

# MYELOMA briefing

A PUBLICATION OF THE MYELOMA INSTITUTE FOR RESEARCH & THERAPY AT THE ARKANSAS CANCER RESEARCH CENTER

## MYELOMA INSTITUTE RECEIVES \$18 MILLION NCI GRANT

The Myeloma Institute for Research and Therapy received a National Cancer Institute grant worth nearly \$18 million in August, the largest research award ever given to the University of Arkansas for Medical Sciences.

The \$17,954,098 grant will fund an ongoing comprehensive research program, entitled "Growth Control of Multiple Myeloma," and will be distributed over a five-year period, concluding in June 2009. The grant is the third consecutive five-year P01 awarded to the Myeloma Institute.

"This grant is a testament to the work of Dr. Barlogie and his group in the myeloma program," said James Y. Suen, M.D., director of the Arkansas Cancer Research Center at UAMS. "All of us at the ACRC salute him for his fierce and relentless pursuit of a cure for multiple myeloma and his amazing accomplishments. We are proud to have the Myeloma Institute as part of our team."

The funds are earmarked for four ongoing research projects as well as four supportive cores at the institute, the first facility in the world created specifically to study and treat this rare form of cancer. *(Details of the projects and cores begin on page 2.)*

"The renewed funding of these projects ensures that the Myeloma Institute will continue to actively develop curative therapy based on sound scientific and clinical research," said Barlogie. "I applaud my colleagues and staff for the excellence of their work and for their diligence in pursuing the breakthroughs

that will one day translate into a cure for myeloma." The P01's novel translational research has been the core of the myeloma program for the past 10 years.



*Bart Barlogie, M.D., Ph.D., Director, Myeloma Institute for Research and Therapy*

"Translational research" is the term used to describe research that translates what goes on in the basic science laboratory directly into improvements in clinical care. Outcomes of the therapies in turn provide ideas for further laboratory refinements and pursuits. Due to P01-funded work performed at UAMS, complete remission rates have increased from less than 5 percent with standard chemotherapy to over 50 percent with high-dose chemotherapy with stem cell rescue. Event-free survival and overall survival have more than doubled.

The overall objective of the P01 research is to improve growth control of multiple myeloma by dissecting and exploiting the molecular and biological consequences of the multiple myeloma – microenvironment interaction.

The four projects to be funded by the NCI grant are:

- "Strategies for Cure in Newly Diagnosed Multiple Myeloma," headed by Barlogie
- "Developmental Therapeutics," project leader Guido Tricot, M.D., Ph.D., director of Clinical Research for the MIRT
- "Elucidating the Role of the Microenvironment in Multiple Myeloma through Global Gene Expression Profiling," project leader John D. Shaughnessy Jr., Ph.D., chief of the Division of Basic Sciences and director of the Lambert Laboratory of Myeloma Genetics, both at the MIRT
- "Targeting Heparan Sulfate for Myeloma Therapy," project leader Ralph Sanderson, Ph.D., ACRC director of research

The supportive cores, which are integral to the entire research program, include:

- "Administration, Data Management and Biostatistics," headed by Barlogie and co-directed by John Crowley, Ph.D., president and chief executive officer of Cancer Research and Biostatistics and director of the Statistical Center of the Southwest Oncology Group at the Fred Hutchinson Cancer Center in Seattle
- "Anatomic and Functional Imaging Core," directed by Ronald Walker, M.D., director of PET Research and co-director of the UAMS Cyclotron Facility
- "Molecular Genetics," directed by Shaughnessy

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## PROJECT 1

### Strategies for Cure in Newly Diagnosed Multiple Myeloma

*Project Leader: Bart Barlogie, M.D., Ph.D.*

*Director, Myeloma Institute for Research and Therapy  
Professor of Medicine and Pathology*

*Co-investigators: Elias Anaissie, M.D., Professor of Medicine; Athanasios Fassas, M.D., Associate Professor of Medicine; Klaus Hollmig, M.D., Assistant Professor of Medicine; Elias Kiwan, M.D., Assistant Professor of Medicine; Raymond Thertulien, M.D., Ph.D., Assistant Professor of Medicine*

The overall goal of Project 1 is to increase the frequency of durable complete remission as a prerequisite for long-term survival, and interpret treatment failure in the context of gene expression profiles of both the multiple myeloma cell and the microenvironment (microenvironment refers to the cellular environment of the bone marrow).

