

AT TWENTY YEARS, MYELOMA INSTITUTE STANDS OUT AS A LEADER

August 2009 marked the 20th anniversary of the first stem cell infusion for treatment of multiple myeloma at UAMS. Now approaching the 8,000th peripheral blood stem cell infusion, or transplant, the Myeloma Institute for Research and Therapy (MIRT) stands out as the world leader in treatment of and research in multiple myeloma.

Unique Focus

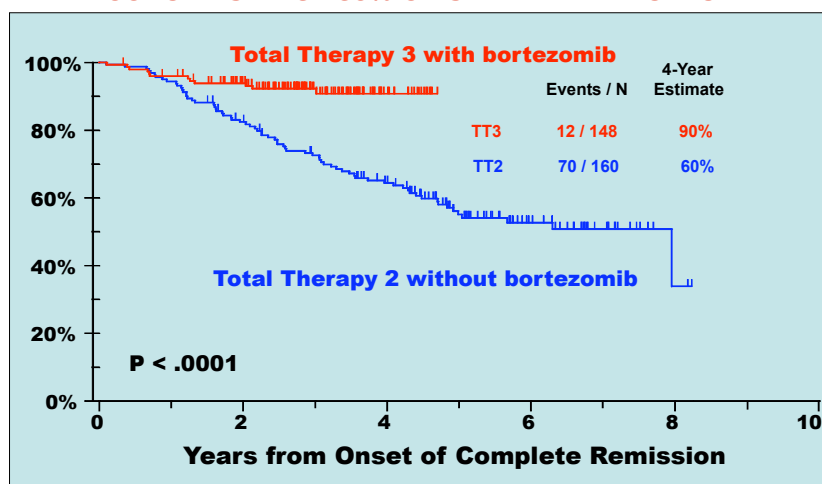
Dr. Bart Barlogie, Director of MIRT, and his colleagues have fundamentally changed the course of multiple myeloma through innovative translational research over the past 20 years. MIRT's program distinguishes itself by its primary focus on one disease and its pursuit of the most appropriate therapies for cure.

Success with Total Therapy Approach

- MIRT has had tremendous success with application of the Total Therapy (TT) approach, by which all currently available agents are applied upfront, resulting in an increase in median survival from 3 years to 6 years with TT1, about 10 years with TT2, and a projected 15 years with TT3, as 90% of such patients are in sustained complete remission at 5 years.
- Molecular characterization of myeloma into distinct subgroups, developed by MIRT scientists,

allows us to identify patients who will benefit the most from specific therapies. Based on unprecedented positive outcome data in TT3 in low-risk myeloma, such patients are randomized in TT4 between standard TT3 and TT3-lite, which is designed to reduce toxicity while maintaining efficacy. High-risk myeloma patients are offered TT5, which investigates whether disease recurrence during previous recovery phases in TT3 can be reduced or eliminated by more dose-dense and less dose-intense therapy.

CURE IS ANTICIPATED FOR THE MAJORITY OF GENOMICALLY DEFINED LOW-RISK MYELOMA CONSTITUTING ~85% OF UNTREATED DISEASE



- TT6, specifically for high-risk multiple myeloma patients who have had prior treatment, utilizes lower doses of chemotherapy drugs and shorter cycles. The premise is that myeloma cells will not have time to re-grow between cycles, resulting in longer remissions.
- A patient diagnosed today with low-risk multiple myeloma can expect to survive more than 10 years.

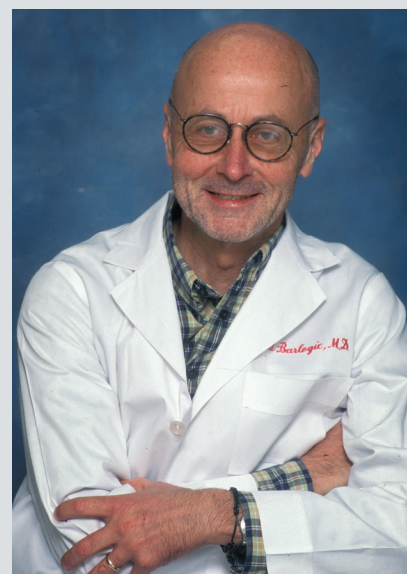
Unprecedented Wealth of Data

- Every new patient's prognosis can be forecast based on actual treatment data.

