MEDICAL COLLEGE OF WISCONSIN
Office of TECHNOLOGY DEVELOPMENT

Patents to Patients®

Harnessing Mitochondrial Telomerase to Treat Cancer & Cardiovascular Disease

MCW Case 1869

Stage of Development: Tested in human tissue

PCT/US2016/049053
Nationalized Aug 2018 in Australia, Canada, China, Europe, Japan, US

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Publications:

Telomerase Counteracts Mito Defect in CT Induced CVD J. Mol. Sci. 2018 19(3), 797

TERT Protects Against Ang-II Endothelial Dysfunction Am J Physiol Heart Circ 2017 Dec; 314: H1053060

Telomerase: a pharmacological target in cancer & CVD Pharmacol Res. 2016 Sept; 111: 422-33

Critical telomerase role in microcirculation Circ. Res.

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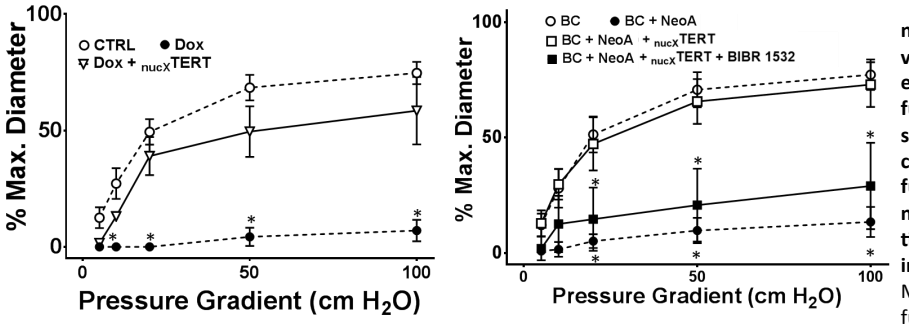
Key Advantages Lead Drug Candidate: nucXTERT

- First-in-Class peptide drug with novel mechanism of action
- **Restores** physiological (1) **vasodilation** in vessels from human subjects with coronary artery disease (CAD) & (2) **endothelial function** in breast cancer patients after chemotherapy (CT)
- **Prevents cardiotoxicity** of general (Doxorubicin) & targeted (Trastuzumab) CT **without decreasing efficacy of CT** and **restores normal function after general & targeted CT**
- Protects against common vascular stressors, including Angiotensin II in vivo (rodents) & ex vivo (rodents and human vessels)
- Validated *in vivo* efficacy without significant toxicity
- Protects from mitochondrial damage & regulates mitochondrial ATP/ROS
- Potential applications in cancer, cardiovascular disease (CVD), neurodegenerative disease & rare/orphan mitochondrial diseases



nucXTERT prevents CT-induced endothelial dysfunction and restores physiological endothelial function after neoadjuvant anti—cancer therapy in breast cancer. Microvascular function was evaluated in (A) isolated arterioles from healthy subjects after ex vivo treatment with Dox (100 nM 15-20h) and (B) from biopsy vessels of subjects without & ~1 month after final anti-cancer therapy. nucXTERT (10 mM) preserved dilator capacity when co-treated with Dox & restored normal dilation to Flow & ACh (not shown) in a telomerase-dependent manner (telomerase inhibitor BIBR 1532 abolished protective effect). Smooth muscle dependent dilation to Papaverine was similar in all groups (not shown). * P<0.05 vs. CTRL 2-way ANOVA RM; N= 3-6.

Mechanism of Action: The impact on aging/cancer of the nuclear-specific, telomere-lengthening effects of telomerase are well-described. However, the physiological implications of non-canonical, extra-nuclear, & non-telomere-lengthening contributions are unclear. The catalytic subunit of telomerase, telomerase reverse transcriptase (**TERT**) regulates levels of mitochondrial-derived reactive oxygen species (mtROS), independent of its nuclear role. Mitochondrial dysfunction plays a central role in CVD, cancer & other mitochondrial myopathies. We have discovered a novel way to manipulate a defense mechanism involving TERT to restore mitochondrial function to manipulate subcellular location (nuclear exclusion) using our **nucXTERT** peptide. **Our approach harnesses the benefits of mitochondrial TERT without increasing the level of nuclear telomerase** which would otherwise lead to tumor growth, immortalization & resistance to chemotherapy via autophagy. This approach decreases nuclear telomerase activity, while preventing mitochondrial dysregulation which plays a key role in both cancer & CVD. **nucXTERT effectively reverses vascular dysfunction in vessels isolated from cancer patients.** The MOA appears to be related to protecting mitochondrial DNA, lowering the production of free radicals, and lowering the release of cell free DNA from the mitochondria.

Meeting a Market Need: The distinct extra-nuclear functions of telomerase & beneficial effects of telomerase activation in the cardiovascular system are underappreciated. Our approach will protect the heart & vasculature from off-target effects of chemotherapies, enabling targeted tumor therapies to be used together with traditional chemotherapy, driving better responses & long-term outcomes for patients. Anthracycline toxicity is therapy-limiting; combining targeted inhibition of tumor drivers (e.g. HER2), with standard therapy is toxic so these therapies must be sequential. Our approach will enable (1) better outcomes with less morbidity from traditional chemotherapy, and (2) concurrent administration of targeted agents. **nucXTERT** will be used in patients receiving cardiotoxic chemotherapies with longitudinal cardiac function parameters serving as endpoints.