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Translational Research Informatics Center (TRI)

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CD34-Positive Cell Therapy for Patients with Critical Limb Ischemia

The Translational Research Informatics Center (TRI) was founded in 2002 as the first data centre in Japan to promote academia-originated medical innovation. The Academic Research Organization (ARO) network was established in 2013 by TRI and is transforming into an Asian ARO network in conjunction with Korea, Taiwan and Singapore. We plan to expand the network globally to Europe and the United States. Our aim is to develop an infrastructure to support the launch of global clinical trials of academia-originated projects and to obtain regulatory approval worldwide.

Peripheral arterial disease (PAD) is commonly referred to as ischemia (or reduced blood supply) of extremities secondary to arterial occlusion due to atherosclerosis (thickening of the artery wall). An additional cause of PAD is vasculitis, such as thromboangiitis obliterans (also known as Buerger's disease), which can also lead to severe limb ischemia. As a consequence of changes in lifestyle, such as diet, the number of patients with arteriosclerosis obliterans (ASO) increased by 23.5% between 2000 and 2010. Globally, there are more than 200 million people living with a spectrum of PAD symptoms that range from asymptomatic to critical. Because patients with ASO frequently present with coronary artery disease and cerebrovascular disease, which affects the blood supply to the brain, ASO should be considered to be a part of polyvascular disease. Critical limb ischemia (CLI) is defined as the most advanced stage of lower limb ischemia. The clinical manifestations comprise rest pain and/or skin ulceration or gangrene, which can lead to the amputation of a limb. In addition, CLI patients are at high risk of cerebrovascular and cardiovascular complications, leading to disease or death. The mortality and major amputation rate 12-months after diagnosis with CLI are reported to be 25% and 30%, respectively. Despite the development of surgical bypass techniques or endovascular intervention, conventional revascularization therapies are not indicated or effective in a significant number of CLI patients. The development of novel strategies to enhance the recovery of blood flow in ischemic limbs is urgently needed for patients with CLI.

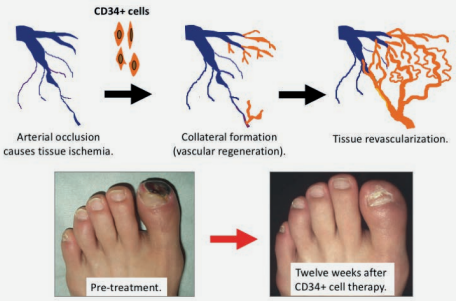

Figure 1. CD34+ cell therapy for critical limb ischemia.

A study[1] published in 1997 identified endothelial progenitor cells (EPCs), which are somatic stem/progenitor cells for vascular regeneration, in adult human peripheral blood as CD34 antigen-positive (CD34+) cells. The primary source of EPCs is bone marrow. EPCs are mobilized from bone marrow into peripheral blood and are incorporated into ischemic tissue for the formation of new blood vessels. The discovery of EPCs guided the development of stem/progenitor cell-based therapies for ischemic cardiovascular diseases. Since then, bone marrow or peripheral blood EPCs have been pre-clinically applied for ischemic cardiovascular diseases including PAD. The promising results from experimental studies in rodents encouraged many investigators to initiate clinical trials.

In a phase I/IIa clinical trial, our group evaluated the safety and feasibility of granulocyte colony stimulating factor (G-CSF)-mobilized CD34+ cells in no-option patients with ASO or thromboangiitis obliterans representing CLI (**see Fig. 1**). CD34+ cells were isolated from a G-CSF-mobilized apheresis product using a magnetic cell sorting system and were then intramuscularly transplanted in a dose-escalating manner into 17 patients (10^5 cells/kg, n=6; $5x10^5$ cells/kg, n=8; or 10^6 cells/kg, n=3). No serious adverse events relating to the cell therapy were observed. For the first 12 months following the cell therapy there were no patient deaths or major limb amputations. The ratio of CLI-free conditions indicating no risk of amputation is generally 25% for 12 months after the initial treatment for CLI. However, the CLI-free ratio was as high as 88% 12 months after the CD34+ cell therapy[2]. A long-term follow-up study showed that the safety and efficacy of CD34+ cell therapy was sustained for up to four years after the initial treatment. The CLI-free ratio was still more than 80% in the fourth year following the treatment[3]. Our phase IIb clinical trial mostly reproduced the favorable clinical outcomes in the phase I/IIa trial, confirming the safety, feasibility and potential effectiveness of CD34+ cell transplantation in CLI patients[4].

Following encouraging experimental results, a phase II/III, multicenter, randomized, clinical trial of CD34+ cell therapy for CLI is in preparation. The clinical trial notification has been accepted by the Pharmaceutical and Medical Device Agency in Japan.

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