“We are charting an ambitious path toward our goal of making a positive impact on the lives of patients with cancer.”
Why do we need better medicines to treat cancer?

According to the American Cancer Society, more than 1.4 million new cancer cases and nearly 560,000 cancer deaths are expected in 2007 in the United States alone. Despite recent remarkable progress, the overall relative survival rate for all cancers is still only 66 percent, and significantly lower for some cancers. Patients who initially respond to current therapies may relapse and find themselves, without options, after treatment failure or drug resistance. Creating new treatment options requires new classes of drugs that target novel pathways. Exelixis is dedicated to the development of novel medicines to meet the challenges and needs of cancer patients now and in the future.

Left, ALAIN MITA, MD, Clinical Investigator, Cancer Therapy and Research Center, Assistant Professor of Medicine, University of Texas Health Science Center at San Antonio.
Right, HEATHER HERMSTAD, XL999 patient.
At Exelixis, we recognize that to advance the treatment of cancer we must increase our understanding of the disease itself. A key component of our strategy is to gain insight into the complex molecular mechanisms that drive the growth, survival, and resistance of cancer cells, and utilize this knowledge to simplify, streamline, and inform the entire drug development process. This approach allows us to be both innovative and strategic while moving quickly in the right direction. We believe that our aggressive, yet thoughtful efforts in the laboratory will help us to make a positive impact on patients in the clinic.

“Our comprehensive research and development engine provides critical insights and knowledge to target the fundamental basis of cancer and other serious illnesses.”

Michael Morrissey, PhD
President, Research and Development
In recent years, insights gleaned from the work of many researchers has dramatically changed how we think about cancer. Whereas cancer once was classified only at the level of cells and tissues, we are now gaining a fundamental understanding of the genes, proteins, and biochemical pathways that drive the disease. At Exelixis, this knowledge is a foundational element of our drug discovery and development strategy.

Recognizing that diverse molecular pathways impact the development, progression, spread, and survival of different cancer types, we are building a pipeline of compounds with unique target profiles. This approach allows us to develop individual drug candidates for those cancer indications and patient populations where the pharmacology of the compound addresses the biology of the disease.

Our ability to take this approach is a result of our extensive expertise in pathway biology, and is supported by an integrated approach to discovery, translational medicine, and clinical development. We believe that extensive discovery research isn’t just good science - it is also critical to good medicine. By understanding target biology and compound activity early on, we seek to identify those patients most likely to benefit from a given drug candidate, and pursue a clearly defined path through the clinic and toward the market.

Our knowledge of MET biology and our ability to incorporate these insights into the clinical development of XL880 exemplifies the power of this approach. XL880 is a potent inhibitor of MET, one of a number of proteins called receptor tyrosine kinases (RTKs) that play important roles in cancer cell growth, metastasis, and survival. MET is directly involved in regulating the proliferation of several types of tumor cells and interacts with other signaling pathways to promote the development of new blood vessels (angiogenesis) necessary to support tumor growth. The MET protein is activated in all patients with the hereditary form of papillary renal cell carcinoma (PRC), and in some patients with gastric cancer, the sporadic form of PRC, and head and neck cancer. Additional data implicate MET as a key molecule in the development of many other tumor types as well. Furthermore, the gene for MET is amplified in certain sub-types of gastric carcinoma. In preclinical studies, XL880 has been shown to cause substantial tumor regression in preclinical models of breast, colon, and non-small cell lung cancer, and glioblastoma.

In the Phase I trial of XL880, tumors in three out of the four PRC patients enrolled in the trial responded to XL880. Based on these results, and the detailed knowledge of the role that MET plays in PRC, the first Phase II trial of XL880 was initiated in this indication. This approach has the potential to provide PRC patients with a new treatment option while providing us with a clear path to market in an indication with significant unmet medical need. There were many additional signals of activity in the Phase I trial, and as a result we have planned a broad Phase II program, initially including trials in gastric cancer and head and neck cancer: two additional biologically relevant indications.

