

The University of Connecticut Health Center

# GENERAL CLINICAL RESEARCH CENTER NEWSLETTER

## OSTEOPOROSIS AND BONE AUGMENTATION/IMPLANT OUTCOMES: AN OBSERVATIONAL STUDY



(Back Row L-R): **David Shafer, DMD, Associate Professor;**  
**Alan Lurie, DDS, PhD, Professor;**  
**David G. Pendrys, DDS, PhD, Associate Professor;**  
**Martin Freilich, DDS, Professor**  
 (Front Row L-R): **Pamela Taxel, MD, Associate Professor;**  
**Susan Reisine, PhD, Professor;**  
**Denise Ortiz, BA, MPH Candidate**

### *Featured PI* **Martin Freilich, DDS** **Professor**

Inadequate bone volume and low bone density create substantial clinical problems for our aging adult population. With the ever-increasing size of the geriatric population, these changes in bone pose particular problems for craniofacial reconstruction and tooth replacement. The replacement of missing teeth with dental implants has become very popular, but is frequently limited by the height and width of the residual alveolar bony ridge that resorbs as a consequence of tooth loss. In the near future, tissue-engineering methods, including cell transplantation and the release of drugs that stimulate bone growth and enhance bone

density, may become available for clinical application.

However, the current standard treatment to increase bone volume is through autogenous graft transplantation. While grafting tends to be successful in young healthy patients, there is evidence that success rates of grafting procedures markedly decrease with age and certain systemic conditions, such as osteoporosis.<sup>1</sup> The efforts of our preclinical research group have focused on utilizing basic bone biology to develop new methods of bone augmentation to solve this common clinical problem.

Our clinical research program brings together preclinical bone augmentation research with research on the specific challenges associated with osteoporosis. This interdisciplinary group of investigators includes Dr. David Pendrys, an epidemiologist; Dr. Pamela Taxel, a bone endocrinologist; Dr. Alan Lurie, an oral and maxillofacial radiologist; Dr. Susan Reisine, a behavioral scientist and Dr. David Shafer, an oral and maxillofacial surgeon. The investigators are fortunate to be working with Ms. Denise Ortiz, the project coordinator, as well as Ms. Lisa Burgio and Ms. Megyn Clement, who are GCRC research dental assistants. While this study will utilize autogenous graft transplantation methods,



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it is envisioned that it will provide a foundation for future clinical studies that deliver bone-stimulating drugs that substitute for graft transplantation, as we have done with our preclinical work.

### Low bone density and bone augmentation:

Osteoporosis is a skeletal disease that compromises bone strength, thereby predisposing those affected to increased risk of fractures and diminished fracture repair. In the United States, there are roughly 10 million women over the age of 50 who have osteoporosis and an additional 34 million with low bone mass or "osteopenia."<sup>2,3,4</sup> Because a statistically significant correlation has been shown between hip and mandible bone mineral density (BMD)<sup>4</sup>, this large population may be at increased risk for complications and low success rates for craniofacial bone augmentation procedures when compared to women with healthy bone. The literature suggests that women with low bone mass or osteoporosis may have compromised outcomes in response to augmentation procedures.<sup>5,6</sup> However, to date, there are no reported studies that have been designed to evaluate the relationship between specific measures of bone metabolism and bone health parameters (e.g., BMD, markers of bone turnover, fracture history) and the success of alveolar bone augmentation procedures. Because osteoporosis is a major public health issue in our aging population, it is critical to understand the relationship between this disorder and bone augmentation/dental implantation.

