As the UAMS Myeloma Institute marks its 25th anniversary this fall, it celebrates world-leading advances in the treatment and even cure of several types of multiple myeloma.

The institute also begins a new chapter under Gareth Morgan, M.D., Ph.D., F.R.C.P., F.R.C.Path., an internationally recognized myeloma clinician and researcher who is settling in as director after Bart Barlogie, M.D., Ph.D., the institute’s founder, stepped down in July to focus on clinical care and research.

Morgan was recruited to UAMS from the Centre for Myeloma Research at the Royal Marsden NHS Foundation Trust and The Institute of Cancer Research in London, Europe’s largest comprehensive cancer institute, where he was director since 2003. He brings a fresh perspective, with plans to further capitalize on the unique elements that distinguish the Myeloma Institute as the world’s foremost myeloma research and treatment center.

Those elements include its cutting-edge genomic approaches to treatment, single-minded purpose and nimbleness as an institute. There’s also great continuity of care, with compassionate staff who hearten patients from around the world with their “incomparable southern hospitality,” Morgan said.

“The people in Arkansas are really friendly and hospitable, and those qualities are reflected in our care,” Morgan said. “I want that to become an emphasis, making the Myeloma Institute about the best science, the best treatment – personalizing our patients’ treatment while supporting their emotional and spiritual needs. Most of all, we want our patients to know that we won’t give up on them even if others have.”

The treatment mainstay for the Myeloma Institute is intensive chemotherapy combined with autologous stem cell rescue, commonly referred to as bone marrow transplantation. It began in 1989 as Total Therapy I, and in subsequent years drugs such as Thalidomide and Velcade were added, improving patient outcomes. In more recent years the institute has used gene expression profiles to risk stratify its treatment by identifying the 15 percent of patients with high-risk disease to better plan their treatment, which is something other centers have not done, Morgan said.

“We’re now taking risk stratification to the next level by identifying genetic features of the cancer, integrating this with the gene expression data to choose the most effective treatments,” he said. “Treatment is customized for each patient to improve their outcome and their chances for cure, and to reduce treatment toxicity.”

Today patients at the Myeloma Institute have many more options for clinical trial participation, often the preferred treatment route, are enhanced when newly diagnosed patients present at the Myeloma Institute without previous treatment. In all cases, we value close partnership with referring physicians to ensure a shared treatment approach and continuity of care. I am honored to be the newly appointed director, and I am especially happy to be in Arkansas, where our people, our science and our treatments offer the very best opportunity for curing patients.

Kind regards,

Gareth Morgan, M.D., Ph.D., F.R.C.P., F.R.C.Path.
Director, Myeloma Institute
Institute receive targeted genomic sequencing to identify so-called hot-spot mutations that drive the proliferation of cancer cells. The institute then identifies drugs on the market or in a clinical trial that can interrupt the signaling pathways responsible for tumor growth (see case study, page 6).

“It’s all about bench to bedside, back to bench,” Morgan said of the institute’s translational research approach to finding cures.

After analyzing the genetic makeup of the tumor cells, a treatment is designed and initiated, and the institute’s clinician investigators examine a subsequent set of the tumor’s genes to learn how effectively the treatment is working. If the patient does not respond to treatment, another treatment combination is designed and administered. The cycle continues until the patient has a good outcome.

As deputy director of the UAMS Winthrop P. Rockefeller Cancer Institute, Morgan envisions a symbiotic relationship between the two institutes. That’s especially true in the realm of clinical trials, he said. Among his first hires was Faith Davies, M.D., F.R.C.Path., as director of the Phase I Clinical Trials Program for the Myeloma Institute and the Cancer Institute. Also an internationally recognized myeloma clinical researcher, Davies joined UAMS from the Institute of Cancer Research in London, where she was a faculty member, and the Royal Marsden Hospital in London, where she was a consultant hematologist. She has served as scientific coordinator of two large United Kingdom myeloma studies and developed a dedicated hematology/oncology clinical trial unit for Phase I, II and III clinical trials in myeloma. She also managed the autologous and allogeneic transplant programs (see story, page 4).

“We have innovative treatments at the Myeloma Institute, and we’ll expand the use of those innovative treatments,” Morgan said. “We have the capacity to develop clinical trials for breast, solid tumors – a variety of tumor types – so that people across the state will have the opportunity to participate in those trials.”

Q&A with Dr. Morgan

Q: Is it important to know the risk status of a patient’s myeloma?

A: Clinically, the outcomes for patients with high-risk (HR) myeloma are very poor and treatment needs to be adapted accordingly. At the Myeloma Institute we utilize specific clinical trials for this group of patients.

Q: What is the best way to define HR behaviors?

A: Gene expression profiling is the only reliable way to define risk status. Interphase FISH, an in-situ genetic test, has been used for this purpose in some centers but it is inaccurate and lacks precision for defining poor clinical outcomes. We use Signal Genetics™, a commercial stage, molecular diagnostic company, for gene expression profiling results on our patients.

Q: Does gene expression profiling reveal anything other than risk status?

A: The results also indicate into which molecular subgroup a patient falls. Seven subgroups (CD-1, CD-2, HY, LB, MF, MS, PR) have been identified by our research team (see heatmap, pie chart, page 3). Based on the subgroup, each of which has a distinct clinical course, we can select the most appropriate treatment regimen and define clinical management. In particular, the MS group benefits from proteasome inhibitors, the CD-2 group is considered good risk even though it is slow to respond, and the MF group has not benefited from the use of proteasome inhibition.

