Stressgen is pioneering innovative immunotherapeutics to treat viral diseases and cancers
2003 Highlights

In 2003, we set the foundation to build a commercial biotechnology company.

- RECEIVED FAST TRACK DESIGNATION FROM THE FDA THAT COULD FACILITATE AN EFFICIENT REGULATORY REVIEW OF HSPE7 FOR RRP

We received U.S. Food and Drug Administration (FDA) approval for a Fast Track Product Development Program for our lead compound, HspE7, in the treatment of patients with recurrent respiratory papillomatosis (RRP). In addition to providing access to a number of FDA programs to enhance HspE7 development, the designation may help the compound be considered for priority review and accelerated approval. Sponsors of products in Fast Track Development programs are also eligible to submit “Rolling Biologics Licensing Applications,” enabling the FDA to commence review of portions of the application before the sponsor submits a complete application.

- ANNOUNCED COMPPELLING CLINICAL RESULTS WITH HSPE7 IN RRP

We released statistically significant results in our Phase II HspE7 clinical trial in patients with RRP. These results support a filing for regulatory approval, a key step on the path towards commercialization.

- ENHANCED PARTICIPATION IN OUR ROCHE COLLABORATION

We restructured our 2002 collaboration with Roche to maximize the potential of our lead product, HspE7. The contractual alliance broadens the scope of the original agreement to provide for multiple indications to be developed in parallel, provides an effective route to market for HspE7, and creates significant value for Stressgen and our shareholders through increased revenues and downstream product rights.

- IDENTIFIED STRONG MANUFACTURING PARTNER: AVECIA LIMITED

In tandem with our clinical efforts, we have taken steps to ensure we have the manufacturing capacity in place to support the maturing HspE7 development and commercialization programs.

- STRENGTHENED FINANCIAL POSITION

We completed a C$20 million financing and received milestones from Roche totaling US$4.5 million. We enter 2004 with a strong balance sheet to support our development programs into 2005.

- SECURED KEY INTELLECTUAL PROPERTY

We strengthened our intellectual property estate with the issuance of both a U.S. and European patent for HspE7. We filed additional patent applications directed to heat shock protein (Hsp) fusions with other viral antigens.

This annual report contains forward-looking statements including discussions of our drug development plans, the therapeutic potential of our products, the possibility of regulatory approval and marketing, and potential revenue from collaborations. Please refer to page 18 regarding risks that could affect the actual outcomes.
Stressgen is seeking to improve human health by creating a new class of proprietary immunotherapeutics, or therapeutic vaccines, that will harness the power of the immune system to treat the millions of patients with chronic viral diseases and cancer. —Daniel L. Korpolinski
Stressgen is developing products that stimulate the body’s own immune system to treat viral diseases and cancers.

HISTORICAL TIMELINE ON EVOLUTION OF VIRAL DRUG DEVELOPMENT

Romans used the word “virus” to describe the kind of stench or poison that arose from swamps.

1796 Jenner develops smallpox vaccine.
1879-1886 Pasteur develops rabies vaccine.
1935 Theiler develops yellow fever vaccine; introduction for use in humans.
1954-1955 Salk and Sabin develop polio vaccines.
1957 Interferon discovered by Isaacs and Lindenmann.
1970 Rubella vaccine introduced for use in humans.
1977 Smallpox is declared eradicated.
1981 Hepatitis B virus vaccine licensed for general use (13 years after studies initiated).
1986 First monoclonal antibody (Orthoclone OKT3) approved by FDA. Recombinant hepatitis B vaccine licensed (11 years after studies initiated).
1991 Intron A, first alfa interferon, is approved by the FDA to treat chronic hepatitis B and hepatitis C.
2007 First therapeutic vaccine for RRP.
Of the many infectious diseases that affect mankind, those spread by viruses cause significant morbidity and mortality. Many viral infections are able to evade detection by the immune system. This ability enables the viruses to persist in the body, triggering chronic symptoms, often for the life of the individual. Over time, viral infections can lead to debilitating and life-threatening medical conditions, including cancer or organ dysfunction and/or failure. In contrast to bacterial infections, where treatment with antibiotics historically has been highly effective, viral infections are often poorly treated by existing drugs. Viruses have also been shown to develop resistance to drugs in many cases. Preventative vaccines are available for some viral diseases, including measles, mumps and rubella, and are routinely given to infants and children. However, for such other widespread viruses as hepatitis C, human papillomavirus (HPV) and human immunodeficiency virus (HIV), no vaccines exist.