In the past five years of the previous P01 funding period, over 600 patients were enrolled in the Total Therapy 2 clinical trial. Patients on the trial were randomized to receive thalidomide or not, and all patients received post-transplant consolidation therapy. The frequency of complete remission was higher for those randomized to thalidomide. For the two-thirds of the patients who did not have cytogenetic abnormalities, 74 percent of the Total Therapy 2 patients remained in complete remission at three years from the onset of complete remission.

The hypothesis for Project 1 is that the microenvironment provides a sanctuary for myeloma cells and that the mechanisms that promote this sanctuary can be deactivated by agents that target both the myeloma cells and the microenvironment. These agents include Thalidomide, dexamethasone, Revimid and Velcade.

There are three major aims of the project:

- 1) Long-term outcomes and obstacles to sustaining complete remission among Total Therapy 2 patients will be assessed.
- 2) Total Therapy 3, a successor to Total Therapy 2, will aim to improve complete remission by incorporating Velcade into induction and consolidation therapies as part of tandem autologous transplants and by interspersing thalidomide and dexamethasone throughout the transplant phase, thereby providing continuous treatment during the treatment free gaps of Total Therapy 2.
- 3) The maturing data from both the Total Therapy 2 and Total Therapy 3 trials will be used to form the basis of Total Therapy 4. Total Therapy 4 will be developed with the goal of introducing risk-adapted therapy based on gene expression profiling.

## PROJECT 2

### Developmental Therapeutics

*Project Leader: Guido Tricot, M.D., Ph.D.*

*Director of Clinical Research, Myeloma Institute for Research and Therapy*

*Professor of Medicine and Pathology*

*Co-investigators: Choon-Kee Lee, M.D., Associate Professor of Medicine; Frits van Rhee, M.D., Ph.D., Associate Professor of Medicine*

The overall goal of Project 2 is to pursue novel immunotherapeutic approaches to augment autologous host responses via cancer/testis antigen vaccination as well as by exploiting allogeneic natural killer and cytotoxic T lymphocyte responses. Novel immunotherapeutic approaches are especially designed for patients with abnormal cytogenetics who do not respond well to high-dose chemotherapy with tandem autologous transplants. The premise is that allogeneic donor T-cells can eradicate myeloma that is resistant to chemotherapy through a graft-versus-myeloma effect.

The hypothesis for Project 2 is that the outcome of high-risk myeloma can be improved by augmenting autotransplant therapy with immunologic manipulations.

Three innovative treatment strategies will be explored:

- 1) Evaluate the efficacy of a non-myeloablative allogeneic transplant following a single autologous transplant in patients with cytogenetic abnormalities. (Non-myeloablative refers to smaller amounts of chemotherapy in less toxic doses.)
- 2) Evaluate whether improved event-free survival and overall survival can be achieved via vaccination with NY-ESO-1 or MAGE-A3 peptides prior to and after autologous transplant in previously treated patients whose myeloma cells express either of these genes.
- 3) Evaluate whether the application of KIR-ligand-mismatched haploidentical donor natural killer (NK) cell infusions followed by an autologous transplant can improve outcome in patients who have either relapsed after transplantation or who have high risk myeloma, as defined by presence of cytogenetic abnormalities. (NK-cells are a subset of immune cells; they are obtained from a family member; they do not cause rejection or graft-versus-host disease. Use of NK-cells has been successfully applied in leukemia.)

