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Correction of Ischemia with p53 Inhibitors: A Novel Therapeutic Approach to Induce Arteriogenesis

Summary

Severe obstruction of the arteries and reduced blood flow (critical limb ischemia (CLI)) is the advanced stage of peripheral artery disease (PAD). Investigators at UMB have found that Pifithrin-α, a p53 pharmacological inhibitor, improves limb perfusion in diabetic animals, suggesting a therapeutic role in CLI. Tumor-suppressing protein p53 mediates anti-angiogenic and anti-proliferative cellular responses to hypoxia, including cell-cycle arrest, cell aging, and apoptosis.

Key Investigator

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Field

Cardiovascular

Technology

P53 inhibitor to mediate critical limb ischemia

Advantages

Novel drug approach to improve limb perfusion

Status

Available for licensing
Sponsored research

Patent Status

US 14/617,149

UMB Docket Reference

RS-2013-040

Market

PAD is estimated to affect 8-12 million Americans and over 200 million worldwide. The number of PAD cases is expected to grow as the population ages and the prevalence of diabetes, obesity, and cardiovascular disease increases. Arteriogenesis or enlargement of pre-existing muscular arteries is the primary mechanism for increasing blood flow in tissues after arterial occlusion. Despite bypass surgery and the use of angioplasty/stenting, more than 100,000 limb amputations are performed annually in the US. As shown in the figure below, vascular disease or dysfunction accounts for a majority of the amputations performed in the US. Standard cardiovascular medications such as anticoagulants, antiplatelet agents, and statins prescribed to reduce the progression of the disease. Endovascular treatments and arterial surgery are the current treatments for CLI. Approximately 600,000 coronary angioplasties and 3.2 million diagnostic and therapeutic peripheral angioplasties are performed every year in the US (American Heart Association, 2007). As a last recourse, amputation may be required. Amputation occurs in about 25% of all CLI patients.

Technology

A method for treating diabetic induced ischemia through the administration of p53 inhibitors (e.g., Pifithrin-α) is described. Clinically relevant *in vivo* mouse models of diabetes and arterial occlusion have shown that p53 negatively regulates enlargement of collateral arteries in response to arterial blockage. The key findings that illustrate the role of p53 as a novel target for correction of diabetic ischemia include:

1. p53 is upregulated in ischemic tissue following hind limb ischemia (HLI) in mice.
2. p53 negatively regulates ischemia-induced angiogenesis and arteriogenesis.
3. Pharmacological augmentation of p53 (with quinacrine) impairs ischemia-induced neovascularization.
4. p53 protein expression is augmented in an experimental model of hyperlipidemia and diabetes following HLI.
5. Administration of the small molecule inhibitor of p53 (pifithrin) systemically markedly improves limb perfusion in diabetic animals.
6. p53 suppresses fluid shear stress-mediated blood flow restoration following arterial occlusion.

Pifithrin nanoparticles are being developed to be used in injectable intramuscular or intra-arterial formulation or as an oral medication. The use of p53 inhibitors could be combined with other therapies, and there is no known direct competition in the clinic.

Technology Status

Pifithrin has been tested in animal models of diabetes and hindlimb ischemia.

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