CEL-SCI Corporation
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Ticker (Exchange)	CVM-NYSE
Recent Price (06/03/2020)	$14.42
52-week Range	$3.70 - $18.00
Shares Outstanding	37.63M
Market Capitalization	$542.7M
Average 10-day volume	885,971
Insider Ownership +>5%	4.48%
Institutional Ownership	21.78%
EPS (Year ended 03/31/20)	($0.25)
Employees	46

CVM (NYSE) One-year Stock Chart

PRODUCT PIPELINE	
MULTIKINE®	
Head and Neck Cancer	Phase 3 Pivotal Study
HPV	Phase 1
LEAPS™ TECHNOLOGY	
CEL-2000	Phase 1 enabling studies
CEL-4000	(NIH Grant)
LEAPS™-COVID-19	Pre-clinical

Source: CEL-SCI Corporation.

COMPANY DESCRIPTION

CEL-SCI Corporation ("CEL-SCI" or "the Company") is a clinical-stage biotechnology company developing **immunotherapy†** technologies to treat cancer, autoimmune, and infectious diseases. The Company is targeting novel therapy candidates that activate and utilize the body's own immune system against disease. CEL-SCI is developing products based on two technologies: (1) Multikine® (Leukocyte Interleukin, Injection), an immunotherapy nearing the end of a global pivotal Phase 3 trial as a **first-line** treatment for head and neck cancer; and (2) LEAPS™ (Ligand Epitope Antigen Presentation System), an immunotherapy vaccine technology platform. The goal of Multikine® is to modulate the body's immune system to create a two-pronged mechanism of action: eliciting the direct killing of tumor cells and **micrometastasis**, limiting the possibility of recurrence, while generating a sustainable anti-tumor response, and rendering tumor cells more susceptible to subsequent radiation and chemotherapy treatments. Multikine® is being developed for **neoadjuvant** administration and could become an integral first-line component of the **standard of care (SOC)** regimen for advanced primary (previously untreated) head and neck cancers. As a neoadjuvant, Multikine® can stimulate the immune system before it is weakened by the toxic cancer therapies, improving its long-term therapeutic effect. The LEAPS™ platform is designed to stimulate the immune system to fight bacterial, viral, and parasitic infections more effectively, as well as autoimmune conditions and cancer. LEAPS™ can be designed to produce a specific natural immune response required for the desired therapeutic effect, depending on the type of LEAPS™ construct used.

KEY POINTS

- CEL-SCI's first indication for Multikine® is as the first treatment immediately following diagnosis (given prior to any other treatment) in advanced primary (previously untreated) **squamous cell carcinoma** of the head and neck. Usually new cancer treatments are given after the initial treatments. CEL-SCI received **Orphan Drug** Status/designation from the FDA for this indication.
- In its most recent Phase 2 clinical trial for Multikine®, CEL-SCI reported a 10.5% **complete response** rate (no clinical or pathology evidence of any remaining cancer) and a 33% improvement in overall survival after only three weeks of treatment, with no reported severe adverse events associated with its use.
- In May 2020, CEL-SCI announced that it had reached the required number of events for the completion of its pivotal Multikine® Phase 3 trial (IT-MATTERS), the largest head and neck cancer study ever conducted. The primary endpoint in the study is a 10% increase in the overall survival of patients treated with the Multikine® treatment regimen + SOC versus patients treated with SOC only. The Company is proceeding with data lock and subsequent analysis of the data and expects to file for regulatory approval in 2021.
- The LEAPS™ technology is being used to develop therapeutics for rheumatoid arthritis (RA) as the lead indication and **COVID 19**.
- CEL-SCI operates a dedicated state-of-the art manufacturing facility with over 73,000 sq. ft. of manufacturing and R&D space.
- As of March 31, 2020, CEL-SCI's cash position was $14.3 million.

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Executive Overview

CEL-SCI Corporation ("CEL-SCI" or "the Company") is a clinical-stage biotechnology company focused on developing immunotherapy products and technologies to treat cancer and infectious diseases that address significant unmet medical needs. The Company aims to develop novel therapies with the potential to activate and utilize the body's own immune system against the disease, while imparting minimal toxicity to normal cells and organ systems. CEL-SCI is focused on developing products based on two innovative technologies: (1) Multikine® (Leukocyte Interleukin, Injection), a next-generation, comprehensive immunotherapy in late Phase 3 development as a first-line treatment for newly diagnosed advanced primary head and neck cancer; and (2) LEAPS™ (Ligand Epitope Antigen Presentation System), a **peptide**-based immunotherapy vaccine technology platform. A summary of the Company's product pipeline based on these proprietary technologies is provided in Figure 1, with greater details in the accompanying pages.

Figure 1

PRODUCT PIPELINE

MULTIKINE®		
Head and Neck Cancer	Neoadjuvant therapy for squamous cell carcinoma of the head and neck	Phase 3 Pivotal Study
HPV	Cervical dysplasia in HIV/HPV co-infected patients	Phase 1

LEAPS™ TECHNOLOGY		
CEL-2000 **CEL-4000**	Rheumatoid Arthitis	Phase 1 enabling studies (NIH Grant)
LEAPS™	COVID-19	Pre-clinical

Source: CEL-SCI Corporation.

MULTIKINE® IMMUNOTHERAPY

The Company's lead product candidate, Multikine®, is an investigational immunotherapy under development for the neoadjuvant treatment of advanced primary (previously untreated) head and neck cancer (squamous cell carcinoma), as well as **cervical dysplasia** in human immunodeficiency virus (HIV) and human papillomavirus (HPV) co-infected patients. Multikine® is comprised of a patented defined mixture of 14 human natural **cytokines** and cellular products, listed in Figure 12 (page 25). The pro-inflammatory cytokine mixture includes **interleukins**, **interferons**, **chemokines**, and other elements of the body's natural mix of defenses against cancer.

Multikine® is being used in a unique way compared to other cancer immunotherapies. Unlike conventional immunotherapies, which have traditionally been administered late in the disease progression (often after surgery, chemotherapy and/or radiation therapy), Multikine® is being developed as a first-line treatment to be given as a neoadjuvant, before any other therapies, as these can weaken the integrity of the immune system. Multikine® is administered locally and stimulates the immune system before it is weakened by both surgery and the toxic therapies that are administered to cancer patients, and by the cancer itself. The goal of Multikine® administration is to modulate the body's healthy immune system to elicit its own anti-tumor response to kill the tumor and the micrometastases that usually causes recurrence. According to CEL-SCI, Multikine® would be the world's first cancer immunotherapy drug to be administered immediately after diagnosis before surgery, which currently is the first of the standard of care (SOC) treatments for this indication.

The first indication being pursued for Multikine® is the neoadjuvant therapy of patients with advanced (stages 3 and 4) primary (untreated) squamous cell carcinoma of the head and neck. The Company has received Orphan Drug Status/designation from the U.S. Food and Drug Administration (FDA) for the neoadjuvant treatment of squamous cell carcinoma of the head and neck. Advanced primary head and neck cancer is a large unmet medical need that currently has only one recommended SOC, which is surgery, followed by either radiation or concurrent radiation/chemotherapy—with the last treatment for this indication approved by the FDA over 50 years ago. The

SOC for this cancer has not changed during the long Phase 3 study. CEL-SCI intends to demonstrate that Multikine® could become an integral first-line component of the current SOC regimen due to its effectiveness and safety profile.

CEL-SCI conducted a series of Phase 1 and Phase 2 clinical trials in over 200 patients throughout the U.S., Europe, Canada, and Israel, which demonstrated that Multikine® was safe and well tolerated, with significant clinical impact. In its most recent Phase 2 clinical trial for Multikine® in advanced primary head and neck cancer, CEL-SCI reported that approximately 10% of patients administered the Multikine® treatment regimen over a three-week period had no clinical or pathologic evidence of any remaining tumor after treatment. The Company also reported a 33% improvement in overall survival of Multikine®-treated patients over that in the literature for the same indication in that same study. In addition, these clinical studies found that Multikine® treatment resulted in positive effect on quality of life observations, including weight gain and reduction in pain, among others. Most importantly, investigators did not report a single severe adverse event associated with the use of Multikine® in any of the completed trials. Multikine® is currently being evaluated in a global pivotal randomized Phase 3 clinical trial (IT-MATTERS), the largest head and neck cancer study ever conducted in this indication.

In early May 2020, CEL-SCI announced that it had reached the required number of events for the completion of the IT-MATTERS Phase 3 trial and is proceeding with preparations for the analysis of the data. The primary endpoint of the study is a 10% increase in the overall survival of patients treated with the Multikine® treatment regimen + SOC versus patients treated with SOC only. The Company expects to file for regulatory approval in 2021.

Furthermore, in addition to the clinical trial results of Multikine® for the treatment of advanced head and neck cancer, early clinical trials have shown Multikine®'s potential as a treatment for cervical dysplasia/neoplasia (pre-cancer and cancer of the cervix).

Multikine® Phase 3 Study (IT-MATTERS)

In 2011, CEL-SCI initiated the Multikine® global pivotal randomized Phase 3 trial (IT-MATTERS) for patients with advanced primary head and neck cancer. The pivotal trial, which is composed of 928 newly diagnosed not yet treated head and neck cancer patients, is an open-label, global, randomized, controlled multi-center Phase 3 study. The IT-MATTERS trial was designed as an event-driven study and requires 298 deaths (events) to occur in the combined comparator arms of the study, to achieve an adequate level of statistical power to prove the survival benefit. It is important to note that the CEL-SCI study was designed to enroll those patients who have the worst survival outcome in head and neck cancer. Their outcome is substantially worse than that of an average head and neck cancer patient and a review of the latest data has shown no improvement in the treatment of these patients during the course of this Phase 3 study. This population's general poor prognosis is likely due to the physical location of the cancer in the oral cavity/soft palate and the low level of human papillomavirus (HPV) involvement in these tumors. The Phase 3 study was started in early 2011, finished full enrollment in September 2016, and reached the required number of deaths in early May 2020. The patients enrolled in the IT-MATTERS study appear to have been living longer than was expected when the study was planned.

Since data from other recent studies indicate that cancer immunotherapy can display a delayed or late survival benefit, CEL-SCI believes that the fact that it took longer than expected to reach the required number of events could be a good sign for the success of the study. Assuming a three-year survival rate of 50% (slightly above historical levels), and taking into account that the last patient was enrolled in September 2016 (well over three years ago), there should have been more than 400 deaths in the approximately 800 patients comprising the two comparator groups used for analysis of the study results (i.e., well above the required 298 events). Following a review in conjunction with outside experts, including analysis of the **Surveillance, Epidemiology, and End Results (SEER)** database (an authoritative source of information on cancer incidence and survival in the United States published by the National Cancer Institute) for the survival of similar head and neck cancer patients in the U.S. during the time of the Phase 3 study, the Company concluded that Multikine® appears to be the only factor capable of producing these results. This conclusion, if proven correct, bodes well for the success of the study.

Another factor that points toward a successful completion of the Phase 3 trial is that in 2017, 2018, 2019, and again in April 2020, the **Independent Data Monitoring Committee (IDMC)**, who is unblinded, reviewed the study's safety and efficacy indicators and recommended that the trial continue until the required number of events have been reached. If the IDMC thought the trial would not be successful, they could have called it "futile" as other IDMCs have done for companies such as Biogen, AbbVie, Mallinckrodt, and Clovis during 2019, or for the very similar Pfizer and Merck 'Javelin' head and neck study in March 2020.

Multikine® Competitive Advantages

Multikine®'s novel intended use as a neoadjuvant first-line treatment, which will be administered prior to initiating the current SOC regimen, its innovative mechanism of action, as well as its safety profile result in significant competitive advantages against other competing therapies.

First-line Treatment. Multikine® is being developed as a neoadjuvant, first-line treatment, to be given to advanced primary (previously untreated) head and neck cancer patients for three weeks before the current intent to cure SOC treatments. The current SOC treatment is normally scheduled and initiated within four weeks of a patient's diagnosis and is comprised of surgery and radiotherapy or surgery followed by concurrent chemo-radiotherapy. Both the SOC and the survival outcome did not change for the type of patients enrolled in CEL-SCI's study during this long Phase 3 study. CEL-SCI's objective is to establish a new intent to cure SOC comprised of Multikine® administered first followed by the current SOC. If Multikine® is approved and becomes part of a new intent to cure SOC, CEL-SCI believes it will be difficult, if not impossible, to conduct studies with other first-line treatments that could compete with Multikine® because ethically, patients could neither be denied nor could the first treatment with Multikine® be delayed, as a critical component of the intent to cure SOC.

Dual Mechanism of Action. Data from Phase 1 and 2 clinical trials suggest that Multikine®, administered locally, has the potential to produce both a direct effect on the tumor, as well as promote the generation of an anti-tumor immune response. The ability of Multikine® to elicit the direct killing of tumor cells allows it to eliminate cancer cells from around the **margin** of the tumor, which might be undetectable and thus not removed during surgery, as well as from the regional lymph nodes. It further reduces the likelihood that cancer cells outside of the main tumor mass will survive, and therefore reduces the possibility of recurrence. Additionally, Multikine® generates a robust and sustainable anti-tumor response and, separately, may render tumor cells more susceptible to subsequent radiation and chemotherapy treatments by promoting tumor cells entry into **cell cycle**. Therefore, the Company believes that the combination of Multikine® with surgery plus radiation/chemotherapy (SOC) should be more successful in eliminating the tumor than the current SOC alone.

Multitarget Flexibility and Additional Indications. Because it is comprised of multiple components, Multikine® is able to target multiple aspects of the tumor. This is unlike **monoclonal antibody (mAb)** therapies or other immunotherapies, which are directed against one specific target. In addition, because Multikine® is not tumor specific, it can potentially be used to address a wide range of solid tumors beyond head and neck cancer. The Company believes that Multikine® may also be useful in treating melanoma, cervical dysplasia/neoplasia, breast, skin, bladder, and prostate cancers.

Safety Profile. During Phase 1 and 2 clinical trials, Multikine® was reported by clinical investigators to be safe and well tolerated in more than 200 patients, with no severe adverse events reported by investigators that were associated with its use. Due to its reported lack of toxicity, it is possible that Multikine® can be combined with other cancer treatments to increase efficacy (e.g., as an adjunct to radiotherapy or chemotherapy). This is a significant advantage, as many immunotherapies are known to be associated with severe toxicities.

Non-Autologous Therapy. A significant limitation of cancer immunotherapies is that many are **autologous** in nature, indicating that they are made from the cancer patient's own tissues and are intended to treat only that patient. This is a costly, time consuming, and labor-intensive process. Multikine® is not an autologous therapy. It can be mass produced to exact specifications at the Company's manufacturing facility near Baltimore, MD and be readily and immediately available for use by physicians for cancer patients. It has a two-year shelf life when stored frozen at minus 20 degrees Celsius (°C).

LEAPS™ (LIGAND EPITOPE ANTIGEN PRESENTATION SYSTEM)

CEL-SCI's second proprietary technology platform, LEAPS™, is an immunotherapeutic/vaccine technology designed to stimulate the immune system to fight bacterial, viral, and parasitic infections more effectively, as well as autoimmune conditions, allergies, transplant rejection, and cancer. Administered as an immunotherapeutic/vaccine, the LEAPS™ compound consists of a small **T or Immune -cell binding ligand (TCBL/ICBL)** linked with a disease-associated peptide **antigen** and is delivered directly to the recipient by injection or mucosal absorption.

Regulation of the immune system is mainly conducted by **T-helper (Th) cells** (differentiated into various cell subsets, including the Th1, Th2, Th17, Th9, and Th22 subsets) as well as **T-regulatory (T-reg) cells**, via the secretion of cytokines. Differentiated Th cell subsets secrete different cytokines. Of particular interest to CEL-SCI are the Th1 and Th17-mediated immune responses. Th1 and Th17 are actively involved in an inflammatory cascade, with Th17 cells known to play an important role in the induction of autoimmune disease and Th1 cells associated with **hypersensitivity immune reactions**, exaggerated or inappropriate immune reactions against an antigen.

The TCBL/ICBL activates the immune system by targeting or binding to an antigen presenting cell, such as a **T-cell** and other immune cells. When a LEAPS™ formulation attaches to a certain T-cell, it causes that cell to activate a particular immune response, altering only select cytokines. Thus, the Company believes that its LEAPS™ technology platform has an advantage over other technologies since LEAPS™ vaccines can be designed to produce an immune response involving the specific T-cells needed for a therapeutic effect, depending on the type of LEAPS™ construct and TCBL/ICBL used. Two TCBLs of particular interest for CEL-SCI are TCBL peptides J (J-LEAPS™) and G (or the modified and more stable version of G, derG [derG-LEAPS™]). Conjugates of these appear to activate different sub-sets of T-cells, with J conjugates eliciting a **Th1 response**, and G conjugates directing a **Th2 response**, promoting **antibody** production. The Company has conducted a series of preclinical animal studies in several disease indications. In these studies, the LEAPS™ candidates have demonstrated efficacy as a therapeutic agent in rheumatoid arthritis (RA), H1N1 influenza infection, and breast cancer. In addition, LEAPS™ constructs have also shown some level of efficacy in myocarditis, lethal herpes simplex virus (HSV1), malaria, and Hepatitis B in preclinical animal studies.

Rheumatoid Arthritis (RA)

Two LEAPS™-based product candidates—CEL-2000 and CEL-4000—have shown the potential to block the progression of RA, a disease that may be driven by different types of inflammatory responses for each individual. Although the initiating events of RA are unknown, the disease is maintained by pro-inflammatory mediators, primarily Th1 and Th17 cell-driven autoimmune responses. CEL-2000, a J-LEAPS™ vaccine, blocked the progression of **collagen induced arthritis (CIA)** by immunomodulation of the Th17 response. CEL-4000, A derG-LEAPS™ vaccine, demonstrated therapeutic efficacy for the **PGIA/GIA** RA mouse models by stopping Th1 driven disease progression.

CEL-2000. CEL-2000 (J-CIIx) combines the J-TCBL with an **epitope** (the part of an antigen that is recognized by the immune system) of type II collagen. Data from animal studies demonstrated that CEL-2000 was effective in the Th17 driven CIA mouse model of RA as a therapy to block the progression of disease. Mice treated with CEL-2000 had much less swelling and inflammation when compared to untreated mice. The efficacy of CEL-2000 was similar to therapy with etanercept (Enbrel®), considered the therapeutic gold standard for RA. The therapeutic effect of CEL-2000 was accompanied by reduced serum levels of pro-inflammatory cytokines and increased levels of regulatory cytokines, showing a redirection away from the Th17 response and towards a Th1 response. Of note, a derG version of this vaccine was ineffective in this model.

CEL-4000. The second candidate being studied against RA is CEL-4000 (derG– PG70), consisting of the derG-TCBL and a **proteoglycan** peptide (PG70). Preclinical data for CEL-4000 indicates that it could be effective against RA cases where a Th1 signature is dominant. CEL-4000 significantly limited disease progression and reduced inflammatory responses in the Th1-driven PGIA and GIA mouse models of RA. Serum cytokine analysis demonstrated a shift from a pro-inflammatory to an anti-inflammatory/regulatory profile, leading to a reduction of pro-inflammatory Th1 and Th17 cells and an increase in the frequency of anti-inflammatory IL10, as well as protective T-reg cells in both models. The J-LEAPS™ version of this vaccine (J-PG70) was not effective in this model.

In May 2019, CEL-SCI announced that a newly discovered LEAPS™ conjugate vaccine, derG-PG275Cit could complement CEL-4000. Results showed that new derG-LEAPS™ conjugate, alone or together with CEL-4000, stopped the progression of RA in the PGIA/GIA model of RA. Results suggest that both conjugates appears to act on different immune pathways as they incorporate distinct PG epitopes involved in arthritis induction. Thus, a combination vaccine containing both LEAPS™ conjugates, CEL-4000 (DerG-PG70), and DerG-PG275Cit, could provide not only broader epitope coverage, but also a greater therapeutic effect than either vaccine alone.

Different Approaches to the Same Goal

The importance of LEAPS™'s ability to modulate the specific pro-inflammatory immune response based on what conjugate is used is demonstrated by the difference in efficacy of the J-TCBL (CEL-2000) and derG-TCBL (CEL-4000) versions of the LEAPS™ vaccines in animal models of disease. The CEL-4000 vaccine was effective in curtailing progression of RA in the Th1-driven PGIA/GIA model, whereas CEL-2000 was effective in blocking the progression of RA in the Th17-driven CIA animal model. It is possible that the failure of some patients to respond to certain therapies may reflect differences in the type of inflammatory response that may be driving their disease. Thus, in the future studies in the development of LEAPS™ vaccines and treatments, the knowledge of the T-cell cytokine profiles that drive a particular patient's disease can facilitate the choice of the use of appropriate LEAPS™ vaccine/treatment. Once the nature of the inflammatory response in a patient has been identified, the patient can be treated with the appropriate LEAPS™ vaccine with either a J-TCBL to counteract a Th17-driven response or a derG-TCBL to counteract a Th1-dominated response.

Rheumatoid Arthritis (RA) Vaccine Grants

Research for the development of the LEAPS™ technology as a treatment for RA has been funded via collaborations with the U.S. National Institutes of Health (NIH), U.S. Army, Navy, and universities. The Company has been awarded two **Small Business Innovation Research (SBIR)** grants from the National Institutes of Health: a $225,000 Phase 1 SBIR grant (July 2014) and a $1.5 million Phase 2 SBIR grant (September 2017). The grants provide funding to advance the LEAPS™ product candidates towards an **Investigational New Drug (IND)** application by funding IND enabling and additional mechanism of action studies, among other preclinical development activities.

COVID-19 Therapeutic Vaccine Candidate

On March 23, 2020, CEL-SCI announced that it signed a collaboration agreement with the University of Georgia's Center for Vaccines and Immunology to develop a LEAPS™ COVID-19 immunotherapy. The Company's treatment is targeted to patients who are at highest risk of dying from COVID-19 due to tissue damage from infection to the lungs. The LEAPS™ peptide technology can be used to construct immunotherapeutic peptides that exhibit both antiviral and anti-inflammatory properties. Consequently, these products not only target the virus infection against which they are directed, but also elicit the appropriate protective response against it.

Predictions of success using the LEAPS™ peptides against COVID-19 coronavirus are based on previous studies that found that LEAPS™-stimulated **dendritic cells (DCs)** were effective in reducing influenza virus (H1N1) replication in the lungs while enhancing survival of infected animals. The study showed the LEAPS™ influenza therapeutic product's ability to enhance the homing of LEAPS™-stimulated DCs into the lungs, resulting in a reduced influenza virus replication in the lungs by activating appropriate T-cell responses rather than an inflammatory response. Of particular interest is LEAPS™ ability to modulate the inflammatory cytokine storm response (to the influenza virus), believed to also be a significant contributor to mortality in severe COVID-19 cases.

Other Conditions and Uses

The LEAPS™ technology platform's efficacy and flexibility has been further validated in pre-clinical testing of additional indications and infectious conditions, including breast cancer, herpes simplex, and as an adjuvant for a malaria vaccine, as well as the Hepatitis B vaccine.

HEADQUARTERS, FACILITIES, AND EMPLOYEES

CEL-SCI was formed as a Colorado corporation in 1983. It is now headquartered in Vienna, Virginia, in close proximity to the FDA, the NIH, and the National Cancer Institute (NCI). CEL-SCI currently employs 46 individuals and operates its own state-of-the art **cGMP** and **BSL-1** manufacturing facility, with over 73,000 sq. ft. of manufacturing and R&D space.

Company Leadership

Management

Geert R. Kersten, Chief Executive Officer (CEO) and Director

Geert Kersten has served in his current leadership role of Chief Executive Officer (CEO) at CEL-SCI since 1995. Mr. Kersten has been with CEL-SCI from the early days of its inception since 1987. He has been involved in the pioneering field of cancer immunotherapy for almost three decades and has successfully led CEL-SCI through many challenging cycles in the biotechnology industry. Mr. Kersten also provides CEL-SCI with significant expertise in the fields of finance and law, with a unique vision of how the Company's Multikine® product will change the way cancer is treated. Prior to CEL-SCI, Mr. Kersten worked at the law firm of Finley & Kumble and worked at Source Capital, an investment banking firm located in McLean, Virginia. He is a native of Germany, graduated from Millfield School in England, and completed his studies in the U.S. Mr. Kersten completed his Undergraduate Degree in Accounting, received an MBA from George Washington University, and a law degree (JD) from American University in Washington, DC. Mr. Kersten is also the inventor of a patent on the potential use of Multikine® in managing cholesterol.

Eyal Talor, Ph.D., Chief Scientific Officer

Eyal Talor joined CEL-SCI in October 1993. In October 2009, Dr. Talor was promoted to Chief Scientific Officer. Prior to this promotion, Dr. Talor was the Senior Vice President of Research and Manufacturing. He is a clinical immunologist with over 26 years of hands-on management of clinical research and drug development for immunotherapy application; pre-clinical to Phase 3 in the biopharmaceutical industry. His expertise includes biopharmaceutical research and development (R&D) and biologics product development, GMP (Good Manufacturing Practices) manufacture, QC (Quality Control) testing, and the design and building of GMP manufacturing and testing facilities. He served as Director of Clinical Laboratories (certified by the State of Maryland) and has experience in the design of pre-clinical and clinical trials (Phase 1 - 3) and GCP (Good Clinical Practices) requirements. He also has broad experience in the different aspects of biological assay development, analytical methods validation, raw material specifications, and QC tests development under FDA/GMP, USP, and ICH guidelines. He has extensive experience in the preparation of documentation for IND (Investigational New Drug) and other regulatory submissions. His scientific area of expertise encompasses immune response assessment. He is the author of over 25 publications and has published a number of reviews on immune regulations in relation to clinical immunology. Before joining CEL-SCI, he was Director of R&D and Clinical Development at CBL, Inc., Principal Scientist - Project Director, and Clinical Laboratory Director at SRA Technologies, Inc. Prior to that, he was a full time faculty member at The Johns Hopkins University, Medical Intuitions; School of Public Health. He has invented technologies that are covered by ten issued patents; on Multikine®'s composition of matter and method of use in cancer and two platform Peptide technologies, Antigen Directed Apoptosis of T-cells ('Adapt') and Ligand Epitope Antigen Presentation System (LEAPS™), for the treatment of autoimmune diseases, asthma, allergy, transplantation rejection and infectious diseases. He also is responsible for numerous product and process inventions as well as a number of pending U.S. and PCT patent applications. He received his Ph.D. in Microbiology and Immunology from the University of Ottawa, Ottawa, Ontario, Canada, and had post-doctoral training in clinical and cellular immunology at The Johns Hopkins University, Baltimore, Maryland. He holds an Associate teaching position at the Johns Hopkins University Medical Institutions.

Dan Zimmerman, Ph.D., Senior Vice President of Research, Cellular Immunology

Daniel H. Zimmerman, Ph.D., is the Senior Vice President of Research, Cellular Immunology for CEL-SCI Corporation, and head of the LEAPS™ technology program. Dr. Zimmerman has invented technologies that are covered by over a dozen U.S. patents as well as many foreign equivalent patents. He is the author of over 40 scientific publications in the area of immunology and infectious diseases. He has been awarded numerous grants from the National Institutes of Health (NIH) and the Department of Defense (DOD). From 1969-1973, Dr. Zimmerman was a Senior Staff Fellow at NIH. For the following 25 years, he continued on at NIH as a guest worker. Dr Zimmerman received a Ph.D. in Biochemistry in 1969, a Masters in Zoology in 1966 from the University of Florida, and a B.S. in Biology from Emory and Henry College in 1963.

John Cipriano, Senior Vice President, Regulatory Affairs

John Cipriano is CEL-SCI's Senior Vice President of Regulatory Affairs for the past 15+ years. Mr. Cipriano brings to CEL-SCI over 30 years of experience in both biotech and pharmaceutical companies. In addition, he held positions at the U.S. FDA as Deputy Director, Division of Biologics Investigational New Drugs, Office of Biologics Research and Review, and was the Deputy Director, IND Branch, Division of Biologics Evaluation, Office of Biologics. Mr. Cipriano completed his B.S. in Pharmacy from the Massachusetts College of Pharmacy in Boston, Massachusetts. He received his M.S. in Pharmaceutical Chemistry from Purdue University in West Lafayette, Indiana.

Patricia B. Prichep, Senior Vice President, Operations

Patricia B. Prichep has over 30 years of experience in business operations and administration. She joined CEL-SCI in 1992 and has been CEL-SCI's Senior Vice President of Operations since March 1994. Between December 1992 and March 1994, Ms. Prichep was CEL-SCI's Director of Operations. Ms. Prichep became CEL-SCI's Corporate Secretary in May 2000. She is responsible for all day-to-day operations of the Company, including human resources and is the liaison with the auditing firm for financial reporting. From June 1990 to December 1992, Ms. Prichep was the Manager of Quality and Productivity for the NASD's Management, Systems and Support Department. She was responsible for the internal auditing and workflow analysis of operations. Between 1982 and 1990, Ms. Prichep was Vice President and Operations Manager for Source Capital, Ltd. She handled all operations and compliance for the company and was licensed as a securities broker. Ms. Prichep received a BA from the University of Bridgeport in Connecticut.

William "Brooke" Jones, Quality Assurance

William "Brooke" Jones has been with CEL-SCI since 1999 and has overall responsibility for Quality Assurance. Mr. Jones began his career in biotechnology in 1978 at the Fort Detrick, NCI- Frederick Cancer Research Center, where he was responsible for GMP compliance of fermentation-based, clinical trial drug products used by the National Cancer Institute (NCI). With nearly 30 years of management experience in biotechnology at such companies as Biogen and Novartis, Mr. Jones brings significant experience (both American and European) in the areas of Quality, Regulatory, and Validation. In addition to his responsibilities at Novartis in the U.S., Mr. Jones was also the Director of Quality Control and Quality Assurance at the Systemix Facility in Lyon, France, where he was involved in developing cell therapy-based clinical trial products derived from the Hematopoetic Stem Cell. Mr. Jones completed his Undergraduate degree in Biology at George Mason University and his Graduate Degree course work in Environmental Biology at Hood College.

Board of Directors

Geert R. Kersten, Chief Executive Officer and Director

Biograph on page 8.

Peter R. Young, Ph.D., Director

Peter R. Young, Ph.D. has been a Director of CEL-SCI since August 2002. Dr. Young has been a senior executive within the pharmaceutical industry in the U.S. and Canada for most of his career, originally in organizations that are now part of Sanofi S.A. Over the last 20 years, he has primarily held positions of CEO or Chief Financial Officer (CFO) and has extensive experience with acquisitions and equity financing. Since November 2001, Dr. Young has been the President of Agnus Dei, LLC, which has acted as a partner in an organization managing immune system clinics which treats patients with diseases such as cancer, multiple sclerosis (MS), and hepatitis. Between 1997 and 2006, Dr. Young was also the President and CEO of SRL Technology, Inc., a company involved in the development of pharmaceutical drug delivery systems. Between 1998 and 2001, Dr. Young was the CFO of Adams Laboratories, Inc., the developer of Mucinex®. Dr. Young received a Ph.D. in Organic Chemistry from the University of Bristol, England after obtaining his bachelor's degree in honors chemistry, mathematics, and economics. Subsequently, he qualified as a Fellow of the Chartered Institute of Management Accountants.

Bruno Baillavoine, Director

Bruno Baillavoine has been a Director of CEL-SCI since June 2015. Since 2017, Mr. Baillavoine has been the Director, Head of Pericles Group UK, the subsidiary of the Paris-based leading French consulting firm, which is an expert in the field of banking, finance, asset management, and insurance, with over 350 institutional clients. He has also been an advisor to the Board of CSL Inc, Combatives Sports League (a U.S. Mix Martial Arts Company) since 2017. Between 2010-2016, Mr. Baillavoine was a partner of Globomass Holdings Limited, a London, England-based developer of renewable energy projects from concept through final operations. From 2012-2016, Mr. Baillavoine was the Executive Chairman of Globomass Holdings. Globomass was acquired by CleanBay Inc. to which Mr. Baillavoine is an advisor to the Board and an investor. Between 1978 and 1982, he was the marketing manager of Ravenhead Ltd., a manufacturer of glass tableware, and part of United Distillers Group (later acquired by Grand Metropolitan). During this time, Mr. Baillavoine became the UK Business Manager, where he restored market share and profit for United Distillers. From 1982 to 1986, Mr. Baillavoine was Group Corporate Planning and Group Marketing Director for Prontaprint, where he expanded the number of shops to 500 locations in four years. Mr. Baillavoine joined Grand Metropolitan Plc between 1986-1988 (now Diageo Plc), an FTSE 100 beverage, food, hotel, and leisure company, as director in the Special Operations division. In this capacity, he developed plans for Grand Met's trouble-shooting division for over 20,000 Grand Met retail outlets. From 1988-1991, he was the Managing Director of Nutri Systems (UK) Ltd., a subsidiary of the U.S.-based provider of professionally supervised weight loss programs. Between 1991 and 1995, Mr. Baillavoine was Director of BET Group plc, a multinational business support services group, and in 1992, was promoted to the Managing Director for the manufacturing businesses. The £2.3 billion turnaround of BET during his tenure is one of the most successful turnarounds of a top 100 FTSE company. Since 1995, Mr. Baillavoine has held a number of CEO positions across a wide range of industries and geographical locations. Mr. Baillavoine has European and American educations (U.S. high school and University of Wisconsin Eau Claire 1972-1976).

Robert Watson, Director

Robert Watson joined Intermedix, Inc. in July 2017 as President of their Preparedness Technology Division. Immediately prior to joining Intermedix, he was the President and Chief Growth Officer of NantHealth, Inc. (Nasdaq: NH) from January 2015 to May 2017. Prior to NantHealth, he was President and CEO of Streamline Health, Inc. (Nasdaq: STRM) from January 2011 to January 2015. Mr. Watson has over 35 years of experience in the healthcare information technology industry as a CEO, board member, and advisor to multiple HCIT companies. He has participated in over 75 acquisitions, raised nearly $750 million in capital, completed three public offerings, and successfully sold four companies. Mr. Watson holds an MBA from the Wharton School of Business at the University of Pennsylvania and a BA degree from Syracuse University.

