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Cellastra Inc

Encoded Gene Vectors for Scarless Healing after Surgery, Burn Injury, and Long Covid

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SUMMARY

Cellastra is currently focused on two global unmet needs: 1) prevention of pathological or excessive scarring and adhesions after surgery and burn injuries and 2) prevention and treatment of pathological tissue damage and fibrosis in lungs or other internal organs after respiratory infections such as COVID-19.

These conditions share many basic pathophysiologic characteristics, which likely can be addressed with our potentially revolutionary CELLEXA technology using an encoded gene vector. When applied locally in the wound area, the vector can transfect cells such as keratinocytes, epithelial cells, and smooth muscle cells. Transfection of these enables the long-term expression (likely for many months) of a natural lactoferrin derivate, ensereptide, which orchestrates a return to homeostasis in perturbated immune and blood clotting systems in a wound area, facilitating scarless healing. Long-term exposure to this and other natural lactoferrin peptides may have played a pivotal role in the innate immune system during the evolution of mammals for millions of years. This long natural selection process may give the peptide "an unfair and unprecedented advantage" in wound healing.

Thus, pathological scarring as well as COVID-19 / Long-Covid share pathophysiological hallmarks such as an immune reaction (often an overreaction), micro-vascular blood clots, and often, over time, secondary infections and sequelae such as scarring/fibrosis. Ensereptide has been shown to have several beneficial effects such as 1) downregulation of hyper-immune response, 2) down regulation of fibrinolysis inhibitors, 3) antimicrobial effects, and 4) anti-scarring effect.

Early non-clinical studies demonstrated that ensereptide had several advantages over lactoferrin and other sub peptides thereof. Ensereptide was about 40-80 times more potent than lactoferrin in terms of antibacterial effects. Furthermore, whereas lactoferrin has a pro-thrombotic effect, ensereptide has a pro-fibrinolytic effect, which reduces the potential for fibrin formation, micro- thrombi and long-term sequelae of scarring/fibrosis. Fibrinolysis not only reduces the potential for development of fibrin plugs /micro-thrombi, but also helps breaking down existing thrombi and splitting fibrin and fibrinogen to degradation products with well-known viscosity reducing, ,anticoagulant and anti- platelet aggregation effects, which may improve microcirculation help prevent new thrombi.

Compelling preclinical data for the vector and the peptide, as well as clinical data for the peptide, under the skin support the potential role for our technology in facilitating wound healing in the skin after burn injuries or surgery and in the lungs and other internal organs after respiratory infections such as COVID-19 and a subsequent syndrome named Long-Covid.

Using a gene vector to program long-term expression /synthesis of the peptide directly at the injury site for many months offers a compelling advantage to explore in well-designed clinical studies, where the vector is applied topically under the skin before surgical wound closure, as a spray of in vitro transfected skin cells on top of a burn injury and as an inhalation followed by an intramuscular injection in patients with Long Covid.

Cellastra has immediate opportunities to advance both projects into government-funded projects in the US (American Rescue Plan funded clinical study in Long Covid) and in Sweden (Vinnova Agency funded clinical study in burn injuries). To take advantage of these unique and time sensitive opportunities, we need seed funding of 5 M USD to contract and complete GMP manufacturing and IND-enabling pharmacology and toxicology studies in 2023 in order to enter clinical phase in early 2024.

OVERVIEW OF THE PROBLEMS

SCARLESS WOUND HEALING

Cellastra has a long-time interest in scarless wound healing and an interest in improving the process or removing the pathological aspects of the process. Wound healing is a natural process after traumatic accidents, surgeries, and burns . Scar formation on the external skin after trauma and adhesions internally in body cavities after surgery are normal processes in wound healing (1). Far too often, the process becomes pathological, and the scars can become hypertrophic or keloid in nature (2), while adhesions can become permanent and result in serious or even fatal outcomes depending on the anatomical sites (3). Examples of severe complications of adhesions are infertility after gynecological surgery (3–5), intestinal obstruction after abdominal surgery (5), and failed back syndrome after spinal surgery (6–8). However, even dermal scars can result in negative consequences ranging from cosmetic issues affecting self-esteem and wellbeing to severe issues such as limitations to mobility, chronic pain, and poor quality of life when a scar is located over a joint.

Pathophysiological considerations

Developing an agent for improving wound healing is complicated by pathophysiological considerations on top of clinical heterogeneity. Preventing infection of a wound site is critical in improving the chances of normal wound healing, as infections result in immunological responses and increase the likelihood of abnormal healing (9). Keeping a surgical site clean is easier than cleaning a wound but result in an increased risk of infection due to breakage of the skin barrier. Even common skin bacteria such as *Staphylococcus epidermidis* can become pathological inside the body (10,11). The normal responses of the body to a wound can become complicated when infection is present in addition to the normal inflammatory response to injury which results in activation and recruitment of immune system elements. Immune cells, especially neutrophils, are recruited to the wound area and release various cytokines and lymphokines, many of which are proinflammatory (12,13). The role of neutrophils appears to be exaggerated in cases of chronic inflammation. Cytokine release can lead to further neutrophil recruitment and further increases in cytokine release, sometimes leading to a cytokine storm locally or even systemically. Good surgical technique is critical, but the heterogeneity of surgical sites, differences in skin among individuals, and the heterogeneity of immune system responses to insult or injury complicate the clinical picture. This, in turn, complicates clinical research studies of wound healing.

Regulatory considerations

Regulatory agencies demand some method of analysis which arrives in a numerical score which can be compared to placebo, preferably, or to another approved treatment (active control). For exterior scars, various scales were developed to score wound healing and scar formation and reconstruction. Of these, the POSAS (14,15) and VSS (16–18) are the most commonly used. However, using these assessment scales in clinical trials is not straightforward as decisions need to be made about how scars are assessed whether a patient serves as his or her own control (opposite sides of body or half a scar treated with each agent), or when assessments are made. A short-term improvement of time to healing (wound covering) may be valuable clinically, but a difference in scar appearance and structure over months certainly is. Of the various well-characterized surgical models to study, an assessment conducted for Cellastra by a Clinical Research Organization (CRO) specializing in dermatology suggested the best was breast augmentation surgery, where both dermal scars and internal capsule formation with visible contracture leading to replacement surgery could be end-points to evaluate. However, with the onset of the SARS-CoV-2 pandemic, such surgeries were

largely halted in the US for over a year. Even breast reconstruction surgery following mastectomy for cancer were largely halted.