In many cases where anti-viral drugs are used, large segments of the population are not effectively treated. The lack of effective anti-viral drug therapies, combined with the ability of viruses to hide from the immune system, has left millions of individuals worldwide suffering from life-long viral infections. Stressgen is pioneering a therapeutic vaccine platform to trigger the immune system to detect and eradicate previously “hidden” virus-infected cells. This novel technology may offer an important solution to the growing worldwide healthcare crisis of viral infections.
Therapeutic vaccines are quite different from the preventative vaccines we are given as children or adults, such as polio or measles vaccines. Preventative vaccines prevent an infection from becoming established and are often designed to trigger antibody responses.

While preventative vaccines are highly effective, there are many serious diseases for which preventative vaccines do not exist or are not effective in all recipients. One of the primary reasons this situation exists today is the lack of approved vaccine technologies that can trigger cellular immunity safely and effectively.

**Therapeutic vaccines** are designed to induce cellular immunity, especially cytotoxic T lymphocyte (CTL) responses, which can eradicate established disease. These cellular immune responses are capable of killing virus-infected or cancer cells and hence can treat established disease. CTL responses are precisely the type of immune responses triggered by Stressgen’s proprietary CoVal™ fusion protein vaccines.

Stressgen’s lead CoVal™ fusion protein product, HspE7, has been tested in Phase II and Phase III clinical trials as a therapeutic vaccine for treating diseases caused by human papillomavirus (HPV). HspE7 has the potential to be the first therapeutic vaccine approved for use in humans, opening the door to follow-on CoVal™ fusion protein products for many other serious viral infections and cancer.

The **immune system** is the body’s primary defense against infection by pathogens such as viruses, bacteria and parasites.

*Stressgen is positioned at the forefront of therapeutic vaccine development and may be one of the first companies to successfully bring a new immunotherapeutic, or therapeutic vaccine, to market.*
THE IMMUNE SYSTEM

HUMORAL (prevents infection)
stimulates antibody production
eliminates extracellular bacteria, viruses and other foreign pathogens

CELLULAR (fights established infections)
stimulates CD4+ and CD8+ (killer T) cell production
clears intracellular pathogens, virus-infected cells and tumor cells

CoVal™ Fusion Protein Therapeutics
Stressgen is advancing a technology platform that has the potential to treat multiple disease targets.

An easy-to-understand animated representation of the CoVal™ fusion therapeutics mechanism of action can be viewed by inserting the disc at left into any computer.

The CD also contains a detailed summary of Stressgen’s unique approach to targeting diseases, as well as a scientific tutorial, a scientific glossary, Stressgen’s Annual Report on Form 10-K for the fiscal year ended December 31, 2003 and other important information.

Stressgen’s fusion technology covalently links a heat shock protein (Hsp) – also known as a stress protein – to an antigen to create a single hybrid molecule. This technology is a platform from which a variety of Hsp fusions can be built, each specific for the treatment of a different disease.
To create therapeutic vaccines, Stressgen takes advantage of the immunostimulatory powers of heat shock proteins (Hsp), also known as stress proteins. Hsp are especially potent triggers for cellular immunity, including cytotoxic T lymphocytes (CTL). CTL, referred to as “killer T cells,” are peptide-specific white blood cells that can recognize and kill infected or cancerous cells, while bypassing normal cells. By stimulating the patients’ own immune system to recognize and eradicate infected cells, therapeutic vaccines may achieve cellular immunity and offer safe, more durable treatment options than currently available drugs.

Stressgen’s CoVal™ fusion protein products are composed of two parts: a stress protein and a protein antigen selected from a virus or cancer cell. The stress protein and antigen are joined or “fused” together covalently using recombinant DNA technology. Each CoVal™ fusion protein represents a new virus or cancer-specific therapeutic vaccine.

The protein antigen that Stressgen fuses to a heat shock protein can be chosen from a wide variety of sources. As a result, the spectrum of diseases that potentially can be treated by CoVal™ fusion immunotherapeutics ranges beyond viral diseases to other types of infections and cancer.

Stressgen is presently developing CoVal™ fusion immunotherapeutics for chronic viral infections with large unmet market and medical needs caused by human papillomavirus (HPV), and has initiated research studies to evaluate stress protein fusions for the treatment of hepatitis B and herpes simplex. In addition, the Company is targeting hepatitis C. The ability of CoVal™ fusion products to elicit a potent and targeted cellular immune response for a given disease may have extraordinary implications in the treatment of a wide range of diseases.
Stressgen’s CoVal™ fusion proteins bring together the target specificity of viral or cancer cell antigens with the unique power of heat shock proteins (Hsp) (also known as stress proteins) to trigger effective immune responses. The Hsp provides heightened cellular immune responses; the antigen provides a specific target for CTL (killer T cell)-mediated destruction of infected or diseased tissues.

