurally diverse and highly potent inhibitors for several new angiogenic and antitumor kinases. This array of early leads in validation and optimization projects should provide a range of opportunities for development candidates and IND compounds over the next few years.

Our Strategy

Our business strategy is to leverage our biological expertise and integrated drug discovery and development capabilities to generate and advance a pipeline of novel compounds to treat cancer and other proliferative diseases. We believe that our gene-to-drug platform will enable us to improve the speed, efficiency and quality of the discovery, development and commercialization process for human therapeutics and other products. Specifically, our business strategy includes the following key elements.

- *Exploit Biological Expertise:* Our biological expertise is a key competitive advantage that we believe applies throughout all aspects of our collaborative relationships and drug discovery efforts. We seek to continually enhance our technology platform through building, in-licensing or acquiring technologies that complement our fundamental knowledge and capabilities, as well as through protecting our proprietary technologies with patents and trade secrets.
- *Selectively Develop Therapeutic Products:* We have invested and plan to continue to invest significant funds in discovering and developing proprietary products, particularly in the area of cancer. We have committed substantial resources to building a world-class drug discovery effort to develop a pipeline of compounds that we anticipate will form the basis of INDs and subsequently advance into clinical trials.
-

Leverage Strategic Collaborations: We have established and intend to continue to pursue commercial relationships and key partnerships with major pharmaceutical, biotechnology and agrochemical companies based on the strength of our technologies, biological expertise and drug discovery and development capabilities. Many of these collaborations provide us with a substantial committed revenue stream in addition to opportunities to receive significant future

S-2

payments, if our collaborators successfully develop and market products that result from our collaborative work. In addition, many of our collaborations have been structured strategically so that we gain access to technology or product opportunities.

- *Acquire Products and Technologies Opportunistically:* We continually evaluate opportunities that may provide us with intellectual property, technologies, products and key personnel that will enhance our development capabilities and product pipeline.

Corporate Collaborations

Based on the strength of our gene-to-drug platform, we have established several commercial collaborations with leading pharmaceutical and biotechnology companies as well as agriculture companies. These include:

- GlaxoSmithKline: small molecule drug discovery and development in the areas of cancer, inflammation and vascular biology;
- Bristol-Myers Squibb: cancer target identification for small molecules and pharmaceutical mechanism of action identification;
- Protein Design Labs: cancer target identification for monoclonal antibodies;
- Merck, Schering-Plough Research Institute, Cytokinetics, Scios and Elan: combinatorial chemistry;
- Bayer Corporation/Bayer CropScience: targets and screening assays for novel crop protection agents and agricultural gene identification;
- Dow AgroScience: agricultural mechanism of action identification; and
- Renessen: seed oil trait gene discovery.

The Exelixis, Inc. logos, Exelixis, Artemis Pharmaceuticals, ACTTAG, Conditional and all other Exelixis product and service names are our trademarks. All other trademarks appearing in this prospectus supplement and the accompanying prospectus are the properties of their respective holders.

S-3

The Offering

Common stock offered by Exelixis	10,000,000 shares
Common stock to be outstanding after the offering	69,874,227 shares
Use of proceeds	To fund clinical development and for working capital and general corporate purposes.
Risk factors	See "Risk Factors" beginning on page S-6 and "Cautionary Note Regarding Forward-Looking Statements" on page S-17 for a discussion of factors you should consider before buying shares of our common stock.
Nasdaq National Market Symbol	"EXEL"

The number of shares of common stock to be outstanding after the offering is based on the number of shares outstanding as of May 31, 2003. As of that date, we had 59,874,227 shares of common stock outstanding, excluding:

- 11,342,114 shares of common stock underlying options and warrants outstanding as of May 31, 2003 at a weighted average exercise price of \$13.26 per share;
- 2,842,813 shares available for future grant under our 2000 Equity Incentive Plan, 696,486 shares available for future issuance under our 2000 Employee Stock Purchase Plan and 1,544,695 shares available for future grant under our 2000 Non-Employee Directors' Stock Option Plan, all as of May 31, 2003; and
- 3,406,536 shares issuable upon conversion of our convertible debt (assuming that the debt had been converted as of May 31, 2003).

S-4

We derived the following information from our audited consolidated financial statements for each of the three years in the period ended December 31, 2002 and from our unaudited consolidated financial statements as of March 31, 2003 and for the three months ended March 31, 2002 and 2003. In the opinion of our management, our unaudited consolidated financial statements include all adjustments, consisting only of normal and recurring adjustments, considered necessary for a fair presentation of the financial information. The following information should be read in conjunction with our consolidated financial statements and related notes incorporated by reference in the accompanying prospectus.

Operating results for the three months ended March 31, 2003 are not necessarily indicative of the results that may be expected for the year ending December 31, 2003. For more details on how you can obtain our SEC reports and other information, you should read the section of the accompanying prospectus entitled "Where You Can Find More Information About Exelixis". The as adjusted consolidated balance sheet data gives effect to the sale of our common stock in this offering, at an assumed offering price of \$8.78 per share, after deducting the estimated underwriting discounts and commissions and estimated offering expenses.

	Year Ended December 31,			Three Months Ended March 31,	
	2000	2001	2002	2002	2003
(in thousands, except per share data)					
Consolidated Statement of Operations Data					
Total revenues	\$ 24,759	\$ 41,006	\$ 44,322	\$ 11,542	\$ 12,330
Total operating expenses	\$ 105,740	\$ 116,320	\$ 132,146	\$ 31,032	\$ 35,637
Net loss	\$ (75,311)	\$ (71,186)	\$ (86,130)	\$ (18,421)	\$ (23,058)
Net loss per share, basic and diluted	\$ (2.43)	\$ (1.53)	\$ (1.52)	\$ (0.33)	\$ (0.39)
Shares used in computing basic and diluted net loss per share	31,031	46,485	56,615	55,654	59,261

March 31, 2003

Actual	As Adjusted
(in thousands)	

Consolidated Balance Sheet Data

Cash, cash equivalents and short-term investments (including restricted cash of \$7,610)	\$ 203,869	\$ 285,981
Working capital	\$ 148,042	\$ 230,154
Total assets	\$ 320,829	\$ 402,941
Long-term obligations, less current portion	\$ 65,024	\$ 65,024
Accumulated deficit	\$ (310,412)	\$ (310,412)
Total stockholders' equity	\$ 155,537	\$ 237,649

S-5

RISK FACTORS

If you purchase shares of our common stock, you will take on financial risk. In deciding whether to invest, you should carefully consider the following factors and the information contained in this prospectus supplement and the accompanying prospectus, including the additional information in our reports and other documents on file with the Securities and Exchange Commission that are incorporated by reference in the accompanying prospectus.

Exelixis has a history of net losses. We expect to continue to incur net losses, and we may not achieve or maintain profitability.

We have incurred net losses each year since our inception, including a net loss of approximately \$23.1 million for the quarter ended March 31, 2003. As of that date, we had an accumulated deficit of approximately \$310.4 million. We expect these losses to continue and anticipate negative operating cash flow for the foreseeable future. The size of these net losses will depend, in part, on the rate of growth, if any, in our license and contract revenues and on the level of our expenses. Our research and development expenditures and general and administrative costs have exceeded our revenues to date, and we expect to spend significant additional amounts to fund research and development in order to enhance our core technologies and undertake product development. In 2001, we acquired XL119, a rebeccamycin analogue that is in Phase 2 clinical development. We anticipate initiating next development steps in late 2003 or early 2004 following discussions with the FDA. As a result, we expect that our operating expenses will increase significantly in the near term, and, consequently, we will need to generate significant additional revenues to achieve profitability. Even if we do increase our revenues and achieve profitability, we may not be able to maintain or increase profitability.

We will need additional capital in the future, which may not be available to us.

Our future capital requirements will be substantial and will depend on many factors, including:

- payments received under collaborative agreements;
- the progress and scope of our collaborative and independent research and development projects;
- our need to expand our product and clinical development efforts as well as develop manufacturing and marketing capabilities to commercialize products;
- the filing, prosecution and enforcement of patent claims; and

- increased costs for clinical and manufacturing activities.

We anticipate that the net proceeds of this offering, our current cash and cash equivalents, short-term investments and funding to be received from collaborators will enable us to maintain our currently planned operations through at least 2005. Changes to our current operating plan may require us to consume available capital resources significantly sooner than we expect. We may be unable to raise sufficient additional capital when we need it, on favorable terms or at all. If our capital resources are insufficient to meet future capital requirements, we will have to raise additional funds. The sale of equity or convertible debt securities in the future may be dilutive to our stockholders, and debt financing arrangements may require us to pledge certain assets and enter into covenants that would restrict our ability to incur further indebtedness. If we are unable to obtain adequate funds on reasonable terms, we may be required to curtail operations significantly or to obtain funds by entering into financing, supply or collaboration agreements on unattractive terms.

S-6

Difficulties we may encounter managing our growth may divert resources and limit our ability to successfully expand our operations.

We have experienced a period of rapid and substantial growth that has placed, and our anticipated growth in the future will continue to place, a strain on our research, administrative and operational infrastructure. As our operations expand domestically and internationally, we will need to continue to manage multiple locations and additional relationships with various collaborative partners, suppliers and other third parties. Our ability to manage our operations and growth effectively requires us to continue to improve our operational, financial and management controls, reporting systems and procedures. In addition, recent SEC rules and regulations have increased the internal control and regulatory requirements under which we operate. We may not be able to successfully implement improvements to our management information and control systems in an efficient or timely manner and may discover deficiencies in existing systems and controls. In addition, acquisitions involve the integration of different financial, internal control and management reporting systems. We may not be able to successfully integrate the administrative and operational infrastructure without significant additional improvements and investments in management systems and procedures.

We are dependent on our collaborations with major companies. If we are unable to achieve milestones, develop products or renew or enter into new collaborations, our revenues may decrease and our activities may fail to lead to commercialized products.

Substantially all of our revenues to date have been derived from collaborative research and development agreements. Revenues from research and development collaborations depend upon continuation of the collaborations, the achievement of milestones and royalties derived from future products developed from our research. If we are unable to successfully achieve milestones or our collaborators fail to develop successful products, we will not earn the revenues contemplated under such collaborative agreements. In addition, some of our collaborations are exclusive and preclude us from entering into additional collaborative arrangements with other parties in the area or field of exclusivity.

We currently have collaborative research agreements with Bayer Corporation, Bristol-Myers Squibb (two agreements), SmithKlineBeecham, Protein Design Labs, Dow AgroSciences, Renessen and Bayer CropScience. Our current collaborative agreement with Bayer Corporation is scheduled to expire in 2008, after which it will automatically be extended for one-year terms unless terminated by either party upon 12-months written notice. Our agreement permits Bayer to terminate our collaborative activities prior to 2008 upon the occurrence of specified conditions, such as the failure to agree on key strategic issues after a period of years or the acquisition of Exelixis by certain specified third parties. Our agreement with Bayer is subject to termination at an earlier date if two or more of our Chief Executive Officer, Chief Scientific Officer, Agricultural Biotechnology Program Leader and Chief Informatics Officer cease to have a relationship with us within nine months of each other. Our mechanism of action collaborative agreement with Bristol-Myers Squibb expires in September 2004. Our cancer collaborative agreement with Bristol-Myers Squibb expires in July 2004. Our recent alliance with SmithKlineBeecham is scheduled to expire in October 2008, but is subject to earlier termination at the discretion of SmithKlineBeecham starting in 2005 if we fail to meet certain diligence obligations. Research funding under our agreement with Protein Design Labs expired in June 2003. Funding under our arrangement with Dow AgroSciences is scheduled to expire in July 2003, after which Dow AgroSciences has the option to renew on an annual basis. Dow has advised us that it intends to renew and we are currently in discussions regarding the terms of a renewal. Our collaborative research arrangement with Bayer CropScience is scheduled to expire in September 2004. The Bayer CropScience arrangement is conducted through a limited liability company, Agrinomics, which is owned equally by Bayer CropScience and Exelixis. Agrinomics is party to a recent collaborative agreement with Renessen, which expires in

S-7

December 2005 but is subject to earlier termination at the discretion of Renessen prior to October 2003. We also have additional agreements providing lower amounts of committed funding with the following chemistry collaborators: Cytokinetics, Inc., Scios Inc., Schering-Plough Research Corporation, Merck & Co., Inc. and Elan Pharmaceuticals.