PXL01 in Hyaluronic Acid Formulation

The Cellastra team was initially interested in developing the peptide ensereptide, also known by the code PXL01, for the prevention of scarring. This 25-amino acid sub peptide of lactoferrin appears to be part of the innate immune system and is more potent than the intact lactoferrin protein (692 amino acids) in many respects. One Swedish company (Promore Pharma) conducted a double-blind, placebo controlled Phase 2 study of PXL01 in hyaluronic acid (HA) in 138 patients and demonstrated an improvement in 4 of 5 endpoints following adhesion formation after flexor tendon repair surgery of the hand (19). Other nonclinical studies by this group demonstrated that ensereptide had properties that would enable scarless wound healing, including reducing infections, counteracting excessive inflammation, and promoting fibrinolysis (20). In March 2017, Cellastra therefore signed an option agreement with Promore Pharma for co-development and marketing rights in North America provided Cellastra was able to secure funding for a Phase 3 registration study in the US at an estimated cost of 12 M USD, as a companion to a Phase 3 trial conducted by Promore Pharma in Europe and Asia.

In January 2018, the option agreement was terminated as Cellastra was unable to find investors for development of prevention of adhesion following flexor tendon repair surgery after tendon rupture, which was considered a niche indication. Furthermore, it was realized that the technology platform using hyaluronic acid (HA) as a slow-release formulation had severe limitations. We recognized that the short-term application of the peptide in a wound was unlikely to result in long-term positive effects. Although HA potentially might contribute positively to wound healing according to some studies (21–23), this was refuted by one clinical study in hand surgery, using HA alone (24). Thus, the Swedish investigators (20) concluded that the utility of HA was likely as a solvent of PXL01 allowing a slow release of the peptide over several days or potentially longer, as the benefit of a single dose administration was shown up to the 6-month endpoint in the Phase 2 study. However, at 9 months follow-up, the benefit no longer reached statistical significance as many patients had dropped out.

Failures of previous anti-scarring drugs

The dilemma with difficulties in demonstrating long-term benefit was not unique to PXL01. Randomized, placebo controlled, blinded studies sponsored by other companies evaluated several other anti-scarring agents in wound healing after surgical procedures. While 6-months results in several of these studies were positive and reached statistical significance, benefit over placebo could no longer be demonstrated at 1-year follow-up, required for regulatory approval. The failure was likely due to insufficient treatment exposure, as treatments in those studies typically were limited to one or a few applications during the first days or weeks after surgery.

The potential for ensereptide as an anti-scarring agent in wound healing was as great or greater than these other agents. However, as the patent for the peptide expired in 2019, Promore Pharma is relying on a patent for hyaluronic acid formulation.

Cellastra's technology platform addresses both issues (duration of treatment exposure and patent protection– see Unfair Advantage below).

PREVENTION AND TREATMENT OF LONG-COVID

Rationale – Pathophysiology of COVID-19, Long Covid share hallmarks with dermal scarring.

The initial intent was to study prevention of scarring after surgery. After examining the mechanisms of action of ensereptide in wound healing and the pathology of abnormal wound healing and that in the lungs after SARS-CoV-2 infection, we were struck by the possibility of using the gene vector administered by inhalation in the treatment of COVID-19. As in wound healing, there were factors associated with SARS-CoV-2 viral infection that were similar, including inflammation and immune system derangement . In addition, fibrin deposition in the vascular space of the lungs led to the development of thrombi and microthrombi which contributed to additional lung damage. In an extensive review of the literature on COVID-19 by one of our team members (Henrik K Kulmala, PhD), we were struck by the common trilogy of factors in the pathogenesis of COVID-19 and the following long-term disease, Long-Covid: Inflammation – Immune Response – Fibrin plugs (thrombi) in micro-vasculature. The primary infection in COVID-19 was in the lungs, in the deep lungs with the early variants and upper lungs with the latest variants. The infection was primarily identified as a novel type of pneumonia. In addition, coronavirus infection was common in the digestive tract, as the virus also was swallowed. Inflammation is a common response to viral infection in all body areas. While acute hyperinflammation with an exaggerated immune response is pathological, chronic inflammation can lead to an exaggerated *pathological immune response and tissue fibrosis*. A common factor in all cases is an immune response to the virus, as asymptomatic cases result when the subject's immune system fights off the virus, but symptomatic and severe cases result from an inadequate immune response. Vaccination aims to induce the immune system to produce antibodies to the Spike (S) protein of the virus, but the original vaccines were based on the old variant S protein and the latest Omicron variants, like XBB.1.5 likely are potentially too mutated to be fully affected by the vaccine (25,26). In some COVID-19 cases, a hyperimmune or deranged immune response is seen, resulting in a cytokine storm. The vasculature is a common link for affected body areas: it can carry the virus and the reactive immune cells. *Excessive clotting and microthrombi* typically induce further tissue damage (inflammation, ischemia), including that in blood vessels. Neutrophils, an integral early part of the immune system response, may participate in the pathology of COVID-19 and Long-Covid (27–30). **A treatment aimed at the underlying pathology could slow the disease process and allow the host immune system to deal with the virus.**

Long-Covid is not a separate disease and follows an infection, especially if the infection was severe. While the illness appears to be heterogeneous, some of this is due to clinical definitions as the disease is defined by its symptoms and clusters of symptoms. In most cases, there is no evidence viral infection is continuing, but the symptoms likely reflect the distribution of virus at the time of active infection and the sites of immune response. Whereas antivirals such as Paxlovid are approved for emergency use in the acute phase of COVID-19 based on evidence of reduced hospitalization and mortality, the rational for their utility for treatment of Long Covid is less clear. *It seems counterintuitive that a 15-day course of antiviral treatment may impact chronic sequelae of tissue damage caused by blood clots and/or a deranged immune system.* **An agent such as inhaled ensereptide encoded vector could potentially be a tool to reduce the spread of virus from an initial respiratory or gastrointestinal site and prevent Long-Covid when administered soon** after infection. Additionally, the vector administered either by inhalation or intramuscular injection could be used to treat the symptoms of Long-Covid once they appear.