Hsp trigger immune responses by targeting dendritic cells (DCs), which are the primary activators of cellular immune responses. Stress proteins are able to trigger potent cellular immune responses, especially CTLs, because DCs possess receptors on their surface which bind to stress proteins. Hence, it is believed that immunization with CoVal™ fusion proteins directs the antigen portion of the fusion to DCs, which in turn trigger antigen-specific CD8+ CTLs. Therefore, CoVal™ fusion proteins may represent a new and highly effective way to stimulate killer T cell responses to viral and cancer antigens.

Stressgen’s lead product, HspE7, is composed of the stress protein Hsp65 from a specific mycobacteria joined to the E7 protein antigen from human papillomavirus (HPV) type 16. Hsp65 was chosen based on abundant scientific evidence that it possessed strong immunostimulatory powers. E7 was chosen because 1) it represents a precise target for an attack against HPV-infected cells in the body, 2) its expression is required to maintain infected cells in a transformed (cancerous) state, and 3) its protein sequence is similar in many types of HPV, which may permit induction of cross-reactive immunity against multiple HPV types. The HPV16 E7 antigen is expressed in many types of HPV infections, such as those that cause precancerous conditions called dysplasia, as well as in cancers associated with HPV. In many cases HPV16 E7 must be expressed for dysplastic and cancer cells to survive. As a result, a virus cannot “switch off” E7 expression to hide from the immune system. The constant expression of the antigen provides an advantageous target for the immune system to destroy infected cells displaying the E7 antigen on their surface.

HspE7 has shown activity in treating a variety of HPV-related conditions. To date, its safety profile has been favorable. In addition, HspE7 activity appears to be independent of CD4+ T helper cells, supporting the potential application of Hsp fusions in the treatment of immunocompromised patients whose CD4+ T helper cells may be depleted or significantly impaired.
HSP FUSION PROTEIN
The Hsp portion of the fusion protein activates a Type 1 (cellular) immune response. In the case of Stressgen’s lead molecule, HspE7, the E7 portion generates an antigen-specific immune response, targeting the immune system to look for the E7 protein of HPV in infected cells.

ANTIGEN PRESENTATION
Hsp receptors on the cell surface enable the Hsp-antigen fusion to enter the dendritic cell. The fusion is processed into small pieces called peptides. Peptides from the E7 antigen are presented on the dendritic cell surface on Class I molecules for presentation to CD8+ T cells.

CYTOTOXIC T LYMPHOCYTE (CTL) RESPONSE
When CD8+ T cells encounter the E7 peptides presented by the dendritic cell, they become activated into CTLs, also known as “killer T cells.” These E7-specific CTL proliferate and search the body for HPV-infected cells displaying the E7 antigen on their surface.

TARGETED CELL DEATH
Once the activated CTL locate these HPV-infected cells, the CTL kill the cells. Only the HPV-infected cells are destroyed, while healthy cells and tissues are spared.
Stressgen is developing its lead product candidate, HspE7, to treat a variety of HPV-related diseases and cancers.

HPV causes the most prevalent sexually transmitted diseases in the world. Approximately 20 million patients in the United States alone are currently infected with HPV, and 5.5 million new HPV infections are reported in the country each year.
Stressgen has completed 11 trials with its lead product, HspE7, in patients with HPV-related diseases, including genital warts; recurrent respiratory papillomatosis (RRP), which occurs in babies born to mothers with HPV; and two pre-cancerous conditions, anal dysplasia and cervical dysplasia.

The focus of Stressgen’s HspE7 development program has evolved to leverage the results from these clinical trials, ensure that the Company captures its broadest potential markets for the product, and capitalize on the resources of third parties interested in using HspE7 to treat specific indications. Because the compound has received Orphan Drug Status and Fast Track Product Development designations from the U.S. Food and Drug Administration (FDA) for the treatment of patients suffering from RRP, and based on Stressgen’s comprehensive evaluations, the Company is targeting RRP as the first market for HspE7.

Stressgen has identified serious, unmet medical indications beyond RRP for which HspE7 might be beneficial. These include high-grade cervical dysplasia in women. The current “gold standard” therapy for this condition is a surgical procedure, known as LEEP (Loop Electrosurgical Excision Procedure), which is invasive, does not always work and can reduce fertility. Stressgen believes HspE7 could prove a viable and long-term alternative to surgery. Stressgen is also looking at ways to help HPV-infected patient groups whose immune systems are not functioning properly. These include those who are HIV-positive, have received organ transplants or are elderly.