If these existing agreements are not renewed or if we are unable to enter into new collaborative agreements on commercially acceptable terms, our revenues and product development efforts may be adversely affected. For example, our agreement with Pharmacia Corporation terminated by mutual agreement in February 2002, which eliminated the opportunity for us to earn approximately \$9.0 million in research revenue in 2002 and 2003. Although we have entered into other collaborations that offset this loss of revenue, we may not be able to enter into a new collaborative agreement on similar or superior financial terms than those under our existing arrangements, and the timing of new collaborative agreements may have a material adverse effect on our ability to continue to successfully meet our corporate goals and milestones.

Conflicts with our collaborators could jeopardize the outcome of our collaborative agreements and our ability to commercialize products.

We are conducting proprietary research programs in specific disease, therapeutic modality and agricultural product areas that are not covered by our collaborative agreements. Our pursuit of opportunities in agricultural and pharmaceutical markets could, however, result in conflicts with our collaborators in the event that any of our collaborators take the position that our internal activities overlap with those areas that are exclusive to our collaborative agreements, and we should be precluded from such internal activities. Moreover, disagreements with our collaborators could develop over rights to our intellectual property. In addition, our collaborative agreements may have provisions that give rise to disputes regarding the rights and obligations of the parties, including the rights of collaborators with respect to our internal programs and disease area research. Any conflict with or among our collaborators could lead to the termination of our collaborative agreements, delay collaborative activities, reduce our ability to renew agreements or obtain future collaboration agreements or result in litigation or arbitration and would negatively impact our relationship with existing collaborators.

We have limited or no control over the resources that our collaborators may choose to devote to our joint efforts. Our collaborators may breach or terminate their agreements with us or fail to perform their obligations thereunder. Further, our collaborators may elect not to develop products arising out of our collaborative arrangements or may fail to devote sufficient resources to the development, manufacture, marketing or sale of such products. Certain of our collaborators could also become our competitors in the future. If our collaborators develop competing products, preclude us from entering into collaborations with their competitors, fail to obtain necessary regulatory approvals, terminate their agreements with us prematurely or fail to devote sufficient resources to the development and commercialization of our products, our product development efforts could be delayed and may fail to lead to commercialized products.

Our potential therapeutic products are subject to a lengthy and uncertain regulatory process that may not result in the necessary regulatory approvals, which could adversely affect our ability to commercialize products.

The FDA must approve any drug before it can be marketed in the U.S. Any products resulting from our research and development efforts must also be approved by the regulatory agencies of foreign governments before the product can be sold in those countries. Before a new drug application can be filed with the FDA, the product candidate must undergo extensive clinical trials, which can take many years and may require substantial expenditures. The regulatory process also requires preclinical testing. Data obtained from preclinical and clinical activities are susceptible to

S-8

varying interpretations, which could delay, limit or prevent regulatory approval. In addition, delays or rejections may be encountered based upon changes in regulatory policy for product approval during the period of product development and regulatory agency review. Completion of clinical trials may take several years or more, but the length of time generally varies substantially according to the type, complexity, novelty and intended use of a product candidate. We currently estimate that typical clinical trials are completed over the following timelines:

Clinical Phase	Estimated Completion Period
Phase 1	1 Year
Phase 2	1-2 Years
Phase 3	2-4 Years

However, the duration and the cost of clinical trials may vary significantly over the life of a project as a result of factors relating to the trial, including, among others, the following:

- the number of patients that ultimately participate in the trial;
- the duration of patient follow-up that seems appropriate in view of the results;
- the number of clinical sites included in the trials; and
- the length of time required to enroll suitable patient subjects.

Any clinical trial may fail to produce results satisfactory to the FDA. The FDA could determine that the design of a clinical trial is inadequate to produce reliable results. Negative or inconclusive results or adverse medical events during a clinical trial could cause a clinical trial to be repeated or development of a product or clinical trial to be terminated. The clinical development and regulatory approval process is expensive and time consuming. Any failure to obtain regulatory approval could delay or prevent us from commercializing products.

Our efforts to date have been primarily limited to identifying targets and developing small molecule compounds against those targets. Significant research and development efforts will be necessary before any of our products directed against such targets can be commercialized. If regulatory approval is granted to any of our products, the approval may impose limitations on the uses for which a product may be marketed. Further, even if regulatory approval is obtained, a marketed product and its manufacturer are subject to continual review, and discovery of previously unknown problems with a product or manufacturer may result in restrictions and sanctions with respect to the product, manufacturer and relevant manufacturing facility, including withdrawal of the product from the market.

Clinical testing of our potential products may fail to demonstrate safety and efficacy, which could prevent or significantly delay regulatory approval.

Clinical trials are inherently risky and may reveal that our potential products are ineffective or have unacceptable toxicity or other side effects that may significantly decrease the likelihood of regulatory approval of the potential product. The regulatory review and approval process is extensive and uncertain and typically takes many years to complete. The FDA requires submission of extensive preclinical, clinical and manufacturing data for each indication for which approval is sought in order to assess the safety and efficacy of the potential product. In addition, the results of preliminary studies do not necessarily predict clinical or commercial success, and larger later-stage clinical trials may fail to confirm the results observed in the preliminary studies. With respect to our own proprietary compounds in development, we have established timelines for manufacturing and clinical development based on existing knowledge of the compound and industry metrics. We have limited experience in conducting clinical studies and cannot provide assurance that any specified timelines with respect to the initiation or completion of clinical studies may be achieved.

S-9

In July 2001, we acquired our XL119 cancer compound, a rebeccamycin analogue, currently in Phase 2 clinical development. This compound was manufactured by Bristol-Myers Squibb, and clinical trials to date have been conducted by the National Cancer Institute, or the NCI. We will have to conduct additional clinical testing in order to meet FDA requirements for regulatory approval. We have no prior experience in conducting clinical trials, and, in conjunction with the NCI, we expect to undertake further clinical development of this compound under our own IND in order to obtain regulatory approval. We are currently in discussions with the FDA regarding a registration clinical trial program. We may not be able to rapidly or effectively assume responsibility for further development of this compound or meet the requirements identified based on our discussions with the FDA. We do not know whether planned clinical trials will begin on time, will be completed on schedule, or at all, will be sufficient for registration or will result in approvable products. Our product development costs

will increase if we have delays in testing or approvals or if we need to perform more or larger clinical trials than planned. If the delays are significant, our financial results and the commercial prospects for our products will be harmed, and our ability to become profitable will be delayed.

We lack the capability to manufacture compounds for clinical trials and rely on third parties to manufacture our potential products, and we may be unable to obtain required material in a timely manner or at a quality level required to receive regulatory approval.

We currently do not have manufacturing capabilities or experience necessary to produce materials for clinical trials, including for our Phase 2 clinical compound, the rebeccamycin analogue, designated XL119. We intend to rely on collaborators and third-party contractors to produce materials necessary for preclinical and clinical testing. We will rely on selected manufacturers to deliver materials on a timely basis and to comply with applicable regulatory requirements, including the FDA's current Good Manufacturing Practices, or GMP. These manufacturers may not be able to produce material on a timely basis or manufacture material at the quality level or in the quantity required to meet our development timelines and applicable regulatory requirements. If we are unable to contract for the production of materials in sufficient quantity and of sufficient quality on acceptable terms, our planned clinical trials may be delayed. Delays in preclinical or clinical testing could delay the filing of our INDs and the initiation of clinical trials that we have currently planned. In addition, our outsourcing efforts with respect to manufacturing clinical supplies will result in a dependence on our suppliers to timely manufacture and deliver sufficient quantities of materials produced under GMP conditions to enable us to conduct planned clinical trials and, if possible, to bring products to market in a timely manner.

We have no experience in developing, manufacturing and marketing products and may be unable to commercialize proprietary products.

Initially, we relied on our collaborators to develop and commercialize products based on our research and development efforts. We have limited or no experience in using the targets that we identify to develop our own proprietary products. Our recent efforts in applying our drug development capabilities to our proprietary targets in cancer are subject to significant risk and uncertainty, particularly with respect to our ability to meet currently estimated timelines and goals for completing preclinical development efforts and filing an IND for compounds developed. In order for us to commercialize products, we would need to significantly enhance our capabilities with respect to product development and established manufacturing and marketing capabilities, either directly or through outsourcing or licensing arrangements. We may not be able to enter into such outsourcing or licensing agreements on commercially reasonable terms, or at all.

S-10

Since our technologies have many potential applications and we have limited resources, our focus on a particular area may result in our failure to capitalize on more profitable areas.

We have limited financial and managerial resources. This requires us to focus on product candidates in specific industries and forego opportunities with regard to other products and industries. For example, depending on our ability to allocate resources, a decision to concentrate on a particular agricultural program may mean that we will not have resources available to apply the same technology to a pharmaceutical project. While our technologies may permit us to work in both areas, resource commitments may require trade-offs resulting in delays in the development of certain programs or research areas, which may place us at a competitive disadvantage. Our decisions impacting resource allocation may not lead to the development of viable commercial products and may divert resources from more profitable market opportunities.

Our competitors may develop products and technologies that make our products and technologies obsolete.

The biotechnology industry is highly fragmented and is characterized by rapid technological change. In particular, the area of gene research is a rapidly evolving field. We face, and will continue to face, intense competition from large biotechnology and pharmaceutical companies, as well as academic research institutions, clinical reference laboratories and government agencies that are pursuing research activities similar to ours. Some of our competitors have entered into collaborations with leading companies within our target markets, including some of our existing collaborators. Our future success will depend on our ability to maintain a competitive position with respect to technological advances.

Any products that are developed through our technologies will compete in highly competitive markets. Further, our competitors may be more effective at using their technologies to develop commercial products. Many of the organizations competing with us have greater capital resources, larger research and development staffs and facilities, more experience in obtaining regulatory approvals and more extensive product manufacturing and marketing capabilities. As a result, our competitors may be able to more easily develop technologies and products that would render our technologies and products, and those of our collaborators, obsolete and noncompetitive.

If we are unable to adequately protect our intellectual property, third parties may be able to use our technology, which could adversely affect our ability to compete in the market.

Our success will depend in part on our ability to obtain patents and maintain adequate protection of the intellectual property related to our technologies and products. The patent positions of biotechnology companies, including our patent position, are generally uncertain and involve complex legal and factual questions. We will be able to protect our intellectual property rights from unauthorized use by third parties only to the extent that our technologies are covered by valid and enforceable patents or are effectively maintained as trade secrets. The laws of some foreign countries do not protect intellectual property rights to the same extent as the laws of the U.S., and many companies have encountered significant problems in protecting and defending such rights in foreign jurisdictions. We will continue to apply for patents covering our technologies and products as and when we deem appropriate. However, these applications may be challenged or may fail to result in issued patents. Our existing patents and any future patents we obtain may not be sufficiently broad to prevent others from practicing our technologies or from developing competing products. Furthermore, others may independently develop similar or alternative technologies or design around our patents. In addition, our patents may be challenged or invalidated or may fail to provide us with any competitive advantages.

We rely on trade secret protection for our confidential and proprietary information. We have taken security measures to protect our proprietary information and trade secrets, but these

S-11

measures may not provide adequate protection. While we seek to protect our proprietary information by entering into confidentiality agreements with employees, collaborators and consultants, we cannot assure you that our proprietary information will not be disclosed, or that we can meaningfully protect our trade secrets.

