Novel Small Molecule Therapeutic for Hemorrhagic Shock

ID 1198

Background
Hemorrhagic shock and tissue hypoxia result in tissue conditions that are at risk of damage upon restored blood circulation. Subsequent oxygen reperfusion increases oxidative species concentrations even further, accelerating the decline of a patient’s systemic health. A patient undergoing severe blood loss suffers hypoxia during which lactic acid and other reactive oxidative species enter the circulatory system. These oxidative species are generated by “electron leakage” from the mitochondria and quickly spread throughout the circulatory system, oxidizing tissues and triggering cell death. Primary causes of hemorrhagic shock include penetrating and blunt trauma, gastrointestinal bleeding, and obstetrical bleeding. Controlling the activity of the reactive oxidative species is as crucial to patient survival as is controlling the bleeding.

Technology Description
Investigators have developed a novel molecular delivery mechanism that allows hemorrhagic shock therapeutics to be targeted directly to the cell’s mitochondria. The lead compound, XJB-5-131, is a targeted nitroxide agent that allows delivery of the antioxidant TEMPO to the mitochondria using a peptide-like fragment of the antibiotic Gramicidin S. This localized concentration of TEMPO was found to provide greater therapeutic effects than those associated with standard TEMPO administration, providing test subjects with significantly longer survival times during prolonged hemorrhaging. This technology platform additionally allows for conjugation of the mitochondria targeting fragment of Gramicidin S to potentially any drug for delivery to the mitochondria for such indications.

Applications
- Treatment of any acute disease or condition that is associated with cellular damage or dysfunction caused by excessive mitochondrial production of reactive oxygen species (ROS):
  - Hemorrhagic shock; septic shock; stroke.

Advantages
- Intravenous treatment increases subject survival time during hemorrhagic shock, providing a greater window for treatment.
- Preserves the protective mucosal lining of the intestine.
- Antioxidant “payload” can be quickly directed to the mitochondria, the source of oxidative stress.
- Lower conjugate drug concentrations can be administered.
- Intravenous application delivers protection to entire circulatory system’s endothelial lining.

Stage of Development
- Proof of concept of the mitochondrial delivery and utility in animals to proven hemorrhagic shock has been established.
- Mouse and rat data available.

US Patents 7,528,174; 7,718,603
US Patent Applications 20110039792

Inventors
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Peter Wipf is the Director of the Combinatorial Chemistry Center (CCC) and the Center for Chemical Methodologies and Library Development (UPCMLD) which are involved in many collaborative projects in Chemical Biology. He is also a founding member of the Center for Medical Countermeasures Against Radiation (CMCR) and the University of Pittsburgh Center for Chemical Diversity (UPCDC).

**Research Interests**

Dr. Wipf’s research focuses on Total Synthesis of Natural Products - the development of new methodology, mechanistic and physical organic experiments, conformational and configurational analysis by spectroscopic and computational methods, and bio-organic and medicinal chemistry.

Organometallic Chemistry will provide most of the new revolutionary techniques for C, C and C-heteroatom bond formations and asymmetric catalysis. Dr. Wipf’s group has had a long tradition in synthetic applications of transition metals. Recently they developed the first general protocol for alkene-alkyne hetero-couplings.

His lab also is interested in the development of new stereoselective methods for the preparation of highly functionalized heterocycles. In particular, they have developed novel protocols for five-membered heterocycle synthesis that have been widely adopted in industry and academe. Research is also conducted on Combinatorial and Solid Phase Synthesis, and Computational Prediction of Macroscopic Properties.

**Selected Publications**