As with RRP, the above indications represent attractive potential commercial opportunities. They may require smaller clinical trials and may qualify for Orphan Drug Status and Fast Track Product Development program designations by the FDA. Stressgen is actively evaluating potential clinical development activities in these areas and await valuable dysplasia data from two ongoing studies – an investigator study and a National Cancer Institute (NCI) trial – which may be available by the fourth quarter of 2004.
GENITAL WARTS are caused by certain types of sexually transmitted HPV. Approximately two-thirds of people who have sexual contact with a partner who has genital warts develop warts themselves, usually within three months of contact. An estimated 500,000 to 1 million new cases occur in the United States each year and while the lesions may spontaneously regress, recurrence is typical even following treatment.

Stressgen’s current agreement with Roche provides exclusive and global rights to Roche to develop a 2nd generation HspE7 compound for genital warts.

RECURRENT RESPIRATORY PAPILLOMATOSIS (RRP), a disease caused by the same types of HPV that cause genital warts, occurs primarily on the larynx and vocal cords of children born to mothers infected with HPV. The papillomas, or warts, occasionally spread into the trachea and lungs. Based on a 1995 survey estimating over 2,000 new cases of pediatric RRP and 3,500 new cases of adult RRP each year in the United States there would be approximately 17,200 patients in the United States. Patients with RRP can die from airway obstruction, cancerous transformation, overwhelming spread of the disease, growth of papillomas in the lungs or complications of surgical treatments. Pediatric patients tend to have about five surgeries per year, and some children have hundreds of procedures during their lifetime. There are no drugs or immunotherapies approved for RRP in the United States. Stressgen is focusing its development resources and efforts on RRP.

CERVICAL INTRAEPITHELIAL NEOPLASIA (CIN), also known as cervical dysplasia, is characterized by abnormal cells in the cervix associated with the malignant transformation of epithelial cells infected with HPV virus. Annually, in the United States more than 1.2 million women are diagnosed with low-grade cervical dysplasia and another 200,000 to 300,000 are diagnosed with high-grade cervical dysplasia in the United States. Worldwide, the problem is much larger.
CIN often precedes cervical cancer, a worldwide public health problem particularly in countries where routine Pap smears are not practiced. American Cancer Society estimates for 2002 predicted that approximately 13,000 women in the United States would be diagnosed and about 4,100 would die from invasive cervical cancer. Globally there are approximately 500,000 new cases of cervical cancer identified each year, resulting in nearly 300,000 deaths. Although death rates from the disease have declined, invasive cervical cancer continues to be associated with extreme morbidity.

An early treatment for CIN involves local surgical techniques, which may not remove all dysplastic cells and do not treat underlying viral infection. In addition, surgery can result in complications such as reduced fertility.

Anal intraepithelial neoplasia (AIN), or anal dysplasia, is characterized by the presence of abnormal cells that may precede anal cancer. Data extrapolated from studies of homosexual and bisexual men and the anal cancer population suggests that there may be 500,000 new cases per year in the United States. Patients are not commonly screened for AIN; however, there is increasing awareness of the condition. No standard therapy exists for AIN.

The U.S. National Cancer Institute (NCI), recognizing the potential of HspE7 to prevent cancers caused by HPV, is sponsoring several clinical trials using the compound in cervical dysplasia and immunocompromised HIV-positive anal dysplasia patients. Data from these trials will help Stressgen plan its next steps in developing HspE7 for cervical and/or anal dysplasia.

Although there are over 100 different types of HPV, most research focuses on the approximately one-third infecting genital epithelial tissue and primarily spread through sexual contact. Low-risk types of HPV typically cause skin warts, the most recognizable sign of genital HPV infection. Other high-risk types of HPV cause cervical and anal dysplasia, which are precursors to cervical and anal cancer.
To Our Shareholders:
In 2003, Stressgen made significant strides in several key areas of our growth, including targeting and advancing our clinical development efforts of our lead compound, HspE7, for the treatment of HPV-related diseases; expanding our product development collaboration with Roche; increasing our breadth of process development and manufacturing capabilities and building our financial strength. We have leveraged opportunities on multiple fronts to ensure that we have the capabilities and resources to drive the clinical development of HspE7’s first indication to the marketplace as quickly as possible for the treatment of recurrent respiratory papillomatosis (RRP).

RRP, one of several severe diseases caused by the human papillomavirus (HPV), strikes both children and adults. Current treatment involves multiple surgical interventions over the lifetime of patients. Data from our completed Phase II RRP clinical trial confirmed the potential for HspE7 to significantly reduce the number of surgeries for the children participating in the study. We look to HspE7 to be an important addition to a physician’s armamentarium to manage patients suffering from RRP, and a host of other serious diseases caused by HPV, including infections in 1) HIV-positive immunosuppressed patients with concomitant HPV disease, 2) women with serious high-grade cervical dysplasia who fail LEEP (Loop Electrosurgical Excision Procedure) surgery, and 3) patients with HPV-related cancers such as cervical, anal and approximately one-third of head and neck cancers. Even excluding other HPV-related diseases, HPV causes disease symptoms in over 1 million new genital warts patients in the United States.