In addition, our competitors may independently develop substantially equivalent proprietary information or may otherwise gain access to our trade secrets.

Litigation or third-party claims of intellectual property infringement could require us to spend substantial time and money and adversely affect our ability to develop and commercialize products.

Our commercial success depends in part on our ability to avoid infringing patents and proprietary rights of third parties and not breaching any licenses that we have entered into with regard to our technologies. Other parties have filed, and in the future are likely to file, patent applications covering genes and gene fragments, techniques and methodologies relating to model systems and products and technologies that we have developed or intend to develop. If patents covering technologies required by our operations are issued to others, we may have to rely on licenses from third parties, which may not be available on commercially reasonable terms, or at all.

Third parties may accuse us of employing their proprietary technology without authorization. In addition, third parties may obtain patents that relate to our technologies and claim that use of such technologies infringes these patents. Regardless of their merit, such claims could require us to incur substantial costs, including the diversion of management and technical personnel, in defending ourselves against any such claims or enforcing our patents. In the event that a successful claim of infringement is brought against us, we may be required to pay damages and obtain one or more licenses from third parties. We may not be able to obtain these licenses at a reasonable cost, or at all. Defense of any lawsuit or failure to obtain any of these licenses could adversely affect our ability to develop and commercialize products.

The loss of key personnel or the inability to attract and retain additional personnel could impair our ability to expand our operations.

We are highly dependent on the principal members of our management and scientific staff, the loss of whose services might adversely impact the achievement of our objectives and the continuation of existing collaborations. In addition, recruiting and retaining qualified scientific and clinical personnel to perform future research and development work will be critical to our success. We do not currently have sufficient executive management and technical personnel to fully execute our business plan. There is currently a shortage of skilled executives and employees with technical expertise, and this shortage is likely to continue. As a result, competition for skilled personnel is intense, and turnover rates are high. Although we believe we will be successful in attracting and retaining qualified personnel, competition for experienced scientists from numerous companies and academic and other research institutions may limit our ability to do so.

Our business operations will require additional expertise in specific industries and areas applicable to products identified and developed through our technologies. These activities will require the addition of new personnel, including management and technical personnel and the development of additional expertise by existing employees. The inability to attract such personnel or to develop this expertise could prevent us from expanding our operations in a timely manner, or at all.

Our collaborations with outside scientists may be subject to restriction and change.

We work with scientific and clinical advisors and collaborators at academic and other institutions that assist us in our research and development efforts. These scientists and advisors are not our employees and may have other commitments that would limit their availability to us.

S-12

Although our advisors and collaborators generally agree not to do competing work, if a conflict of interest between their work for us and their work for another entity arises, we may lose their services. In addition, although our advisors and collaborators sign agreements not to disclose our confidential information, it is possible that valuable proprietary knowledge may become publicly known through them.

Social issues may limit the public acceptance of genetically engineered products, which could reduce demand for our products.

Although our technology is not dependent on genetic engineering, genetic engineering plays a prominent role in our approach to product development. For example, research efforts focusing on plant traits may involve either selective breeding or modification of existing genes in the plant under study. Public attitudes may be influenced by claims that genetically engineered products are unsafe for consumption or pose a danger to the environment. Such claims may prevent our genetically engineered products from gaining public acceptance. The commercial success of our future products will depend, in part, on public acceptance of the use of genetically engineered products, including drugs and plant and animal products.

The subject of genetically modified organisms has received negative publicity, which has aroused public debate. For example, certain countries in Europe are considering regulations that ban products or require express labeling of products that contain genetic modifications or are "genetically modified". Adverse publicity has resulted in greater regulation internationally and trade restrictions on imports of genetically altered products. If similar action is taken in the U.S., genetic research and genetically engineered products could be subject to greater domestic regulation, including stricter labeling requirements. To date, our business has not been hampered by these activities. However, such publicity in the future may prevent any products resulting from our research from gaining market acceptance and reduce demand for our products.

Laws and regulations may reduce our ability to sell genetically engineered products that we or our collaborators develop in the future.

We or our collaborators may develop genetically engineered agricultural and animal products. The field-testing, production and marketing of genetically engineered products are subject to regulation by federal, state, local and foreign governments. Regulatory agencies administering existing or future regulations or legislation may prevent us from producing and marketing genetically engineered products in a timely manner or under technically or commercially feasible conditions. In addition, regulatory action or private litigation could result in expenses, delays or other impediments to our product development programs and the commercialization of products. The FDA has released a policy statement stating that it will apply the same regulatory standards to foods developed through genetic engineering as it applies to foods developed through traditional plant breeding. Genetically engineered food products will be subject to premarket review, however, if these products raise safety questions or are deemed to be food additives. Our products may be subject to lengthy FDA reviews and unfavorable FDA determinations if they raise questions regarding safety or our products are deemed to be food additives.

To date, the FDA has not required genetically engineered agricultural products to be labeled as such, provided that these products are as safe and have the same nutritional characteristics as conventionally developed products. The FDA may reconsider or change its policies, and local or state authorities may enact

labeling requirements, either of which could have a material adverse effect on our ability or the ability of our collaborators to develop and market products resulting from our efforts.

We use hazardous chemicals and radioactive and biological materials in our business. Any claims relating to improper handling, storage or disposal of these materials could be time consuming and costly.

Our research and development processes involve the controlled use of hazardous materials, including chemicals and radioactive and biological materials. Our operations produce hazardous waste products. We cannot eliminate the risk of accidental contamination or discharge and any resultant injury from these materials. Federal, state and local laws and regulations govern the use, manufacture, storage, handling and disposal of hazardous materials. We may be sued for any injury or contamination that results from our use or the use by third parties of these materials, and our liability may exceed our insurance coverage and our total assets. Compliance with environmental laws and regulations may be expensive, and current or future environmental regulations may impair our research, development and production efforts.

In addition, our collaborators may use hazardous materials in connection with our collaborative efforts. To our knowledge, their work is performed in accordance with applicable biosafety regulations. In the event of a lawsuit or investigation, however, we could be held responsible for any injury caused to persons or property by exposure to, or release of, these hazardous materials used by these parties. Further, we may be required to indemnify our collaborators against all damages and other liabilities arising out of our development activities or products produced in connection with these collaborations.

We expect that our quarterly results of operations will fluctuate, and this fluctuation could cause our stock price to decline, causing investor losses.

Our quarterly operating results have fluctuated in the past and are likely to fluctuate in the future. A number of factors, many of which we cannot control, could subject our operating results and stock price to volatility, including:

- recognition of upfront licensing or other fees;
- payments of non-refundable upfront or licensing fees to third parties;
- acceptance of our technologies and platforms;
- the success rate of our discovery efforts leading to milestone payments and royalties;
- the introduction of new technologies or products by our competitors;
- the timing and willingness of collaborators to commercialize our products;
- our ability to enter into new collaborative relationships;
- the termination or non-renewal of existing collaborations;
- the timing and amount of expenses incurred for clinical development and manufacturing of our products;
- the impairment of acquired goodwill and other assets; and
- general and industry-specific economic conditions that may affect our collaborators' research and development expenditures.

A large portion of our expenses, including expenses for facilities, equipment and personnel, are relatively fixed in the short term. In addition, we expect operating expenses to increase significantly during the next year. Accordingly, if our revenues decline or do not grow as anticipated due to the expiration of existing contracts or our failure to obtain new contracts, our inability to meet milestones or other factors, we may not be able to correspondingly reduce our operating expenses.

Failure to achieve anticipated levels of revenues could therefore significantly harm our operating results for a particular fiscal period.

Due to the possibility of fluctuations in our revenues and expenses, we believe that quarter-to-quarter comparisons of our operating results are not a good indication of our future performance. As a result, in some future quarters, our operating results may not meet the expectations of stock market analysts and investors, which could result in a decline in the price of our stock.

Our stock price may be extremely volatile.

We believe the trading price of our common stock will remain highly volatile and may fluctuate substantially due to factors such as the following:

- the announcement of new products or services by us or our competitors;
- the failure of product candidates in clinical trials by us or our competitors;
-

quarterly variations in our or our competitors' results of operations;

- failure to achieve operating results projected by securities analysts;
- changes in earnings estimates or recommendations by securities analysts;
- developments in the biotechnology industry;
- acquisitions of other companies or technologies; and
- general market conditions and other factors, including factors unrelated to our operating performance or the operating performance of our competitors.

These factors and fluctuations, as well as general economic, political and market conditions, may materially adversely affect the market price of our common stock.

In the past, following periods of volatility in the market price of a company's securities, securities class action litigation has often been instituted. A securities class action suit against us could result in substantial costs and divert management's attention and resources, which could have a material and adverse effect on our business.

We are exposed to risks associated with acquisitions.

We have made, and may in the future make, acquisitions of, or significant investments in, businesses with complementary products, services and/or technologies. Acquisitions involve numerous risks, including, but not limited to:

- difficulties and increased costs in connection with integration of the personnel, operations, technologies and products of acquired companies;
- diversion of management's attention from other operational matters;
- the potential loss of key employees of acquired companies;
- the potential loss of key collaborators of the acquired companies;
- lack of synergy, or the inability to realize expected synergies, resulting from the acquisition; and
- acquired intangible assets becoming impaired as a result of technological advancements or worse-than-expected performance of the acquired company.

S-15

Mergers and acquisitions are inherently risky, and the inability to effectively manage these risks could materially and adversely affect our business, financial condition and results of operations.

If product liability lawsuits are successfully brought against us, we could face substantial liabilities that exceed our resources.

We may be held liable if any product our collaborators or we develop causes injury or is found otherwise unsuitable during product testing, manufacturing, marketing or sale. Although we intend to obtain general liability and product liability insurance, this insurance may be prohibitively expensive, or may not fully cover our potential liabilities. Inability to obtain sufficient insurance coverage at an acceptable cost or to otherwise protect ourselves against potential product liability claims could prevent or inhibit the commercialization of products developed by our collaborators or us.

Our headquarters facilities are located near known earthquake fault zones, and the occurrence of an earthquake or other catastrophic disaster could cause damage to our facilities and equipment, which could require us to cease or curtail operations.

Given our headquarters location in South San Francisco, California, our facilities are vulnerable to damage from earthquakes. We are also vulnerable worldwide to damage from other types of disasters, including fire, floods, power loss, communications failures and similar events. If any disaster were to occur, our ability to operate our business at our facilities would be seriously, or potentially completely, impaired. In addition, the unique nature of our research activities could cause significant delays in our programs and make it difficult for us to recover from a disaster. The insurance we maintain may not be adequate to cover our losses resulting from disasters or other business interruptions. Accordingly, an earthquake or other disaster could materially and adversely harm our ability to conduct business.

Future sales of our common stock may depress our stock price.

If our stockholders sell substantial amounts of our common stock (including shares issued upon the exercise of outstanding options and warrants) in the public market, the market price of our common stock could fall. These sales also might make it more difficult for us to sell equity or equity-related securities in the future at a time and price that we deemed appropriate. For example, following an acquisition, a significant number of shares of our common stock held by new stockholders may become freely tradable or holders of registration rights could cause us to register their shares for resale. Sales of these shares and other shares of common stock held by existing stockholders could cause the market price of our common stock to decline.

Some of our existing stockholders can exert control over us, and their interests could conflict with the best interests of our other stockholders.

Due to their combined stock holdings, our officers, directors and principal stockholders (stockholders holding more than 5% of our common stock) acting together, may be able to exert significant influence over all matters requiring stockholder approval, including the election of directors and approval of significant corporate transactions. In addition, this concentration of ownership may delay or prevent a change in control of our company, even when a change may be in the

best interests of our stockholders. In addition, the interests of these stockholders may not always coincide with our interests as a company or the interests of other stockholders. Accordingly, these stockholders could cause us to enter into transactions or agreements that you would not approve of.

