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Pitt ID: 02241, 02580, 03015

Novel Inhibitors of NADPH Oxidase

Background

The deleterious role of high levels of ROS (a.k.a. oxidative stress) has been widely demonstrated for many disorders in the cardiovascular system as well as in cancer and neurodegenerative diseases. A major culprit of cellular ROS generation is a 2-electron transfer to molecular oxygen which is catalyzed by family of enzymes, referred to as NADPH oxidase (Nox). There are seven isoforms of Nox (Nox1, Nox2, also referred to as gp91phox, Nox3, Nox4, Nox5 and Duox1/2) which differ in the type of ROS generated [superoxide anion ($O2^{\bullet-}$) vs. hydrogen peroxide (H_2O_2)], cellular components/subunits required, intracellular localization or tissue distribution and a lot of research is being carried out to develop isoform-specific Nox inhibitors that, in turn, can be used as (a) tools to delineate the role of this class of enzymes in normal and pathological cellular signaling pathways; and (b) therapeutic agents to abolish pathological ROS production, and reverse or reduce disease progression. The widely touted failure of clinical trials of traditional antioxidant vitamins (flawed for multiple reasons) strongly endorses the development of specific inhibitors of these major tissue sources of ROS.

Dr. Patrick Pagano, a professor in the Department of Pharmacology and Chemical Biology at the University of Pittsburgh, is broadly recognized for his pioneering work studying Nox enzymes and examining the role of reactive oxygen species (ROS) and, in particular, superoxide anion and hydrogen peroxide in the modulation of vascular tone, inflammation, and remodeling. Stemming from the early discoveries on Nox and ROS, Dr. Pagano was the first to develop specific cell- and tissue-permeant peptidic and adenoviral inhibitor of NADPH oxidase, which is widely considered the most specific NADPH oxidase inhibitor available. These and his other more recently developed inhibitors of novel isoforms of NADPH oxidase are expected to provide a platform for the development of new therapies aimed at treating hypertension and other cardiovascular diseases.

Technologies

Pitt ref # 02241: Gp91ds-tat (Nox2ds-tat) is a selective peptide inhibitor of Nox 2 that finds potential therapeutic use in stroke and ischemia/reperfusion injury

Gp91ds-tat is a selective[1] peptidic Nox2 inhibitor developed in the lab of Dr. Pagano in 2001. This peptide is designed to mimic the docking sequence on Nox2 that is important for its interaction with p47phox. The peptide also contains a short amino acid region corresponding to HIV-tat protein that provides inhibitor with the capacity to cross plasma membrane and block subunit assembly and thus superoxide generation.

In the first published article[2] related to Gp91ds-tat, Dr. Pagano and his team demonstrated that Gp91ds-tat attenuated angiotensin II (AngII)-induced vascular $O2^{\bullet-}$ production and blood pressure elevation in mice. Subsequently, numerous studies[3-6] demonstrated the effectiveness of this chimeric peptide inhibitor to attenuate or abolish ROS levels in normal or diseased tissue, consistent with the expression of Nox2. Gp91ds-tat (aka Nox2ds-tat) is now one of the most studied peptide inhibitors of Nox2 with approximately 1000 publications referencing this inhibitor* and has shown immense potential in ameliorating cardiopulmonary diseases. * Google Scholar – August 28, 2017

University of Pittsburgh has filed patent application on the therapeutic use of Gp91ds-tat in cardiovascular disorders such as stroke and ischemia/reperfusion injury.

IP: US patent application # 15/441,359 pending.

Pitt ref # 02241: Aerosolized Gp91ds-tat (Nox2ds-tat), finds potential therapeutic applications in treatment of cardiopulmonary diseases

As a new delivery mechanism, Dr. Pagano has developed aerosolized Gp91ds-tat and has demonstrated that aerosolized version of Gp91ds-tat markedly attenuates right ventricular hypertrophy in hypoxia-induced pulmonary hypertension in mice models. This along with other studies performed clearly suggest potential clinical applications of aerosolized Gp91ds-tat in treating conditions of the heart, lungs, or blood vessels connecting the heart and the lungs such as pulmonary hypertension, pulmonary fibrosis, acute lung injury, ischemia/reperfusion injury, and ventricular hypertrophy[7,8].

IP: US Patent # US8962570 B2 and US9585933 B2 issued.

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Pitt ref # 02580: Therapeutic use of NoxA1ds, a novel inhibitor of Nox1, in hypertension and cancer

A team of researchers led by Dr. Pagano recently developed and characterized a Nox1-specific peptidic inhibitor NoxA1ds, which prevents the interaction of NoxA1 with Nox1. The first sets of data on this inhibitor showed attenuation of VEGF-induced O2•−-mediated wound closure of the pulmonary endothelial cells[9] and stretch-induced ROS production in smooth muscle cells[10].
IP: US Patent # US9187528 B2 and US9770481 B2 issued.

Pitt ref # 03015: Novel small drug like molecules as highly selective Nox2 inhibitors

The technology identifies two highly efficacious and selective inhibitors of Nox2 that display no effect on Nox 1, 4, or 5. The inhibitors are bridged tetrahydroisoquinolines that are synthesized in 2-3 steps from commercially available materials and were assessed for specificity and effectiveness across a range of Nox isoforms[11]. An acceptable selective Nox2 probe would not only be inactive against other Nox isoforms but should also lack non-specific effects such as inhibition of another major source of $O2^{\bullet-}$ in mammalian cells or ability to scavenge $O2^{\bullet-}$. The two small compounds were identified as highly selective Nox2 inhibitors and did not show any significant effect on ROS. It is also shown that these compounds displayed considerably lower IC50 values (~30 nM) when tested in a cell-free system. Although early, these data suggest that bridged tetrahydroquinolines represent a new group of compounds with potential to serve as a platform for developing therapeutic agents for the treatment of Nox2-dependent oxidative stress disorders.
IP: US patent # US9796681 B2 issued; US patent application # US 15/708,341 pending.

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