- MIRT's comprehensive database on more than 8,400 patients contains detailed baseline and follow-up information that is unsurpassed. It comprises Magnetic Resonance Imaging (MRI) data (approximately 7,000 at baseline and more than 35,000 at follow-up) and PET-CT data at baseline (2,000) and after therapy. Metaphase cytogenetics data from every diagnostic bone marrow specimen (more than 80,000) has allowed us to document clonal evolution and the development of treatment-induced Myelodysplastic Syndrome in the context of specific therapies. Gene Expression Profiling (GEP) samples (more than 1,500 at baseline and more than 5,000 at follow-up) have been obtained to address research questions relating to disease evolution in the context of the bone marrow micro-environment.
- MIRT has a large patient referral base; tight, long-term follow-up; integrated basic-clinical investigation; statistical power to interpret current findings in the context of historical patients with comprehensive annotations of clinical course and therapeutic interventions; and availability of samples and laboratory correlates in our database.
- MIRT has followed almost 600 patients for more than 10 years. MIRT is the only center with such long-term follow-up and instantaneous access to outcome data in the context of unique patient characteristics. This enables us to identify, almost instantaneously, patients who might be candidates for novel agents targeting unique pathways because of their genomic and other characteristics.
- Adequately large sample size is critical in order for myeloma therapeutic trials to have an impact on clinical practice. MIRT has maintained an annual referral of approximately 250 newly diagnosed, untreated patients, who are thus eligible for TT4 or TT5.

Advanced Diagnostics

- Treatments are administered within the context of the most refined diagnostic tools in radiologic imaging (MRI, PET-CT) and in molecular genetics profiling (DNA micro-array, interphase FISH, polymerase-chain-reaction (PCR) assay for residual disease).
- MIRT scientists have combined powerful technologies (such as Gene Expression Profiling), unique animal models (such as the SCID-hu mouse, developed by our scientists), and an unsurpassed and unique wealth of patient samples toward developing cure.



In 1989 Dr. Bart Barlogie came to the University of Arkansas for Medical Sciences from the University of Texas M. D. Anderson Cancer Center. Since then, he and his colleagues have fundamentally changed the course of multiple myeloma through innovative translational research.

The Bottom Line

Dr. Barlogie and his team of scientists and clinicians continue to push the envelope, pursuing all levels of translational investigation with one overriding goal: to advance cure in patients with multiple myeloma.

MANY BREAKTHROUGHS THAT HAVE CHANGED THE STANDARD OF CARE HAVE COME FROM THE MYELOMA INSTITUTE:

- Application of thalidomide, only the third independently active treatment for multiple myeloma after the discovery of melphalan and glucocorticoids in the 1960s.
- Molecular characterization of the disease, enabling identification of patients who will benefit the most from specific therapies. Patients have begun to receive therapies targeted to their specific myeloma subtype, allowing them to receive enough treatment to elicit cure with the minimum amount of side effects. Origins of disease relapse are being elucidated through the further study of focal lesions of myeloma growth in bone.
- Discovery that a patient's bone is not only a target of myeloma, but also an active participant in myeloma progression, partly accounting for its resistance to therapies. This has therapeutic consequences for myeloma as well as other diseases.

CASTLEMAN'S DISEASE RESEARCH LAB NAMED FOR GRATEFUL PATIENT

In 2004, Greg Pacheco's life took an unexpected turn when he was diagnosed with a very rare condition known as Castleman's Disease. Pacheco has since become a leading advocate for unraveling the biology of the disease and developing curative treatment.

Pacheco and his wife, Charlyn, along with a host of family members and friends, secured \$120,000 in donations for the purchase of equipment for Castleman's Disease research at the Myeloma Institute. To honor his efforts and his fight against the disease, the lab was named the Gregory Pacheco Laboratory for Castleman's Research at a dedication ceremony this past spring.

"Thanks to Greg and Charlyn's efforts, we are another step closer to finding new and more effective treatments for Castleman's Disease, as well as unlocking the causes of this rare condition," said Frits van Rhee, M.D., Ph.D., director of clinical research at the Myeloma Institute.

