MOLECULAR GENETICS OF FAMILIAL TUMORAL CALCINOSIS AND THE ROLE OF FIBROBLAST GROWTH FACTOR 23

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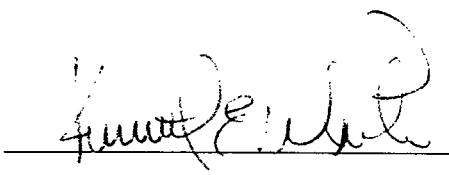
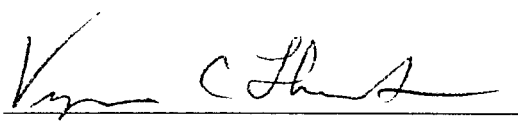


Kenneth E. White, PhD, Chair



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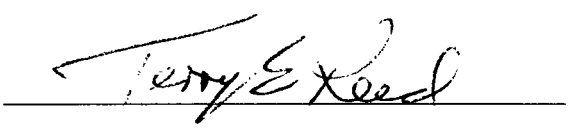

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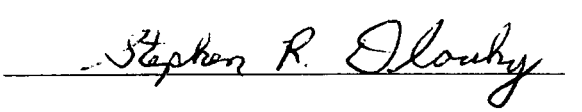
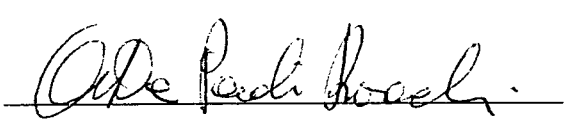


Stephen R. Dlouhy, PhD



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ABSTRACT

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MOLECULAR GENETICS OF FAMILIAL TUMORAL CALCINOSIS AND THE ROLE OF FIBROBLAST GROWTH FACTOR 23

The regulation of serum phosphate concentrations is dependent upon complex and yet to be fully understood interactions between endocrine pathways. Disruptions within these pathways result in mis-regulation of phosphate homeostasis and lead to clinical disorders. Phosphate homeostasis is a central biological process required to maintain normal growth and development as well as sustain bone composition. The kidneys play the lead role in serum phosphate regulation. Phosphate, like most other ions and molecules, is secreted into the filtrate at the kidney glomerulus. Through reabsorption, phosphate re-enters the circulation via the actions of a sodium/phosphate co-transporter type IIa (NPT2a) in the apical membrane of proximal tubule cells. In disorders of hypo- and hyperphosphatemia, the normal regulation of NPT2a activity is disturbed.

Fibroblast growth factor 23 (FGF23) is a circulating polypeptide produced mainly in osteoblasts, and is vital to the process of phosphate homeostasis, exemplified by human disorders caused by mutations in the *FGF23* gene. Autosomal dominant hypophosphatemic rickets (ADHR) is the result of stabilizing mutations in *FGF23*. ADHR mutations prevent cleavage and inactivation of the FGF23 protein. Failure to inactivate FGF23 results in the inability to reabsorb phosphate, and manifests in

hypophosphatemia, loss of bone mass, and rickets or osteomalacia. The clinical mirror-image of ADHR is the autosomal recessive disorder, familial tumoral calcinosis (TC). TC can be the result of homozygous inactivating mutations in *FGF23* or its upstream regulators. Without FGF23 activity, NPT2a remains active longer, and abnormal amounts of phosphate are reabsorbed into the bloodstream. TC patients suffer from hyperphosphatemia and ectopic and vascular calcifications. These disorders demonstrate that FGF23 plays a regulatory role in the absorption of phosphate from the filtrate in the proximal tubule. However, much remains unknown about the FGF23 polypeptide, its processing, regulation, required co-factors and molecular mechanism of activity. This research clarifies the role of key residues and domains in FGF23 post-translational processing, co-factor interactions, as well as receptor activation, and tests the central hypothesis that cellular processing and activity of FGF23 are dependent upon critical residues and structural domains.

Kenneth E. White, PhD, Chair

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