Five year UCHC clinical study: We are currently recruiting subjects for a descriptive/observational study to evaluate surgical bone augmentation/dental implant placement outcomes among postmenopausal women with varying degrees of bone density measurement representative of the aging population. Our long-range goal is to test new methods to guide new bone formation at alveolar ridge sites. The objective of this study is to utilize a clinical study model to test the association between specific measures of bone health (including the diagnosis of osteoporosis)

and the successful integration of new bone from bone augmentation procedures. We plan to accomplish the objectives of this study by pursuing two specific aims: 1) To generate a descriptive estimate of the two-year success rate of bone augmentation followed by dental implant placement in postmenopausal women with normal to osteoporotic bone density; and 2) To explore potential associations between bone health parameters (e.g., BMD, biochemical markers of bone turnover, fracture history and vitamin D levels) and implant failure.

We expect this research to provide critical data on success/failure rates of augmentation procedures among women with healthy and impaired bone health. This will enable us to plan studies of how best to enhance success rates among older, postmenopausal women. The study will also provide new data on the potential role of bone turnover markers as predictors of implant success. Such data may be of critical importance to the clinician in identifying and managing patients at high risk of implant failure.

Background: Tooth loss and subsequent bone resorption is seen in a significant proportion of the population over the age of 50 years, including post-menopausal women.<sup>7,8</sup> Depending on racial grouping, 65-80 % of postmenopausal women experience significantly reduced BMD, with 25-40 % diagnosed with osteoporosis.<sup>9,10</sup> It is known that osteoporosis is also evident in the jaws,<sup>11,12,13,14</sup> with significant correlations found between lower jaw and hip bone mineral density.<sup>15</sup> Although the modern standard of care for tooth replacement is the placement of the dental implant, as noted earlier, because bone resorption often follows tooth loss,<sup>16,17</sup> bone augmentation procedures are frequently needed prior to implant placement.

Autogenous (from the same patient) bone transplanted in the form of block grafts generally harvested from intraoral donor sites (such as the posterior lower jaw or the chin<sup>18</sup>) are secured with screws into deficient sites months prior to implant placement.<sup>19</sup> High success rates (90 ± 5%) are consistently reported in healthy

patients.<sup>20</sup> These grafts carry bone forming cells and bone inductive substances into areas that are likely deficient in these components. Less invasive procedures, such as alveolar ridge expansion<sup>21, 22</sup> and dehiscence repair with autogenous bone chips,<sup>23</sup> can sometimes be used, allowing for simultaneous implant placement. Both techniques have advantages in terms of reduced treatment time, patient comfort and simplicity of the technique and also demonstrate high success rates in healthy patients.<sup>24, 25, 26, 27, 28</sup> While many studies demonstrate the high success rate of bone augmentation, there is little evidence demonstrating the success of bone augmentation procedures in patients with low BMD or osteoporosis.

Bone augmentation requires vigorous activity of a critical mass of osteoblast precursors and osteoblasts. As a consequence of menopause and substantially decreased ovarian estrogen production there is a decrease in the production of osteoblasts and osteoblast proteins (IGF, TGF $\beta$ , BMP, Type I collagen) and an increased production of IL-6, RANK-ligand and other cytokines. A complex signaling pathway stimulates the differentiation of osteoclasts, which are directly responsible for bone resorption.<sup>29, 30</sup> These changes lead to a decrease in BMD and may compromise bone augmentation efforts.<sup>31, 32, 33</sup> Bone density is reliably evaluated from dual energy x-ray absorptiometry (DEXA). Micro-architectural deterioration and low bone density scores characterize the World Health Organization's definition of osteoporosis (WHO Technical Report Series 843, WHO, Geneva, 1994.).

The biochemical markers of bone formation and bone resorption are frequently called markers of "bone turnover." Bone-specific alkaline phosphatase (ALP, BAP), procollagen type I C propeptide (PICP) and procollagen type I N propeptide (PINP) are markers of bone formation. PINP and PICP terminals are cleaved off and can be measured in the blood to reflect bone formation. Aminoterminal cross-linking telopeptide of bone collagen (NTX), carboxyterminal cross-linking telopeptide of

bone collagen (CTX) and pyridinoline (PYD) are useful markers of bone resorption.

