



The Bone Disease

Program of Texas

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A collaborative research and clinical program of Baylor College of Medicine and The University of Texas M. D. Anderson Cancer Center

MISSION

The Bone Disease Program seeks to improve the prevention and treatment of all degenerative bone diseases, including osteoporosis, osteomalacia, Paget's disease, and cancer metastases to bone, by translating basic science findings to more effective treatment and prevention options.

The Bone Disease Program of Texas

Robert F. Gagel, MD

Director, Bone Disease Program of Texas
Professor and Head, Division of Internal Medicine
M. D. Anderson

Gerard Karsenty, MD, PhD

Co-Director, Bone Disease Program of Texas
Professor of Molecular and Human Genetics
Baylor College of Medicine

Pamela Jones

Program Director, Bone Disease Program of Texas
M. D. Anderson

Program Advisory Committee

Lawrence C. B. Chan, DSc, MBBS

Betty Rutherford Chair for Diabetes Research
Professor of Medicine and Molecular and Cellular Biology
Chief, Division of Diabetes, Endocrinology and Metabolism
Department of Medicine
Baylor College of Medicine

Stephen B. Greenberg, MD

Distinguished Service Professor and Chair
Department of Medicine
Baylor College of Medicine

Margaret L. Kripke, PhD

Executive Vice President and Chief Academic Officer
M. D. Anderson

Christopher Logothetis, MD

Professor and Chair, Genitourinary Medical Oncology
M. D. Anderson

Steven Teitelbaum, MD

Wilma and Roswell Messing Professor
of Pathology and Immunology
Washington University
St. Louis, Missouri

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Kirby Attwell

Allan Bailey

Mary Bass

Karen Calvert

Irene Franz

Gloria Hicks

Jennie Hull

John Lollar

Sandy Soriero

Suzi Swanson

Pat Thomas

Jerry Trzeciak

L. M. "Skip" Vaughan, Jr.

Marilyn M. Wright



Bone is a complex organ containing two cell types with opposite functions. The osteoclasts resorb or selectively degrade bone, whereas the osteoblasts make bone. Their concerted function is called bone remodeling, which maintains healthy bone mass between the end of puberty and menopause in women, and until about age 50 in men. Bone is an organ affected by multiple and frequent diseases, of which degenerative bone disease (including osteoporosis) and cancer metastasis are the most prevalent and the most devastating. Metabolic bone disease involves abnormal changes within bone cells, while bone metastasis is the spread of cancer cells to the bone.

In the United States today, 10 million individuals already are suffering from bone disease and almost 34 million more are estimated to have low bone mass, placing them at increased risk for osteoporosis and fractures. Bone metastasis, which occurs most often when breast, prostate, lung, kidney, myeloma and thyroid cancers spread to bones, is the primary cause of death in prostate cancer, and is one of the most frequent causes of pain in individuals with cancer.



Karen Calvert:
A Walking Miracle.
See inside.



As The Bone Disease Program of Texas enters its fourth year, it is important to reflect upon how this program has changed the face of bone research and clinical care in Houston and the State of Texas. The program has provided a focal point for interactions of physicians and scientists interested in bone health, yet there are many opportunities remaining to be explored. Prior to the development of this program, there was substantial research and clinical activity related to bone health in the Texas Medical Center, but with little organization or focus. The creation of this umbrella organization has provided a much needed research focus, developed seminars for both clinical and research activities, and supported core facilities for bone research. Most importantly, it has provided legitimacy to the topic of bone health. Under this umbrella, researchers and clinicians in the program developed increasing expertise and reputations in this field. Along the way we have made significant contributions to the field of bone biology and would like to highlight a few in this report.

Perhaps the most important research observations have been regarding the roles of the central and peripheral nervous system in the regulation of bone formation and the development of specific insights regarding this important process. Scientists in Dr. Gerard Karsenty's laboratory at Baylor College of Medicine have provided a road map for how the brain, specifically the hypothalamus, acts through the sympathetic nervous system to regulate local bone formation. Work in the Karsenty laboratory has identified a series of complex hormonal and nerve interactions that define both the physical characteristics of the skeleton and the amount of bone formed. These studies are groundbreaking in that they advance the novel concept that the nervous system, in fact, controls skeletal growth and development.