UNFAIR ADVANTAGE

As ensereptide had potent pharmacological effects and was known to be safe, it seemed to be a promising anti-scarring peptide to further develop. One of us (Brad Thompson, PhD) came up with a novel idea, discussed further below, to use an adeno-associated virus 6 (AAV6) vector to transfect cells in the wound area to produce the multi-potent peptide locally for many months. This would overcome the concerns with short treatment exposure with a peptide formulated in hyaluronic acid. It would also be the foundation for a new proprietary technology platform both for ensereptide and for new analogues thereof with potentially longer half-life in the blood circulation. A novel triple-mutant AAV6.2FF vector was found to be superior to natural AAV6 vector both after intramuscular and pulmonary administration (31). Such vectors generally cause less immune response in hosts and have other characteristics which make them superior as vectors.

The new study for Cellastra demonstrated that intramuscular injection of this vector encoded for the ensereptide gene of interest linked to human IgG (for assay purposes) resulted in long-term production of the peptide in mice (32). Furthermore, in postmortem studies of mice sacrificed on Day 77, the tagged peptide could be demonstrated in blood as well as in lungs and some other organs. A patent application was submitted for the use of this peptide and related longer half-life analogues in scarless wound healing, as discussed below.

Additional studies of the vector were conducted in mice and larger animals to examine the long- term expression of a monoclonal antibody and safety of the AAV6.2FF vector (33,34). The vector proved to be safe with minimal evidence of inflammation at the intramuscular injection sites and expression of the protein could be measured in blood for more than two years (study ongoing).

The potential for long-term expression of ensereptide (many months up to a year or more) gives the CELLEXA gene vector platform enabling long-term in vivo expression /synthesis of a peptide at the site of injury unfair and unprecedented advantages over conventional treatment paradigms using manufactured drugs administered topically, orally, or by injection.

SAFETY OF THE AAV GENE VECTOR

It is important to note that AAV does not generally get into the cell nucleus and induce permanent changes to the host genome. Also, AAV is a nonpathogenic virus commonly found in nature. In practice in gene therapy, the viral genetic material is removed during processing and only the capsid (essentially an empty shell) and some regulatory elements are used to carry the gene of interest into the cell. Rather than being incorporated into the nucleus, the vector is taken up into a structure known as an episome. The genetic material is read and the code is translated into the intended peptide, which is then released from the cell. Transfection results in the production of the peptide for the lifespan of the transfected cell, or about 30 days for many cells. The material is not replicated if the cell divides, but is split between the progeny resulting in a decrease in peptide production over time. Nevertheless, FDA requires at least five years of follow-up of any subject treated with a gene therapy agent to monitor for any long-term effects of the agent.

UTILITY OF THE CELLEXA PLATFORM

Thus, ensereptide delivered locally after transfection by viral gene vector could be used as a stand-alone or add on treatment in the acute and chronic phase of COVID/ Long-Covid to prevent and treat many of the symptoms of COVID-19 and Long-Covid to stop further excess cytokine release, thrombi formation, tissue damage, encourage infection free, scarless healing, and prevent fibrosis. Future in vitro and in vivo studies would clarify which mechanisms are most effective in COVID-19.

Since the activity of the peptide is not specific to the viral sequence but directed toward an innate immune response, treatment of other viral respiratory infections with the vector also might be effective in reducing the pathology. A current example is respiratory syncytial virus (RSV), which is known for seasonally causing severe infections among young children in the US and also is severe or fatal among the elderly, most of whom have weakened immune systems. Another example is "the triple pandemic" where COVID-19 coincides with RSV and influenza as reported in late 2022.

MANUFACTURING OF AAV GENE VECTOR

Another consideration with gene therapy is the expense of manufacturing the gene vector according to GMP. While it is relatively easy to manufacture batches in the laboratory using stacks of culture plates containing the cells used in the manufacture, the process of purifying the material and ensuring it is free of any contaminants, such as viruses, bacteria, and partially filled or empty capsids, is expensive. Any drug administered parenterally to humans must be a sterile product. Also, manufacturing the large quantities required for definitive animal or human studies requires different manufacturing methods which then need to be optimized and the product characterized. It is possible to use a smaller engineering batch in the initial experiments, recognizing that this early product may not be the same as the final product intended for clinical trials. Since this situation is common in clinical trials, it is accepted practice. However, the cost still amounts to a few million dollars just for the manufacturing. This has led to extremely high treatment costs for rare genetic diseases. However, for larger indications such as wound healing and Long-Covid, the cost would be expected to be acceptable as cost of goods are dramatically reduced with scale-up production.

PATENTS

The AAV6.2FF vector, which has been awarded a US patent, is characterized by lower immunogenicity, higher transgenic expression in muscle (>100-fold) and lung (49-fold) at 24 hours. 10-fold greater expression in the lung at 21 days and significantly increased expression on Days 1, 7, and 14 in muscle, and robust expression maintained at high levels throughout a 6-month study period compared with native AAV6 (14). Cellastra has licensed patent rights to the triple mutant AAV6.2FF vector from University of Guelph, ON, Canada (US Patent 10,806,802B2 (granted October 30, 2020; granted in Canada in 2021).

The composition of matter patent of ensereptide expired in July 2019 so development of the peptide would not be protected by patent. However, Virlexa and Scarlexa are protected by a USPTO patent filing (July 2018) and the subsequent continuation in part (CIP) filing on May 14, 2021. The CIP filing has composition of matter claims for the vector encoded for endogenous expression /production of a broad range of lactoferrin sub-peptides, including ensereptide and potentially superior analogues thereof. This CIP filing is based on results from an in vivo study in mice receiving intramuscular administration of the triple mutant AAV6.2FF vector encoded for ensereptide demonstrating rapid and robust expression of IgG Fc-tagged ensereptide. A telephone call with USPTO in October 2022 indicated that the patent would be issued in the near future. The global PCT patent filing was submitted in July 2019 but will be updated with the data from the CIP application in the US as soon as the US patent has been granted. These patents were assigned to Cellastra by the inventor.

An independent law firm specializing in Life Science Law was contracted to make a Freedom to Operate analysis for Cellastra. After a thorough review of the related patent landscape, they issued a privileged and confidential report and concluded: "In our opinion, based upon the foregoing analysis, none of the issued patent claims discussed herein will be found to be infringed."