Milestones

In the past 18 months, the Company has achieved significant milestones, as highlighted below. Potential upcoming milestones are outlined thereafter.

Recent Milestones

- On May 4, 2020, the Company reached the targeted threshold of 298 events (deaths) required to conduct the data evaluation for its pivotal Phase 3 head and neck cancer study of Multikine®.
- On April 23, 2020, the Independent Data Monitoring Committee (IDMC) for CEL-SCI's Phase 3 clinical trial of Multikine® announced that it completed its most recent review of the Phase 3 study data, agreeing to continue the trial without change until the appropriate number of events have occurred.
- On March 26, 2020, the Company announced the closing of the offering of 630,500 shares of its common stock at a price of $12.22 per share, for total gross proceeds of approximately $7.7 million. Additionally, the Company has granted the underwriter a 45-day option to purchase up to 94,575 additional shares to cover over-allotments.
- On March 23, 2020, CEL-SCI announced that it had signed a collaboration agreement with the University of Georgia's Center for Vaccines and Immunology to develop LEAPS™ COVID-19 immunotherapy.
- In December 2019, the Company raised gross proceeds of approximately $5.5 million through an underwritten public offering of 606,395 shares of its common stock at a price of $9.07 per share. In January 2020, the underwriters fully exercised the over-allotment option of an additional 90,959 shares, bringing the total gross proceeds to approximately $6.325 million.
- On May 11, 2019 and July 3, 2019, CEL-SCI presented new data on its LEAPS™ therapeutic treatment for RA. The work was performed in conjunction with researchers at Rush University Medical Center, Chicago, Illinois.
- The U.S. Patent and Trademark Office granted CEL-SCI two patents for its LEAPS™ technology during fiscal 2019.
- In March and July 2019, two scientific articles regarding CEL-SCI's LEAPS™ program were published: (1) The Journal of Clinical & Cellular Immunology published "Why Don't We Have a Vaccine Against Autoimmune Diseases?" and (2) International Immunopharmacology published "Lessons From Next Generation Influenza Vaccines For Inflammatory Disease Therapies".
- On June 28, 2019, CEL-SCI joined the broad-market Russell 3000® Index, effective after the U.S. market opened on July 1, 2019. The Company raised approximately $14.5 million during fiscal 2019 through the exercise of warrants.

Potential Future Milestones

- Announce results from the Multikine® Phase 3 clinical trial in head and neck cancer (2020).
- File for regulatory approval of Multikine® in head and neck cancer (2021).
- FDA approval of Multikine® as neoadjuvant therapy in first-line patients with advanced head and neck cancer (2022).
- Results of animal studies for COVID 19 treatment vaccine (2020).

Intellectual Property

Patents and other proprietary rights are essential to CEL-SCI's business. CEL-SCI files patent applications to protect its technologies, inventions, and improvements to its inventions that the Company considers important to the development of its business. CEL-SCI'S intellectual property (IP) portfolio covers its proprietary technologies, including Multikine® and LEAPS™, by multiple issued patents and pending patent applications in the U.S. and in key foreign markets.

Multikine® is protected by a U.S. patent, which is a **composition-of-matter** patent issued in May 2005 that, in its current format, expires in 2023. Additional composition-of-matter patents for Multikine® have been issued in Germany, China, Japan, and three in Europe. In addition to the patents that offer certain protections for Multikine®, the method of manufacture for Multikine®, a complex biological product, is held by CEL-SCI as a trade secret. Figure 2 (page 13) lists the Company's IP portfolio as it relates to Multikine®.

LEAPS™ is protected by patents in the U.S. issued in February 2006, April 2007, August 2007, January 2019, and March 2019. The LEAPS™ patents include overlapping claims, with composition of both matter (new chemical entity), process, and methods-of-use to maximize and extend the coverage in their current format. One issued U.S. application is a joint application with Northeast Ohio Medical University (Neoucom), and CEL-SCI will share the ability to use the patent, unless CEL-SCI licenses the rights to the patent from Neoucom. CEL-SCI has four patent applications pending in the U.S. and one in Europe for LEAPS™, which, if issued, would extend protection through 2034, subject to any potential patent term extensions. Figure 3 (page 14) lists the Company's IP portfolio as it relates to LEAPS™.

Figure 2

INTELLECTUAL PROPERTY - MULTIKINE®

	Filing Date	Application #	Country	Status	Patent #	Issue Date	Expiration
CS-120	Method of Pre-Sensitizing Cancer Prior to Treatment with Radiation/Chemotherapy and a Novel Cytokine Mixture						
CS-120	7/3/2003	10/611,914	USA	Granted	6,896,879	5/24/2005	9/2/2023
CS-120	7/1/2004	PCT/US04/020998	PCT	Nationalized			
CS-120	7/1/2004	200480025403.6	PCT-China	Granted	200480025403.6	5/25/2011	7/1/2024
CS-120/CIP	6/28/2005	PCT/US05/22678	PCT	Nationalized			
CS-120/CIP	6/28/2005	5789138.4	PCT-Europe	Granted	1,773,368	5/4/2016	6/28/2025
CS-120/CIP	6/28/2005	2007-519321	PCT-Japan	Granted	5,122,279	11/2/2012	6/28/2025
CS-120/CIP	6/28/2005	60 2005 049 252.6	PCT-Germany	Granted	1,773,368	5/4/2016	6/28/2025
CS-120/CIP	6/28/2005	5789138.4	PCT-France	Granted	1,773,368	5/4/2016	6/28/2025
CS-120/CIP	6/28/2005	2 581 978	PCT-Spain	Granted	1,773,368	5/4/2016	6/28/2025
CS-122	A Method for Altering the Cd4/Cd8 Ratio and the Mononuclear Cellular Infiltrate into a Tumor						
CS-122	6/3/2005	PCT/US05/019263	PCT	Nationalized			
CS-122	6/3/2005	5756247.2	PCT-Europe	Granted	1,753,452	10/28/2015	6/3/2025
CS-122	6/3/2005	60 2005 047 788.8	PCT-Germany	Granted	1,753,452	10/28/2015	6/3/2025
CS-122	6/3/2005	5756247.2	PCT-France	Granted	1,753,452	10/28/2015	6/3/2025
CS-122	6/3/2005	5756247.2	PCT-Spain	Granted	1,753,452	10/28/2015	6/3/2025
CS-122	6/3/2005	5756247.2	PCT-Italy	Granted	1,753,452	10/28/2015	6/3/2025
CS-122	6/3/2005	5756247.2	PCT-UK	Granted	1,753,452	10/28/2015	6/3/2025
CS-123	Method for Managing Cholesterol with a Serum-Free and Mitogen Free Cytokine Mixture						
CS-123	7/29/2005	PCT/US05/26819	PCT	Nationalized			
CS-123	7/29/2005	5775596.9	PCT-Europe	Granted	1,773,395	6/22/2011	7/29/2025
CS-123	7/29/2005	5775596.9	PCT-Germany	Granted	1,773,395	6/22/2011	7/29/2025
CS-124	Method for Modulating HLA Class II Tumor Cell Surface Expression with a Cytokine Mixture						
CS-124	5/10/2006	PCT/US06/018055	PCT	Nationalized			
CS-124	5/10/2006	6770164.9	PCT-Europe	Granted	1,879,618	10/4/2017	5/10/2026
CS-124	5/10/2006	6770164.9	PCT-France	Granted	1,879,618	10/4/2017	5/10/2026
CS-124	5/10/2006	6770164.9	PCT-Germany	Granted	1,879,618	10/4/2017	5/10/2026
CS-124	5/10/2006	6770164.9	PCT-UK	Granted	1,879,618	10/4/2017	5/10/2026

Source: CEL-SCI Corporation.

Figure 3

INTELLECTUAL PROPERTY - LEAPS™

	Filing Date	Application #	Country	Status	Patent #	Issue Date	Expiration
CS-110	Peptide Constructs for Treating Autoimmune and Related Diseases						
CS-124	10/27/2000	PCT/US00/41647	PCT	Nationalized			
CS-124	4/26/2002	10/111,602	USA	Granted	7,199,216	4/3/2007	7/13/2022
CS-124	1/19/2007	11/625,202	USA-Cont.	Pending			
CS-111	Methods of Preparation and Composition of Peptide Constructs Useful for Treatment						
CS-111	10/27/2000	PCT/US00/41646	PCT	Nationalized			
CS-111	4/26/2002	10/111,645	USA	Granted	6,995,237	2/7/2006	9/17/2021
CS-111	12/12/2005	11/298,718	USA-Cont.	Granted	7,256,254	8/14/2007	9/17/2021
CS-127	Methods of Preparation and Composition of Peptide Constructs Useful for Treatment of Rheumatoid Arthritis						
CS-127	3/14/2008	61/036,566	USA-Prov.	Converted to PCT			
CS-127	9/26/2008	61/100,383	USA-Prov.	Converted to PCT			
CS-127	3/16/2009	PCT/US09/37312	PCT	Nationalized			
CS-127	3/16/2009	12/922,687	USA	Pending			
CS-127	9/14/2010	9718824.7	PCT-Europe	Granted	2,254,588	10/11/2017	3/16/2029
CS-127	9/14/2010	9718824.7	PCT-UK	Granted	2,254,588	10/11/2017	3/16/2029
CS-127	9/14/2010	9718824.7	PCT-France	Granted	2,254,588	10/11/2017	3/16/2029
CS-127	9/14/2010	9718824.7	PCT-Germany	Granted	2,254,588	10/11/2017	3/16/2029
CS-130R	Method for Inducing an Immune Response Against Avian, Swine, Spanish, H1N1, H5N9 Influenza Viruses						
CS-130R	12/13/2010	61/422,474	USA-Prov.	Converted to PCT			
CS-130R	12/13/2011	PCT/US11/64746	PCT	Nationalized			
CS-130R	6/13/2013	13/994,092	USA	Granted	10,238,747	3/26/2019	5/14/2032
CS-1334	Method for Inducing an Immune Response for Treatment of Cancer and Autoimmune Diseases or Conditions						
CS-1334	5/24/2012	PCT/US12/39474	PCT	Nationalized			
CS-1334	11/25/2013	14/122,240	USA	Granted	10,179,164 B2	1/15/2019	5/24/2032
CS-1325	Method for Inducing an Immune Response and Formulations Thereof						
CS-1325	5/24/2012	PCT/US12/39473	PCT	Nationalized	(Ownership-CEL-SCI/NIH)		
CS-1325	11/25/2013	14/122,238	USA	Granted	10,179,174 B2	1/15/2019	5/24/2032
CS-136	Methods of Preparation and Composition of Peptide Cnstructs Useful for Treatment of Rheumatoid Arthritis						
CS-136PROV2.3	4/28/2014	PCT/US2014/035757	PCT	Nationalized			
CS-136PROV2.3	10/23/2015	14787690.8	PCT-Europe	Pending	(Ownership-CEL-SCI/Rush		
CS-136PROV2.3	1/25/2016	14/907,520	PCT-USA	Pending	(Ownership-CEL-SCI/Rush		
CS-138/R	Peptides and Conjugates for Treatment of Arthritis						
CS-138/R	5/11/2019	62/846,609	USA-Prov.	Pending	(Ownership-CEL-SCI/Rush		

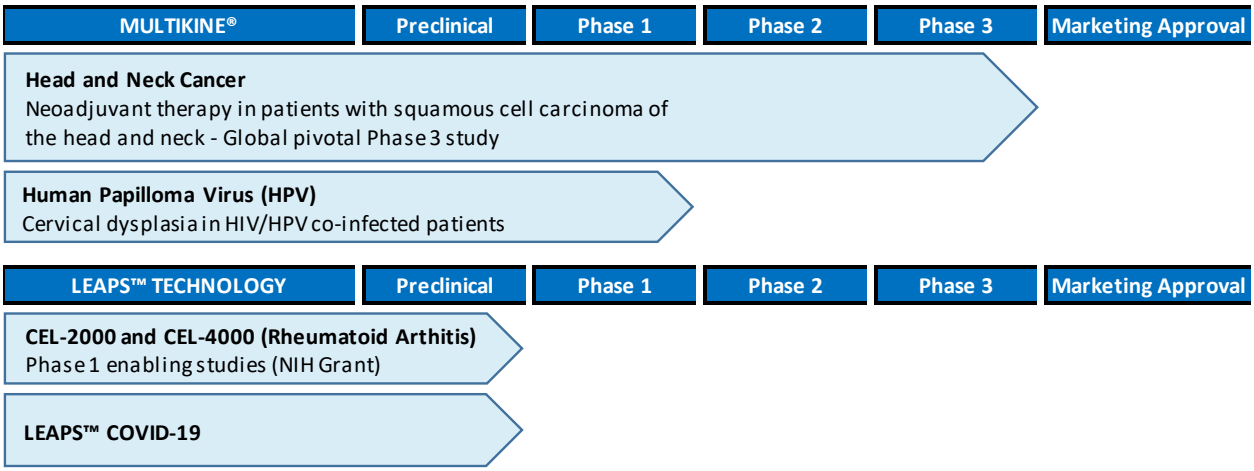
Source: CEL-SCI Corporation.

Core Story

CEL-SCI Corporation ("CEL-SCI" or "the Company") is a clinical-stage biotechnology company involved in the research and development of immunotherapy products and technologies to treat cancer, autoimmune, and infectious diseases that address significant unmet medical needs. The Company's vision is to change the way cancer and other diseases are treated, as it strives to develop novel therapies with the potential to activate and utilize the body's own immune defense system against the disease, while delivering minimal toxicity to normal cells and organ systems. The Company is currently focused on developing product candidates based on two innovative technologies, as shown in Figure 4: (1) Multikine® (Leukocyte Interleukin, Injection), a next-generation, comprehensive immunotherapy in Phase 3 as a first-line treatment for head and neck cancer; and (2) LEAPS™ (Ligand Epitope Antigen Presentation System), a peptide-based immunotherapy vaccine technology platform.

Figure 4

PRODUCT PIPELINE



Source: CEL-SCI Corporation.

The Company's lead product candidate, Multikine®, is an investigational immunotherapy under development for the treatment of certain head and neck cancers, as well as cervical dysplasia in human immunodeficiency virus (HIV) and human papillomavirus (HPV) co-infected patients. Multikine® is currently in a global pivotal randomized Phase 3 clinical trial for patients who are newly diagnosed (not yet treated) with advanced cancer of the head and neck, for which the Company has received Orphan Drug Status/designation from the U.S. Food and Drug Administration (FDA). The Phase 3 trial is the largest head and neck cancer study ever conducted and is taking place in the U.S. and 23 other countries. The Company believes that advanced primary head and neck cancer is a large unmet medical need that has only one recommended standard of care (SOC), with the last FDA approval for advanced primary head and neck cancer made over 50 years ago.

In May 2020, CEL-SCI announced that it had reached the required number of events for the completion of its Phase 3 trial. The Company is proceeding with the preparation for analysis of the data and expects to file for regulatory approval in 2021.

Multikine® is being used differently than other cancer immune therapies. The investigational therapeutic agent is given locally at the site of the tumor as a first-line treatment, before surgery, radiation and/or chemotherapy (as these therapies are known to weaken the immune system). The goal is to modulate the body's immune system to use its own anti-tumor response to kill the tumor and micrometastases that usually cause recurrence of the cancer and to do so before surgery, radiation, and chemotherapy have severely weakened the immune system. According to CEL-SCI, if approved, Multikine® would be the world's first cancer immunotherapy drug to be administered prior to surgery and immediately following diagnosis.

In addition to Multikine®, CEL-SCI is also developing LEAPS™, a propriety vaccine technology platform. LEAPS™ is a new class of drug that acts early to treat autoimmune and infectious diseases. Using LEAPS™, the Company has developed two investigational therapeutic vaccine product candidates, CEL-2000, and CEL-4000, under development to treat rheumatoid arthritis (RA) as well as a therapeutic candidate for COVID-19. CEL-SCI was awarded a Phase 2 Small Business Innovation Research (SBIR) grant of $1.5 million from the National Institutes of Health (NIH) in September 2017. This grant will provide funding to allow CEL-SCI to advance its first LEAPS™ product candidate, CEL-4000, towards an Investigational New Drug (IND) application.

CEL-SCI's Manufacturing Facility

CEL-SCI operates a dedicated state-of-the art facility with over 73,000 sq. ft. of manufacturing and R&D space available. The cGMP and BSL-1 facility was built specifically for Multikine® and produced multiple clinical lots of its investigational biological product candidate to supply the Phase 3 clinical trial. Upon commercial approval, CEL-SCI intends to manufacture Multikine® in a proprietary manner in the same commercial scale-ready manufacturing facility. The facility has passed quality systems review by a **European Union Qualified Person (QP)** on several occasions and has been inspected by the QP for the manufacture and release of Sterile Medicinal Products (per ICH and EU directives).

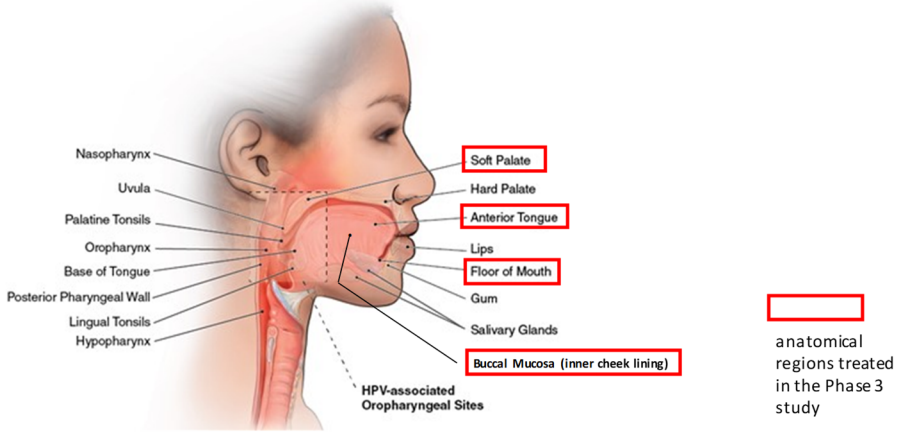
CEL-SCI believes that manufacturing is a strategic asset. According to the Company, manufacturing in-house helps protect its IP and allows for more control when working with the FDA and other regulators to secure approval of Multikine®. Multikine® is a complex **biologic** requiring special manufacturing, and the Company has spent over 10 years and over $80 million developing and validating the Multikine® manufacturing process, acquiring significant "know how" as well as trade secrets. This can not only produce competitive advantages but signifies a significant barrier to entry for any future similar or generic competitive technologies.

HEAD AND NECK CANCER

Head and neck cancer is the sixth most frequently occurring cancer worldwide. Approximately 90% of head and neck cancers originate in the squamous cells—thin, flat cells that line the mucosal surfaces (mouth, nose, and throat) of the head and neck (and other mucosal surfaces)—and are thus called squamous cell carcinomas. As depicted in Figure 5, this group of cancers includes cancer of the oral cavities (cheeks, lips, gums, tongue, hard and soft palate, and mouth floor), salivary glands, paranasal sinuses and nasal cavity, pharynx, larynx (voice box), and lymph nodes. In total, there are more than 30 locations in the head and neck for cancer to develop (Sources: American Dental Association). Cancers of the brain, eye, and thyroid are not typically classified as head and neck cancers. Most squamous cell carcinomas are traditionally considered tobacco and alcohol exposure related. However, high risk human papillomaviruses (HPV), mainly HPV type 16 (HPV16), have recently been recognized as causally related to a subset of oropharyngeal squamous cell carcinomas (Source: *PLoS One*, 13(2), 2018).

Figure 5

COMMON HEAD AND NECK CANCER SITES



Source: Centers for Disease Control and Prevention (CDC).

Often cancer begins in one area, such as the tongue, and spreads to other adjacent anatomical areas, including the lymph nodes. This effect is known as tumor **metastasis** and is associated with cancer recurrence and decreased survival. Metastasis and cancer recurrence are significant clinical issues in head and neck cancers. The American Cancer Society estimates that 10% to 40% of patients whose oral cancer was considered "cured" will likely develop cancer of the oral cavity again (a local recurrence) or of a nearby organ, such as the larynx, esophagus (regional recurrence), or lung (distal recurrence). This number increases for patients diagnosed at a late stage disease, such as the CEL-SCI study, where even after successful treatment and remission, 30% to 60% will develop recurrent local cancer or second primary cancers (Source: *Annals of Oncology*, Vol. 30 (5):744–756, 2019). The recurrence rate affects the five-year survival of the disease. In the U.S., the 5-year relative survival rate for head and neck cancers in general is 65% (for all the types of head and neck cancer, encompassing all stages at diagnosis). Although this constitutes a 28% increase from the 1975-1977 levels (53% five-year survival rate), this improvement considerably lags the 40% increase in five-year survival rate for overall cancer during the same period (Source: American Cancer Society's *Cancer Facts and Figures 2020*).

However, there are some head and neck cancer sites that have a worse outcome than others. CEL-SCI's Phase 3 study focuses on patients with Stage III-IVa cancer (advanced) in anatomical locations of the head and neck that are known to present a worse prognosis (cancers of the anterior tongue, soft palate, floor of the mouth, and cheek). An analysis conducted by external statistical experts using the SEER data base found that the combined overall survival of the 'SEER' population having the same characteristics of the specific type of patients enrolled in the Phase 3 study (type of cancer, tumor stage, location, etc.) was found to be 47% at three years and about 37% at five years. This analysis reflects the U.S. (SOC) treatment during the time of the Company's Phase 3 trial. Treatment has not gotten better and the SOC has not changed during this long Phase 3 study. While Keytruda® was approved for head and neck cancer in 2019, it was not approved to be used for advanced primary patients; it was approved to be used for recurrent patients and those who cannot have surgery as a first treatment.

CEL-SCI believes that the low rate of long-term survival from head and neck cancers is due to inadequacies in the treatment regimen that composes the current SOC. The current SOC for head and neck cancer patients is surgery followed by radiation or concurrent radiochemotherapy. However, if after surgery, patients still exhibit micrometastases around the area of the tumor or in the adjacent or distally located lymph nodes, surgery is followed by concurrent radiation and chemotherapy. Nevertheless, surgeries, radiation, and chemotherapy often miss outlying tumor cells that are located around the margins of the tumor (causing local recurrence) or in the lymph nodes (responsible for regional recurrence). Additionally, concurrent radiation and chemotherapy subjects patients to high levels of toxicity, which can cause severe side effects or even death. Another side effect of these (SOC) treatments is immunosuppression, which negatively impacts the efficacy of utilizing immunotherapy after SOC and chemotherapy.

CEL-SCI's comprehensive cancer immunotherapeutic approach with Multikine® (further detailed on pages 25-43) has already been shown in early studies to address both local and regional cancer recurrences by eliminating tumor cells from these areas before the patient undergoes first-line SOC therapies. If Multikine® treatment is successful, patients in the future may not need to receive as intensive a radiation/chemotherapy regimen following surgery, potentially lessening significant toxicity to the body. Consequently, the Company believes that Multikine® could become a new routine and vital addition to the SOC regimen, administered before surgery, when the immune system has not yet been suppressed by subsequent treatments. CEL-SCI also believes that providing Multikine® prior to initiating radiation or chemotherapy could enhance the effects of these treatments by making the residual cancer cells more susceptible to both radiation and chemotherapy. Greater details of Multikine®'s novel mode of action are presented on pages 27-30.

Incidence, Prevalence, and Market Size

Worldwide, head and neck cancer is the sixth most common cancer in the world and is expected to account for more than 650,000 occurrences and 330,000 deaths in 2020 (Source: the Head and Neck Cancer Alliance). In the U.S., head and neck cancers account for approximately 3% of all cancers, representing over 53,000 new cases and over 10,000 deaths each year, while Europe accounts for approximately 150,000 cases annually (Sources: American Cancer Society and *PLoS One*, 13(2), 2018). Figure 6 lists the estimated new cancer cases and deaths in the U.S. for several types of head and neck cancer during 2020.

Figure 6

HEAD & NECK CANCERS STATISTICS

	Estimated New Cases			Estimated Deaths		
	Both Sexes	Male	Female	Both Sexes	Male	Female
All Cancer Types	1,806,590	893,660	912,930	606,520	321,160	285,360
Oral Cavity and pharynx	53,260	38,380	14,880	10,750	7,760	2,990
Tongue	17,660	12,960	4,700	2,830	1,980	850
Mouth	14,320	8,430	5,890	2,660	1,690	970
Pharynx	17,950	14,630	3,320	3,640	2,820	820
Other Oral cavity	3,330	2,360	970	1,620	1,270	350

Source: American Cancer Society, Inc. (2020)

The oncology market is one of the largest pharmaceutical markets and, with the introduction of improved treatments, it is expected to continue to expand. Globally, the oncology market is forecast to grow at an average annual growth rate of 12.3% to $196.2 billion in 2026, up from $77.3 billion in 2018 (Source: Coherent Market Insights' *Oncology Drugs Market Analysis*, December 2018). Specifically, the global market for head and neck cancer is expected to reach $4.5 billion by 2027, growing at CAGR 17.3%, driven by a rising epidemic of HPV-associated head and neck cancer, and the anticipated approval of novel immunotherapy options (Source: iHealthcareAnalyst, Inc.'s *Head and Neck Squamous Cell Carcinoma Market by Drug Class*, February 2020).

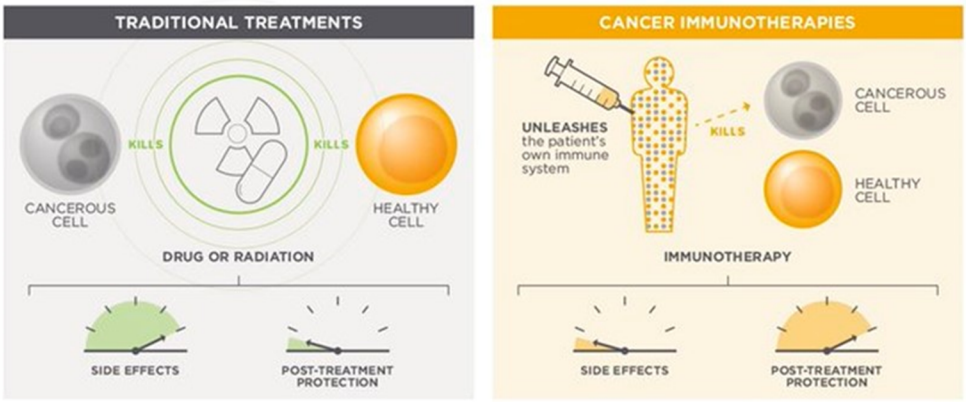
IMMUNOTHERAPY

Healthcare companies are focused on developing new cancer therapies with improved efficacies and more favorable safety profiles, in part due to the severe toxicities and stagnant survival rates associated with many current cancer treatments. Specifically, companies are attempting to create treatments that selectively address only the cancer cells without damaging surrounding healthy cells. One prominent method, called immunotherapy, utilizes the body's own immune system to fight the disease.

Immunotherapy, or biological therapy, is a type of cancer treatment that boosts the body's natural defenses to fight cancer. It uses substances made by the body or in a laboratory to improve immune system function, helping the body fight cancer by eliciting the following effects: (1) stop or slow the growth of cancer cells; (2) stop cancer from spreading to other parts of the body; and (3) help the immune system work better at destroying cancer cells.

Immunotherapies also provide significant advantages over conventional cancer treatments, such as chemotherapy or radiation. Since immunotherapy can train the immune system to recognize and remember cancer cells, this "immune memory" may result in longer-lasting remissions. Clinical studies on long-term overall survival have shown that the beneficial responses to cancer immunotherapy treatment are maintained even after treatment is completed. Furthermore, since cancer immunotherapy is focused on the immune system and may be more targeted than conventional cancer treatments, it normally presents a better safety profile when it comes to side effects. Conventional chemical or radiological cancer therapy normally affects both the cancerous cells as well as healthy tissues, which results in common side effects, such as hair loss and nausea, but also can cause immunosuppression, weakening the body's immune system and affecting the body's post-treatment protection against infections and recurrent cancers, as illustrated in Figure 7 (page 19) (Source: Cancer Research Institute).

Figure 7
IMMUNOTHERAPY VS. CHEMOTHERAPY



Source: Adaptive Biotechnologies.

As part of its normal function, the immune system detects and destroys abnormal cells and most likely prevents or curbs the growth of many cancers. However, on its own, the body's immune system cannot typically eliminate all cancers. This is due to several causes: (1) development of **tumor tolerance**; (2) inadequate immune responses; and (3) the cancer cell's ability to ward off an attack. Since cancer cells are not physically introduced to the body as foreign substances, but rather are derived from the body's own cells, the immune system does not always recognize cancer cells as foreign. When the immune system views cancer cells as part of the "self," the effect is called tumor tolerance. Moreover, even if the immune system distinguishes tumor cells from the "self" and attempts to attack them, the response is often inadequate because it is too weak to destroy cancer cells, is not targeted to the correct body region, or is not utilizing the most effective "killer" cells. In addition, tumors protect themselves against discovery by secreting substances that suppress the activation of the body's anti-tumor killer cells, eliminating cellular components that the immune system uses to recognize diseased or cancerous cells, and not expressing cell-surface molecules that are typically needed for an immune cell to induce **apoptosis** of the cancer cell. These tumor defense mechanisms allow cancer cells to grow into a large tumor mass.

Outside stimulation with immunotherapies designed to overcome the immune system's natural limitations can both enable recognition of a tumor as a foreign diseased entity and increase the efficacy of killer cells at combating the cancer. Immunotherapies and biological agents encompass passive and active therapies. These therapies differ based on mechanisms of action and effect on the immune system but have many of the same limitations.

- *Passive Agents.* Passive immunotherapies do not stimulate the immune system to eradicate diseased cells. Rather, components of the immune system are formulated *ex vivo* and then administered to patients.

- *Active Agents.* An active immunotherapy triggers the immune system to attack cancer cells. Primary examples of active immunotherapies include cancer vaccines, which aim to cause the immune system to react against a select antigen; cellular therapies, a technique designed to improve upon distinct parts of the immune system; and **adjuvant**s, which are given in conjunction with another treatment.

Types of Cancer Immunotherapies

The most conventional immunotherapy approaches are described in the accompanying section, followed by an in-depth description of CEL-SCI's novel immune simulator and comprehensive immunotherapy, Multikine®.

Monoclonal Antibodies (mAbs)

Monoclonal antibodies (mAbs) are one of the more widely used passive immunotherapies. Antibodies are produced naturally by a person's body to help the immune system recognize germs that cause disease, such as bacteria and viruses, and mark them for destruction. Monoclonal antibodies consist of a single antibody type that has been engineered to recognize and bind to one particular antigen. Antigens are the substances on diseased cells, viruses, fungi, bacteria, and toxins that signal a foreign entity. mAbs are highly specific in that they target and attach only to defined antigenic sites on a select cell. After binding to the predetermined antigen on the surface of a diseased cell, the mAbs induces apoptosis of that cell.

Some mAbs mark cancer cells so that the immune system will better recognize and destroy them. An example is rituximab, which binds to a protein present on some types of cancer cells, causing the immune system to kill them. Other mAbs bring T-cells close to cancer cells, helping the immune cells kill the cancer cells. In addition, some mAb technologies, called **immunomodulatory** mAbs, are considered active therapy as they operate by interacting with components of the immune system in order to elicit a novel response or reinstate an existing anticancer immune response (Source: *Oncotarget*. Vol. 5(24): 12472–12508, 2014). Yet, mAbs do not always function as anticipated and are associated with several limitations, including usage, antigen expression, mutated tumor cells, and toxicity, as briefly described below.

- *Usage.* After chemotherapy and radiation, the immune system is weakened and the effectiveness of mAbs therapy is limited. Yet, many mAbs are not administered as a first-line therapy, or if they are, are given in conjunction with a SOC and not before the SOC is employed.

- *Antigen Expression.* The same antigen is not always expressed on every patient's cancer. For instance, Genentech, Inc.'s (DNA-NYSE) Herceptin® treats metastatic breast cancer that possesses **human epidermal growth factor receptor 2 (HER2+)**; however, only approximately 25% of breast cancer patients have HER2+ on their tumors (Source: Genentech, Inc.). CEL-SCI believes that developing an antigen-targeted therapy for each subgroup of patients within a cancer indication could likely be a costly endeavor.

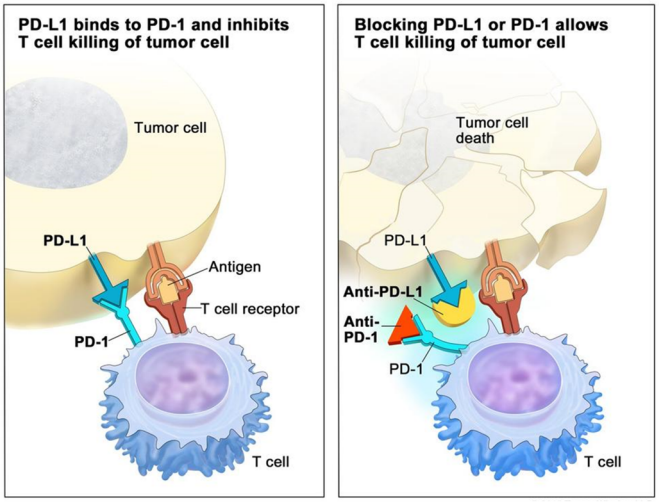
- *Mutations and Toxicity.* As a result of chemotherapy and radiation, tumor cells can mutate. The target antigens on the tumor's surface can change, limiting the effectiveness of the targeted mAbs therapy. In addition, mAbs have not always been as pure, specific, or as safe in practice as they had been thought to be. When administered systemically in high doses, some mAbs therapies are more toxic than expected. In contrast, Multikine® has not been found to be toxic.