S-16

CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS

Some of the statements in this prospectus supplement, the accompanying prospectus and the documents incorporated by reference are forward-looking statements. These statements are based on our current expectations, assumptions, estimates and projections about our business and our industry, and involve known and unknown risks, uncertainties and other factors that may cause our or our industry's results, levels of activity, performance or achievement to be materially different from any future results, levels of activity, performance or achievements expressed or implied in or contemplated by the forward-looking statements. Words such as "believe", "anticipate", "expect", "intend", "plan", "will", "may", "should", "estimate", "predict", "potential" and "continue", or the negative of such terms or other similar expressions, identify forward-looking statements. In addition, any statements that refer to expectations, projections or other characterizations of future events or circumstances are forward-looking statements. Our actual results could differ materially from those anticipated in such forward-looking statements as a result of several factors more fully described under the caption "Risk Factors" and in the documents incorporated by reference. The forward-looking statements made in this prospectus supplement and the accompanying prospectus speak only as of the date on which the statements are made.

S-17

USE OF PROCEEDS

We expect to receive approximately \$82.1 million in net proceeds from the sale of 10,000,000 shares of common stock in this offering (or \$94.5 million if the underwriters exercise their option to purchase additional shares in full), after deducting estimated underwriting discounts and commissions and offering expenses payable by us. These amounts are based on an assumed offering price to the public of \$8.78 per share.

We anticipate using the net proceeds to us from the sale of the common stock in this offering to fund clinical development and for working capital and general corporate purposes. We may also use a portion of the net proceeds to acquire or invest in businesses, products and technologies that are complementary to our own, although we are not currently planning or negotiating any such transactions.

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

S-18

PRICE RANGE OF COMMON STOCK

Since April 11, 2000, our common stock has been quoted and traded on the Nasdaq National Market under the symbol "EXEL". The following table sets forth, for the periods indicated, the reported high and low intraday sales prices per share of our common stock on the Nasdaq National Market:

	<u>High</u>	<u>Low</u>
Year ended December 31, 2001		
First Quarter	\$ 16.25	\$ 6.00
Second Quarter	19.00	7.25
Third Quarter	19.28	9.61
Fourth Quarter	17.47	10.60
Year ended December 31, 2002		
First Quarter	\$ 16.72	\$ 10.88
Second Quarter	13.56	5.63
Third Quarter	7.45	3.50
Fourth Quarter	9.41	2.95
Year ending December 31, 2003		
First Quarter	\$ 8.03	\$ 5.01
Second Quarter (through June 11, 2003)	9.41	6.52

The last reported sale price of our common stock on the Nasdaq National Market on June 11, 2003 was \$8.78. As of June 11, 2003, there were approximately 1,026 stockholders of record of our common stock.

DIVIDEND POLICY

We have never declared or paid cash dividends on our capital stock. We currently intend to retain earnings, if any, to support the development of our business and do not anticipate paying cash dividends for the foreseeable future.

S-19

CAPITALIZATION

The following table sets forth as of March 31, 2003:

- our actual unaudited cash, cash equivalents, short-term investments and capitalization; and
- our actual unaudited cash, cash equivalents, short-term investments and capitalization as adjusted to give effect to this offering of our common stock using the amounts set forth under "Use of Proceeds" and assuming the underwriters do not exercise their option to purchase additional shares of our common stock.

This table should be read in conjunction with the financial statements and the related notes incorporated by reference in the accompanying prospectus.

	As of March 31, 2003	
	Actual	As Adjusted
	(in thousands, except share and per share data)	
Cash, cash equivalents and short-term investments (including restricted cash of \$7,610)	\$ 203,869	\$ 285,981
Capital lease obligations, net of current portion	\$ 4,545	\$ 4,545
Notes payable and bank obligations, net of current portion	5,110	5,110
Convertible promissory note and loan	55,000	55,000
Total long-term debt	64,655	64,655
Stockholders' equity:		
Preferred stock, \$0.001 par value; 10,000,000 shares authorized; no shares issued, actual and as adjusted	—	—
Common stock, \$0.001 par value; 100,000,000 shares authorized; 59,659,276 shares issued and outstanding, actual; and 69,659,276 shares issued and outstanding, as adjusted	60	70
Additional paid-in-capital	465,534	547,636
Notes receivable from stockholders	(843)	(843)
Deferred stock compensation, net	(648)	(648)
Accumulated other comprehensive income	1,846	1,846
Accumulated deficit	(310,412)	(310,412)
Total stockholders' equity	155,537	237,649
Total capitalization	\$ 220,192	\$ 302,304

S-20

DILUTION

The net tangible book value of our common stock on March 31, 2003 was approximately \$83.5 million, or approximately \$1.40 per share. Net tangible book value per share is equal to the amount of our total tangible assets, less total liabilities, divided by the aggregate number of shares of common stock outstanding. Dilution in net tangible book value per share represents the difference between the amount per share paid by purchasers of shares of common stock in this offering and the net tangible book value per share of our common stock immediately after this offering. After giving effect to the sale of 10,000,000 shares of common stock in this offering at an assumed public offering price of \$8.78 per share, and after deducting estimated underwriting discounts and commissions and offering expenses, our net tangible book value at March 31, 2003 would have been approximately \$165.7 million, or approximately \$2.38 per share. This represents an immediate dilution of \$6.40 per share to new investors purchasing shares of common stock in this offering. The following table illustrates this dilution:

Assumed public offering price per share	\$ 8.78
Net tangible book value per share as of March 31, 2003	\$ 1.40
Increase per share attributable to new investors	0.98
Net tangible book value per share as of March 31, 2003 after giving effect to this offering	2.38
Dilution per share to new investors	\$ 6.40

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

- 11,264,344 shares of common stock underlying options and warrants outstanding at a weighted average exercise price of \$13.40 per share;

- 4,539,723 shares issuable upon conversion of our convertible debt (assuming that the debt had been converted as of March 31, 2003).

UNDERWRITING

Exelixis and the underwriters for the offering named below have entered into an underwriting agreement with respect to the shares being offered. Subject to certain conditions, each underwriter has severally agreed to purchase the number of shares indicated in the following table.

Underwriters	Number of Shares
Goldman, Sachs & Co.	
SG Cowen Securities Corporation	
Total	10,000,000

The underwriters are committed to take and pay for all of the shares being offered, if any are taken, other than the shares covered by the option described below unless and until this option is exercised.

If the underwriters sell more shares than the total set forth in the table above, the underwriters have an option to buy up to an additional 1,500,000 shares from Exelixis to cover such sales. They may exercise that option within 30 days of the date of this prospectus supplement. If any shares are purchased pursuant to this option, the underwriters will severally purchase shares in approximately the same proportion as set forth in the table above.

The following table shows the per share and total underwriting discounts and commissions to be paid to the underwriters by Exelixis. Such amounts are shown assuming both no exercise and full exercise of the underwriters' option to purchase 1,500,000 additional shares.

Paid by Exelixis

	No Exercise	Full Exercise
Per share	\$	\$
Total	\$	\$

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

Exelixis and each of its directors and executive officers have agreed not to dispose of or hedge any shares of the common stock or any securities convertible into or exchangeable for shares of the common stock during the period 90 days after the date of this prospectus supplement, subject to certain permitted exceptions, except with the prior written consent of Goldman, Sachs & Co. This agreement does not apply to an existing 10b5-1 sales plan of Exelixis' chief executive officer (under which approximately 2,500 shares are expected to be sold each week during the 90-day lock-up period) or to Exelixis' existing equity incentive plans. Goldman, Sachs & Co., in its sole discretion, may release any of the securities subject to these lock-up agreements at any time without notice.

The common stock is quoted on the Nasdaq National Market under the symbol "EXEL".

In connection with this offering, the underwriters may purchase and sell shares of 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 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 shares 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 additional shares pursuant to the option granted to them. "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 stock in the open market after pricing that could adversely affect investors who purchase in the offering. Stabilizing transactions consist of various bids or purchases made by the underwriters in the open market for the purpose of preventing or retarding a decline in the market price of the common stock while the offering is in progress.

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 underwriters have repurchased shares sold by or for the account of such underwriter in stabilizing or short covering transactions.

Purchases to cover a short position and stabilizing transactions may have the effect of preventing or retarding a decline in the market price of the common stock, and together with the imposition of a penalty bid, may stabilize, maintain or otherwise affect the market price of the common stock. As a result, the price of

the common stock may be higher than the price that otherwise might exist in the open market. If these activities are commenced, they may be discontinued by the underwriters at any time. These transactions may be effected on the Nasdaq National Market, in the over-the-counter market or otherwise.

Each underwriter has represented, warranted and agreed that: (i) it has not offered or sold and, prior to the expiry of a period of six months from the closing date, will not offer or sell any shares 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 have not resulted and will not result in an offer to the public in the United Kingdom within the meaning of the Public Offers of Securities Regulations 1995; (ii) it has only communicated or caused to be communicated and will only communicate or cause to be communicated any invitation or inducement to engage in investment activity (within the meaning of section 21 of the Financial Services and Markets Act 2000, or FSMA) received by it in connection with the issue or sale of any shares in circumstances in which section 21(1) of the FSMA does not apply to Exelixis; and (iii) it has complied and will comply with all applicable provisions of the FSMA with respect to anything done by it in relation to the shares in, from or otherwise involving the United Kingdom.

The shares may not be offered, sold, transferred or delivered in or from The Netherlands, as part of their initial distribution or as part of any re-offering, and neither this prospectus supplement and the accompanying prospectus nor any other document in respect of this offering may be distributed or circulated in The Netherlands, other than to individuals or legal entities which include, but are not limited to, banks, brokers, dealers, institutional investors and undertakings with a treasury department, who or which trade or invest in securities in the conduct of a business or profession.

No underwriter has offered or sold, or will offer or sell, in Hong Kong, by means of any document, any shares other than to persons whose ordinary business it is to buy or sell shares or debentures, whether as principal or agent, or under circumstances which do not constitute an offer to the public within the meaning of the Companies Ordinance (Cap. 32) of Hong Kong, nor has it

S-23

issued or had in its possession for the purpose of issue, nor will it issue or have in its possession for the purpose of issue, any invitation or advertisement relating to the shares in Hong Kong (except as permitted by the securities laws of Hong Kong) other than with respect to shares which are intended to be disposed of to persons outside Hong Kong or to be disposed of only to persons whose business involves the acquisition, disposal, or holding of securities (whether as principal or as agent).

This prospectus supplement has not been registered as a prospectus with the Monetary Authority of Singapore. Accordingly, this prospectus, the accompanying prospectus and any other document or material in connection with the offer or sale, or invitation or subscription or purchase, of the shares may not be circulated or distributed, nor may the shares be offered or sold, or be made the subject of an invitation for subscription or purchase, whether directly or indirectly, to persons in Singapore other than under circumstances in which such offer, sale or invitation does not constitute an offer or sale, or invitation for subscription or purchase, of the shares to the public in Singapore.

Each underwriter has acknowledged and agreed that the shares have not been registered under the Securities and Exchange Law of Japan and are not being offered or sold and may not be offered or sold, directly or indirectly, in Japan or to or for the account of any resident of Japan, except (1) pursuant to an exemption from the registration requirements of the Securities and Exchange Law of Japan and (ii) in compliance with any other applicable requirements of Japanese law. As part of the offering, the underwriters may offer shares in Japan to a list of 49 offerees in accordance with the above provisions.

Exelixis estimates that its share of the total expenses of this offering, excluding underwriting discounts and commissions, will be approximately \$420,000.

The underwriting compensation will not exceed 8%.

Exelixis has agreed to indemnify the several underwriters against certain liabilities, including liabilities under the Securities Act of 1933.

