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RESEARCH GOALS: The overall goal of our research is to identify of the cellular and molecular mechanisms that control skeletal development and repair. Cell and mouse models with specific alterations in these pathways are being used to study the role of growth factors and hypoxia inducible factors during bone development and following skeletal injury.

RESEARCH SUMMARY AND SIGNIFICANCE: Our lab is studying the mechanisms of action of insulin, insulin-like growth factor and growth hormone in bone and skeletal muscle. Mice and their cells with specific alterations in the components of these pathways have been created and are being used to identify the interplay between these growth factors. In a separate project, we are investigating the hypothesis that the osteoblast and osteocytes are positioned in bone to sense and respond to fluctuations in oxygen and nutrient supply and thereby play key roles in regulation of angiogenesis and blood flow when bone is under normal physiological conditions, and in response to pathological signals. Osteoblast cell models and genetically altered mice are being used to study the role of hypoxia inducible factors during bone development and following skeletal injury. This information will then be used to generate new diagnostic and therapeutic modalities.

CURRENT PROJECTS:

1. Defining Insulin Actions in Bone.
2. Oxygen Sensing and Osteogenesis
3. The GH/IGF-1 Pathway in Skeletal Muscle

RECENT PUBLICATIONS:

1. Wang Y, Wan C, Deng L, Liu X, Cao X, Gilbert SR, Bouxsein ML, Faguere M-C, Guldberg RE, Gerstenfeld LC, Haase VH, Johnson RS, Schipani E, **Clemens TL**. The hypoxia-inducible factor α pathway couples angiogenesis to osteogenesis during skeletal development. *J Clin Invest* 2007;117:1616-1626, [PMCID: PMC1878533](#).
2. Fulzele K, DiGirolamo DJ, Liu Z, Xu J, Messina JL, **Clemens TL**. Disruption of the IGF-1 Receptor in Osteoblasts Enhances Insulin Signaling and Action. *J Biol Chem* 2007;282:25649-25658, [PMID: 17553792](#).
3. DiGirolamo DJ, Mukherjee A; Fulzele K; Gan Y; Cao X; Frank SJ; **Clemens TL**. Mode of Growth Hormone Action in Osteoblasts. *J Biol Chem* 2007;282:31666-74, [PMID: 17698843](#).
4. Wan C, Gilbert SR, Wang Y, Cao X, Shen X, Ramaswamy G, Jacobsen KA, Alaql ZS, Eberhardt AW, Gerstenfeld LC, Einhorn TA, Deng L, **Clemens TL**. Activation of the hypoxia inducible factor-1 α pathway accelerates bone regeneration. *Proc Nat'l Acad Sci USA* 2008;105:686-691, [PMID: 18184809](#).
5. Mak KK, Bi Y, Wan C, Chuang P-T, **Clemens T**, Young M and Yang Y. Hedgehog signaling in mature osteoblasts regulates bone formation and resorption by controlling *PTHrP* and *RANKL* expression. *Dev Cell*. 2008 May;14(5):674-88, [PMID: 18477451](#).

6. Tang Y, Liu Z, Zhao L, Wu D, **Clemens T** and Cao X. Smad7 Stabilizes β -catenin Binding to E-cadherin Complex and Promotes Cell-Cell adhesion. *J Biol Chem* 2008;283:23956-3963, [PMID: 18593713](#).
7. Riddle RC, Khatri R, Schipani E, **Clemens TL**. Role of Hypoxia-Inducible Factor-1 α in Angiogenic-Osteogenic Coupling. *J Mol Med* 2009 87:583-90.
8. Zhang F, Qiu T, Wu X, Wan C, Shi W, Wang Y, Chen J, Wan M, **Clemens TL**, Cao X. Sustained BMP Signaling in Osteoblasts Stimulates Bone Formation by Promoting Angiogenesis and Osteoblast Differentiation. *J Bone Miner Res.* 2009 Mar 3. [In Press]
9. Shen X, Wan C, Ramaswamy G, Mavalli M, Wang Y, Duvall CL, Deng LF, Guldberg RE, Eberhart A, **Clemens TL**, Gilbert SR. Prolyl hydroxylase inhibitors increase neoangiogenesis and callus formation following femur fracture in mice. *J Orthop Res.* 2009 Mar 31. . [In Press]
10. Fan Y, Menon RK, Cohen P, Hwang D, **Clemens T**, Digirolamo DJ, Kopchick JJ, Leroith D, Trucco M, Sperling MA. Liver-specific Deletion of the Growth Hormone Receptor Reveals Essential Role of GH Signaling in Hepatic Lipid Metabolism. *J Biol Chem.* 2009 May 21. . [In Press]