The XL880 development strategy is a paradigm for how we expand and advance our clinical pipeline. We identify interesting targets, elucidate the biology of these targets and their pathways, select and optimize compounds with compelling target inhibition profiles, and then evaluate these compounds in biologically relevant patient populations.

We have developed other inhibitors for many of the targets and pathways that are key drivers of human tumors. For example, the RAS/RAF/MEK/ERK pathway, which is frequently activated in human tumors and is required for transmission of growth-promoting signals from numerous RTKs, is inhibited by both XL281 and XL518. Activating mutations in RAS and RAF occur in 30 percent of all tumors and in approximately 60 percent of melanomas, respectively. Another important pathway frequently disregulated in human tumors, and which contributes to tumor pathology is the PI3K pathway. Exelixis compounds XL418, XL147, and XL765 all target this pathway at different points. XL228 is a potent inhibitor of BCR-ABL, which is activated in chronic myelogenous leukemia (CML). Currently marketed inhibitors of this target provide an effective therapy for CML. However, these patients treated with these inhibitors have exhibited drug-resistance, which have been associated with the development of mutations in the gene for BCR-ABL. XL228 has been shown in preclinical studies to retain high potency against these mutants of BCR-ABL, which have become resistant to the current generation of inhibitors.

We have developed other inhibitors for many of the targets and pathways that are key drivers of human tumors. For example, the RAS/RAF/MEK/ERK pathway, which is frequently activated in human tumors and is required for transmission of growth-promoting signals from numerous RTKs, is inhibited by both XL281 and XL518. Activating mutations in RAS and RAF occur in 30 percent of all tumors and in approximately 60 percent of melanomas, respectively. Another important pathway frequently disregulated in human tumors, and which contributes to tumor pathology is the PI3K pathway. Exelixis compounds XL418, XL147, and XL765 all target this pathway at different points. XL228 is a potent inhibitor of BCR-ABL, which is activated in chronic myelogenous leukemia (CML). Currently marketed inhibitors of this target provide an effective therapy for CML. However, these patients treated with these inhibitors have exhibited drug-resistance, which have been associated with the development of mutations in the gene for BCR-ABL. XL228 has been shown in preclinical studies to retain high potency against these mutants of BCR-ABL, which have become resistant to the current generation of inhibitors.

These are just a few examples of Exelixis compounds that are being developed to address specific alterations in genes and proteins that are important for the growth and survival of tumor cells, and for the development of resistance to current therapies.

The insights we have accumulated around these targets and our knowledge of the roles that they play in specific cancer indications help define our clinical strategies. By keeping biology integral to the process, even as we advance into and through the clinic, we believe that we can increase the likelihood that we – and patients – will succeed.
“With our integrated approach to R&D, we are leveraging data across the development continuum. Disease biology shapes our clinical strategies and provides a clear path to the market, while clinical data inform our drug discovery initiatives.”

Gisela M. Schwab, MD
Senior Vice President and Chief Medical Officer

The fields of medical and molecular oncology are highly dynamic, driven by discoveries in the lab and experience in the clinic. At Exelixis, we are establishing a seamlessly integrated R&D organization with the critical mass to leverage data effectively and the flexibility to incorporate new insights into our strategies. By making rational and data-driven decisions at each point along the drug development continuum, we strengthen the entire process. Extensive target characterization enhances our ability to select indications and patient populations in which our drug candidates are most likely to provide benefit, and our experiences in the clinic help us identify additional areas of unmet medical need on which we can focus future discovery and development efforts.
Our belief in the value of an integrated research and development process is itself based on a growing body of data from numerous product candidates in our pipeline. The strategies we have used in advancing compounds such as XL647, XL784, XL820, and XL880 highlight the value of this approach.

With XL647, we also thought to develop a single compound that would simultaneously inhibit EGFR, HER2, and VEGFR2 with high potency. Each of these targets is impacted individually by currently approved cancer therapies. While these therapies have provided clinical benefit in some cancer indications, there is substantial room for improvement, and for more potent compounds. In addition, tumors in many patients treated with RTK inhibitors ultimately become resistant to the drugs through mutation of the RTK. XL647 was designed as a second-generation inhibitor that retains activity against most of the mutations that confer resistance to some of the first-generation compounds currently on the market.