In the ordinary course of their respective businesses, the underwriters have from time to time performed, and may in the future perform, certain investment banking and advisory services for Exelixis for which they have received, and may receive, customary fees and expenses. In addition, the Chairman of the board of directors of Exelixis is an employee of SG Cowen, one of the underwriters in this offering.

LEGAL MATTERS

The validity of the common stock offered hereby will be passed upon for us by Cooley Godward LLP, Palo Alto, California, and for the underwriters by Sullivan & Cromwell LLP, Los Angeles, California.

EXPERTS

Ernst & Young LLP, independent auditors, have audited our consolidated financial statements for the years ended December 31, 2001 and 2002 included in our annual report on Form 10-K for the year ended December 31, 2002, as set forth in their report, which is incorporated by reference in the accompanying prospectus and given upon their authority as experts in accounting and auditing.

The consolidated financial statements for the year ended December 31, 2000 incorporated in the accompanying prospectus by reference to the Annual Report on Form 10-K for the year ended December 31, 2002 have been so incorporated in reliance on the report of PricewaterhouseCoopers LLP, independent accountants, given on the authority of said firm as experts in accounting and auditing.

S-24

PROSPECTUS

\$150,000,000

Exelixis, Inc.

COMMON STOCK

Exelixis, Inc. may offer from time to time, in one or more issuances, shares of common stock under this prospectus. We will offer the shares of our common stock in an amount and on terms that market conditions will determine at the time of the offering. Please read any prospectus supplements and this prospectus carefully before you invest in our common stock. This prospectus may not be used to sell shares of our common stock unless accompanied by a prospectus supplement.

Our common stock trades on the Nasdaq National Market under the symbol EXEL. On July 27, 2001, the last reported sale price of our common stock was \$18.60 per share.

See "Risk Factors" beginning on page 3 to read about factors you should consider before buying shares of our common stock.

NEITHER THE SECURITIES AND EXCHANGE COMMISSION NOR ANY STATE SECURITIES COMMISSION HAS APPROVED OR DISAPPROVED THESE SECURITIES OR DETERMINED IF THIS PROSPECTUS IS TRUTHFUL OR COMPLETE. ANY REPRESENTATION TO THE CONTRARY IS A CRIMINAL OFFENSE.

Prospectus dated August 7, 2001

TABLE OF CONTENTS

	Page
ABOUT THIS PROSPECTUS	1
EXELIXIS	1
RISK FACTORS	3
CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS	13
USE OF PROCEEDS	13
PLAN OF DISTRIBUTION	14
DESCRIPTION OF CAPITAL STOCK	14
LEGAL MATTERS	17
EXPERTS	17
WHERE YOU CAN FIND MORE INFORMATION ABOUT EXELIXIS	17

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

Exelixis, Artemis Pharmaceuticals, ACTTAG, the Exelixis, Inc. logos and all other Exelixis product and service names are registered trademarks or trademarks of Exelixis, Inc. in the U.S. and in other selected countries. All other brand names or trademarks appearing in this prospectus are the property of their respective holders.

ABOUT THIS PROSPECTUS

This prospectus is part of a registration statement on Form S-3 that we filed with the Securities and Exchange Commission utilizing a "shelf" registration process. Under this shelf process, we may offer from time to time the shares of our common stock described in this prospectus in one or more offerings for up to a total amount of \$150,000,000. This prospectus provides you with a general description of our common stock that we may offer. Each time we use this prospectus to offer shares of our common stock, we will provide a prospectus supplement that will contain specific information about the terms of that offering. The prospectus supplements may also add, update or change information contained in this prospectus. You should read both this prospectus and any prospectus supplement together with additional information described below under the heading "Where You Can Find More Information About Exelixis."

EXELIXIS

We believe that we are a leader in the discovery and validation of high-quality novel targets for several major human diseases, and a leader in the discovery of potential new drug therapies, specifically for cancer and other proliferative diseases. Our mission is to develop proprietary products by leveraging our integrated discovery platform to increase the speed, efficiency and quality of pharmaceutical and agricultural product discovery and development.

Through our expertise in biology and drug discovery built upon a foundation of comparative genomics and model system genetics, we are able to find new drug targets that we believe would be difficult or impossible to uncover using other experimental approaches. Our pharmaceutical research identifies novel genes and proteins expressed by those genes that, when changed, either decrease or increase the activity in a specific disease pathway in a therapeutically relevant manner. These genes and proteins then represent either potential product targets or drugs that may treat disease, or prevent disease initiation or progression.

Specifically in cancer, the remarkable evolutionary conservation of the biochemical pathways between humans and "lower" organisms strongly supports the use of simple model systems, such as fruit flies, nematode worms, zebrafish and mice to identify key members of critical cancer pathways that can then be targeted for drug discovery. We expect to develop new cancer drugs by exploiting the underlying "genetic liabilities" of tumor cells to provide specificity in targeting these cells for destruction, while leaving normal cells unharmed. We have discovered and are further developing a number of small molecule drug targets in addition to monoclonal antibody drug targets. Molecules developed against these targets may selectively kill cancer cells while leaving normal cells unharmed, and may provide alternatives to current cancer therapies.

1

While our proprietary programs focus on drug discovery and development, we believe that our proprietary technologies are valuable to all other industries whose products can be enhanced by an understanding of DNA or proteins, including the agrochemical, agricultural and diagnostic industries. Many of these industries have shorter product development cycles and lower risk than the pharmaceutical industry, while at the same time generating significant sales with double-digit product margins. By partnering with leading companies in multiple industries, we are able to diversify our business risk, while at the same time maximizing our future revenue stream.

We are a Delaware corporation. Our principal executive offices are located at 170 Harbor Way, South San Francisco, California 94080, and our telephone number is (650) 837-7000. In this prospectus, "Exelixis," "we," "us," and "our" refer to Exelixis, Inc., unless the context otherwise requires.

2

RISK FACTORS

You should carefully consider the following risk factors, in addition to other information included or incorporated by reference in this prospectus, before making an investment decision. The risks described below are not the only risks we face. Additional risks that we do not yet know of or that we currently think are immaterial may also impair our business operations. If any of the events or circumstances described in the following risks actually occurs, our business may suffer, the trading price of our common stock could decline and you may lose all or part of your investment.

We have a history of net losses. We expect to continue to incur net losses, and we may not achieve or maintain profitability.

We have incurred net losses each year since our inception, including a net loss of approximately \$12.7 million for the three months ended March 31, 2001. As of that date, we had an accumulated deficit of approximately \$142.8 million. We expect these losses to continue and anticipate negative cash flow for the foreseeable future. The size of these net losses will depend, in part, on the rate of growth, if any, in our license and contract revenues and on the level of our expenses. Our research and development expenditures and general and administrative costs have exceeded our revenues to date, and we expect to spend significant additional amounts to fund research and development in order to enhance our core technologies and undertake product development. As a result, we expect that our operating expenses will increase significantly in the near term and, consequently, we will need to generate significant additional revenues to achieve profitability. Even if we do increase our revenues and achieve profitability, we may not be able to sustain or increase profitability.

We will need additional capital in the future, which may not be available to us.

Our future capital requirements will be substantial, and will depend on many factors including:

- payments received under collaborative agreements;
- the progress and scope of our collaborative and independent research and development projects;
- our ability to successfully continue development of a recently acquired cancer compound;
- our need to expand our other proprietary product development efforts as well as develop manufacturing and marketing capabilities to commercialize products; and
- the filing, prosecution and enforcement of patent claims.

We anticipate that our current cash and cash equivalents, short-term investments and funding to be received from collaborators will enable us to maintain our currently planned operations for at least the next two years. Changes to our current operating plan may require us to consume available capital resources significantly sooner than we expect. For example, our newly acquired cancer product from our recent relationship with Bristol Myers-Squibb will require significant resources for development that were not in our operation plans prior to acquiring the cancer product. We may be unable to raise sufficient additional capital when we need it, on favorable terms, or at all. If our capital resources are insufficient to meet future capital requirements, we our capital resources are insufficient to meet future capital requirements, we will have to raise additional funds. The sale of equity or convertible debt securities in the future may be dilutive to our stockholders, and debt financing arrangements may require us to pledge certain assets and enter into covenants that would restrict our ability to incur further indebtedness. If we are unable to obtain adequate funds on reasonable terms, we may be required to curtail operations significantly or to obtain funds by entering into financing, supply or collaboration agreements on unattractive terms.

3

Difficulties we may encounter managing our growth may divert resources and limit our ability to successfully expand our operations.

We have experienced a period of rapid and substantial growth that has placed, and our anticipated growth in the future will continue to place, a strain on our administrative and operational infrastructure. As our operations expand, we expect that we will need to manage multiple locations, including locations outside the

United States, and additional relationships with various collaborative partners, suppliers and other third parties. Our ability to manage our operations and growth effectively requires us to continue to improve our operational, financial and management controls, reporting systems and procedures. We may not be able to successfully implement improvements to our management information and control systems in an efficient or timely manner and may discover deficiencies in existing systems and controls. In addition, acquisitions involve the integration of different financial and management reporting systems. We may not be able to successfully integrate the administrative and operational infrastructure without significant additional improvements and investments in management systems and procedures.

We are dependent on our collaborations with major companies. If we are unable to achieve milestones, develop products or renew or enter into new collaborations, our revenues may decrease and our activities may fail to lead to commercialized products.

Substantially all of our revenues to date have been derived from collaborative research and development agreements. Revenues from research and development collaborations depend upon continuation of the collaborations, the achievement of milestones and royalties derived from future products developed from our research. If we are unable to successfully achieve milestones or our collaborators fail to develop successful products, we will not earn the revenues contemplated under such collaborative agreements. In addition, some of our collaborations are exclusive and preclude us from entering into additional collaborative arrangements with other parties in the area or field of exclusivity.

We currently have collaborative research agreements with Bayer, Bristol-Myers Squibb (two agreements), Dow AgroSciences, Aventis and Protein Design Labs. Our current collaborative agreement with Bayer is scheduled to expire in 2008, after which it will automatically be extended for one-year terms unless terminated by either party upon 12-month written notice. Our agreement permits Bayer to terminate our collaborative activities prior to 2008 upon the occurrence of specified conditions, such as the failure to agree on key strategic issues after a period of years or the acquisition of Exelixis by certain specified third parties. In addition, our agreements with Bayer are subject to termination at an earlier date if two or more of our Chief Executive Officer, Chief Scientific Officer, Agricultural Biotechnology Program Leader and Chief Informatics Officer cease to have a relationship with us within six months of each other and we are unable to find replacements acceptable to Bayer. The first of our collaborative agreements with Bristol-Myers Squibb expires in September 2002. The funded research term of second arrangement, entered into July 2002, expires in July 2005. Our collaborative agreement with Dow AgroSciences is scheduled to expire in July 2003, after which Dow AgroSciences has the option to renew on an annual basis. Our collaborative research arrangement with Aventis is scheduled to expire in June 2004. Aventis has the right to terminate the research arrangement prior to the expiration date, provided that it pays the annual research funding amount due for the year following termination. Thereafter, the arrangement renews annually unless Aventis terminates automatic renewal prior to the scheduled date of renewal. The Aventis arrangement is conducted through a limited liability company, Agrinomics, which is owned equally by Aventis and Exelixis. Aventis may surrender its interest in Agrinomics and terminate the related research collaboration prior to the scheduled expiration upon the payment of the subsequent year's funding commitment. Bayer and Aventis recently announced an exclusive negotiation period for acquisition were to occur. Our agreement with Protein Design

4

Labs is scheduled to expire in May 2003. Protein Design Labs has a unilateral right to renew for 12 and six month periods thereafter. The five-year term of the convertible promissory note entered into as part of this arrangement is unaffected by whether or not Protein Design Labs renews. If these existing agreements are not renewed or if we are unable to enter into new collaborative may be adversely affected.

