Hypercalcemia is a common disorder defined as a serum calcium concentration higher than the normal range of 8.5 - 10.5 mg/dL. The most common causes of hypercalcemia are over-secretion of parathyroid hormone (PTH) from one or more enlarged parathyroid glands, which can lead to primary hyperparathyroidism (PHPT), or hypercalcemia due to humoral hypercalcemia of malignancy (HHM). PTH is an 84 amino acid peptide that regulates calcium and phosphate homeostasis through activation of its receptor, PTHR1. PTHrP has close homology to the N-terminal region of PTH and also activates PTHR1, inducing similar biological actions. Activation of PTHR1, a class B G-protein coupled receptor expressed in bone and kidney, leads to an increase in cAMP and PKA activation, inducing gene expression changes of important modulators of bone homeostasis. In the kidney, it increases renal phosphate excretion and calcium reabsorption. Hyperactivation of PTHR1 due to high levels of either PTH or PTHrP results in increased calcium release from the bone matrix, as well as increased calcium reabsorption in the kidney, causing hypercalcemia. Surgery is the first line therapy for PTHrP, but patients that cannot or choose not to have surgery are prescribed calcimimetics and/or bisphosphonates. Calcimimetics decrease circulating calcium levels but have no effect on bone homeostasis, while bisphosphonates improve bone homeostasis but have little effect on circulating calcium. HHM patients are prescribed bisphosphonates or denosumab, both of which possess undesirable side effects. We hypothesize that blocking PTH/PTHrP action via a PTHR1 antagonist may provide an improved therapeutic mechanism to treat PTHrP and HHM, and potentially other diseases of hypercalcemia.

Using an iterative medicinal chemistry approach, Crinetics has identified several nonpeptide PTHR1 molecules suitable for evaluation in human clinical trials. Candidate molecules are being evaluated in a battery of safety studies to select the optimal therapeutic for hypercalcemia caused by PHPT and HHM. Currently, ANT-1 and other potential PTHR1 antagonists’ pharmacokinetic plasma profile in preclinical species. ANT-1 suppresses ionized calcium in rat models of PTH- and PTHrP-induced hypercalcemia. ANT-1 is also potent in functional antagonist assays targeting PTHR1 from other species. ANT-1 potently inhibits PTH binding to the human and rat PTH type-1 receptors. ANT-1 is also potent in functional antagonist assays targeting human and rat PTHR1. ANT-1 has good drug-like properties and is orally bioavailable. Using an iterative medicinal chemistry approach, Crinetics has identified several nonpeptide PTHR1 antagonists that inhibit hypercalcemia in a rat model and could be a viable treatment for hypercalcemia in humans.