We believe that HspE7 has the potential to be a front-runner in a totally new class of drugs, therapeutic vaccines, to treat viral diseases and cancer by mobilizing the immune system to target diseased cells. Successful commercialization of HspE7 could provide a major advance in the management of HPV-related diseases. With the introduction of HspE7, we believe our Company and our shareholders can make a major contribution to the treatment of HPV-related diseases.

ADVANCING HSPE7 IN CLINICAL DEVELOPMENT
Over the recent past and in 2003, we gathered increasing clinical evidence to support our belief that HspE7 will treat multiple diseases caused by HPV, including genital warts, RRP, cervical dysplasia, anal dysplasia and various cancers.

We recently completed an open-label Phase II trial in 27 pediatric patients with RRP who required frequent and painful surgery for their papillomas. Treatment with HspE7 increased the time interval between required RRP surgeries and thereby reducing the frequency of surgery in patients with moderate and severe RRP. In fact, the median interval of all surgeries reported following treatment suggests that the 27 children treated in the trial would experience 87 fewer surgeries during the first year post-treatment. Most significantly, the high level of statistical significance in a small population and the internal consistency of the RRP data according to a variety of measures suggest that results to be obtained in a carefully designed pivotal trial are likely to be robust and reproducible. These extremely ill children with RRP have to repeatedly undergo surgeries under anesthesia. A reduction in the number of these procedures will be a welcome benefit for the children, their caregivers and the physicians who treat them.

Stressgen has been granted Orphan Drug Status and Fast Track Product Development designations from the U.S. Food and Drug Administration (FDA) for HspE7 in the treatment of patients suffering from RRP. Based on our findings from the clinical trials conducted to date, advice from an ad hoc clinical advisory board, market research and our experience with the regulatory approval process, Stressgen is targeting RRP as the first market for HspE7. We plan to begin a pivotal RRP trial with HspE7 and anticipate submitting a Biologics License Application (BLA) for the indication in mid-2007.
We also recently completed our Phase III anal dysplasia trial in which HspE7 was used to treat high-grade anal dysplasia patients, a precursor to anal cancer. This trial was designed to test the proposition that HspE7 produces a pathological response rate superior to placebo in anal dysplasia. In addition, this trial was designed to evaluate the proposition that an adjudicated read of pathological assessment would be a viable primary endpoint in a pivotal Phase III trial. This trial was not intended to be a pivotal trial.

The final analysis showed that the drug exceeded the treatment effect that it was intended to detect. However, the anticipated placebo effect doubled as estimated from previous Phase II trials and as had been predicted by experts through studies of natural history, and thus there was no difference between drug and placebo. The 28 percent discordance in the adjudicated pathological assessment of biopsies makes it very difficult to interpret these results.

Nonetheless, HspE7 reproduced Phase II results in the secondary endpoint of Physician’s Global Assessment (PGA). PGA, a blinded assessment, represents a scoring by the treating physician of overall patient outcomes and takes into account variables such as extent and depth of disease as well as pathological analysis of biopsies. PGA reached statistical significance for anal dysplasia at six months with 80 percent of patients showing improvement. These results were in line with PGA responses in the previous Phase II anal dysplasia study. In the additional secondary endpoint measuring global assessment in the patients with concomitant genital warts, HspE7 demonstrated an increasing treatment advantage and became statistically significant at 48 weeks. These results are consistent with the beneficial effect in genital warts observed in previous Phase II studies, i.e., 80 percent complete responses at 48 weeks. Finally, patients in this Phase III study were followed up to 24 months and 73 percent who achieved complete remission were in complete remission at the end of the study. Similarly, 70 percent of the complete responders in our Phase II study were in complete remission at the 24 month observation point.

ENHANCING VALUE THROUGH OUR COLLABORATIONS
During 2003, we broadened and restructured our HspE7 collaboration with our partner Roche. This restructuring was designed to increase the potential of revenue flowing into Stressgen, to broaden HPV disease targets, to equalize resource allocation by both companies, and to take advantage of Stressgen’s experience to lead the clinical development of HspE7 down a faster commercialization pathway. In our new agreement, Stressgen will develop the current 1st generation HspE7, now in clinical trials, for all HPV indications except genital warts. Roche has the right to independently develop a 2nd generation technology – one with a unique and separate HspE7 formulation – to treat genital warts. This new structure allows full utilization of each company’s expertise and resources to develop HspE7 for multiple indications on parallel tracks.