In the development of XL647, we sought to develop a single compound that would simultaneously inhibit EGFR, HER2, and VEGFR2 with high potency and with similar kinetics. In addition, we designed our inhibitor to make unique binding contacts with these targets so it would retain activity against the mutations that confer resistance to many of the first-generation inhibitors. Iterative screening and medicinal chemistry guided by knowledge of the atomic structures of the targets and the drug resulted in the identification of XL647 as a compound that met our stringent criteria. In this manner, the discovery of XL647 was predicated on these two indications.

As clinical data helped to shape the discovery and early development of XL647, our understanding of target and disease biology is guiding the Phase II program for this compound. EGFR and HER2 are known to be overexpressed in many cases of non-small cell lung cancer (NSCLC) and breast cancer. Based on this biology, our Phase II development program for XL647 is focused on these two indications.

A Phase II trial of XL647 in untreated patients with advanced (Stage IIIb or IV) NSCLC already has been initiated. Incorporating demographic information about EGFR expression and sensitivity of different EGFR variants to inhibition, this study has been designed to include an enriched patient population known to be more responsive to EGFR inhibition.

A second Phase II trial in NSCLC has been designed similarly. It has become evident that many patients who initially respond to EGFR inhibitors develop drug resistance associated with specific EGFR mutations, and subsequently experience relapse of their disease. Because XL647 has been shown in preclinical studies to retain patient activity against these mutant forms of EGFR, we are planning a Phase II trial of XL647 in NSCLC patients who have relapsed following an initial response to erlotinib, an approved EGFR inhibitor. This trial is expected to begin in 2007. Matching the activity of XL647 with the biology of specific patient populations may provide a more direct path to the market.

XL784, which is being evaluated in a Phase II trial in patients with diabetic kidney disease, is a potent inhibitor of the metalloprotease enzymes ADAM-10 and MMP-2. Oral administration of XL784 in preclinical models dramatically reduced kidney damage as a result of either diabetes or hypertension. XL784 may provide a novel approach to preserving or slowing the loss of kidney function in patients with proteinuria associated with diabetic kidney disease. We anticipate results from this Phase II trial in 2007.

XL820, which is expected to enter Phase II development in 2007, inhibits multiple RTKs involved in tumor cell growth and angiogenesis, including KIT. Mutational activation of KIT is causative for most cases of gastrointestinal stromal tumor (GIST). Based on the potent inhibition of KIT by XL820 in preclinical studies, and the clinical efficacy of approved KIT inhibitors, GIST is a compelling indication for XL820 Phase II trials. Moreover, XL820 is active against many mutant forms of KIT associated with resistance to current therapies.

XL880 demonstrates how we incorporate biomarkers into our development strategies. Early on in the development of XL880 we identified a number of pathways and proteins that are affected by inhibition of MET. In the Phase I trial of XL880, we analyzed these biomarkers in numerous tumor samples and observed changes that were consistent with MET inhibition. These data provided initial evidence that XL880 was capable of effectively inhibiting its key target in human tumors. Biomarkers may also help guide treatment strategies by making it possible to assess patient response early in treatment.

At Exelixis, we have built an innovative research and development organization that combines the critical mass and resources of a large pharmaceutical company with the speed and agility more typical of the biotechnology industry.
Value has a unique meaning to each of Exelixis’ stakeholders. For patients, it is having new and better treatment options. For investors, it is gaining a return on their investment. For the Exelixis team, it is making a positive impact on the lives of patients with cancer. We are pursuing a business strategy designed to create value by any definition. Diversifying our pipeline in terms of compounds and ownership reduces our risk of failure while allowing us to retain a significant portion of our programs’ potential over the long term. Targeting diverse cancer indications gives us the opportunity to help many patients, and strategic partnerships bring in critical resources that may enable us to bring new therapies to these patients more rapidly. And what could be more valuable than that?

“Our diverse pipeline, world-class R&D capabilities, and our balance of partnered and proprietary programs combine to enhance our ability to bring new therapies to patients in need, while creating value for our investors.”

