

National Cancer Institute (<http://www.cancer.gov/>)

The National Cancer Institute (NCI) is part of the National Institutes of Health (NIH), which is one of 11 agencies that comprise the U.S. Public Health Service (PHS) in the Department of Health and Human Services (HHS). The NCI, established under the National Cancer Institute Act of 1937, is the Federal Government's principal agency for cancer research and training.

The National Cancer Institute coordinates the National Cancer Program, which conducts and supports research, training, health information dissemination, and other programs with respect to the cause, diagnosis, prevention, and treatment of cancer, rehabilitation from cancer, and the continuing care of cancer patients and the families of cancer 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.

National Cancer Institute Awards P01 Grant to the Myeloma Institute

The Myeloma Institute has received continuous P01 grant funding for the Project Program "Growth Control of Multiple Myeloma" since 1993. **The grant has been renewed at the amount of \$19.5 million for an additional 5 years, resulting in 20 consecutive years of uninterrupted funding.** 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 P01's novel translational research has been the core of the UAMS myeloma program. "Translational research" is the term used to describe research that bridges what goes on in the basic science laboratory with developments in clinical care. Breakthroughs in the laboratory are translated into clinical care therapies; outcomes of the therapies in turn provide ideas for further laboratory refinements and pursuits.

The Arkansas Approach to Studying and Treating Multiple Myeloma

From the inception of the myeloma program at UAMS in 1989, our physician-scientist team has been totally committed toward

- furthering insights in disease biology, genetics, gene expression profiling (GEP);
- refining diagnostic and staging tools (MRI and FDG-PET-CT);
- and advancing therapeutics through intense translational research

The structure of our P01 program project has afforded discoveries that were critically dependent on

- a large patient referral base;
- tight, long-term follow-up;
- integrated basic–clinical investigation;
- and statistical power to interpret findings in the context of historical patients with comprehensive annotations of clinical course and therapeutic interventions as well as availability of samples and laboratory correlates in our database

Unlike any other myeloma (MM) research program, the Arkansas approach is uniquely focused on the "total" treatment of patients, not just from the point of view of our Total Therapy (TT) strategy of applying all currently available agents upfront, but also in reference to our long-term follow-up of patients.

We have generated an unprecedented treasure of bone marrow samples annotated according to the phase of therapy at the time of procurement. We have GEP studies of MM and the bone marrow stroma from over 1000 cases and more than 70,000 metaphase karyotypes from more than 7000 individuals with MM. Additionally, MRI and PET-CT studies have been performed for almost all patients, leading to the recognition of focal lesion (FL) disease with unique biological and molecular characteristics. This wealth of data has allowed us to validate a GEP-based risk index and has provided evidence for a MM- bone marrow microenvironment (ME) interaction that is associated with both GEP-defined risk and molecular subgroup classification.

An adequately large sample size is critical for MM therapeutic trials to have a significant impact on clinical practice. The Myeloma Institute has maintained an annual referral of about 250 newly diagnosed, untreated patients, who are thus eligible for Total Therapy. Other trials have been available for patients presenting with renal failure, advanced age, or hematopoietic compromise.

Overall Long-Term Objectives & Hypotheses of “Growth Control in Multiple Myeloma”

The overall objective of the P01 Program Project is to understand MM growth in the context of its interaction with the ME in order to translate this knowledge into smarter MM growth control in patients.

We hypothesize that **MM subjugates various ME components, perhaps in a MM subtype-specific manner, and that such MM-induced ME imprints may become an irreversible force contributing to MM's resistance to cure.** This hypothesis and those outlined below for each project will be pursued by translational, basic, and clinical research conducted by 4 projects and supported by 5 cores.

Project 1: Strategies for Cure in Newly Diagnosed Multiple Myeloma

Principal Investigator: Bart Barlogie, M.D., Ph.D, director of the Myeloma Institute

Project 1 is pursuing two new Total Therapy approaches (TT4 and TT5). For the first time, newly diagnosed patients are assigned to different therapeutic trials based on their MM-GEP-defined risk index and based on the hypothesis that **better growth control of MM can be achieved by using risk-based treatment strategies.** The emphasis in **TT4 for low-risk MM** is on decreasing treatment-related morbidity while retaining and potentially enhancing efficacy by the addition of bortezomib and thalidomide to fractionated melphalan-based transplants. Low-risk patients are randomized between the highly successful standard Total Therapy 3 (S-TT3) and a TT3-lite version (L-TT3) with reduced induction and consolidation cycles and a 4-day fractionated melphalan (MEL) transplant regimen to which has been added VTD (bortezomib, thalidomide, dexamethasone); this is designed to exploit the synergism between the individual components of therapy documented pre-clinically and clinically. Maintenance in both arms is with VRD (lenalidomide).

