



# Creating Life Stories

Placental Cell Therapies By Pluristem



## Pluristem Therapeutics Inc.

(NasdaqCM: PSTI; TASE: PLTR) is a clinical-stage biotechnology company developing cell therapies for a variety of ischemic and inflammatory conditions. Pluristem's cell products are derived from placentas habitually discarded following childbirth. Pluristem collects and then expands placental-derived cells using a unique, proprietary, three-dimensional (3D) technology platform that enables the efficient, controlled production of commercial quantities of therapeutic PLacental eXpanded (PLX) cells. PLX cells act within a patient's body by secreting therapeutic chemokines, cytokines and growth factors in response to signals from inflamed and ischemic tissues. PLX cells are an off-the-shelf product that require no tissue matching prior to administration. Clinical data from 3 Phase I/II studies strongly suggest that PLX-PAD cells are safe and can significantly improve patient health.

Pluristem has a strong intellectual property position, 160-person team, strong balance sheet, and GMP certified manufacturing and research and development facilities of over 40,000 square feet. The company maintains strategic relationships with major pharmaceutical companies and research institutions around the globe.

## Vision

**To become the world leader in developing and manufacturing cell therapy products**





Did you know that  
me being born  
could help people  
all over the world?



### Pluristem's 3D Expansion Technology:

Pluristem's PLX cells are mesenchymal - like adherent stromal cells (ASCs) derived from full term placentas. These cells are expanded in Pluristem's proprietary bioreactors, which create a three-dimensional (3D) microenvironment to optimize cell expansion and modification.

Each bioreactor is at the heart of a fully automated and self-contained system. Multiple systems operate in parallel within the company's state-of-the-art, GMP-certified manufacturing facilities. The precisely controlled systems allow PLX cells to be mass-produced with batch-to-batch consistency for a fraction of the cost of the industry's standard method of expanding cells in petri dishes or tissue flasks.

### "The Process is the product"

Pluristem's 3D expansion technology allows for the production of different PLX cell products. These products are each derived from the same placental ASCs, but differ in their secretomes; the differentiation is accomplished by the strict manipulation and control of the cell's growth environment.

PLX-PAD, Pluristem's first product, is in clinical trials for cardiovascular, orthopedic and pulmonary indications. PLX-RAD, Pluristem's second product, is in pre-clinical development for hematological indications.



# Powered by Pluristem



Following child-birth, cells are extracted from the Placenta



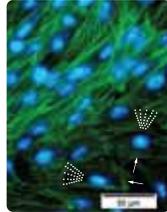
Cell growth in a proprietary platform in a State-of-the-art GMP manufacturing facility



PLX cells are frozen & stored, readily available for use



The proteins released by the PLX cells help the body heal itself, creating life stories



PLX cells release therapeutic proteins in response to signals within the patient's body



Point of care thawing device, to assure cells' quality, prior to administration



## Business Strategy:

Pluristem's goal is to provide patients, doctors and healthcare decision makers around the globe with "off-the-shelf", standardized, high quality, regulatory-approved PLX cell therapy products that need no matching prior to administration for a variety of inflammatory and ischemic conditions.

Our business strategy includes establishing partnerships with pharmaceutical companies for assistance in developing and marketing PLX cell products. These pharmaceutical partnerships include out-licensing agreements as was done with United Therapeutics Corp. (NASDAQ: UTHR) who licensed our PLX cells for the treatment of Pulmonary Hypertension. Additionally, Pluristem has collaborated with CHA Bio & Diostech (Kosdaq: CHA) for the development and commercialization of PLX cells for the treatment of intermittent claudication (IC) and

Critical Limb Ischemia (CLI). Commercialization with CHA will lead to a joint venture co-owned by CHA and Pluristem.

These relationships will leverage Pluristem's expertise in the efficient manufacture of high quality PLX cells using the company's proprietary, scalable, 3D cell manufacturing platform. This platform facilitates the cost-effective, mass production of PLX cells. Pluristem's strategy in negotiating collaborations is to retain control of the manufacture of our PLX cell products and associated intellectual property.

