

# Symptom Research Awarded NIH P01 Grant

Under the direction of Charles Cleeland, PhD, the Department of Symptom Research has spent the past several years developing new approaches to the management of treatment-related symptoms, working always toward its goals to reduce the symptom burden of cancer therapy, increase treatment tolerability, and reduce symptomatic late effects for cancer survivors. Now the department's efforts are beginning to pay off, with recent awards of funding for sustained, major research in pursuit of these goals.

In addition to an AstraZeneca "Center of Excellence" award to study the development and mechanisms of treatment-related neuropathy and other symptoms in patients beginning cancer therapy, the renewal of a long-standing National Institutes of Health (NIH)-funded R01 that will be the first-ever large-scale study to use a Bayesian adaptive trial design to evaluate combinations of symptom-focused therapies, and a new NIH R21 grant to compare the cytokine-driven symptom burden produced by two radiation techniques in patients with non-small cell lung cancer, the Department of Symptom Research was recently awarded a multimillion-dollar NIH P01 Program Project grant to study the mechanisms underlying disease-related and treatment-related symptoms in multiple myeloma. This multidisciplinary, multidepartment Program Project, to be led by Dr. Cleeland as Principal Investigator, includes four R01-sized projects and three supporting cores.

## Rationale for the Program Project

Patients with cancer have multiple symptoms, such as pain, fatigue, sleep disturbance, and poor appetite that cause significant distress, impair function and rehabilitation, and may cause treatment delays or premature treatment termination. These symptoms are produced by both the cancer and its therapy. Growing evidence indicates that some symptoms may cluster together and share common physiological mechanisms, creating a "symptom burden" that is the subjective counterpart of tumor burden.

Multiple myeloma, an incurable but treatable cancer of the plasma cell, is an excellent disease for studying the interaction between cancer, treatment, and symptoms. According to PI Cleeland, "Proinflammatory cytokines play a major role in the development of the disease. Aggressive treatments exacerbate production of proinflammatory cytokines and, in recent years, we've learned much more about agents for inflammatory blockade that make mechanistic symptom control a real possibility in the trajectory of this disease.

Early treatment for multiple myeloma is often accompanied by some improvement in disease-related symptoms (bone pain, anemia-related fatigue, sleep disturbance), but this is counterbalanced by the onset of new symptoms (such as neuropathic pain) known to arise from such treatments as thalidomide and bortezomib. Because patients with multiple myeloma have a 3-to-5-year median survival after diagnosis, maintaining a balance between minimum symptom burden and compliance with aggressive therapies is essential.

"Since inflammation plays a presumptive role in the development of multiple myeloma, and correlations between increases in markers of disease and inflammation are well-known, it's essential that our Program Project investigate the interaction between inflammatory pathways activated by disease, the modulation of inflammation and symptoms by curative therapies,

and the role of therapeutic modulation of inflammation with the intent of reducing symptom burden," says Cleeland.

The significance of this Program Project is that it will address the degree to which inflammation is responsible for a wide variety of symptoms in cancer. Recent studies of rheumatoid arthritis, Crohn's disease, and depression have suggested that inflammation plays a central role in the production of multiple symptoms in diseases other than cancer, and that reduction of inflammation by targeted cytokine therapies produces amelioration of pain and other symptoms. What is not known is whether these cytokines actually cause the emergence of symptoms and symptom clusters. Verifying such a causal relationship would support the development of symptom management strategies based on underlying symptom mechanisms (such as bisphosphonates for bone pain and erythropoietin for fatigue) rather than on the use of empiric treatments (such as opioids for pain and stimulants for fatigue).

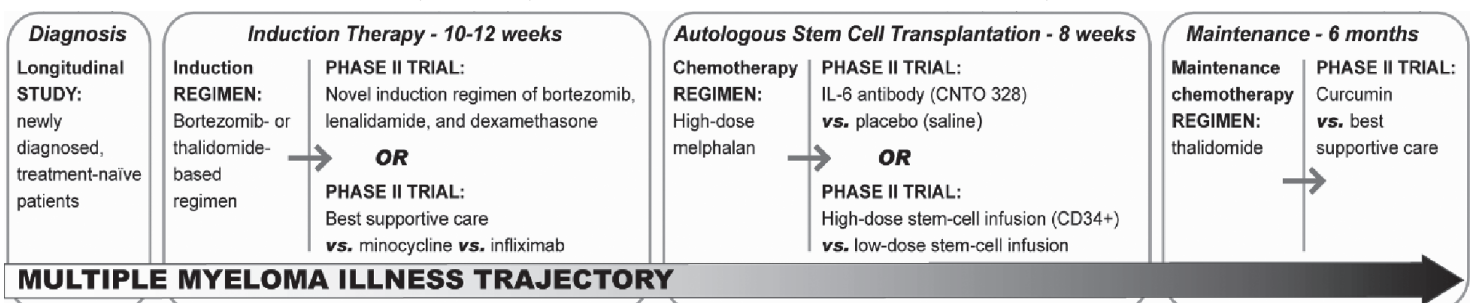
Notes Cleeland, "The recent development of targeted therapies, especially for components of the inflammatory response, underscores the timeliness of our Program Project. Such therapies may allow for reduction in symptom burden at the same time that disease control improves." And when the cancer is incurable, as is multiple myeloma, the balance between the side effects of aggressive treatment and optimal function becomes critical.