Other work emanating from the program has focused on regulation of the osteoblast, which is the bone-forming cell. Work from the Karsenty laboratory has established that the WNT signaling system is one of the key elements in regulating bone formation. Karsenty and M. D. Anderson investigator, Dr. Benoit deCrombrugge, have elucidated the regulatory factors involved in the creation of osteoblasts from more primitive stem cells. These

investigators have identified the two major regulators controlling this differentiation pathway, RUNX2 and osterix. In a series of elegant studies, Drs. Karsenty and de Crombrugge and colleagues, have shown that these factors are absolutely essential for normal formation and mineralization of the skeleton. Other work has focused on the mechanism by which bone is resorbed and turned over. Studies from Dr. Bryant Darnay's laboratory at M. D. Anderson have defined the signaling system of RANK and its ligand by which osteoclasts, the cells that break down bone, are formed and mediate bone resorption. Importantly, Dr. Darnay has developed agents that disrupt this pathway and may be useful clinically for treatment of specific bone diseases.

There have been advances on the clinical side of the program as well. Together with my colleagues from M. D. Anderson's Department of Endocrine Neoplasia and Hormonal Disorders and Medical Breast Oncology, we completed a study to examine a serious side effect of intravenous bisphosphonates characterized by bone deterioration in the jaw. Our review of 4,000 M. D. Anderson patients showed that this side effect, though serious, is quite rare. In another study Maria Cabanillas, MD, Department of General Internal Medicine and Department of Leukemia, determined that patients with acute lymphoblastic leukemia have profound bone loss during their treatment for acute leukemia. More importantly, she has determined that this group of patients has significant Vitamin D deficiency, one factor that is known to be responsible for robust bone loss. Her current studies focus on correction of several hormone deficiencies in patients with leukemia and the development of strategies for prevention of bone loss.

The Bone Disease Program of Texas continues to provide an organizational hub for groundbreaking clinical and laboratory research in this burgeoning field. The items in this publication are representative of the breadth of the accomplishments of the bone community in Houston.

**Bone
Disease
Program
of Texas
Enters Its
Fourth
Year**

Robert F. Gagel, MD
Director, The Bone Disease Program of Texas
Professor and Head, Division of Internal Medicine
The University of Texas M. D. Anderson Cancer Center

Investing in the Future: Rolanette & Berdon Lawrence Bone Research Awards



In March, 2006, The Bone Disease Program of Texas established a competitive research award for young Baylor College of Medicine and M. D. Anderson investigators active in bone research. The Rolanette and Berdon Lawrence Bone Research Awards were named to honor the couple for their generous support of the Bone Disease Program through an initial \$2 million donation and their continued philanthropic leadership in the community. The \$45,000 award provides initial funding for promising laboratory, pre-clinical, translational or clinical studies in metabolic or metastatic bone disease. Eligible projects include research development in the areas of bone metastases, bone health in cancer patients, bone formation and bone biology. The award program emphasizes hypothesis-driven research with high potential for future external funding and will advance the goal of reducing the incidence and morbidity of bone disease.

Five finalists were chosen from a larger pool of outstanding young investigators. Applicants represented a wide range of medical specialties and approaches to bone research (see inset). A panel of external reviewers evaluated the proposals and presentations, and two investigators, Drs. Roy Morello and Krishna Sinha were selected for funding.

Award winners Drs. Krishna Sinha and Roy Morello join Mr. and Mrs. Lawrence (seated) and director Dr. Robert Gagel (center)

Role of Collagen Prolyl 3-Hydroxylation in Bone Formation and Human Disease



Roy Morello, PhD, Assistant Professor, Baylor College of Medicine, Department of Molecular and Human Genetics

Osteogenesis imperfecta is a devastating childhood bone disease characterized by a low bone mass at birth. In the most severe form of this disorder, children die young because of fractures of their rib cage and other bones, making it impossible for them to breathe normally. In less severe cases, these youngsters develop

fractures of multiple bones during childhood and adolescence, which causes considerable bony deformities and long-term problems. The majority of children with this disorder have a defect in the type-1 collagen gene that leads to weakness of the skeleton; however, a small percentage of patients with this disorder have no such identifiable type-1 collagen abnormality. Dr. Roy Morello from Baylor College of Medicine's Department of Molecular and Human Genetics and his mentor Brendan Lee, MD, PhD, have identified a protein that they believe may explain the cases without a primary abnormality of type-1 collagen. The CRTAP (cartilage-associated protein) gene is responsible for the addition of a chemical group to collagen that allows collagen molecules to interact, thereby creating a stronger protein matrix in which bone mineral calcium can aggregate. Dr. Morello believes that a defect in this gene is responsible for the cases of osteogenesis where there is no primary type-1 collagen defect, and proposes to develop a mouse model in which the CRTAP gene is mutated to examine the effect of such abnormalities on normal bone formation and mineralization. He hopes to use these findings to develop treatments for children with this form of a severe and disabling bone disease.