Biochemical markers have been used primarily to assess the rate of bone turnover in research and clinical settings and to evaluate future fracture risk as well as response to treatment of osteoporosis.<sup>34, 35, 36</sup> There is evidence of an association between low BMD and high bone turnover.<sup>37</sup> Furthermore, studies have shown that women with low bone mass, history of prior fracture and high bone turnover are at a higher risk of fracture.<sup>38, 39, 40, 41, 42, 43, 44</sup> Low bone mass and high bone turnover may also be associated with failure of bone augmentation.

Both cell culture and animal models have demonstrated the different response of bone regeneration in healthy and pathological conditions.<sup>45, 46, 47</sup> These findings and the known decrease in bone cell numbers and activity along with differences in biomechanical and micro-architectural deterioration also associated with this systemic bone disorder may create a substantial biological challenge at the site of bone augmentation attempts in aged or osteoporotic bone.<sup>48</sup> In general, the relationship between low BMD and augmentation success is not well explored and additional research in this area is of critical importance.<sup>49</sup> Recent reports have attempted to show an association between bone graft/dental implant loss and factors such as smoking, advanced age and low bone density with mixed conclusions.<sup>50, 51, 52</sup> However, these studies had a relatively small number of "cases" or failed implants and an even smaller number of patients with low bone density/osteoporosis in their sample populations. Larger, prospective studies of subjects with low bone mass and density are needed to clarify the relationship between systemic bone disorders and alveolar bone augmentation/dental implant placement.

Study methods Through the recruitment, treatment and evaluation of 120 subjects, our study will attempt to address these limitations in the literature. All participants will receive bone augmentation, implant placement and prosthetic treatment based upon their specific presenting clinical situation, as guided by specific criteria

that are part of the study protocol. The choice of the augmentation method and the timing of implant placement are based upon the alveolar ridge width in the edentulous area. The three surgical augmentation methods to be used in this study are: 1) autogenous intraoral block graft (less than 3 mm initial ridge width); 2) selective ridge expansion/combined with implant placement (3–4 mm initial ridge width); or 3) implant placement combined with dehiscence repair with autogenous bone chips covered by collagen membrane (5–6 mm ridge width). Ridge width assessment and consequent choice of surgical method will be made utilizing 3-D radiographic analysis at the treatment planning exam and will be visually verified at the time of surgical entry. Prosthetic procedures to fabricate artificial crowns will begin three months after placement of the implant.

Survival of the implant will be the primary outcome measure of success. However, success will be secondarily assessed by other relevant clinical outcomes, clinical efficiency, as well as patient satisfaction, pain and quality of life. Descriptive analyses will also explore potential predictive associations between bone health parameters and bone augmentation/implant success, both individually and jointly. Data from this study will provide information on differential implant success rates for women possessing a spectrum of bone mineral density. Our long-range goal is to identify the most important predictors of success of bone augmentation/implant placement among patients with compromised bone health and/or unfavorable local alveolar architecture. We will then develop and test the best methods to use in delivering these therapies, including the application of new techniques with which to guide alveolar bone formation at deficient osseous sites.

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## NOTES FROM THE GCRC PROGRAM DIRECTOR



**Henry R. Kranzler, M.D.**

Professor of Psychiatry,  
GCRC Program Director

As you may have heard, plans were being made by the Health Center administration to move the General Clinical Research Center (GCRC; which since its inception 14 years ago has been located in the main Health Center building) to the Dowling North Building. The Clinical Trials Unit (CTU), and the Office of Clinical and Translational Research (OCTR) were also to be relocated there. The move was intended to consolidate clinical research and administrative activities in a single building, in an effort to synergize those activities and establish a Clinical and Translational Science Institute (CTSI) at UHC. The CTSI will be the basis for a Clinical and Translational Science Award (CTSA) application to NIH. By the time UHC submits its first CTSA application, which is planned for either June or October 2008, as many as 32 institutions will have been awarded a CTSA, so the competition will be keen.

