Project Summary/Abstract
I am seeking a Mentored Research Scientist Development Award from the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) to facilitate my progression to an independent investigator in the genetics of osteoporosis. I am an epidemiologist with a strong background in quantitative methods and experience with osteoporosis epidemiology and genetic association studies. My recent work with Drs. Eric Orwoll and Robert Klein has focused on understanding how discoveries of genetic associations with BMD in mouse models can be translated to fill gaps in knowledge of the genetic regulation of bone phenotypes in human populations. The K01 award will allow me to develop a deeper understanding of bone physiology and metabolism, functional evaluation of genetic variants, and expertise in statistical genetics. My long-term goal is to combine population-based studies with investigations in the mechanisms of skeletal metabolism to propel discoveries of the genetic contributions to osteoporosis in aging men and women.

The career-development goals of this award period are to gain a deeper understanding of bone physiology and metabolism and to build expertise in statistical genetics and in techniques for functional characterization of gene mutations. The plan has oversight by my primary mentor, Dr. Eric Orwoll, and my co-mentors, Drs. Robert Klein, José Luis Millán and Bruce Weir. They have helped to define the training program, including coursework, directed reading, practical training and observations, and will provide continuing advice. Further support and feedback will be provided by my division and department chairs—for academic career advice—and by Osteoporotic Fractures in Men (MrOS) and Study of Osteoporotic Fractures (SOF) investigators for the specific scientific activities related to skeletal genetics. The environment includes the laboratories of these mentors at OHSU (Orwoll and Klein), Sanford | Burnham Medical Research Institute (Millán), and Unversity of Washington (Weir), as well as the international team of investigators on the MrOS and SOF cohort studies of musculoskeletal outcomes.

The research proposal focuses on characterizing alkaline phosphatase (*ALPL*) gene mutations for their effect on enzyme activity *in vitro* and on their associations with BMD in two large, well characterized cohorts of men and women. Preliminary data in mice and human studies point to this bone mineralization candidate gene, and we have found that it harbors multiple rare variants and appears to be associated with BMD and fracture risk. The long-term goal of this research is to understand how rare variants in *ALPL* contribute to bone physiology and osteoporosis and how they interact with other genes involved in mineralization. The study design and analytic methods developed through this work will also be applicable to the study of rare variants in other musculoskeletal candidate genes in the future.