Characterization of NO66, an Osx Interacting Protein During Osteoblast Differentiation and Bone Formation

Krishna M. Sinha, PhD, Instructor M. D. Anderson, Department of Molecular Genetics

Krishna Sinha, PhD, an investigator in M. D. Anderson's Department of Molecular Genetics, and his mentor, Dr. Benoit deCrombrugge, identified a gene/protein necessary for normal mineralization of the skeleton, which he named osterix. Mice in which this gene has been deleted failed to mineralize the skeleton. The question of how osterix deficiency causes a lack of mineralization led Dr. Krishna to look for proteins that interact with osterix. He identified the protein NO66, which is a novel protein not previously linked to any physiologic function, and found it interacts with osterix and inhibits its activity. Dr. Sinha has proposed a series of rationally designed studies to understand how this protein regulates bone formation and mineralization. This is a particularly exciting piece of work because of its therapeutic potential, as regulation of NO66 could be used as a treatment for osteoporosis and other disorders in which bone formation is decreased.

Rolanette and Berdon Lawrence Bone Research Award Finalists

Dickkopf-1 (DKK-1) Interaction with Osterix and Its Role in Osteosarcoma Pathogenesis and Tumorigenesis
Nadezhda V. Koshkina, PhD
Assistant Professor, Pediatrics, M. D. Anderson

The Role of VEGF and VEGFR on Osteoclastogenesis and Prostate Tumor Growth in Bone
Khalid A. Mohamedali, PhD
Instructor, Experimental Therapeutics, M. D. Anderson

Characterization of NO66, an Osx Interacting Protein, During Osteoblast Differentiation and Bone Formation
Krishna M. Sinha, PhD
Instructor, Molecular Genetics, M. D. Anderson

Role of Collagen Prolyl 3-Hydroxylation in Bone Formation and Human Disease
Roy Morello, PhD, Assistant Professor,
Molecular and Human Genetics, Baylor College of Medicine

Activator Protein-1 (AP-1) and Late Endochondral Bone Formation
Qiping Zheng, MD, PhD
Assistant Professor, Molecular and Human Genetics
Baylor College of Medicine



Magnus Hook, PhD, Institute of Biosciences and Technology, The Texas A & M University Health Science Center, Houston.

The external selection committee:
Steven Teitelbaum, MD, Wilma and Roswell Messing Professor of Pathology and Immunology, Washington University School of Medicine, St. Louis, Missouri; Dianna Milewicz, MD, PhD, Division of Medical Genetics, The University of Texas Health Science Center – Houston; and

The Bone Disease Program, through mechanisms such as the Rolanette and Berdon Lawrence Bone Research Awards, is committed to fostering groundbreaking research and supporting talented, young investigators in bone research careers.

Steven Teitelbaum, MD Headlines Annual Retreat Program

On Friday, March 17, 2006, members of the Bone Disease Program of Texas met for the program's 4th annual scientific retreat. The retreat was held in the Texas Medical Center and had a record attendance of over 60 participants from Baylor College of Medicine, M. D. Anderson, UT Health Science Center Houston, and Rice University.

Steven Teitelbaum, MD, Messing Professor of Pathology, Department of Pathology and Immunology, at Washington University in St. Louis, gave the keynote address. His talk, titled "Osteoclasts, Integrins and Osteoporosis," focused on his laboratory's recent discovery that the bone-degrading capacity of osteoclasts depends upon their physical interaction with receptor proteins on the bone surface. Blocking these receptors, known as integrins, also prevents osteoporosis. This effect was demonstrated when mice bred by the researchers without genes for the major integrins developed increased bone mass. Phase II clinical trials in humans are now underway for drugs that target the integrins.