Dr. van Rhee is one of the country's leading experts in Castleman's Disease, a benign condition of the lymph nodes with symptoms that include extreme fatigue, night sweats, skin irritation, inflammation and shortness of breath. The Myeloma Institute is one of the country's leading referral centers.

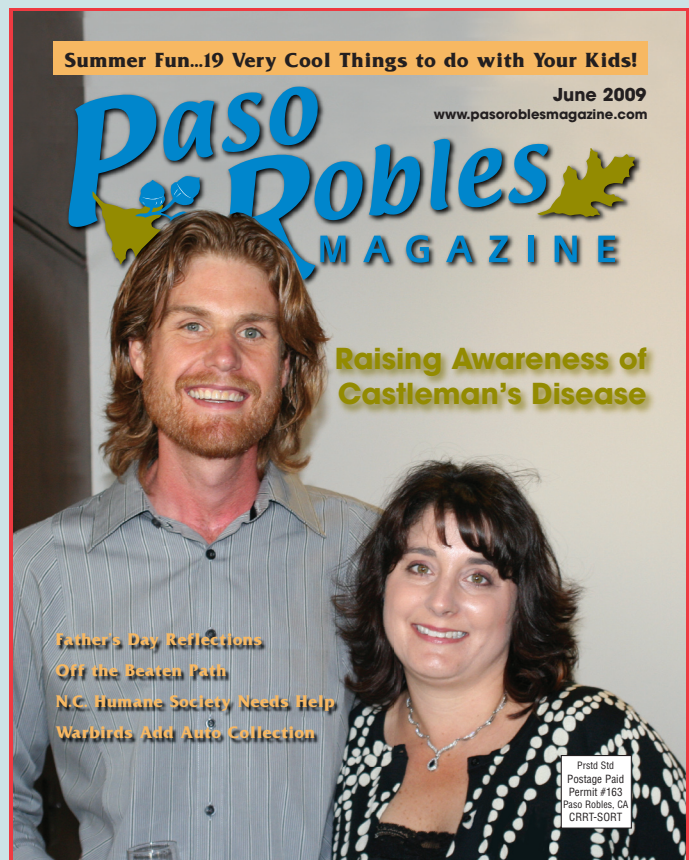
It is unknown how many people have Castleman's Disease, but the Myeloma Institute treats about 50 patients with the condition. Dr. van Rhee's research includes examining the genetic differences that predispose a person to Castleman's and determining whether those differences — if they exist — affect how individuals respond to treatment.

Pacheco travels from Paso Robles, Calif. to Little Rock about once a month to receive intravenous antibody treatment supervised by van Rhee and his team. Pacheco has maintained this rigorous schedule for more than four years.

The drug he receives, which is in the clinical trial stage, is called MRA (humanized anti-human interleukin-6 receptor monoclonal antibody); it is designed to block the interaction between the immune protein known as Interleukin 6 (IL-6)

and its receptor. Castleman's patients overproduce IL-6, which causes the debilitating symptoms.

"Dr. van Rhee gave me my life back," Pacheco said. "For about a year before I was diagnosed with Castleman's, my exhaustion was so severe that I could barely walk from my front door to my car. Now, I'm able to share quality time with my family again."



Greg and Charlyn Pacheco are honored on the cover of Paso Robles Magazine.

The Pachecos have established a nonprofit organization called C.A.R.E. (Castleman's Awareness and Research Effort). The foundation's goals are to raise funds for research, raise awareness about the disease, and give other patients and their families hope that someday there might be a cure.

Thanks to Greg and Charlyn's efforts, we are another step closer to finding new and more effective treatments for Castleman's Disease!

FIFTH BIKE RIDE FOR A GOOD CAUSE – FORWARD AND NORTHWARD

Al Wolfson has once again pulled off an amazing 210 mile bike ride – his 5th - to raise awareness of multiple myeloma and funds for research. His previous four rides yielded \$58,000 from friends and colleagues; this year's ride brings the grand total to more than \$75,000, with additional donations still on the way.

What motivates Al? This is what he tells his supporters...

