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# NOVEL COMPOSITIONS FOR EXPLORING THERAPEUTICS IN DISEASES WITH MITOCHONDRIAL DYSFUNCTION

## TECHNOLOGY DESCRIPTION

Mitochondria have been identified as a culprit driving numerous diseases and pathologies, including metabolic disorders, neurodegenerative diseases, and aging. This wide impact is due to mitochondria's essential role in several different important biological functions. One of the most critical and best known is their role in generating ATP, the energy currency of a cell, which is produced by oxidative phosphorylation. An inevitable consequence of this process is the production of reactive oxygen species (ROS). ROS can arise from 11 distinct sites along the electron transport chain, which have been characterized by Buck's investigators. The relative contribution of ROS from these different sites varies and can be altered by biological changes in and/or outside of the mitochondria.

Buck investigators have identified one of these sites of ROS generation to be of particular importance: site $I_Q$ (the ubiquinone-binding site in respiratory complex I). A high-throughput screen enabled our scientists to identify high-affinity site-specific suppressors of site $I_Q$ electron leak (now called S1QELs; pronounced ''cycles'') that do not inhibit electron flow and therefore do not disrupt oxidative phosphorylation. Subsequently, our scientists discovered that site $I_Q$ is one of the main contributors to superoxide-$H_2O_2$ production in isolated mitochondria and in several cell lines. Several chemotypes were identified in this screen that can serve as critical tools in interrogating the importance of site $I_Q$ as a therapeutic target. Buck investigators have validated the importance of modulating site $I_Q$ production of ROS with S1QELs in several different disease animal models.

## APPLICATIONS

This foundational research can serve as a launching platform for drug discovery and development in a wide range of diseases in the aging field and beyond.

## PUBLICATIONS

Use of S1QELs and S3QELs to link mitochondrial sites of superoxide and hydrogen peroxide generation to physiological and pathological outcomes, *Biochem Soc Trans*, 2019, Watson et al.

Riding the tiger – physiological and pathological effects of superoxide and hydrogen peroxide generated in the mitochondrial matrix, *Crit Rev Biochem Mol Biol*, 2020, Brand.

Mitochondrial generation of superoxide and hydrogen peroxide as the source of mitochondrial redox signaling, *Free Radic. Biol. Med,* 2016, Brand.

Suppressors of Superoxide-H2O2 Production at Site IQ of Mitochondrial Complex I Protect against Stem Cell Hyperplasia and Ischemia-Reperfusion Injury, *Cell Metab,* 2016, Brand et al.

Suppression of superoxide/hydrogen peroxide production at mitochondrial site IQ decreases fat accumulation, improves glucose tolerance and normalizes fasting insulin concentration in mice fed a high-fat diet, *Free Radic. Biol. Med,* 2023, Watson et al.

## PATENT STATUS

PCT application pending

## CASE NUMBER

BI 500

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