



# TGEN: FOCUS

## Cystic Fibrosis

*Focus*

*Recent Achievements*

*Future Objectives*

**ADDRESS UNDERLYING  
GENETIC DEFECT  
CAUSING DISEASE**

**PRESENTED AND PUBLISHED  
POSITIVE PHASE II  
CLINICAL RESULTS**

**FORMED COLLABORATION WITH  
CF FOUNDATION  
AND INITIATED PHASE IIB  
CLINICAL TRIAL**

**COMPLETE PHASE IIB  
PATIENT ENROLLMENT**

## AIDS Vaccine

*Focus*

*Recent Achievements*

*Future Objectives*

**DEVELOP A PREVENTATIVE  
AIDS VACCINE**

**PRESENTED FINAL PRECLINICAL  
DATA SUPPORTING CLINICAL  
TRIAL INITIATION**

**INITIATED PHASE I TRIAL**

**EXTENDED COLLABORATION WITH  
IAVI/CCRI THROUGH 2006**

**COMPLETE PHASE I  
DOSE ESCALATION  
PATIENT ENROLLMENT**

## Rheumatoid Arthritis

*Focus*

*Recent Achievements*

*Future Objectives*

**DEVELOP A LOCALLY  
ADMINISTERED TNF- $\alpha$  INHIBITOR**

**PRESENTED FINAL PRECLINICAL  
DATA SUPPORTING CLINICAL  
TRIAL INITIATION**

**INITIATED PHASE I TRIAL**

**COMPLETE PATIENT ENROLLMENT**

# Dear Fellow Shareholders



*Key executives left: Todd E. Simpson, CFO;  
H. Stewart Parker, President & CEO;  
Barrie J. Carter, Ph.D., Chief Scientific Officer*

Targeted Genetics is a company with diverse technologies and broad potential for the development of novel therapies to treat serious diseases. In 2003 the challenge we set for ourselves was to focus on those programs within our portfolio that we believe have the greatest potential for near-term success. Every member of the Targeted Genetics team worked hard to enable us to execute on a strategic plan set forth at the beginning of the year. I am pleased to share with you our progress in 2003 and our vision for the future.

At the start of 2003 we implemented a strategic plan designed to focus our development efforts and financial resources on advancing three key programs: tgAAVCF for the treatment of cystic fibrosis, tgAAC09 to prevent AIDS and tgAAC94 for the treatment of rheumatoid arthritis. The other key objective of our plan was to secure additional financial resources to fund the development of these programs. We met our objectives in each program area and in our corporate development activities.

Our most advanced product candidate is tgAAVCF for the treatment of cystic fibrosis (CF). tgAAVCF uses our adeno-associated virus (AAV) vector system to deliver a functional copy of the gene that is deficient in CF patients, and is designed to address the underlying cause of this genetic disease. In April 2003 we announced a collaboration with the Cystic Fibrosis Foundation to advance the development of tgAAVCF. The focus of the collaboration is to conduct a 100-patient Phase IIb clinical trial to evaluate the efficacy of tgAAVCF in patients with mild to moderate CF. The CF Foundation is providing \$1.7 million to cover the external costs of this study, which was initiated in July 2003.

The Phase IIb trial of tgAAVCF, the largest and most advanced trial of an AAV-based product candidate ever conducted, is being undertaken based on the promising results of a Phase II study that was completed in 2002. The results of the completed study were presented at the American Society of Gene Therapy (ASGT) annual meeting in June 2003. In this Phase II study, we demonstrated a clean safety profile and a statistically significant improvement in lung function 30 days after treatment with tgAAVCF. The Phase IIb study is designed to confirm this observation in a larger population of CF patients.