Pluristem believes the company's innovative research and development expertise in cell therapies combined with its high quality, efficient manufacturing technology will be the "engine" that drives this platform technology towards the successful development of many PLX cell therapy products.



# Pluristem's Product Candidate Pipeline:

Therapeutic Area	Indication	Phase	Partner	Global Market Potential
Cardiovascular	Critical Limb Ischemia (CLI)	Phase 1 complete	CHAVANCE License for South Korea	\$ 12B
	Intermittent Claudication (IC)	Phase 2 in progress	CHAVANCE License for South Korea	\$ 6B
	Buerger's Disease*	Phase 1 complete		\$ 1.5B
	Acute Myocardial Infarction (AMI)	Pre-Clinical		\$ 16B
	Diastolic Heart Failure	Pre-Clinical complete		\$ 8B
Orthopedic	Muscle Injury	Phase 2 efficacy complete**		\$ 1B
	Tendon Injury	Pre-Clinical complete		\$ 6B
Pulmonary	Pulmonary Hypertension	Phase 1 in progress	United Therapeutics License Internationally	\$ 3B
	Pulmonary Fibrosis	Proof of Concept complete		\$ 4B
Women's Health	Preeclampsia	Pre-Clinical complete		\$ 2.5B
Hematology	Acute Radiation Syndrome	Pre-Clinical in progress		\$ 1B
	Graft versus Host Disease (GvHD)	Pre-Clinical complete		\$ 0.25B
	Chemotherapy Induced BM Hypoplasia	Proof of Concept complete		\$ 0.5B
	Bone Marrow Transplant Failure***	Compassion Treatment complete		\$ 0.5B
Central Nervous System (CNS)	Neuropathic Pain	Pre-Clinical complete		\$ 3B
	Ischemic Stroke	Pre-Clinical complete		\$ 8B
	Multiple Sclerosis	Proof of Concept complete		\$ 8B

\*CLI Phase 1 (IIa) trial data support proceeding directly to Phase II

\*\*Phase 2 efficacy completed, safety ongoing

\*\*\*Compassionate Use Treatments-Human Data

Proof of Concept | Pre-Clinical | Phase 1 | Phase 2 | Phase 3 | Market

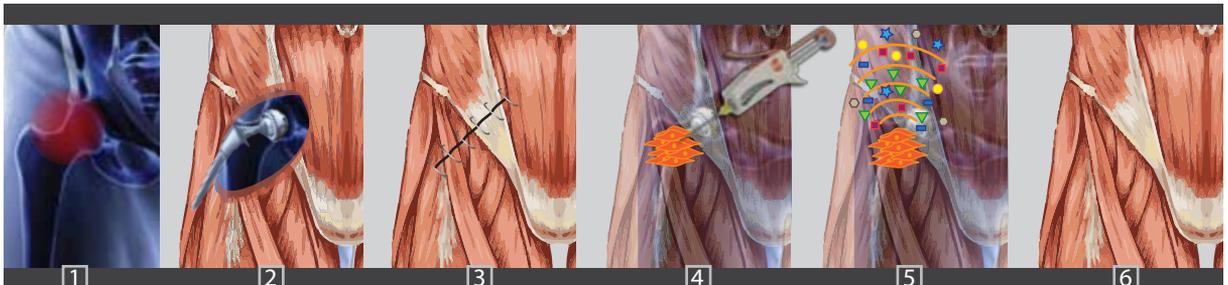
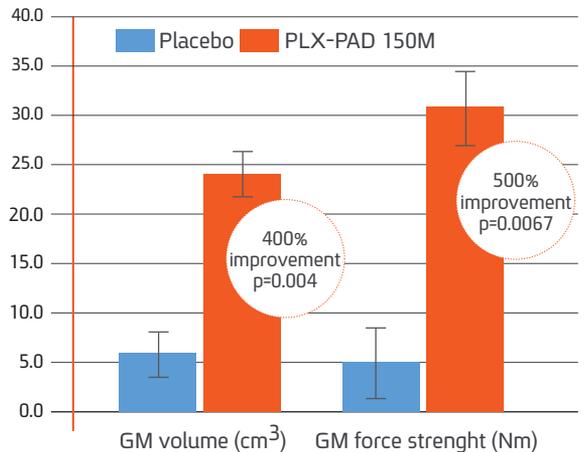
FDA orphan drug status designation, Buerger's Disease & Aplastic Anemia

