

Summer Student Research Program  
Project Description

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**PROJECT TITLE (200 Characters max):**

*Role of insulin mimetic agent upon osseous healing in non DM rat*

**HYPOTHESIS:**

Insulin has both direct and indirect effects on bone. *In vitro*, insulin has been shown to stimulate proliferation of rat osteoblastic cells through their insulin receptors {Hickman, 1989 #106; Levy, 1986 #59}. *In vitro* studies have also proved insulin directly increases collagen production by osteoblasts {Kream, 1985 #128}. In fetal rat calvaria, Insulin increased collagen synthesis in the central bone; however, only high insulin concentrations increased collagen synthesis in the periosteum. IGF-I, which activates similar receptors as insulin, also stimulates collagen synthesis and cell proliferation in osteoblasts {Gabbitas, 1994 #56; Machwate, 1994 #61}.

**Hypothesis:** insulin plays a fundamental role in bone formation.

**PROJECT DESCRIPTION (Include design, methodology, data collection, techniques, data analysis to be employed and evaluation and interpretation methodology)**

More than one million operations are performed in the United States each year for reconstructive surgery, trauma, or abnormal skeletal defects. Large amounts of autologous bone stock, and alternatively, large bulk allograft is needed for these surgical procedures. Application of autogenous bone graft is the standard technique used to facilitate the arthrodesis process. Iliac crest graft harvesting remains today's gold standard, with approximately 340,000 procedures done annually. Autogenous bone grafting is associated with notable morbidity: including scarring; increased surgical time; prolonged hospitalization; delayed rehabilitation; increased blood loss; increased infection risk; and surgical complications (i.e. fracture, hematoma, neuroma etc.). Complications arise in up to 31 % of the procedures and 27% of the patients continue to feel pain at 24 months post-surgery {Kim, 2009 #1093; Gupta, 2001 #1095; Schwartz, 2009 #1094}. At times, the quantity of available graft is suboptimal and still necessitates augmentation with allograft. For these reasons, an impetus exists to develop and validate an alternative process capable of achieving the performance of iliac crest graft, while eliminating the associated morbidity and complications.

Alternatively, large bulk allograft has been utilized for reconstructive needs. Little is understood about the coordination of events leading to successful union. It is evident that bone healing involves the regulation of cellular chemotaxis, proliferation, and differentiation. Several signaling molecules have been identified which regulate the cascade of events in a time dependent fashion leading to the repair of bone tissue {Dimitriou, 2005 #776}. The key growth factors characterized in the fracture site are TGF- $\beta$ 1, TGF- $\beta$ 2, BMP-2, BMP-3, BMP-4, and BMP-7 (OP-1), PDGF, and acidic and basic FGF (FGF-1 and FGF-2) {Joyce, 1991 #44; Linkhart, 1996 #618}.

The local effect of insulin administration on bone *in vivo* has proved difficult to quantify, attributable to the systemic effects of insulin, particularly hypoglycemia {Stuck, 1932 #1090}. Local injection of insulin over one hemicalvariae of an adult mouse was used to demonstrate the

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direct effect of insulin on bone {Cornish, 1996 #126}. Indices of bone formation significantly increased in insulin-treated samples compared to untreated hemicalvariae. Indices of bone resorption declined while mineralized bone area increased in insulin-treated animals. The direct action of insulin on bone may contribute to increased bone density seen in obesity in addition to the osteopenia appreciated in type I diabetes\_ {Einhorn, 1988 #55}. Puche et al. reported an increase in calcium and phosphorus plasma levels when crystalline insulin was administered to thyroparathyroidectomized rats {Puche, 1973 #782}. These studies suggest insulin plays a fundamental role in bone formation.

This study investigated the effects of local insulin in a non-critical size femoral defect rat model. The *in vivo* release kinetics of local insulin delivery was investigated to examine possible hypoglycemic side effects of local insulin treatment. Microradiographic, histologic, and histomorphometric outcome parameters were also evaluated the non-critical size femoral defect model to determine the effect of local insulin on new bone growth.

### SPONSOR'S MOST RECENT PUBLICATIONS RELEVANT TO THIS RESEARCH:

*Beam H et al Lin SS, JOR 2002*

*Gandh, A et al Lin SS BONE 2005*

THIS PROJECT IS:  Clinical     Laboratory     Behavioral     Other

THIS PROJECT IS CANCER-RELATED

Please explain Cancer relevance

THIS PROJECT IS HEART, LUNG & BLOOD- RELATED

Please explain Heart, Lung, Blood relevance

THIS PROJECT EMPLOYS RADIOISOTOPES

THIS PROJECT INVOLVES THE USE OF ANIMALS

PENDING                       APPROVED                       IACUC PROTOCOL #06041

THIS PROJECT INVOLVES THE USE OF HUMAN SUBJECTS

PENDING                       APPROVED                       IRB PROTOCOL # M

THIS PROJECT IS SUITABLE FOR:

UNDERGRADUATE STUDENTS                       ENTERING FRESHMAN   
SOPHMORES                       ALL STUDENTS

THIS PROJECT IS WORK-STUDY:            Yes             or            No

THIS PROJECT WILL BE POSTED DURING ACADEMIC YEAR  
FOR INTERESTED VOLUNTEERS?:    Yes             or            No

WHAT WILL THE STUDENT LEARN FROM THIS EXPERIENCE?

*The student shall learn basic skills of animal husbandry, surgeries as well the technique for outcome analysis of histology, radiographic and mechanical testing*