## A Brief Look at the Program Project

The Program Project will bring together four preclinical and patient-based studies, including: longitudinal symptom measurement using self-report measures and symptom-cytokine associations of such symptoms as pain, fatigue, depression, sleep disturbance, and decreased appetite that are characteristically reported in patients with multiple myeloma (Projects 1 and 2); longitudinal assessment of sensory-motor impairments documenting the duration and extent of neuropathy over the multiple myeloma disease trajectory (Project 3); and clinical trials of cytokine-modulating agents that can potentially modify the severity of cancer-related symptoms or prevent their occurrence entirely (Projects 1 and 4).

The studies build on preliminary data from the Program Project's participating investigators showing that dysregulation of inflammatory cytokines is key to the development of symptom burden produced by a variety of cancer therapies. The overall hypothesis to be tested in this Program Project is that increases in specific proinflammatory cytokines, especially IL-1, IL-6, and TNF- $\alpha$ , along with activation of their precursor, NF- $\kappa$ B, are associated with the emergence of individual symptoms or clusters of treatment-related symptoms, and that modulation of these inflammatory pathways will reduce both the prevalence and severity of symptoms.

A project of this nature necessitates a broadly based integrated and multidisciplinary team with expertise in longitudinal symptom assessment, immunology, quantitative motor and sensory assessment, and animal models of symptoms and disease where mechanisms of symptom expression can be examined. Especially essential is the development of statistical models that can account for the relationship of symptom and biological variables over time. Components of the individual projects will follow patients with multiple myeloma from diagnosis through induction therapy, transplantation, and maintenance therapy (see diagram below).



## Project Leaders

- Charles S. Cleeland, PhD, Program Principal Investigator, Project 1 Leader, and Administrative Core Director; McCullough Professor of Cancer Research and Chair of the Department of Symptom Research
- Xin Shelley Wang, MD, MPH, Project 1 Co-Leader; Associate Professor in the Department of Symptom Research
- Bharat Aggarwal PhD, Project 2 Leader; Ransom Horne Jr. Professor in Cancer Research, Professor and Chief of the Cytokine Research Section
- Patrick M. Dougherty, PhD, Project 3 Leader; Professor in the Department of Anesthesiology and Pain Medicine
- Sergio A. Giralt, MD, Project 4 Leader; Professor and Deputy Chair in the Department of Stem Cell Transplantation and Cellular Therapy at M. D. Anderson, with a joint appointment in the Myeloma Section, and Medical Director of Transplantation Services
- Valen E. Johnson, PhD, Biostatistics & Data Management Core Director; Professor and Deputy Chair in the Department of Biostatistics
- James M. Reuben, PhD, Laboratory Core Director; Director of the Human Cancer Cytokine Laboratory supported by the Cancer Center Support Grant and Associate Professor of Hematopathology with a joint appointment in the Department of Symptom Research

Drs. Cleeland and Wang will focus on describing the symptoms associated with induction and maintenance therapy for multiple myeloma and, in collaboration with Dr. Giralt and Sheeba Thomas, MD (Lymphoma & Myeloma), will conduct clinical trials that test methods for reducing the high level of symptom burden produced by allogeneic stem cell transplantation. Dr. Dougherty will study the development of neuropathy in both animal models and patients. Dr. Aggarwal will evaluate the role of NF- $\kappa$ B in the development of the symptom cascade and will join with Drs. Cleeland and Wang to evaluate the role of curcumin, a component of the spice turmeric, for the control of symptoms associated with chronic cancer treatment. Drs. Johnson and Reuben will provide statistical and laboratory support to all projects.

The long-term objectives of the Program Project are to characterize the basic mechanisms underlying cancer treatment-induced symptom burden, to focus on cytokines and immune mediators, and to provide a rationale for mechanism-driven symptom management. As Cleeland says, "Having the ability to reduce symptom burden or even prevent these consequences from therapy would be of potential benefit to thousands of cancer patients and survivors by improving the tolerability of treatment and reducing posttreatment residual symptoms."