"This is not a personal quest, but one I make for Dr. Barlogie and the Myeloma Institute. Although I do not have multiple myeloma [Al has MGUS], there was a time when I feared I might. This seeming curse has turned into a mission for me, as I have seen fear in the eyes of new patients and the relief that so many have found through the single minded devotion and relentless scientific rigor of Dr. Barlogie, his fellow doctors and research team, and his dedicated support staff. Having witnessed what they do, I resolved to help them, and I've been riding my bike each year ever since.

My first ride was from Buffalo to Pittsburgh; my second was from Pittsburgh to Buffalo. It was during my third ride from Toronto to Algonquin Park that I was inspired to keep heading north, deeper into the wintry area of the world I've viewed with fascination since childhood, until I reached James Bay (the southern arm of Hudson Bay where the Hudson Bay Company set up shop to undertake its trading enterprises in the New World in the 17th century). Something about the vast spaces, long winter nights, northern lights, bears, wolves and moose always drew me.

In planning this year's trip, from North Bay, Ontario to Cochrane, Ontario, I realized that James Bay could not be reached by road. Cochrane is literally at the end of paved



roads heading north from Toronto. I was, however, able to reach the shore of James Bay by train, incredibly named "The Polar Bear Express," from Cochrane to Moosonee, Ontario. From Moosonee (and its companion town of Moose Factory where the tall ships came to enable the Hudson Bay Company to first establish itself in the fur trade) one can hire a boat to traverse the 9 kilometers from the twin towns to the shore of James Bay. After all of these rides, it was a great feeling to get there.

I have a few sore muscles, but not so many for a 60 year old. What is not sore is my sense of gratitude to you for your tremendous and often repeated generosity. There have been small donations and larger ones, but no matter what the size of the gifts, I can guarantee that you have made a difference in saving lives and helping thousands of people. I don't know Dr. Barlogie's religion, but if he was Catholic he'd be a saint. His warmth and skill have given care, hope, and comprehension to so many, including me. He is a wonderful person, and so, my friends, are you."

The Myeloma Institute extends warm thanks to Al and his friends. We are deeply grateful and moved.

YOUTH TURNS BIRTHDAY INTO FUNDRAISER FOR RESEARCH



Two years ago Kendall Gary of Lewisville, Texas, passed up presents on her 10th birthday in exchange for donations from family and friends. Her father, Don Gary, a long-term patient at the Myeloma Institute, proudly presented \$1,095 to Dr. Bart Barlogie on behalf of his daughter.

This year, on the occasion of her 12th birthday, Kendall once again raised more than \$1,000. Through her determination and the advances made by MIRT researchers, we have no doubt that Kendall and her father will share many more happy birthdays.

Thanks, Kendall!

SUPPORT MYELOMA CURE: GIVE TO THE ANNUAL CAMPAIGN

The momentum of scientific discovery at the Myeloma Institute keeps our program pushing forward.

The pace of sound translational research can never be too fast.

Your donation will help break barriers.

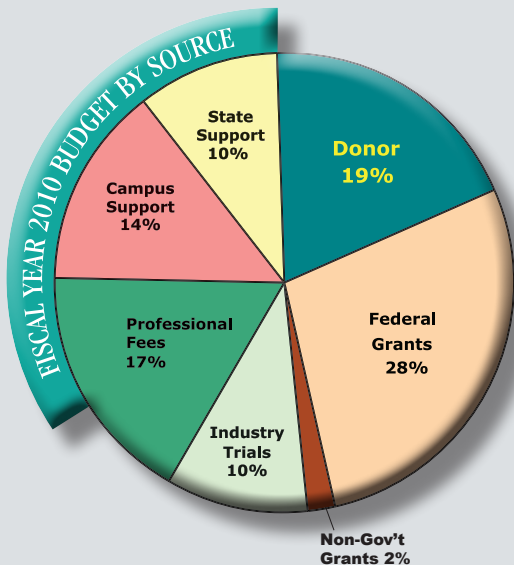
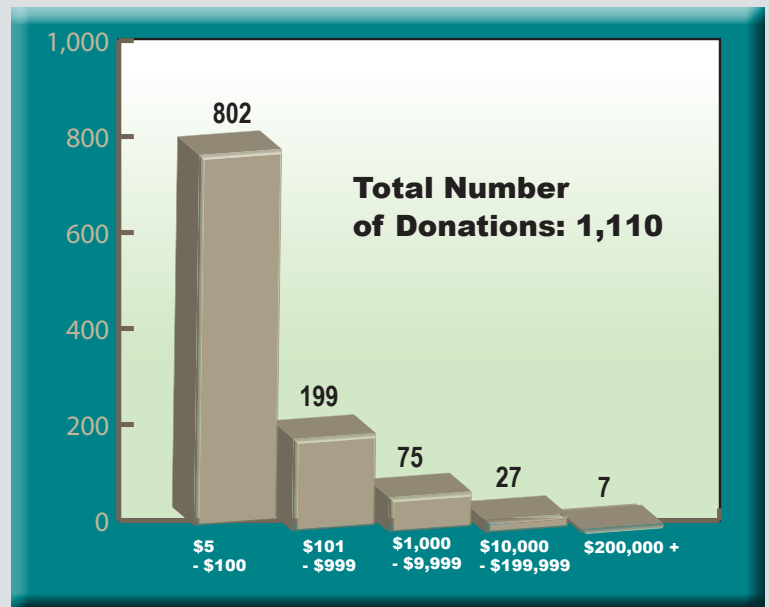
Your donation will help advance cure.