The Facts about Osteoporosis

- Osteoporosis is the most common degenerative disease in developed countries. This disease is characterized by loss of bone and increased skeletal fragility, leading to an increased number of fractures.
- Osteoporosis is one manifestation of the aging process. Everyone will be affected by this disease at some point in his or her life—the only question is the degree of severity. In both men and women, bone loss occurs with aging and causes spine and hip fractures during middle and older age. The increase of 5 to 10 years of life expectancy over the past 50 years has made osteoporosis a common and distressing health problem for many otherwise healthy individuals.
- If preventative steps are not taken, bone loss begins long before symptoms of the disease are apparent.
- In the U.S., osteoporosis is responsible for more than 1.5 million fractures annually. One in two women and one in eight men over age 50 will have an osteoporosis-related fracture in their lifetime. The consequences of these fractures are devastating. For example, one-fourth of those who were ambulatory before their hip fracture require long-term care afterward; and about one-fourth of hip fracture patients age 50 and over die in the year following their fracture due to the dramatic change in their lifestyle.
- Osteoporosis is a major public health concern. The estimated national direct expenditures by physicians, hospitals and nursing homes for osteoporosis-associated fractures totaled \$15 billion in 2000. Experts estimate that this cost is going to rise 5 to 10 percent per year as the baby-boomer population ages.
- To date, only one bone-forming drug exists (teriparatide). This drug is approved for use in post-menopausal women with osteoporosis; however, its safety in other patient populations, including cancer, has not been established.
- A number of drugs are widely used to stop the destruction of bone, including bisphosphonates and SERMs (selective estrogen receptor modulators).
- Cancer patients face additional challenges to bone health. Recent advances in treatment regimens for breast and prostate cancer have greatly improved patient survival; however, these therapies can weaken bones. Increasingly, patients who are otherwise cured, or whose cancer is successfully managed for years, are developing osteoporosis at an accelerated rate due to cancer treatment.

Beta Blockers May Prevent Osteoporosis

Gerard Karsenty, MD, PhD, Baylor College of Medicine Professor of Molecular and Human Genetics, and his colleagues demonstrated in mice that the sympathetic nervous system mediates the resorption or destruction of bone through a special receptor on bone cells. This effect is responsible for the development of osteoporosis in female mice after removal of their ovaries, which initiates a menopausal state. Preventing the sympathetic nervous system from activating this receptor could prevent osteoporosis following menopause. Karsenty's group provided the background for this recent discovery a few years ago when he demonstrated that one of the main functions of leptin, a hormone initially thought only to regulate appetite, is to regulate bone formation. Dr. Karsenty's lab then showed that the sympathetic nervous system mediated only the bone formation and not the appetite-related function of leptin.

In their most recent study, they showed that leptin also affects bone destruction or resorption to maintain a constant rate of bone remodeling. This action was also found to be mediated by the sympathetic nervous system through the *Adrb2* receptor present on bone cells. Female mice lacking this receptor make more bone than normal mice, and they do not lose bone when their ovaries are removed. These findings have highly significant clinical implications, especially as the mice studied remained lean and did not demonstrate an increased appetite. Drugs to inhibit the sympathetic nervous system, called beta blockers, are already commonly used for treating high blood pressure. These beta blockers reduce blood pressure by targeting similar receptors in heart muscle cells. The development of a beta blocker that would block leptin receptors on bone without affecting heart function could lead to development of a safe and effective agent to prevent bone loss due to osteoporosis.

Dr. Karsenty is also studying the effect of beta blockers on men who have undergone surgical castration as treatment for prostate cancer. This study is being carried out in collaboration with The University of Texas M. D. Anderson Cancer Center.



Dr. Gerard Karsenty, receives the 2006 Edith and Peter O'Donnell Award for achievements in medicine from The Academy of Medicine, Engineering and Science of Texas.

On hand to present the awards was Texas dignitary Senator Kay Bailey Hutchison.

As this publication goes to press, we bid adieu to Dr. Karsenty. He will be leaving Baylor College of Medicine this summer to become Chair of the Department of Genetics and Development at Columbia University College of Physicians and Surgeons, New York. We are truly grateful for the many outstanding scientific contributions he has made to bone disease research during his long tenure with Baylor and for his role in co-founding the Bone Program. We wish him all the best in his new endeavor.

Targeting Osteoclasts in Bone Metastasis

Identifying the fundamental cellular, molecular, and genetic mechanisms controlling cell growth and differentiation is essential for understanding the evolution of disease and cancer. Identification of these processes and the gene products that modulate differentiation and cellular growth may provide novel targets for molecular therapeutics for cancer intervention. The Bone Disease Program of Texas underscores this theme in its understanding of basic research to provide novel therapeutics for the treatment of bone-related cancer and diseases.

