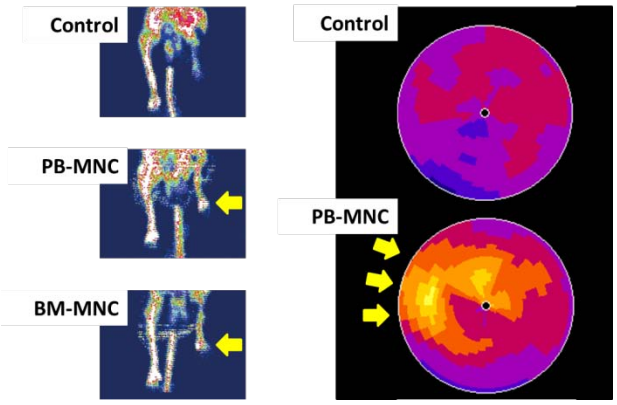
Therapeutic Neovascularization for Severe Ischemic Heart / Limb diseases

Overview

Cardiovascular ischemic diseases are the leading cause of morbidity and mortality in the industrialized world despite the considerable evolution of medicine in this field. Meanwhile great progress has been made in our knowledge of the physiology and pathology relating to how blood vessels are formed in ischemic tissues. Thus, therapeutic angiogenesis has been developed as a way to ameliorate ischemic burden with the use of growth factors or angiogenesis-promoting cells.

Our Bench-to-Bedside Approach in 2001

In 2001, when we started our first approach to develop therapeutic angiogenesis, most research focused on endothelial progenitor cells (EPC), the bone marrow-derived cells that are capable of differentiating into vascular endothelium. Transplantation of Bone marrow mononuclear cells (BMMNC) or Pharmacologically-mobilized peripheral blood stem cells (PBSC) were beginning to show efficacy as therapeutic angiogenesis in numerous animal models. But we interpreted [?]these results differently. Although some of these cells may become endothelial cells, most of them would stay as immune cells that are capable of producing various pro-angiogenic growth factors. We found that peripheral blood mononuclear cells (PBMNC) had such paracrine effect comparable to that of BMMNC, resulting in excellent capacity to induce neovascularization in animal models of hind limb or myocardial ischemia. Because we thought it risky to take out BMMNC from, or to administer stem cell-stimulating factors into, severely ill patients, we decided not to stick to stem/progenitor cell theory, and instead applied naïve PBMNC as a therapeutic tool.



PBMNC for Critical limb ischemia: a Clinical Trial

In 2002, we started a clinical trial of autologous PBMNC implantation for patients with critical limb ischemia (CLI). Our early cases showed the feasibility of PBMNC therapy to relieve severe rest pain and ischemic ulcers (Minamino et al. Lancet 2002). A Phase I/II trial that recruited 26 patients showed excellent outcomes (Tateno et al. Circ Res 2006), in that nearly 70% of the patients experienced improvements in their ischemic burdens without being exposed to any severe adverse events. From these results, PBMNC therapy was approved by the Japanese Ministry of Health, Labor and Welfare as a type of Highly Advanced Medicine. Also, we started a randomized-crossover clinical trial of PBMNC therapy for patients with severe intermittent claudication. A phase-I/II dose escalation trial of PBMNC for un-graftable coronary artery disease is also ongoing. CAM, equipped with a GMP-quality Cell Processing Center, is at the center of the trial

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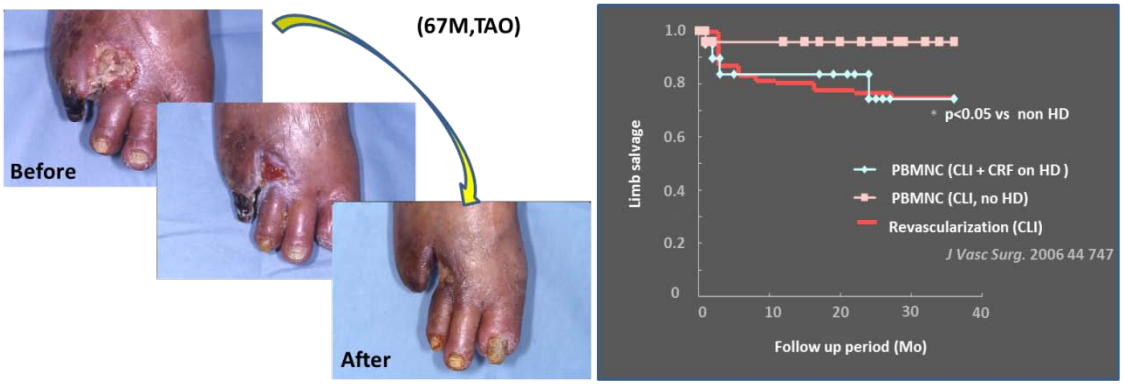
In 2008 we reported on the long-term efficacy of PBMNC for CLI (Moriya et al. Circ. Cardiovasc. Interv. 2009). Altogether, 42 patients (34 men, 8 women; average age 61 +/- 14 years) underwent 94 transplantations. Early phase (~6 months) success, defined by improvement in either rest pain, ischemic ulcer, or walking distance, was achieved in 76% (32/42) of the patients. During the long-term follow-up (average 30+/- 10 months range 6-50 months), 85% (17/20) of the responding patients did not experience relapse of ischemic ulcers, and 89% (23/26) remained rest pain free.

Limb salvage was 91% (4/42) at 6 Mo, and 97% (33/34) during the late follow-up period. These outcomes were comparable to that of conventional revascularization therapy. Thus, we believe PBMNC can be a good choice for those patients who are not eligible for revascularization strategies.



How can we improve clinical efficacies? From Bedside-to-Bench investigations

From our clinical data, we found that angiogenic growth factors and cytokines in the serum, including VEGF and IL-1beta, increase transiently after cell transplantation, and that these elevations correlate very well with clinical outcomes. If we could see how these factors increased after the cell therapy, it would be a good clue to improve the clinical efficacies. So we decided to go back to the bench (Tateno et al. Circ Res 2006).

With IL-1be-ta KO mice, we found that many of the angiogenic factors are produced by muscle tissue. Bone marrow or muscle cell transplantation experiments showed that growth factors produced by muscle cells determine the fate of the ischemic limb. From in-silico and in-vitro investigations we learned that factor Y, which is a trans-membrane receptor found in muscle and vessel cells, might play a pivotal role. Mice lacking factor Y in their muscle tissue did not respond to PBMNC transplantation.

Now that we found a key molecule… From Bench-to-Bedside investigations

Strikingly, factor X, the ligand for the receptor Y, was found to be attenuated in PBMNC of the non-responding patients. This strongly suggests that either factor X or factor Y or bothcould be novel therapeutic target(s) to treat non-responding cases. To verify these results, and to pave the way for upcoming translational research, we are making full use of CAM's resources. Our experience is a good example of how CAM may serve to promote advanced medicine by integrating clinical practice and outstanding basic research.