Checkpoint Inhibitors

Checkpoint inhibitors are immunomodulatory therapies that work by exposing cancer cells to the immune system for attack. Adaptive immune cells, like T-cells, are selective components of the immune system attacking specific antigens. T-cells roam the body looking for foreign cells by using proteins receptors located on their surface to exchange signals with other cells and help them differentiate healthy cells from cancer cells. During this exchange of signals, called a checkpoint, cell surface proteins bind together with the T-cell, telling the immune system they are normal cells and sending an "off" signal to the T-cell. However, because cancer cells are the body's own mutated cells, the immune system does not always recognize them as foreign. Many types of cancer cells can send deceptive signals at checkpoints that bind to the protein receptors of the T-cells, making them appear as normal cells.

Checkpoint inhibitors work by blocking the receptors that cancer cells use to send signals to T-cells. This prevents the "off" signal from being sent, allowing the T-cells to kill cancer cells, as seen in Figure 8. When the signal is blocked, T-cells may be better able to differentiate a cancer cell from a healthy cell and launch an attack. However, because checkpoint inhibitors stimulate the immune system, they may cause immune cells to attack healthy cells, triggering a variety of side effects. Although relatively well tolerated, given the mechanism of action for these agents, most side effects are immune-related and result from an overactive immune system (Source: Cancer Research Institute).

Figure 8
CHECKPOINT INHIBITORS



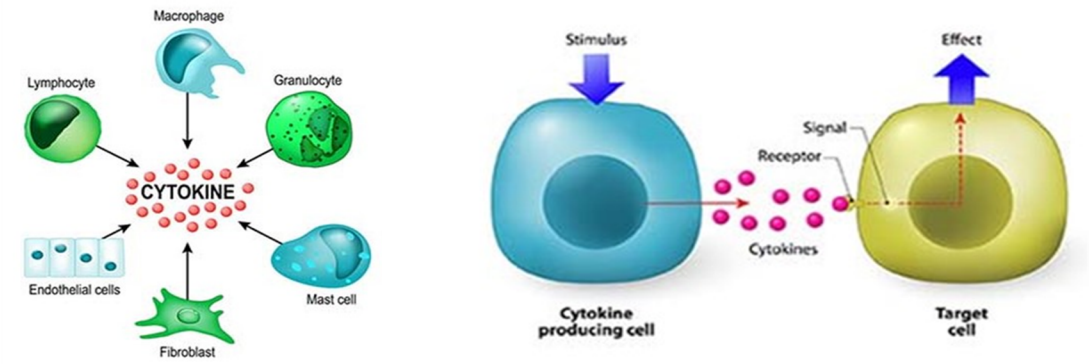
Source: NIH's National Cancer Institute.

In 2011, the FDA approved the first checkpoint inhibitor immunotherapy for the treatment of cancer—ipilimumab (Yervoy®) for melanoma. As of 2020, seven checkpoint inhibitors have been approved for multiple cancer types, targeting the PD-1, PD-L1, and CTLA-4 immune checkpoints (Figure 10, page 22). In particular, two check point inhibitors have received FDA approval for the treatment of head and neck cancer: Pembrolizumab (Keytruda®) by-Merck & Co., for the treatment of head and neck squamous cell cancer; and Nivolumab (Opdivo®), by Bristol-Myers Squibb, for the treatment of patients with recurrent or metastatic squamous cell carcinoma of the head and neck. Due to their potential to enhance the effectiveness of immune responses, many different checkpoint inhibitors are currently being evaluated, both alone and in combination with other treatments, in a variety of cancer types in clinical trials (Source: ONS Voice).

Cytokine Immunomodulatory Therapy

Cytokines are protein molecules that help regulate and direct the immune system. Cells release cytokines, which act as messengers to other cells and are crucial in controlling the growth and activity of other immune system cells and blood cells, as depicted in Figure 9. Cytokines play a key role in controlling the body's immune and inflammation responses. They also help to boost anti-cancer activity by sending signals that can help make abnormal cells die and normal cells live longer (Source: American Cancer Society).

Figure 9
CYTOKINES



Source: microbenotes.com.

Taken as a family, cytokines regulate virtually all biological functions. Thus, these messenger molecules can be used as cancer therapeutic agents by trying to harness the biological potency of specific cytokines to elicit novel or strengthen pre-existent tumor-targeting immune responses, and to prevent or manage chemotherapy side effects. To accomplish this, specific cytokines are synthesized in the lab and injected in larger doses than the body would normally produce. The two most common cytokines used in cancer therapy are interleukins (IL) and interferons (INF).

Interleukins (IL) are a group of cytokines that act as chemical signals between white blood cells. There are more than a dozen interleukins, including Interleukin 2 (IL-2), which is also called T-cell growth factor. IL-2 is naturally produced by the body to help fight infection and prevent autoimmune diseases. IL-2 boosts the number of white blood cells in the body, including **natural killer (NK) cells**. Increasing these cells can cause an immune response against cancer. IL-2 also helps B cells (another type of white blood cell) produce certain substances that can target cancer cells. IL-2 can be used as a single drug treatment or can be combined with chemotherapy or with other cytokines. A man-made version of IL-2, Aldesleukin (Proleukin®), is approved to treat advanced kidney cancer and metastatic melanoma. Other interleukins, such as IL-7, IL-12, and IL-21, continue to be studied for use against cancer too, both as adjuvants and as stand-alone agents.

Interferons (IFN) are immune proteins that help the body resist virus infections and cancers. The types of interferon are named after the first 3 letters of the Greek alphabet: IFN-alfa, IFN-beta, and IFN-gamma. Only IFN-alfa is used to treat cancer as it boosts the ability of certain immune cells to attack cancer cells. It may also slow the growth of cancer cells directly, as well as the blood vessels that tumors need to grow (Source: American Cancer Society). Currently, there are four FDA-approved cytokine immunotherapies for the treatment of subsets of patients with kidney cancer, leukemia, lymphoma, melanoma, and sarcoma. Figure 10 lists the approved immunotherapies—both checkpoint inhibitors and cytokine therapies—approved by the FDA.

Figure 10
SELECTED FDA APPROVED IMMUNOMODULATORS

Checkpoint inhibitors			
Compound	**Brand Name**	**Target**	**Indication**
Atezolizumab	(Tecentriq®)	PD-1/PD-L1 pathway	Some types of bladder cancer, breast cancer, and lung cancer
Avelumab	(Bavencio®)	PD-1/PD-L1 pathway	Some types of bladder cancer, kidney cancer, and Merkel cell carcinoma
Cemiplimab	(Libtayo®)	PD-1/PD-L1 pathway	Some types of cutaneous squamous cell carcinoma, a type of skin cancer
Durvalumab	(Imfinzi™)	PD-1/PD-L1 pathway	Some types of bladder cancer and lung cancer
Ipilimumab	(Yervoy®)	CTLA-4 pathway	Some types of melanoma and liver cancer
Nivolumab	(Opdivo®)	PD-1/PD-L1 pathway	Some types of bladder cancer, colorectal cancer, head and neck cancer, kidney cancer, liver cancer, lung cancer, lymphoma, and melanoma
Pembrolizumab	(Keytruda®)	PD-1/PD-L1 pathway	Some types of bladder cancer, cervical cancer, colorectal cancer, esophageal cancer, head and neck cancer, kidney cancer, liver cancer, lung cancer, lymphoma, melanoma, and stomach cancer, as well aspatients with cancers of any type that present with a certain genetic mutation (MSI-high).
Cytokines			
Compound	**Brand Name**	**Target**	**Indication**
Aldesleukin	(Proleukin®)	IL-2/IL-2R pathway	Some types of kidney cancer and melanoma
Interferon alfa-2a:		IFNAR1/2 pathway	Some types of leukemia and sarcoma
Interferon alfa-2b	(Intron A®)	IFNAR1/2 pathway	Some types of leukemia, lymphoma, melanoma, and sarcoma
Peginterferon alfa-2b	(Sylatron®/PEG-Intron®)	IFNAR1	Some types of melanoma

Source: Cancer Research Institute.

Cancer Vaccines

Unlike traditional vaccines intended to directly prevent diseases such as polio, smallpox, or measles, cancer vaccines do not prevent cancer but are used to treat specific cancers and prevent conditions that may cause cancer. Vaccines for cancer come in two categories: prophylactic and therapeutic. There are currently four vaccines that are approved by the FDA that can help prevent cancer (prophylactic), in addition to three FDA-approved vaccines for the treatment of cancer (therapeutic), as seen in Figure 11.

Figure 11
FDA-APPROVED CANCER VACCINES

Prophylactic		
Name	Protects against HPV strains	Can help prevent the development of HPV-related:
Cervarix® (HPV)	16 and 18	Anal, cervical, head and neck, penile, vulvar, and vaginal cancers
Gardasil® (HPV)	16, 18, 6, and 11	Anal, cervical, head and neck, penile, vulvar, and vaginal cancers
Gardasil-9® (HPV)	16, 18, 31, 33, 45, 52, 58, 6, 11	Anal, cervical, head and neck, penile, vulvar, and vaginal cancers
HEPLISAV-B (HBV)	HBV	Liver cancer
Therapeutic		
Name	Type	
Bacillus Calmette-Guérin	Weakened bacteria	Approved for patients with early-stage bladder cancer
Sipuleucel-T (Provenge®)	Autologous dendritic cells	Approved for prostate cancer
talimogene laherparepvec (T-VEC, or Imlygic®)	Oncolytic (virus based)	Approved for melanoma that cannot be operated on

Source: Cancer Research Institute.

Prophylactic or preventative vaccines attack viruses that may cause cancer. The human papillomavirus (HPV) vaccine, for example, targets the high-risk strains of HPV responsible for most cases of cervical cancer and linked to some throat, anal, vaginal, vulvar, and penile cancers. The hepatitis B virus (HBV) vaccine targets the disease that has been linked to an increased risk for liver cancer in people who have chronic (long-term) infections with the virus. Thus, vaccinating certain people against HPV and HBV could have a positive effect in protecting against the types of cancers linked to each condition.

Therapeutic cancer vaccines are a type of immunotherapy that treats cancer by stimulating the immune system to attack cancer in a specific location of the body. Unlike cancer prevention vaccines, cancer treatment vaccines are designed to get the immune system to attack a disease that already exists. Therapeutic cancer vaccines either delay or stop cancer cell growth, shrink the tumor, and prevent tumor growth. They work by presenting the immune system with antigens it will recognize as foreign or dangerous.

Some cancer treatment vaccines are made up of cancer cells, parts of cells, pure antigens (certain proteins on the cancer cells), or even modified bacteria or viruses. Sometimes a patient's own immune cells are removed and exposed to these substances in the lab to create the vaccine. Once the vaccine is ready, it is injected into the body to increase the immune response against cancer cells.

Cellular Therapies

Cellular therapy is the use of cells to repair or replace tissue. For cancer patients, cellular therapy involves the removal of certain immune cells from the patient, which are then modified in a laboratory to better attack the specific cancer cells, replicated in cell culture, and then administered back to the patient. Cellular therapies can be customized to the patient so that the engineered cells are trained specifically for the type of tumor present in the patient's body. In this way, this technique aims to improve upon the patient's current immune abilities to make the immune system more likely to kill cancer cells.

The most common cellular therapy used for cancer is **T-cell transfer therapy**, which is a treatment that boosts the natural ability of T-cells to fight cancer. There are two main types of T-cell transfer therapy: tumor-infiltrating **lymphocytes** (or TIL) therapy and CAR T-cell therapy.

- TIL therapy uses T-cells called tumor-infiltrating lymphocytes that are found in the tumor. Doctors test these lymphocytes in the lab to find out which ones best recognize a patient's tumor cells and then these selected lymphocytes are treated with substances that make them grow to large numbers quickly before injecting them back into the patient. The idea behind this approach is that the lymphocytes that are in or near the tumor have already shown the ability to recognize a patient's tumor cells.

- CAR T-cell therapy is similar to TIL therapy, but the T-cells are changed so that they make a type of protein known as CAR before they are grown and administered. CAR stands for chimeric antigen receptor. CARs are designed to allow the T-cells to attach to specific proteins on the surface of the cancer cells, improving their ability to attack the cancer cells (source: NIH's National Cancer Institute).

The process of growing a patient's T-cells in a lab can take two to eight weeks. During this time, a patient may be treated with chemotherapy and/or radiation therapy to get rid of other immune cells. Reducing a cancer patient's immune cells helps the transferred T-cells be more effective. However, in the same way that autologous vaccines may be costly and difficult to mass produce, CEL-SCI believes that cellular therapies, since they require cells from the patient, could also have high costs and limited abilities for commercial scale manufacturing. Furthermore, the infusion of billions of cells into the patient could cause adverse reactions. The Company also believes that certain tumor-infiltrating agents may not always grow well in cell culture, thereby not reaching the quantity or engineered quality that is needed for efficacy against tumors.

Adjuvants

An adjuvant is any agent that may increase the efficacy or potency of a treatment. As it relates to biologic products, adjuvants are substances usually injected with antigens to enhance or modify the body's immune response. When administered in conjunction with a cancer vaccine or mAb treatment, adjuvants are intended to increase the effectiveness of the treatment by augmenting the body's immune response. When chemotherapy is administered to a patient prior to or following surgery to remove the patient's cancer, it is considered either a neoadjuvant or adjuvant therapy depending upon when it is given.

The toxicity of adjuvants may vary depending on what substance is being used and its route of administration. Some adjuvants cannot be administered more than a few times sequentially to humans and others can only be administered as a percutaneous injection through the skin. Some commonly used adjuvants for use in cancer treatments include aluminum sulfate (Alum), keyhole limpet hemocyanin (KLH), incomplete Freund's adjuvant (IFA), QS21, Detox-B, dinitrophenyl (DNP), and granulocyte-**macrophage** colony-stimulating factor (GM-CSF).

Comprehensive Immunotherapy: Multikine®

CEL-SCI has designed a novel type of biological immunotherapy—an immune stimulator called Multikine®—that acts as a comprehensive immunotherapeutic agent. The Company believes that Multikine® more closely mimics natural immune functions as it leverages the functions of both passive and active immunotherapies to accomplish the following two goals:

- Activate the immune system to produce a more robust and sustainable anti-tumor response; and
- Cause a direct, multi-targeted elimination of tumor cells.

Multikine® is an immunotherapy product candidate comprised of a patented defined mixture of 14 human natural cytokines and cellular products, listed in Figure 12. The pro-inflammatory cytokine mixture includes interleukins, interferons, chemokines, and colony-stimulating factors, which contain elements of the body's natural mix of defenses against cancer. Research at the U.S. National Institutes of Health (NIH) has shown the vast majority of Multikine®'s cytokine components to be biologically/immunologically active, potentially simulating the natural immune system to mount an immune rejection episode, including tumor rejection.

Figure 12
MULTIKINE® COMPONENTS

▪ Interleukin 1 α (IL-1 α)	▪ Tumor Necrosis factor α (TNF-α)	▪ Granulocyte-colony stimulating factor (G-CSF)
▪ Interleukin 1 β (IL-1β)	▪ Tumor Necrosis factor β (TNF-β)	▪ Granulocyte-macrophage colony-stimulating factor (GM-CSF)
▪ Interleukin 2 (IL-2)	▪ Interleukin 6 (IL-6)	▪ Macrophage Inflammatory Protein 1α (MIP-1α)
▪ Interleukin 3 (IL-3)	▪ Interleukin 8 (IL-8)	▪ Macrophage Inflammatory Protein 1β (MIP-1β)
▪ RANTES (CCL5)	▪ Interferon Gamma (IFN-γ)	

Source: CEL-SCI Corporation.

The Company believes that available immunotherapies, as well as those currently being developed, are limited by their abilities to target only one or two specific tumor-associated antigens. Conversely, Multikine®'s multitargeted therapy effect is directed at several targets on the cancer cell and activates multiple cellular components of the immune system in order to more effectively fight cancer. Multikine® kills tumor cells and, at the same time, activates a robust anti-tumor immune response.

The first indication CEL-SCI is pursuing for Multikine® is for the neoadjuvant therapy in patients with squamous cell carcinoma of the head and neck (advanced primary head and neck cancer). CEL-SCI has completed Phase 1 and Phase 2 clinical trials with Multikine® and is in the final stages of a global pivotal randomized Phase 3 trial. Data from Phase 1 and Phase 2 clinical trials indicates that Multikine® may help the immune system "see" the tumor and then attack it, enabling the body's own anti-tumor immune response to fight the tumor. Furthermore, no severe toxicity was reported as being associated with Multikine® during the clinical trials. The Company plans to capitalize on the full potential of Multikine®'s multi-target capabilities to assess the immunotherapy for treating cervical dysplasia in HIV/HPV co-infected patients (has completed a Phase 1), as well as other solid cancer targets, including breast, skin, bladder, and cervical cancers, and melanoma.

In June 2007, the FDA granted Multikine® Orphan Drug status as a neoadjuvant therapy in head and neck cancer, which may enable an accelerated approval process. Results of the Phase 1 and Phase 2 trials are presented on pages 31-34 and a description of the pivotal Phase 3 trial is provided on pages 35-40.

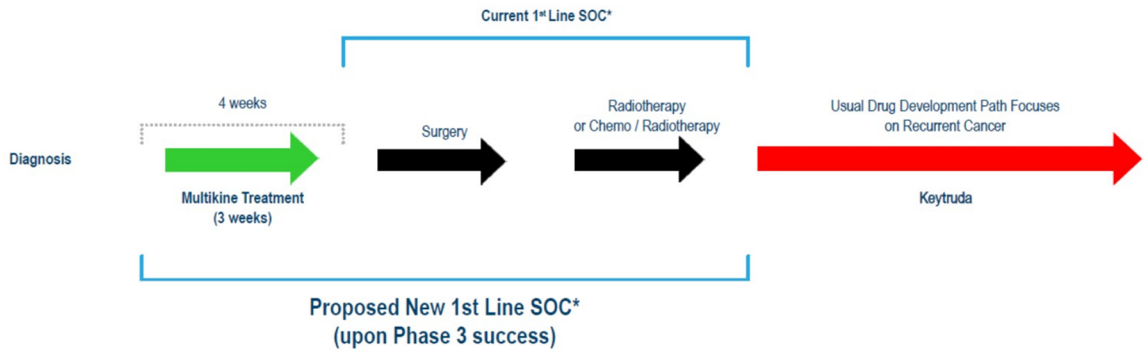
MULTIKINE®: A NOVEL FIRST-LINE TREATMENT

Multikine®'s first indication is for advanced (stages 3 and 4) primary (not yet treated) head and neck cancer. This was selected as CEL-SCI believes there is a large, unmet medical need among head and neck cancer patients as a whole, and for this very prevalent cancer in particular. According to the Company, the last FDA approval of a therapy for the treatment of advanced primary head and neck cancer was over 50 years ago. In addition, there is only one SOC for this type of cancer.

Multikine® is being used in a different way than the other cancer immunotherapy options. Unlike conventional immunotherapies, which have traditionally been administered late in the disease process (often after chemotherapy and radiation therapy), Multikine® is being developed as a first-line treatment to be given to patients before any other therapy options, including surgery, radiation, or chemotherapy is initiated. (i.e., as a neoadjuvant). CEL-SCI designed Multikine® for use in this manner because the Company believes that one of the primary impediments to immunotherapy efficacy has been that these products are traditionally administered after the immune system has already been ravaged by the disease and destroyed by current first-line treatments (e.g., chemotherapy, radiation, or surgery). In later cancer stages, the immune system is less likely to wage an effective anti-tumor response because it has been weakened by both the toxic therapies and the cancer itself. On the contrary, Multikine® is able to stimulate the immune system before it is weakened by surgery, chemotherapy, or radiation, resulting in an effective anti-tumor response.

There is one recommended SOC for advanced primary head and neck cancer, which did not change during the Company' long Phase 3 trial: surgery followed by either radiation or concurrent radiation/chemotherapy. After diagnosis, many patients have an average of four weeks of preparation before surgery. Multikine® is administered to previously untreated, newly diagnosed head and neck cancer patients in the period between diagnosis and surgery. Delay of surgery is not permitted because it is an "intent to cure" treatment. Therefore, Multikine® can only be given for three weeks. During this four-week period, the Multikine® investigational treatment regime is administered locally around the tumors and near the draining lymph nodes for three weeks, five times per week. As such, the three-week Multikine® treatment regimen falls within this waiting period (from diagnosis to surgery) and does not delay surgery or any other treatment related to the SOC. Instead, it provides patients with a proactive approach to treatment while waiting for surgery. To the Company's knowledge, there are no other comprehensive anticancer immunotherapies being developed for first-line treatment in this manner. CEL-SCI believes that Multikine® has a chance to establish itself as an integral part of a new first line SOC for head and neck cancers if approved, as illustrated in Figure 13.

Figure 13
MULTIKINE® PROTOCOL



Source: CEL-SCI Corporation.

MULTIKINE®'S MECHANISM OF ACTION

Micrometastases around the tumor and in the lymph nodes are a major cause of cancer recurrence. The American Cancer Society estimates that up to 40% of patients whose oral cancer was considered "cured," will likely develop recurrent local cancer or second primary cancers, with this number going up to 60% for patients diagnosed at a late stage disease (Source: *Annals of Oncology*, Vol. 30 (5):744–756, 2019). Cancer treatment today involves aggressive surgery, including the removal of the affected organ or area, as well as radiation or radio-chemotherapy due to fear that tumor micrometastases will survive the first round of cancer treatments and cause tumor recurrence.

Multikine®'s primary function in cancer treatment is to eliminate cancer cells from around the margin of the tumor as well as from the regional lymph nodes. By clearing the local and regional tumor metastases, Multikine® improves surgeons' abilities to easily remove all of the tumor. The effect of clean tumor margins also decreases the likelihood that doctors will miss cancer that has begun to spread outside of the main tumor mass and reduces the chances of recurrence. In addition, Multikine® is thought to make residual cancer cells more susceptible to subsequent radiation and chemotherapy treatments.

Clinical and pathology data from Phase 1 and Phase 2 clinical trials suggest that Multikine® has the potential to elicit both active and passive immunity, producing both a direct effect on the tumor, as well as activating the immune system to produce an effective and sustainable anti-tumor immune response. Figure 14 summarizes Multikine®'s novel mode of action, which enables this complex biologic to comprehensively marshal an effective anti-tumor attack. A description of each of Multikine®'s functions follows.

Figure 14
FUNCTIONS OF MULTIKINE®

- Causes a direct, targeted killing of tumors
- Acts on multiple targets on the cancer cell
- Activates the immune system to produce a more robust and sustainable anti-tumor response
- Works to impede cancer recurrence
- Renders residual tumor cells susceptible to radiation or chemotherapy

Source: CEL-SCI Corporation.

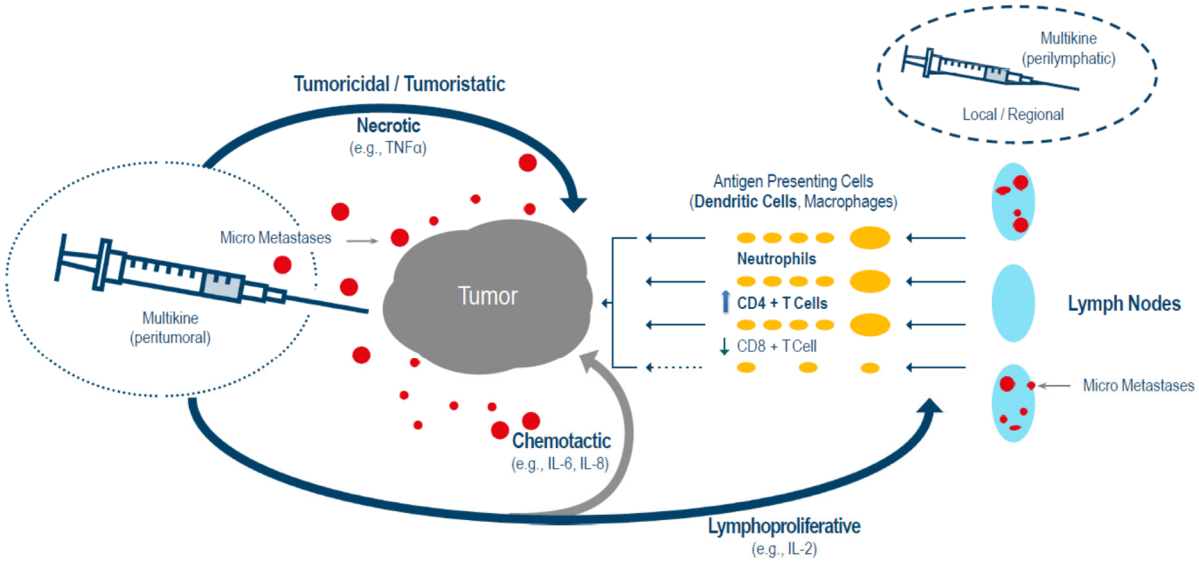
Multikine®—Direct Killing of Tumor Cells

Whereas mAbs and many other immunotherapies are targeted at a specific tumor antigen or are formulated from a single cell type, CEL-SCI's Multikine® is composed of a mixture of cytokines. Cytokines are proteins produced by the immune system cells that affect cell behavior and communication, with an important role in regulating the immune response. Traditionally, single cytokine therapies, such as commercial **erythropoietin (EPO)**, have been highly effective for indications with a clear cause and effect relationship. For example, EPO injections stimulate production of red blood cells in patients who have a deficiency of EPO and therefore cannot produce enough of their own red blood cells. However, for complex diseases like cancer, CEL-SCI believes that a single-cytokine approach is less effective than a combination of multiple cytokines with varied functions that can address cancer's numerous causes, and effectively marshal an anti-tumor immune response.

Multikine®'s patented and reproducible cytokine mixture (a complex biologic) contains natural pro-inflammatory interleukins, interferons, chemokines, colony-stimulating factors, and other cytokines, which are biologically active and simulate a healthy immune response. Since Multikine® is produced in a proprietary culture of healthy primary normal donor cells, the natural cytokine mixture produced and present in Multikine® is thought to have a similar proportion to that found in a natural, healthy immune system. By incorporating all of these active molecules rather than just one cytokine, CEL-SCI is able to mimic the natural immune system more closely. This is the basis for the Company's decision to classify Multikine® as an immune simulator. Moreover, the activity of each of these cytokines contributes to Multikine®'s ability to kill cancer cells (Source: *The Journal of Clinical Oncology* May 2005). The believed order of Multikine®'s functions in marshalling the immune system to mount an effective anti-tumor response is summarized on the accompanying page and depicted in Figure 15 (page 28).

Figure 15

MULTIKINE® MECHANISM OF ACTION: CLEAN TUMOR MARGINS; IMPROVE PATIENT OUTCOME



Source: CEL-SCI Corporation.

(1) **Tumor necrosis factor** alpha (TNFα), a cytokine produced by activated **monocytes** and macrophages that can destroy tumors, aids Multikine®'s ability to cause **necrosis** of cancer cells by attacking the tumor, causing it to release tumor antigens.

(2) The antigen-presenting cells, such as dendritic cells (of the treated individual), transport the tumor antigens to the lymph nodes, where Multikine®'s **lymphoproliferative** cytokines induce replication of tumor-specific T-cells to target cancer in the lymph nodes, and have them ready for recruitment to the tumor site.

(3) Subsequently, Multikine®'s **chemotactic** factors recruit anti-tumor specific **CD-4+** T-cells (T-helper cells or Th) from the local lymph nodes, changing the balance of CD-4+ to **CD-8+** T-cells in the tumor microenvironment. The tumor-infiltrating CD-4+ T-cells further instigate a local an anti-tumor response, culminating in tumor cell death and necrosis.

(4) Lastly, Multikine® recruits neutrophils from circulation to destroy tumor cell nests. Other cytokines in Multikine®, or those secreted on-site in the tumor microenvironment by the tumor-infiltrating lymphocytes, induce local fibrosis.

Multikine®—Acts on Multiple Targets

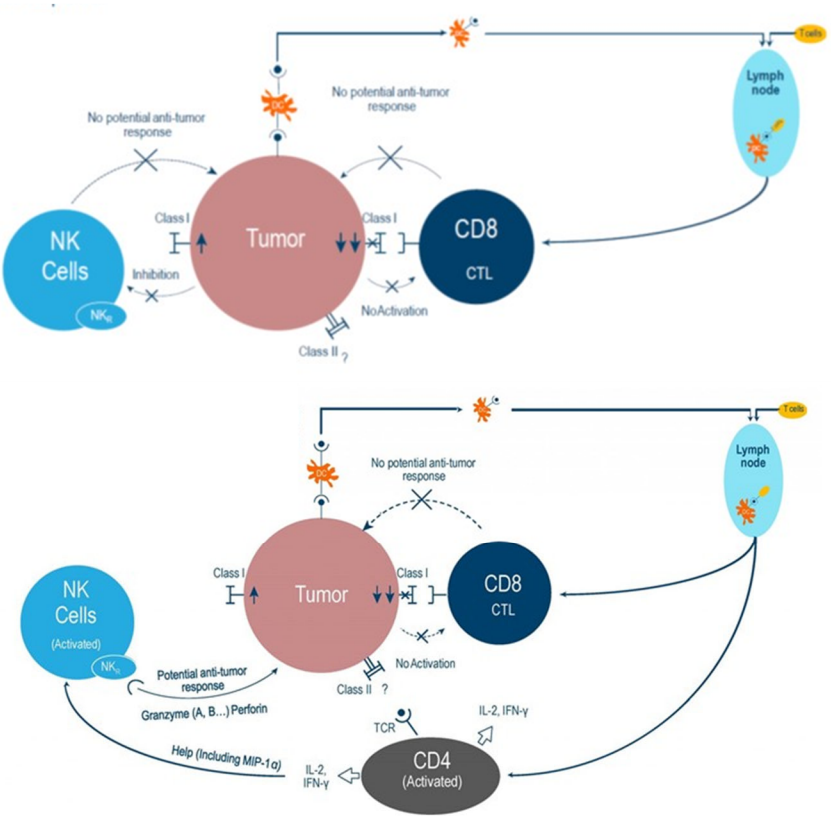
Having multiple elements in its composition enables Multikine® to correct a range of immune deficits and target multiple aspects of the tumor that are required for its destruction. This is unlike mAb therapies or some active immunotherapies, which are directed against and react with one specific target. In addition, because Multikine® is not tumor specific, it can potentially be used to address a wide range of solid tumors beyond head and neck cancer.

Multikine®—Produces a Robust and Sustainable Anti-Tumor Response

Typically, the immune system sends its CD-8+ T-cells and NK cells to defend against cancer cells. However, due to the tumor tolerance mechanisms, the tumor is able to block these immune cells, making them unable to trigger an effective anti-tumor immune response (illustrated in the top part of Figure 16, page 29). Multikine® leverages CD-4+ cells (Th-cells) instead. Th-cells are believed to enable a more robust anti-tumor response through tumor infiltrating CD4+, CD8+ and NK cells, while also facilitating the immune system's recognition of cancerous cells, thereby functionally "breaking" tumor tolerance.

Figure 16

MULTIKINE® ANTI-TUMOR EFFECT

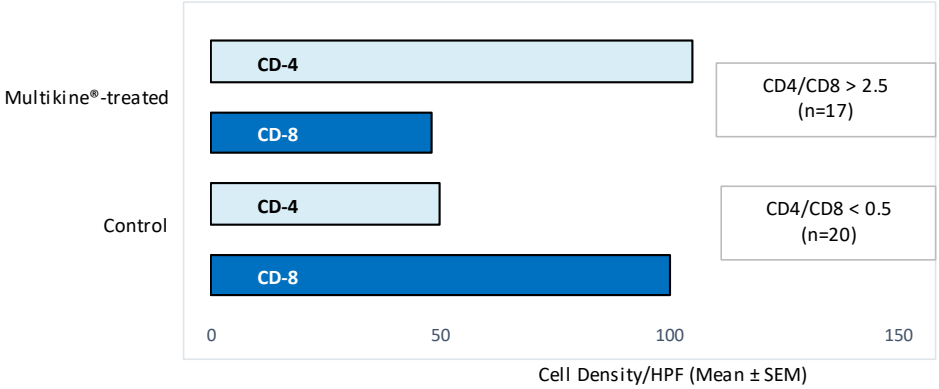


Source: CEL-SCI Corporation.

Involving Th cells in the anti-tumor response is of clinical significance as the tumor is able to shut down the infiltrating CD-8+ cells, but preliminary evidence seems to suggest an inability to shut down the Th-cell. In addition, CD-4+ cells appear to help break "tumor tolerance," thereby potentially allowing the immune system to recognize and destroy tumor cells. The effect of Th-cells in one aspect is similar to that of checkpoint inhibitors, where Th-cells circumvent the inhibitory signal the tumor sends to NK cells, activating the tumor-residing NK cells and allowing them to mount an effective anti-tumor response (bottom part of Figure 16).

Figure 17

MULTIKINE® EFFECT ON HOST CD-4/CD-8 CELL DENSITY



Sources: CEL-SCI Corporation and the Journal of Clinical Oncology (2005).

Figure 17 (page 29) shows Multikine®'s effect at decreasing relative quantities of CD-8+ T-cells and increasing CD-4+ T-cells in patients with oral squamous cell carcinoma versus a control group. The matched control group was drawn from matched pathology repository samples of patients who did not receive Multikine®. In addition to improving the CD-4/CD-8 ratio, a three-week regimen of Multikine® treatment resulted in two complete responses, indicating the effective elimination of all cancer cells in these two patients as determined by **histopathology**. CEL-SCI's Phase 2 trial also reported that Multikine® stimulates a sustained anti-tumor immunological response that continues for up to 54 days after cessation of Multikine® administration.