George A. Scangos, PhD
President and Chief Executive Officer
Exelixis is advancing multiple drug candidates toward the market in order to build a vibrant and sustainable business. In the process, we intend to capitalize on the amazing opportunities for improved therapeutics that result from a growing body of knowledge about disease pathways and improvements in drug discovery technologies. We are supported in this ambitious effort by a broad and renewable pool of drug candidates, the intellectual and financial resources to develop them, and the flexibility to thrive in the dynamic environment of oncology drug development.

Our approach matches the target inhibition profile of an individual drug candidate with well-defined patient populations that are not well served by currently approved therapies which has the potential to provide a clear path to product approval and for Exelixis by potentially shortening the time to establishing a sustainable revenue stream.

Exelixis is advancing by speeding new therapies to the market, and for Exelixis by offering partnerships we executed in 2006 with Bristol-Myers Squibb (BMS) and Genentech, Inc. The BMS partnership is a broad alliance to discover and develop three novel oncology compounds, while the Genentech collaboration is focused on the development of XL538, a small-molecule inhibitor of MEK. In both collaborations, we have the option to co-promote compounds commercialized in the United States and will receive royalties on any compounds commercialized in other territories. Thus, we utilize partnerships as an alternative pathway toward the market. This approach is exemplified by the partnerships we executed in 2006 with Bristol-Myers Squibb Company (BMS) and Genentech, Inc.

Our agreement with Symphony Capital Partners, L.P., also highlights our ability to enhance our development capabilities and reduce our financial risk. Through this transaction, we have accessed $80 million in external capital to fund Phase II programs for XL647, XL784, and XL999. The transaction gives us the ability to regain rights to these compounds for later-stage clinical trials, while off-loading the financial risk if we do not consider them past Phase II.

As we focus on long-term value for all our stakeholders, we are aware that creating a sustainable business requires a renewable portfolio of successful, proprietary products. The strength of our pipeline allows us to diversify risk over multiple compounds, partnerships, and clinical financing vehicles, while enabling us to execute transactions in which we retain increasing equity in partnered programs.

For example, our GlaxoSmithKline (GSK) partnership has been focused on 12 programs, of which GSK may select up to three. Exelixis retains rights to the programs not selected by GSK, and can develop them or leverage them into additional partnerships. We also will receive milestones and royalties on any of the selected programs that GSK may commercialize. Our 2005 collaboration with Genentech provides us with milestones and royalties for any cancer therapies commercialized under the agreement, but gives us the option for profit sharing in the field of inflammation or the field of tissue growth and repair. Building additional value, our most recent collaborations – with Genentech around MEK and with BMS in oncology drug development – are profit-sharing alliances in which we have retained significant equity in multiple potential product opportunities. Of the 16 compounds now in the Exelixis pipeline, we retain full rights to up to ten and we have retained significant share of the profits from the six partnered compounds. With so many high-quality compounds, we have the uncommon ability to leverage partnerships for more rapid growth while simultaneously advancing proprietary programs that are the key to our future as an independent, sustainable organization that will have a positive impact on patients.

Our full funding strategy – executing on existing partnerships, establishing new alliances, utilizing clinical funding vehicles, and accessing equity financing – has secured more than $500 million in cash in the past two years. Significantly, over 70 percent of this funding was not raised through public offerings. This retains value for our investors today without limiting our ability to create value for patients and our company tomorrow and in the future.

### Pipeline: The strength of our drug discovery and development capabilities has enabled us to build a robust pipeline of promising therapeutic candidates. With 12 compounds in clinical development – and at least three more expected to enter the clinic each year for the foreseeable future – we have diverse opportunities to create value through partnerships and by advancing products toward the market.
Advancing better medicines
to treat cancer.

Our goal is to develop drugs that fundamentally improve the lives of cancer patients.
In everything we do – in the lab, in the clinic, in the boardroom – we strive to find ways to do things better.
Ways to work smarter and move faster.
Better ways to better medicines.

