Pharmaceutical therapies and drug screening methods for the treatment of Ventilator-Induced Diaphragmatic Dysfunction (VIDD)

Critically ill patients often require breathing assistance provided by a mechanical ventilator (MV). While treatment with these devices has greatly improved patient outcomes, it is often associated with a loss in muscle fiber from the diaphragm, leading to Ventilator-Induced Diaphragmatic Dysfunction (VIDD). Unfortunately, there are few therapies for VIDD. This technology links a leaky calcium channel, Ryanodine Receptor 1 (RyR1) to the development of VIDD. Building on these findings, the technology also describes validated pharmaceutical interventions for VIDD, as well as a method for screening novel therapeutics to treat and even prevent VIDD.

Small molecules to treat and prevent sarcoplasmic reticulum (SR) leakage through RyR1

This technology demonstrates an association between MV, oxidative stress, and rapid remodeling of the sarcoplasmic reticulum (SR) transmembrane calcium channel RyR1 within the diaphragm. After remodeling, RyR1 can no longer efficiently associate with calstabin1, a protein that forms a macromolecular complex with RyR1, to prevent resting calcium leakage. The technology further identifies pharmaceutical agents that enhance the RyR1-calstabin1 interaction to prevent resting calcium leakage and restore efficient muscle contraction. The technology proposes delivery methods of these compounds for therapeutic intervention of VIDD as well as a biochemical assay for screening new compounds that increase the interaction of RyR1 with calstabin1.

This technology has been extensively validated using in vivo and ex vivo murine and porcine models of VIDD. In addition, it has been tested in humans who underwent mechanical ventilation and brain death prior to organ harvesting. Biochemical simulations were used to validate the molecular mechanisms of pharmaceutical intervention.
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Applications:

- Treatment of VIDD patients
- Prevention of VIDD in patients undergoing MV
- Drug Discovery
- Biochemical assay to determine the presence and degree of VIDD in at-risk patients
- Animal models for lung disease and VIDD

Advantages:

- Identifies RyR1 as a target for VIDD treatment
- Broadly applicable to patients on MV to prevent the occurrence of VIDD
- May decrease the weaning time for long-term MV patients
- Has been validated in human, porcine and murine models to confirm efficacy of the therapeutics
- Provides methods to discover new VIDD therapeutics

Patent Information:

Patent Pending (WO/2015/014666)

Tech Ventures Reference: IR CU14121

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