## Validation of PLX Platform:

**Orthopedic Diseases & Sports Medicine** – In a 20 patient, randomized, double-blind, placebo-controlled Phase I/II trial conducted in Germany, PLX cells met both primary endpoints. First, the cells were demonstrated to be safe. For the primary efficacy endpoint of the study, which was the change in the maximal voluntary isometric contraction force of the gluteal muscle at six months after total hip replacement, both PLX-PAD treated patient groups showed efficacy, with the group receiving the 150 million cell dose displaying a statistically significant 500% improvement over the placebo group ( $p=0.0067$ ). Patients treated at the 300 million cell dose showed a 300% improvement over the placebo ( $p=0.18$ ).

An analysis of the macrostructure of the gluteal muscle using magnetic resonance imaging (MRI) indicated an increase in muscle volume in those patients treated with PLX-PAD cells versus the placebo group. This efficacy endpoint was demonstrated in both PLX-PAD treated patient groups, with the group receiving the 150 million cell dose displaying a statistically significant superiority over the placebo group. Patients treated at the 150 million cell dose showed an approximate 300% improvement over the placebo in the analysis of muscle volume ( $p=0.004$ ). Patients treated at the 300 million cell dose showed an approximate 150% improvement over the placebo in the change of muscle volume ( $p=0.19$ ).

**Table 1:** Change of Maximal Contraction Force and the Muscle Volume of Gluteal Muscle (At 6 months)



**Diagram 1:** Proposed Mechanism of Action (MOA) Muscle Injury

HGF ★ IL-8 ■ VEGF ● Angiogenin ▼ IL-10 ○ IL-6 ■

1. Degenerative arthritis of the hip
2. Hip replacement surgery
3. Suturing of the gluteal muscle
4. Administration of PLX-PAD cells into the injured muscle
5. PLX-PAD cells receive inflammatory and regenerative signals from the injured muscle,

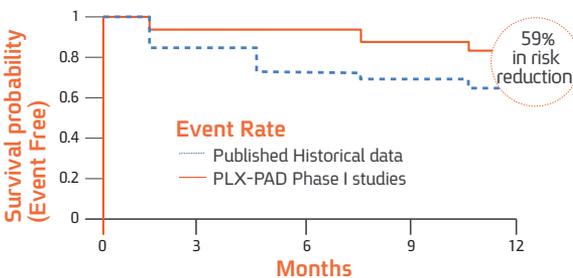
secretes pro-angiogenic, immuno-modulatory and trophic factors causing paracrine effect (on neighbouring cells) and endocrine effect (on distant tissues through the blood stream)

6. Increase of muscle volume and strength, following PLX-PAD treatment

**Cardiovascular Disease** - Treatments for the entire spectrum of peripheral artery disease (PAD) from early stage intermittent claudication (IC) to Buerger's disease and Critical Limb Ischemia (CLI) are being investigated.

Two Phase I/II safety/dose-finding clinical trials at multiple sites in the U.S. and Germany for CLI demonstrated that PLX-PAD cells were safe, even if two doses are given to patients from the same placental source, and that no matching is required prior to administration. Also, PLX-PAD cells were found to potentially be effective in reducing the incidence of amputation in CLI patients. The FDA and EMA require the primary endpoint for pivotal CLI clinical trials to be Amputation Free Survival (AFS) at one year. In our studies, an AFS rate of 85% was observed which contrasts to a 66% historical rate.