To Our Shareholders
Seven years ago, Exelixis turned its focus onto developing and commercializing first-in-class or best-in-class therapies. This was not a move away from our foundational competencies in pathway biology, but a strategic decision to use that foundation to build a vibrant company that would bring improved therapies to patients and provide a new value proposition to investors. We addressed this goal with energy and critical mass and have created significant momentum. We have attained a level of productivity that is among the best in the industry and we continue to strive for excellence in everything that we do.

In 2006, we made substantial progress in all aspects of our business, finishing the year with four programs in Phase II clinical trials, six programs in or about to enter Phase I trials, three new partnerships, and a record amount of cash on hand. We are very pleased to welcome Gisela M. Schwab, MD, to Exelixis as senior vice president and chief medical officer. Dr. Schwab has more than 14 years of industry experience in drug development, including extensive expertise in building and managing teams and in directing diverse aspects of product development, leading to worldwide product registration. Her addition to the Exelixis team will strengthen our development capabilities, helping to ensure seamless integration of our discovery, research and development infrastructure from bench to bedside.

Progress in the Clinic

Rapidly and thoughtfully moving our compounds through clinical development is our most important goal. In 2006, we initiated Phase II programs for XL784, XL647 and XL880. The XL784 Phase II trial is being conducted in type II diabetes patients with moderate levels of proteinuria, which is a sign of impaired renal function. We will measure the ability of XL784 to reduce proteinuria over a three-month period, and anticipate that we will have data from this trial in 2007. Both XL647 and XL880 are being evaluated in a variety of cancer indications, and we expect the first Phase II results to be available during 2007 as well.

Each of these Phase II trials has been designed to match the target inhibition profile of a specific compound with the biology of defined indications and patient populations. Ultimately, we believe that this approach will allow us to generate proof-of-concept data for these programs in 2007, with results that identify indications, with clear paths to product approval and commercialization.

We also reported promising data from multiple Phase I trials, and these results provide a compelling rationale for the Phase II programs that we’ve already initiated as well as those that we expect to initiate in 2007. We continued to expand the pipeline with investigational new drug (IND) application filings for XL228, XL281, and XL588. Combined with the IND applications for XL418 and XL347 filed in January and March of 2007 respectively, we now have 12 compounds in clinical development.

Developing cutting-edge therapies is not without its challenges, and in the third quarter of 2006 we received new data that impacted the Phase II trials for XL999. On the one hand, there were encouraging signs that XL999 has the potential to provide benefit to patients with lung cancer and acute myelogenous leukemia. However, our internal safety monitoring board became concerned with the frequency of cardiovascular events experienced in October by patients in the program, and by November 1, we suspended enrollment in all XL999 trials pending analysis and further data analysis. We determined that patients already enrolled in the Phase I and II trials could continue to receive XL999 and the U.S. Food and Drug Administration (FDA) later agreed with this determination. After extensive review of the data, we submitted a proposed action plan to the FDA in January 2007, and we are working with the FDA to restart clinical evaluation. We believe that XL999 has the potential to provide a risk-to-benefit profile that may make this compound an attractive treatment option for patients with a variety of cancers.

As we enhance our ability to navigate these challenges and to manage our diverse and growing clinical pipeline effectively, we are making a significant investment in our existing R&D infrastructure. At the beginning of 2007, we integrated the drug discovery and drug development groups into a seamless and efficient R&D organization under the leadership of Michael Morrissey PhD, president, research and development. We also were very pleased to welcome Gisela M. Schwab, MD, to Exelixis as senior vice president and chief medical officer. Dr. Schwab has more than 14 years of industry experience in drug development, including extensive expertise in building and managing teams and in directing diverse aspects of product development, leading to worldwide product registration. Her addition to the Exelixis team will strengthen our development capabilities, helping to ensure seamless integration of our discovery, research and development infrastructure from bench to bedside.

New Alliances

High-value partnerships are a pillar of our strategies to advance promising drug candidates and fund our proprietary programs. In 2006, Exelixis established new partnerships with Daichi Sankyo Company, Bristol-Myers Squibb Company (BMS), and Genentech, Inc. Each of these alliances were designed to achieve three objectives: create access to additional resources that can enhance a program’s development; generate significant near-term revenue; and provide us with the opportunity to advance a program’s success through milestone payments and royalties or profit-sharing provisions.

