2026 ICVBM / CMMRF Update

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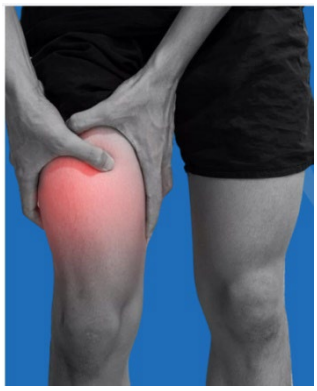
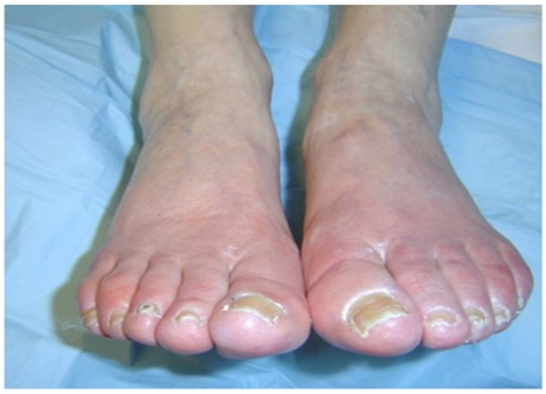
1. **Peripheral Arterial Disease (PAD)**.
    a. PAD is caused by hardening of the arteries of the leg due to build up of atherosclerotic plaque. This plaque eventually limits blood flow to the muscle and skin of the leg causing pain, and in more severe cases, gangrene of the foot. PAD presents in three different scenarios: asymptomatic, claudication (pain in the calf muscles with walking), and chronic limb threatening ischemia. PAD is more common than coronary artery disease in the US and affects 8.5 million Americans and 202 million people worldwide. With the rise in diabetes the number of patients with PAD is increasing.
    b. ***BREAKTHROUGH***! Our pioneering work in cell therapy to prevent leg amputations in patients with severe PAD has led to approval of using autologous[1] bone marrow cells in patients with all forms of PAD in Europe. This effort was a result of a collaboration with the ICVBM, support from the CMMRF, and an industry sponsor, Zimmer-Biomet Inc. (Warsaw, IN) who developed the MarrowStim™ device that can separate the stem cell fraction from a patient's own bone marrow. Safety of using autologous bone marrow cells was established in the landmark MOBILE Trial, a multicenter study led by the ICVBN. The MarrowStim™ product will be available in Europe to all patients with PAD and we are working with Zimmer-Biomet to obtain US Food and Drug Administration approval in the US.
    c. **Claudication** is the most common form of PAD and represents about 35% of the PAD population. Claudication is pain in the muscle of the leg when walking as the exercising muscle does not get enough oxygen due to decreased blood flow. Characteristically this pain goes away when the patient rests. About 20% of Americans suffer from claudication and it has a significant negative impact on quality of life and work productivity. The ***current recommendations*** by the American Heart Association and the Society for Vascular Surgery for treating patients with claudication is risk factor management, which is stopping smoking, controlling blood pressure, and treating cholesterol with a statin medication. Surgical bypass and angioplasty are ***not recommended*** as first line treatment because these interventions are associated with complications (wound infection,



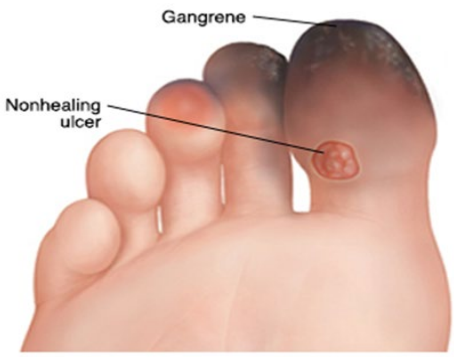
[1] Definition: autologous; adjective; derived from the same individual; involving one individual as both donor and recipient.

bleeding, pain) and ultimately fail leaving the patient with worse blood puts the patient at risk for an amputation. Currently, there are no effective treatments to improve the symptoms of patients with claudication. At the Indiana Center for Vascular Biology and Medicine we participated in the PACE Trial (Patients with Intermittent Claudication Injected with ALDH Bright Cells) through the National Institutes of Health. This multi-center trial showed an improvement in walking distance in the cell treated group, however it was not significant when compared to the placebo group. Thus, the ICVBM is testing induced pluripotent stem cells (iPSC) that have the to stimulate new blood vessel growth for the next generation clinical trial.

d. Chronic limb threatening ischemia, (CLTI), is the most severe form of PAD and is characterized by foot pain and tissue loss (gangrene. CLTI is a significant risk for amputation of the leg and has a quality of life equivalent to terminal cancer.