Bone metastasis is the second most common cancer-related metastasis and is not only a major therapeutic challenge but also significantly decreases patients' quality of life. It affects 80-90% of patients with advanced prostate cancer or breast cancer, and up to 30% of patients with cancer of the lung, colon, stomach, bladder, uterus, rectum, thyroid, or kidney. The mechanism of bone metastasis is not well understood. RANKL has been identified as an essential regulator of the formation and activation of bone-destroying osteoclasts and plays a role in metastatic bone cancer. Bryant Darnay, PhD, Department

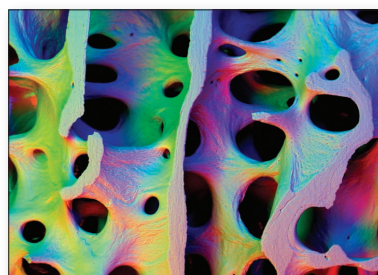
of Experimental Therapeutics, along with other scientists at M. D. Anderson is investigating the manipulation of RANKL, its receptor (RANK), and the signaling machinery within the osteoclast to prevent bone loss caused by osteoporosis and malignant tumors in animal models.

By understanding the mechanisms by which RANK and RANKL mediate their effects on the bone resorbing cells, it may be possible to develop effective new therapeutic approaches to treat bone-related diseases. The work from Dr. Darnay's laboratory at M. D. Anderson has defined the signaling system by which osteoclasts are formed and mediate bone resorption. His research has defined novel mechanisms that relay the signals from the outside of the cell to cause osteoclast maturation. Recently, his laboratory has developed novel agents that block osteoclast differentiation and function, of which one has been patented. Importantly, Dr. Darnay's observations and his expertise in osteoclast biology, along with other activities of clinicians at M. D. Anderson, will provide the basis for clinical evaluation of these new agents in bone metastasis.

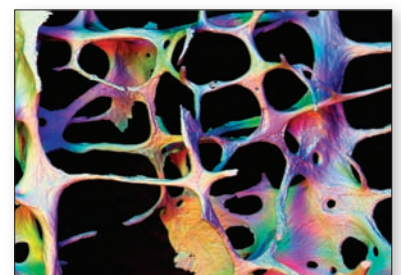
The Facts about Bone Metastases

Bone metastases occur when cancer cells break off from a primary tumor site, enter the bloodstream and reach bones.

- Breast, prostate, lung, kidney and thyroid cancers are most likely to spread to bones.
- Bone metastasis is the primary cause of death in prostate cancer, which is the most common cancer in American males. It also is a common problem in myeloma, leukemia and other forms of cancer.
- Bone metastasis is one of the most frequent causes of pain in individuals with cancer.
- Bone metastasis not only causes fractures but also increases blood calcium concentration to a level that can greatly reduce a cancer patient's quality of life and even become life-threatening.
- Our understanding of the process of cancer metastasis to the bone is still limited. This lack of understanding hinders our ability to design effective methods to prevent or control the process; however, recent discoveries about the interactions between cancer cells and normal bone cells hold promise that additional research will translate into new drugs in the near future.



Normal Bone
(courtesy of Alan Boyde)



Osteoporotic

Vitamin D – Exploring Its Role in Osteoporosis and Cancer

The laboratory of Sara Peleg, PhD, Associate Professor in M. D. Anderson's Department of Endocrine Neoplasia and Hormonal Disorders, focuses on the nuclear receptor for vitamin D. Nuclear receptors are transcription factors that function as transmitters of signals delivered by small lipophilic molecules such as steroid hormones and retinoids. These signals regulate embryonic development, cellular differentiation, and organ physiology.

The physiologic role of vitamin D is to regulate calcium homeostasis and bone remodeling. Bone remodeling effects of vitamin D include activation of osteoclasts, which cause bone resorption, as well as induction of maturation and differentiation of bone-forming osteoblasts. Therefore, significant efforts have been made to develop synthetic vitamin D analogues, or deltanoids, to treat metabolic and metastatic bone disease without inducing excessive bone resorption or hypercalcemia. To that end, Dr. Peleg and her colleagues have developed the concept of hybrid vitamin D deltanoids, which are synthetic compounds that combine two types of building blocks—one to reduce calcemia, and the other to promote cellular differentiation. Because both of these deltanoid actions are mediated through the transcriptional activities of the vitamin D receptor (VDR), Dr. Peleg and her colleagues are studying how modifications in the structure of deltanoids may change the profile of their VDR-mediated biological activities.

Biochemical studies performed by this group determined the relationship between deltanoid structures and their contact points in the VDR's ligand-binding pocket. They showed that the mode of interaction in the ligand-binding pocket has a fundamental effect on the outer shape of the VDR, and a direct impact on its interactions with cellular proteins (transcription coregulators) that modulate the level and spectrum of VDR transcriptional activities. Importantly, the change in the mode of interaction of several hybrid deltanoids with the VDR caused a cell-selective recruitment of VDR nuclear chaperones and transcription coregulators. Furthermore, *in vitro* and *ex-vivo* studies with hybrid deltanoids have revealed that they induce transcriptional activity of the VDR in a cell- and tissue-selective fashion.