Recently, however, plans to renovate the space at Dowling North so that the GCRC can move there have been put on hold. However, the Dental Clinical Research Center (DCRC), a GCRC core, was recently moved temporarily from Dental Clinic 10 to Dental Clinic 4 in the main building to accommodate the establishment of the Dental Implant Center. Renovations are underway to provide a new, permanent location for the DCRC in the L building in the coming year.

The specific reasons for the decision to delay in moving the GCRC have not been made public yet. Further, the potential still exists for such a move to occur. In response to my request for input on the potential move, some investigators have voiced the concern that, since Dowling North is less accessible to them, the move would limit their ability to conduct clinical research, given their clinical and other responsibilities that occur largely in the main building. There is also concern over the adequacy of the facilities available at Dowling North, including decreased access for research subjects, particularly those who are ill or aged. Health Center administration has assured us that, if the move occurs, all necessary modifications will first be made to accommodate the activities of the GCRC and CTU. Despite the temporary reprieve, I remain concerned that the plans be adequately considered prior to the GCRC moving to Dowling North or to another location on the UCHC campus. I welcome any questions or comments that you may have related to this matter.

### **DATA AND SAFETY MONITORING PLANS**

by Kathleen Salomone, APRN, MSW  
Research Subject Advocate (RSA)

In 1998 and 2000, NIH issued policies on Data and Safety Monitoring for Clinical Trials. Those policies outline the requirements for data and safety monitoring of clinical trials supported by NIH funds. In addition, The National Center for Research Resources (NCRR), the NIH Center that funds GCRCs, requires all GCRC-supported protocols to have a Data and Safety Monitoring Plan that is approved by the GCRC Scientific Advisory Committee and by the Institutional Review Board. A common misconception is that a data and safety monitoring plan (DSMP) is required only for clinical trials. Monitoring the ongoing study plays an essential role in protecting the safety of participants and assuring the integrity of research; hence developing an

effective monitoring plan is of paramount importance for all clinical studies.

The UCHC IRB application includes Appendix B, The Data and Safety Monitoring Plan. Although not required for all UCHC IRB applications, it is required when requesting support/resources from the GCRC. Thus, Appendix B must be included with the IRB application and the GCRC application when support/resources are sought from the GCRC. Once approved, the UCHC IRB stamps the Appendix B valid through the expiration date of the protocol. The GCRC is required to maintain a copy of the current IRB-approved DSMP. The investigator should review the DSMP for accuracy at least annually, as the monitoring plan may change. The DSMP must be submitted to the IRB and the GCRC annually for approval. It is also important to maintain documentation showing that the data and safety monitoring plan is being followed.

NCRR also requires all protocols that place subjects at significant risk have an independent Data and Safety Monitoring Board (DSMB). The use of a DSMB should be noted in the UCHC IRB application/ Appendix B. When a DSMB is used, the UCHC IRB application should also include the DSMB Charter and membership roster, identifying the Chairperson of the Board. Some important characteristics of a DSMB include:

- members are not affiliated with the study
- no fewer than three members
- meet annually, at a minimum
- may have an open and closed portion of the meeting. The PI and/ or study staff attend the open session only
- submit all DSMB reports to the IRB and to the GCRC Research Subject Advocate

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For more detailed information on DSMBs including a template for a DSMB Charter see: <http://resadm.uhc.edu/hspo/irb/files/CurrentForms/AppendixBInstructionsRevised081505.doc>

If you are applying for GCRC funding and need assistance or have questions regarding the development of a DSMP/B, please contact Kathy Salomone, GCRC RSA at 679-3276 or [Salomone@nso.uhc.edu](mailto:Salomone@nso.uhc.edu)

### THE GCRC CONGRATULATES

**Christopher Carroll, M.D.** on having received the Alfred Soffer Award of the American College of Chest Physicians for the retrospective arm of his study entitled, "β-Adrenergic Receptor Polymorphisms: Implications for the Treatment of Status Asthmaticus in Children". This study was supported by the GCRC. Dr. Carroll, a pediatrician at Connecticut Children's Medical Center, received one of two of these awards for "outstanding original scientific research".