The Sankyo collaboration is focused on developing cardiovascular therapies targeted against the mineralocorticoid receptor (MR), a target validated by the approval of two MR inhibitors for the treatment of hypertension and congestive heart failure. We received a $20 million upfront payment and are entitled to receive research funding, and substantial development, regulatory, and commercialization milestone payments, as well as double-digit royalties on the sales of any products commercialized under the collaboration. This partnership with Sankyo complements partnerships with BMS and Wyeth that we signed late in 2005, both of which are also focused on the development of new treatments for cardiovascular diseases. These three alliances, together with a number of earlier stage projects, provide Exelixis with an exciting program in cardiovascular disease that we intend to develop in collaboration with pharmaceutical partners.

The BMS partnership that we signed in December 2006 is a broad alliance to discover and develop novel oncology compounds. We received a $10 million upfront payment, and we expect to receive $20 million in milestone payments for each of three IND-ready compounds that BMS selects to develop. If Exelixis opts to co-promote compounds commercialized in
the United States, we will receive half of the profits for those compounds. And we will receive royalties on sales of any compounds commercialized outside the United States. This is our fourth collaboration with BMS, and over time the companies have demonstrated the ability to work seamlessly together and to make rapid progress on our collaborative objectives.

Our newest collaboration with Genentech is focused on the development of XL250, a small-molecule inhibitor of MEK. Genentech paid us $40 million in upfront and milestone payments at signing and has the option to develop the compound after we complete a Phase I trial. If Genentech exercises its option, it will conduct and finance all subsequent clinical trials. We will co-commercialize the compound and will share in the profits. This is an innovative partnership with a leading oncology company, and we are pleased to have Genentech as a partner. This is our second collaboration with Genentech, and over time I believe that both companies have gained respect for the quality of work done by the other.

The upfront and near-term milestone payments alone from these deals secured $120 million, and they may generate significant revenue in the future. Yet their value to our company is more than just financial. They also provide important validation of the quality of our compounds and our processes. The multiple collaborations we have with both BMS and Genentech speak to our ability to execute on our plans and programs. Both partners were willing to pay substantial upfront payments because of the high quality of our compounds and our demonstrated ability to execute on our objectives.

Our future business development activities will focus on high-value alliances that allow us to capitalize more fully on our investments in our world-class discovery infrastructure.

Managing our Financial Resources for Success

We are pursuing a four-pillar financing strategy through the achievement of milestones in existing partnerships, establishing new alliances, utilizing clinical funding vehicles, and accessing the equity markets. In the past two years, this strategy has secured over $500 million, with limited dilution to our shareholders, while allowing us to retain ownership of a majority of the compounds in our pipeline. Through partnering and the successful completion of a Phase II trial of XL201 in October 2006 that raised net proceeds of $90.5 million, we finished 2006 with $263 million in cash – our highest cash balance ever. And that did not include $75 million that we received in early January 2007 as a result of the collaborations we signed in December 2006. We believe this demonstrates the value that pharmaceutical companies and investors place on our promising programs and our ability to continually review and expand our pipeline.

Focusing on Milestones

Although I am proud of everything that Exelixis achieved in 2006, we are looking forward and are focused on our ambitious objectives for 2007. These include generating proof-of-concept data in the Phase II programs for XL418, XL784, XL109 and XL880, initiating Phase II programs for XL201 and XL184; advancing the Phase I trials for XL844, XL283, XL228, and XL158; and bringing four new compounds into Phase I clinical trials. Already in 2007 we have filed INDs for XL418, a dual inhibitor of AKT and S6K, which are important nodes in the PI3K pathway, and XL147 which also potently inhibits the PI3K pathway. We expect to file two additional INDs by the end of 2007.

As we enter 2007, we intend to build additional momentum toward our goal, moving with the force and energy we need to make a positive impact on patients, on our company, and on you, our investors.