We made significant progress in the development of tgAAC09, our first AAV-based vaccine candidate. tgAAC09 is the subject of a collaboration among Targeted Genetics, the International AIDS Vaccine Initiative (IAVI) and Columbus Children's Research Institute (CCRI) at Children's Hospital in Columbus, Ohio. In March 2003 we extended the original three-year collaboration to support regulatory filings, initiation of a Phase I clinical trial and other milestones, and we have now extended this collaboration through the end of 2006.

Promising tgAAC09 preclinical data were presented at ASGT and supported advancing this product candidate into a Phase I trial, which was initiated in December 2003. This study will evaluate the safety and immune-stimulating potential of tgAAC09 in healthy volunteers. Targeted Genetics' vaccine is unique in that it may elicit a dual immune response important in preventing disease, and utilizes a single-shot vaccine approach, which is ideal for developing nations. We are very excited about the potential of tgAAC09 to have a positive impact on the global HIV/AIDS pandemic and also look forward to leveraging the

knowledge we gain through its development into opportunities for other AAV-based vaccines.

Throughout 2003 we completed the preclinical studies of tgAAC94 to support regulatory filings and initiate clinical trials. Data from these studies were presented at ASGT, and demonstrated that use of tgAAC94 resulted in a significant reduction in ankle and hind paw swelling as well as a clean safety profile. tgAAC94 uses an AAV vector to deliver a DNA sequence encoding a potent inhibitor of tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) directly into affected joints in patients with rheumatoid arthritis. Several anti-TNF- $\alpha$  therapies already are approved and show clinical and commercial success. Rheumatologists, however, still believe that about 25 to 40 percent of people with RA still suffer from pain in one or more joints, despite currently available therapies. We believe tgAAC94 may have potential therapeutic benefit in this patient category. In the future, we also will consider additional disease targets for tgAAC94, where local expression of a TNF- $\alpha$  inhibitor may have a therapeutic benefit.

We are very excited about the opportunity that tgAAC94 presents as a product candidate that is complementary to existing or novel protein therapies. In January 2004, we received regulatory approval from the U.S. Food & Drug Administration (FDA) and Health Canada to initiate a Phase I clinical trial, and we initiated the study in March.

Our success in meeting our program development objectives helped us to achieve our corporate development goals. There is significant enthusiasm within the CF community for tgAAVCF, and data from our earlier Phase II study was key to establishing a collaboration with the CF Foundation to provide us with the funding to advance the clinical development of this promising AAV-based CF therapy while reducing our expenditures related to this program. Similarly, the preclinical data for tgAAC09 that we generated with our collaborators at CCRI resulted in the March 2003 extension of the IAVI/CCRI collaboration. This extension provided us with financial support that enabled us to complete our regulatory filing and initiate a clinical development program for this innovative vaccine candidate. The ongoing success of the program led to a three-year extension of the collaboration, which we announced at the beginning of 2004. This extension provides funding in 2004 of up to \$10.7 million to support manufacturing of tgAAC09 for the Phase I clinical trial and preclinical studies to evaluate the utility of various HIV antigens in a multi-component AIDS vaccine.

Our presentations of data at ASGT generated renewed interest in our company among investors. Coupled with a resurgence in the biotechnology equity market, this enthusiasm for our programs and technology enabled us to raise \$17.5 million through a public offering of our stock in June 2003. In February 2004 we were able to raise an additional \$25.5 million in the equity markets, enhancing our financial resources and providing the capital we need to continue advancing our development programs. Throughout 2003 we took several other steps to strengthen our financial position, including a \$4.8 million equity investment under our research and development agreement with Biogen, Inc. (now Biogen IDEC); converting \$9.4 million in outstanding convertible debt, which was held by Elan Corporation, plc under a collaborative agreement established in 1999, into equity; and entering into a contract manufacturing agreement with Genvec, Inc.

Our contract manufacturing agreement with Genvec demonstrated our ability to leverage our expertise in biologics manufacturing and our existing manufacturing infrastructure, including our Regulatory Affairs and Quality expertise, to provide contract manufacturing services to other companies at times when we are not utilizing our manufacturing capacity for our own needs. We believe that this approach will enable us to derive near-term revenue from our state-of-the-art manufacturing facilities as we continue to develop our promising product pipeline.