Multikine®—Works to Impede Cancer Recurrence

CEL-SCI believes that Multikine® harnesses the immune system to prevent the recurrence of cancer in particular areas. Multikine® is injected ½ daily dose **peritumorally** (around the tumor) and ½ daily dose **perilymphatically** (in the vicinity of the nearby draining lymph nodes). These areas are most likely to be the site of future cancer recurrences. Multikine® is not injected into the tumor. Multikine® seeks to primarily eliminate those tumor cells that are likely to be missed in surgery because those cancer cells are thought to be the cause of death for many patients. One key goal is to create "clean margins" before they cause recurrence. A clean margin is essentially an area around the edge of a tumor excised by surgery that has been deemed free of any remaining cancer cells by a pathologist.

As Multikine® is believed to activate the patient's own immune system while it is still strong (before surgery, radiation, and chemotherapy), the body has the capacity to find and kill tumor micrometastases thought to be responsible for recurrence. Therefore, the Company believes that the combination of its immunotherapy drug Multikine® with surgery plus radiation/chemotherapy should be more successful in eliminating all of the tumor cells than the current standard therapies of surgery plus radiation/chemotherapy, alone.

Cleaning the tumor margin and rendering the regional lymph nodes 'tumor-free' offers another added benefit: patients who do not have cancer cells that have spread or are capable of spreading to the lymph nodes are less likely to require treatment with a combined radiation/chemotherapy regimen after surgery, or might possibly need a lower dose treatment. Radiation is still associated with toxicity but diminishing the need for concurrent chemotherapy decreases the risk of high levels of toxicity, which could result in life-long side effects or death.

Multikine®—Renders Residual Tumor Cells Susceptible to Other Treatments

CEL-SCI believes that using Multikine® as a first-line treatment can destroy a large number of cancer cells and possibly increase the susceptibility of the remaining cancer cells to further treatments by promoting the tumor cells' entry into the cell cycle (*The Laryngoscope*, 2003). Certain stages of the cell cycle are more susceptible to radiation than others, and non-cycling or slowly cycling cells are less likely to move into the susceptible stages. As a result, radiation and chemotherapy must be administered multiple times (five times a week for six to seven weeks of radiation) in order to target the full range of tumor cells. As the cumulative effect of radiation and chemotherapy doses increase in the later weeks of treatment, complications are more likely to arise, and they are more likely to be severe with possible permanent damage to normal tissue. Accordingly, therapies that can increase the susceptibility of cancer cells to radiation or chemotherapy could be highly beneficial components of cancer care.

Through its Phase 1 and Phase 2 clinical trials, Multikine® has shown that it may induce tumor cells to enter into the cell cycle. CEL-SCI believes that after Multikine® administration, radiation may possibly be able to kill a larger number of tumor cells in the first radiotherapy cycle versus approximately 5% to 10% of tumor cells estimated to be susceptible to radiotherapy at any given time in patients treated with only the SOC (Source: *Anticancer Research* 2002). Moreover, since Multikine® is not known to be toxic, it would not likely add further toxicity to that produced by the radiation or chemotherapy treatments. As a result, chemotherapy and radiation could prove to be significantly more effective.

CLINICAL TRIAL RESULTS OF MULTIKINE®

CEL-SCI has conducted a series of Phase 1 and Phase 2 clinical trials in over 200 patients throughout the U.S., Europe, Canada, and Israel, which have shown that Multikine® was safe and well tolerated, with significant clinical impact. A summary of these trials is provided in Figure 18.

Figure 18
MULTIKINE® CLINICAL STUDIES

Phase	Indication	No. of subjects	Countries	Published paper
Phase 1/2	Head & Neck Cancer Recurrent	16	U.S. & Canada	N/A
Pilot Study	Head & Neck Cancer Recurrent	4	U.S.	Arch Otolaryngol Head and Neck Surgery
Phase 1/2	Head & Neck Cancer Pre-surgery	12	Israel	Arch Otolaryngol Head and Neck Surgery
Phase 2	Head & Neck Cancer Pre-surgery	28	Canada	N/A
Phase 2	Head & Neck Cancer Pre-surgery	31	Hungary	Laryngoscope, ASCO Annual Meeting
Phase 2	Head & Neck Cancer Pre-surgery	21	Hungary	ASCO, Journal of Clinical Oncology and Oral Oncology
Phase 2	Head & Neck Cancer Pre-surgery	30	Poland & Czech Republic	N/A
Pilot Study	Prostate Cancer Pre-Surgery Treatment	5	U.S.	Seminars in Oncology
Pilot Studies	Different cancer tumors	54	U.K. & others	Lymphokine
Phase 1	Cervical Dysplasia in HPV Induced Cervical Cancer	8	U.S.	Annals of the 33rd International Congress of the Society of Gynecological Oncologists
Phase 1/2	HIV	15	U.S.	Antiviral Therapy
Total Patients		**224**		

Source: CEL-SCI Corporation.

Based on its most recent Phase 2 clinical trial for Multikine® in advanced head and neck cancer, CEL-SCI reported that approximately 10% of patients administered the Multikine® treatment regimen over a three-week period had no clinical or pathology evidence of any remaining cancer after treatment. The Company also reported a 33% improvement in overall survival of Multikine®-treated head and neck cancer patients in the same study. CEL-SCI views these findings as significant because its Phase 3 trial is designed to replicate the Multikine® treatment regimen utilized in this Phase 2 trial. In addition, these earlier clinical studies also found Multikine® to result in positive quality of life anecdotal observations, including weight gain and reduction in pain, ability for patients to open their mouths more easily, and ability of patients with tongue cancer to move their tongues again within a few days of treatment initiation. Furthermore, in addition to the clinical trial results of Multikine® for the treatment of advanced head and neck cancer, Multikine® has preliminarily shown the potential for biological activity (in early clinical trials) in cervical dysplasia/neoplasia (pre-cancer and cancer of the cervix) and prostate cancer.

Most importantly, there has not been severe adverse event associated with the use of Multikine® reported in any of the Company's early trials. Conversely, traditional cancer therapies (e.g., chemotherapy and radiation) as well as some newer mAb treatments are associated with many toxicities and potentially severe side effects. Further summations of the results of CEL-SCI's largest and most significant trials are presented on pages 32-35, followed by a description of the Company's ongoing Phase 3 trial.

Phase I/II Trial results
Source: The Laryngoscope, Vol. 113 (12):2,206-2,217, 2003.

A multicenter Phase I/II trial of 54 patients (27 treated with Multikine® and 27 in the control group) with advanced primary oral squamous cell carcinoma studied the effects of escalating doses of Multikine® over a two-week period. Trial participants were assigned to one of several groups: (1) eight patients who received the lowest Multikine® dose—400 international units (IU), three times a week; (2) 12 patients who received 800 IU of Multikine® three times a week; and (3) seven patients who received 800 IU of Multikine® five times a week. Multikine® was injected into the tumor margin.

In conjunction with Multikine® administration, the treatment regimen included a single intravenous infusion of low-dose **cyclophosphamide** (a sub-chemotherapeutic dose) three days before the first Multikine® injections, and oral **indomethacin** three times a day until 24 hours before surgery. These products help to increase the effectiveness of Multikine®'s effect. Patients also consumed multivitamins containing zinc sulfate daily throughout the treatment regimen until 24 hours before surgery. Between days 21 and 28 after the initial injection of Multikine®, patients had their tumors surgically removed. Two to four weeks after the surgeries (dependent on surgical wound healing), patients were given standard radiation therapy.

This trial confirmed that Multikine® can stimulate T-cells to migrate into **cancer cell nests** and that oral squamous cell carcinoma is an immunogenic tumor. In addition, researchers found that Multikine® induced a high proportion of the tumor cell population to enter the cell cycle process, which may enhance the efficacy of follow-up radiation or chemotherapy treatments. As published in the *Laryngoscope* in December 2003, the authors/investigators concluded that Multikine®'s novel ability to propel tumor cells into the cell cycle could be a result of the drug's synergistic cytokine mixture, which functions in different manners on the immune system and tumor.

Moreover, it was discovered that Multikine®-treated patients did not have an increase in recurrence at 24 months versus the control group (selected from the same institution—for comparison to the Study patients). In fact, one group of eight patients from one of the recruiting centers who were administered the Multikine® treatment regimen did not have a single incidence of recurrence by 24 months.

Phase 2 Trial
Journal of Clinical Oncology, Vol. 23 (15):3421-3432, 2005.

Expanding on its Phase I/II trials, CEL-SCI completed a Phase 2 multicenter study in 39 patients with oral squamous cell carcinoma. Nineteen of these patients had previously untreated head and neck cancer and were assigned to a Multikine® treatment regimen that closely resembled the protocol used in the Phase I/II trial. However, rather than injecting Multikine® only around the tumor, in this trial, investigators/physicians injected Multikine® both peritumorally and in the vicinity of the local draining lymph node.

The remaining 20 patients in this study consisted of a historical control group. The investigators and study pathologists selected patients for pathologic evaluation from the pathology specimen repository of the National Institute of Oncology (Budapest, Hungary). The control group was matched to the active treatment arm based on tumor size, location, and disease stage, as well as patient gender and age. Of note, no systemic or local toxicity or severe adverse events related to Multikine® were reported by investigators in this trial.

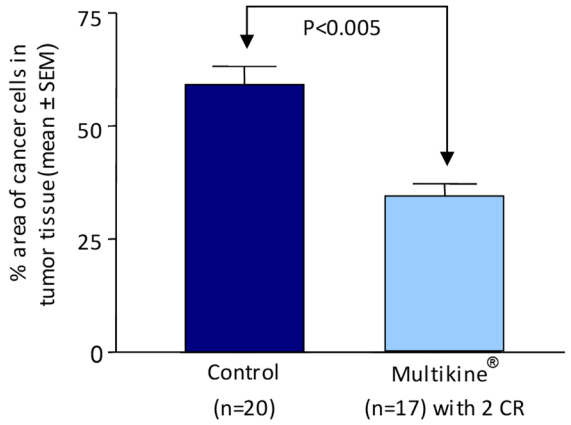
Tumor Response

As determined by histopathology, Multikine® eliminated tumors in 2 of 19 individuals administered three weeks of Multikine® therapy. In these two patients, it was not possible to detect any cancer tissue in the surgically resected tumor mass, and thus, were considered to be complete responders (i.e., exhibiting 100% tumor reduction). Two other patients had major responses, with a greater than 50% reduction in tumor volume, with four more patients having a minor response, which is characterized by a greater than 30% (but less than 50%) reduction in tumor volume. Only one patient experienced a progression of their disease; the remaining 10 individuals exhibited stable disease. As a result, the Company's **objective response rate** (4 of 19 patients) was 21%, and the overall response (8 of 19 patients) was 42%.

The investigators determined the efficacy of these tumor responses through histopathology, a science that studies microscopic changes in diseased tissues. The Company also found that the Multikine® treatment regimen was associated with a lower percentage of cancer cells, by area, in the tumor tissue than was the control (as seen in Figure 19). Data indicate that in the Multikine®-treated group, the proportion of the connective tissue (versus cancer cells) in tumor tissue was significantly increased compared to those of the control patients, indicating a reduction of cancer cell nest area. This can be seen in Figure 20, where the left Figure (control group) shows peritumoral (around the tumor) fibrous collagen rim while the right Figure (Multikine® group) shows an accumulation of interstitial collagen fibers between cancer cell nests.

Figure 19

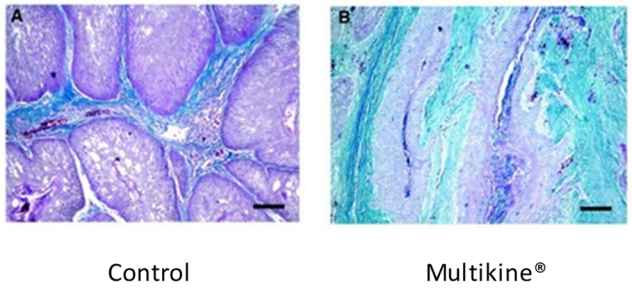
MULTIKINE®'S ANTI-TUMOR EFFECT



Sources: CEL-SCI Corporation and the Journal of Clinical Oncology.

Figure 20

MULTIKINE®'S ANTI-TUMOR EFFECT



Source: Journal of Clinical Oncology (May 2005).

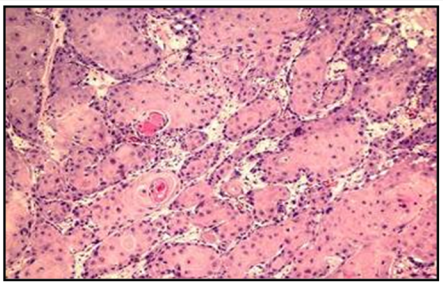
In addition, CEL-SCI was able to demonstrate that Multikine® stimulated a significant increase in tumor-infiltrating CD-4+ T-cells, while also decreasing the prevalence of CD-8+ T-cells. Involving CD-4+ cells in the anti-tumor response is of clinical significance as these immune cells can help counter the induction of tumor tolerance, allowing the body to recognize tumor cells and mount an effective anti-tumor response. Histopathology showed that the intratumoral CD4:CD8 ratio was low (< 1) in patients not treated with Multikine® (control). An increase in tumor-infiltrating CD4+ and a decrease of CD8+ T-cells was observed in the Multikine®-treated patients, leading to a significantly higher intratumoral CD4:CD8 ratio (> 2.5).

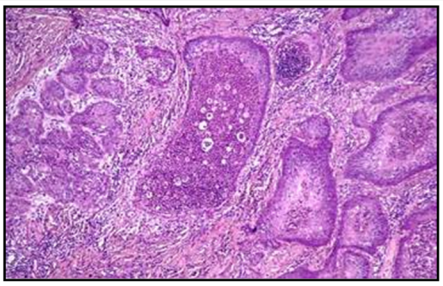
Recruiting CD-4+ T-cells to the tumor site with the use of Multikine® resulted in breaking tumor tolerance and inducing an anti-tumor response culminating in tumor necrosis. This effect is shown in Figure 21 (page 34), which compares a matched control patient with a tumor (Panel A) to a patient whose tumor was treated with Multikine® prior to surgery (Panel B). Microscopic necrosis was markedly more frequent in the Multikine®-treated group compared with the control group. These changes may reflect the aftermath of an effective anti-tumor immune response raised against the cancer, induced by Multikine® treatment regimen neoadjuvant administration.

Figure 21

HISTOLOGICAL APPEARANCE OF NECROSIS WITH MULTIKINE®

Panel A: Control	Panel B: Multikine® Treated
The epithelial nests of oral squamous cell carcinoma lack necrosis.	The entire cancer nest is necrotic, containing debris and leukocytes.





Sources: CEL-SCI Corporation and the Journal of Clinical Oncology (May 2005).

The authors/investigators also noted that immunohistopathologic changes could be observed in the tumor 14 to 54 days after Multikine® treatment was discontinued. This finding supports the belief that Multikine® stimulates immune-mediated processes that continue after treatment with Multikine® has ended.

Phase 2 Trial Results Overview

An overview of key results from the Multikine® Phase 2 trial is provided on Figure 22.

Figure 22

MULTIKINE® PHASE 2 TRIAL RESULTS

After 3 weeks of Multikine® Administration		
Of the evaluable patients - 10.5% of patients had no remaining cancer cells	The remaining treated patients had about a 50% average reduction in the number of cancer cells	42.1% Overall Response Rate (RECIST) in Phase 2 study

Sources: CEL-SCI Corporation and the Journal of Clinical Oncology (May 2005).

Phase 2 Follow-up Analysis

Approximately three years after the Phase 2 study was completed, CEL-SCI applied for and received permission to request the investigators obtained the patients' and their families' consents for a follow-on survival follow-up study. Survival results in this final "Proof of Concept" Phase 2 study were compared to results from 55 clinical trials in the same patient population (Advanced Primary SCCHN) who were treated only with standard of care and any other follow-on treatment.

In the follow-up analysis, patients who received Multikine® treatment regimen as first-line investigational therapy, followed by surgery and radiotherapy, were reported by the clinical investigators to have had a 63.2% overall survival (OS) rate at a median of 3.33 years from surgery. This number was compared to the overall survival rate that was calculated based upon a review of 55 clinical trials conducted in the same cancer population (with a total of 7,294 patients studied) and reported in the peer reviewed scientific literature between 1987 and 2007. Review of this literature showed an approximate survival rate of 47.5% at 3.5 years from treatment. Therefore, the results of CEL-SCI's final Phase 2 study were considered to be favorable, resulting in a 33.1% improvement in the overall survival rate versus patients administered only the SOC (as gleaned from the literature). Figure 23 (page 35) summarizes the results.

Figure 23
MULTIKINE® TREATMENT EFFECT: PHASE 2 CLINICAL RESULTS

	Standard of Care +/- All Other Treatment Modalities	Multikine® + Standard of Care	% Improvement over the Standard of Care
Overall Survival (at 3.3 Years from treatment)	47.5%[1]	63.2%[2]	33.1%[3]

[1] Survey of 55 clinical trials; advanced primary H&N cancer (published 1987 – 2007)

[2] Multikine® Treatment: Phase 2 Clinical Trial (Timar et al, JCO, 23(15): May 2005)

[3] Talor et al, Oral Oncology Supplement (2) No. 1, May 2007

Source: CEL-SCI Corporation.

Clinical and histopathology data collected during Phase 2 clinical trials of Multikine® indicate that Multikine® appears to have reduced the number of recurrences of tumors in the treated head and neck cancer patients beyond that which would otherwise normally be expected in this same patient population based on literature reports. First-line neoadjuvant Multikine® treatment improved the two-year local-regional control rates (recurrence around the tumor [local] and in the lymph nodes [regional]) over previously published local-regional control rates. The median local-regional control at two years (based on the Company's analysis of scientific literature) was approximately 73%. Conversely, Multikine® with the SOC increased this value to roughly 79%.

The results of the various histopathology analyses from multiple Phase 1 and 2 studies with Multikine® suggest a clear benefit to the patients. The overall survival data from the last Phase 2 study, even though the number of patients is not large, confirms that Multikine® appears to confer a clinical benefit to patients with no added toxicity and raising no safety issues. Following these Phase 2 results, CEL-SCI had discussions with a group of U.S. KOLs (experts in head and neck cancer) who reviewed the Phase 1 and 2 data and concurred with CEL-SCI's viewpoint that Multikine® should move into Phase 3 development. As a result, CEL-SCI decided to meet with the FDA and other regulators to discuss the Phase 3 trial. The FDA and 23 other regulators concurred with CEL-SCI's Phase 3 protocol and allowed it to proceed.

The FDA recommended that CEL-SCI consider having its own dedicated manufacturing facility for Multikine®, a Complex Biologic, because it was made clear that the same manufacturing facility ought to be supplying both the Phase 3 study and the commercial product. Supplying the Phase 3 study product from a contract manufacturing facility and supplying commercial product from a different facility was deemed to introduce too large of a regulatory and other risks. Based upon the above, CEL-SCI management determined that the risk/benefit weighed heavily in favor of building the Multikine® manufacturing facility before the Phase 3 study was launched.

IT-MATTERS: MULTIKINE®'S GLOBAL PHASE 3 HEAD AND NECK CANCER STUDY
(clnicaltrials.gov: NCT01265849).

In 2011, CEL-SCI initiated its global pivotal randomized Multikine® Phase 3 trial for patients with advanced primary (not yet treated) squamous cell carcinoma of the oral cavity and soft palate, accruing patients having tumors located in the worst areas for head and neck cancer in terms of prognosis. The ongoing pivotal trial is an open-label, global, randomized, controlled multi-center global Phase 3 study of the effects of Multikine® in newly diagnosed advanced primary (previously untreated) head and neck cancer, which represents a recognized unmet medical need. In the Phase 3 clinical trial, Multikine® is given as a first-line treatment before surgery, radiation, or concurrent radio-chemotherapy. To the Company's knowledge, this study is thought to be the first Phase 3 study in the world in which immunotherapy is given to patients in a neoadjuvant setting. Of note, because of Multikine®'s Orphan Drug status in the U.S., it is anticipated that only its IT-MATTERS pivotal study is expected to be necessary for Multikine®'s marketing approval.

The study is being conducted in the following 24 countries on 3 continents, with a total of approximately 100 sites:

(1) North America: U.S. and Canada,

(2) Europe: UK, Austria, France, Spain, Italy, Hungary, Poland, Russia, Ukraine, Belarus, Serbia, Croatia, Bosnia, Turkey, and Romania; and

(3) Asia and the Far East: Israel, Taiwan, Malaysia, Philippines, India, Sri Lanka, and Thailand.

End Points

Figure 24
IT-MATTERS ENDPOINTS

Primary Endpoint
Overall Survival (10% improvement over SOC alone)
Secondary Endpoint:
Progression Free Survival Local/Regional Control Safety Histopathology of Tumor infiltrate Quality of Life
Tertiary Endpoint:
TumorResponse

Source: CEL-SCI Corporation.

The primary objective of this Phase 3 trial is to evaluate the efficacy of Multikine® therapy given prior to SOC, as evaluated by overall survival. The primary endpoint is overall survival with a 10% advantage in the Multikine® regimen treated group expected at a median follow-up time of three years versus SOC alone. Secondary objectives are to determine Multikine®'s effect on the cumulative incidence of local-regional control (which measures the spread of metastases and spread of the disease outside the head and neck area), progression-free survival, tumor histopathology, and quality of life. Additionally, CEL-SCI seeks to further confirm Multikine®'s safety. Tumor response is a tertiary outcome in this immunotherapy study. Figure 24 provides an overview of the study's endpoints.

The trial was designed as an event-driven study, and as such, the study requires for 298 deaths (events) to have occurred among the two comparator arms of the study to prove an overall survival benefit for Multikine®. In early May 2020, CEL-SCI announced that it had reached the required number of events for the completion of its Phase 3 trial.

Enrollment

Nine hundred twenty-eight (928) newly diagnosed (and not yet treated) head and neck cancer patients were enrolled in this Phase 3 study globally, with patients followed post-treatment for protocol-specific outcomes. The last patient was enrolled in the study in September 2016. Approximately 135 patients were enrolled in the study from 2011 to 2013, about 195 were enrolled in 2014, about 340 in 2015, and about 260 in 2016. To the Company's knowledge, its IT-MATTERS trial constitutes the world's largest Phase 3 trial in advanced primary head and neck cancer. To qualify for the study, patients had to meet strict inclusion criteria, including having Stage III and IVa of one of the following head and neck cancers: (1) oral cavity: tongue (oral portion only), floor of mouth, or cheek; or (2) soft palate.

Since CEL-SCI's Phase 3 study focuses on patients with Stage III-IVa cancer (advanced) in locations that are believed to present a worse prognosis (cancers of the anterior tongue, soft palate, floor of the mouth, and cheek), as this segment of the advanced primary squamous cell carcinoma of the head and neck (SCCHN) cancer patients displays a significantly worse five-year survival rate than the general head and neck cancer population. For perspective, while the five-year relative survival rate for all head and neck cancers (regardless of the stage at diagnosis or tumor location) is 65%, an analysis conducted by external statistical experts found the overall survival of the specific type of patients enrolled in the IT-MATTERS Phase 3 study (type of cancer, tumor stage, location, etc.) based on the U.S. government SEER database to be 47% at three years and about 37% at five years. This analysis reflects treatment of U.S. patients during the time of the Company's Phase 3 trial. Thus, treatment outcome for this patient population has not gotten better during the course of the Phase 3 trial—a clear unmet medical need.

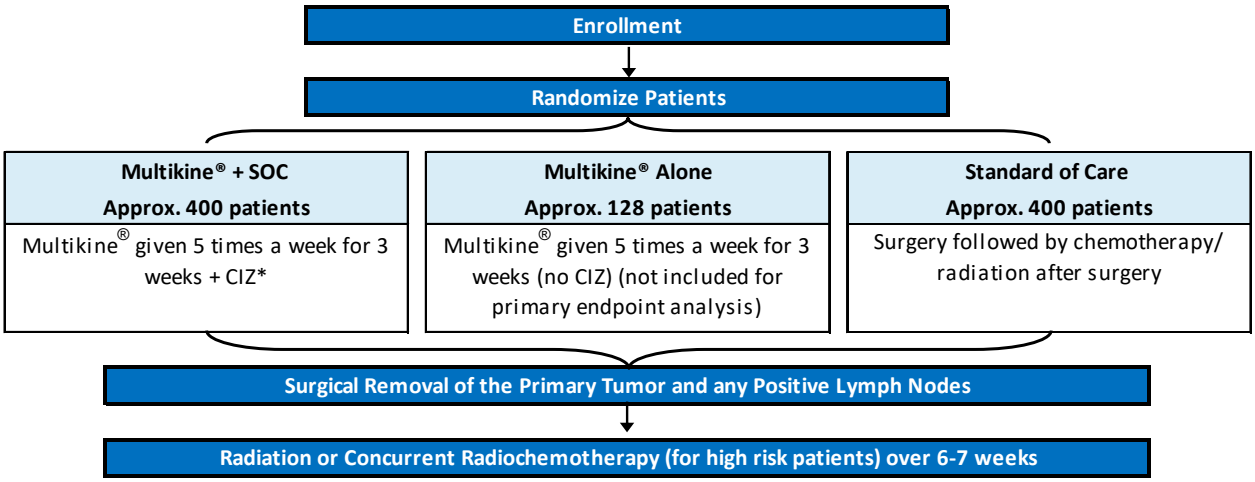
Treatment Protocol

To mitigate its risk, CEL-SCI is using the same treatment regimen in its Phase 3 study that was used in Phase 2, which produced a 33% increase in overall survival. The Multikine® treatment regimen consists of the investigational therapy being injected five times a week for three weeks around the tumor (peri-tumorally) as well as in the vicinity of the local draining lymph nodes (peri-lymphatically) prior to SOC treatments. In addition to Multikine®, just as was done in the Phase 2 studies, the treatment regimen also consists of low-dose administration of non-chemotherapeutic cyclophosphamide (once, 3-days before the Multikine® injection schedule begins), and indomethacin, and Zinc multivitamin (collectively referred to as CIZ treatment). CIZ is added to decrease tumor suppressor mechanisms and thought to enhance Multikine® activity.

After three weeks of Multikine® injections, patients followed the same treatment regimen as the SOC group, undergoing surgery to remove the tumor and any cancer-positive lymph nodes as well as subsequent radiation or concurrent radiation/chemotherapy treatments for up to six to seven weeks after surgery. As shown in Figure 25, patients are randomized into three groups within the study: (1) Multikine® treatment regimen plus CIZ followed by SOC; (2) Multikine® alone (no CIZ) followed by SOC; and (3) SOC alone.

Figure 25

PHASE 3 TRIAL DESIGN



*CIZ: Cyclophosphamide 300 mg/m2 (x1,day -3); Indomethacin 25mg tid (day 1 to 24 hrs prior to surgery) + Zinc (as Multivitamin)

Source: CEL-SCI Corporation.

The trial design calls for a 3:1:3 randomization among three groups, resulting in approximately 400 patients in each of group 1 (Multikine® + CIZ + SOC) and group 3 (SOC alone). The overall survival comparison is made between groups 1 and 3 (800 total patients), with the determination if the study's primary end point has been met occurring when there are a total of 298 deaths in those two groups combined. The primary purpose of the smaller Group 2, which was requested by the FDA, is to gain additional information on the mechanism of action and toxicity of Multikine®.

Length of Study and Estimated Completion

Successful cancer immunotherapy can display a delayed or late survival benefit, the same survival benefit that Multikine® is attempting to prove to become part of the SOC for advanced head and neck cancer. In contrast, a time driven study is designed to end the study at a certain time point (e.g., two years after the last drug was administered). Under the 'time-driven' scenario, the study may end before the survival benefit could materialize. To avoid this problem, the Multikine® study was designed as an 'event-driven' study and must wait for a certain number of events to occur before concluding the trial. The advantage of this type of study design is the hope that the delayed survival benefit of Multikine® can be captured. Therefore, to prove a 10% improvement in overall survival, the study requires CEL-SCI to wait until 298 events (deaths) have occurred, and a successful Multikine® outcome is expected to delay the death rate and thus delay the end of the study.

Further compounding this issue is the fact that in an event-driven study, researchers need an adequate level of statistical power to prove that the drug works. If the study ends short of the required 298 events, even in the presence of an apparent significant survival benefit, the Company may lack the required statistical power to prove the efficacy of Multikine®. It is important to note that stopping for efficacy is typically not recommended in cases where the therapy is novel. Waiting until statistical power is met is extremely important if seeking to change SOC. Clinicians take this very seriously since there is a burden of proof that a novel therapy must meet in order for widespread acceptance (which is how a new SOC is developed). Part of this burden of proof is to rule out the likelihood of false positives—which is what the power number (298) does. If the trial stops for efficacy prior to reaching this number, then a significant number of clinicians and decision-makers may consider the results to be a false positive.

The Phase 3 study protocol assumed an overall survival rate of approximately 55% at three years for the SOC treatment group alone, as the Company assumed an improvement in the SOC efficacy over time would result in an increase in survival rate. However, an analysis conducted by external statistical experts for the Company using the Surveillance, Epidemiology, and End Results data base (SEER), which is an authoritative source for cancer statistics in the U.S. (providing information on cancer statistics in an effort to reduce the cancer burden among the U.S. population) shows that the SOC for this patient population has not resulted in an improvement in survival.

This result is in line with scientific literature that does not suggest an improvement in survival rates for the type of patients enrolled in the Company's Phase 3 study over the past 10 years. In contrast with declines of death rates for the most common cancers, death rates rose over the past decade for patients with cancer in specific sites within the oral cavity and pharynx (Source: American Cancer Society's *Cancer Facts and Figures 2020)*

Figure 26
SEER-BASED OVERALL SURVIVAL ESTIMATE

Year	OS Estimate	95% Confidence Bound
1	71.42%	(69.84%, 72.92%)
2	53.86%	(52.09%, 55.59%)
3	**46.59%**	(44.74%, 48.42%)
4	41.98%	(40.02%, 43.93%)
5	**36.75%**	(34.475%, 39.03%)

Source: CEL-SCI Corporation.

When the Company, with the help of external statistical experts, looked at the SEER data and the U.S. survival in the general U.S. population for patients having the specific type of patients enrolled in the Phase 3 study (type of cancer, tumor stage, location, etc.) during the study years, and who were treated with the same SOC, it found that the combined overall survival for these patients was about 47% at three years and about 37% at five years (Figure 26) compared to the initial estimate of 55% survival at three years as estimated over 10 years ago before the initiation of the Phase 3 study.

According to this analysis, the study should have reached the required number of events well before the May 2020 actual completion date. The last patient was enrolled more than three years ago (and for some patients over nine years ago). The two groups used for the primary end point analysis accounted for about 800 patients (400 patients in the Multikine® + CIZ + SOC group and 400 in the SOC alone group). Even assuming a three-year 50% survival rate, it should have resulted in 400 deaths in the combined groups (800 x 50%), well above the required 298 events, even if Multikine® had no effect. CEL-SCI believes the fact that it took this long to reach the required number of events could be a good sign for the success of the study.

CEL-SCI conducted a review, in conjunction with outside experts, of the possible reasons or factors, other than the Multikine®-treatment regimen, which might be contributing to what appears to be a better than expected survival in this Phase 3 study. It concluded that, since no other factor appeared to be able to produce this result, Multikine® should be responsible for the patients living longer—a conclusion that if proven true, bodes well for the success of the study.

One of the factors that the Company assessed was the possibility that the introduction in late 2016 of Keytruda® and Opdivo® (two new cancer immunotherapy drugs for recurrent head and neck cancer), may be responsible for the lower-than-expected death rate in the study. However, Keytruda® and Opdivo® show a survival benefit of about three additional months in head and neck cancer once the initial treatment has failed and the tumor recurs. Since patients in the trial entered/completed treatment between 3.5 and 9 years ago, a three-month survival benefit could not account for the delay in reaching the required number of events. In addition, these drugs are not available in many countries where patients were enrolled in the study.

Another factor that the Company assessed was the possibility that the apparent increased survival rate in the Phase 3 trial could have been related to a large dropout of patients, since that would have reduced the sample size from which events can be collected. However, the Company does not think that this was the case. Even though CEL-SCI is blinded to the study results, the Independent Data Monitoring Committee (IDMC) and select members of the CRO have unblinded information and the IDMC periodically reviewed Multikine®'s safety and efficacy data. A large dropout rate would have resulted in the CRO who ran the study reporting a problem (which never happened).

In addition, in its review and recommendations of the trial, the IDMC would have considered the dropout rate and is required to advise the Company to enroll more patients if its unblinded review shows that the study may lack power or not be able to conclude in a reasonable time. They have not done so. In October 2019, the IDMC recommended continuing the stay and said that they reviewed "progression free and overall survival and limited demographic and safety data available for the aforementioned protocol." As recently as April 2020 the IDMC recommended "… continuing the trial without change".

The issue of event-driven studies taking longer than originally planned is not a new one. Another example of this type of occurrence can be found in the development of Ipilimumab (Yervoy®) in front-line metastatic melanoma by Bristol Myers (approved in 2011). The estimated time for the study was three years, but after that period, the company had only approximately 85% of the anticipated number of events, an event rate that would put the end of the study within six months. However, the event rate (death rate) was decreasing, a clear sign that the delayed survival benefit was in action. The study continued for an additional two years for it to reach the remaining required events, with the planned three-year study becoming a five-year study. Since then, Yervoy® has become a blockbuster drug, with sales of $1.33 billion and $1.49 billion in 2018 and 2019, respectively.

Independent Data Monitoring Committee (IDMC) Overview

Another key factor that points towards a successful completion of the trial is the fact that during the long term follow up of the study's patients (while all subjects had completed treatments), in 2017, 2018, 2019, and again in April 2020, the IDMC reviewed safety results and efficacy indicators and recommended that the trial continue until the required number of events have occurred.

While CEL-SCI is blinded to the study results, the regulators, the IDMC and select members of the CRO have unblinded information. Throughout the course of the Phase 3 trial, the IDMC is required to periodically review Multikine® safety and efficacy data, but until the 298 number of events is reached, may only announce a recommendation to add patients (i.e., increase sample size), stop, or continue the trial. In October 2019, the IDMC recommended to "continue the trial until the appropriate number of events has occurred." In April 2020, the committee reiterated this stand, stating that it "agrees with continuing the trial without change." Since the study has been going on for over nine years, and is finally near to its end, the IDMC should have a fairly clear idea whether it can be successful or not. If it could not be successful, they could have called it "futile" as other IDMCs did for Biogen, AbbVie, Mallinckrodt, and Clovis during 2019, or the similar Pfizer and Merck 'Javelin' head and neck study in March 2020.

