# Buck Institute Technology Summary

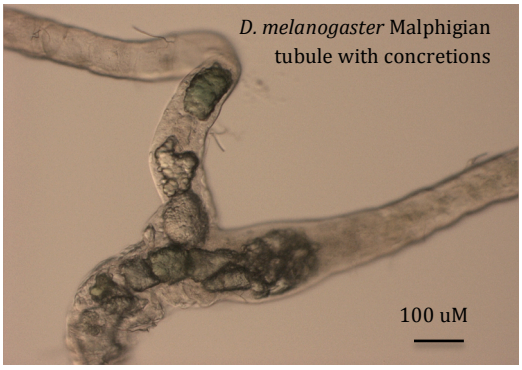
## Zinc as a potential therapeutic target for biomineralization-associated diseases

### Buck Institute Case No. BI-405

*Background*

Biomineralization, the processes by which organisms form minerals, occurs through normal physiologic processes that are carefully regulated by complex pathways. However, if not properly regulated, biomineralization can damage surrounding tissues and lead to a number of pathological conditions such as kidney stones, atherosclerosis and neurodegenerative disorders. Biomineralization-associated pathologies have long attracted the attention of the medical community although the mechanism is not well understood. Investigations on key biomineralization processes especially the initiating steps will provide insights in strategies against disease progression.

Calcification has been linked to biomineralization and calciferous deposits are associated with pathologies including kidney tubule blockage, kidney stone formation and arteriosclerotic plaques. However, the source of calcification is still unknown. The Kapahi group at the Buck Institute and others have shown that the fruit-fly Malphigian tubule is a good model for the mammalian kidney tubule to study calcification in the biomineralization process.




*The Technology*

Using both fruit fly Malphigian tubule calcium concretions and human renal biopsy material, the Kapahi lab found that zinc plays an important role in calcification to initiate biomineralization. Specifically, dietary zinc supplementation and zinc transporter knockdown showed an essential role for zinc in concretion formation. The Kapahi group screened genes implicated in calcification-associated human diseases for their ability to induce mineralized concretions and found a target gene xanthine dehydrogenase (XDH). Then they used a XDH mutant fly strain fed on a high protein diet to increase tubule

concretion formation. Supplementation with (N,N,N',N'-Tetrakis-(2-pyridylmethyl) ethylenediamine (TPEN) resulted in reduction of concretion in these mutant flies. TPEN was identified as a chelating agent that binds zinc and specifically modulates the activity of at least one zinc transporter polypeptide of a cell in the disease-associated tissue. In this way, it effectively reduces the formation of mineral deposit in tissues. Thus, TPEN can modulate the nucleation of a mineral concretion and could potentially be used as a therapeutic for biomeralization-related diseases.

### *Opportunity*

Findings from the Kapahi group deepen our understanding of mechanisms that regulate the mineralization process in the kidney. This understanding is essential for the development of novel therapeutic strategies to prevent or inhibit ectopic mineralization in other human tissues. The Kapahi lab has identified a role of zinc in the pathological biomineralization process and that TPEN is one promising therapeutic candidate through manipulation of zinc. Research continues at the Buck in terms of this new approach to target zinc-mediated biomeralization–thought to play a role in a diverse range of diseases such as kidney stones, atherosclerosis and neurodegenerative disease. The Buck seeks interested partners who can collaborate and further develop compounds involved in calcification processes to treat biomineralization-associated diseases.

The Buck Institute is the only free-standing institute dedicated to aging and age-related research in the United States. We actively partner with industry to develop therapeutics, diagnostics or tools that make a difference. For more information on this or another technology or opportunity, please contact:

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