The steps that we took in the laboratory, the clinic and in the business during 2003 provide us with tremendous opportunities for success in the year ahead and the resources to achieve our goals. Already in 2004 we have expanded our IAVI/CCRI collaboration, raised \$25.5 million in the public equity market and initiated clinical development of tgAAC94. Over the next 18 months our main objective is to complete current clinical trials in our three core development programs while we remain opportunistic about seeking out and evaluating additional opportunities for partnerships, out-licensing and strategic transactions. We will continue to focus on realizing the potential of our programs and technology, striving to create value — for patients, for our company and for you, our shareholders.

Sincerely,



H. Stewart Parker

*President and Chief Executive Officer*

# Program Overview

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For more than a decade Targeted Genetics has been at the forefront of innovation in the development of multiple gene delivery systems and novel gene-based therapies for serious diseases. We believe that gene-based therapies will become a therapeutic class that will find important use as a new weapon in the war against disease, and we are committed to realizing the clinical and commercial potential of our gene delivery technologies. As part of that commitment, we have focused many of our resources on, and gained significant expertise in, the preclinical development, clinical and regulatory affairs and manufacturing of our innovative gene-based product candidates. In parallel with these efforts, we have amassed a large portfolio of intellectual property covering various aspects of our technologies and product development programs. Our current product development efforts are focused in the areas of cystic fibrosis, AIDS prophylaxis and rheumatoid arthritis.

## *Cystic Fibrosis Program*

Cystic fibrosis (CF) is a genetic disease that results from a lack of function of the cystic fibrosis transmembrane regulator (CFTR) gene. Despite advances in treating the symptoms of the disease, the median age of survival for CF patients is in the early thirties. Lung function in patients with CF declines at an average rate of about 2 percent per year, ultimately resulting in lung failure and death. There is a clear, unmet need for new therapies that address the root cause of the disease and reduce or eliminate the progressive decline in lung function. Approximately 60,000 people worldwide have CF, including 30,000 individuals in the United States.

Targeted Genetics' program to treat the underlying cause of CF is the most advanced CF gene therapy program under development. Our product candidate for the treatment of CF, tgAAVCF, uses an AAV vector to deliver the DNA sequence encoding CFTR to cells within the lung. tgAAVCF is designed to deliver the CFTR gene sequence into the cell where it directs the production of the CFTR protein. This protein inserts into the cell membrane where it functions as a chloride channel and helps to normalize the flow of water and chloride ions. Targeted Genetics believes that

tgAAVCF may be able to restore sufficient chloride channel function to reduce or eliminate the cycle of inflammatory events that lead to progressive lung failure. Data from a Phase II clinical trial completed in 2003 demonstrated a statistically significant improvement in a key measure of lung function 30 days after administration of tgAAVCF compared with placebo. A number of patients receiving tgAAVCF in this study experienced a sustained improvement in lung function throughout the course of the study that was not observed in patients receiving placebo.

These promising data are the first to show that gene transfer of CFTR can produce significant improvement in the lung function of CF patients. Along with a good safety profile, these data provide the foundation upon which to examine the impact of tgAAVCF on lung function in a larger group of patients. In June 2003, in collaboration with the CF Foundation, we initiated a Phase IIb study that is designed to enroll up to 100 patients with mild-to-moderate CF. The study will assess the safety and impact on lung function, inflammation and changes in biologic markers from repeated doses of tgAAVCF compared with placebo. The CF Foundation is providing funding to cover the external costs associated with this trial. Our 2004 objective for this study is to complete patient enrollment and dosing by year-end.