Dr. Peleg's lab is translating its *in vitro* findings into preclinical studies using animal models of osteoporosis and prostate cancer-induced metastatic bone disease. The results of their research provide a foundation for the design of deltanoids that will have sufficient target cell and target gene specificity to be both potent and safe drugs for treatment of human disease.

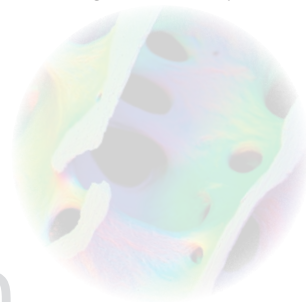
Osterix Plays Major Role in Bone

Holder of the Paul and Mary Haas Chair in Genetics in Honor of Amanda Marie Whittle, Dr. Benoit de Crombrugge is trying to understand the molecular signals that turn on bone formation and regulate activity in the osteoblasts. In 2002, de Crombrugge and his colleagues discovered a gene that regulates a major molecular switch required for bone formation in mice.

Mice that lack this gene can develop to a certain point, making so-called preosteoblast cells, but no bone. In the mutant mice, these pre-osteoblasts are arrested in their differentiation. Scientists named this master gene osterix and showed that its role is to turn on whole sets of genes that lead to bone formation. Scientists are looking for the specific genes that are turned on by osterix and are searching for external signals that tell osterix to set in motion the chain of events that leads to bone formation. That knowledge, de Crombrugge says, could lead to drugs that stimulate bone formation in areas where bone density is decreased, particularly in cancer patients whose bones are thinned by metastatic disease, and perhaps as a treatment for osteoporosis.

Shared Laboratories Expand with Influx of New Equipment

In late 2005, the Bone Disease Program received almost a half million dollars in earmarked congressional funds to purchase key equipment for shared resources at Baylor College of Medicine and The University of Texas M. D. Anderson Cancer Center. The density and hardness of bone makes it a difficult substance to sample, image, and analyze, necessitating special equipment for bone studies. Investigators will benefit from the purchase of the latest in high-tech cutting instruments for sampling bone in small animals. Newly acquired high resolution cameras allow scientists to detect structural changes in the bone samples of laboratory animals, and sophisticated software for bone analysis will provide the analytical results. In the final stages of development is a high resolution, digital X-ray imaging system with bone densitometry and body composition measurements. Bone Program scientists will be among the first in the nation to utilize this technology. The advantage of this system is that it can be used on live small animals, like mice and rats, allowing researchers to make multiple measurements *in situ* during the life of the animal. This capability avoids the need to sacrifice animals to measure these factors, therefore saving time, money, and animals.



Vitamin D Deficiency in Acute Leukemia

Vitamin D is a hormone that is found in few foods, but fortunately is produced in the skin by exposure to sunlight. The observation that patients in northern latitudes had a higher

Clinical

Research

incidence and mortality from cancer was first made in the 1940's. There are many epidemiologic studies that implicate sun exposure and vitamin D levels with a number of types of cancers including breast, prostate, and colon cancers.

Vitamin D is also a potent differentiator of cells, meaning that it can make immature cells become mature cells. Immature leukemic cells, known as blasts, can be made to mature into normal cells when exposed to vitamin D *in vitro*. Vitamin D plays a key role in maintaining a healthy, mineralized skeleton.

In a study led by Maria Cabanillas, MD, Assistant Professor, General Internal Medicine, clinicians examined 58 new patients with acute lymphoblastic leukemia (ALL) and lymphocytic

lymphoma who presented to M. D. Anderson between April 2004 and February 2006. Only 19% of patients had adequate stores of vitamin D in their blood. Vitamin D deficiency was present in 66% of patients, and borderline levels were present in 15% of patients. It is unclear as to why vitamin D deficiency is so prevalent in this group of patients, but possible causes are low sunlight exposure and poor nutrition. This study has also shown that patients with ALL

have substantial bone loss during therapy, up to 15% over a six month period. Vitamin D deficiency is likely to be one contributing factor. Because vitamin D is a differentiating agent in leukemic cell lines, it is also possible that vitamin D deficiency may play a pathogenic role in the development of leukemia.

