Small Molecule Inhibitors of Cardiovascular and Renal Ectopic Calcification
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SUMMARY
UCLA researchers in the Department of Medicine have discovered that administration of small molecule inhibitors of ENPP1 or functional antagonists of PPI can substantially attenuate ectopic calcification. This suggests that ENPP1 and PPI can be potential pharmacological targets when developing therapeutics for pathological ectopic calcification.

BACKGROUND
Pathological calcification of soft tissues, or ectopic calcification, is common in diseases such as diabetes and chronic kidney disease. It is also common to see ectopic calcification with general aging. For example myocardial calcification is observed in the aging heart and in patients with diabetes, renal disease, and myocardial injury secondary to ischemia or inflammation (Rostand et al., 1988). Calcification within the heart muscle is also one of the most common underlying causes of heart blocks where calcification and fibrosis of the conduction system interrupt smooth propagation of electrical impulses (Lev, 1964). Cardiac pump dysfunction and arrhythmias can also occur depending on the extent and anatomic site of calcification and calcified myocardial scars have been reported to cause refractory ventricular tachycardia. Cardiac calcification is also a prognostic indicator of poor outcomes following myocardial infarction or myocarditis (Stallion et al., 1994).

UCLA researchers have now elucidated the underlying mechanism for this process and are developing a set of pharmacological targets and small molecules to inhibit and potentially reverse ectopic calcification. The target is ENPP1, which is an enzyme that regulates mineralization and is differentially expressed in fibroblasts of hearts post-injury. ENPP1-mediated generation of PPI in bone augments mineralization via hydrolysis of PPI to generate Pi and subsequent hydroxyapatite formation. The UCLA team has shown that similar mechanisms underlie ectopic cardiac calcification. Administration of small molecules that inhibit ENPP1 led to significantly decreased ectopic cardiac calcification and preservation of post injury cardiac function.

APPLICATIONS
Treatment of ectopic calcification in the heart. A similar mechanism likely underlies other types of ectopic calcification in kidneys and the vasculature although this remains to be further validated.

ADVANTAGES
These small molecules are the only drugs that have shown efficacy to retard or reverse ectopic calcification.

STATE OF DEVELOPMENT
All three molecules have been tested and shown outstanding efficacy in mouse models and with valve cells isolated from patients with calcific valve disease.

PATENT STATUS
Patent Pending

RELATED MATERIALS

ADDITIONAL TECHNOLOGIES BY THESE INVENTORS
- Wnt1 for the Treatment of Peripheral Vascular Disease and the Repair of Heart

INVENTORS
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OTHER INFORMATION
KEYWORDS
Small molecule, inhibitor, ENPP1, PPI, ectopic calcification, pharmacological target, pathological mineralization, myocardial calcification, cardiovascular, therapeutics

CATEGORIZED AS
- Medical
  - Disease: Cardiovascular and Circulatory System
  - Therapeutics

RELATED CASES
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