

## DIRECTOR'S NOTES

The CMBD has an active and highly successful Pilot and Feasibility (P&F) Program. The goal of this program is to develop new research focusing on basic, clinical and translational research in bone biology and disease. It employs a review process similar to the NIH. Funding for these P&F projects is provided through two avenues: 1) the NIH/NIAMS Research Core Center grant and 2) the UAB University-Wide Center grant.

The P&F Program provides resources to develop programs for independent funding (e.g., R01) within two to three years. Since its inception in 1997, ten UAB faculty have received funding from this program, four of whom are currently receiving CMBD funding. All six P&F principal investigators (PIs) who have completed their funding cycle and two of the four currently funded PIs now have independent extramural funding (33 grants totaling \$13,715,911 in direct costs). Further evidence of the impact of this P&F Program is that these ten faculty have published 258 peer-reviewed manuscripts.

An RFA will be announced in January/February 2004 for funding of two new P&F projects to begin on May 1, 2004.

The successful recruitment of Thomas L. Clemens, PhD enhances research in bone disease at UAB. Dr. Clemens begins his employment on January 1, 2004 as Professor and Director, Division of Molecular and Cellular Pathology, Department of Pathology. He brings with him a strong research program focused on mechanisms and consequences of parathyroid and related hormone actions, and is a leading authority on the use of animal models for dissecting molecular mechanisms of bone disease. Upon his arrival, Dr. Clemens will be recruiting new faculty in the bone field, further strengthening the Center. Below is a synopsis of his research program.

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## GENETIC MOUSE MODELS FOR STUDY OF ANABOLIC AGENTS IN BONE

My laboratory specializes in the use of animal models to study bone biology and disease. An example is our recent studies on the mechanism of action of insulin-like growth factor-I (IGF-I). IGF-I exerts profound anabolic effects on bone and has been postulated to mediate the anabolic actions of parathyroid hormone and to amplify other osteogenic signals. However, the cellular and molecular mechanisms that mediate the anabolic actions of IGF-I have been difficult to address experimentally primarily due to the complexity of the IGF-I system: IGF-I is produced both systemically by the liver under the control of growth hormone as well in local tissue compartments, and its activity is modulated by multiple IGF binding proteins and specific proteases. To provide a more physiological context to study the paracrine biology of the skeletal actions of IGF-I, our laboratory has developed several mouse models in which genetic alterations have been introduced to examine the consequence of increased or decreased IGF-I signaling in cells of the osteoblast lineage. We found that mice with targeted overexpression of IGF-I in osteoblasts have an increased bone formation rate and increased trabecular and cortical bone volume. Remarkably, these changes occur without an increase in the total number of osteoblasts suggesting that locally produced IGF-I exerts its anabolic effects primarily by increasing the activity of resident osteoblasts. To examine the consequence of decreased IGF-I signaling in bone, the Cre/loxP recombination system was used to disrupt selectively the *Igf1r* gene in mouse osteoblasts. Mutant mice lacking the IGF-1R in osteoblasts showed a severe reduction in trabecular bone caused by a markedly impaired mineral apposition rate. Surprisingly, despite defective IGF-signaling, the mutant osteoblasts were able to mature and deposit osteoid normally, but ultimately failed to perform their final function, namely to mineralize bone matrix. These findings have prompted a rethinking of the mechanisms of IGF-I action in bone and underscored the value of genetically altered mouse models for study of IGF-I and other growth factors in bone.

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