Beginning of the Trial: Recruiting Issues with the initial CRO and FDA Clinical Hold

The Company encountered two issues while conducting the Phase 3 clinical trial: recruiting issues with the original CRO and an FDA clinical hold notice. Initially, CEL-SCI hired Pharmanet in 2010 (which was acquired by inVentiv in 2011) to manage the IT-MATTERS trial. The enrollment process fell behind and Pharmanet was unable to deliver on its recruiting commitments during the 2011 to 2013 period. CEL-SCI subsequently replaced the CRO with two new clinical development companies, ICON Inc. (ICON) and Ergomed Clinical Research Limited (Ergomed) to complete the study. In addition, the Company filed an arbitration suit against their former CRO, and in June 2018, an arbitrator made a final ruling that the former CRO had materially breached its contract with CEL-SCI and awarded CEL-SCI $2.9 million in damages.

Furthermore, in September 2016, the FDA put the Multikine® head and neck cancer Phase 3 study on a partial clinical hold, but the agency allowed the 928 patients already enrolled to continue to receive treatment and be monitored. The FDA letter cited unreasonable and significant risk of illness, the absence of prompt reports to the IDMC, errors in the investigator brochure, and deficiencies in the protocol. The partial clinical hold became a full clinical hold in May 2017 because it became clear to the agency that all study treatments had been concluded. In August 2017, after a full review of the study and clinical data provided to the FDA by the study CROs, the FDA lifted the hold, allowing the Company to continue with its Phase 3 trial with no changes or restrictions to the study or the protocol. According to the Company, since the FDA allowed all patients to complete planned treatment with Multikine®, placing the IND on hold did not delay the Phase 3 trial and all protocol-specified data collection continued as described in the protocol without change.

In summer of 2016, CEL-SCI submitted a request to the FDA to increase the study sample size. This was done because in the spring of 2016, when the annual report was filed with the FDA, the Company noted that the total number of death events in the study was lagging behind that which was expected. In early 2017, when the new annual report was filed with the FDA, CEL-SCI learned that the number of death events had caught up to a level where no new patients were needed to be added to the study. Based on that new information obtained in early 2017, CEL-SCI withdrew its 2016 request to the FDA for additional patients in the study in early Spring 2017.

Creating a New Standard of Care Therapy

Through its Phase 3 trial, CEL-SCI intends to demonstrate that Multikine® can be a successful first-line component of the current SOC regimen administered before a patient undergoes surgery. Figure 27 compares the SOC to CEL-SCI's Multikine® regimen (demonstrated through earlier clinical trials) and summarizes Multikine®'s added benefit to each stage.

Figure 27

THE IMPACT OF MULTIKINE® ON STANDARD THERAPIES FOR HEAD AND NECK CANCER

	Treatment Order			Survival Outcome
Standard Therapy		Surgery	Chemotherapy/ radiation after surgery	Three-year survival is approximately 50%
Multikine® plus Standard Therapy	Multikine® pretreatment for three weeks	Surgery following Multikine®	Radiation/ chemotherapy after Multikine®/surgery	Clinical results: 63.2% survival at ~3.5 years post surgery
Impact of Multikine® plus the Standard Therapy on the Cancer	Eliminates tumor cells around the tumor and in lymph nodes	Better margins around the tumor, which facilitates surgical removal of the tumor	Could enhance the effectiveness of radiation or chemotherapy after surgery	Improvement of 33% in overall survival over the standard therapy—data from follow-up study of the Phase 2 trial

Sources: CEL-SCI Corporation, the Journal of Clinical Oncology (May 2005), and the Laryngoscope (Dec. 2003).

CEL-SCI designed its pivotal Phase 3 trial to evaluate the performance of Multikine® treatment regimen + SOC against the SOC alone. Commercializing Multikine® as the first SOC therapy for newly diagnosed patients could provide the Company with opportunities to receive reimbursement coverage for its product candidate. In addition, CEL-SCI believes that the market for first-line therapies in cancer patients following initial diagnosis is significantly larger than the market for medications aimed at the treatment of recurring cancer. The Company views the initial market for cancer treatment first, immediately after diagnosis (in the neoadjuvant setting) as can be done with Multikine®, to have limited to no competition, especially should Multikine® become part of the SOC treatment regimen and shown to extend life. A successful Phase 3 trial could result in Multikine® becoming an integral part of a new SOC, which could positively influence adoption and usage of Multikine®.

Multikine®: Platform for Additional Indications

Although the initial focus is on head and neck cancer, CEL-SCI believes that due to the multi-targeted nature of the candidate's mode of action, Multikine® may reach beyond being a head and neck cancer treatment. Because it functions by mobilizing the immune system to mount a robust anti-tumor response and the specificity of the response comes from the patient's own tumor, CEL-SCI believes that it could also be proven effective for other solid tumors. In this way, Multikine® is similar to a platform technology, creating a foundation from which further applications can be developed. In addition to head and neck cancer, Multikine® may also be useful in treating melanoma, as well as breast, skin, bladder, and cervical cancers. Data from CEL-SCI's clinical trials has also shown previous biological activity in cervical dysplasia/neoplasia and prostate cancer.

Initially, the Company plans to capitalize on the full potential of Multikine®'s multi-target capabilities to assess the immunotherapy for treating cervical dysplasia. Specifically, CEL-SCI conducted a Phase I study in women with cervical dysplasia/neoplasia who were co-infected with both Human Immunodeficiency Virus (HIV) and HPV. The presence of HIV causes immunosuppression, which diminishes the body's ability to clear HPV on its own. As a result, women co-infected with both diseases are more likely to develop cervical cancer. Approximately 83% of HIV-positive women are co-infected with HPV (Source: the *Journal of the National Cancer Institute*). This trial returned favorable initial clinical results, showing a decrease by 75% in the number of HPV types in the trial's participants and significant lesion improvement by histology.

Moreover, at two dose levels—200 IU and 400 IU five times per week for two weeks with a two-week break over a six-week period—no severe adverse events related to Multikine® were reported in this trial. The Multikine® regimen was well tolerated by all patients. Future growth in terms of Multikine® could include extending the labeled indications to encompass treatment of other solid tumors, such as breast, skin, bladder, or cervical cancers. CEL-SCI further expects that Multikine® may be used for other indications due to its favorable safety profile (which is unusual for cancer treatments and potential efficacy).

Development Agreements for Multikine®

In order to support its Phase 3 trial of Multikine®, as well as advance its global marketing efforts, the Company has executed key development agreements, including with clinical trial partners (as shown in Figure 28) as well as international distribution partners.

Figure 28
PHASE 3 TRIAL PARTNERS

National Institutes of Health, USA	Teva Pharmaceutical Industries Ltd., Israel	Orient Europharma Co. Ltd., Taiwan	Ergomed PLC, UK
Genetic and molecular markers from tumor samples derived from Phase 3 study patients	Licensee for several countries	Licensee for several Far Eastern countries	CRO that completed Phase 3 patient enrollment, contributed up to $12 million towards the cost of the Phase 3 study
About 100 top medical research institutes, universities, and hospitals around the world participating in the Phase 3 study			

Source: CEL-SCI Corporation.

COMPETITIVE ADVANTAGES OF MULTIKINE®

A summary of Multikine®'s competitive advantages is provided in Figure 29, followed by a brief description of each key benefit.

Figure 29
COMPETITIVE ADVANTAGES OF MULTIKINE®

- As a potential first-line treatment for head and neck cancer, it addresses an intact immune system that has not been depleted by earlier treatments
- Combines both passive and active immunotherapy activity into one comprehensive treatment, which means that no external antigens are needed
- Works by enhancing and activating the body's own immune systeme, with the potential to produce a more robust and sustainable anti-tumor response, while causing a direct, multi-targeted elimination of tumor cells
- May enhance subsequent radiation and chemotherapy and also prevent the recurrence of cancer
- May have use in additional solid tumor indications as Multikine® is not tumor specific
- Demonstrated safety profile in over 200 patients (no severe adverse event were reported in any of Multikine® clinical trials)
- Non-toxic, so it can be combined with other anticancer treatments without adding toxicity
- As a non-autologous therapy, Multikine® is ready to use "off-the-shelf" and does not need customization, making large scale manufacturing at a reasonable cost possible
- Granted Orphan Drug status by the FDA

Sources: CEL-SCI Corp., Laryngoscope, Journal of Clinical Oncology, and Crystal Research Associates, LLC.

First-line Treatment

Multikine® is being developed as a first-line treatment to be given to patients before any other therapy options, like surgery, radiation, or chemotherapy, are initiated. Utilizing Multikine® in this manner allows the immunotherapy candidate to augment/stimulate the immune system before it is weakened by surgery, chemotherapy, or radiation, and as a result, still has an intact immune system to stimulate.

Another advantage of using Multikine® as a first-line treatment is that any competing product must be able to accommodate the three-week protocol that Multikine® uses, as any delay of the SOC therapies would be inappropriate and unethical as they are potentially curative on their own. As such, the idea that Multikine® is in competition with the currently FDA approved immunotherapies (e.g., Keytruda®, Opdivo®, CAR-T, and many more) is inaccurate as these therapies are administered over many months, which would result in a delay in SOC if used as a first line treatment. Further, the extreme toxicities that may be associated with these new products would preclude their use in patients that are potentially curable by the current SOC alone. In addition, if following approval, Multikine® gets accepted as part of a new SOC for its patient population (as is the Company's objective), CEL-SCI believes that developing new competing first-line treatments might be difficult. Any clinical trial of future first-line candidates would not be able to delay SOC therapies to avoid ethical concerns. Thus, if Multikine® is accepted as SOC, that would mean that any competing product might not be able to take its place as a neoadjuvant therapy, making comparisons between Multikine® and any new product in development extremely difficult.

Active and Passive Immunotherapy Activity

According to CEL-SCI, Multikine® more closely mimics natural immune functions, leveraging both passive and active immunotherapies to produce a more robust and sustainable anti-tumor response, while causing a direct, multi-targeted elimination of tumor cells. The Company believes that available immunotherapies, as well as those currently being developed, are limited by their abilities to target only one or two specific tumor-associated antigens.

Conversely, Multikine®'s multitargeted therapy effect is directed at several targets on the cancer cell and activates multiple cellular components of the immune system in order to more effectively fight cancer. Having multiple elements in its composition enables Multikine® to correct a range of immune deficits and target multiple aspects of the tumor that are required for its destruction. This is unlike mAb therapies or some active immunotherapies, which are directed against and react with one specific target.

Effect on Radiation, Chemotherapy, and Recurrence of Cancer

As Multikine® activates the patient's own immune system while it is still strong (before surgery, radiation, and chemotherapy), the body has the capacity to find and kill tumor micrometastases thought to be responsible for recurrence. Therefore, CEL-SCI believes that the combination of Multikine® with surgery plus radiation/chemotherapy should be more successful at eliminating all of the tumor cells than the current standard therapies of surgery plus radiation/chemotherapy alone.

Flexibility and Additional Indications

Because Multikine® is not tumor specific, as it functions by mobilizing the immune system to mount a robust anti-tumor response with the specificity of the response coming from the patient's tumor, it can be used to address a range of solid tumors and conditions beyond head and neck cancer. The Company believes that Multikine® may also be useful in treating melanoma, cervical dysplasia/neoplasia, and breast, skin, bladder, and prostate cancers.

Safety Profile

During early clinical trials, Multikine® proved to be safe and well tolerated in more than 200 patients, with no severe adverse events associated with its use reported by investigators. Due to its lack of toxicity, it is possible that Multikine® can be combined with other cancer treatments to increase efficacy without added harm to patients (e.g., as an adjunct to chemotherapy and radiation). This is a significant advantage, as many passive immunotherapies and adjuvants are known to be associated with severe toxicities. Moreover, administering Multikine® in conjunction with other first-line treatments instead of as a monotherapy may benefit late-stage patients.

Non-Autologous Therapy

A significant limitation of the targeted immunotherapies cited on pages 20-24 is that many of these are autologous in nature, indicating that they are made from the cancer patient's own tissues and are intended to treat only that patient. This is a costly, labor-intensive process. Multikine® is not an autologous therapy. Multikine® can be mass produced like other pharmaceuticals to exact specifications under cGMP and is an "off-the-shelf" product that can be readily and immediately available and used by physicians for patients.

Multikine®: Orphan Drug Status

Under the Orphan Drug Act, the FDA may grant orphan drug designation to drugs or biologics intended to treat a rare disease or condition that affects fewer than 200,000 individuals in the U.S., or if it affects more than 200,000 individuals in the U.S., there is no reasonable expectation that the cost of developing and making the drug for this type of disease or condition will be recovered from sales in the U.S. Orphan drug status in the European Union has similar, but not identical, requirements and benefits.

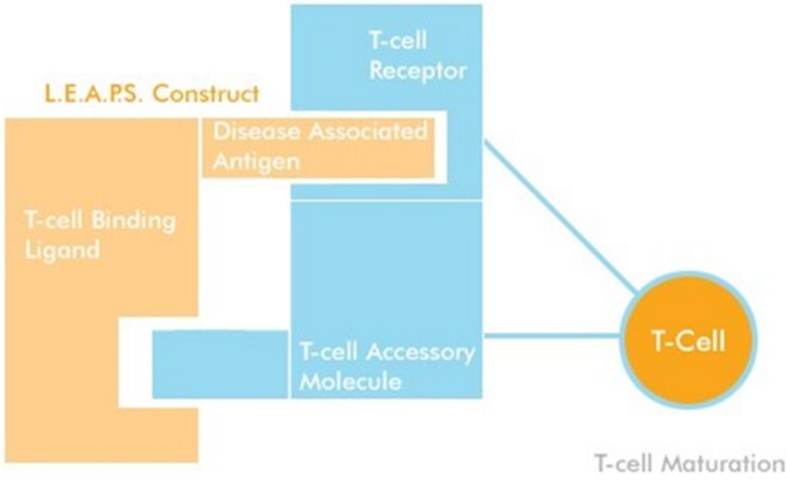
In June 2007, the FDA granted Multikine® Orphan Drug status as a neoadjuvant therapy in patients with squamous cell carcinoma of the head and neck, establishing another significant competitive advantage for the immunotherapy candidate. As an Orphan Drug, Multikine® benefits from several policies that standard therapies in development cannot access.

LEAPS™ (Ligand Epitope Antigen Presentation System) Technology

CEL-SCI's second proprietary technology platform, LEAPS™ (Ligand Epitope Antigen Presentation System), is a preclinical technology designed to stimulate the human immune system to fight bacterial, viral, and parasitic infections more effectively, as well as autoimmune conditions, allergies, transplantation rejection, and cancer. LEAPS™ is a patented, T-cell modulation delivery technology designed to stimulate antigen-specific immune responses in T-cells using synthetic peptides. The proprietary peptides immunogens are designed and synthesized by CEL-SCI to target specific disease and conditions.

Administered as a vaccine, the LEAPS™ compound consists of a small T and Immune -cell binding ligand (TCBL/ICBL) linked with a small, disease-associated peptide antigen (Figure 30), and is delivered directly to the recipient's immune system by injection or mucosal absorption. According to the Company, the LEAPS™ technology may provide a new method to treat and prevent certain diseases by enhancing the T-cell responses to that particular antigen, acting earlier in the pathway of the specific disease.

Figure 30
SCHEMATIC REPRESENTATION OF A LEAPS™ CONSTRUCT



Source: CEL-SCI Corporation.

The ability to generate a specific immune response is important because many diseases are often not treated and cured effectively due to the body's selection of the "inappropriate" immune response. The capability to specifically reprogram an immune response may offer a more effective approach than existing vaccines and drugs in attacking an underlying disease.

This platform technology has been shown in several animal models to preferentially direct immune response to a cellular (e.g. T-cell), humoral (antibody), or mixed pathway. It has the potential to be utilized in diseases for which antigenic epitope sequences have already been identified, such as a number of infectious diseases, some cancers, autoimmune diseases, allergic asthma, and select CNS and other diseases (e.g., Alzheimer's).

THE IMMUNE SYSTEM

The immune system is a network of cells, tissues, and organs that are designed to defend the body against foreign or dangerous substances. Substances that stimulate an immune response in the body are called antigens. Antigens are primarily microorganisms (e.g., bacteria, viruses, and fungi), parasites (e.g., worms), cancer cells, or even transplanted organs and tissues. As the body detects antigens, it produces an immune response aimed at attacking and destroying the substance. This attack involves a variety of **leukocytes** (white blood cells) that work together to destroy invaders. The main leukocytes involved in the immune process are lymphocytes. The two major classes of lymphocytes are B-cells and T-cells, which are also known as B-lymphocytes and T-lymphocytes, respectively.

B-cells

The major function of B-cells is the production of antibodies in response to the presence of antigens. Antibodies are specialized proteins that recognize and bind to one particular antigen. Antibodies binding to a foreign substance are critical as a means of signaling other cells to engulf, kill, or remove that substance from the body. The antibodies attach to foreign antigens to mark them for destruction by T-cells or other immune cells.

T-cells

Unlike B-cells, T-cells do not recognize free-floating antigens. Rather, T-cells' surfaces contain specialized receptors that can detect fragments of antigens on the surface of infected or cancerous cells. T-cells have two major roles in immune defense: (1) direct and regulate immune responses; and (2) directly attack infected cells. Regulation of the immune system is mainly conducted by T-helper (Th) cells (CD4 cells), which is done via the secretion of cytokines. Some cytokines stimulate nearby B-cells to produce antibodies while others activate T-cells, such as the killer T-cell (cytotoxic killer cells), which destroy certain antigens or antigen-infected cells.

T-helper cells differentiate into various effector T-cell subsets, including the well-defined Th1 and Th2 subsets as well as the more recently discovered Th17, Th9, and Th22 subsets (Figure 31). Differentiated T-helper cell subsets secrete different cytokines. Most T-helper cells belong to one of these subsets. However, approximately 10% of Th cells become T-regulatory (T-reg) cells, charged with aiding the regulation of immune system response (Source: Biology-pages.info).

Figure 31
T-HELPER CELLS

	Th1	Th2	Th17	Th9	Th22	Treg
Cytokines Produced	IFNγ	IL-4	IL-17	IL-9	IL-22	IL-10 TGFβ
Function	Intracellular Infections (Cellular)	Extracellular Infections (Humoral)	Extracellular Infections (Humoral)	Extracellular Infections (Humoral)	Extracellular Infections (Humoral)	Regulation

Source: PLOS Pathogens.

LEAPS™ CONSTRUCT

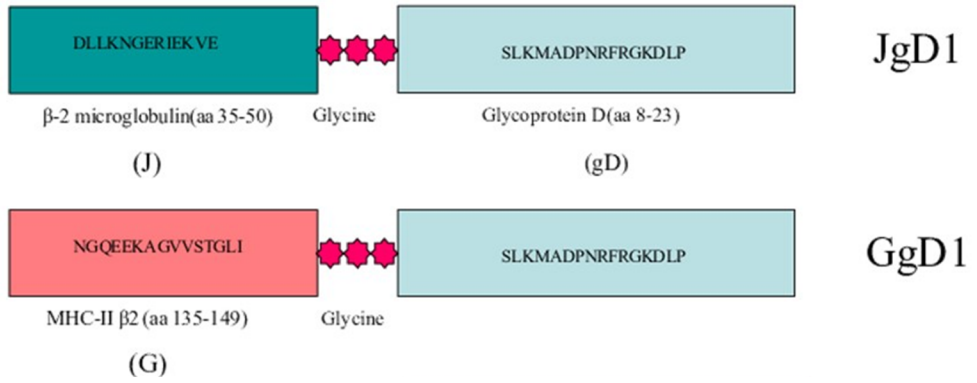
The major goal for preparing a successful vaccine is to elicit the proper immune response to the antigen of interest and avoid excessive inflammation or even suppression of immune responses to achieve the desired outcome. The goal of the LEAPS™ technology is to direct the nature of the immune response to one that is appropriate for the disease to be prevented or treated. As such, the Company's technology aims to remedy situations where the body's immune system has generated an inappropriate response to a particular antigen—reprogramming the immune response to be more effective.

LEAPS™ TCBL/ICBL Epitopes

The concept behind the LEAPS™ technology is to directly mimic cell/cell interactions on the T-cell surface using synthetic peptides. LEAPS™ vaccines consist of a combination of a small peptide (referred to as a T-cell binding ligand or TCBL or immune cell binding ligand - ICBL) that activates the immune system by targeting or binding to an antigen presenting cell, such as a dendritic cell (example of ICBL) or to a T-cell (TCBL), with another small peptide containing a disease associated epitope. LEAPS™ creates a hetero-conjugate containing both a TCBL and a disease specific epitope, combining adjuvant/activating and antigen/immunizing activities into one relatively small peptide.

When a LEAPS™ formulation attaches to a certain T-cell, it causes that cell to activate a particular immune response. The Company can vary the immune response depending on the type of LEAPS™ construct and TCBL used. Two TCBLs of particular interest for CEL-SCI are TCBL peptides J and G (or the modified and more stable version of G, derG). Conjugates of these appear to activate different sub-sets of T-cells. J is a short fragment from β-microglobulin, which elicits a Th1 response, and G is a modified fragment from MHC II β-chain, which directs to a Th2 response. Figure 32 illustrates examples of the J and G TCBL peptides attached to a Herpes Simple Virus (HSV) epitope (gD).

Figure 32
LEAPS™ TCBL CONSTRUCT EXAMPLES



Source: Journal of Vaccines and Vaccination.

When LEAPS™ stimulates a Th1 response, the Th1 cells react with high cytotoxic T-cell activity relative to the amount of antibody production. Th1 cells secrete IL-2, interferon-γ, and IL-12. Th1 cells kill antigen-presenting cells and are associated with vigorous delayed-type hypersensitivity reactions. Th2 cells, on the other hand, synthesize and secrete IL-4, IL-5, IL-6, and IL-10—cytokines that influence B-cell development and antibody production when LEAPS™ stimulates a Th2 response, Th2 cells cause high antibody production relative to the amount of cytotoxic T-cell activity.

Mechanism of Action

The concept behind the LEAPS™ technology is to directly mimic cell/cell interactions on the T-cell surface using synthetic peptides. When a LEAPS™ formulation attaches to a certain T-cell, it causes that cell to activate a particular immune response, altering only select cytokines specific for each disease model. Thus, the Company believes that its LEAPS™ technology platform has an advantage over other peptide epitope-based technologies because LEAPS™ vaccines can be designed to produce either a cellular response or antibody mediated response (humoral), involving the specific T-cells and immune cells needed for an optimal response for that particular condition.

The combination of a small peptide that activates the immune system with another small peptide from a disease-related protein allows the LEAPS™ vaccines to activate precursors to differentiate and become more mature cells that can initiate and direct appropriate T-cell responses. For example, J-LEAPS™ vaccines (LEAPS™ vaccines using the J conjugate) interacts with human monocytes and mouse bone marrow DC precursors to promote their maturation into DCs that promote T-cell responses with the Th1 phenotype. Dendritic cells (DC) are the bridge between the innate and adaptive immune systems. Mature DCs direct the nature of an immune response by producing different cytokine environments while presenting antigen to T-cells. During the development of an adaptive immune response, DCs play an extremely important role in initiating T-helper cells differentiation. Thus, by demonstrating that the J TCBL molecule can activate precursor DCs, it shows that the LEAPS™ technology platform can act earlier in the pathway of the specific disease, recruiting the immune system at the earlier stages.

RESULTS OF PRECLINICAL STUDIES

The Company and its collaborators have conducted a series of preclinical animal challenge studies in several disease indications, of which key results are summarized on the accompanying pages. Challenge studies entail the administration of a chemical substance or an antigen in order to assess the reaction, whether documenting the occurrence of normal physiological responses or to evoke an immunologic response in a previously sensitized subject. In these studies, the LEAPS™ candidates have demonstrated protection against lethal herpes simplex virus (HSV1) and H1N1 influenza infection, as a prophylactic or therapeutic agent. They have also shown some level of efficacy in animals in two autoimmune conditions, curtailing and sometimes preventing disease progression in arthritis and myocarditis animal models.

Furthermore, even though the various LEAPS™ vaccine candidates have not yet been given to humans, they have been tested in vitro with human cells. In these studies, LEAPS™ constructs have induced similar cytokine responses that were seen in these animal models, which may indicate that the LEAPS™ technology could translate to humans. In addition to the development of product candidates for conditions that currently do not have an available vaccine, CEL-SCI's believes that the LEAPS™ technology may even be a significant alternative to the vaccines currently available on the market.

Rheumatoid Arthritis (RA)—Preclinical Product Candidate (CEL-2000, CEL-4000)

The LEAPS™ technology platform has been used to develop immunoprotective and immunomodulating small peptide vaccines for infectious and autoimmune diseases. Several products are currently in various stages of development at the pre-clinical stage (in animal challenge efficacy studies). In particular, two LEAPS™-based product candidates—CEL-2000 and CEL-4000—have shown the potential to block the progression of RA by modulation of specific immune responses. CEL-2000, a J-LEAPS™ vaccine similar to those that provide protection against HSV-1 and therapy for HER-2 antigen bearing breast cancer tumors and autoimmune myocarditis, modulate the Th17 inflammatory response. In contrast, CEL-4000, a derG-LEAPS™ vaccines, provides antigen specific cessation of Th1 driven disease progression.

For RA, the efficacy of CEL-2000 and CEL-4000 LEAPS™ vaccines was demonstrated by therapeutic cessation of disease progression in their respective mouse models and modulation of T-cells and serum cytokines away from inflammation and towards a healthier balance. With both CEL-2000 and CEL-4000, single epitope LEAPS™ vaccines appear to evoke therapeutic immune responses against a multiple epitope driven disease in their respective animal models for at least 35 days or more.

Research for the development of the LEAPS™ technology as a treatment for RA has been funded via collaborations with the U.S. National Institutes of Health (NIH), U.S. Army, Navy, and universities. Specifically, CEL-SCI has received two Small Business Innovation Research (SBIR) grants from the NIH for a total of $1.725 million. With the support of these grants, CEL-SCI is developing CEL-2000 and CEL-4000 as potential RA therapeutic vaccines. CEL-2000 and CEL-4000 have the potential to become a personalized, disease-specific therapy, that is significantly less expensive and acts at an earlier step in the disease process than current therapies. In addition, they may be useful in patients not responding to existing RA therapies.

According to the Company, while its initial autoimmune studies with LEAPS™ focus on RA, LEAPS™ vaccines could be applied to other autoimmune conditions driven by Th1 or Th17 cytokines. Further discussions of product candidates CEL-2000 and CEL-4000, along with a description of the preclinical studies for LEAPS™ in RA are found on pages 50-54.

Influenza Virus

Influenza requires annual immunizations due to the numerous strains of virus and its propensity to create new strains through mutation or re-assortment of the genomic strands. The annual "flu" shot is meant to provide protection by generating antibodies to the prevalent strain of virus. However, manufacturing of these vaccines are based on epidemiologic prediction of the expected predominant influenza strain for the following year. Since the influenza virus is constantly undergoing mutations and changes, new variants of the virus may emerge from year to year, which might make the vaccine effectiveness vary each year according to the ability of epidemiologists to correctly predict the prevalent strain each season (Source: *International Immunopharmacology*, Vol. 74, 2019).

As an alternative to antibody protections for influenza, T-cell response-based vaccines (such as LEAPS™) target the infected cell rather than the free virus and are not as strain dependent. Following this strategy, CEL-SCI conducted efficacy studies to assess LEAPS™ in the treatment of H1N1 (swine flu), an infectious disease caused by type A strains of the influenza virus.

During the studies, DCs were stimulated into maturation with a J-LEAPS™ base conjugated with 15 to 30 amino acid–long peptides derived from influenza virus and were subsequently injected into influenza-infected mice. Scientists found that LEAPS™-stimulated DCs were effective in reducing influenza virus replication in the lungs while enhancing survival of infected animals. The LEAPS™ conjugate enhanced the homing of influenza-peptide–bearing DCs to the lungs, which is the site of infection. Additionally, they promoted a Th1 based immune response, augmenting influenza-specific T-cell responses in the lungs and reducing the severity of disease by limiting excessive cytokine responses, which are known to contribute to morbidity and mortality following influenza virus infection (Source: *The Journal of Clinical Investigation*, Vol. 123(7):2850-2861, 2013).

Using the LEAPS™ technology, CEL-SCI created a potential peptide treatment for H1N1 (swine flu)-hospitalized patients, which contains epitopes known to be associated with immune protection against influenza in animal models. This LEAPS™ flu treatment is designed to focus on the conserved, non-changing epitopes of the different strains of Type A Influenza viruses (H1N1, H5N1, H3N1, etc.), including "swine", "avian or bird", and "Spanish Influenza", in order to minimize the chance of viral escape by mutations from immune recognition. Because of this, the Company views its H1N1 LEAPS™ treatment as a potential pandemic flu treatment.

Herpes Simplex

The herpes simplex virus is both an oral and a sexually transmitted disease that can cause blister-like lesions around the mouth and lips, eye infections, encephalitic brain infections, neonatal infections, and genital herpes, among other effects. An estimated 3.7 billion people (or 67% of the population) under age 50 have herpes simplex virus type 1 (HSV-1) infection globally, while another 491 million people aged 15-49 (13% of the population) have herpes simplex virus type 2 (HSV-2) infection (Source: World Health Organization [WHO]). In the U.S. it is estimated that 47.8% and 11.9% of people have HSV-1 and HSV-2, respectively (Source: Centers for Disease Control and Prevention [CDC]).

A viable herpes vaccine could certainly provide a lucrative financial windfall for the company that develops it. At this time, there is no major clinical trial under way for a vaccine to prevent the sexually transmitted disease. The herpes virus has more complicated DNA than most infections and has ways to go undetected by our immune system, much like many cancer cells. Since vaccines work by stimulating the human immune system, this makes it more difficult to develop an inoculation for herpes. Furthermore, it is believed that a vaccine against HSV infection would not only help to promote and protect millions of people from that particular disease, but it could also potentially have an impact on slowing the spread of HIV (Source: Healthline's *Why We Still Don't Have a Herpes Vaccine*, May 2019). In murine models, the Company's LEAPS™ technology delayed the onset of disease signs, diminished the severity of the herpes, decreased mortality rates, and reduced disease progression.

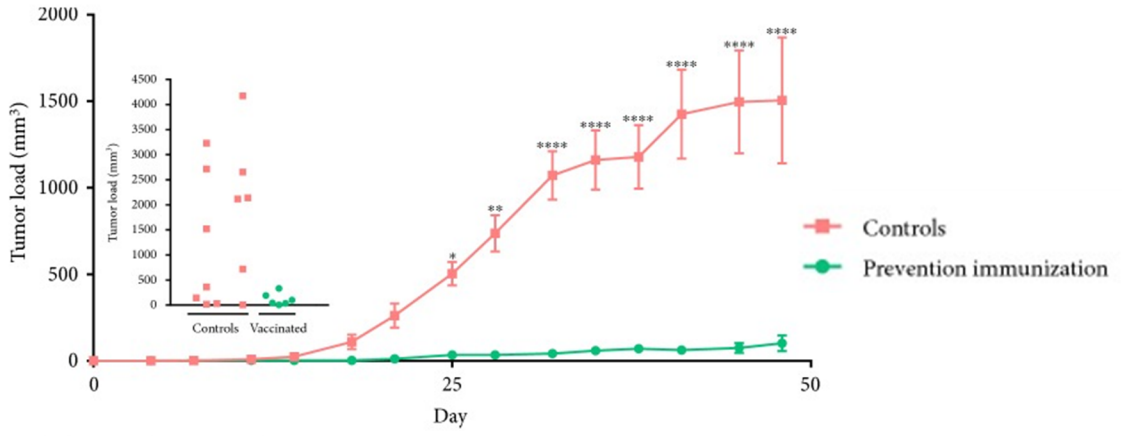
Breast Cancer

The Company conducted a proof-of-concept study to test the ability of a LEAPS™ vaccine (J-HER) to prevent or treat breast cancer HER-2/neu-expressing tumors in mouse models. The vaccine was tested for its ability to elicit prophylactic and therapeutic responses in mice challenged with TUBO cells (Source: *Journal of Immunology Research*, Vol. 2017:1-8, 2017). The prototype J-HER breast cancer vaccine was prepared by covalent attachment of the J-immune cell binding ligand (J-TCBL) to a murine T-cell epitope from HER-2/neu. The J-TCBL was chosen for its potential to promote Th1/Tc1 responses.

This pilot project demonstrated that when administered as a prophylactic vaccination, the immune response elicited by J-HER was sufficient to prevent the initial development of tumor outgrowth in the TUBO breast cancer tumor model. Unimmunized mice developed measurable tumors within 14 days after injection of cancer cells into the abdomen, with tumor growth extended into the abdomen and through the skin. In contrast, for the J-HER-immunized mice, there was minimal evidence of tumor development or disease signs over the course of the trial, 48 days after injection of TUBO cells. Figure 33 shows tumor volume for control and treated mice at day 48 following cancer cell injection (end of experiment), while the inset shows total tumor size for individual mice. Despite eliciting protection, antibody production in J-HER-immunized mice to HER-2-neu was less than that in unimmunized mice. This is consistent with the lack or limited antibody generation by J-TCBL-based LEAPS™ vaccines

Figure 33

LEAPS™ EFFECT ON TUMOR LOADS



Source: Journal of Immunology Research.