TT5 for high-risk MM is pursuing a strategy of delivering timely and consistently effective therapies by avoiding host tolerance-exhausting high-dose approaches. Patients receive dose-dense but less dose-intense therapy with 8-drug combination regimens: dose-reduced, fractionated MEL80-VRD-PACE is employed for both transplants, between which is sandwiched MEL20-VTD-PACE without stem-cell support. Maintenance is with monthly alternating M-VD and R-VD for 3 years. In this fashion, it is hoped that complete remission (CR) rates will be sustained by continuously administering highly synergistic and more tolerable combination therapies, with an overall 50% reduction in total melphalan dose (from 400 mg/m² in previous TT1, TT2, and TT3 regimens to 200 mg/m²). If this approach works for high-risk MM, it will subsequently be applied to low-risk disease.

Project 1 will also address the mechanisms underlying the success in TT3 for advancing the outcomes of low-risk MM versus failing patients with high-risk MM. Extended follow-up over the next 5 years of this newly awarded grant cycle will enable us to test the hypothesis that **therapeutic success in TT3 compared with TT2 can be explained in the context of MM-ME interaction revealed by GEP studies of both MM and the ME.** Based on a large patient population remaining on TT2 and TT3 protocols, with high compliance rates of frequent MM and ME GEP analyses, important insights related to our hypothesis are anticipated through longitudinal studies.

Project 2: Developmental Therapeutics

Principal Investigator: Frits van Rhee, M.D., Ph.D., director of clinical research at the Myeloma Institute

Project 2 is focused on strategies aimed at improving therapy for relapsed patients with high-risk MM by employing Natural Killer (NK)-based cytotherapy in the allogeneic setting

Poor outcomes in high-risk MM may originate from highly resistant tumor subpopulations that rapidly expand upon elimination of the drug-sensitive myeloma cells. Immunotherapy with *ex vivo*-expanded and -activated allogeneic natural killer (exp-allo-NK) cells may induce cure by eliminating drug-resistant cells. Our initial clinical experience and pre-clinical studies provide a platform to design more effective allo-NK cell therapy, which will be tested in patients with relapsed high-risk MM, as these patients have the poorest outcome with currently available treatment options. **Project 2 will test the hypothesis that allo-NK cell therapy can be rendered more effective for drug-refractory MM by modulating myeloma and NK cell interactions to favor NK cell activation.**

Project 3: Tumor Cell-Microenvironment Interactions in the Molecular Pathogenesis of Multiple Myeloma

Principal investigator: John Shaughnessy, Ph.D., director of basic research at the Myeloma Institute and director of the Donna D. and Donald M. Lambert Laboratory of Myeloma Genetics

Project 3 is focused on novel observations of DKK1-expressing myeloma cells and CYR61/CNN1-expressing components of the ME toward defining

- novel pathogenetic mechanisms of MM progression from monoclonal gammopathy of undetermined significance (MGUS), and
- therapeutic approaches of re-establishing Wnt/ β -catenin signaling in mesenchymal cells (MSCs)/osteoblasts by bortezomib and other agents.

Based on *in vitro* and *in vivo* preliminary work in MM cell lines and primary MM PCs, **we hypothesize that deregulation of Wnt/ β -catenin signaling in both the ME and MM tumor cells is a fundamental and critical event in the natural history of MM, and, as such, may provide the framework for innovative therapeutic strategies.**

Project 4: Targeting the Microenvironment for Myeloma Growth Control

Principal investigator: Shmuel Yaccoby, Ph.D.

Project 4 addresses two aspects of the same overall hypothesis suggesting that increased osteoclast activity in lytic/focal lesions is a critically adverse determinant of long-term survival favoring dissemination of myeloma cells, while stimulation of bone formation creates an inhospitable environment for myeloma cells, preventing their progression during remission and dissemination to uninvolved bone marrow and extramedullary sites upon relapse. **The goal of Project 4 is to determine if MM growth can be suppressed and disease relapse prevented by stimulating osteoblastogenesis and whether efforts at defining osteoclast-secreted proteases and their role in MM dissemination may lead to novel therapeutic interventions.** Using a mouse model system in the context of TT-like treatments, Project 4 will determine the effects of increased bone formation by anabolic agents (e.g., PTH, anti-DKK1) and/or osteoblast precursors (e.g., MSC, placenta-derived cells) on prevention of relapse and tumor metastasis as well as the roles of osteoclast-produced serine proteases in MM bone disease, tumor growth, egress from bone marrow, and dissemination. In addition, the study will investigate potential therapeutic benefits of combined approaches to simultaneously increase osteoblast activity and decrease osteoclast activity. **The long-term goal is to identify and validate targeted therapies associated with osteoclast and osteoblast functions in myelomatous bones to develop novel interventions.**

The P01 funded research includes several shared cores that support the projects:

Core A: Administration, biostatistics and research coordination

Co-directors: Bart Barlogie and 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 Hutchinson Cancer Research Center in Seattle

Core B: Cell Analysis and Specimen Banking

Core director: Joshua Epstein, D.Sc.

Core C: Genomics and Proteomics

Core director: John Shaughnessy

Core D: SCID-hu and In-vivo Modeling

Core director: Shmuel Yaccoby

Core E: Experimental Cellular Pathology

Core director: William Bellamy, Pharm.D., Ph.D.