Please use the enclosed envelope for your contribution.

SUMMARY OF GIVING IN FISCAL YEAR 2009 (JULY 1, 2008 – JUNE 30, 2009)

Donations for myeloma genetics & proteomics research	\$2.72 million
Donations for general myeloma research	\$764,000
Donations for the patient support fund*	\$37,610
Other, including unrestricted donations	\$548,390
Total donations	\$4.07 million

*Since November 2008 more than \$11,000 has been disbursed from the Susan & Richard Speer Patient Support Fund. These funds have helped many Myeloma Institute patients with housing, food, and other expenses, making it possible for them to be treated when their financial resources were limited.



Note: We will not mail an additional annual campaign appeal. Please make your annual contribution now.

Volunteer OPPORTUNITIES AT THE MYELOMA INSTITUTE

Volunteers are an integral part of the Myeloma Institute team. They help patients navigate from one appointment to the next, they chat with patients to provide friendship and ease their anxiety, and they make sure that waiting areas are inviting and comfortable. Myeloma Institute volunteers can select work hours and jobs that match their schedules and interests.

If you are interested in joining this very special group, please contact the Department of Volunteer Services at the Winthrop P. Rockefeller Cancer Institute at (501) 686-8286 or visit <http://cancer.uams.edu/?id=4433&sid=2>. Let them know that you would like to volunteer at the Myeloma Institute.



Long-time MIRT volunteer
Esther Crauford

NEW INPATIENT UNIT OFFERS COMFORT WITH STYLE

Earlier this year, the myeloma/stem cell transplant inpatient unit moved into a brand new hospital wing (F7) with rooms that combine some of the best elements of simple design, efficiency, and space. Larger than the rooms on the former unit, they include plenty of cupboards for storage and an expansive countertop. Each room features a new state-of-the-art hospital bed, private, wheelchair-friendly bathroom, and large picture window.

Sleep Sofas for Caretakers

As a bonus for caretakers, every room includes a sofa that converts into a double bed. Flat screen TVs and wireless connection are standard. In the words of Glenda Ainsworth, caretaker from Laurel, Mississippi, the rooms are “quiet, big, and comfortable.”

A Sense of Calm

The atmosphere on the unit is peaceful. Colors throughout are soothing, the simulated wood flooring exudes warmth, and the lighting is soft. Hallways are wide, and there is a feeling of spaciousness.



Efficiency

Nurses, doctors, and pharmacists enjoy greatly improved work areas, including computer stations between patient rooms that are designed for privacy and efficiency. Nurses can be within close proximity of patients at all times. Angled windows with privacy blinds allow staff to check on patients without disturbing them. Souraya Irani, a unit charge nurse, notes that the windows definitely enhance her ability to keep tabs on how patients are doing.