We recently announced the reacquisition, effective February 2002, of future rights to research programs in metabolism and alzheimer's disease previously licensed exclusively to Pharmacia Corporation. Pharmacia will retain rights to targets under the existing agreement selected prior to the reacquisition date, subject to the payment of milestones for certain of those targets selected and royalties for future development of products against or using those targets but will have no other obligations to make payments to the Company, including approximately \$9 million in annual funding that would otherwise be payable for two years if the Company had not elected to reacquire rights to the research at this time. Although we anticipate entering into future collaborations involving either or both of these programs, there can be no assurance that we will be able to enter into new collaborative agreements or that such collaborations will provide revenues equal to or exceeding those otherwise obtainable under the Pharmacia collaboration.

Conflicts with our collaborators could jeopardize the outcome of our collaborative agreements and our ability to commercialize products.

We intend to conduct proprietary research programs in specific disease and agricultural product areas that are not covered by our collaborative agreements. Our pursuit of opportunities in agricultural and pharmaceutical markets could, however, result in conflicts with our collaborators in the event that any of our collaborators takes the position that our internal activities overlap with those areas that are exclusive to our collaborative agreements, and we should be precluded from such internal activities. Moreover, disagreements with our collaborators could develop over rights to our intellectual property. In addition, our collaborative agreements may have provisions that give rise to disputes regarding the rights and obligations of the parties. Any conflict with our collaborators could lead to the termination of our collaborative agreements, delay collaborative activities, reduce our ability to renew agreements or obtain future collaboration agreements or result in litigation or arbitration and would negatively impact our relationship with existing collaborators.

We have limited or no control over the resources that our collaborators may choose to devote to our joint efforts. Our collaborators may breach or terminate their agreements with us or fail to perform their obligations thereunder. Further, our collaborators may elect not to develop products arising out of our collaborative arrangements or may fail to devote sufficient resources to the development, manufacture, market or sale of such products. Certain of our collaborators could also become our competitors in the future. If our collaborators develop competing products, preclude us from entering into collaborations with their competitors, fail to obtain necessary regulatory approvals, terminate their agreements with us prematurely or fail to devote sufficient resources to the development and commercialization of our products, our product development efforts could be delayed and may fail to lead to commercialized products.

We are deploying unproven technologies, and we may not be able to develop commercially successful products.

You must evaluate us in light of the uncertainties and complexities affecting a biotechnology company. Our technologies are still in the early stages of development. Our research and operations thus far have allowed us to identify a number of product targets for use by our collaborators and our own internal development programs. We are not certain, however, of the commercial value of any of our current or future targets, and we may not be successful in expanding the scope of our research into new fields of pharmaceutical or pesticide research, or

5

other agricultural applications such as enhancing plant traits to produce superior crop yields, disease resistance or increased nutritional content. Significant research and development, financial resources and personnel will be required to capitalize on our technology, develop commercially viable products and obtain regulatory approval for such products.

We have no experience in developing, manufacturing and marketing products and may be unable to commercialize proprietary products.

We recently acquired a product (Rebeccamycin) directed against cancer under our recent collaborative agreement with Bristol Myers-Squibb. Clinical development of Rebeccamycin to date has been conducted by the National Cancer Institute, or the NCI, and manufacturing of this product has been the responsibility of Bristol Myers-Squibb. Rebeccamycin has recently completed Phase I clinical studies and is in early Phase II clinical trials being conducted by the NCI. We are currently in negotiations with the NCI to use the results of the clinical studies they have conducted to date and to determine what additional studies, if any, will be conducted by the NCI or us. There can be no assurance that we will successfully agree upon further development plans, the respective rights and obligations of the parties to conduct additional clinical studies or the timing of such studies. In addition, there can be no assurance that the clinical studies conducted to date will support further clinical development or be accepted by the FDA in conjunction with any application for product approval submitted to the FDA for Rebeccamycin. Moreover, although Bristol Myers-Squibb has provided the NCI with sufficient quantities of Rebeccamycin, development necessary for product approval will require us to either develop internal manufacturing capabilities or retain a third party to manufacture the product. In addition, we have recently hired a new Senior Vice President responsible for clinical development of this product, as well as any new potential products that we may develop. As a result, we have limited experience in clinical development and no experience in manufacturing potential drug products. Accordingly, the development of Rebeccamycin is subject to significant risk and uncertainty, particularly with respect to our ability to successfully develop, manufacture and market Rebeccamycin as a product.

With respect to products developed against our proprietary drug targets, we will rely on our collaborators to develop and commercialize products based on our research and development efforts. We have limited or no experience in using the targets that we identify to develop our own proprietary products. Our recent success in applying our drug development capabilities to our proprietary targets in cancer are subject to significant risk and uncertainty, particularly with respect to our ability to meet currently estimated timelines and goals for completing preclinical development efforts and filing an Investigational New Drug Application for compounds developed. In order for us to commercialize products, we would need to significantly enhance our capabilities with respect to product development, and establish manufacturing and marketing capabilities, either directly or through outsourcing or licensing arrangements. We may not be able to enter into such outsourcing or licensing agreements on commercially reasonable terms, or at all.

Since our technologies have many potential applications and we have limited resources, our focus on a particular area may result in our failure to capitalize on more profitable areas.

We have limited financial and managerial resources. This requires us to focus on product candidates in specific industries and forego opportunities with regard to other products and industries. For example, depending on our ability to allocate resources, a decision to concentrate on a particular agricultural program may mean that we will not have resources available to apply the same technology to a pharmaceutical project. While our technologies may permit us to work in both areas, resource commitments may require trade-offs resulting in delays in the development of certain programs or research areas, which may place us at a competitive disadvantage. Our

decisions impacting resource allocation may not lead to the development of viable commercial products and may divert resources from more profitable market opportunities.

Our competitors may develop products and technologies that make ours obsolete.

The biotechnology industry is highly fragmented and is characterized by rapid technological change. In particular, the area of gene research is a rapidly evolving field. We face, and will continue to face, intense competition from large biotechnology and pharmaceutical companies, as well as academic research institutions, clinical reference laboratories and government agencies that are pursuing research activities similar to ours. Some of our competitors have entered into collaborations with leading companies within our target markets, including some of our existing collaborators. Our future success will depend on our ability to maintain a competitive position with respect to technological advances.

Any products that are developed through our technologies will compete in highly competitive markets. Further, our competitors may be more effective at using their technologies to develop commercial products. Many of the organizations competing with us have greater capital resources, larger research and development staffs and facilities, more experience in obtaining regulatory approvals and more extensive product manufacturing and marketing capabilities. As a result, our competitors may be able to more easily develop technologies and products that would render our technologies and products, and those of our collaborators, obsolete and noncompetitive.

If we are unable to adequately protect our intellectual property, third parties may be able to use our technology, which could adversely affect our ability to compete in the market.

Our success will depend in part on our ability to obtain patents and maintain adequate protection of the intellectual property related to our technologies and products. The patent positions of biotechnology companies, including our patent position, are generally uncertain and involve complex legal and factual questions. We will be able to protect our intellectual property rights from unauthorized use by third parties only to the extent that our technologies are covered by valid and enforceable patents or are effectively maintained as trade secrets. The laws of some foreign countries do not protect intellectual property rights to the same extent as the laws of the U.S., and many companies have encountered significant problems in protecting and defending such rights in foreign jurisdictions. We will continue to apply for patents covering our technologies and products as and when we deem appropriate. However, these applications may be challenged or may fail to result in issued patents. Our existing patents and any future patents we obtain may not be sufficiently broad to prevent others from practicing our technologies or from developing competing products. Furthermore, others may independently develop similar or alternative technologies or design around our patents. In addition, our patents may be challenged, invalidated or fail to provide us with any competitive advantages.

We rely on trade secret protection for our confidential and proprietary information. We have taken security measures to protect our proprietary information and trade secrets, but these measures may not provide adequate protection. While we seek to protect our proprietary information by entering into confidentiality agreements with employees, collaborators and consultants, we cannot assure you that our proprietary information will not be disclosed, or that we can

meaningfully protect our trade secrets. In addition, our competitors may independently develop substantially equivalent proprietary information or may otherwise gain access to our trade secrets.

Litigation or third party claims of intellectual property infringement could require us to spend substantial time and money and adversely affect our ability to develop and commercialize products.

Our commercial success depends in part on our ability to avoid infringing patents and proprietary rights of third parties, and not breaching any licenses that we have entered into with regard to our technologies. Other parties have filed, and in the future are likely to file, patent applications covering genes and gene fragments, techniques and methodologies relating to model systems, and products and technologies that we have developed or intend to develop. If patents covering technologies required by our operations are issued to others, we may have to rely on licenses from third parties, which may not be available on commercially reasonable terms, or at all.

Third parties may accuse us of employing their proprietary technology without authorization. In addition, third parties may obtain patents that relate to our technologies and claim that use of such technologies infringes these patents. Regardless of their merit, such claims could require us to incur substantial costs, including the diversion of management and technical personnel, in defending ourselves against any such claims or enforcing our patents. In the event that a successful claim of infringement is brought against us, we may be required to pay damages and obtain one or more licenses from third parties. We may not be able to obtain these licenses at a reasonable cost, or at all. Defense of any lawsuit or failure to obtain any of these licenses could adversely affect our ability to develop and commercialize products.

The loss of key personnel or the inability to attract and retain additional personnel could impair our ability to expand our operations.

We are highly dependent on the principal members of our management and scientific staff, the loss of whose services might adversely impact the achievement of our objectives and the continuation of existing collaborations. In addition, recruiting and retaining qualified scientific personnel to perform future research and development work will be critical to our success. We do not currently have sufficient executive management and technical personnel to fully execute our business plan. There is currently a shortage of skilled executives and employees with technical expertise, and this shortage is likely to continue. As a result, competition for skilled personnel is intense and turnover rates are high. Although we believe we will be successful in attracting and retaining qualified personnel, competition for experienced scientists from numerous companies, academic and other research institutions may limit our ability to do so.

Our business operations will require additional expertise in specific industries and areas applicable to products identified and developed through our technologies. These activities will require the addition of new personnel, including management and technical personnel and the development of additional expertise by existing employees. The inability to attract such personnel or to develop this expertise could prevent us from expanding our operations in a timely manner, or at all.

Our collaborations with outside scientists may be subject to restriction and change.

We work with scientific advisors and collaborators at academic and other institutions that assist us in our research and development efforts. These scientists are not our employees and may have other commitments that would limit their availability to us. Although our scientific advisors and collaborators generally agree not to do competing work, if a conflict of interest between their work for us and their work for another entity arises, we may lose their services. In addition, although our scientific advisors and collaborators sign agreements not to disclose our confidential information, it is possible that valuable proprietary knowledge may become publicly known through them.

Our potential therapeutic products are subject to a lengthy and uncertain regulatory process that may not result in the necessary regulatory approvals, which could adversely affect our ability to commercialize products.

The Food and Drug Administration, or FDA, must approve any drug or biologic product before it can be marketed in the U.S. Any products resulting from our research and development efforts must also be approved by the regulatory agencies of foreign governments before the product can be sold outside the U.S. Before a new drug application or biologics license application can be filed with the FDA, the product candidate must undergo extensive clinical trials, which can take many years and may require substantial expenditures. The regulatory process also requires preclinical testing. Data obtained from preclinical and clinical activities are susceptible to varying interpretations, which could delay, limit or prevent regulatory approval. In addition, delays or rejections may be encountered based upon changes in regulatory policy for product approval during the period of product development and regulatory agency review. The clinical development and regulatory approval process is expensive and time consuming. Any failure to obtain regulatory approval could delay or prevent us from commercializing products.

Our efforts to date have been primarily limited to identifying targets. Significant research and development efforts will be necessary before any products resulting from such targets can be commercialized. If regulatory approval is granted to any of our products, this approval may impose limitations on the uses for which a product may be marketed. Further, once regulatory approval is obtained, a marketed product and its manufacturer are subject to continual review, and discovery of previously unknown problems with a product or manufacturer may result in restrictions and sanctions with respect to the product, manufacturer and relevant manufacturing facility, including withdrawal of the product from the market.