Effective immunologic approaches, in combination with autologous transplantation, should provide superior disease control in high-risk myeloma patients. Once these approaches prove to be successful, they can be applied to standard-risk patients to further improve their outcome.

## PROJECT 3

### Elucidating the Role of the Microenvironment in Multiple Myeloma through Global Gene Expression Profiling

*Project Leader: John D. Shaughnesy, Jr., Ph.D.*

*Director, Donna D. and Donald M. Lambert Laboratory of Myeloma Genetics*

*Chief, Division of Basic Sciences, Myeloma Institute for Research and Therapy*

*Associate Professor, Department of Medicine*

*Co-investigator: Fenghuang Zhan, Ph.D., Assistant Professor of Medicine*

The goal of Project 3 is to define molecular signatures of disease initiation, evolution, and resistance/relapse by studying gene expression profiles of the microenvironment (cells in the bone marrow where myeloma cells proliferate) and myeloma cells, and by examining the molecular consequences of interactions between the microenvironment and myeloma cells.

Molecular profiling of cancers has revealed that gene expression signatures of patient cancer cells are predictors of disease progression.

The hypothesis for Project 3 is that gene expression profiling of the microenvironment will enable us to identify key molecular mechanisms through which the microenvironment contributes to disease survival.

The two primary aims of the project will rely on samples obtained through clinical research of projects 1 and 2:

- 1) Identify and validate genes involved in a pathogenetic crosstalk between the microenvironment and myeloma that contribute to disease survival.
- 2) Develop and validate gene expression profiling as a prognostic indicator of clinical outcome to form a basis for selecting optimal treatment modalities.

The bone marrow microenvironment is a complex mixture of cells, each with a distinct gene expression profile. However, with the large sample groups obtained through the clinical research of projects 1 and 2, it is expected that recurring patterns found in myeloma will provide insight into the key molecular signals that contribute to disease progression. Elucidating the key gene expression profile signatures in myeloma disease evolution will provide clinically relevant information that can be used to develop targeted therapies and ultimately improve treatment outcome.

Microarray technology is used to decode the genetic profile of multiple myeloma cells by determining which genes are “turned on” or “turned off.” Myelomas can be classified into different groups according to these gene profiles.

## PROJECT 4

### Targeting Heparan Sulfate for Myeloma Therapy

*Project Leader: Ralph Sanderson, Ph.D.*

*Director of Research, Arkansas Cancer Research Center, UAMS*

*Professor of Pathology*

*Co-investigator: Yang Yang, M.D., Ph.D., Assistant*

*Professor of Pathology*

The overall goal of project 4 is to target heparan sulfate as a novel therapeutic approach for myeloma. Although heparan sulfate is generally thought to inhibit tumor progression, recent discoveries in our lab indicate that heparan sulfate promotes cancer growth. There is mounting evidence that important differences in heparan sulfate structure exist among individual tumors, even tumors of the same type, and that these differences in structure underlie differences in heparan sulfate function.

Syndecan-1 is a proteoglycan having multiple heparan sulfate chains attached to the core protein. Syndecan-1 is present on the outside surface of myeloma tumor cells and acts to control the growth and metastasis of tumor cells within the bone. In addition to being attached to the surface of tumor cells, syndecan-1 molecules can be released from the cell surface and accumulate in the bone marrow and blood of myeloma patients. High levels of syndecan-1 in the bone marrow and blood is an indicator of poor prognosis. Syndecan-1 has been shown to promote growth and metastasis of myeloma tumors in living tissue. Shed syndecan-1 in the bone marrow is in a prime position to facilitate the activities of many of the heparan sulfate-binding growth factors that drive myeloma progression. Thus, heparan sulfate represents a unique target for myeloma therapy.

The hypothesis of project 4 is that interfering with heparan sulfate function or availability within the bone marrow microenvironment will inhibit myeloma growth. By blocking the normal function of heparan sulfate there is an opportunity to interfere with multiple signaling pathways that drive myeloma progression.