Side Effects of IV Bisphosphonates

Osteonecrosis of the jaw is a rare disorder that is found in approximately 3% of cancer patients who have radiation to the head, neck and jaw. Patients experience jaw pain, toothache, exposed bone, and possibly altered sensation and recurrent soft-tissue infection. Affected tissues heal poorly, if at all. Over the past several years, reports have emerged that patients who are treated with intravenous bisphosphonates (and occasionally with oral bisphosphonates) have developed this condition in the absence of exposure to radiation therapy, which is already known for bone effects. Other studies have shown that almost all of these patients with osteonecrosis of the jaw have been treated with intravenous bisphosphonates. To assess the extent of this problem and better understand the causes, Dr. Ana Hoff, in collaboration with Drs. Robert Gagel and Gabriel Hortobagyi, reviewed the charts of all patients treated with intravenous bisphosphonates at the M. D. Anderson. The investigators

reviewed the medical records of 4,000 patients who received intravenous bisphosphonates and identified 31 patients who had developed osteonecrosis of the jaw. Most importantly, they determined that the majority of these patients had either a dental procedure such as a tooth being pulled or an implanted tooth, a poor-fitting denture, a bony outgrowth in the mouth, or trauma to the jaw or maxilla that precipitated the bony problem. These studies showed clearly that patients treated with very large doses of bisphosphonates for years are at highest risk for development of this uncommon but problematic condition. Most importantly, the results of the study provided insight into ways to avoid development of this problem and guidelines for dentists and oral surgeons to prevent this disorder.

Prevention of Bone Loss in Bone Marrow Transplant Patients

Patients with hematologic malignancies who undergo bone marrow transplantation are at high risk of bone loss. Bone loss occurs early and most rapidly during the first three months after the transplantation. Over 50% of patients receiving a transplant will develop graft versus host disease (GVHD). High-dose treatment with glucocorticoids (steroids) in these patients may also contribute to significant bone loss. Huifang Lu, MD, PhD, a rheumatologist in M. D. Anderson's General Internal Medicine Department, will conduct a study using intravenous bisphosphonates for the prevention of bone loss in this patient population.

Teriparatide in the Treatment of Postoperative Hypocalcemia

Mimi Hu, MD, Clinical/Research Endocrinology Fellow, Baylor College of Medicine and University of Texas M. D. Anderson Cancer Center, will conduct a trial in head and neck surgical patients to examine the effect of short-term administration of teriparatide, a synthetic form of human parathyroid hormone (PTH) and its effect on calcium levels. M. D. Anderson performs more than 400 thyroidectomies and extensive neck dissections for head and neck cancer annually, with an estimated 15-30% incidence of postoperative hypocalcemia. Hypocalcemia due to hypoparathyroidism is a common occurrence in patients after total thyroidectomy or extensive neck dissections, and often may require readmission for treatment. Complications with muscle spasms, seizures and vocal hoarseness may develop. Hospitalizations can be prolonged to allow for standard therapy using calcium and vitamin D. Teriparatide (PTH 1-34) mimics endogenous parathyroid hormone in that it increases renal reabsorption of calcium, increases 1,25-dihydroxyvitamin D3 synthesis, and mobilizes calcium out of the skeleton. It is currently available for treatment of osteoporosis in patients who usually have normal calcium levels. Dr. Hu and colleagues hypothesize that short-term use of PTH-1-34 will be effective in head and neck surgical patients in preventing symptoms due to low calcium levels, and may shorten the length of hospital stays or prevent additional readmissions for treatment of hypocalcemia.



Dr. Cabanillas and board member, Allan Bailey, discuss her research findings at March retreat.

Living with Bone Loss



Calvert at the Houstonian's Resolution Shape Up Program

In her early thirties, Calvert, along with her husband, Monte, received some long-anticipated, wonderful news. Calvert was pregnant with their first child. Because of difficulties with earlier pregnancies and concern about an existing immunologic disorder (lupus), she was placed on bed rest, cortisone-like drugs and a blood thinner. Within five months, she was losing height as her spine had begun to collapse. Calvert spent the last two months prior to delivery in the hospital. Doctors surmised that her profound bone loss was due to a combination of corticosteroid therapy for lupus and inactivity.

Following the caesarean delivery of her son, Justin, doctors placed Calvert in a full body cast and recommended an aggressive daily physical therapy plan that included water therapy. Recovery was challenging for Calvert because she was extremely fragile. Dr. Robert Gagel, M. D. Anderson endocrinologist, and director of The Bone Disease Program of Texas, said Calvert's bones looked like those of a 100-year old woman. At the time of her first appointment with Dr. Gagel, Calvert had fractured virtually every vertebral body in her spine and intense back pain kept her confined to a wheelchair. "I was a china doll in a china case, lying in bed waiting for my bones to break," says Calvert.