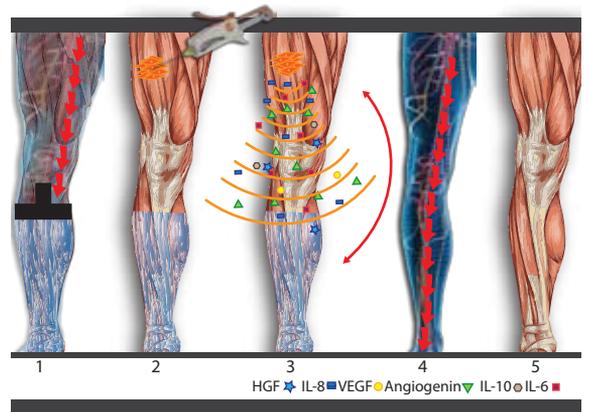
**Table 2:** Cumulative Event-Rate Comparison



Following our successful Phase I/II trials in CLI, a 150 patient placebo-controlled, double-blind, randomized, dose escalating trial in the U.S., Europe and Israel in IC is currently underway. PLX-PAD cells are given intramuscularly (IM) into the patient's afflicted limb. The twelve-month endpoint for the study will be

the distance the patient is able to walk on a treadmill. Additionally, CHA Bio & Diostech has received regulatory approval in South Korea for a Phase II study using PLX-PAD cells in the treatment of IC and intends to pursue South Korean regulatory approval for a phase II/III CLI study using PLX-PAD cells.

**Diagram 2:** Proposed Mechanism of Action (MOA) ) Peripheral Artery Disease (PAD)



1. Blood vessels' occlusion below the knee leads to lower leg ischemic condition
2. PLX-PAD cells are administered IM to the injured limb and signals from both the ischemic tissues and the cells are generated
3. In a response to the environmental stimuli, PLX-PAD secretes pro-angiogenic, immuno-modulatory and trophic factors that reach the ischemic organ via the blood stream
4. The blood supply to the lower leg is restored
5. The ischemic leg regenerates, following PLX-PAD treatment

**Pulmonary Diseases** - Pluristem has out-licensed the company's PLX-PAD cells to United Therapeutics Corp. (NASDAQ:UTHR) for the indication of Pulmonary Hypertension (PH). Pre-clinical studies have been completed and regulatory approval has been obtained to initiate a Phase I trial using PLX-PAD cells intravenously (IV) in Australia.

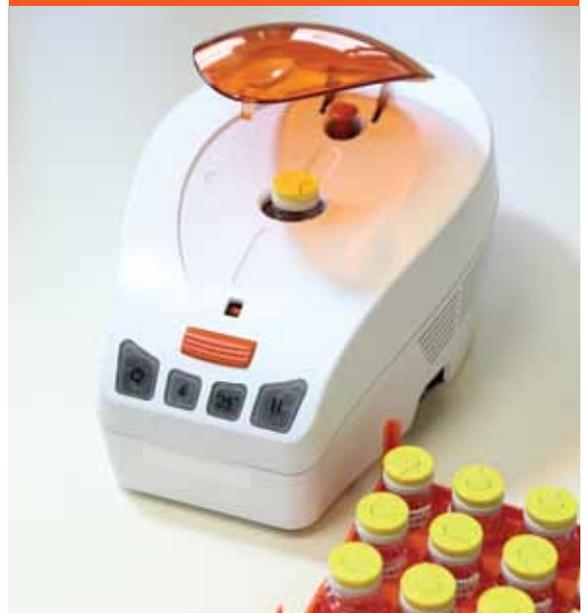
Favorable pre-clinical studies have also been conducted for the indication of pulmonary fibrosis.

