Vascular calcification (VC) is typical in aging, several genetic and metabolic disorders. It is now recognized as a strong and independent predictor of cardiovascular events and mortality, not only in diabetic and chronic kidney disease (CKD) patients, but even in the general population. VC is classified into two distinct types based on location in the arterial wall; intimal and medial. Elastin-associated medial arterial calcification (MAC) is more specific to CKD and contributes significantly to cardiovascular mortality in these patients. It is responsible for loss of vessel elasticity, increased arterial stiffness, increased pulse pressures and systolic blood pressure, and left ventricular hypertrophy ultimately causing arrhythmias and heart failure.

Current clinical practice is mostly focused on prevention and retardation of VC progression. Most patients with CKD remain underdiagnosed, and those diagnosed have already heavily calcified vessels. As such, they are undertreated since preventative strategies no longer work at this stage. Unfortunately, there is no FDA-approved treatment available that reverses calcification in countless CKD patients. A treatment strategy, which promotes resorption of calcified lesions in arteries, while simultaneously avoiding demineralization from normally calcified tissues (i.e., bones and teeth) remains an urgent health care need. Chelating agents bind to metal cations, can dissolve and “wash away” calcium deposits if delivered in close proximity to the calcification sites. Amongst chelating agents known for their affinity to Ca, we found that EDTA chelates Ca from hydroxyapatite better than others. In our laboratory, we have developed a unique targeting mechanism by using nanoparticles to deliver chelating agents and other drugs to degraded elastin, a characteristic feature of VC. We take this approach forward in clinically relevant animal models of CKD.

First, we tested the targeted nanoparticle-based EDTA chelation therapy in a rat model of adenine-induced renal failure. The targeted nanoparticles delivered EDTA to the sites of vascular calcification and reversed mineral deposition without any unpleasant side effects. Furthermore, we validated the adenine-CKD model in mice to monitor MAC in vivo, and explore the phenotypic and functional alterations associated with it. We were able to target our nanoparticle delivery system to calcified arteries in these mice. The mouse model will help us to test whether our EDTA chelation therapy tangibly improves arterial function by restoring vascular health. Lastly, we investigated the possibility of using an ex vivo organ culture model of VC as a simpler, and relatively easier model to assess if EDTA chelation therapy promotes vessel homeostasis. The work presented here represents another major step towards the development of targeted EDTA chelation therapy as an unconventional therapeutic approach to reverse pathological calcifications in CKD patients.