### UPCOMING GCRC SEMINARS

**Tuesday, March 11, 2008**

**Thiruchandurai V. Rajan, M.D.**  
Professor, Department of Pathology &  
Laboratory Medicine  
University of Connecticut Health Center  
Farmington, CT

**“The Intra-Uterine Environment  
and Adult Health”**

12:00 noon –1:00 p.m.  
Academic Research Building - EG-013

**Monday, March 17, 2008**

**William Hersh, M.D.**

Professor and Chair, Department of Medical  
Informatics and Clinical Epidemiology  
Oregon Health and Science  
Portland, OR

**“Informatics: An Essential Tool and  
Science for Translational Research”**

12:00 noon –1:00 p.m.  
Onyuke Dining Room

**Tuesday, April 22, 2008**

**Roger S. Thrall, MD.**

Professor, Department of Immunology  
University of Connecticut Health Center  
Farmington, CT

**“Regulatory Lymphocytes in a Mouse  
Model of Asthma”**

12:00 noon –1:00 p.m.  
Academic Research Building - EG-013

**Tuesday, May 13, 2008**

**Lance Bauer, M.D.**

University of Connecticut Health Center

**Tuesday, May 27, 2008**

**Bruce Liang, M.D.**

University of Connecticut Health Center

**Tuesday, June 3, 2008**

**Jonathan A. Ship, M.D.**

NYU School of Medicine

**Tuesday, June 10, 2008**

**Mark Litt, M.D.**

University of Connecticut Health Center

*Upcoming seminars are posted on our website at:  
(<http://gcr.uhc.edu/training/gcrcseminar.html>)*

*All GCRC seminars are sponsored by the University  
of Connecticut School of Medicine Office of  
Continuing Medical Education. You can receive one  
hour per session of category 1 credit for attending  
this educational session.*

## NEW CLINICAL RESEARCH IN THE GCRC

Genetic Influences on Responsiveness to  
Albuterol in Children with Bronchiolitis  
*P.I. - Christopher Carroll, M.D.*

Anti-Inflammatory Intervention in Radiation-  
induced Oral Mucositis  
*P.I. - Rajesh Lalla, B.D.S., Ph.D.*

Topiramate Treatment of Problem Drinkers  
*P.I. - Henry Kranzler, M.D.*

Behavioral and Physiological Responses to  
Race-Related Stress in Diabetic Women  
*P.I. - Julie Wagner, Ph.D.*

Pharmacogenetic Testing for Warfarin Therapy  
*P.I. - Min Fang, M.D., Ph.D.*

## RECENT GCRC PUBLICATIONS

Abu-Hasaballah K, James A, Aseltine RH Jr.  
Lessons and Pitfalls of Interactive Voice  
Response in Medical Research. *Contemp.  
Clin. Trials*, 28:593-602, 2007.

Alessi SM, Hanson T, Wieners M, Petry NM.  
Low-cost Contingency Management in  
Community Clinics: Delivering Incentives  
Partially in Group Therapy. *Exp. Clin.  
Psychopharmacol.* 15:293-300, 2007.

Bauer LO, Covault J, Harel O, Das S, Gelernter  
J, Anton R, Kranzler HR. Variation in  
GABRA2 Predicts Drinking Behavior in  
Project MATCH subjects. *Alcohol Clin.  
Exp. Res.* 31:1780-7, 2007.

Litt MD, Kadden RM, Kabela-Cormier E, Petry  
N. Changing Network Support for Drinking:  
Initial Findings from the Network Support  
Project. *J. Consult. Clin. Psychol.* 75:542-  
55, 2007.

Taxel P, Kaneko, H, Lee SK, Aguila HL, Raisz  
LG, Lorenzo JA. Estradiol Rapidly Inhibits  
Osteoclastogenesis and RANKL Expression  
in Bone Marrow Cultures in Postmenopausal  
Women: A Pilot Study. *Osteoporosis Int.*  
19(2):193-9, 2008.



