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# Smart cells that heal

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## Innovative Israeli cell therapy could step up treatment of CLI.

Lars Norgren, emeritus professor at Örebro University in Sweden, and a member of the CLI study steering committee; Prof. Nikol Sigrid senior consultant of the Department of Clinical and Interventional Angiology at the St. Georg Asklepios Hospital in Hamburg, Germany and Pluristem co-CEO Zami Aberman. (photo credit: Courtesy)

Imagine if every time you walked, climbed the stairs or exercised, you experienced burning pain of the lower leg or feet. And what if this throbbing continued even when you sat down or slept?

This is the painful reality of some 8.5 million Americans, including 12-20% of individuals over the age of 60, who are suffering from peripheral arterial disease (PAD), according to the Centers for Disease Control and Prevention.

PAD is caused by fatty deposits in the leg arteries that obstruct blood flow. The disease is often a result of smoking, diabetes, heavy weight, cardiovascular problems or hypertension. According to Prof. Sigrid Nikol, senior consultant of the Department of Clinical and Interventional Angiology at the St. Georg Asklepios Hospital in Hamburg, Germany, two-thirds of diabetic patients that she sees develop vascular diseases.

PAD is a chronic disease. In the beginning, the clinical signs and symptoms include pain after walking short distances, which are relieved at rest. This is known as intermittent claudication or IC. Eventually, it can progress to the ominous stage of critical limb ischemia (CLI), characterized by severe pain at rest, non-healing skin wounds, tissue necrosis, and poor quality of life, with a high risk of amputation and likely even death. Between five million and six million patients in the US and Europe suffer from CLI.

But now, PAD patients might have new hope, thanks to the work of a Haifa-based biotherapeutic company, Pluristem Therapeutics.

In January, leading physicians and clinical trial teams from Europe were in Israel for Pluristem's most recent Phase III clinical trial to help those suffering from CLI. This new

trial is testing Pluristem's PLXPAD cellular therapy on 246 American and European patients. The trial, paid for in large part by the European Union, is focused on using PLX-PAD to treat CLI patients with tissue loss that are unsuitable for revascularization, either because of their vessel anatomy, or because they are too ill. According to the European Society for Vascular Surgery, up to 40% of patients are unsuitable for revascularization and experience up to a 40% amputation rate after one year.



*Lars Norgren, emeritus professor at Örebro University in Sweden, and a member of the CLI study steering committee; Prof. Nikol Sigrid senior consultant of the Department of Clinical and Interventional Angiology at the St. Georg Asklepios Hospital in Hamburg, Germany and Pluristem co-CEO Zami Aberman. (photo credit: Courtesy)*

Some 246 patients are taking part in the multinational study from Germany, England, the US, Poland, Hungary, Czech Republic and Austria. Patients are receiving multiple intramuscular injections in the affected leg twice at eight-week intervals, with a randomization ratio of 2:1.

Pluristem CEO Zami Aberman explained that PLX-PAD cells are extracted from the placenta in Pluristem's proprietary platform located in the company's manufacturing facility in Haifa. The PLX cells are then frozen and stored, readily available for use, requiring no tissue or genetic match between the cells and the patient. The secreted proteins, administered through intramuscular injections, initiate a self-healing process in the patient's body.

"The PLX-PAD cells are smart cells with the ability to sense the needs of the patients and respond," said Aberman. "PLX-PAD was found to reduce inflammation, stimulate the growth of collateral blood vessels, and stimulate the repair of damaged muscles in patients with PAD."

“Most importantly, there are indications that treatment with PLX-PAD may prevent amputation and ultimately death,” said Lars Norgren, emeritus professor at Örebro University in Sweden, and a member of the CLI study steering committee.

“Simply put, an amputation-free survival is what we hope for and expect,” Norgren said, “Whether Pluristem’s approach is the best remains to be proven,” said Norgren, “but I am optimistic.”

Norgren said that today there is no medical treatment that doctors know of that heals CLI, though many attempts have been made. For example, previous research indicated that autologous stem cell therapy – when the cells are taken from the patient’s body and reinjected into his or her leg – looked promising in pre-clinical trials. But when Phase III trials of autologous stem cell therapy took place, the solution failed.

Nikol, who was involved in these autologous studies, said she believes one of the reasons that autologous stem cell therapy did not work is that these cells were being taken from patients who were already sick.

“The progenitor cells in these patients is low – for sure lower than in healthy patients,” said Nikol. A progenitor cell is a biological cell that, like a stem cell, tends to differentiate into a specific type of cell, but is already more specific than a stem cell and is pushed to differentiate into its “target” cell.

She said the other problem with autologous therapy is that the cell extraction is a procedure that puts the patient at risk. Doctors don’t have control over the extracted cells, which means that this procedure could lead to infection or other safety risks, Nikol said.

One reason Pluristem’s PLXPAD cell therapy is so desirable is that the placenta cells being used in the therapy are better quality, said Norgren. The cells are derived from the placentas of young, healthy women following fullterm delivery. These cells can be stored for years and administered to patients via a very standardized procedure that does not put them at risk, said Nikol. Further, said Norgren, Pluristem’s cells can be administered off-the-shelf without tissue matching.

This newest Phase III study comes on the heels of a Phase II IC clinical trial, which included partners in the United States, Europe, Israel and South Korea.

The Phase II trial included 172 patients, of whom some 30% received placebo treatment. The other 70% received courses of PLX-PAD intramuscularly three months apart. The results of that study are expected to be published around June this year.

“We are seeing many regulators around the world trying to fasttrack therapies like PLX-PAD because they want to get these products to the market for patients that really have no other medical solution,” said Aberman.

In addition to these two clinical trials, Pluristem was also recently accepted into the US's FDA expanded access program, which allows Pluristem to treat patients with this serious, life-threatening condition who do not meet the enrollment criteria for the clinical trial in progress.

Pluristem has generated hope for all patients who currently have no other medical solution, said Aberman "I'm excited," said Norgren. "They have found something new, and this is perhaps the way to go."

*This article was written in cooperation with Pluristem Therapeutics.*