More importantly, therapeutic administration of J-HER one week after challenge with breast cancer cells limited the spread of the tumors and the morbidity and the mortality in the challenged mice. Mice were treated with the J-HER vaccine one week after initiation of tumor development by subcutaneous injection of breast cancer cells. Vaccine treatments were repeated every two weeks after the initial treatment. Unlike the untreated mice, J-HER-treated mice appeared otherwise healthy and tumor morbidity and mortality were significantly reduced. Mice treated with J-HER showed a lag in the development of tumors compared to untreated mice. Mortality was delayed and more mice survived compared to untreated mice.

The ability to elicit responses that prevent spread of the TUBO tumor by J-HER suggests its utility as a neoimmunoadjuvant therapy to surgery. Individual or mixtures of J-LEAPS™ vaccines can be readily prepared to include different CD8+ T-cell epitopes to optimize tumor therapy and customize treatment for individuals with different HLA types.

Other Conditions and Uses

The LEAPS™ technology has also been tested for other infectious conditions. In early preclinical testing, the LEAPS™ technology showed promise in use as a potential adjuvant to a malaria vaccine, as well as the Hepatitis B vaccine and decreasing morbidity and mortality in animal model of Influenza (H1N1).

PRODUCT CANDIDATES – CEL-2000 AND CEL-4000 FOR RHEUMATOID ARTHITIS

The LEAPS™ technology platform has been used to develop immunoprotective and immunomodulating small peptide vaccines for infectious and autoimmune diseases. Several products are currently in various stages of development at the pre-clinical stage (in animal challenge efficacy studies). In particular, two LEAPS™-based product candidates—CEL-2000 and CEL-4000—have shown the potential to block the progression of autoimmune diseases by immunomodulation of ongoing pathogenic responses.

CEL-2000, a J-LEAPS™ vaccine, blocks the progression of collagen induced arthritis (CIA) by immunomodulation of the Th17 response during RA. CEL-4000, A derG-LEAPS™ vaccine (using a more stable version of the G-TCBL called derG), demonstrated therapeutic efficacy for the proteoglycan (PG)-induced arthritis (PGIA) and PG G1-domain-induced arthritis (GIA) (PGIA/GIA) mouse models of RA by providing antigen specific cessation of Th1 driven disease progression. Figure 34 provides a comparison of both product candidates.

Figure 34

CEL-2000 and CEL-4000 COMPARISON

	TCBL	Epitope	Modulation	Arthritis mouse model
CEL-2000	J	Type II collagen	Th17	Collagen Induced Arthritis (CIA)
CEL-4000	derG	proteoglycan (PG)	Th1	PG-induced arthritis (PGIA) and PG G1-domain-induced arthritis (GIA)

Sources: CEL-SCI Corporation, and Crystal Research Associates, LLC.

Disease progression in the CIA model mimics human disease in terms of joint pathology, inflammation, bone erosion, bone remodeling, cartilage alterations, and pannus formation. The disease in this model is driven by Th17 immune responses, as indicated by the generation of IL17. The PGIA and GIA models in adult female mice are predominantly driven by Th1 responses producing IFNy. The PGIA and GIA models resemble human RA more than other animal models in that disease is induced in older females (Source: *Journal of Clinical and Cellular Immunology*. Vol. 10(1): 574, 2019).

Rheumatoid Arthritis (RA) Vaccine Grants

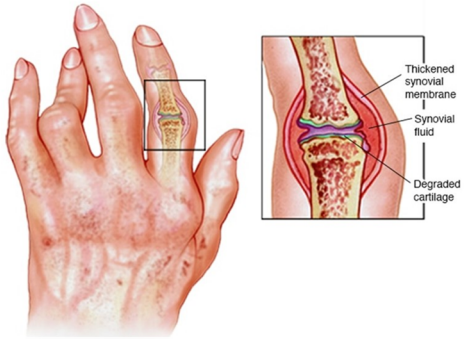
Research for the development of the LEAPS™ technology as a treatment for RA has been funded via collaborations with the U.S. National Institutes of Health (NIH), U.S. Army, Navy, and universities. In July 2014, CEL-SCI announced that it has been awarded a Phase 1 Small Business Innovation Research (SBIR) grant in the amount of $225,000 from the National Institute of Arthritis Muscoskeletal and Skin Diseases, which is part of the National Institutes of Health. The grant funded the development of CEL-SCI's LEAPS™ technology as a potential treatment for RA.

On September 2017, CEL-SCI was awarded a Phase 2 SBIR grant in the amount of $1.5 million from the National Institute of Arthritis Muscoskeletal and Skin Diseases. This grant will provide funding to allow CEL-SCI to advance its first LEAPS™ product candidate, CEL-4000, towards an Investigational New Drug (IND) application, by funding GMP manufacturing, IND enabling studies, and additional mechanism of action studies, among other preclinical development activities.

Overview

Rheumatoid arthritis (RA) is an autoimmune disorder characterized by chronic inflammation and systemic destruction of the peripheral joints. RA affects over 1.3 million Americans and as much as 1% of the worldwide population and is one of the most common autoimmune disorders (Source: RheumatoidArthritis.org). RA occurs when the immune system attacks the synovium, the lining of the membranes that surround the joints. The resulting inflammation causes a painful swelling, which can eventually destroy the joint cartilage and bone, resulting in bone erosion and joint deformity (Figure 35).

Figure 35
RHEUMATOID ARTHRITIS



Source: Mayo Clinic.

RA can affect more than just the joints. The inflammation associated with RA can damage other parts of the body and a wide variety of body systems, including the skin, eyes, lungs, heart, and blood vessels (Source: Mayo Clinic).

RA Mechanisms of Action

RA is a very heterogeneous disease that may have different initiators and be driven by different types of inflammatory responses for each individual. Although the initiating events of RA are unknown, the disease is maintained by pro-inflammatory mediators produced during T-helper (primarily Th1 and Th17) cell-driven autoimmune responses (Source: *Vaccine*, Vol. 35: 4048–4056, 2017).

T-helper cells, generally Th1 or Th17, become actively involved in an inflammatory cascade, featured in the dysregulation of the production of inflammatory and regulatory cytokines. Th17 cells, which produce the inflammatory cytokine IL-17, are involved in inflammation and host defense against extracellular pathogens and has been shown to play an important role in the induction of autoimmune tissue injury. Th1 cells, which secrete IL-2, interferon-γ, and IL-12, kill antigen-presenting cells and are associated with vigorous delayed-type hypersensitivity reactions (immune responses that are exaggerated or inappropriate against an antigen).

Key antigens suggested to be inducers of RA as it relates to the Company's technology are collagen II and proteoglycan (PG), which can induce RA-like disease in mice and elicit potent T-cell responses (Source: *Journal of Clinical and Cellular Immunology*. Vol. 10(1): 574, 2019).

RA Treatments and Vaccines

Current treatment for RA largely focus on alleviating symptoms (through the use steroids and anti-inflammatory drugs, including NSAIDS) or delaying disease progression through the use of disease-modifying antirheumatic drugs (DMARDs), including biologics. The most recent advances in treatment have come from biologics targeting specific components of the immunological inflammatory pathway. Biologics suppress elements of the immune system in order to curtail the inflammatory process by targeting the cytokines or cell surface receptors that are responsible for maintaining the autoimmune and inflammatory disease processes.

Although somewhat more selective, this is also an ablative therapy that leaves the patient deficient in certain types of immune protection, increasing the risk of infections and other potentially severe side effects. Since the anti-cytokine and receptor blocking approach is not selective, it can delete essential immune protections against diseases, such as tuberculosis and cancers, putting the treated individual at risk for these diseases. In addition, these therapies are expensive and must be administered by specialists on a regular schedule. Furthermore, DMARDs do not provide a universal therapy for everyone, with their ineffectiveness for 30% to 50% of RA patients demonstrating the need for new approaches to therapy (Source: *Expert Review of Vaccines*, Vol. 14(6):1-18, 2015).

An alternate approach is to actively modulate the ongoing aberrant immune response with a vaccine, so that the immune response no longer promotes disease. Chronic autoimmune diseases result from tissue-damaging inflammation that is initiated by improperly regulated immune responses to self-antigens.

Ideally, an RA therapeutic vaccine would consist of an immune modulation therapy that enhances the regulatory and therapeutic immune response while curtailing the pro-inflammatory responses associated with RA. This method of immune modulation is preferable to anti-cytokine or receptor blocking, as it actively redirects the immune response away from the disease-causing actions, instead of generically removing an important component of the immune system.

An additional problem for an RA vaccine is that different approaches may be required for modulating the disease driving T-cell response, since the inflammatory response driving disease (whether Th1 or Th17) may be different in different individuals (Source: *International Immunopharmacology*, Vol.74, 2019).

Product Candidate CEL-2000

Of the different vaccine approaches that has been suggested, the LEAPS™ approach is unique in that the vaccine can be designed to define the direction of the subsequent antigen-specific response toward Th1, Th2, Th17, or Treg cells depending upon the attached TCBL. One such construct is CEL-SCI's product candidate, CEL-2000 (J-CIIx). This LEAPS™ conjugate combines the J-TCBL with an epitope of type II collagen, which is also known to have T-cell responsiveness in human RA patients.

The data from animal studies demonstrated that CEL-2000 was effective in the Th17-driven CIA mouse model of RA as therapy to block the progression of disease after disease initiation, showing that it could be used as an effective treatment against RA associated with the Th17 response, with fewer administrations than those required by other anti-RA treatments currently on the market. The therapeutic effect of CEL-2000 was accompanied by reduced serum levels of pro-inflammatory cytokines.

C-2000 Study Overview
Journal of Vaccines and Vaccinations, Vol. 3:5, 2012.

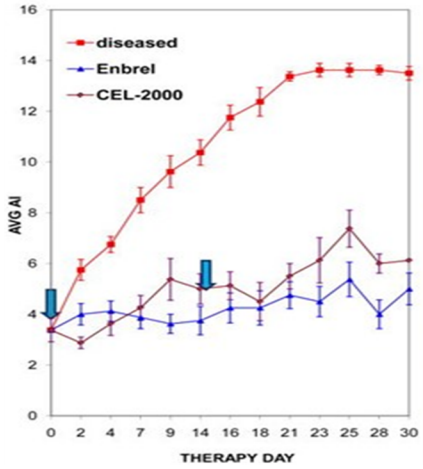
The collagen-induced arthritis (CIA) model was used to demonstrate the ability of a J-LEAPS™ conjugate to therapeutically treat RA. Following the CIA model protocol, mice received two injections of 100µg bovine collagen three weeks apart. Thirty-one days following the first injection, the mice were grouped and assessed via an arthritic index (AI) score. CEL-2000 therapy was initiated after grouping of mice on day 31 of study, after the onset of disease symptoms. J-LEAPS™ conjugate CEL-2000 (100nmol) was administered on days 0 and 14 after grouping. Control groups were either untreated or treated with TNF-α receptor antagonist, etanercept (Enbrel®), every other day.

Mice with CIA developed notable swelling and inflammation of the paws and ankles, including cell infiltration and destruction of the joints. Mice treated with CEL-2000 had much less swelling of the paws, as measured by an arthritic index (AI) score compared to untreated mice. The efficacy indicated by the favorable AI score was similar to therapy with etanercept (Enbrel®), an anti- TNF-α biologic used in the clinic to treat RA in man and considered the therapeutic "gold standard", as seen in Figure 36 (page 53). The Figure shows the average AI score of CEL-2000 treated, untreated, and etanercept (Enbrel®)-treated mice following administration of CEL-2000 (arrows). At the end of the study, histopathological examination of ankles and paws following treatment also showed a lack of disease progression due to vaccination that blocked bone or cartilage erosion and damage.

The effect of CEL-2000 on disease progression was also assessed through evaluation of serum cytokine levels taken 10 days after initiation of therapy. Analysis of serum cytokines in treated and untreated mice showed a redirection away from the Th17 response (untreated) and towards a Th1 response (CEL-2000 treated), with a relative decrease in inflammatory cytokines TNF-α and IL-17, IL-6, and increased levels of IFNγ and IL10, a regulatory cytokine. The increase in IL-12p70 but decrease in IL-12p40 suggests a decrease in IL-23, an inducer of the Th17 response. Similar to the therapeutic effect as measured via AI score, serum cytokine results following biweekly CEL-2000 treatments were comparable to those for mice treated every other day with the TNFα antagonist, etanercept (Enbrel®, Figure 37 [page 53]).

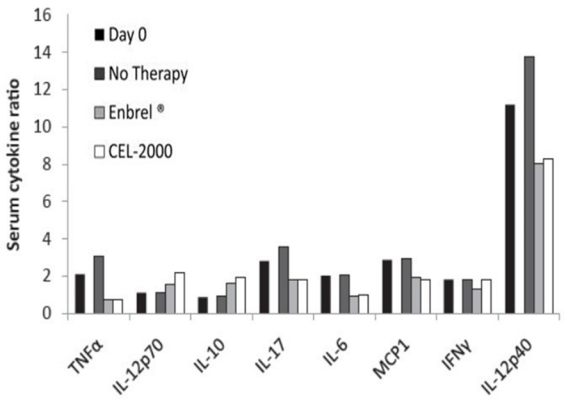
Of note, neither a mixture of the unconjugated J-TCBL nor a DerG version of this vaccine was effective in this RA model.

Figure 36
CEL-2000 RA SCORES



Source: Journal of Vaccines and Vaccinations.

Figure 37
CEL-2000 SERUM CYTOKINES



Source: Journal of Vaccines and Vaccinations.

Product Candidate CEL-4000

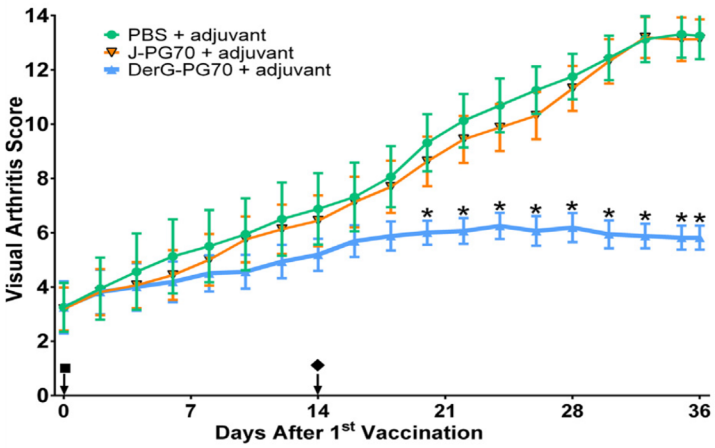
The second product candidate being studied against RA is CEL-4000 (derG– PG70), consisting of the derG-TCBL and the immunodominant PG peptide (PG70) from human proteoglycan. The preclinical data for CEL-4000 indicates it could be effective against RA cases where a Th1 signature cytokine (IFN-γ) is dominant. CEL-4000 stopped progression of disease and reduced Th1 as well as Th17-related cytokine and inflammatory responses in the Th1 driven PGIA and GIA mouse models of RA. The J-LEAPS™ version of this vaccine (J-PG70) was not effective in this model. The importance of a vaccine's ability to modulate the specific disease-driving proinflammatory immune response within an individual is demonstrated by the difference in efficacy of the J-ICBL (Th1 promoting) and G-ICBL (Th2/ Treg promoting) versions of the CEL-2000 and CEL-4000 LEAPS™ vaccines in the CIA and PGIA/GIA mouse models.

C-4000 Study Overview
Vaccine, Vol. 35: 4048–4056, 2017

In this study, CEL-SCI tested the therapeutic efficacy its LEAPS™ vaccines technology in two Th1 cell-driven mouse models of RA, cartilage proteoglycan (PG)-induced arthritis (PGIA), and PG G1-domain-induced arthritis (GIA). For the study, the immunodominant PG peptide PG70 was attached to a DerG or J immune cell binding peptide, and the DerG-PG70 (CEL-4000) and J-PG70 LEAPS™ vaccines were administered to the mice after the onset of PGIA or GIA symptoms. As indicated by the VA scores, treatment with the DerG-PG70 (CEL-4000) vaccine significantly limited disease progression within three weeks in in both PGIA (Figure 38 [page 54]) and GIA models, while J-PG70 had no significant effects compared to control. Importantly, the CEL-4000 vaccine effectively curtailed arthritis symptoms in GIA despite its more aggressive disease course compared to PGIA.

Figure 38

ARTHRITIS SCORE IN PGIA MODEL



Source: Vaccine

In vitro spleen cell-secreted and serum cytokines from CEL-4000-treated mice demonstrated a shift from a pro-inflammatory to an anti-inflammatory/regulatory profile. Treatment of PGIA or GIA mice with the CEL-4000 vaccine led to a reduction of pro-inflammatory Th1 and Th17 cells and an increase in the frequency of anti-inflammatory IL10-producing as well as protective Treg cells in both models.

As in RA, the inflammatory disease in both the PGIA and GIA models is driven and sustained primarily by Th1 but also by Th17 cells and cytokines produced by them. CEL-4000 treatment promoted a more balanced, less inflammatory cytokine responses by increasing Th2 (IL4+ and IL10+) and Treg cells and reducing Th1 and Th17 cells in PGIA, and to a somewhat lesser extent in the GIA system.

CEL-2000 and CEL-4000 – Different Approaches to the Same Goal

The inflammatory response driving RA, whether Th1 or Th17, may be different in different individuals. Failure of some patients to respond to certain therapies may reflect differences in the initiators and responses driving their disease. Thus, different approaches may be required for treating the disease, according to the underlying mechanisms of action for each case.

The importance of a LEAPS™' ability to modulate the specific disease-driving pro-inflammatory immune response within an individual is demonstrated by the difference in efficacy of the J-TCBL (Th1 promoting) and derG-TCBL (Th2/ Treg promoting) versions of the CEL-2000 and CEL-4000 LEAPS™ vaccines in the CIA and PGIA/GIA mouse models. The CEL-4000 (derG-PG70) vaccine was effective in curtailing progression of RA driven by Th1 responses whereas CEl-2000 (J-CIIx) was effective in blocking the progression of RA in the Th17-driven CIA model.

As such, knowledge of signature T-cell cytokine phenotypes that drive the patient's disease can facilitate the choice of the appropriate LEAPS™ vaccine therapy. These results suggest that once the nature of the inflammatory autoimmune response in a patient with RA has been identified (e.g., by analyzing prominent serum cytokines levels), then this patient can be treated with the appropriate LEAPS™ vaccine with either a J-TCBL to counteract a Th17-driven inflammatory response or a derG-TCBL to counteract a Th1-dominated inflammatory response.

New Epitope Discovery
Journal of Immunology, Vol. 202 (1):133.4, 2019

In May 2019, CEL-SCI announced that a newly discovered LEAPS™ conjugate vaccine acts alone and can complement CEL-4000 therapeutically when administered in combination to an animal model of RA. The data was initially presented at the American Association of Immunologists 103rd Annual Meeting (Immunology 2019).

CEL-4000 (derG-PG70) and a newly discovered LEAPS™ conjugate, derG-PG275Cit, were evaluated alone and in combination in the PGIA and GIA mouse model of RA. Mice were immunized with either one or two different derG LEAPS™ vaccines containing PG epitopes (PG70 or PG275Cit) subcutaneously after signs of arthritis were noted. Mice were examined twice weekly for arthritis progression. At study end, serum antibodies to the vaccine epitopes and splenic T-cell responses to PG G1 domain were determined.

Results showed that new derG LEAPS™ conjugate (derG-PG275Cit), alone or together with CEL-4000 (derG-PG70), modulated the inflammatory response and stopped the progression of RA. derGPG275Cit was effective in providing protection but did not induce significant serum antibodies, whereas CEL-4000 (alone or with derGPG275Cit) induced both protection and antibodies. Results suggest mechanistically different immune responses to the two vaccines. Both derG-LEAPS™ conjugates appears to act on different immune pathways by a different mechanism from each other. In addition, these vaccines incorporate distinct epitopes that are located in distant regions of the PG molecule involved in arthritis induction. Thus, a combination vaccine containing both LEAPS™ conjugates CEL-4000 (derG-PG70) and derG-PG275Cit could offer advantages in case one epitope or another was missing in the disease inducing situation. The combination of the two RA vaccines provided not only broader epitope coverage, but also a greater therapeutic effect than either vaccine alone.

LEAPS™ COVID-19

On March 23, 2020, CEL-SCI announced that it had signed a collaboration agreement with the University of Georgia's Center for Vaccines and Immunology to develop a LEAPS™ COVID-19 immunotherapy. The Company's treatment is targeted for patients who are at highest risk of dying from COVID-19 due to tissue damage from infection to the lungs. The LEAPS™ peptide technology can be used to construct immunotherapeutic peptides that exhibit both antiviral and anti-inflammatory properties. Consequently, these products not only target the virus infection against which they are directed, but also elicit the appropriate protective response against it.

Predictions of success using the LEAPS™ peptides against COVID-19 coronavirus are based on previous studies that found that LEAPS™-stimulated dendritic cells (DCs) were effective in reducing influenza virus replication in the lungs while enhancing survival of infected animals. The study showed the LEAPS™ influenza therapeutic product's ability to enhance the homing of LEAPS™-stimulated DCs into the lungs, resulting in a reduced influenza virus replication in the lungs by activating appropriate T-cell responses rather than an inflammatory response. Of particular interest is LEAPS™ ability to modulate the inflammatory cytokine storm response to the influenza virus, believed to be a significant contributor to mortality in severe COVID-19 cases.

It is suggested, based on studies with H1N1, that a LEAPS™ COVID-19 immunotherapy may reduce or arrest the progression of the virus infection and prevent tissue damage from inflammation resulting from lung infection by the virus. By stimulating the correct immune responses to the COVID-19-causing virus without producing unwanted inflammatory responses associated with lung tissue damage, LEAPS™ immunotherapy may be particularly beneficial to those patients who are at highest risk of dying from COVID-19. Although individuals of all ages are susceptible to COVID-19 infection, the elderly and individuals with compromised lung function or immune system are at highest risk for severe morbidity and mortality. It is believed that, in most cases, onset of symptoms takes between two- and 14-days post infection—a period of time that may allow intervention for those at highest risk and with a known exposure.

The proposed LEAPS™ peptides are directed towards antigens within the nucleoprotein of COVID-19 that elicit **cytolytic** T-cell responses. Unlike other antigens, which are important for antibody-based vaccines, these antigens are less variable between viral strains and less likely to change in response to antibodies elicited by prior infection or other vaccines. Cytolytic T-cell responses attack the virus infected cellular "factories" within the infected host in order to eliminate the source of virus and help subdue the infection.

The University of Georgia Center for Vaccines and Immunology brings together a diverse, world-renowned team of experts in the areas of infectious disease, veterinary medicine, ecology, and public health. The university's world-class biocontainment research resources are coupled with the expertise of CVI investigators who focus on translational studies to test and assess the efficacy of vaccines and immunotherapies in development by industry, governmental, and academic institutions.

Investment Highlights

- CEL-SCI Corporation is a clinical-stage biotechnology company focused on developing immunotherapy products and technologies to treat cancer and infectious diseases that address significant unmet medical needs. The Company aims to develop novel therapies with the potential to activate and utilize the body's own immune system against the disease.
- The Company is focused on developing product candidates based on two innovative technologies: (1) Multikine® (Leukocyte Interleukin, Injection), a next-generation, comprehensive immunotherapy; and (2) LEAPS™ (Ligand Epitope Antigen Presentation System), an immunotherapy vaccine technology platform.
- CEL-SCI's lead product candidate, Multikine®, is an investigational immunotherapy in Phase 3 studies for patients with squamous cell carcinoma of the head and neck (advanced primary head and neck cancer), for which the Company has received Orphan Drug Status from the FDA. CEL-SCI intends to demonstrate that Multikine® could become an integral first-line component of the current standard of care (SOC) regimen due to its effectiveness and safety profile. Multikine® is also being studied for the treatment of cervical dysplasia in human immunodeficiency virus (HIV) and human papillomavirus (HPV) co-infected patients.
- Multikine® modulates the body's immune system through a dual mechanism of action: eliciting the direct killing of tumor cells and micrometastasis (limiting the possibility of recurrence), while generating a sustainable anti-tumor response, and possibly rendering tumor cells more susceptible to subsequent radiation and chemotherapy.
- Multikine® is being developed as a first-line treatment for advanced primary head and neck cancer, to be given as a neoadjuvant, prior to other therapy options (chemotherapy and radiation therapy). Multikine® augments/stimulates the immune system before it is weakened by both the toxic therapies and the cancer itself. According to CEL-SCI, Multikine® would be the world's first cancer immunotherapy drug to be administered prior to surgery.
- In its most recent Phase 2 clinical trial for Multikine®, CEL-SCI reported a 10.5% complete response rate (no clinical or pathology evidence of any remaining cancer) and a 33% improvement in overall survival. Most importantly, there has been no severe adverse events associated with the use of Multikine®.
- Multikine® is currently in a pivotal Phase 3 clinical trial (IT-MATTER), the largest head and neck cancer study ever conducted. In May 2020, CEL-SCI announced that it had reached the required number of events for the completion of its Phase 3 trial. The Company is proceeding with the analysis of the data and expects to file for regulatory approval in 2021.
- CEL-SCI's second proprietary technology platform, LEAPS™, is a vaccine technology platform designed to stimulate the immune system to fight bacterial, viral, and parasitic infections more effectively, as well as autoimmune conditions, transplant rejection, and cancer. Research for the development of the LEAPS™ technology as a treatment for RA has been funded in part via two Small Business Innovation Research (SBIR) grants from the National Institutes of Health totaling $1.725 million.
- The LEAPS™ technology is being used to develop therapeutic agents for rheumatoid arthritis (RA) as the lead indication, as well as for COVID-19 in collaboration with the University of Georgia's Center for Vaccines and Immunology.
- The inflammatory response driving RA may be different in different individuals, with failure of some patients to respond to certain therapies reflecting these differences. The LEAPS™ platform can be designed to produce a specific natural immune response depending on the type of construct used. Thus, once the nature of the inflammatory response has been identified, the patient can be treated with the appropriate LEAPS™ vaccine.
- CEL-SCI operates a dedicated state-of-the art manufacturing facility with over 73,000 sq. ft. of manufacturing and research and development (R&D) space. The Phase 3 trial was supplied from this facility, reducing regulatory risks at time of approval.
- As of March 31, 2020, CEL-SCI's cash position was $14.3 million. The Company has no debt, no convertible notes, and a clean balance sheet.

Competition

The development and commercialization of new drug and biological products is highly competitive. CEL-SCI faces competition from leading pharmaceutical companies, specialty pharmaceutical companies, and biotechnology companies worldwide. Potential competitors also include academic institutions, government agencies, and other public and private research organizations that conduct research, seek patent protection, and establish collaborative arrangements for research, development, manufacturing, and commercialization.

MULTIKINE® COMPETITIVE LANDSCAPE

According to the Company, the most common misconception with respect to Multikine® is that it is in competition with all of the FDA approved immunotherapies (e.g., Keytruda®, Opdivo®, and other checkpoint inhibitors). In contrast to Multikine®, these immunotherapies are indicated only for patients whose cancers have recurred following standard of care (SOC) treatment or those patients with cancer where surgery is no longer an option. Similarly, none of the other treatment options for head and neck cancer, such as targeted therapies (e.g., EGFR inhibitors like Erbitux® [cetuximab]), and monoclonal antibodies have been approved as neoadjuvants. Furthermore, the extreme toxicities that are associated with these new products would preclude their use in pre-SOC settings. For perspective, no severe adverse events associated with the use of Multikine® was recorded during its clinical trials, where Multikine® proved to be safe and well tolerated in more than 200 patients.

Multikine® is being developed as a first-line treatment to be given to patients following initial definitive diagnosis and before any other therapy options, administered in the four-week period that normally occurs between diagnosis and surgery. Any new therapy must be able to accommodate this protocol, as any delay of the intent to cure SOC treatment would be unethical. However, if following approval, Multikine® gets accepted as part of a new SOC (as is the Company's objective), CEL-SCI believes that development of competing treatments might be difficult. Any clinical trial of future first-line candidates would not be able to delay SOC therapies, which would include Multikine® as its initial treatment, to avoid ethical concerns, and which would mean that they might not be able to take Multikine®'s place as part of the SOC, making comparisons with Multikine® extremely difficult. In addition, Multikine® is a complex biologic requiring special manufacturing, and the Company has spent over 10 years developing and validating its manufacturing process. This signifies a significant barrier to entry for any future similar or generic competitive technologies. A clinical trial of interest to CEL-SCI is from Merck Sharp & Dohme Corp, described below.

pembrolizumab—Merck Sharp & Dohme Corp. (NCT03765918)

A Phase 3 study is assessing the effectiveness of pembrolizumab (Pembro) given prior to surgery and pembrolizumab in combination with SOC radiotherapy given post-surgery in treating naïve participants with newly diagnosed Stage III / IVA, advanced head and neck squamous cell carcinoma. The Phase 3 study, which started in 2018, is estimated to be completed in 2026.

LEAPS™ COMPETITIVE LANDSCAPE

Multiple drug classes are available for the treatment of RA, with the global RA therapeutic market estimated at $58 billion in 2018 (Source: VisionGain's *Global Rheumatoid Arthritis Drugs Market Forecast* 2020-2030, 2020). A popular treatment strategy for RA involves pharmacotherapy with disease-modifying antirheumatic drugs (DMARDs), supported by non-steroidal anti-inflammatory drugs (NSAIDs) and/or corticosteroids to provide pain relief and control inflammation. Common DMARDs include methotrexate (Trexall, Otrexup, Rasuvo), leflunomide (Arava), and hydroxychloroquine (Plaquenil). However, the ability of these treatment regimens to suppress disease progression and joint destruction is limited for a large number of patients. Regarding COVID-19, while the Company's immunotherapy treatment (vaccine) is in animal modeling at present, a number of companies have already advanced into human trials for their COVID-19 vaccine candidates.

Biological agents are a newer class of DMARDs that can target parts of the immune system that triggers inflammation to cause joint and tissue damage. Biological agents include inhibitors of tumor necrosis factor (TNF), which block the activity of key inflammatory mediators, giving rise to the main characteristics of RA; as well as checkpoint inhibitors, which inhibit the production of inflammatory cytokines. However, since this drug suppresses parts of the immune system, they enhance the possibility of infections and other diseases. These include infliximab (Remicade®), adalimumab (Humira®), etanercept (Enbrel®), golimumab (Simponi®), certolizumab pegol (Cimzia®), abatacept (Orencia®), and rituximab (Rituxan®), among others. In addition, Janus Kinase (JAK) inhibitors, such as Tofacitinib (Xeljanz), Filgotinib, and baricitinib are recently approved by the FDA.

The Company faces competition from vaccine technology platforms and vaccine-centric companies that could be developing competing technologies in some of the same indications pursued by CEL-SCI. The list is not intended to be an exhaustive collection, but rather is believed to be representative of the type of competition CEL-SCI may encounter as it seeks to further develop and commercialize its product candidates.

Akshaya Bio Inc. (private)

Akshaya is a privately-held development stage biotechnology company developing innovative therapeutics for infectious diseases and cancer. Akshaya's proprietary Chimigen® Platform Technology uses dendritic cell receptor-targeted molecules to develop a portfolio of agents, which have therapeutic as well as prophylactic applications. The Chimigen® Platform is a flexible platform vaccine technology designed to elicit both humoral and cellular immune responses in hosts. Using its proprietary technology, Akshaya's product candidates include an H1, H5, and pan-influenza prophylactic vaccine as well as a cancer immunotherapy vaccine for breast, ovarian, and colorectal cancer. Akshaya is located in Edmonton, Alberta, Canada.

GlaxoSmithKline plc (GSK-NYSE)

GlaxoSmithKline plc is a global pharmaceutical company engaged in the discovery, development, and marketing of pharmaceutical products, vaccines, over-the-counter (OTC) medicines, and health-related consumer products. It operates through four segments: Pharmaceuticals, Pharmaceuticals R&D, Vaccines, and Consumer Healthcare. Its vaccine portfolio includes products for HPV (Cervarix®) and Influenza (Fluarix®, FluLaval®, and Pandemrix®), among others. In addition, the company's therapeutic drug pipelines includes candidates for head and neck squamous cell carcinoma (GSK3359609 – Phase 1-2) as well as RA (GSK3196165 [otilimab] – Phase 3). GlaxoSmithKline is headquartered in Brentford, the United Kingdom.

Merck & Co, Inc. (MRK-NYSE)

Merck provides healthcare solutions worldwide. The company offers therapeutic and preventive products, including its vaccines for HPV (Gardasil®), Ebola (Erbevo®), and Rotovirus (Rotateq®). In addition, the company its developing its check point inhibitor, Keytruda®, for multiple oncology targets, in addition to its current indications, which include melanoma, small cell lung cancer, and head and neck squamous cell carcinoma, among others. The company is headquartered in Kenilworth, New Jersey.

Novavax, Inc. (NVAX-NASDAQ)

Novavax is a late-stage biotechnology company focused on the discovery, development, and commercialization of vaccines to prevent serious infectious diseases. The company's lead vaccine candidates include NanoFlu, a nanoparticle seasonal influenza vaccine in Phase 3 clinical trial, as well as a nanoparticle vaccine candidate for Ebola in Phase 1. Both these vaccine candidates utilize the company's proprietary Matrix-M™ adjuvant technology. Matrix-M™ is used to enable a vaccine to enhance the amplitude of the immune response with much lower doses of antigen. The vaccine platform technology stimulates strong antibody and cell-mediated immune responses of both Th1 and Th2 types induced by low antigen doses, as well as potent cellular responses, including cytotoxic T lymphocytes. Novavax is headquartered in Gaithersburg, Maryland.

Sanofi (SNY-NASDAQ)

Sanofi is a diversified global healthcare company with extensive lines of prescription medicines and vaccines, as well as consumer health products. Its product offerings include the vaccines Flublok® and Fluzone® for influenza, as well as therapeutic products Kevzara® for RA and Libtayo® for metastatic cutaneous squamous cell carcinoma. Sanofi is headquartered in Paris, France.

Historical Financial Results

Figures 39, 40, and 41 provide CEL-SCI's Condensed Statements of Operations, Condensed Balance Sheets, and Condensed Statements of Cash Flows for the period ending March 31, 2020.