## *AIDS Vaccine Program*

In 2003 alone, 3 million people died of AIDS. More than 40 million people around the world are now living with HIV infection, and HIV/AIDS is one of the greatest medical, economic and social challenges in many parts of the developing world. More than 70 percent of the population in sub-Saharan Africa is living with HIV/AIDS, and it is estimated that 45 million people in the developing world will become infected in less than a decade. In collaboration with IAVI and CCRI, we are developing a vaccine capable of preventing the onset of AIDS. In keeping with IAVI's mission of addressing the HIV/AIDS pandemic in the developing world, the collaboration is focused on development of a vaccine that is not only safe and effective but also can be manufactured and administered in a simple and cost-effective manner.

## Program Overview continued

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A key challenge to developing an effective prophylactic AIDS vaccine has been to identify an approach capable of stimulating both B-cells and T-cells of the immune system. B-cells secrete antibodies that help to block viral infection, while T-cells help to eliminate cells that have become infected. tgAAC09 is a recombinant vaccine candidate that uses an AAV vector to deliver select genes from HIV. Preclinical studies of AAV-based vaccines against SIV, a virus that infects monkeys and is similar to HIV, have generated very promising data. In addition to a clean safety profile, these vaccines have induced robust and durable B-cell and T-cell responses following vaccination, reduced the amount of virus present in the blood after vaccinated animals have been challenged with infectious SIV and increased long-term survival for animals challenged with SIV infection after a single inoculation with the vaccine.

Based on the strength of these preclinical data, we initiated a Phase I clinical trial of tgAAC09 in late 2003. This trial is being conducted in healthy volunteers and is designed to evaluate the safety of tgAAC09 as well as the ability of the vaccine candidate to stimulate an immune response. The randomized, double-blind, placebo-controlled, dose escalation study will evaluate three escalating doses of tgAAC09 in up to 50 subjects. The costs of the clinical trial, manufacturing of tgAAC09 for the trial and preclinical studies of additional vaccine candidates are funded by IAVI. In 2004, we intend to complete enrollment in the dose-escalation portion of the Phase I study.

### *Rheumatoid Arthritis Program*

More than 2 million people in the United States alone are living with rheumatoid arthritis (RA). RA is an autoimmune disorder in which the immune system inappropriately attacks normal tissue in the joints. This leads to painful swelling, loss of mobility in the joint and the destruction of joint tissue over time. Over the past decade, advances in drug discovery and development have identified tumor necrosis factor alpha (TNF- $\alpha$ ) as a key mediator of disease-related inflammation and tissue damage. Several systemically administered TNF- $\alpha$  inhibitors have been approved for the treatment of inflammatory autoimmune diseases. These therapies have proven to be successful and are projected to garner

revenues in excess of \$7 billion by 2011. Although anti-TNF therapies have significantly improved the lives of many patients with RA, approximately 25 to 40 percent of patients treated with anti-TNF therapies do not achieve total resolution of their RA symptoms. We are using our gene delivery technologies to develop an anti-TNF therapy that can be locally administered and targeted to joints with persistent arthritic symptoms. Our product candidate, tgAAC94, utilizes our AAV vector technology to deliver the DNA sequence encoding a potent inhibitor of TNF- $\alpha$  known as TNFR:Fc, and is formulated for direct injection into affected joints.

Preclinical studies in a rat model of arthritis demonstrated that direct injection of AAV vectors containing the TNFR:Fc gene into an affected joint improved a number of disease parameters. These improvements include a reduction in arthritis severity, circulating TNF- $\alpha$  levels and levels of other inflammatory cytokine molecules within the treated joint; the prevention of cartilage and bone degradation; and positive effects in the treated joint as well as in other non-injected joints in the same animal.

Based on these promising data, Targeted Genetics initiated a Phase I clinical trial of tgAAC94 in March 2004. The double-blind, placebo-controlled, dose escalation trial is designed to assess the safety of tgAAC94 injection into a single joint of patients with RA. Secondary endpoints of the study include the presence of TNFR:Fc protein in serum and other symptoms of disease, such as swelling and tenderness in injected joints. We intend to complete patient enrollment and dosing in this study in the first quarter of 2005.