Assuming that all HspE7 development and commercial milestones are achieved and Roche exercises its rights to certain other CoVal™ fusion product candidates, the payments to Stressgen, excluding royalty payments or sales-based payments, will be US$227 million, in addition to the US$21.5 million received from Roche to date. Potential payments of up to US$15 million may be provided to us in 2005. We believe this restructured agreement adds significant value to our business. In the agreement, Stressgen captures top line revenue for three years from product sales in the United States and Canada, starting with the first U.S. BLA approval. In year four, Stressgen will receive significant royalty streams in both the United States and the rest of the world. These new terms provide a major advance in potential revenue streams and royalties, or sales-based payments, compared to our original agreement signed in June 2002.

In another collaboration, we have two clinical trial agreements with the U.S. National Cancer Institute (NCI) for the co-development of HspE7 for the treatment of dysplasia and cancer. Under the agreements, Stressgen provides clinical-grade supplies of HspE7 and is able to use any resulting trial data. The NCI’s support includes creating a general development plan, soliciting research protocols, recruiting investigators and funding the trials. The collaboration with the NCI enables studies of HspE7 for the treatment of dysplasias and pre-cancerous lesions to progress, while Stressgen uses its resources to advance RRP.

Two trials now underway may provide sufficient Phase II data to support pivotal Phase III trials for HspE7 in HIV-positive immunosuppressed patients with concomitant HPV infection, and for women with serious high-grade cervical dysplasia who fail LEEP surgery. Successful pivotal trials could see new label indications for these serious HPV-related diseases.
INCREASING OUR MANUFACTURING CAPABILITIES
To better utilize resources of both partners, Stressgen has reacquired control of the manufacturing process, for both clinical trial supplies and commercial product, for the 1st generation HspE7 therapeutic vaccine now in advanced clinical trials. Under the current agreement, Roche has responsibility for the manufacture of 2nd generation HspE7 for genital warts. To meet our BLA filing target, we have contracted Avecia Limited to complete development of the commercial process and provide clinical supplies for our Phase III RRP, and other HspE7 clinical trials. Avecia’s management and experience in the scale-up of biologics, coupled with its modern manufacturing facility to meet the market needs for commercial products, gives us confidence that we will meet the Company’s target for marketing HspE7. The program is on schedule, and we have already developed and validated a bioassay for the release testing of HspE7, a major step in the manufacturing process. Similar to our restructured agreement with Roche, the Avecia contract demonstrates management’s ability to work with collaborators and to search for better ways to keep Stressgen’s development program on track. Finally, commercial-grade material available from Avecia will produce clinical supplies for multiple Phase III trials for other indications, as well as drug for the market if HspE7 is approved for sale.

BUILDING FISCAL STRENGTH THROUGH FINANCING AND BIOREAGENTS
We enter 2004 with the financial resources to aggressively fund our development programs into 2005. The strength of our balance sheet is due in part to US$4.5 million paid in 2003 from Roche as an equity investment and a development milestone payment, an aggregate US$17 million paid by Roche in development work under our original collaboration, and a C$20 million equity financing we completed in December 2003. These dollars, coupled with an average C$2 million per year contribution from our bioreagent business, and a potential US$15 million from Roche in 2005 from our newly restructured Roche partnership, lead us to believe that we will be able to maintain a solid financial picture as we move forward in the development of HspE7 and of our CoVal™ technology platform.

Despite downward pressure that the challenging economic environment presented, our bioreagent business remained profitable in 2003. Both our U.S. and Canadian dollar denominated sales increased by 4 and 10 percent respectively, aided by the introduction of several higher priced, kit-based research products. The weakening U.S.

dollar was the principal reason reported bioreagent sales were 6 percent lower in 2003 compared to 2002. We continue to view the bioreagent business as an asset and a source of cash for our therapeutic development business. With a strengthening economy, we expect the business can be grown through new product introductions or developed to attract capital from strategic partners.

DEMONSTRATED MULTIPLE PRODUCT POTENTIAL OF COVAL™ FUSION PRODUCTS AND TECHNOLOGY PLATFORM
HspE7 represents one of several potential commercial products that can be developed utilizing our proprietary technology platform. In 2003, we announced progress with our CoVal™ fusion protein for hepatitis B known as HspBcor. Repeatedly, HspBcor has been able to overcome tolerance in hepatitis B-infected transgenic mice by eliciting a specific CTL response, an observation critical for moving our HspBcor program forward towards clinical development.