Figure 39
CONDENSED STATEMENTS OF OPERATIONS (Unaudited)
THREE MONTHS ENDED MARCH 31, 2020 and 2019

	2020	2019
Grant income	$ 298,726	$ 150,769
Operating Expenses:		
Research and development	4,402,347	2,832,546
General and administrative	2,558,522	1,624,823
Total operating expenses	6,960,869	4,457,369
Operating loss	(6,662,143)	(4,306,600)
Other income	18,448	18,216
Loss on derivative instruments	(3,049,027)	(967,171)
Other non-operating gains (losses)	934,511	(730,823)
Interest expense, net	(253,407)	(461,303)
Net loss	(9,011,618)	(6,447,681)
Modification of warrants	(21,734)	—
Net loss available to common shareholders	$ (9,033,352)	$ (6,447,681)
Net loss per common share		
BASIC	$ (0.25)	$ (0.22)
DILUTED	$ (0.25)	$ (0.22)
Weighted average common shares outstanding		
BASIC	36,165,050	29,113,910
DILUTED	36,165,050	29,113,910

Source: CEL-SCI Corporation.

Figure 40
CONDENSED BALANCE SHEETS (Unaudited)

ASSETS	March 31, 2020	September 30, 2019
Current Assets:		
Cash and cash equivalents	$ 14,329,870	$ 8,444,774
Receivables	62,289	62,765
Prepaid expenses	565,246	524,953
Supplies used for R&D and manufacturing	849,548	782,363
Total current assets	15,806,953	9,814,855
Finance lease right of use assets	12,741,195	—
Operating lease right of use assets	899,508	—
Property and equipment, net	3,286,273	15,825,636
Patent costs, net	312,380	311,586
Deposits	1,670,917	1,670,917
Total Assets	$ 34,717,226	$ 27,622,994
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current Liabilities:		
Accounts payable	$ 1,139,914	$ 1,586,478
Accrued expenses	316,866	34,432
Due to employees	675,408	709,442
Derivative instruments, current portion	2,156,857	674,442
Lease liabilities, current portion	977,264	—
Other current liabilities	5,000	14,956
Total current liabilities	5,271,309	3,019,750
Derivative instruments, net of current portion	4,067,436	5,813,868
Finance lease obligations, net of current portion	12,232,493	13,508,156
Operating lease obligations, net of current portion	812,479	—
Other liabilities	125,000	147,553
Total liabilities	22,508,717	22,489,327
Commitments and Contingencies		
STOCKHOLDERS' EQUITY		
Preferred stock, $.01 par value-200,000 shares authorized; -0- shares issued and outstanding	—	—
Common stock, $.01 par value - 600,000,000 shares authorized; 37,336,411 and 35,231,776 shares issued and outstanding at March 31, 2020 and September 30, 2019, respectively	373,365	352,318
Additional paid-in capital	379,943,932	358,507,603
Accumulated deficit	(368,108,788)	(353,726,254)
Total stockholders' equity	12,208,509	5,133,667
TOTAL LIABILITIES AND STOCKHOLDERS' EQUITY	$ 34,717,226	$ 27,622,994

Source: CEL-SCI Corporation.

Figure 41
CONDENSED STATEMENTS OF CASH FLOWS (Unaudited)
SIX MONTHS ENDED MARCH 31, 2020 and 2019

	2020	2019
Net loss	$ (14,486,778)	$ (5,201,779)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation and amortization	951,831	316,083
Share-based payments for services	347,227	511,424
Equity based compensation	3,581,204	1,104,490
Common stock contributed to 401(k) plan	79,896	72,124
Shares issued for settlement of clinical research costs	—	1,290,000
Loss (Gain) on derivative instruments	2,282,518	(4,589,135)
Capitalized lease interest	—	64,432
(Increase)/decrease in assets:		
Receivables	476	(4,579)
Prepaid expenses	96,951	(74,741)
Supplies used for R&D and manufacturing	(67,185)	(115,774)
Increase/(decrease) in liabilities:		
Accounts payable	(765,872)	(1,489,234)
Accrued expenses	20,110	82,580
Due to employees	(34,034)	245,074
Other liabilities	3,438	(1,057)
Net cash used in operating activities	(7,990,218)	(7,790,092)
CASH FLOWS FROM INVESTING ACTIVITIES:		
Purchases of property and equipment	(752,797)	(160,920)
Expenditures for patent costs	(13,996)	(67,661)
Net cash used in investing activities	(766,793)	(228,581)
CASH FLOWS FROM FINANCING ACTIVITIES:		
Proceeds from issuance of common stock	12,917,632	—
Payments of stock issuance costs	(190,553)	(80,224)
Proceeds from the purchase of stock by officers and directors	184,990	—
Proceeds from exercises of warrants	2,069,272	3,305,387
Proceeds from exercises of options	49,898	—
Payments on obligations under finance lease	(389,132)	(2,521)
Net cash provided by financing activities	14,642,107	3,222,642
NET INCREASE (DECREASE) IN CASH AND CASH EQUIVALENTS	5,885,096	(4,796,031)
CASH AND CASH EQUIVALENTS, BEGINNING OF PERIOD	8,444,774	10,310,044
CASH AND CASH EQUIVALENTS, END OF PERIOD	$ 14,329,870	$ 5,514,013

Source: CEL-SCI Corporation.

Recent Events

May 11, 2020—CEL-SCI Corporation reported financial results for the quarter ended March 31, 2020 and provided an update on clinical developments.

May 4, 2020—Announced that it has been notified that the Company has reached the targeted threshold of 298 events (deaths) required to conduct the data evaluation for its pivotal Phase 3 head and neck cancer study of Multikine® immunotherapy. The database is now being prepared for database lock. Once the database has been locked, the final analysis of the trial results can be performed. CEL-SCI will continue to remain blinded to the study results throughout this process. CEL-SCI will be advised of the results when the analysis is complete, and the study results will be announced to the public and investors at that time.

April 23, 2020—Announced that the Independent Data Monitoring Committee (IDMC) for the Company's pivotal Phase 3 head and neck cancer study of its investigational immunotherapy Multikine® has completed its recent review of the Phase 3 study data. The IDMC meets periodically to review the safety and efficacy of the ongoing Phase 3 study. The data from all 928 enrolled patients were provided to the IDMC by the clinical research organization (CRO) responsible for data management of this Phase 3 study.

April 8, 2020—Announced that there are two options to access the virtual meeting webcast—as a "Guest" or join as a "Shareholder". The 2020 Annual Meeting was held on April 17, 2020 with Geert Kersten, the Company's Chief Executive Officer.

March 30, 2020—Announced that the location of its 2020 Annual Meeting of Shareholders will be changed and a virtual format via a live online webcast will be added.

March 26, 2020—Announced the closing of the offering of 630,500 shares of its common stock at a price of $12.22 per share, for total gross proceeds of approximately $7.7 million, before deducting underwriting discounts and other offering expenses payable by the Company. The Company has also granted the underwriter a 45-day option to purchase up to 94,575 additional shares to cover over-allotments. Aegis Capital Corp. acted as the sole book-running manager for the offering.

March 24, 2020—Announced that due to demand, the underwriter has agreed to increase the size of its previously announced offering and purchase on a firm commitment basis 630,500 shares of common stock of the Company, at a price to the public of $12.22 per share, representing a 5% discount to the closing price per share. The closing of the offering is expected to occur on or about March 26, 2020, subject to customary closing conditions. Aegis Capital Corp. is acting as the sole book-running manager for the offering.

March 23, 2020—Announced that it has signed a collaboration agreement with the University of Georgia's Center for Vaccines and Immunology to develop LEAPS™ COVID-19 immunotherapy. CEL-SCI's immunotherapy candidate aims to treat patients at highest risk of dying from COVID-19. The collaboration will commence with pre-clinical studies based on the experiments previously conducted with LEAPS™ immunotherapy in collaboration with the National Institutes for Allergies and Infectious Diseases (NIAID) against another respiratory virus, H1N1, involved in the 2009 H1N1 flu pandemic. Those successful studies demonstrated that LEAPS™ peptides, given after virus infection has occurred, reduced morbidity and mortality in mice infected with H1N1. It is suggested, based on studies with H1N1, that a LEAPS™ coronavirus-SARS-CoV-2 immunotherapy may reduce or arrest the progression of the SARS-CoV-2 virus infection and prevent tissue damage from inflammation resulting from lung infection by the virus. By stimulating the correct immune responses to the COVID-19-causing virus without producing unwanted inflammatory responses associated with lung tissue damage, the LEAPS™ immunotherapy may be particularly beneficial in those patients who are at highest risk of dying from COVID-19.

March 9, 2020—Announced that it is developing an immunotherapy with the potential to treat the COVID-19 coronavirus using its patented LEAPS™ peptide technology. The LEAPS™ peptides will utilize conserved regions of coronavirus proteins to stimulate protective cell mediated T-cell responses and reduce viral load. The LEAPS™ peptide technology can be used to construct immunotherapeutic peptides that exhibit both antiviral and anti-inflammatory properties. Consequently, these products not only target the virus infection against which they are directed, but also elicit the appropriate protective response(s) against it. Predictions of success using the LEAPS™ peptides against COVID-19 coronavirus are based on previous studies conducted in collaboration with the National Institutes for Allergies and Infectious Diseases (NIAID) with another respiratory virus, pandemic influenza (H1N1). In those studies, LEAPS™ peptides elicited protection of mice from morbidity and mortality after the introduction of infection by activating appropriate T-cell responses rather than an inflammatory response.

February 26, 2020—Issued a letter to its shareholders, which will be sent to the Company's shareholders along with the proxy to the upcoming annual meeting.

February 10, 2020—Reported financial results for the quarter ended December 31, 2019 and provided an update on clinical developments.

February 6, 2020—Announced that Geert Kersten would be presenting at the 2020 BIO CEO & Investor Conference in New York, NY on Monday, February 10, 2019 at 3:45 p.m.

January 10, 2020—Announced that Geert Kersten will be attending two upcoming healthcare investor conferences in San Francisco and New York: the 38th Annual JP Morgan Healthcare Conference, January 13-16, 2020 in San Francisco, CA and BIO CEO & Investor Conference, February 10-11, 2020 in New York, NY.

January 7, 2020—Announced the full exercise of the over-allotment option granted to the underwriters with respect to 90,959 additional shares of common stock in connection with its previously announced underwritten public offering of 606,395 million shares, bringing total gross proceeds from the offering to approximately $6.325 million. Aegis Capital Corp. acted as the sole book-running manager for the offering.

December 27, 2019—Announced the closing of an underwritten public offering of 606,395 shares of its common stock at a price of $9.07 per share, for total gross proceeds of approximately $5.5 million, before deducting underwriting discounts and other offering expenses payable by the Company. Additionally, the Company has granted the underwriter a 45-day option to purchase up to 90,959 additional shares to cover over-allotments. Aegis Capital Corp. acted as the sole bookrunner for the offering. This offering was made pursuant to an effective shelf registration statement on Form S-3 (No. 333-226558) previously filed with the U.S. Securities and Exchange Commission.

December 24, 2019—Announced the pricing of an underwritten public offering with gross proceeds to the Company expected to be approximately $5.5 million before deducting underwriting discounts and other estimated offering expenses. The proposed offering equates to 606,395 shares of the Company's common stock at a price of $9.07 per share. The Company also granted the underwriters a 45-day option to purchase up to 90,959 additional shares of common stock to cover over-allotments at the public offering price.

December 23, 2019—Announced that it intends to offer shares of its common stock for sale in an underwritten public offering. In addition, the Company expects to grant the underwriter a 45-day option to purchase up to an additional 15% of the shares of common stock offered in the public offering solely to cover over-allotments.

December 16, 2019—Reported financial results for the fiscal year ended September 30, 2019 and provided an update on clinical developments.

December 6, 2019—Announced that it will be presenting at the 12th annual LD Micro Main Event on Tuesday, December 10, 2019. Geert Kersten will be presenting and meeting with investors.

October 29, 2019—Announced that Geert Kersten was presenting at the Dawson James Securities Small Cap Growth Conference on Tuesday, October 29th.

October 15, 2019—Announced that the Independent Data Monitoring Committee (IDMC) for the Company's pivotal Phase 3 head and neck cancer study of its investigational immunotherapy Multikine® (Leukocyte Interleukin, Injection) has completed its recent review of the Phase 3 study data. The IDMC meets periodically to review the safety and efficacy of the ongoing Phase 3 study.

September 3, 2019—Announced that Geert Kersten was scheduled to present at the H.C. Wainwright 21st Annual Global Investor Conference on Tuesday, September 10th.

August 14, 2019—Reported financial results for the quarter ended June 30, 2019 and provided an update on clinical developments.

July 23, 2019—Announced that a review titled, "Lessons From Next Generation Influenza Vaccines For Inflammatory Disease Therapies" was published in the peer reviewed scientific journal *International Immunopharmacology*. This review was authored by Dr. Zimmerman of CEL-SCI, Dr. Rosenthal of Northeast Ohio Medical University and Roseman University and two other CEL-SCI scientists. This review proposes a new approach to treating autoimmune and inflammatory diseases based on lessons from new generation influenza vaccines.

July 8, 2019—Announced that one of its key collaborators from Rush University Medical center, Dr. Adrienn Markovitz an Assistant professor in the department of Orthopedic Surgery, presented new LEAPS™ data at i-Chem2019, International Conference on Immunity and Immunochemistry in San Francisco, California on Wednesday July 3, 2019. The title of her presentation was "Vaccination with DerG LEAPS™ peptide conjugates incorporating distinct PG (aggrecan) epitopes protects by different immune mechanisms in the PG G1 domain induced mouse model of rheumatoid arthritis". Dr. Markovitz also presented a poster on other aspects of her work on modulation of autoimmune arthritis by the tyrosine phosphatase enzyme SHP-1, and identification of immunogenic citrullinated proteoglycan epitopes that may play a role in this disease in mice and humans.

June 10, 2019—Announced that the Company is set to join the broad-market Russell 3000® Index at the conclusion of the 2019 Russell indexes annual reconstitution, effective after the U.S. market opens on July 1, according to a preliminary list of additions posted June 7. Annual Russell indexes reconstitution captures the 4,000 largest U.S. stocks as of May 10, ranking them by total market capitalization.

June 3, 2019—Announced that it will be presenting at the 9th annual LD Micro Invitational on Tuesday, June 4th. Geert Kersten will be giving the presentation.

May 14, 2019—Reported financial results for the quarter ended March 31, 2019.

May 13, 2019—Announced that Daniel Zimmerman, Ph.D., Senior Vice President of Research, Cellular Immunology, presented new LEAPS™ data at the American Association of Immunologists 103rd Annual Meeting (Immunology 2019) in San Diego, California on Saturday, May 11, 2019. The title of his presentation is "Therapeutic vaccination by two DerG LEAPS™ conjugates incorporating different PG (aggrecan) epitopes protect by different immune mechanisms in the PG G1 domain induced mouse model of rheumatoid arthritis". The work was performed in conjunction with researchers at Rush University Medical Center, Chicago, Illinois. CEL-4000 and a newly discovered LEAPS™ conjugate, DerG-PG275Cit, were evaluated alone and in combination in the sister model of proteoglycan [PG] induced arthritis (PGIA) called recombinant PG G1 domain-induced arthritis (GIA), an autoimmune mouse model of RA.

May 8, 2019—Announced issuance of a shareholder letter. Phase 3 head and neck cancer study is continuing, and the Company is moving forward with its RA product development. Since January 1, CEL-SCI has received approximately $9.6 million from the conversion of warrants to finance our ongoing projects.

March 29, 2019—Announced that the IDMC for the Company's pivotal Phase 3 head and neck cancer study of its investigational immunotherapy Multikine® has completed its recent review of the Phase 3 study data. The data from all 928 enrolled patients were provided to the IDMC by the clinical research organization (CRO) responsible for data management of this Phase 3 study.

Risks and Disclosures

This Executive Informational Overview® (EIO) has been prepared by CEL-SCI Corporation ("CEL-SCI" or "the Company") with the assistance of Crystal Research Associates, LLC ("CRA") based upon information provided by the Company. CRA has not independently verified such information. Some of the information in this EIO relates to future events or future business and financial performance. Such statements constitute forward-looking information within the meaning of the Private Securities Litigation Act of 1995. Such statements can only be predictions and the actual events or results may differ from those discussed due to the risks described in CEL-SCI's statements on its financial and other reports filed from time to time.

The content of this report with respect to CEL-SCI has been compiled primarily from information available to the public released by the Company through news releases, presentations, Annual Reports, and other filings. CEL-SCI is solely responsible for the accuracy of this information. Information as to other companies has been prepared from publicly available information and has not been independently verified by CEL-SCI or CRA. Certain summaries of activities and outcomes have been condensed to aid the reader in gaining a general understanding. CRA assumes no responsibility to update the information contained in this report. In addition, CRA has been compensated by the Company in cash of thirty-five thousand U.S. dollars for its services in creating this report and for updates.

Investors should carefully consider the risks and information about CEL-SCI's business. Investors should not interpret the order in which considerations are presented in this or other filings as an indication of their relative importance. In addition, the risks and uncertainties overviewed herein are not the only risks that the Company faces. Additional risks and uncertainties not presently known to CEL-SCI or that it currently believes to be immaterial may also adversely affect the Company's business. If any of such risks and uncertainties develops into an actual event, CEL-SCI's business, financial condition, and results of operations could be materially and adversely affected, and the trading price of the Company's shares could decline.

This report is published solely for informational purposes and is not to be construed as an offer to sell or the solicitation of an offer to buy any security in any state. Past performance does not guarantee future performance. Additional information about CEL-SCI as well as copies of this report, can be obtained by calling (703) 506-9460.

CEL-SCI has identified material weaknesses in its internal control over financial reporting which could, if not remediated, result in material misstatements in CEL-SCI's financial statements.

CEL-SCI's management is responsible for establishing and maintaining adequate internal control over its financial reporting, as defined in Rule 13a-15(f) under the Exchange Act. Company management has identified material weaknesses in the internal control over financial reporting as of September 30, 2016. A material weakness is a deficiency, or a combination of deficiencies, in internal control over financial reporting, such that there is a reasonable possibility that a material misstatement of CEL-SCI's annual or interim financial statements will not be prevented or detected on a timely basis.

CEL-SCI discovered an error in the way it accounted for the lease for its manufacturing facility. The accounting error was determined to be a material weakness in CEL-SCI's internal control over financial reporting as of September 30, 2016 relating to CEL-SCI's financial close process for non-routine transactions, including the accounting for leases and the assessment of impairment of long-lived assets. The errors were identified during the course of the preparation of its financial statements and other financial data for its fiscal year ended September 30, 2017, as well as its assessment of its disclosure controls and procedures and internal control over financial reporting as of that date. This resulted in CEL-SCI filing an amended 10-K/A for the year ended September 30, 2016, that disclosed these material weaknesses and the impact of the restatement to the previously issued financial statements. These material weaknesses continue to exist, and CEL-SCI is in the process of remediating these material weaknesses.

If the remedial measures CEL-SCI has begun implementing that are designed to address these material weaknesses are insufficient to address these material weaknesses, or if additional material weaknesses or significant deficiencies in CEL-SCI's internal control are discovered or occur in the future, the Company's financial statements may contain material misstatements and CEL-SCI could be required to restate its financial results.

CEL-SCI has incurred significant losses since inception and anticipates that it will continue to incur significant losses for the foreseeable future and may never achieve or maintain profitability.

The Company has a history of net losses, expects to incur substantial losses, and have negative operating cash flow for the foreseeable future, and may never achieve or maintain profitability. CEL-SCI has relied principally upon the proceeds from the public and private sales of its securities to finance its activities to date. To date, CEL-SCI has not commercialized any products or generated any revenue from the sale of products and does not expect to generate any product revenue for the foreseeable future. CEL-SCI does not know whether or when it will generate product revenue or become profitable.

The Company is heavily dependent on the success of Multikine®, which is under clinical development. It cannot be certain that Multikine® will receive regulatory approval or be successfully commercialized even if it receives regulatory approval. Multikine® is CEL-SCI's only product candidate in late-stage clinical development, and its business currently depends heavily on its successful development, regulatory approval, and commercialization. The Company has no drug products for sale currently and may never be able to develop approved and marketable drug products. Even if it succeeds in developing and commercializing one or more of its product candidates, CEL-SCI expects to continue to incur significant operating and capital expenditures as it:

- continues to undertake preclinical development and clinical trials for product candidates;
- seeks regulatory approvals for product candidates; and
- implements additional internal systems and infrastructure.

To become and remain profitable, CEL-SCI must succeed in developing and commercializing its product candidates, which must generate significant revenue. This will require the Company to be successful in a range of challenging activities, including completing preclinical testing and clinical trials of its product candidates, discovering or acquiring additional product candidates, obtaining regulatory approval for these product candidates, and manufacturing, marketing, and selling any products for which the Company may obtain regulatory approval. CEL-SCI is only in the preliminary stages of most of these activities. The Company may never succeed in these activities and, even if it does, may never generate revenue that is significant enough to achieve profitability. Even if it does achieve profitability, it may not be able to sustain or increase profitability on a quarterly or annual basis. Failure to become and remain profitable could depress the value of the Company and could impair its ability to raise capital, expand its business, maintain its research and development efforts, diversify its product offerings, or even continue its operations. A decline in the value of the Company could cause its stockholders to lose all or part of their investment.

CEL-SCI will require substantial additional capital to remain in operation. A failure to obtain this necessary capital when needed could force the Company to delay, limit, reduce, or terminate its product candidates' development or commercialization efforts.

The Company expects to continue to expend substantial resources for the foreseeable future developing Multikine®, LEAPS™, and any other product candidates or technologies that it may develop or acquire. These expenditures will include costs associated with research and development, potentially obtaining regulatory approvals, and having its products manufactured, as well as marketing and selling products approved for sale, if any. In addition, other unanticipated costs may arise. Because the outcome of the Company's current and anticipated clinical trials is highly uncertain, CEL-SCI cannot reasonably estimate the actual amounts necessary to successfully complete the development and commercialization of its product candidates.

CEL-SCI's future capital requirements depend on many factors, including:

- the rate of progress of, results of, and cost of completing Phase 3 clinical development of Multikine® for the treatment of certain head and neck cancers;
- the results of CEL-SCI' s applications to and meetings with the FDA, the EMA, and other regulatory authorities and the consequential effect on its operating costs;
- assuming favorable Phase 3 clinical results, the cost, timing, and outcome of CEL-SCI's efforts to obtain marketing approval for Multikine® in the United States, Europe, and in other jurisdictions, including the preparation and filing of regulatory submissions for Multikine® with the FDA, the EMA, and other regulatory authorities;
- the scope, progress, results, and costs of additional preclinical, clinical, or other studies for additional indications for Multikine®, LEAPS™, and other product candidates and technologies that CEL-SCI may develop or acquire;
- the timing of, and the costs involved in obtaining regulatory approvals for LEAPS™ if clinical studies are successful;
- the cost and timing of future commercialization activities for CEL-SCI's products, if any of its product candidates are approved for marketing, including product manufacturing, marketing, sales, and distribution costs;
- the revenue, if any, received from commercial sales of CEL-SCI's product candidates for which the Company receives marketing approval;
- the cost of having its product candidates manufactured for clinical trials and in preparation for commercialization;
- CEL-SCI's ability to establish and maintain strategic collaborations, licensing, or other arrangements and the financial terms of such agreements; and
- the costs involved in preparing, filing, and prosecuting patent applications and maintaining, defending, and enforcing its intellectual property rights, including litigation costs, and the outcome of such litigation; and the extent to which CEL-SCI acquires or in-license other products or technologies.

If adequate funds are not available on a timely basis, CEL-SCI may be required to delay, limit, reduce, or terminate preclinical studies, clinical trials, or other development activities for Multikine®, LEAPS™, or any other product candidates or technologies that it develops or acquire, or delay, limit, reduce, or terminate its sales and marketing capabilities or other activities that may be necessary to commercialize CEL-SCI's product candidates. Due to recurring losses from operations and future liquidity needs, there is substantial doubt about the Company's ability to continue as a going concern without additional capital becoming available. The doubt about CEL-SCI's ability to continue as a going concern could have an adverse impact on the Company's ability to execute its business plan, result in the reluctance on the part of certain suppliers to do business with it, or adversely affect CEL-SCI's ability to raise additional debt or equity capital.

The costs of CEL-SCI's product candidate development and clinical trials are difficult to estimate and will be extremely high for many years, preventing the Company from making a profit for the foreseeable future, if ever.

Clinical and other studies necessary to obtain approval of a new drug can be time consuming and costly, especially in the U.S., but also in foreign countries. CEL-SCI's estimates of the costs associated with future clinical trials and research may be substantially lower than what the Company actually experiences. It is impossible to predict what CEL-SCI will face in the development of a product candidate, such as Multikine®. The purpose of clinical trials is to provide both the Company and regulatory authorities with safety and efficacy data in humans. It is relatively

common to revise a trial or add subjects to a trial in progress. The difficult and often complex steps necessary to obtain regulatory approval, especially that of the FDA and the EMA, involve significant costs and may require several years to complete. The Company expects that it will need substantial additional financing over an extended period of time in order to fund the costs of future clinical trials, related research, and general and administrative expenses. The extent of the Company's clinical trials and research programs are primarily based upon the amount of capital available to it and the extent to which the Company receives regulatory approvals for clinical trials. CEL-SCI has established estimates of the future costs of the Phase 3 clinical trial for Multikine®, but those estimates may not prove correct.

An adverse determination in any future legal proceedings could have a material adverse effect on CEL-SCI.

The Company may be the target of claims asserting violations of securities fraud and derivative actions, or other litigation or arbitration proceedings in the future. Any future litigation could result in substantial costs and divert management's attention and resources. These legal proceedings may result in large judgments or settlements against it, any of which could have a material adverse effect on the Company's business, operating results, financial condition, and liquidity.

Compliance with changing regulations concerning corporate governance and public disclosure may result in additional expenses.

Changing laws, regulations, and standards relating to corporate governance and public disclosure may create uncertainty regarding compliance matters. New or changed laws, regulations, and standards are subject to varying interpretations in many cases. As a result, their application in practice may evolve over time. The Company is committed to maintaining high standards of corporate governance and public disclosure. Complying with evolving interpretations of new or changing legal requirements may cause CEL-SCI to incur higher costs as the Company revises current practices, policies, and procedures, and may divert management's time and attention from potential revenue-generating activities to compliance matters. If CEL-SCI's efforts to comply with new or changed laws, regulations, and standards differ from the activities intended by regulatory or governing bodies due to ambiguities related to practice, the Company's reputation may also be harmed. Further, its board members, chief executive officer, and other executive officers could face an increased risk of personal liability in connection with the performance of their duties. As a result, CEL-SCI may have difficulty attracting and retaining qualified board members and executive officers, which could harm its business.

The Company hopes to expand its clinical development capabilities in the future, and any difficulties hiring or retaining key personnel or managing this growth could disrupt its operations.

CEL-SCI is highly dependent on the principal members of its management and development staff. If the Phase 3 Multikine® clinical trial is successful, the Company expects to expand its clinical development and manufacturing capabilities, which will involve hiring additional employees. Future growth will require CEL-SCI to continue to implement and improve its managerial, operational, and financial systems and to continue to retain, recruit, and train additional qualified personnel, which may impose a strain on the Company's administrative and operational infrastructure. Competition for qualified personnel in the biopharmaceutical field is intense. CEL-SCI is highly dependent on its ability to attract, retain, and motivate highly qualified management and specialized personnel required for clinical development. Due to its limited resources, CEL-SCI may not be able to effectively manage the expansion of its operations or recruit and train additional qualified personnel. If the Company is unable to retain key personnel or manage its future growth effectively, CEL-SCI may not be able to implement its business plan.

If product liability or patient injury lawsuits are brought against the Company, it may incur substantial liabilities and may be required to limit clinical testing or future commercialization of Multikine® or its other product candidates.

CEL-SCI faces an inherent risk of product liability as a result of the clinical testing of Multikine® and other product candidates and will face an even greater risk if it commercialize any of its product candidates. For example, CEL-SCI may be sued if Multikine® or LEAPS™ product candidates, or any other future product candidates, allegedly cause injury or are found to be otherwise unsuitable during clinical testing, manufacturing or, if approved, marketing or sale. Any such product liability claims may include allegations of defects in manufacturing, defects in design, a failure to warn of dangers inherent in the product candidate, negligence, strict liability, and a breach of warranties. Claims could also be asserted under state consumer protection acts.

Furthermore, Multikine® is made, in part, from components of human blood. There are inherent risks associated with products that involve human blood, such as possible contamination with viruses, including hepatitis or HIV. Any possible contamination could cause injuries to patients who receive contaminated Multikine® or could require CEL-SCI to destroy batches of Multikine®, thereby subjecting the Company to possible financial losses, lawsuits, and harm to its business. If CEL-SCI cannot successfully defend itself against product liability claims, it may incur substantial liabilities or be required to limit or cease the clinical testing or commercialization of its product candidates, if approved. Even a successful defense would require significant financial and management resources.

Regardless of the merits or eventual outcome, liability claims may result in:

- decreased demand for Multikine® or the Company's other product candidates, if approved;
- injury to CEL-SCI's reputation;
- withdrawal of existing, or failure to enroll additional, clinical trial participants;
- costs to defend any related litigation;
- a diversion of management's time and resources;
- substantial monetary awards to trial participants or patients;
- product candidate recalls, withdrawals, or labeling, marketing, or promotional restrictions;
- loss of revenue;
- inability to commercialize Multikine® or the Company's other product candidates; and
- a decline in the price of CEL-SCI's common stock.

Although the Company has product liability insurance for Multikine® in the amount of $10 million, the successful prosecution of a product liability case against CEL-SCI could have a materially adverse effect upon its business if the amount of any judgment exceeds its insurance coverage. Any claim that may be brought against the Company could result in a court judgment or settlement in an amount that is not covered, in whole or in part, by its insurance or that is in excess of the limits of its insurance coverage. CEL-SCI's insurance policies also have various exclusions, and the Company may be subject to a claim for which it has no coverage. CEL-SCI may have to pay any amounts awarded by a court or negotiated in a settlement that exceeds its coverage limitations or that are not covered by its insurance, and CEL-SCI may not have, or be able to obtain, sufficient capital to pay such amounts. CEL-SCI commenced the Phase 3 clinical trial for Multikine® in December 2010. Although no claims have been brought to date, participants in its clinical trials could bring civil actions against the Company for any unanticipated harmful effects allegedly arising from the use of Multikine® or any other product candidate that the Company may attempt to develop.

The Company's commercial success depends, in part, upon attaining significant market acceptance of its product candidates, if approved, among physicians, patients, healthcare payors, and major operators of cancer clinics.

Even if the Company obtains regulatory approval for its product candidates, any resulting product may not gain market acceptance among physicians, healthcare payors, patients, and the medical community, which are critical to commercial success. Market acceptance of any product candidate for which CEL-SCI receives approval depends on a number of factors, including:

- the efficacy and safety as demonstrated in clinical trials;
- the timing of market introduction of such product candidate as well as competitive products;
- the clinical indications for which the drug is approved;
- the approval, availability, market acceptance, and reimbursement for the companion diagnostic;
- acceptance by physicians, major operators of cancer clinics, and patients of the drug as a safe and effective treatment;
- the potential and perceived advantages of such product candidate over alternative treatments, especially with respect to patient subsets that are targeted with such product candidate;
- the safety of such product candidate seen in a broader patient group, including its use outside the approved indications;
- the cost of treatment in relation to alternative treatments;
- the availability of adequate reimbursement and pricing by third-party payors and government authorities;
- relative convenience and ease of administration;
- the prevalence and severity of adverse side effects; and
- the effectiveness of its sales and marketing efforts.

If CEL-SCI's product candidates are approved but fail to achieve an adequate level of acceptance by physicians, healthcare payors, and patients, the Company will not be able to generate significant revenues and may not become or remain profitable.

RISKS RELATED TO GOVERNMENT APPROVALS

CEL-SCI's product candidates must undergo rigorous preclinical and clinical testing and regulatory approvals, which could be costly and time-consuming and subject the Company to unanticipated delays or prevent it from marketing any products.

The Company's product candidates are subject to premarket approval from the FDA in the U.S., the EMA in the European Union, and by comparable agencies in most foreign countries before they can be sold. Before obtaining marketing approval, these product candidates must undergo costly and time consuming preclinical and clinical testing, which could subject CEL-SCI to unanticipated delays and may prevent it from marketing its product candidates. There can be no assurance that such approvals will be granted on a timely basis, if at all. Clinical testing is expensive and can take many years to complete, and its outcome is inherently uncertain. Failure can occur at any time during the clinical trial process. The results of preclinical studies and early clinical trials of CEL-SCI's product candidates may not be predictive of the results of later-stage clinical trials. A number of companies in the biopharmaceutical industry have suffered significant setbacks in advanced clinical trials due to lack of efficacy or

adverse safety profiles, notwithstanding promising results in earlier trials. The Company's current and future clinical trials may not be successful.

Although CEL-SCI is no longer treating patients and simply following the patient's per the protocol of the Phase 3 clinical trial for Multikine®, the Company may experience delays in its the clinical trial and does not know whether the clinical trials need to be redesigned. Clinical trials can be delayed for a variety of reasons, including delays related to:

- the availability of financial resources needed to commence and complete its planned trials;
- obtaining regulatory approval to commence a trial;
- reaching agreement on acceptable terms with prospective contract research organizations (CROs) and clinical trial sites, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and trial sites;
- obtaining Institutional Review Board (IRB) approval at each clinical trial site;
- recruiting suitable patients to participate in a trial;
- having patients complete a trial or return for post-treatment follow-up;
- clinical trial sites deviating from trial protocol or dropping out of a trial;
- adding new clinical trial sites; or
- manufacturing sufficient quantities of the Company's product candidate for use in clinical trials.