# Corporate Information

## Board of Directors

Jeremy Curnock Cook  
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Executive Chairman  
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*Chairman and Chief Executive Officer  
NeoRx Corporation*

Joseph M. Davie, Ph.D., M.D.  
*Former Senior Vice President, Research  
Biogen, Inc.*

Louis P. Lacasse  
*President  
GeneChem Management, Inc.*

Nelson L. Levy, Ph.D., M.D.  
*Chairman and Chief Executive Officer  
CoreTechs Corporation*

H. Stewart Parker  
*President, Chief Executive Officer  
Targeted Genetics Corporation*

Mark P. Richmond, Ph.D., D.Sc.  
*Former Director of Research  
Glaxo plc*

## Management

H. Stewart Parker  
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Barrie J. Carter, Ph.D.  
*Executive Vice President  
Chief Scientific Officer*

Todd E. Simpson  
*Vice President, Finance and Administration  
Chief Financial Officer*

Pervin Anklesaria, Ph.D.  
*Vice President, Product Development*

Richard W. Peluso, Ph.D.  
*Vice President, Process Sciences  
and Manufacturing*

B.G. Susan Robinson  
*Vice President, Business Development*

Jonathan K. Wright, J.D.  
*General Counsel*

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*President  
CellExSys*

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*Senior Director, Intellectual Property*

David J. Poston  
*Senior Director, Finance*

Haim Burstein, Ph.D.  
*Senior Director, Product Discovery*

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*Director, Operations*

Alison E. Heald, M.D.  
*Director, Clinical Affairs*

Ralph W. Paul, Ph.D.  
*Director, Technology Evaluation*

Rae Saltzstein  
*Director, Regulatory Affairs  
and Quality*

Ryan Takeya  
*Director, Manufacturing*

Barbara Thorne, Ph.D.  
*Director, Process Development*

## Corporate Headquarters

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## Transfer Agent and Registrar

Mellon Investor Services  
85 Challenger Road  
Ridgefield Park, New Jersey 07660  
Telephone 1.800.522.6645

## Shareholder Inquiries

Inquiries regarding the company and its activities may be directed to the communications department at 206.521.7392. Communications concerning stock and transfer requirements, lost certificates and changes of address should be directed to the transfer agent.

## Legal Counsel

Orrick, Herrington & Sutcliffe LLP  
Seattle, Washington

## Independent Auditors

Ernst & Young LLP  
Seattle, Washington

## Corporate Information

News releases, corporate governance documents and SEC filings are available on the Internet at [www.targetedgenetics.com](http://www.targetedgenetics.com).

## Stock Listing

Targeted Genetics' common stock is traded on the NASDAQ SmallCap Market under the symbol TGEN.

## Common Stock

As of March 19, 2004, there are approximately 26,000 holders of Targeted Genetics' common stock. Targeted Genetics has never paid dividends and the company does not anticipate paying dividends in the foreseeable future.

## Annual Meeting

The annual meeting of shareholders will be held at 9:00 a.m. on Thursday, May 20, 2004, at the Washington Athletic Club, 1325 Sixth Avenue, Seattle, Washington.

This Annual Report contains forward-looking statements. Forward-looking statements are based on the opinions and estimates of management at the time the statements are made and are subject to known and unknown risks and uncertainties and inaccurate assumptions that could cause actual results to differ materially from those expected or implied by the forward-looking statements. Our actual results could differ materially from those anticipated in the forward-looking statements for many reasons, including the risks described under "Factors Affecting Our Operating Results, Our Business and Our Stock Price" in our Annual Report on Form 10-K for the year ended December 31, 2003, and in the filings we make with the Securities and Exchange Commission from time to time. You should not place undue reliance on these forward-looking statements, which speak only as of the date of this Annual Report.