Our successes with HspE7 and our preclinical studies with HspBcor suggest that the immunotherapeutics we create by covalently linking a heat shock protein to an antigen are effective in stimulating the immune system to recognize the specific-linked antigen and fight the disease. Our technology platform will potentially provide multiple CoVal™ fusion products to treat a variety of unmet medical needs in viral infections such as herpes simplex, hepatitis B and hepatitis C, and cancer. HspE7 for HPV infection represents the first in a family of products utilizing this novel proprietary technology.

VALUING YOUR SUPPORT
The progress we made this year would not have been possible without the hard work and dedication of everyone at and connected with Stressgen. As such, I would like to thank my colleagues for their continued commitment toward advancing our first therapeutic to market. I also thank our directors for their guidance and leadership, and our shareholders, who have continued to support us throughout the year. On behalf of the Board of Directors, thank you all. I look forward to shaping and sharing Stressgen’s continuing accomplishments with you.

Sincerely,
Daniel L. Korpolsinski
Director, President and Chief Executive Officer
March 4, 2004
Disease Targets

Stressgen is developing a preclinical pipeline of CoVal™ fusion proteins for other large market viral infections. It is concentrating its early-stage research efforts on the treatment of hepatitis B and herpes simplex viruses, and is evaluating the use of its technology to develop a fusion protein to treat infections caused by hepatitis C virus. Treatments for cancer, bacterial and fungal diseases are possibilities for future development.

HPV-RELATED DISEASES AND CANCERS

Current estimates of the costs of genital HPV-related diseases make HPV the second most costly sexually transmitted disease after HIV infection. HspE7 has the potential to reduce or eliminate recurrence and treat chronic conditions in people already infected with HPV.

HEPATITIS B VIRUS (HBV)

Although safe and effective preventative vaccines exist for HBV, the United States has an estimated 1 million to 1.25 million cases of chronic HBV; between 140,000 and 320,000 new cases each year; and an estimated 4,000 to 5,000 HBV-related deaths annually. Worldwide, about 1 million deaths are attributable to HBV each year. Due to the large infected population and small percentage of the public being vaccinated for the disease, the need for new and effective therapies for chronic HBV infection remains great.

HEPATITIS C VIRUS (HCV)

HCV infects an estimated 290 million people worldwide and 3.9 million people in the United States (1.8 percent of the population), with 8,000 to 10,000 U.S. deaths attributed to HCV annually. Researchers predict that over the next 10 to 20 years, chronic HCV infection will become a major burden on the health care system as patients progress to end-stage liver disease. Currently there is no vaccine or available therapy to eradicate the virus or do more than delay the progression of the disease.

HERPES SIMPLEX VIRUS (HSV)

The cause of genital herpes, HSV-2, is now detectable in about one in five persons 12 years of age or older in the United States. An estimated 45 million Americans are already infected with genital herpes, with an additional 500,000 to 1 million new cases estimated to occur each year. Except in newborns, genital herpes is not life threatening. Nonetheless, it is distressing and can contribute to the spread of other sexually transmitted diseases.
Index of Selected Financial Statements

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Note Regarding Forward-Looking Statements

The forward-looking statements in this annual report involve risks and uncertainties, including the discussions of collaborations, revenue, product development efforts and the future of our products. Actual results may differ materially from our current expectations due to factors including uncertainties associated with the development of therapeutics, the risk that we will not obtain regulatory approval for our products and our need for additional financing. Please see our Annual Report on Form 10-K, which is included on the enclosed CD-ROM and is available from our Investor Relations department, for a more detailed discussion of these and other risks.
Selected Consolidated Financial Data

The following table summarizes certain selected consolidated financial data for each of the five years in the period ended December 31, 2003. The information presented is not necessarily indicative of the results of future operations and should be read in conjunction with the consolidated financial statements and related notes thereto and with “Management’s Discussion and Analysis of Financial Condition and Results of Operations,” included in the Company’s 2003 Annual Report on Form 10-K. Our consolidated results include those of our subsidiaries, including a U.S. subsidiary, which provides management, research and development services, and a Barbados subsidiary, which is responsible for HspE7 development.

### Consolidated Statement of Operations Data

**(In thousands of Canadian dollars, except per share amounts)**

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### Consolidated Balance Sheet Data

**(In thousands of Canadian dollars)**

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<tbody>
<tr>
<td>Cash and short-term investments</td>
<td>$52,090</td>
<td>$46,013</td>
<td>$62,682</td>
<td>$70,567</td>
<td>$16,477</td>
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<tr>
<td>Total assets</td>
<td>56,430</td>
<td>54,815</td>
<td>67,789</td>
<td>74,325</td>
<td>19,852</td>
</tr>
<tr>
<td>Long-term obligations</td>
<td>2,672</td>
<td>3,606</td>
<td>578</td>
<td>1,036</td>
<td>1,467</td>
</tr>
</tbody>
</table>
Corporate Governance
Management and the Board of Directors believe that Stressgen’s corporate governance practices are in line with those established by The Toronto Stock Exchange. The mandate of the Board of Directors is to provide advice and guidance to the management of the Company and represent the best interest of shareholders. The directors are kept informed of the Company’s operations at meetings of the board, its committees and through reports and analysis by management.