THE CELLASTRA TEAM

The Team at Cellastra currently may seem pretty barebones and top heavy with executives with a proven ability to get medical products approved and to roll up their sleeves and do the work. Until we get outside funding, we have by necessity been relying on equity grants as the sole compensation which has worked well but is far from ideal. Most importantly, the various members act as a Team and accomplish the missions, whether assigned or implied, often in innovative ways. Each member of the Team has a desire to succeed and a strong belief that they are doing their part to aid humanity. The members act harmoniously and complement each other's strengths, recognizing where they have weaknesses and seeking support. In seeking support and quotes from outside vendors, we have formed personal and professional bonds with the various scientists, sometimes challenging them to find new and better ways and never being afraid to ask dumb questions

Each of the company's officers has generalized scientific and medical capabilities in drug and biological development as well as specific prior research interests. Prior interest in central nervous system diseases, disorders, and their treatment is a common theme and could prove useful as Long-Covid appears to affect central functioning.

Dr. Karl Mettinger, MD, PhD, Cofounder, President and CEO, is a visionary entrepreneur from the Karolinska Institute, Stockholm, where he was an associate professor of Neurology and helped start the first stroke unit in Europe where completed cross-disciplinary blood coagulation and cardiovascular studies in young stroke patients. He also met with the Swedish Prime Minister Olof Palme and Industry leaders and the Secretary of the Nobel Foundation and became Cofounder and President of the Swedish Stroke Society, a research and patient support organization with today 10,000 members in 74 chapters under the auspices of Queen Silvia of Sweden. As an accomplished clinical research executive in the Life Science Industry for more than 35 years, he has helped guiding many projects to their endpoints leading to global market approvals in companies such as Kabi/Pharmacia (acquired by Pfizer for 60 B), IVAX (acquired by TEVA for 7.5 B and Pharmacyclics (acquired by AbbVie for 21B). **Dr. Henrik Kulmala, PhD, Executive VP of Regulatory / Product Development** is a neuroscientist initially researching neurological diseases. After obtaining his PhD in Neuropharmacology from University of Chicago he served as an Assistant Professor at Northeastern Ohio Medical University. He has subsequently served in the Life Science industry and has more than 35 years' experience guiding projects involving some 75 molecules, many to US IND and initial clinical trials, as well as many projects to marketing applications including the multibillion blockbuster Prograf for liver transplantation (Fujisawa/ Astellas). **Dr Vinod Kumar, MD, Chief Medical Officer, Executive VP,** is an accomplished distinguished physician and neuroscientist, who has more than 20 years' experience in the industry and was Head of Neuroscience Section and Global Medical Director at Novartis for 16 years, and previously Professor of Psychiatry and Neurology at University of Illinois and University of Miami.

We have an active Board who meets by Zoom about every month, actively discussing plans and options**. Dr Brad Thompson, PhD, Chairman and Chief Technology Officer**, is a virologist and inventor who was head of Biotechnology for the Alberta Research Council. He served as CEO in several prominent biotechnology companies in Canada and was Director and Chair of BIOTECanada. The board also includes **Sven Andreasson, Director M Sc. Business** from Stockholm School of Economics, with a long career as President Pharmacia International (acquired by Pfizer for 60 B and CEO of several Swedish and Belgian companies including Isconova, acquired by Novavax, Rockville where he currently serves as Sr VP Corporate Development. **Daniel Quintero**, Director, Legal Counsel, is Founding and Managing Partner of Prometheus Partners LLP, a law firm for the Innovative Mind and Financial Services, and previously had a distinguished career

as the General Counsel and Corporate Secretary of Sony Optiarch America, where he concurrently served as Senior Managing Counsel and Director for Sony Electronics Inc. and oversaw Sony's Law Department in Silicon Valley. Our CFO is **Bruce Phillips, Director, CPA** with a distinguished career from Ernst & Young and other companies and currently Managing Partner and Head of Accounting Cloud Solutions at Aprio Cloud operating Globally. **Dr Kent Persson, PhD, Cofounder, Director**, is an accomplished Molecular Biologist who earned his PhD in Sweden completed his post doc in gene expression at University of California, San Francisco and subsequently worked more than 20 years in the industry including Bio-Rad and OctaPharma. He is currently a Senior consultant at Complyit, a Swedish consulting firm serving the Life Science Industry.

Our Scientific Advisory Board includes world leading experts in burn injuries, tissue regeneration and gene therapy. This board includes **Professor Folke Sjoberg**, Professor of Burn Surgery and Critical Care at Linkoping University Hospital and the President Elect of the International Society for Burn Injuries. **Professor Christopher Evans**, is currently Director of the Rehabilitation Medicine Research at Mayo Clinic. He has won numerous awards including the Orthopedic Research Society Excellence in Tissue Regeneration Award. **Dr. Magda Forsberg, PhD** from Uppsala University in Sweden, did a Postdoctoral Fellowship in Reprogramming and Neurobiology at the Karolinska Institutet in Sweden, where she became an Assistant Professor and worked on the development of cell replacement therapy for neuro-degenerative diseases, focusing on stem cell biology, cell differentiation, and clinical applications. Dr. Forsberg is currently President & CEO of DVL-op MEDICO Inc., an orthopedic device company.

The CEO has interviewed some distinguished younger individuals for senior management roles, but we are hampered by lack of funding for salaries. With initial funding, the focus will be on manufacturing the viral gene vector, a process taking a year or more. Thus, persons more expert in CMC issues and in business development are forecast as initial hires. **For Facilities, Employes and organization chart see Appendix 1.**

MILESTONES AND FINANCIALS

MILESTONE 1: MANUFACTURING AND IND-ENABLING PRECLINICAL STUDIES. ABOUT 12 MONTHS - $5M

The first milestone to meet is FDA filing of an IND for Virlexa, our initial project. This requires sufficient data on the chemistry, manufacturing, and controls (CMC) of the product and basic nonclinical pharmacology and toxicology data. To achieve this, we need to initiate a manufacturing project at one of the vendors who have submitted bids to Cellastra and to use product from the initial engineering batch for some preclinical studies, to include proof of concept efficacy and safety studies (in vitro and in vivo). We also need to manufacture small quantities of the peptide, ensereptide, and develop an assay in biological and other fluids. The total cost for this initial phase is estimated to be $5 million, the bulk of it for manufacturing.

MILESTONE 2: COMPLETE PHASE 2 -OBTAIN AN EUA (EMERGENCY USE AUTHORIZATION) IN LONG- COVID – 12 MONTHS

The second milestone would be initiation of a Phase 1 clinical study and then completion of the Phase 1 portion of the study. We propose to conduct continuous clinical trials in which the study continues directly into Phase 2. Depending on the efficacy and safety determined in the Phase 1-2 study, we may next submit an Emergency Use Authorization application (EUA) in Long-Covid, with a Phase 3 confirmatory trial and a full application (BLA) to follow.