Social issues may limit the public acceptance of genetically engineered products, which could reduce demand for our products.

Although our technology is not dependent on genetic engineering, genetic engineering plays a prominent role in our approach to product development. For example, research efforts focusing on plant traits may involve either selective breeding or modification of existing genes in the plant under study. Public attitudes may be influenced by claims that genetically engineered products are unsafe for consumption or pose a danger to the environment. Such claims may prevent our genetically engineered products from gaining public acceptance. The commercial success of our future products will depend, in part, on public acceptance of the use of genetically engineered products including drugs and plant and animal products.

The subject of genetically modified organisms has received negative publicity, which has aroused public debate. For example, certain countries in Europe are considering regulations that may ban products or require express labeling of products that contain genetic modifications or are "genetically modified." Adverse publicity has resulted in greater regulation internationally and trade restrictions on imports of genetically altered products. If similar action is taken in the U.S., genetic research and genetically engineered products could be subject to greater domestic regulation, including stricter labeling requirements. To date, our business has not been hampered by these activities. However, such publicity in the future may prevent any products resulting from our research from gaining market acceptance and reduce demand for our products.

Laws and regulations may reduce our ability to sell genetically engineered products that our collaborators or we develop in the future.

Our collaborators or we may develop genetically engineered agricultural and animal products. The field-testing, production and marketing of genetically engineered products are subject to

regulation by federal, state, local and foreign governments. Regulatory agencies administering existing or future regulations or legislation may prevent us from producing and marketing genetically engineered products in a timely manner or under technically or commercially feasible conditions. In addition, regulatory action or private litigation could result in expenses, delays or other impediments to our product development programs and the commercialization of products.

The FDA has released a policy statement stating that it will apply the same regulatory standards to foods developed through genetic engineering as it applies to foods developed through traditional plant breeding. Genetically engineered food products will be subject to premarket review, however, if these products raise safety questions or are deemed to be food additives. Our products may be subject to lengthy FDA reviews and unfavorable FDA determinations if they raise questions regarding safety or our products are deemed to be food additives.

The FDA has also announced that it will not require genetically engineered agricultural products to be labeled as such, provided that these products are as safe and have the same nutritional characteristics as conventionally developed products. The FDA may reconsider or change its policies, and local or state authorities may enact labeling requirements, either of which could have a material adverse effect on our ability or the ability of our collaborators to develop and market products resulting from our efforts.

We use hazardous chemicals and radioactive and biological materials in our business. Any claims relating to improper handling, storage or disposal of these materials could be time consuming and costly.

Our research and development processes involve the controlled use of hazardous materials, including chemicals, radioactive and biological materials. Our operations produce hazardous waste products. We cannot eliminate the risk of accidental contamination or discharge and any resultant injury from these materials. Federal, state and local laws and regulations govern the use, manufacture, storage, handling and disposal of hazardous materials. We may be sued for any injury or contamination that results from our use or the use by third parties of these materials, and our liability may exceed our insurance coverage and our total assets. Compliance with environmental laws and regulations may be expensive, and current or future environmental regulations may impair our research, development and production efforts.

In addition, our collaborators may use hazardous materials in connection with our collaborative efforts. To our knowledge, their work is performed in accordance with applicable biosafety regulations. In the event of a lawsuit or investigation, however, we could be held responsible for any injury caused to persons or property by exposure to, or release of, these hazardous materials use by these parties. Further, we may be required to indemnify our collaborators against all damages and other liabilities arising out of our development activities or products produced in connection with these collaborations.

We expect that our quarterly results of operations will fluctuate, and this fluctuation could cause our stock price to decline, causing investor losses.

Our quarterly operating results have fluctuated in the past and are likely to fluctuate in the future. A number of factors, many of which we cannot control, could subject our operating results and stock price to volatility, including:

- recognition of license, milestone or other fees;
- payments of licensing fees to third parties;
- acceptance of our technologies and platforms;

- the success rate of our discovery efforts leading to milestones and royalties;
- the introduction of new technologies or products by our competitors;
- the timing and willingness of collaborators to commercialize our products;
- our ability to enter into new collaborative relationships;
- the termination or non-renewal of existing collaborations; and
- general and industry-specific economic conditions that may affect our collaborators' research and development expenditures.

A large portion of our expenses, including expenses for facilities, equipment and personnel, are relatively fixed in the short term. In addition, we expect operating expenses to increase significantly during the next year. Accordingly, if our revenues decline or do not grow as anticipated due to the expiration of existing contracts or our failure to obtain new contracts, our inability to meet milestones or other factors, we may not be able to correspondingly reduce our operating expenses. Failure to achieve anticipated levels of revenues could therefore significantly harm our operating results for a particular fiscal period.

Due to the possibility of fluctuations in our revenues and expenses, we believe that quarter-to-quarter comparisons of our operating results are not a good indication of our future performance. As a result, in some future quarters, our operating results may not meet the expectations of stock market analysts and investors, which could result in a decline in the price of our stock.

Our stock price may be extremely volatile.

We believe the trading price of our common stock will remain highly volatile and may fluctuate substantially due to factors such as the following:

- the announcement of new products or services by us or our competitors;
- quarterly variations in our or our competitors' results of operations;
- failure to achieve operating results projected by securities analysts;
- changes in earnings estimates or recommendations by securities analysts;
- developments in the biotechnology industry;
- acquisitions of other companies or technologies; and
- general market conditions and other factors, including factors unrelated to our operating performance or the operating performance of our competitors.

These factors and fluctuations, as well as general economic, political and market conditions, may materially adversely affect the market price of our common stock.

In the past, following periods of volatility in the market price of a company's securities, securities class action litigation has often been instituted. A securities class action suit against us could result in substantial costs and divert management's attention and resources, which could have a material and adverse effect on our business.

We are exposed to risks associated with acquisitions.

We have made, and may in the future make, acquisitions of, or significant investments in, businesses with complementary products, services and/or technologies. Acquisitions involve numerous risks, including, but not limited to:

- difficulties and increased costs in connection with integration of the personnel, operations, technologies and products of acquired companies;
- diversion of management's attention from other operational matters;
- the potential loss of key employees of acquired companies;
- the potential loss of key collaborators of the acquired companies;
- lack of synergy, or the inability to realize expected synergies, resulting from the acquisition; and
- acquired intangible assets becoming impaired as a result of technological advancements or worse-than-expected performance of the acquired company.

Mergers and acquisitions are inherently risky, and the inability to effectively manage these risks could materially and adversely affect our business, financial condition and results of operations.

Currency fluctuations may impair our financial results.

With our acquisition of Artemis, some of our operating expenses are denominated in foreign currencies. To the extent that our operating expenses are denominated in foreign currencies, our operating results may be adversely affected by changes in exchange rates. Given the substantial volatility of currency exchange rates, and constantly changing currency exposures, we cannot predict the effect of exchange rate fluctuations on our future operating results. Although we engage in foreign currency hedging transactions from time to time, these hedging transactions can be costly, and therefore, we do not attempt to cover all potential foreign currency exposures. These hedging techniques do not eliminate all of the effects of foreign currency fluctuations on anticipated revenue.

If product liability lawsuits are successfully brought against us, we could face substantial liabilities that exceed our resources.

We may be held liable if any product our collaborators or we develop causes injury or is found otherwise unsuitable during product testing, manufacturing, marketing or sale. Although we intend to obtain general liability and product liability insurance, this insurance may be prohibitively expensive, or may not fully cover our potential liabilities. Inability to obtain sufficient insurance coverage at an acceptable cost or to otherwise protect ourselves against potential product liability claims could prevent or inhibit the commercialization of products developed by our collaborators or us.

Our facilities are located near known earthquake fault zones, and the occurrence of an earthquake or other catastrophic disaster could cause damage to our facilities and equipment, which could require us to cease or curtail operations.

Given our location, our facilities are vulnerable to damage from earthquakes. We are also vulnerable to damage from other types of disasters, including fire, floods, power loss, communications failures and similar events. If any disaster were to occur, our ability to operate our business at our facilities would be seriously, or potentially completely, impaired. In addition, the unique nature of our research activities could cause significant delays in our programs and make it

difficult for us to recover from a disaster. The insurance we maintain may not be adequate to cover our losses resulting from disasters or other business interruptions. Accordingly, an earthquake or other disaster could materially and adversely harm our ability to conduct business.

Future sales of our common stock may depress our stock price.

If our stockholders sell substantial amounts of our common stock (including shares issued upon the exercise of outstanding options and warrants) in the public market, the market price of our common stock could fall. These sales also might make it more difficult for us to sell equity or equity-related securities in the future at a time and price that we deemed appropriate. In October 2000, a significant number of shares of our common stock held by existing stockholders became freely tradable, subject in some instances to the volume and other limitations of Rule 144. Sales of these shares and other shares of common stock held by existing stockholders could cause the market price of our common stock to decline. In addition, up to 1.7 million shares of our common stock held by former investors in Artemis will become freely tradable in August 2001 following the expiration of a 90-day lock-up for shares acquired in the Artemis acquisition.

Some of our existing stockholders can exert control over us, and may not make decisions that are in the best interests of all stockholders.

Due to their combined stock holdings, our officers, directors and principal stockholders (stockholders holding more than 5% of our common stock) acting together, may be able to exert significant influence over all matters requiring stockholder approval, including the election of directors and approval of significant corporate transactions. In addition, this concentration of ownership may delay or prevent a change in control of our company, even when a change may be in the best interests of our stockholders. In addition, the interests of these stockholders may not always coincide with our interests as a company or the interests of other stockholders. Accordingly, these stockholders could cause us to enter into transactions or agreements that you would not approve.

CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS

Some of the statements in this prospectus and the documents incorporated by reference are forward-looking statements. These statements are based on our current expectations, assumptions, estimates and projections about our business and our industry, and involve known and unknown risks, uncertainties and other factors that may cause our or our industry's results, levels of activity, performance or achievement to be materially different from any future results, levels of activity, performance or achievements expressed or implied in or contemplated by the forward-looking statements. Words such as "believe," "anticipate," "expect," "intend," "plan," "will," "may," "should," "estimate," "predict," "potential," "continue," or the negative of such terms or other similar expressions, identify forward-looking statements. In addition, any statements that refer to expectations, projections or other characterizations of future events or circumstances are forward-looking statements. Our actual results could differ materially from those anticipated in such forward-looking statements as a result of several factors more fully described under the caption "Risk Factors" and in the documents incorporated by reference. The forward-looking statements made in this prospectus relate only to events as of the date on which the statements are made.

USE OF PROCEEDS

Unless otherwise indicated in the prospectus supplement, the net proceeds from the sale of common stock offered by this prospectus will be used for general corporate purposes, including capital expenditures and to meet working capital needs. These purposes may also include repaying indebtedness. In addition, from time to time we may evaluate the acquisition of businesses,

products and technologies for which a portion of the net proceeds may be used; however, we currently are not planning or negotiating any such transactions. Pending such uses, we may invest the net proceeds in interest-bearing securities.

PLAN OF DISTRIBUTION

We may sell the common stock offered under this prospectus:

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

We may sell the common stock offered under this prospectus from time to time in one or more transactions:

- at a fixed price or prices, which may be changed from time to time;
- at market prices prevailing at the times of sale;
- at prices related to such prevailing market prices; or
- at negotiated prices.

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

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

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

We may grant underwriters who participate in the distribution of our common stock an option to purchase additional shares of common stock to cover over-allotments, if any, in connection with the distribution.

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

DESCRIPTION OF CAPITAL STOCK

Our authorized capital stock consists of 100,000,000 shares of common stock, \$0.001 par value per share, and 10,000,000 shares of preferred stock, \$0.001 par value per share.

