Novel epigenetic therapy for Prader Willi Syndrome

Unmet Need

Prader-Willi Syndrome (PWS) is a rare and complex genetic disorder affecting an estimated 1 in 10,000 to 30,000 infants. Primarily caused by a paternal chromosome 15q11-q13 deletion, PWS presents a myriad of physical, behavioral, and cognitive challenges that manifest throughout development. These include hypotonia (weak muscle tone), delayed growth, and feeding difficulties during infancy, followed by the onset of hyperphagia (insatiable hunger) in early childhood often leading to obesity and type 2 diabetes. Intellectual disability, learning impairments, stubbornness, anger, and obsessive-compulsive disorders are common behavioral and mental challenges. PWS additionally leads to underdeveloped genitals and incomplete puberty, resulting in sterility. Presently, there is no cure for PWS, and existing treatments address individual symptoms, necessitating a complex and burdensome regimen. There is a need for genetic therapies for PWS that can address the root cause of the disease and comprehensively mitigate the multitude of symptoms through a single treatment.

Technology

Duke inventors have developed an epigenetic therapy for Prader-Willi Syndrome (PWS) using G9a (a histone H3 methyltransferase) small molecule inhibitors. This therapy is intended to be a pharmacological intervention administered to patients with PWS. Specifically, the G9a inhibitors are designed to prevent the methylation of H3K9 in PWS patients. This treatment enables the expression of otherwise silenced critical PWS associated genes from the maternal chromosome, compensating for the paternal deletion. These has been demonstrated through the
identification of G9a inhibitors through high-content screening of over 9000 small molecules in cultured human fibroblast cells and further testing in both human fibroblasts and PWS mouse models. Treated mice exhibited improved survival and growth compared to untreated counterparts.

**Other Applications**

This technology could also serve as a proof-of-concept for other genetic imprinting disorders such as Angelman Syndrome.

**Advantages**

- First-in-class epigenetic therapy targeting root cause of PWS
- Offers comprehensive symptom relief in one regimen
- Has the potential for sustained symptom relief compared to current methods