Considering the urgency in the development of an effective treatment for Long-Covid, Cellastra has approached leaders for White House Covid Task Force as the Biden Administration has set aside $1.5B from the American Rescue Fund for research and clinical studies in Long-Covid, the RECOVER INITIATIVE. This has two components, an observational study to study the causes, mechanisms in the natural course and epidemiology of Long-Covid, and a clinical trials component which includes both solicitation of drug candidates as well as a support center for execution and oversight of the clinical trials. We are in communication with the White House to see if we can get funding for our clinical development of Virlexa in Long-Covid. They have encouraged us to stay in touch and update them on our progress and timelines for manufacturing and IND enabling studies.

DEVELOPMENT OF SCARLEXA

Scarlexa could continue in parallel or be licensed out. Cellastra is a partner in the Center for Advanced Medical Products (CAMP) funded by a 50 M SEK grant which among several projects in includes a clinical study in patients with burn injuries where our vector would be used to transfect skin cells in vitro prior to them being sprayed as a suspension on top of the wound to explore scarless healing potential in a small Phase 1-2 study (10-20 patients). Our obligation is to provide GMP quality gene vector which would be taken from the same batch as the batch used for the inhalation device for Virlexa. Only a small quantity of vector will be needed for this study.

LONG-TERM PROJECTIONS

The projected costs for complete development of both projects are shown in the following table. These figures are based on estimates obtained from various vendors for specific studies.

Project	Item	Year 1	Year 2	Year 3	Year 4	Total
VIRLEXA	**CMC**	$3,384	$1,200	$1,200	$1,200	$6,984
	Preclinical	$1,600				$1,600
	Clinical					
	Phase 1		$1,191			$1,191
	Phase 2		$1,696			$1,696
	Phase 3		$6,000			$6,000
	Regulatory		$700	$3,500		$4,200
	TOTAL	**$4,984***	**$10,787****	**$4,700**	**$1,200**	**$21,671**
SCARLEXA	**CMC**	$2,950	$1,200	$1,200	$1,200	$6,550
	Preclinical	$950	$750			$1,700
	Clinical					
	Phase 1		$1,600***			$1,600
	Phase 2		$1,700	$1,700		$3,400
	Phase 3			$3,500	$3,500	$7,000
	Phase 3 confirm			$3,500	$3,500	$7,000
	Phase 3 2nd Indication				$7000	$7,000

	Regulatory		$250		$3,500	$3,750
	TOTAL	**$3,900**	**$5,500**	**$9,900**	**$18,700**	**$38,000**
External Projects Total		$8,884	$16,297	$14,600	$19,900	$59.671
Internal Operations Total		$2,132	$3,911	$3604	$4776	$14323
Grand Total		***$11,016***	***$20,208***	***$18,104***	***$24,676***	***$73,994***

*Milestone 1 Seed Funding; **Milestone 2 Phase 1-3 studies could potentially be funded by US Government; *** funded by Swedish Government Vinnova Agency

MARKET AND COMPETITION

MARKET AND TREATMENT OPTIONS FOR DERMAL SCARRING

Scarlexa is a gene vector to be applied into or under to the skin in the wound area and is evaluated for prevention of dermal scarring after surgery and burn injuries. Based on published preclinical and clinical studies using PXL01 (Ensereptide), we selected a gene vector encoded to enable endogenous synthesis of this promising anti-scaring peptide for development.

Scarlexa is programmed with the code for the anti-scarring peptide Ensereptide. When applied directly in the wound area after surgery or burn injuries, Scarlexa enables long-term synthesis (expression) and local exposure to peptide for several weeks or months, which is believed to be critical for robust scar prevention. Cellastra's portfolio also includes gene vectors encoded for Ensereptide fused with an IgG Fc fragment enabling a longer half-life and measurement of expression in vivo. By contrast, previous attempts to develop scar prevention agents have failed to show long-term benefit, most likely due to treatment being limited to just the first few days or weeks after surgery.

Proposed routes of administration in Burn Injuries and Post-op Scar Prevention

For burn injuries, Cellastra is proposing to explore Scarlexa by spraying in vitro transfected skin cells /keratocytes on the top of a burn injury, to see if incidence of hypertrophic scarring can be reduced from the current over 70% rate. If promising results are obtained, this could lead to registration studies in burn injuries and other dermal scarring indications in collaboration with partners in the burn / wound care aesthetic surgery industry. Such a study might quickly prove the value of the platform in dermal wound healing and would be simpler from a regulatory aspect as treatment would be in vitro to cells which are then further processed under GMP protocols.

For post-op scar prevention Cellastra is proposing to apply Scarlexa under the skin before wound closure or potentially injected into the skin or musculature in the wound area.

Target Indications for Scarlexa

Burn injuries is natural first choice as Cellastra has entered an agreement with a Swedish Consortium (CAMP = Center for advanced medical Products) funded by the Vinnova government Agency. Where Cellastra will provide study drug for a Phase 1-2 study of burn injury patients admitted to the National Burn Center in Linkoping University Hospital with Professor Folke Sjoberg, an international leader in the field. There are three compelling reasons to be part of this study: 1) a majority of these patient have long term suffering of hypertrophic scarring; 2) there are no effective treatment options on the market; 3) transfecting the skin cells (keratinocytes) in vitro in the laboratory provides a unique opportunity to evaluate if the anti-scarring peptide is clinically meaningful and safe.

If the results are positive Cellastra may consider out licensing Scarlexa to a large pharma company that is a leader in surgical wound healing. The global market for a product that improves wound

healing and prevents or limits scarring is huge, easily in the billions of dollars annually. However, in order to obtain regulatory approval for a product, one needs to demonstrate efficacy using a clinical endpoint acceptable to regulatory agencies and clinically relevant. For this reason, there are a limited number of options chosen for clinical trials of scar prevention in wound healing. Of these, Cellastra chose scar prevention after breast augmentation surgery, in which external scars are troublesome in some patients who develop hypertrophic scarring and/or internal scars resulting in capsular contraction in some 15% to 45% of patients (35). These may be severe in about 10% and require reoperation. In 2019, before the pandemic, there were 270,000 breast implant procedure in the US and 1.5 million globally and after a temporary decline the numbers are back at these levels and expected to grow with an annual growth rate (AGR) of 6.5%.