Doctors found Calvert's case particularly difficult because she did not readily absorb calcium and required high doses of a specific vitamin D analog to begin to remineralize bone. Calvert persevered with physical therapy while doctors isolated the endocrine problems. Within months, her bones began to recover.

"I am a walking miracle," says Karen Calvert, Bone Disease Program of Texas' board member and osteoporosis patient.

Eleven years have passed since that time. As a result of the assault on her skeleton, Calvert permanently lost six inches in height, but the treatment that Calvert received has significantly reduced her fracture risk. In fact, she has a substantial improvement in her spine and hip density – as much as 65% increased density in her spine.

The days of wheelchair confinement are long gone. Like most moms, Calvert runs between school activities for her son, a challenging job, and numerous social activities. She continues to take care of her bones by exercising regularly, taking calcium supplements, Vitamin D, and parathyroid hormone 1-34. Calvert is an active voice for the prevention of bone loss because she knows all too well that some loss is permanent. Calvert is also the voice of hope for those who are already experiencing problems. She knows, first hand, that effective treatment is available.

Her remarkable experience led Calvert to become a member of The Bone Disease Program of Texas' Development Advisory Board. Says Calvert, "Thanks to the expertise of the bone doctors like Dr.

Gagel, I have had the opportunity to be a mother to my son and be fully involved in his life. That's a miracle. How do you repay a miracle?"



Editor's Note: "Karen's situation is unique in its severity, but there are many other individuals, age 50 or older, who suffer from spine and hip fractures and are undiagnosed or under-treated. The Bone Disease Program sends a strong message of hope that they, like Karen, can continue to enjoy life."

Partners in the Bone Disease Program of Texas

We gratefully acknowledge the generosity of the following individuals, foundations and corporations who contributed between June of 2005 and June of 2006.

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The Bone Disease Program of Texas - Participants

Arthur Beaudet, MD
Chairman, Department of
Molecular and Human Genetics
Baylor College of Medicine

Maria Cabanillas, MD
Assistant Professor
General Internal Medicine
M. D. Anderson

Dianna Cody, PhD
Associate Professor
Imaging Physics
M. D. Anderson

Gilbert Cote, PhD
Associate Professor
Endocrine Neoplasia
and Hormonal Disorders
M. D. Anderson

Bryant Darnay, PhD
Assistant Professor
Experimental Therapeutics
M. D. Anderson

Benoit deCrombrughe, MD
Paul and Mary Haas Chair
Professor, Molecular Genetics
M. D. Anderson

Patricia Ducy, PhD
Assistant Professor
Molecular and Human Genetics
Baylor College of Medicine

Isaiah Fidler, PhD, DVM
Chair and Professor
Cancer Biology
M. D. Anderson

Ana Hoff, MD
Assistant Professor
Endocrine Neoplasia and
Hormonal Disorders
M. D. Anderson

Gabriel Hortobagyi, MD
Chair and Professor
Breast Medical Oncology
M. D. Anderson

Jeorg Jacoby, PhD
Instructor
Experimental Therapeutics
M. D. Anderson

Nora JanJan, MD
Professor, Radiation Oncology
M. D. Anderson

Brendon Lee, MD, PhD
Associate Professor
Molecular and Human Genetics
Baylor College of Medicine

Sue Hwa Lin, PhD
Professor
Molecular Pathology
M. D. Anderson

Huifang Lu, MD
Assistant Professor
General Internal Medicine
M. D. Anderson

Paul Mathew, MD
Assistant Professor
Genitourinary Medical
Oncology
M. D. Anderson

Roy Morello, PhD
Assistant Professor
Molecular and Human Genetics
Baylor College of Medicine

William A. Murphy, Jr., MD
Professor
Diagnostic Radiology
M. D. Anderson

Nora Navone, MD, PhD
Associate Professor
Research, Genitourinary
Medical Oncology
M. D. Anderson

Sara Peleg, PhD
Associate Professor
Endocrine Neoplasia and
Hormonal Disorders
M. D. Anderson

Rena Sellin, MD
Professor
Endocrine Neoplasia and
Hormonal Disorders
M. D. Anderson

Steven Sherman, MD
Associate Professor and Chair
Endocrine Neoplasia and
Hormonal Disorders
M. D. Anderson

Krishna Sinha, PhD
Instructor
Molecular Genetics
M. D. Anderson

Steven Waguespack, MD
Assistant Professor
Endocrine Neoplasia and
Hormonal Disorders
M. D. Anderson

Alan Yasko, MD
Professor
Orthopedic Oncology
M. D. Anderson

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