The two aims of project 4 are to:

- 1) Determine if modifying or neutralizing heparan sulfate function or inhibiting normal heparan sulfate expression will inhibit myeloma growth.
- 2) Employ new techniques in mass spectrometry to define the structure and ligand-binding capabilities of syndecan-1 heparan sulfate isolated from individual patients.

It is likely that understanding heparan sulfate structure/function signatures of tumors will lead to a new level of patient stratification that will help guide and determine diagnosis, treatment, and prognosis.

The supporting cores are listed below:

### Administration, Data Management, and Biostatistics

*Core Leader: Bart Barlogie, M.D., Ph.D.*

*Co-leader: John Crowley, Ph.D., President and CEO, Cancer Research and Biostatistics,*

*Director, Statistical Center, Southwest Oncology Group, Fred Hutchinson Cancer Center, Seattle, WA*

This core is designed to provide administrative support to all projects so that research activities are coordinated; manage the overall data infrastructure; and provide biostatistics support to link study design, data collection, measurement, and analysis to the research hypotheses and questions under investigation.

### Anatomic and Functional Imaging Core

*Core Director: Ronald Walker, M.D.*

*Director of PET Research, Co-Director of UAMS Cyclotron Facility*

The overall goal of the Anatomic and Functional Imaging Core is to provide the P01 projects with an extensive array of research-based imaging technologies as a means to improve myeloma diagnosis, prognosis and treatment.

The aims of the core are to:

- 1) Offer anatomic and functional imaging for myeloma patients and animal models.
- 2) Perform guided biopsies providing rapid and accurate visual assessment of disease distribution in the skeletal system and soft tissues, which will allow investigators to identify the most metabolically active regions (sentinel lesions).
- 3) Maintain and correlate databases from anatomic and functional imaging studies.

### Molecular Genetics

*Core Director: John Shaughnessy, Jr., Ph.D.*

*Director, Donna D. and Donald M. Lambert Laboratory of Myeloma Genetics*

*Chief, Division of Basic Sciences, Myeloma Institute for Research and Therapy*

*Associate Professor, Department of Medicine*

The overall goal of the Molecular Genetics Core is to provide a highly specialized molecular shared resource that will serve established research projects.

The aims of the core are to:

- 1) Assist in the conduct of research related to molecular genetics as proposed in each P01 project. Specifically, gene expression profiling (GEP), fluorescence in situ hybridization (FISH) and G-banded cytogenetics will be performed on patient samples.
- 2) Maintain and correlate data from molecular genetics studies. Data mining and statistical analyses of GEP, FISH and cytogenetics will be analyzed and developed into predictive models in collaboration with biostatistical analyses.

### Cell Analysis and Sample Banking

*Core Leader: Joshua Epstein, DSc*

*Basic Scientist, Myeloma Institute for Research and Therapy*

*Professor, Department of Medicine*

The Cell Analysis Core is designed to centralize common procedures for the P01 projects. These procedures include sample acquisition and banking, cell sorting, analytical flow cytometry, and histology and immunohistochemistry.

### New Protocol Already Showing Signs Of Success

Carol Pepe calls it luck. Dr. Guido Tricot calls it the next step to finding a cure for multiple myeloma. "It" is Total Therapy 3, a unique protocol begun by Myeloma Institute for Research and Therapy physicians in February



*Guido Tricot, M.D.*

that addresses the issue of the myeloma microenvironment. Unlike its predecessors, TT3 incorporates Velcade, a proteasome inhibitor, in an effort to target myeloma cells as well as the environment in which they grow.

"There were a lot of questions asked in Total Therapy 2. More than enough patients have been enrolled in that study to adequately answer those questions, so now we're asking some different questions," explained Tricot, MIRT's director of clinical research. "Until now, we've mainly paid attention to killing the myeloma cells. If we want to have a successful treatment, we think we also have to deal with the microenvironment, to make sure that the cells cannot regrow."