Another target indication is C-section, which has become increasingly common and is currently used globally in about 30 million women every year (including 1.4 million procedures in the US and about 6 million in China). C-section may cause hypertrophic or cosmetically challenging scarring in up to a third of Caucasian women and two thirds of Chinese women (16). In addition, the scars may be accompanied by internal adhesions causing bowel obstruction or infertility. Hypertrophic scars can lead to numerous complications including pain, persistent itching, and limitations on mobility.

Competing Agents in Dermal Scarring

The majority of products designed to allow for more normal healing and prevent scarring are devices, such as surgical meshes, and over the counter (OTC) products. Most topical products to date are OTC or "cosmeceutical" products with very limited clinical evidence of benefit and no regulatory approvals. There are many failed trials of pharmaceutical agents in wound healing.

There are few biotech agents that have been in development to prevent dermal scarring and two, AZX 100 and Justina recently failed, as short-term improvement could not be confirmed at 12 months follow-up. One of the limitations was that these agents were only applied immediately after surgery with no maintenance treatment. Another product, RXI 109, was evaluated in a Phase 2 study, but the design using within-patient control made it difficult to interpret the results and further development is apparently on hold. Ensereptide formulated in high molecular weight hyaluronic acid was used successfully as a single application after tendon repair surgery; however, treatment exposure of a few days may prove to be too short to achieve long-term effect in dermal scarring. Thus, there do not appear to be any current competing biotech development programs.

THE COVID MARKET

Some have declared that the COVID-19 pandemic is over, but that clearly is not the case. The rise of Omicron as the predominant variant in November of 2021 was followed by waves of this variant and subvariants sweeping through globally. Currently, the XBB.1.5 subvariant, first found in New York, is sweeping through the northeast US while other subvariants (e.g., CH.1.1) are arising. Due to various mutations in the structure of the two important structures of this subvariant, the S protein and the receptor binding domain or RBD, this subvariant is the most immune evasive and probably the most contagious viral variant yet seen. It is highly likely that another wave of infection will sweep the US, possibly annually, as there is little long-term protection from prior infection or vaccination to the XBB.1.5 subvariant and probably others. The wave of infections in China now are due to an Omicron variant and the large number of cases makes it highly likely that new subvariants with better immune escape and stronger infection characteristics will arise. It is fortunate, perhaps, that the Omicron variants are less deadly that the prior variants such as Delta, but deaths, severe disease requiring hospitalization, and even cases of Long-Covid will increase with additional infections. COVID-19 cases, hospitalizations, and deaths are lower now in the US than the peaks, but certainly not a zero

levels. Reporting of results has decreased and testing appears to be at a low point, not necessarily due only to a reduction in the number of cases. The hope that vaccines would end the pandemic has faded and current interest in vaccination in the US is low. It is likely that annual vaccinations for COVID-19 with vaccines tailored for the current variant(s) will become established practice as FDA recently stated.

COVID-19 Treatment Options

Numerous specific drugs were developed during the pandemic, but many had little efficacy, and most have been removed from the market in the US. Few drugs are left to fight the pandemic.

There are two major regions of the SARS-CoV-2 virus that are critical to its infectiveness, the Spike (S) protein and the receptor-binding domain (RBD). Antibodies to either of these amino acid sequences can decrease the infectivity and pathogenicity of the virus. The host immune system is the primary method of combatting an infection. People who fight off an infection generally develop antibodies against parts of both RBD and S protein regions, whereas the vaccines were developed toward known amino acid sequences in the S protein only. All viruses mutate and the mutations can occur anywhere in the viral capsid. A change in one amino acid for another can cause major or minor changes in the folding of the protein and the binding required for internalization of the virus into host cells. Multiple changes can affect viral behavior in many ways; those which are not beneficial to the virus spreading and replicating generally disappear as they are replaced by viruses with more infective features. This should be apparent to anyone looking at the waves of infections worldwide in the pandemic and the designations given the viral variants responsible for these, such as Alpha, Beta, Gamma, Delta, and Omicron. Host mortality is not a beneficial feature for the virus, as it decreases the number of circulating virus particles in the population. Increased infectivity of hosts and organ systems and decreased incubation time can drive mutation. This is evident from the predominance of the various Omicron subvariants since November 2021 and the rapid rise and fall in population infection rates of these subvariants. Omicron appears less lethal than Delta, but also more infective with a shorter incubation time.

Vaccines

The current Omicron variants seen globally are extremely immune evasive, responding little to the original vaccines (designed against the S protein of original variants) and to prior infection. Only the bivalent vaccine is expected to have some, but limited, efficacy, as it was developed against an original Omicron variant. While the vaccine can be modified to recognize major changes in the S protein, these modifications take months under the current system to be tested for efficacy and safety and the virus keeps mutating rapidly. The current XBB.1.5 variant went from first detected to predominant in just a matter of weeks. Annual vaccination with a vaccine designed against expected circulating variants likely will be needed in the future, for years to come. Even in the best situations, a vaccine is not 100% effective and often is much less effective, as seen annually with influenza vaccines (FDA wants 50% or better efficacy), and many people don't bother getting a vaccine. A vaccine is dependent on the host immune system to generate antibodies, and elderly, immunosuppressed individuals, and people with some diseases have a weaker immune system. Vaccines are not considered to be competitive for Virlexa and prior vaccination is not a contraindication to treatment with the vector.

Monoclonal Antibodies

All of the monoclonal antibodies, designed against an S protein sequence, are now ineffective and none are currently available in the US. *Convalescent serum,* derived from sera of individuals who

fought off an infection, is probably still somewhat effective mainly as it included antibodies against multiple regions of the viral capsid, not just the S protein. However, this is a limited option. Evusheld (tixagevimab co-packaged with cilgavimab) is not currently authorized for use in the U.S. until further notice by the Agency (26 January 2023).

Oral Antivirals

Oral antiviral treatments are in development and Pfizer's Paxlovid and Merck's Lagevrio obtained Emergency Use Authorization (EUA) by the FDA based on promising results with five-day dosing in large Phase 3 studies with about 2000 and 1400 patients, respectively, showing about 90% reduction in hospitalization and reduced death rates. Since approval, treatment with Paxlovid was reported to be followed by a viral rebound in many cases, in which patients again tested positive for the virus after negative testing. Because of probable interactions with >150 drugs at liver cytochrome P450 systems, Paxlovid must be used with caution in many patients, especially the elderly and immunocompromised subjects who likely are on many medications. Paxlovid appears to be one of the few options in patients with COVID-19 currently as the target of this drug (an enzyme) does not appear to have mutated with the viral variants. Another option for some patients who are hospitalized or at high risk of being hospitalized or having severe disease is Veklury (remdesivir), an RNA polymerase inhibitor. These agents likely could be used concomitantly with Virlexa.