Patient enrollment, a significant factor in the timing of clinical trials, is affected by many factors, including the competence of the CRO running the study, size, and nature of the patient population, the proximity of patients to clinical sites, the eligibility criteria for the trial, the design of the clinical trial, competing clinical trials and clinicians' and patients' perceptions as to the potential advantages of the drug being studied in relation to other available therapies, including any new drugs that may be approved for the indications the Company is investigating. Furthermore, CEL-SCI relies on CROs and clinical trial sites to ensure the proper and timely conduct of its clinical trials and while the Company has agreements governing their committed activities, it has limited influence over their actual performance.

CEL-SCI could also encounter significant delays and/or need to terminate a development program for a product candidate if physicians encounter unresolved ethical issues associated with enrolling patients in clinical trials of its product candidates in addition to existing treatments that have established safety and efficacy profiles. Further, a clinical trial may be suspended or terminated by CEL-SCI, one or more of the IRBs for the institutions in which such trials are being conducted, by CEL-SCI upon a final recommendation by the Independent Data Monitoring Committee, or IDMC, with which the Company agrees for such trial, or by FDA or other regulatory authorities, due to a number of factors, including failure to conduct the clinical trial in accordance with regulatory requirements or CEL-SCI's clinical protocols, as a result of inspection of the clinical trial operations or trial site(s) by FDA or other regulatory authorities, the imposition of a clinical hold or partial clinical hold, unforeseen safety issues or adverse side effects, failure to demonstrate a benefit from using a product candidate, changes in governmental regulations or administrative actions or lack of adequate funding to continue the clinical trial.

The occurrence of any one or more of these events would have significant and severe material consequences for CEL-SCI and could impact its ability to continue as a going concern. If the Company experiences termination of, or delays in the completion of any clinical trial of its product candidates, the commercial prospects for its product candidates will be harmed, and its ability to generate product revenues will be delayed. In addition, any delays in completing its clinical trials will increase costs, slow product development and approval process, and jeopardize the

Company's ability to commence product sales and generate revenues. Any of these occurrences may harm the Company's business, prospects, financial condition, and results of operations significantly. Many of the factors that cause, or lead to, a delay in the commencement or completion of clinical trials may also ultimately lead to a delay or the denial of regulatory approval for CEL-SCI's product candidates.

Even if CEL-SCI obtains regulatory approval for its investigational products, the Company will be subject to stringent, ongoing government regulation.

If CEL-SCI's investigational products receive regulatory approval, either in the U.S. or internationally, those products will be subject to limitations on the approved indicated uses for which the product may be marketed or to the conditions of approval, and may contain requirements for potentially costly post marketing testing, including Phase 4 clinical trials, and surveillance of the safety and efficacy of the investigational products. CEL-SCI will continue to be subject to extensive regulatory requirements. These regulations are wide-ranging and govern, among other things:

- product design, development, and manufacture;
- product application and use adverse drug experience;
- product advertising and promotion;
- product manufacturing, including good manufacturing practices record keeping requirements;
- registration and listing of the Company's establishments and products with the FDA, EMA, and other state and national agencies;
- product storage and shipping;
- drug sampling and distribution requirements;
- electronic record and signature requirements; and
- labeling changes or modifications.

CEL-SCI and any of its third-party manufacturers or suppliers must continually adhere to federal regulations setting forth requirements, known as current, Good Manufacturing Practices (GMPs) and their foreign equivalents, which are enforced by the FDA, the EMA, and other national regulatory bodies through their facilities inspection programs. If the Company's facilities, or the facilities of its contract manufacturers or suppliers, cannot pass a pre-approval plant inspection or fail such inspections in the future, the FDA, EMA, or other national regulators will not approve the Company's marketing applications for its product candidates, or may withdraw any prior approval.

In complying with cGMP and foreign regulatory requirements, CEL-SCI and any of its potential third-party manufacturers or suppliers will be obligated to expend time, money, and effort in production, record-keeping, and quality control to ensure that its product candidates meet applicable specifications and other requirements. If CEL-SCI does not comply with regulatory requirements at any stage, whether before or after marketing approval is obtained, the Company may be subject to, among other things, license suspension or revocation, criminal prosecution, seizure, injunction, fines, be forced to remove a product from the market or experience other adverse consequences, including restrictions or delays in obtaining regulatory marketing approval for such products or for other product candidates for which it seeks approval. This could materially harm CEL-SCI's financial results, reputation, and stock price. Additionally, CEL-SCI may not be able to obtain the labeling claims necessary or desirable for product promotion.

If CEL-SCI or other parties identify adverse effects after any of its products are on the market, or if manufacturing problems occur, regulatory approval may be suspended or withdrawn. CEL-SCI may be required to reformulate its products, conduct additional clinical trials, make changes in product labeling or indications of use, or submit additional marketing applications to support any changes. If the Company encounters any of the foregoing problems, its business and results of operations will be harmed, and the market price of its common stock may decline. The FDA and other governmental authorities' policies may change, and additional government regulations may be enacted that could prevent, limit, or delay regulatory approval of the Company's product candidates. If it is slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if CEL-SCI is not able to maintain regulatory compliance, the Company may lose any marketing approval that it may have obtained, which would adversely affect its business, prospects, and ability to achieve or sustain profitability. CEL-SCI cannot predict the extent of adverse government regulations, which might arise from future legislative or administrative action. Without government approval, CEL-SCI will be unable to sell any of its product candidates.

CEL-SCI's product candidates may cause undesirable side effects or have other properties that could delay or prevent their regulatory approval, limit the commercial profile of an approved label, or result in significant negative consequences following marketing approval, if any.

Undesirable side effects caused by CEL-SCI's product candidates could cause the Company or regulatory authorities to interrupt, delay, or halt clinical trials and could result in a more restrictive label or the delay or denial of regulatory approval by the FDA or other comparable foreign authorities. Results of its clinical trials could reveal a high and unacceptable severity and/or prevalence of these or other side effects. In such an event, CEL-SCI's trials could be suspended or terminated, and the FDA or comparable foreign regulatory authorities could order the Company to cease further development of, or deny approval of, its product candidates for any or all targeted indications. The drug-related side effects could affect patient recruitment or the ability of enrolled patients to complete the trial or result in potential product liability claims. Any of these occurrences may harm the Company's business, financial condition, and prospects significantly.

Additionally, if one or more of CEL-SCI's product candidates receives marketing approval, and the Company or others later identify undesirable side effects caused by such products, a number of potentially significant negative consequences could result, including:

- regulatory authorities may withdraw approvals of such product;
- regulatory authorities may require additional warnings on the label;
- CEL-SCI may be required to create a medication guide outlining the risks of such side effects for distribution to patients;
- the Company could be sued and held liable for harm caused to patients; and
- CEL-SCI's reputation may suffer.

Any of these events could prevent the Company from achieving or maintaining market acceptance of the particular product candidate, if approved, and could significantly harm its business, results of operations, and prospects.

CEL-SCI relies on third parties to conduct its preclinical and clinical trials. If these third parties do not successfully carry out their contractual duties and meet regulatory requirements, or meet expected deadlines, the Company may not be able to obtain regulatory approval for or commercialize its product candidates and its business could be substantially harmed.

The Company has relied upon and plans to continue to rely upon third-party CROs to prepare for, conduct, monitor, and manage data for its preclinical and clinical programs. CEL-SCI relies on these parties for all aspects of the execution of its preclinical and clinical trials, and although the Company diligently oversees and carefully manages its CROs, the Company directly controls only certain aspects of their activities and relies upon them to provide timely, complete, and accurate reports on their conduct of CEL-SCI's studies. Although such third parties provide support and represent the Company for regulatory purposes in the context of its clinical trials, ultimately CEL-SCI is responsible for ensuring that each of its studies is conducted in accordance with the applicable protocol, legal, regulatory, and scientific standards, and its reliance on the CROs does not relieve CEL-SCI of its regulatory responsibilities.

CEL-SCI and its CROs acting on its behalf, as well as principal investigators and trial sites, are required to comply with Good Clinical Practice (GCP) and other applicable requirements, which are implemented through regulations and guidelines enforced by the FDA, the Competent Authorities of the Member States of the European Economic Area (EEA), and comparable foreign regulatory authorities for all of its products in clinical development. Regulatory authorities enforce these GCPs through periodic inspections of trial sponsors, principal investigators, and trial sites. If CEL-SCI or any of its CROs fail to comply with applicable GCPs or other applicable regulations, the clinical data generated in its clinical trials may be determined to be unreliable and the Company may therefore need to enroll additional subjects in its trials, or the FDA, EMA, or comparable foreign regulatory authorities may require the Company to perform an additional clinical trial or trials before approving its marketing applications.

Moreover, if CEL-SCI or any of its CROs, principal investigators, or trial sites fail to comply with applicable regulatory and GCP requirements, then the Company, its CROs, principal investigators, or trial sites may be subject to enforcement actions, such as fines, warning letters, untitled letters, clinical holds, civil or criminal penalties, and/or injunctions. CEL-SCI cannot assure investors that upon inspection by a given regulatory authority, such regulatory authority will determine that any of its clinical trials comply with GCP regulations. In addition, clinical trials must be conducted with product produced under GMP regulations. Failure to comply with these regulations may require CEL-SCI to delay or repeat clinical trials, which would delay the regulatory approval process.

If any of the Company's relationships with its third-party CROs terminate, CEL-SCI may not be able to enter into arrangements with alternative CROs or do so on commercially reasonable terms. In addition, the Company's CROs are not its employees, and except for remedies available to it under Company agreements with such CROs, CEL-SCI cannot control whether or not they devote sufficient time and resources to CEL-SCI's on-going clinical, nonclinical, and preclinical programs. If CROs do not successfully fulfill their regulatory obligations, carry out their contractual duties, or obligations or meet expected deadlines, if they need to be replaced or if the quality or accuracy of the clinical data they obtain is compromised due to the failure to adhere to Company clinical protocols, regulatory requirements, or for other reasons, its clinical trials may be extended, delayed, or terminated, and the Company may not be able to obtain regulatory approval for or successfully commercialize its product candidates.

As a result, results of operations and the commercial prospects for the Company's product candidates would be harmed, its costs could increase, and its ability to generate revenues could be delayed. Switching or adding additional CROs involves additional cost and requires management's time and focus. In addition, there is a natural transition period when a new CRO commences work. As a result, delays may occur, which can materially impact the Company's ability to meet its desired clinical development timelines. Though CEL-SCI diligently oversees and carefully manages its relationships with CROs, there can be no assurance that CEL-SCI will not encounter similar challenges or delays in its clinical development in the future or that these delays or challenges will not have a material adverse impact on its business, financial condition, and prospects.

CEL-SCI has obtained orphan drug designation from the FDA for Multikine® for neoadjuvant, or primary, therapy in patients with squamous cell carcinoma of the head and neck, but the Company may be unable to maintain the benefits associated with orphan drug designation, including the potential for market exclusivity.

Under the Orphan Drug Act, the FDA may grant orphan drug designation to a drug or biologic intended to treat a rare disease or condition, which is defined as one occurring in a patient population of fewer than 200,000 in the U.S., or a patient population greater than 200,000 in the U.S. where there is no reasonable expectation that the cost of developing the drug or biologic will be recovered from sales in the U.S. In the U.S., orphan drug designation entitles a party to financial incentives, such as opportunities for grant funding towards clinical trial costs, tax advantages, and user-fee waivers. In addition, if a product that has orphan drug designation subsequently receives the first FDA approval for the disease for which it has such designation, the product is entitled to orphan drug exclusivity, which means that the FDA may not approve any other applications, including a full Biologics License Application (BLA) to market the same biologic for the same indication for seven years, except in limited circumstances, such as a showing of clinical superiority to the product with orphan drug exclusivity or where the manufacturer is unable to assure sufficient product quantity.

Even though the Company has received orphan drug designation for Multikine® for the treatment of squamous cell carcinoma of the head and neck, it may not be the first to obtain marketing approval of a product for the orphan-designated indication due to the uncertainties associated with developing pharmaceutical products. In addition, exclusive marketing rights in the U.S. may be limited if the Company seeks approval for an indication broader than the orphan-designated indication, or may be lost if the FDA later determines that the request for designation was materially defective or if CEL-SCI is unable to assure sufficient quantities of the product to meet the needs of patients with the rare disease or condition.

Further, even if the Company obtains orphan drug exclusivity for a product candidate, that exclusivity may not effectively protect the product candidate from competition because different drugs with different active moieties can be approved for the same condition. Even after an orphan product is approved, the FDA can subsequently approve another drug with the same active moiety for the same condition if the FDA concludes that the later drug is safer, more effective, or makes a major contribution to patient care. Orphan drug designation neither shortens the development time or regulatory review time of a drug nor gives the drug any advantage in the regulatory review or approval process.

Failure to obtain or maintain adequate coverage and reimbursement for CEL-SCI's product candidates, if approved, could limit the Company's ability to market those products and decrease its ability to generate revenue.

Sales of the Company's product candidates will depend substantially, both domestically and abroad, on the extent to which the costs of its product candidates will be paid by health maintenance, managed care, pharmacy benefit, and similar healthcare management organizations, or reimbursed by government authorities, private health insurers and other third-party payors. CEL-SCI anticipates that government authorities and other third-party payors will continue efforts to contain healthcare costs by limiting the coverage and reimbursement levels for new drugs. If coverage and reimbursement are not available, or are available only to limited levels, the Company may not be able to successfully commercialize its product candidates. Even if coverage is provided, the approved reimbursement amount may not be high enough to allow it to establish or maintain pricing sufficient to realize a return on its investment. It is difficult to predict at this time what third-party payors will decide with respect to the coverage and reimbursement for CEL-SCI's product candidates.

Foreign governments often impose strict price controls, which may adversely affect the Company's future profitability.

CEL-SCI intends to seek approval to market Multikine® in both the U.S. and foreign jurisdictions. If the Company obtains approval in one or more foreign jurisdictions, it will be subject to rules and regulations in those jurisdictions relating to Multikine®. In some foreign countries, particularly in the European Union, prescription drug pricing is subject to governmental control. In these countries, pricing negotiations with governmental authorities can take considerable time after the receipt of marketing approval for a drug candidate. Coverage and reimbursement decisions in one foreign jurisdiction may impact decisions in other countries.

To obtain reimbursement or pricing approval in some countries, CEL-SCI may be required to conduct clinical trials that demonstrate its product candidate is more effective than current treatments and compare the cost-effectiveness of Multikine® to other available therapies. If reimbursement of Multikine® is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, the Company may be unable to achieve or sustain profitability.

Healthcare legislative reform measures may have a material adverse effect on CEL-SCI's business and results of operations.

In the U.S., there have been and continues to be a number of legislative initiatives to contain healthcare costs that may result in more limited coverage or downward pressure on the price the Company may otherwise receive for its product candidates. For example, in March 2010, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, or collectively, the Affordable Care Act, was passed, which substantially changes the way healthcare is financed by both governmental and private insurers, and significantly impacts the U.S. pharmaceutical industry.

Much of CEL-SCI's intellectual property is protected as trade secrets or confidential know-how, not as a patent.

The Company considers proprietary trade secrets and/or confidential know-how and unpatented know-how to be important to its business. Much of its intellectual property pertains to the Company's manufacturing system, certain aspects of which may not be suitable for patent filings and must be protected as trade secrets and/or confidential know-how. This type of information must be protected diligently by CEL-SCI to protect its disclosure to competitors, since legal protections after disclosure may be minimal or non-existent. Accordingly, much of the value of this intellectual property is dependent upon the Company's ability to keep its trade secrets and know-how confidential.

To protect this type of information against disclosure or appropriation by competitors, CEL-SCI's policy is to require its employees, consultants, contractors, and advisors to enter into confidentiality agreements with the Company. However, current or former employees, consultants, contractors, and advisers may unintentionally or willfully disclose the Company's confidential information to competitors, and confidentiality agreements may not provide an adequate remedy in the event of unauthorized disclosure of confidential information. Enforcing a claim that a third party obtained illegally, and is using, trade secrets and/or confidential know-how is expensive, time consuming, and unpredictable. The enforceability of confidentiality agreements may vary from jurisdiction to jurisdiction.

In addition, in some cases a regulator considering the Company's application for product candidate approval may require the disclosure of some or all of CEL-SCI's proprietary information. In such a case, the Company must decide whether to disclose the information or forego approval in a particular country. If unable to market the Company's product candidates in key countries, CEL-SCI's opportunities and value may suffer. Failure to obtain or maintain trade secrets and/or confidential know-how trade protection could adversely affect the Company's competitive position. Moreover, its competitors may independently develop substantially equivalent proprietary information and may even apply for patent protection in respect of the same. If successful in obtaining such patent protection, CEL-SCI's competitors could limit the Company's use of such trade secrets and/or confidential know-how.

CEL-SCI may be subject to claims challenging the inventorship or ownership of its patents and other intellectual property.

The Company may also be subject to claims that former employees, collaborators, or other third parties have an ownership interest in its patents or other intellectual property. The Company may be subject to ownership disputes in the future arising, for example, from conflicting obligations of consultants or others who are involved in developing its product candidates. Litigation may be necessary to defend against these and other claims challenging inventorship or ownership. If the Company fails in defending any such claims, in addition to paying monetary damages, it may lose valuable intellectual property rights, such as exclusive ownership of, or right to use, valuable intellectual property. Such an outcome could have a material adverse effect on CEL-SCI's business. Even if the Company is successful in defending against such claims, litigation could result in substantial costs and be a distraction to management and employees.

RISKS RELATED TO THE COMPANY'S COMMON STOCK

An investor may experience future dilution as a result of future equity offerings or other equity issuances.

The Company expects that significant additional capital will be needed in the future to continue its planned operations. To raise additional capital, CEL-SCI may in the future offer additional shares of its common stock or other securities convertible into or exchangeable for Company common stock. To the extent the Company raises additional capital by issuing equity securities, its stockholders may experience substantial dilution. If CEL-SCI sells common stock, convertible securities, or other equity securities, investment in CEL-SCI's common stock will be diluted. These sales may also result in material dilution to the Company's existing stockholders and new investors could gain rights superior to existing stockholders.

The Company's outstanding options and warrants may adversely affect the trading price of its common stock.

CEL-SCI's outstanding options and warrants could adversely affect its ability to obtain future financing or engage in certain mergers or other transactions, since the holders of options and warrants can be expected to exercise them at a time when the Company may be able to obtain additional capital through a new offering of securities on terms more favorable to it than the terms of the outstanding options and warrants. For the life of the options and warrants, the holders have the opportunity to profit from a rise in the market price of the Company's common stock without assuming the risk of ownership. The issuance of shares upon the exercise of outstanding options and warrants will also dilute the ownership interests of existing stockholders.

CEL-SCI's ability to utilize its net operating loss carryforwards and certain other tax attributes may be limited.

Under Section 382 of the Internal Revenue Code of 1986, as amended, if a corporation undergoes an "ownership change" (generally defined as a greater than 50% change (by value) in its equity ownership over a three-year period), the corporation's ability to use its pre-change net operating loss carryforwards and other pre-change tax attributes to offset its post-change income may be limited. As a result of its public offerings and other transactions, CEL-SCI may experience ownership changes in the future based on subsequent shifts in its stock ownership, some of which are outside its control. As a result, the Company's ability to use its pre-change net operating loss carryforwards and other pre-change tax attributes to offset U.S. federal taxable income may be subject to limitations, which could result in increased tax liability.

Since the Company does not intend to pay dividends on its common stock, any potential return to investors will result only from any increases in the price of its common stock.

At the present time, CEL-SCI intends to use available funds to finance its operations. Accordingly, while payment of dividends rests within the discretion of the Company's board of directors, no common stock dividends have been declared or paid by it and CEL-SCI has no intention of paying any common stock dividends in the foreseeable future. Additionally, any future debt financing arrangement may contain terms prohibiting or limiting the number of dividends that may be declared or paid on its common stock. Any return to the Company's investors will therefore be limited to appreciation in the price of its common stock, which may never occur. If the Company's stock price

does not increase, its investors are unlikely to receive any return on their investments in the Company's common stock.

The price of CEL-SCI's common stock has been volatile and is likely to continue to be volatile, which could result in substantial losses for Company shareholders.

CEL-SCI's stock price has been, and is likely to continue to be, volatile. As a result of this volatility, investors may not be able to sell shares at or above its current market price. The market price for the Company's common stock may be influenced by many factors, including:

- actual or anticipated fluctuations in CEL-SCI's financial condition and operating results;
- actual or anticipated changes in CEL-SCI's growth rate relative to its competitors;
- competition from existing products or new products or product candidates that may emerge;
- development of new technologies that make CEL-SCI's technology less attractive;
- changes in physician, hospital, or healthcare provider practices that may make CEL-SCI's product candidates less useful;
- announcements by CEL-SCI, its partners, or its competitors of significant acquisitions, strategic partnerships, joint ventures, collaborations, or capital commitments;
- developments or disputes concerning patent applications, issued patents, or other proprietary rights;
- the recruitment or departure of key personnel;
- failure to meet or exceed financial estimates and projections of the investment community or that CEL-SCI provides to the public;
- actual or anticipated changes in estimates as to financial results, development timelines, or recommendations by securities analysts;
- variations in CEL-SCI's financial results or those of companies that are perceived to be similar;
- changes to coverage and reimbursement levels by commercial third-party payors and government payors, including Medicare, and any announcements relating to reimbursement levels;
- general economic, industry, and market conditions; and
- the other factors (described in this Risk section).

The provision of CEL-SCI's amended bylaws requiring exclusive venue in the U.S. District Court for Delaware for certain types of lawsuits may have the effect of discouraging lawsuits against the Company and its directors and officers.

Article X of the Company's amended bylaws provides that stockholder claims brought against CEL-SCI, or its officers or directors, including any derivative claim or claim purportedly filed on its behalf, must be brought in the U.S. District Court for the district of Delaware and that with respect to any such claim, the laws of Delaware will apply. The exclusive forum provision may limit a stockholder's ability to bring a claim in a judicial forum the stockholder finds favorable for disputes with the Company or its directors or officers, and may have the effect of discouraging lawsuits with respect to claims that may benefit the Company or its stockholders.

Glossary

Adjuvant—A secondary treatment in addition to the primary therapy that often speeds or improves the action of the primary therapy.

Antibody—Immune system-related proteins produced by B-cells in response to the presence of antigens. Their function is to recognize and attach to antigens, marking them for other components of the immune system to destroy.

Antigen—A substance that stimulates the production of an antibody when introduced into the body. Antigens include toxins, bacteria, foreign blood cells, and transplanted organs, among other substances.

Apoptosis—Programmed cell death. This physiological process is necessary for the elimination of superfluous, diseased, or damaged cells and the formation of new cells.

Autologous—A treatment in which the donor and recipient are the same person. Autologous immunotherapy normally involves the removal of immune cells from a person, which are altered and later given back to that same person.

Biologic—Vaccines, blood products or derivatives, allergenic products, serums, toxins, antitoxins, and other similar products used to prevent, treat, or cure disease or injury.

BSL-1—Biosafety level 1, suitable for work with well-characterized agents which do not cause disease in healthy humans.

Cancer Cell Nest—A mass of cells extending from a common center seen in cancerous growths.

CD-4+—T-helper cells (CD-4+) are immune cells that express the CD4 protein on the surface.

CD-8+—Cytotoxic T-cells (CD-8+) are immune cells that express the CD8 protein on the surface. Some CD-8+ cells recognize and kill cancerous cells and those infected by intracellular pathogens (e.g., bacteria, viruses, and mycoplasma).

Cell Cycle—An ordered cycle of complex events, where cells proceed to cell division from a resting state.

Cervical Dysplasia—Dysplasia is the presence of abnormal cells in the cervix that may indicate a precancerous condition. Neoplasia is the pathological process that results in a tumor.

cGMP—Refers to the Current Good Manufacturing Practice regulations enforced by the FDA. cGMPs provide for systems that assure proper design, monitoring, and control of manufacturing processes and facilities.

Checkpoint Inhibitors—A form of cancer immunotherapy that targets immune checkpoints, key regulators of the immune system that, when stimulated, can dampen the immune response to an immunologic stimulus.

Chemokines—Any of a class of cytokines with functions that include attracting white blood cells to sites of infection.

Chemotactic—Pertaining to the attraction and repulsion of living protoplasm to a chemical stimulus.

Collagen Induced Arthritis (CIA)—The collagen-induced arthritis (CIA) mouse model is the most commonly studied autoimmune model of rheumatoid arthritis (RA). Autoimmune arthritis is induced in this model by immunization with an emulsion that includes type II collagen (CII).

Complete Response—The disappearance of all signs of tumor.

Composition of Matter—Relates to chemical compositions and may include mixtures of ingredients as well as new chemical compounds.

COVID-19—An illness caused by a virus that can spread from person to person. Coronaviruses are members of the coronavirus family. Seven members of the coronavirus family can make people ill, one of which is the new coronavirus strain SARS-CoV-2, which causes COVID-19.

Cyclophosphamide—A drug used for immunosuppression and destruction of cancer cells.

Cytokines—Small proteins released by cells that have a specific effect on cell interactions, communications, and behavior. Cytokines include interleukins, lymphokines, and cell signal molecules, such as tumor necrosis factor (TNF) and interferons, which trigger inflammation and respond to infections.

Cytolytic—Causing the dissolution, degeneration, or destruction of cells.

Dendritic Cell (DC)—A special type of antigen-presenting cell that activates T-cells.

Epitope—A region on the surface of an antigen that is capable of eliciting an immune response. An epitope is a site on the surface of an antigen molecule to which a single antibody molecule binds.

Erythropoietin (EPO)—A cytokine that stimulates differentiation of bone marrow stem cells, accelerates cell maturation, and maintains the level of circulating erythrocytes.

European Union Qualified Person (QP)—A technical term used in European Union pharmaceutical regulation. The regulations specify that no batch of medicinal product can be released for sale or supply prior to certification by a QP that the batch is in accordance with the relevant requirements.

First-Line—The first type of therapy given for a condition or disease.

Histopathology—The study of cell and tissue pathology and microscopic changes typical of disease.

Human Epidermal Growth Factor Receptor 2 (HER2+)—A protein involved in normal cell growth. HER2/neu may be made in larger than normal amounts by some types of cancer cells, including breast, ovarian, bladder, pancreatic, and stomach cancers. This may cause cancer cells to grow more quickly and spread to other parts of the body.

Hypersensitivity Immune Reactions—Refers to undesirable reactions produced by the normal immune system, including allergies and autoimmunity.

Immunomodulatory—The modulation or control of the immune system response, caused by either natural or man-made substances. Man-made immunomodulators aim to activate or suppress functions of the body's immune system to achieve a desired therapeutic effect.

Immunotherapy—Also called biologic therapy, is a type of cancer treatment that boosts the body's natural defenses to fight cancer. It uses substances made by the body or in a laboratory to improve or restore immune system functions.

Independent Data Monitoring Committee (IDMC)—A committee established by the sponsor to assess at intervals the progress of a clinical trial, safety data, and critical efficacy variables and recommend to the sponsor whether to continue, modify, or terminate the trial.

Indomethacin—A drug that belongs to the family of drugs called nonsteroidal anti-inflammatory drugs (NSAIDs). Indomethacin reduces pain, fever, swelling, and redness. It is also being used to reduce tumor-induced suppression of the immune system and to increase the effectiveness of anticancer drugs.

Interferons—A group of signaling proteins made and released by host cells in response to the presence of several viruses. In a typical scenario, a virus-infected cell will release interferons causing nearby cells to heighten their anti-viral defenses.

Interleukins—A group of naturally occurring proteins (*cytokines*) that mediate communication between cells. Interleukins regulate cell growth, differentiation, and motility. They are particularly important in stimulating immune responses, such as inflammation.

Investigational New Drug (IND)—Refers to the Food and Drug Administration's (FDA) program by which a pharmaceutical company obtains permission to ship an experimental drug across state lines (usually to clinical investigators) before a marketing application for the drug has been approved. The FDA reviews the IND for safety to assure that research subjects will not be subjected to unreasonable risk.

Leukocytes—Also known as white blood cells, they are small, colorless cells that circulate in the blood and body fluids and are involved in counteracting foreign substances and disease.

Lymphocytes—A type of leukocyte (white blood cell) that develops from stem cells in the bone marrow and helps protect the body from infection and cancer. There are three main types known as T-cells, B-cells, and natural killer cells. Lymphocytes are part of the body's immune defense and act to recognize antigens, produce antibodies, and destroy cells that could cause damage.

Lymphoproliferative—Referring to the proliferation of the bone marrow cells that give rise to lymphoid cells and reticuloendothelial cells.

Macrophage—A type of white blood cell that surrounds and kills microorganisms, removes dead cells, and stimulates the action of other immune system cells.

Margin—The edge or border of the tissue removed in cancer surgery. The margin is described as "negative" or "clean" when the pathologist does not find any cancer cells at the edge of the tissue, suggesting that all of the cancer has been removed. The margin is described as "positive" or "involved" when the pathologist finds cancer cells at the edge of the tissue, i.e., all cancer has not been removed.

Metastasis—The migration of cancer cells from the original tumor site. Metastasis also is the term used for a secondary cancer growing at a distant site.

Micrometastases—A metastatic tumor cell that is too small to be identified in a scan.

Monoclonal antibodies (mAb)—Any of a class of artificial antibodies produced in the laboratory. Monoclonal antibodies are extremely specific for a particular location in the body. This type of antibody recognizes only one type of antigen and is sometimes used as an immunotherapy to treat diseases such as cancer.

Monocytes—Large white blood cells that ingest other cells and foreign particles. When a monocyte enters tissue, it develops into a macrophage.

Natural killer (NK) cells—Also known as NK cells, they are a type of lymphocyte (a white blood cell) and a component of innate immune system. NK cells play a major role in the host-rejection of both tumors and virally infected cells.

Necrosis—A type of cell death where cells swell and break open, releasing their contents and damaging neighboring cells thereby provoking inflammation. Necrosis is often caused by infection or the interruption of blood supply.

Neoadjuvant—Treatment given before the primary treatment.

Objective Response Rate—Proportion of patients with reduction in tumor burden of a predefined amount.

Orphan Drug—Designation given to a medication that may treat either a rare disease that affects fewer than 200,000 people or a common disease that has been ignored because it is less prominent in the U.S. than in developing nations.

Perilymphatic—Surrounding or adjacent to a lymphatic node or vessel.

Peritumoral—Surrounding or adjacent to a tumor.

PGIA/GIA—Proteoglycan (PG)-induced arthritis (PGIA) and PG G1-domain-induced arthritis (GIA) are two RA mouse models that use proteoglycan as antigen. The PGIA and GIA models in adult female mice are predominantly driven by Th1 responses and resemble human RA in that disease is induced in older females.

Peptide—Any of various natural or synthetic compounds containing two or more amino acids linked by the carboxyl group of one amino acid to the amino group of another.

Proteoglycan—A compound consisting of a protein bonded to glycosaminoglycan groups, present especially in connective tissue.

Small Business Innovation Research (SBIR)—A U.S. Government program, coordinated by the Small Business Administration, intended to help certain small businesses conduct research and development (R&D). Funding takes the form of contracts or grants**.**

Squamous Cell Carcinoma—Cancer that begins in squamous cells, which are thin, flat cells resembling fish scales. Squamous cells are found in the tissue that forms the surface of the skin, the lining of the hollow organs of the body, and the passages of the respiratory and digestive tracts.

Standard of Care (SOC)—A diagnostic and treatment process that a clinician should follow for a certain type of patient, illness, or clinical circumstance. For head and neck cancer, the standard of care is surgery followed by radiation or concurrent radiation and chemotherapy, depending upon the severity of the cancer and its likelihood of spreading or recurring.

Surveillance, Epidemiology, and End Results (SEER)—An authoritative source for cancer statistics in the U.S. The Surveillance, Epidemiology, and End Results (SEER) Program provides information on cancer statistics in an effort to reduce the cancer burden among the U.S. population.

T-cell—A lymphocyte of a type produced or processed by the thymus gland and actively participating in the immune response. There are 3 main types of T-cells: cytotoxic (CD-8), helper (CD-4), and regulatory. Each of them has a different role in the immune response.

T or Immune Cell-Binding Ligand (TCBL/ICBL)—A ligand is a molecule that binds to a site on a target protein to serve a biological purpose. A T-cell or immune cell-binding ligand is a ligand that binds to the T-cell receptor (TCR), a protein complex found on the surface of T-cells, or immune cells, respectively, which produces an immunomodulatory signal or action.

T-cell Transfer Therapy—A type of immunotherapy in which T-cells are taken from the patient's blood or tumor tissue, grown in large numbers in the laboratory, and then given back to the patient to help the immune system fight the cancer. Sometimes, the T-cells are changed in the laboratory with the goal of improving immune functionality and characteristics.

Th1 Response—An acquired immune response characterized by high cytotoxic T-cell activity relative to the amount of antibody production. The Th1 response is promoted by Th1 helper T-cells.

Th2 Response—An acquired immune response characterized by high antibody production relative to the amount of cytotoxic T-lymphocyte activity. The Th2 response is promoted by Th2 helper T-cells.

T-helper (Th) Cells—Immune cells involved in cell-mediated immunity and function as "helpers" by regulating the overall immune response to antigen presence. Also known as CD4+ cells, Th cells help the activity of other immune cells by releasing cytokines, regulating the immune responses.

T-regulatory (T-reg) Cells—Immune cells that have a role in regulating or suppressing other cells in the immune system. T-regs control the immune response to self and foreign particles (antigens) and help prevent excessive reactions and autoimmune disease.

Tumor Necrosis Factor (TNF)—A cytokine with a key role in the body's immune response by promoting inflammation, controlling the production of other pro-inflammatory molecules, and helping cells heal or repair themselves. TNF-α acts as a cytolytic and cytostatic agent on several cell types. TNF α is a subgroup of molecules capable of initiating signaling cascades that increase cell proliferation, differentiation, and apoptosis.

Tumor Tolerance—A process by which growing tumors, which have mutated proteins and altered antigen expression, prevent elimination by the host immune system.

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