Common Stock

As of May 31, 2001, there were 48,533,903 shares of Exelixis common stock outstanding, held of record by approximately 923 stockholders. The holders of common stock are entitled to one vote for each share held of record on all matters submitted to a vote of the stockholders. Accordingly, holders of a majority of the shares of common stock entitled to vote in any election of directors

14

may elect all of the directors standing for election. Subject to preferences that may be applicable to any preferred stock outstanding at the time, the holders of outstanding shares of common stock are entitled to receive ratably any dividends out of assets legally available therefor as our board of directors may from time to time determine. Upon liquidation, dissolution or winding up of Exelixis, holders of common stock are entitled to share ratably in all assets remaining after payment of liabilities and the liquidation preference of any then outstanding shares of preferred stock. Holders of common stock have no preemptive or conversion rights or other subscription rights. There are no redemption or sinking fund provisions applicable to the common stock. All outstanding shares of Exelixis common stock are, and all shares of Exelixis common stock to be outstanding upon the closing of this offering will be, fully paid and nonassessable.

Preferred Stock

Our board of directors has the authority to issue up to 10,000,000 shares of Exelixis preferred stock, in one or more series and to determine the rights, preferences, privileges and restrictions of the preferred stock, including dividend rights, conversion rights, voting rights, terms of redemption, liquidation preferences, sinking fund terms and the number of shares constituting any series or the designation of any series. The issuance of Exelixis preferred stock could diminish the voting power of holders of Exelixis common stock, and the likelihood that holders of Exelixis preferred stock will receive dividend payments and payments upon liquidation may have the effect of delaying, deferring or preventing a change in control of Exelixis. We have no present plans to issue any shares of Exelixis preferred stock.

Warrants

As of May 31, 2001, the following warrants to purchase an aggregate of 496,220 shares of Exelixis common stock were outstanding:

- a warrant to purchase 71,428 shares of common stock at an exercise price of \$1.13 per share. The warrant expires on April 14, 2005;
- three warrants to purchase an aggregate of 106,875 shares of common stock at an exercise price of \$4.00 per share. The warrants expire on April 14, 2005;
- three warrants to purchase an aggregate of 78,750 shares of common stock at an exercise price of \$13.00 per share. The warrants expire on April 14, 2005;
- 13 warrants to purchase an aggregate of 166,251 shares of common stock at an exercise price of \$20.00 per share. The warrants expire on December 31, 2001;
- a warrant to purchase 29,167 shares of common stock at an exercise price of \$20.98 per share. The warrant expires on December 31, 2001; and
- two warrants to purchase an aggregate of 43,750 shares of common stock at an exercise price of \$20.00 per share. The warrants expire on September 30, 2004.

The warrants contain provisions for the adjustment of the exercise price and the aggregate number of shares that may be issued upon the exercise of the warrants if a stock dividend, stock split, reorganization, reclassification or consolidation occurs.

Registration Rights

Holders of an aggregate of 23,199,818 shares of common stock and holders of warrants to purchase an aggregate of 71,428 shares of common stock will be entitled to rights to register these shares under the Securities Act. These rights are provided under the fourth amended and restated securityholders' agreement, dated January 28, 1999, under the fourth amended and restated

registration rights agreement, dated February 26, 1999, and under agreements with similar registration rights. If we propose to register any of our securities under the Securities Act, either for our own account or for the account of others, the holders of these shares with registration rights are entitled to notice of the registration and are entitled to include, at our expense, their shares of common stock in the registration and any related underwriting, provided, among other conditions, that the underwriters may limit the number of shares to be included in the registration and in some cases, exclude these shares entirely. In addition, the holders of these shares may require us, at our expense and on not more than two occasions, to file a registration statement under the Securities Act with respect to their shares of common stock, and we will be required to use our best efforts to effect the registration. Further, the holders may require us, at our expense, to register their shares on Form S-3 when this form is available. In addition, in connection with our sale of shares of common stock to Bristol-Myers Squibb on July 17, 2001 we have agreed to file a resale registration statement on Form S-3 for the 600,600 shares purchased by Bristol-Myers Squibb within 45 days of the purchase date.

Delaware General Corporation Law and Certain Charter Provisions.

In general, Section 203 of the Delaware General Corporation Law prohibits a publicly-held Delaware corporation from engaging in any business combination with any interested stockholder for a period of three years following the date that the stockholder became an interested stockholder unless:

- prior to that date, the corporation's board of directors approved either the business combination or the transaction that resulted in the stockholder becoming an interested stockholder;
- upon consummation of the transaction that resulted in the stockholder becoming an interested stockholder, the interested stockholder owned at least 85% of the voting stock of the corporation outstanding at the time the transaction commenced, excluding those shares owned by persons who are directors and also officers, and by employee stock plans in which shares held subject to the plan will be tendered in a tender or exchange offer; or
- on or subsequent to that date, the business combination is approved by the corporation's board of directors and is authorized at an annual or special meeting of stockholders, and not by written consent, by the affirmative vote of at least two-thirds of the outstanding voting stock not owned by the interested stockholder.

Section 203 defines "business combination" to include:

- any merger or consolidation involving the corporation and the interested stockholder;
- any sale, transfer, pledge or other disposition involving the interested stockholder of 10% or more of the assets of the corporation;
- subject to exceptions, any transaction that results in the issuance or transfer by the corporation of any stock of the corporation to the interested stockholder; and
- the receipt by the interested stockholder of the benefit of any loans, advances, guarantees, pledges or other financial benefits provided by or through the corporation.

In general, Section 203 defines an interested stockholder as any entity or person beneficially owning 15% or more of the outstanding voting stock of the corporation and any entity or person affiliated with or controlling or controlled by the entity or person.

Our certificate of incorporation requires that any action required or permitted to be taken by our stockholders must be effected at a duly called annual or special meeting of stockholders and may not be effected by a consent in writing. Additionally, our certificate of incorporation:

- substantially limits the use of cumulative voting in the election of directors;
- provides that the authorized number of directors may be changed only by resolution of its board of directors; and
- authorizes its board of directors to issue blank check preferred stock to increase the amount of outstanding shares.

Our bylaws provide that candidates for director may be nominated only by our board of directors or by a stockholder who gives written notice to us no later than 60 days prior, nor earlier than 90 days prior, to the first anniversary of the last annual meeting of stockholders. Our board of directors currently consists of ten members, divided into three classes. As a result, a portion of the board of directors will be elected each year. The board of directors may appoint new directors to fill vacancies or newly created directorships. The restated bylaws also limit who may call a special meeting of stockholders.

Delaware law and these charter provisions may have the effect of deterring hostile takeovers or delaying changes in control of our management, which could depress the market price of our common stock.

Transfer Agent and Registrar

The transfer agent and registrar for Exelixis common stock is Mellon Investor Services LLC.

EXPERTS

The consolidated financial statements incorporated in this prospectus by reference to the Annual Report on Form 10-K for the year ended December 31, 2000, have been so incorporated in reliance on the report of PricewaterhouseCoopers LLP, independent accountants, given on the authority of said firm as experts in auditing and accounting.

WHERE YOU CAN FIND MORE INFORMATION ABOUT EXELIXIS

You should rely only on the information provided or incorporated by reference in this prospectus or any prospectus supplement. We have authorized no one to provide you with different information. We are not making an offer of these securities in any state where the offer is not permitted. You should not assume that the information in this prospectus or any prospectus supplement is accurate as of any date other than the date on the front of the document.

We have filed with the SEC a registration statement on Form S-3 to register the common stock offered by this prospectus. However, this prospectus does not contain all of the information contained in the registration statement and the exhibits and schedules to the registration statement. We strongly encourage you to carefully read the registration statement and the exhibits and schedules to the registration statement.

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

Fifth Street, N.W., Washington, DC 20549 or at the SEC's other public reference rooms located in New York, New York and Chicago, Illinois. You can request copies of these documents by contacting the SEC and paying a fee for the copying cost. Please call the SEC at 1-800-SEC-0330 for further information on the public reference rooms. Our SEC filings are also available to the public from the SEC's website at www.sec.gov.

The SEC allows us to "incorporate by reference" the information contained in documents that we file with them, which means that we can disclose important information to you by referring to those documents. The information incorporated by reference is considered to be part of this prospectus. Information in this prospectus supersedes information incorporated by reference that we filed with the SEC prior to the date of this prospectus, while information that we file later with the SEC will automatically update and supersede this information. We incorporate by reference the documents listed below and any future filings we will make with the SEC under Sections 13(a), 13(c), 14 or 15(d) of the Securities Exchange Act of 1934.

The following documents filed with the SEC are incorporated by reference in this prospectus:

1. Our Annual Report on Form 10-K for the year ended December 31, 2000;
2. Our Quarterly Report on Form 10-Q for the quarter ended March 31, 2001;
3. Our Current Reports on Form 8-K, filed on May 15, 2001 pursuant to Item 2 of such report, on July 18, 2001 and on July 26, 2001 pursuant to Item 5 of such report; and
4. The description of our common stock set forth in our registration statement on Form 8-A, filed with the SEC on April 6, 2000.

We will furnish without charge to you, on written or oral request, a copy of any or all of the documents incorporated by reference, including exhibits to these documents. You should direct any requests for documents to Exelixis, Inc., Attention: Investor Relations, 170 Harbor Way, P.O. Box 511, South San Francisco, California 94083, telephone: (650) 837-7000.

No dealer, salesperson or other person is authorized to give any information or to represent anything not contained in the prospectus and the prospectus supplement. You must not rely on any unauthorized information or representations. The prospectus and the prospectus supplement are an offer to sell only the shares offered hereby, but only under circumstances and in jurisdictions where it is lawful to do so. The information contained in the prospectus and the prospectus supplement is current only as of their respective dates.

TABLE OF CONTENTS

Prospectus Supplement

	Page
About This Prospectus Supplement	S-i
Prospectus Supplement Summary	S-1
Risk Factors	S-6
Cautionary Note Regarding Forward-Looking Statements	S-17
Use of Proceeds	S-18

Price Range of Common Stock	S-19
Dividend Policy	S-19
Capitalization	S-20
Dilution	S-21
Underwriting	S-22
Legal Matters	S-24
Experts	S-24

Prospectus

About This Prospectus	1
Exelixis	1
Risk Factors	3
Cautionary Note Regarding Forward-Looking Statements	13
Use of Proceeds	13
Plan of Distribution	14
Description of Capital Stock	14
Legal Matters	17
Experts	17
Where You Can Find More Information About Exelixis	17

10,000,000 Shares

Exelixis, Inc.

Common Stock



**Goldman, Sachs & Co.
SG Cowen**

QuickLinks

[ABOUT THIS PROSPECTUS SUPPLEMENT](#)
[PROSPECTUS SUPPLEMENT SUMMARY](#)

[Exelixis, Inc.](#)

[The Offering](#)

[Summary Consolidated Financial Data](#)

[RISK FACTORS](#)

[CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS](#)

[USE OF PROCEEDS](#)

[PRICE RANGE OF COMMON STOCK](#)

[DIVIDEND POLICY](#)

[CAPITALIZATION](#)

[DILUTION](#)

[UNDERWRITING](#)

[LEGAL MATTERS](#)

[EXPERTS](#)

[TABLE OF CONTENTS](#)

[ABOUT THIS PROSPECTUS](#)

[EXELIXIS](#)

[RISK FACTORS](#)

[CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS](#)

[USE OF PROCEEDS](#)

[PLAN OF DISTRIBUTION](#)

[DESCRIPTION OF CAPITAL STOCK](#)

[LEGAL MATTERS](#)

[EXPERTS](#)

[WHERE YOU CAN FIND MORE INFORMATION ABOUT EXELIXIS](#)

[TABLE OF CONTENTS Prospectus Supplement](#)