Recently, it was announced that a US Government has funded placebo-controlled Phase 3 study (n=1700 patients) to evaluate a 15-day dose regimen of Paxlovid as a potential treatment of patients with Long Covid. The study is expected to start in January 2023 and to complete enrollment in a year. If the study shows long- term effectiveness and safety with careful monitoring of potential drug-drug interactions, it seems likely that Paxlovid may be used in combination with novel and complimentary treatment modalities such as Virlexa; however, Virlexa is aimed for prevention rather than treatment.

Interferon Lambda

Among predominantly vaccinated outpatients with COVID-19 in Canada and Brazil, the incidence of hospitalization or an emergency department visit (observation for >6 hours) was significantly lower among those who received a single dose of pegylated interferon lambda than among those who received placebo (36). This study showed promising results for an old drug in 2022-23.

THE CASE FOR VIRLEXA

Proposed routes of administration in Long-Covid

In addition, we propose to explore utility in COVID/ Long-Covid using inhalation, potentially combined with an intramuscular administration:

1) **One inhalation of Virlexa may bind to heparan sulfate in the ACE-2 receptors on the epithelial cells of the lung, which is the site of invasion of the SARS-COV-2 virus causing COVID-19. This will enable targeted transfection of the cells at the injury site and turn the lung epithelium into a temporary bioreactor (surface about 100 sqm = the size of a racquet ball court).**
2) **The inhaled dose will likely also be distributed to surrounding structures such as the epithelium of nasal cavities, the olfactory pathways for smell and taste, to the brainstem as wells as to esophagus/upper gastrointestinal tract. This may help stop invasion of the CNS, the bowels. other organ systems.**

3) **Ensereptide produced in close vicinity to the viral attack points seems an unprecedented advantage, particularly considering the continuous resupply of an agent with multimodal effects against the perturbations caused by insult: antimicrobial, anti-immune, anti-thrombotic, and anti-fibrotic.**

4) **Thus, Virlexa engineered ensereptide seems a uniquely useful weapon to prevent infections, tissue damage, and fibrosis in respiratory, esophageal-upper gastrointestinal, and nasal/olfactory/CNS, which seems to be of paramount importance to prevent acute and long-term pathology and symptoms related to these organs.**

5) **The full benefit of one inhalation will last for at least 30 days (= the life span of epithelial cells) but will decrease over the next few months as cells divide or die off.**

6) **An intramuscular injection of the vector may be given on Day 1 or Day 30 to enable long-term expression of ensereptide over several months, and likely up to a year or more, as the same gene vector has been shown to enable expression of another protein, a monoclonal antibody, for more than two years in a sheep model.**

Virlexa is intended for the prevention or treatment of Long-Covid. Whereas antivirals such as Paxlovid are approved for emergency use in the acute phase of COVID-19 based on evidence of reduced hospitalization and mortality, the rational for their utility for treatment of Long-Covid is less clear. It seems counterintuitive that a 15-day course of antiviral treatment may impact chronic sequelae of tissue damage caused by blood clots and/or deranged immune system. An agent such as inhaled ensereptide-encoded vector may reduce the initial tissue damage and help prevent fibrosis in the lungs. In addition, it could potentially be a tool to reduce the spread of virus from an initial respiratory, nasal or gastrointestinal site and prevent Long-Covid affecting CNS and internal organs when administered soon after infection. Additionally, the vector administered either by inhalation or intramuscular injection could be used to treat the symptoms of Long-Covid once they appear.

It is difficult to estimate the number of subjects with long-COVID in any country or in the world. Since the diagnosis is by exclusion of other etiologies in patients who have recovered from COVID-19, some studies provide an incidence rate at various times after infection. The incidence generally decreases with time since primary infection, but, so far, never reaches zero. General estimates initially were that 37% to 50% of patients recovering from COVID-19 get long-Covid, but the current incidence may be lower. Some of the reported difference in incidence may be related to whether patients were hospitalized with severe COVID-19 or not, as severe disease is more likely to be followed by Long-Covid. The incidence of Long-Covid from the Omicron variant may be in the range of 4-5% of COVID-19 patients (37). Given the huge surge in cases globally due to the Omicron variant, the incidence of Long-Covid is expected to increase and potentially be a huge medical burden for years. Some 5% or more of patients now infected are likely to get the disease, on top of the 18 million estimated cases in the US (in 2022) and over 150 million cases globally.

For Marketing Projections see Appendix 2.

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APPENDIX 1 FACILITIES AND ORGANIZATION

EMPLOYEES

Cellastra has the highly qualified personnel in place to initiate the development program and potentially to submit an IND or CTA or both. The plan is to rely on contract manufacturing (CDMO) and research organizations (CRO) to conduct the required activities. Oversight of CDMO and CRO activities would require additional Cellastra personnel.

We are currently working with a recruiter in UK specializing in Gene and Cell therapy companies and have started interviews to identify candidates for CBO/COO position. The plan is also to seek young and experienced talent to secure future growth.

