Docket #: S23-552

Treating Cardiac Dysfunction with 15-PGDH Inhibition

Stanford researchers have found that inhibiting 15-prostaglandin dehydrogenase (15-PGDH), which breaks down prostaglandin E2 (PGE2), can improve cardiac function in diseased and aged hearts.

Dilated cardiomyopathy (DCM) is a life-threatening condition characterized by ventricle expansion and thinning of the cardiac wall, which lead to cardiac failure. PGE2, known for its vasodilatory and anti-inflammatory effects, could be a potential treatment for DCM. However, PGE2's short half-life restricts therapeutic effects to the site of injection. Also, direct PGE2 administration may exceed physiological levels.

The Blau Lab at Stanford University explored an alternative method to increase PGE2 levels in the heart. Previously, they used the small molecule SW033391 (SW) to inhibit the PGE2 degrading enzyme 15-PGDH and achieved skeletal muscle rejuvenation. Building on this, they explored 15-PGDH inhibition for increasing PGE2 levels in the heart. A month of daily intraperitoneal injection of SW in two mouse models of DCM resulted in significant improvements in cardiac function, as measured by fractional shortening and left ventricular ejection fraction. Additionally, the same treatment in aged wildtype mice led to metabolic rejuvenation, as indicated by changes in mitochondrial gene expression and cardiac glucose uptake. 15-PGDH inhibition has the potential to treat a broad spectrum of cardiac disorders.

Stage of Development
Proof of concept – in vivo data

Applications

- Cardiovascular diseases of genetic and non-genetic etiology
- Dilated cardiomyopathy

- Cardiac hypertrophy
- Aging-associated dysfunction

Advantages

- Directly targets the heart tissue and improves cardiac function, as opposed to current drugs that treat hypertension and heart rate
- Fewer adverse effects than direct PGE2 administration
- Inhibitors with long half-life or gene therapy can be used for systemic benefits
- Inhibition effects localized to diseased cardiac tissues with high 15-PGDH

Publications

- Bakooshli, M. A., Wang, Y. X., et al. (2023). Regeneration of neuromuscular synapses after acute and chronic denervation by inhibiting the gerozyme 15-prostaglandin dehydrogenase. *Science translational medicine, 15*(717), eadg1485.

Patents

- Published Application: WO2025170936

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