### REMINDER TO INVESTIGATORS

Remember to acknowledge the GCRC grant  
on all manuscripts and abstracts as follows:

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University of Connecticut Health Center,  
Farmington, CT



## RECRUITMENTS

### SMOKERS

A research study at the University of  
Connecticut Health Center is evaluating a  
medication for smoking cessation. All visits and  
study medication (active drug or inactive  
placebo) are **free of charge**. After an initial  
screening visit, there will be 11 additional  
weekly visits.

**We are seeking smokers who are:**

- **between 18 and 65 years of age**
- **smoking at least 10 cigarettes per day**

This research is under the direction of  
Cheryl Oncken,  
Associate Professor of Medicine.

Please call **(860) 679-3136** for more  
information about this study.

IRB Number: 06-114-1

## ARE YOU YOUNG AND HEALTHY AND INTERESTED IN KNOWING ABOUT YOUR BONE HEALTH?

Healthy Women 20 to 30 years of age with regular menstrual periods needed for a Medical Research Study at University of Connecticut Health Center.

### To qualify, you must be:

- Healthy - Age 20 to 30 years
- Having regular menstrual periods
- Not a smoker
- Not on birth control pills
- Not pregnant within last 6 months or breastfeeding
- Willing to come to the health center for two visits

**You will receive blood work and a bone density at no cost!**

### For more information, call:

Paula Gendreau, RN at 860-679-8074 or Harriet Zawistowski at 860-679-1658

IRB# 07-206-1

## HELP US LEARN MORE ABOUT

The effects of estrogen and progesterone on the anterior cruciate ligament (ACL) and the achilles tendon

We are seeking females between the ages of 18-30. Who are:

- Taking a monophasic birth control pill for at least the last three months.
- Participants should be active, non-smokers.
- Able to commit to Study duration of one month, which includes nine visits to the GCRC.

In this study, we hope to clarify the effect of birth control pills on both ACL laxity (stretchiness) and the extensibility of the

Achilles tendon. Upon completion of the study, participants will receive \$120. If you are interested or know of someone interested in participating in the study please contact Paula Gendreau at (860) 679-8074 or Harriet Zawistowski at (860) 679-1658.

This research is being conducted by  
Thomas H. Trojian, M.D.,  
Department of Family Medicine  
(IRB #04-170)

## HEALTHY ADULT MEN NEEDED FOR ALCOHOL STUDY

Healthy males, 21-45 years old, with no history of substance dependence or psychiatric illness, are needed for a UConn Health Center study to evaluate whether the effects of an FDA approved medication, dutasteride, and genetic variation modify the effects of a moderate dose of alcohol. Although dutasteride (Avodart™) is FDA approved for the treatment of bladder problems in men with an enlarged prostate, it is not FDA approved for the purpose of this study.

The study involves blood samples, interviews, questionnaires, and four 9-hour sessions where you will be asked to consume placebo or alcohol drinks (containing the equivalent of 4-6 standardized alcohol beverages, based on your body weight). Two to four days prior to each alcohol session you will attend a brief office visit to take dutasteride or matching placebo capsules. \$485 paid for full participation.

**For information call 860-679-4186**

IRB# 06-218

**GCRC PHONE NUMBERS**  
**(860) 679-4145 - ADMINISTRATION**  
**(860) 679-3666 - CLINIC**  
**(860) 679-1636 - STUDY LINE**

# General Clinical Research Center Newsletter

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Harriet Zawistowski, BGS, CCRP	Clinical Research Assistant

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*This Newsletter is a publication brought to you  
by the Staff of the GCRC*

## **General Clinical Research Center Newsletter**

**General Clinical Research Center  
UCONN Health Center, MC-3805  
263 Farmington Avenue  
Farmington, CT 06030**