Stock Listing
The Company’s common shares are traded on The Toronto Stock Exchange under the symbol “SSB.”

Annual General Meeting
The Annual General Meeting of Shareholders will be held on Wednesday, May 12, 2004, at 1:00 p.m. at the Pan Pacific Hotel in Vancouver, British Columbia.

Independent Auditors
Deloitte & Touche LLP
San Diego, CA

Transfer Agent and Share Registrar
Computershare Trust Company of Canada
Computershare
510 Burrard Street
Vancouver, British Columbia V6C 3B9
Telephone (Investor Services): 1-800-564-6253

Shareholder Inquiries

Alternatively, please contact:
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350-4243 Glanford Avenue
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Stressgen Biotechnologies, Inc.
6055 Lusk Boulevard
San Diego, CA 92121
USA
Telephone: 858-202-4900
Fax: 858-450-6849

Internet Site: www.stressgen.com
Email: ir@stressgen.com

Corporate Profile
Stressgen Biotechnologies Corporation (TSX:SSB) is a public biopharmaceutical company focused on the discovery, development, and commercialization of innovative, proprietary immunotherapeutics for the treatment of infectious disease and cancer. The Company’s proprietary platform technology is based on the covalent bonding of a stress protein, also called a heat shock protein (Hsp), to proteins such as viral or cancer antigens. The resulting CoVal™ fusion proteins are designed to stimulate immune responses to the disease-specific antigen present in the fusion. By targeting immune responses to a specific antigen, CoVal™ fusion proteins use the body’s immune system to combat infectious diseases or cancer.

Stressgen recently completed a Phase II trial with HspE7, its lead product candidate, to treat children with a serious disease called recurrent respiratory papillomatosis (RRP) caused by the same HPV types, 6 and 11, that cause genital warts. The data from this trial were highly statistically significant, supporting the Company’s decision to initiate a pivotal Phase III trial in RRP patients. HspE7 may also have applications in other indications caused by HPV, including genital warts, cervical dysplasia, cervical cancer and anal dysplasia. The U.S. Food and Drug Administration has granted Orphan Drug Status and designated HspE7 as a Fast Track Product Development program for the treatment of patients suffering from RRP. Stressgen is evaluating other CoVal™ fusion candidates for the treatment of viral infections caused by hepatitis B and herpes simplex viruses, and is targeting hepatitis C.
Corporate Directory

Management

Daniel L. Korpolski
President & Chief Executive Officer

Gregory M. McKee
Vice President, Corporate Development and
Chief Financial Officer

Marvin I. Siegel, Ph.D.
Executive Vice President, Research & Development

John R. Neefe, M.D.
Senior Vice President, Clinical Development

Howard T. Holden, Ph.D.
Vice President, Regulatory Affairs and Compliance

Lee Mizzen, Ph.D.
Vice President, Scientific Affairs

Bruce M. Berger, M.D.
Vice President, Clinical Development

Ariel Louwrier, Ph.D.
Director, Operations-Bioreagents

Board of Directors

Joann Data, M.D., Ph.D.\textsuperscript{1,3}
Senior Vice President, Regulatory Affairs
and Quality Assurance
Amylin Pharmaceuticals

Kenneth Galbraith, CA\textsuperscript{2}
Current President
Gigha Consulting Ltd.
Former Executive Vice President & CFO
QLT Inc.

Elizabeth Greetham, B.Sc., M.A.\textsuperscript{2}
Current President
ACCL Financial Consultants
Former Chairman & Chief Executive Officer
DrugAbuse Sciences, Inc.

Daniel L. Korpolski
President & Chief Executive Officer
Stressgen Biotechnologies Corporation

Ian Lennox\textsuperscript{1,2}
President & Chief Executive Officer
Drug Discovery & Development Sector
MDS Inc.

Margot Northey, Ph.D., M.A.\textsuperscript{3}
Former Dean of Queen’s School of Business
Queen’s University
Kingston, Ontario

Jay M. Short, Ph.D.\textsuperscript{1}
President & Chief Executive Officer
Diversa Corporation

(1) Compensation Committee
(2) Audit Committee
(3) Governance Committee
Stressgen is pioneering innovative immunotherapeutics to treat viral diseases and cancers