TT3 involves treating patients under 75 who have received no more than a single cycle of chemotherapy with thalidomide, dexamethasone and Velcade, along with tandem stem-cell transplants. With already nearly 100 patients enrolled in the protocol, Tricot expects to have no problem in accruing 300 by the middle of 2006.

Pepe was one of the first to sign up for the program. A special education teacher in Frenchtown, N.J. who dealt with autistic children, she was diagnosed with myeloma in December 2003 and after doing some research, decided MIRT was the best possible place to seek treatment. After being evaluated in February, she and Tricot decided she was a perfect candidate for TT3.

Following her second transplant in September, Pepe is now in remission and considers herself extremely fortunate. "I really respect and admire Dr. Tricot. I feel lucky to have him for my doctor,"

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## \$18 Million Grant *(continued from page 1)*

- “Cell Analysis and Sample Banking,” directed by Joshua Epstein, D.Sc., MIRT senior scientist

### NCI, NIH Provide Funding For Research

The National Institutes of Health (NIH) is one of the world's most highly ranked medical research centers. An agency of the Department of Health and Human Services, the NIH is the federal government's foundation for health research. Its mission is the pursuit through science of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce illness and disability. The NIH provides leadership and direction to programs designed to improve health by conducting and supporting research.

The National Cancer Institute (NCI) is one of 20 institutes under the umbrella of the NIH. The mission of the NCI is to eliminate suffering and fatality due to cancer. The NCI aims to achieve this goal by the year 2015. NCI researchers work to integrate scientific discoveries through interdisciplinary collaborations; accelerate development of treatment interventions and new technology through translational research; and ensure the delivery of these interventions for application in clinical and public health programs.

The NCI conducts and supports research related to the cause, diagnosis, prevention, and treatment of cancer. The NCI supports a broad range of research

to expand scientific discovery at the molecular and cellular level, within a cell's microenvironment, and in relation to human and environmental factors that influence cancer development and progression. Each year, almost 5,000 principal investigators lead research projects that result in improved methods to combat cancer. Program experts at the NCI provide guidance and oversight for research conducted at universities and teaching hospitals. Proposals are selected for funding by peer review, a rigorous process by which scientific experts evaluate new proposals and recommend the most scientifically meritorious for funding. The NCI also promotes translational research and intervention development through collaborative partnerships. Discovery of a new tool that first helps to understand the underlying mechanism of cancer may eventually be used to help diagnose it, and then may be further developed to help treat it. The largest collaborative research activity of the NCI is the Clinical Trials Program for testing interventions for preventing cancer, diagnostic tools, and cancer treatments. The NCI supports over 1,300 clinical trials a year involving more than 200,000 patients.

### What is a P01 Grant?

A P01 Research Program Project grant supports a broadly based, multidisciplinary program which has a specific major objective or basic theme. It is often a long-term program. A P01 research program project generally involves the

organized efforts of relatively large groups whose members are conducting research projects that are designed to elucidate the various components of the major objective. Each research project is typically under the leadership of an established investigator. P01 projects are expected to demonstrate essential elements of unity and interdependence through research activities directed toward and contributing to a well-defined research program goal.

In Fiscal Year 2002 there were 993 P01 awards, with an average award amount of \$1,392,771. The amount awarded to the Myeloma Institute that year was \$3,298,384. In Fiscal Year 2003 the NCI invested \$26.3 million in myeloma research; \$4.1 million, or 15.7%, was awarded to the Myeloma Institute.

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### New Protocol *(continued from page 3)*

she said. “I had no complications and all of my treatments went smoothly. I don't know that I would have had these results if I had gone elsewhere.”

Patients like Pepe benefit from being involved in protocols like TT3 because of the strict guidelines followed over the course of the treatment, according to Tricot. “Protocols like this are more regimented. Everybody needs to be treated the same way. Otherwise, you don't learn anything.”

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