A la Carte Menu

Perhaps one of the most welcome features is the Nutrition Ambassador Program, a new dietary service. An “ambassador” from the Nutritional Services Department is on the unit one

hour before each mealtime to consult with patients and take meal orders. Patients can order just about anything they want – they are not limited to the standard daily menu. Being able to order right before the meal is served enables patients to make selections that truly match their appetites. Juice and coffee are offered first thing in the morning before breakfast arrives. Patient response to this new program has been very enthusiastic.



While a stay in the hospital is hardly a vacation, it should be as pleasant as possible. F7, a unit of calm and efficiency with elements of comfort and convenience, offers an improved environment for patient care and healing.

MYELOMA INSTITUTE WELCOMES NEW STAFF

Abeer Said Al-Qaisi, MD, is a hospitalist on the inpatient unit. Dr. Al-Qaisi completed a residency in Internal Medicine at St. Vincent Hospital in Indianapolis and a Family Practice internship at Indiana University School of Medicine. She received her medical degree from Jordan University of Science and Technology School of Medicine.

Alejandro Restrepo, MD, is a hospitalist on the inpatient unit. Dr. Restrepo completed a fellowship in Transplant Infectious Diseases at Massachusetts General Hospital, a fellowship in Infectious Diseases at the University of Rochester Medical Center and a residency in Internal Medicine at Geisinger Medical Center in Danville, Penn.

Kristen Carter, APN, received a Bachelor of Science in Nursing from the University of Arkansas at Monticello and a Master of Nursing Science and Adult Acute Care Nurse Practitioner certification from UAMS. Her experience

includes patient care nursing in surgical, coronary and cardiac intensive care units.

Sarah Williams, APN, received a Bachelor of Science in Nursing from UAMS and a Master of Science in Nursing from the University of Central Arkansas. She has experience in rehabilitation and oncology nursing.

Alaina Wakefield, APN, received her Bachelor of Science in nursing from Arkansas State University and a Master of Science in Nursing from the University of Central Arkansas. Her previous focus was in cardiovascular intensive care.

Michael Fear, RN, joined the Myeloma Institute as the Outpatient Clinic Manager. Mr. Fear has had extensive nursing and supervisory experience since earning his nursing degree in 1991.

TP53 deletion is not an adverse feature in multiple myeloma treated with total therapy 3

British Journal of Haematology. 2009 Aug 21 [Epub ahead of print]

PMID: 19702643

DelTP53, a poor-risk feature in TT2, was examined for its prognostic consequences in TT3. DelTP53 did not affect rate or duration of complete response, nor did it compromise survival or event-free survival in patients with genomically defined low-risk myeloma.

Complete remission in multiple myeloma examined as time-dependent variable in terms of both onset and duration in total therapy protocols

Blood. 2009 Aug 13;114(7): 1299-305.

PMID: 19515721

This study addresses the importance of not only attaining complete remission (CR) but also the timing of onset and duration of CR. Survival was favorably affected both by achieving CR early in the course of treatment and by sustaining CR for prolonged durations. The results provide a basis for assessing the issue of CR consolidation, especially in high-risk disease, in order to prospectively determine the critical time required in order for CR status to be actively sustained.

F18-fluorodeoxyglucose positron emission tomography in the context of other imaging techniques and prognostic factors in multiple myeloma

Blood. 2009 Sep 3;114(10):2068-76.

PMID: 19443657

F18-fluorodeoxyglucose positron emission tomography (FDG-PET) is a powerful tool to investigate the role of tumor metabolic activity and its suppression by therapy for cancer survival. Suppression of focal lesions as determined by FDG-PET prior to transplantation was identified as an independent favorable prognostic

variable, reflecting the importance of complete suppression of tumor metabolism in myeloma—regardless of gene-array defined risk—for durable disease control and survival.

Gene expression profiling of plasma cells at myeloma relapse from tandem transplantation trial Total Therapy 2 predicts subsequent survival

Blood. 2009 Jun 25;113(26):6572-5.

PMID: 19389881

Results presented here indicate that the predictive power of gene expression profiling (GEP)-defined risk, developed in Total Therapy 2 (TT2) and validated in another front-line setting of Total Therapy 3, extends to post-relapse survival after TT2, unrelated to the salvage therapies employed. Recognizing that GEP-risk status increases at relapse in a sizeable proportion of patients, GEP analysis should be repeated upon treatment failure so that salvage strategy can be selected according to this powerful risk-discriminating tool.