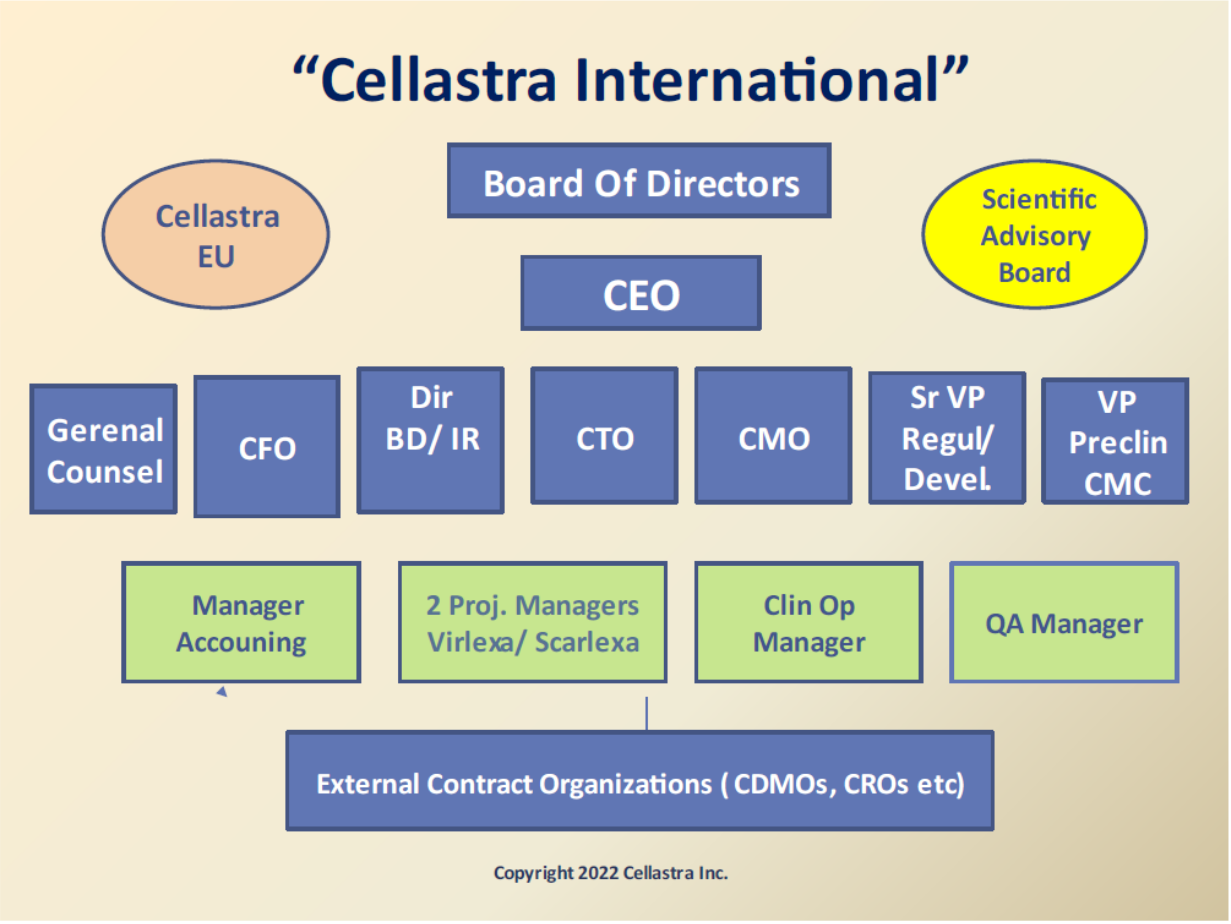
Expansion of Cellastra staff also might include the following positions to be added during the first year:

- VP or Director of CMC & Preclinical Regulatory Affairs (Gene therapy background)
- Manager of Clinical Operations Director or VP of Business Development (BD) Investor Relations (IR)
- Manager Quality Affairs (inspections and audits)
- Project Manager of Therapeutic Areas
- Executive Vice President R&D
- Administrative Assistant(s)

FACILITIES

Cellastra's headquarters at 201 Spear Street, Suite 1100, San Francisco, CA 94105. This is a premiere venue, with access to conference and meeting rooms and offices with flexibility to expand as needed. This is a convenient location in the midst of San Francisco Downtown Financial District about 1-2 blocks from Bart, Ferry Terminal and the new 4.2 B Transbay Terminal project. The building has Bay views, garage and is located next to the refurbished Embarcadero Promenade. The vendor also offers access to meeting rooms in more than 70 cities around the US.

ORGANIZATIONAL CHART



APPENDIX 2 MARKET PROJECTIONS

VIRLEXA

- VIRLEXA: Indication: Prevention of Long COVID in High-Risk Patients (may be expanded to other age groups later)
- US: Based on current CDC statistics (November. 2022 compare with November 2021) on average about 2 M cases / month and 24 M cases/year,
- Assuming similar recurrence pattern as for influenza
- A conservative projection is that on average there are 6 M high risk patients (25%) available annually
- Globally (based on WHO Statistics) there would be a minimum of 240 M cases and 60M high risk patients annually
- Capture Rate: 25%
- Paxlovid has a price tag of $500 for a five day treatment course and thus likely $1,000 for a two week treatment course.
- Assuming a price tag for Virlexa of $1,000/patient in US and $500 Globally, the US market has a market value of $1.5 B/Year. The global market would have a value of $7.5B/Year.

SCARLEXA – PREVENTION OF DERMAL SCARRING AFTER BURNS AND SURGERY – MAY BE OUTLICENSED

INDICATION 1: BREAST IMPLANT -PREVENTION OF DERMAL SCARRING AND INTERNAL CAPSULE CONTRACTION

- US: 270, 00 patients /Year in 2019 before the pandemic(American Society of Plastic Surgeons, 2020)
- Package price in US; 4, 10,000-15,000, includes implant, surgery and anesthesia, paid by the patient. Not reimbursable.
- Embrace silicon sheet developed at Neodyn, Stanford as an OTC product with limited documentation cost up to $84/month and $504 for 6 months.
- Capture rate of 33% and rice tag of $1,500 the US market has a value of $135M
- Globally: 1.5M patients/Year (International Society of Aesthetic Plastic Surgeons, 2020). With a capture rate of 33% and price tag of $1,000/patient the global market is $500 M/Year. AGR is 6.5%

Indication 2: C-Section - Prevention of dermal scarring and potentially internal adhesions as an add-on indication after long term follow-up}

- US: Currently 1.5M cases/Year (CDC 2022)
- Capture rate of 20 percent and a price tag of $500 the US market would be worth

$150M/ Year.

- Globally: 35M cases/Year (WHO, 2022). With a capture rate of 20 percent and a price tag of $500/ patient the lobal market would be worth $3.5B AGR is 6%

Indication 3: Breast reconstruction surgery – Prevention of hypertrophic scarring

- In 2018, there were about 101,000 such procedures in the US and 81% of them used breast implant (https://effectivehealthcare.ahrq.gov/products/breast-reconstruction-mastectomy/protocol). This indication represents a great humanitarian need and the procedure is reimbursed by according to Federal Law.
- As of 2016, >40% of women in the U.S. who underwent mastectomy had reconstruction.
- Immediate reconstruction is the most common practice in the U.S., selected for approximately 75% of patients compared with delayed reconstruction.
- Autologous reconstruction (AR) requires a larger operation than implant-based reconstruction, leads to greater scarring, and may lead to long-term sequelae in the area of flap harvest and to more major complications, such as wound dehiscence and delayed healing.
- Currently not part of our business plan