RESEARH CENTER
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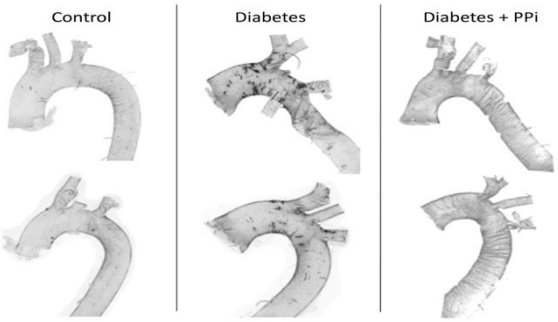
TECHNOLOGY OFFER

TOWARD A PREVENTION THERAPY OF DIABETES-ASSOCIATED CALCIFICATION

PYROPHOSPHATE, AN ENDOGENOUS METABOLITE INHIBITS PATHOLOGICAL CALCIFICATION. ORAL USE OF THIS COMPOUND PROMISES NOVEL THERAPIES IN CALCIFICATION PATHOLGIES.



*Proof-of-concept experiment indicating that the diabetes-associated calcification **("Diabetes")** of the aorta can be prevented by oral supplementation of pyrophosphate **("Diabetes+PPi")** in the animal model developed. **"Control"** demonstrates minimal calcification in the aorta of the non-diabetic animals.*

About 10% of the population has diabetes mellitus (DM), and the prevalence of diabetes keeps rising. DM accelerates atherosclerosis, peripheral arterial disease is a major complication and the leading cause of amputation among diabetics. Vascular calcification is an independent predictor of cardiovascular and overall mortalities in patients with type 2 diabetes. To examine this pathogenesis in more detail, we developed a diabetic mouse model exhibiting diabetes-associated cardiovascular pathology, such model was not available earlier. Our diabetic mice develop accelerated and increased calcification in their aortas and kidneys compared to age-matched controls, providing a unique tool to investigate diabetes-related vascular calcification and to develop intervention.

SOLUTION

Our results show that under diabetic conditions, plasma pyrophosphate (PPi) levels decrease in our mice indicating that PPi may play an important role in the prevention of diabetes-related calcification. To directly address this pathogenesis, we executed an oral PPi replacement therapy. We accomplished a proof-of-concept experiment proving that oral supplementation of PPi was able to inhibit DM-associated calcification in the animal model. The successful outcome of this experiment provides the preclinical basis of a mechanism-based first-in-class therapy for DM-associated calcification.

BENEFITS

Ongoing clinical trials: Human trials using oral pyrophosphate to reduce calcification are registered and started in pseudoxanthoma elasticum [NCT04868578, clinicaltrials.gov] in France and in systemic sclerosis [NCT04966416, clinicaltrials.gov] in Hungary. These trial provide encouraging examples that this treatment is safe and doable.

APPLICATION

In order to initiate a clinical trial first pharmacokinetic data should be generated in our animal model and then on a well characterized diabetes cohort to establish the optimal salt-form, dose and formulation.

TRL 5 SMALL SCALE PROTOTYPE

SEEKING FOR PARTNER TO DEVELOP CLINICAL TRIAL

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INTELLECTUAL PROPERTY: Granted Patent EP 3512530 B1 "Oral Pyrophosphate for Use in Reducing Tissue Calcification" and US11504395B2 (same title). The invention was developed in research collaboration of the Research Center for Natural Sciences (RCNS) and the Netherland Cancer Institute (NKI) in 2016. The contributions to the invention of the respective employees of the two institutions are 85% (RCNS) and 15% (NKI). The patent was filed by NKI in September 2016, who undertakes to create the conditions for exploitation mainly through licensing agreements.

PUBLICATIONS

Dedinszki D, Szeri F, Kozák E, Pomozi V, Tőkési N, Mezei TR, Merczel K, Letavernier E, Tang E, Le Saux O, Arányi T, van de Wetering K, Váradi A. (2017) Oral administration of pyrophosphate inhibits connective tissue calcification. *EMBO Mol Med*. **9**:1463-1470.

Kozák E, Fülöp K, Tőkési N, Rao N, Li Q, Terry SF, Uitto J, Zhang X, Becker C, Váradi A, Pomozi V. (2022) Oral supplementation of inorganic pyrophosphate in pseudoxanthoma elasticum. *Exp Dermatol*. **31**:548-555.