Cytogenetic abnormalities in multiple myeloma: poor prognosis linked to concomitant detection in random and focal lesion bone marrow samples and associated with high-risk gene expression profile

British Journal of Haematology. 2009

Jun;145(5):637-41. PMID: 19344415

The clinical significance of cytogenetic abnormalities (CA) present in randomly sampled (RS) or focal lesion (FL) bone marrow sites was examined in 419 untreated multiple myeloma patients. The novel finding of this study relates to the discovery that the adverse prognostic consequences of CA requires the detection of CA at both RS and FL sites, a circumstance linked in turn to a predominance of high-risk and PR (Proliferation) gene expression profiling designations in RS sites.

The ephrinB2/EphB4 axis is dysregulated in osteoprogenitors from myeloma patients and its activation affects myeloma bone disease and tumor growth

Blood. 2009 Aug 27;114(9):1803-12.

PMID: 19597185

This study suggests that mesenchymal stem cells (MSCs) from multiple myeloma patients underexpress the cell-surface ligand ephrinB2 and its receptor, EphB4, and that myeloma cells negatively regulate their expression in MSCs. Dysregulation of these factors may contribute to uncoupling of bone remodeling in MM lytic lesions. Therefore, approaches to up-regulate expression of endogenous EphB4 and ephrinB2 in osteoprogenitors or exogenously increase EphB4 levels may help restore coupling of bone remodeling and simultaneously inhibit myeloma tumor growth, bone disease, and angiogenesis.

Inhibitor of DASH proteases affects expression of adhesion molecules in osteoclasts and reduces myeloma growth and bone disease

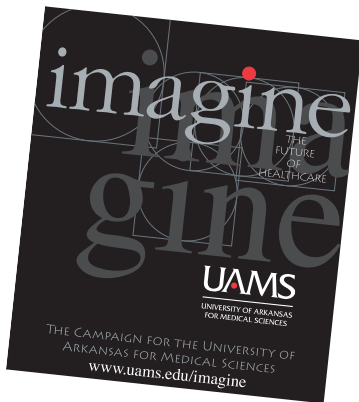
British Journal of Haematology 2009

Jun;145(6):775-87. PMID:19388929

Dipeptidyl peptidase IV activity and/or structure homologues (DASH) are serine proteases implicated in tumorigenesis. We previously found that a DASH protease, fibroblast activation protein was involved in osteoclast-induced myeloma growth. Here we further demonstrated expression of various adhesion molecules in osteoclasts cultured alone or cocultured with myeloma cells, and tested the effects of DASH inhibitor, PT-100, on myeloma cell growth, bone disease, osteoclast differentiation and activity, and expression of adhesion molecules in osteoclasts. These data support the idea that certain DASH proteases are involved in the pathogenesis of myeloma and its associated bone disease.

Full text of articles can be accessed via PMID number at <http://www.ncbi.nlm.nih.gov/pubmed>

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MAJOR GRANT AWARDED TO MYELOMA INSTITUTE

The National Cancer Institute (NCI) has awarded the Myeloma Institute a competitive renewal of a Program Project (P01) grant amounting to more than \$19.5 million over five years. "Growth Control in Multiple Myeloma," funded continuously for the past 15 years, has supported intensive translational research, enabling the Myeloma Institute to develop curative therapies.

In its review of the grant application, the NCI noted that "the major strengths of the Program are the disease focus, the large patient population, the well-established infrastructure through the Myeloma Institute for Research and Therapy, the excellent productivity during the current funding period, and the strong expertise of the investigative team in MM [multiple myeloma] treatment and in the study of MM biology."

The Myeloma Institute is grateful to the many donors who support research and other endeavors at the Myeloma Institute.

If you would like to make a contribution, please use the enclosed remittance envelope.

If you have any questions, contact Betty Tucker, Director of Development, at 501-526-2873 or TuckerBettyA@uams.edu.

Myeloma Briefing is a publication of the Myeloma Institute for Research and Therapy, Bart Barlogie, MD, PhD, Director.

Myeloma Briefing is mailed to patients, referring physicians, supporters and friends, and can be found on the Myeloma Institute website at <http://myeloma.uams.edu/news/newsletters.asp>

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