Rest Pain



Tissue Loss

e. Surgical interventions have provided excellent results in treating CLTI however up to 30% of patients with CLTI will not be candidates for angioplasty or bypass and the only treatment option for relief of pain or removal of an infected ulcer is amputation. Over 153,000 amputations are performed each year ranking as the 6th costliest operation at 10.6-billion-dollar expense to our health care system.

f. Diabetic patients are especially at risk for limb amputation due to infection and more extensive hardening of the arteries. The incidence of diabetes and its vascular complications continues to rise each year.

g. The American Heart Association has recently noted that amputations due to PAD and diabetes has increased over the past ten years. The AHA issued a policy statement that there needs to be an international effort to reduce amputations by 20% by the year 2030.

h. With the support of the CMMRF the ICVBM is addressing the critical need for effective therapies to prevent amputations and has been the international leader in this field, beginning with the landmark MOBILE trial over twenty five years ago.

i. With research funds we have created two polygenic diabetic mouse models of CLTI and we are testing new cell types and preparations, In addition, we have been able to purchase specialized equipment that can measure leg muscle strength and walking function in mice, thus providing a more comprehensive analysis of the effects of mesenchymal stromal cell therapy.

j. With the Mason's research funds, we have purchased the Buchi Encapsulator. This device encapsulates cells [2]which protects them from getting cleared by the recipient's immune system yet still allows the cells to secrete growth factors that stimulate new blood vessels to grow.

k. A recent paper in Nature Medicine showed that encapsulated human islet cells when injected into a diabetic mouse survived for 175 days and controlled the mouse's blood sugar.

l. We plan to use this encapsulating shield for our MSC spheroids. If the cells can survive longer, they may be more effective in restoring blood flow to the leg and promote wound healing.

m. What is even more exciting is that the Buchi encapsulator is a sterile system and thus whatever we create can be used in humans in clinical trials.

n. This $90k investment for the Buschi device produced preliminary data to support a new 5-year National Institutes of Health research grant for $3.7 million dollar grant " *Human Vertebral Body Mesenchymal Stromal Cells from Organ Donors For Limb Preservation in a Murine Model of Diabetic Hindlimb Ischemia."* This is an excellent return on the CMMRF investment.

o. Working with a biotechnology company from Australia, Cynata Therapeutics, the ICVBM has received approval from the US Food and Drug Administration to use their iPSC mesenchymal stem cells in clinical trials to prevent amputations in CLTI.

2. **Abdominal Aortic Aneurysms**.

a. Abdominal Aortic Aneurysms (AAA) are a pathologic dilatation of the aorta, the main blood vessel from the heart, that leads to rupture and death if untreated.

b. AAA is the 13th leading cause of death in the U.S. but its incidence is probably much higher as it has no symptoms until it ruptures. Of those patients who rupture half die before reaching the hospital, half will die after emergent surgery, so that ruptured AAA has a 75% mortality rate.

c. Approximately 200,000 new AAAs are diagnosed each year and surgical repair is indicated only when the AAA grows to a diameter of 5.5 cm. Thus, many patients with smaller AAA's must wait

[2] Mesenchymal stem cells but also other cell types, such as beta cells that secrete insulin and can control diabetes.

for years before repair and describe it as if having a ticking time bomb in their abdomen.

d. There are no current medical strategies to prevent or suppress AAA expansion and rupture to avoid surgery
e. The ICVBM completed a First in Man clinical trial in which veterans with small AAA's were given anti-inflammatory stem cells to see if this would prevent the AAA from getting larger. The trial reached its declared primary endpoint showing a significant increase in the "good" regulatory T-cells and a decrease in the "bad" Th17 cells. Also, the study showed the patients in the high cell dose group had a reduction in aneurysm volume! The study was hoping to show that MSCs merely slowed the growth of the aneurysm but this data suggests that high doses of MSCs may cause the aneurysm to shrink. This is a major breakthrough and the results have been presented in a plenary lecture at the annual conference of the Society of Vascular Surgery and the American Heart Assoiciation, from which we have received several prestigious awards**.**
f. Based on these results we are designing a larger Phase II multi-center clinical trial.
g. We have demonstrated that those aortic aneurysms are a result of an auto-immune response to proteins in the aorta, specifically to a protein called elastin. Working with collaborators at Northwestern University we are using state of the art nanoparticle technology that will in essence be a "reverse vaccine" that will prevent patients from developing this immune response and prevent aneurysms from even starting.
h. Dr. Leckie has also invented a skin test that may identify patients at risk for AAA before the aneurysm actually develops. This will allow treatment to suppress aortic inflammation and prevent the AAA from starting.
i. We are working with a company for a skin patch that will prevent these immune responses that cause AAA formation.