**Hematological Diseases** - Following positive data from the use of PLX cells in animals and humans in stimulating hematopoiesis in diseased or injured bone marrow, Pluristem intends to pursue the development of PLX-RAD for enhancing the engraftment of Hematopoietic Stem Cells (HSCs) after allogeneic bone marrow transplantation (BMT). Additionally, via a relationship with the National Institute of Allergy and Infectious Diseases (NIAID), a Division of the Department of Health and Human Services, National Institutes of Health (NIH), PLX-RAD cells are being evaluated for the treatment of Acute Radiation Syndrome (ARS). Following positive animal results, NIAID has recommended extending and expanding the scope of their investigation towards developing our PLX-RAD cells as a treatment for ARS. Favorable pre-clinical studies have also been conducted for the indication of Graft versus Host Disease (GvHD) following BMT.

**Women's Health (Preeclampsia)** - Following successful preclinical studies using PLX-PAD in animal models of preeclampsia, Pluristem plans to file for regulatory approval to begin a Phase I/II study.

### Regulatory and Clinical Affairs Strategy

Pluristem's development strategy is to hold open discussions with regulators at all stages of development from pre-preclinical trials to the more advanced regulatory stages. Pluristem utilizes this strategy in working with the U.S. Food and Drug Administration (FDA) as well as the European Medicines Agencies (EMA), Germany's Paul Ehrlich Institute (PEI), and the Israeli Ministry of Health. In addition, Pluristem's partners expand the regulatory strategy in working with Australian and South Korean regulatory authorities.





### Intellectual Property:

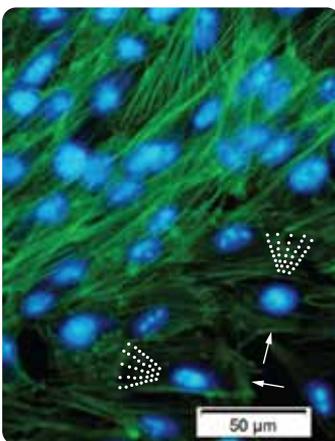
Pluristem's IP portfolio currently includes 27 issued patents and over 100 pending patent applications. Pluristem has developed a four-tier strategy to protect its IP. The base tier includes the purchase of the core patent surrounding the company's 3D cell expansion technology initially developed at the Weizmann Institute of Science and the Technion-Israel Institute of Technology. Further patent applications have been filed based on the company's advances in the 3D expansion technology for ASCs. These include methods of culture as well as dedicated instruments in support of the company's cell manufacturing and delivery plan. The second tier relates to the company's filing of "composition-of-matter" patent applications surrounding the unique PLX cells produced by the company's 3D expansion technology. The third tier consists of the filing of patents surrounding the unique instruments and devices invented by Pluristem and the fourth tier consists of the filing of "method of treatment" patents surrounding the therapeutic use of Pluristem's PLX cells for different indications.

### Pluristem's Advantages:

- 3 Phase I/II clinical studies confirmed safety and efficacy of the PLX-PAD cells
- PLX cells are a drug delivery platform that releases numerous therapeutic proteins effective for a variety of inflammatory and ischemic medical conditions
- Pluristem's novel, proprietary 3D expansion technology permits the manufacture of different PLX products such as PLX-PAD and PLX-RAD. These "tailored" PLX cell products possess specific secretomes with unique anti-inflammatory, angiogenic, tissue regeneration and/or cytoprotective properties
- Utilizing this 3D expansion process, Pluristem is able to manufacture commercial quantities of PLX cells at a fraction of the cost of growing an equivalent number of cells in the traditional "2D" approach
- PLX cell administration requires no donor-patient matching and is an off-the-shelf product
- Comprehensive IP coverage (27 granted patents & over 100 pending applications)
- Clinical development plans recognized by the FDA, Germany's Paul Ehrlich Institute (PEI), the Israeli Ministry of Health, the Korea's Ministry of Food and Drug Safety, and the Australian authorities
- GMP certified manufacturing facilities that enable batch-to-batch consistency and the capability for mass production of PLX cell therapies
- Strong balance sheet

Readily Available  
Cell Therapies





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