Q: Do you use sequencing data at the Myeloma Institute?

A: Yes, we use it to look for a range of mutations that can help us target treatment. For example, we have been able to target the RAS pathway and achieve successful response, as described in the case report in this issue. The data can also inform us of other treatment strategies and can help us identify approaches for cure for patients who are difficult to treat.

Gareth Morgan, M.D., Ph.D., F.R.C.P., F.R.C.Path., is director of the UAMS Myeloma Institute.
Early Intervention Critical in Myeloma Bone Manifestations

By Maurizio Zangari, M.D.

Ninety percent of multiple myeloma patients develop bone lesions during the course of the disease, with 60 percent experiencing pathologic fractures, mostly in the spine, and 3 percent experiencing cord compression.

Myeloma bone disease (MBD) is specifically characterized by a suppression of osteoblastic activity, increased osteoclast function, and a decrease in serum vitamin D25 levels. Multiple mechanisms have been associated with myeloma bone disease, including the markedly increased receptor activator of the NFkB ligand signaling pathway, which plays a critical role in normal bone remodeling in myeloma patients, and suppression of the WNT pathway by the specific inhibitor DKK1, which is expressed by myeloma cells.

Proteasome inhibitor drugs clearly have a new role in re-establishing the loss of bone anabolic activity experienced by myeloma patients. At the UAMS Myeloma Institute, comprehensive baseline skeletal evaluations include bone survey, MRI, CT-PET, and bone density studies coupled with appropriate vitamin hormonal levels. Genetic testing of the most important bone related pathways from biopsy samples are routinely evaluated, and, as appropriate, samples are sent to specialized laboratories that focus on the identification of specific therapeutic targets involved in MBD.

Preservation of the functional capacity of the patient is critical. Early interventions such as kyphoplasty and bisphosphonate therapy are implemented and novel agents with specific bone anabolic properties are employed.

Zangari is an internationally recognized expert in multiple myeloma and myeloma bone disease.

Researchers at the Myeloma Institute have used global gene expression profiling (GEP) of purified myeloma cells to discover that seven different molecular defects can cause the disease known as myeloma. This discovery helps explain why some patients respond well to certain therapies while others do not. The heatmap above represents the expression level of 700 genes in myeloma cells from 351 newly diagnosed myeloma patients. A red color means the gene is expressed at high levels and green means the gene is low. Each disease subtype is characterized by the unique over (red) or under (green) expression of 100 genes, creating the “staircase” appearance of the figure.
Myeloma Institute Leads Development of UAMS Clinical Trials Unit

By Faith Davies, M.D., F.R.C.Path.

The clinical landscape for myeloma patients has changed dramatically over the last 20 years, with the UAMS Myeloma Institute being pivotal in the development of many of the new anti-myeloma therapies. To ensure that patient outcomes continue to improve and that patients have access to innovative therapies, we are embarking on a new initiative to develop a dedicated phase I clinical trials unit. This unit will offer novel therapeutic agents to myeloma patients as well as to the wider hematology/oncology patient population in the UAMS Winthrop P. Rockefeller Cancer Institute. The unit will have dedicated inpatient and outpatient facilities, allowing for the comprehensive assessment of new anti-cancer therapies, including pharmacokinetic and pharmacodynamics analysis, as well as state-of-the-art imaging and molecular diagnostics.

With the recent advances in the understanding of myeloma biology, it is becoming increasingly evident that myeloma can be subdivided based on a number of genetic and biological markers, and many of these markers are potential therapeutic targets. Therefore, at any point, a portfolio of studies will be open to accrual in the unit, allowing for the matching of patients to appropriate studies and a personalized approach to therapy. Additionally, the unit will be able to run both commercial- and investigator-led phase I studies to ensure that promising basic research findings from the Myeloma Institute and other UAMS programs can be translated quickly into the clinical environment for patient benefit.

By embarking on this initiative we are committed to delivering clinical-research-driven care that is integrated, pioneering and world-class, and which, most importantly, embraces the essentials of high quality and patient focus with the overarching goal of curing myeloma.

Davies is a professor of medicine and director of the phase I clinical trials unit.

ALLOGENEIC TRANSPLANT PROGRAM ON THE HORIZON

Yogesh Jethava, M.D., has been named director of an allogeneic transplantation program in development for the Myeloma Institute and Winthrop P. Rockefeller Cancer Institute at UAMS. An assistant professor in the Division of Hematology/Oncology in the College of Medicine, Jethava expects the program to be operational in January 2015. A dedicated inpatient unit with 12 rooms, all with high efficiency particulate air (HEPA) filters and some with laminar airflow barriers for ultra-high-risk patients, will be staffed by nurses with extensive specialized training.

The allogeneic stem cell transplant program will serve Arkansas and adjoining states, which lack this treatment option for eligible patients with acute myeloid leukemia, myelodysplastic syndrome, acute lymphocytic leukemia, lymphomas and, occasionally, myeloma. Jethava expects about 60-70 transplants per year when the program is fully functional.

“The addition of an allogeneic transplantation program here will enable UAMS to provide more comprehensive cancer treatment options to patients,” Jethava said.

Jethava shares the same vision for curing malignant hematological disorders as Myeloma Institute Director Gareth Morgan, M.D., Ph.D., F.R.C.P., F.R.C.Path., and institute founder Bart Barlogie, M.D., Ph.D. He enjoys working as part of a team with the patients, caregivers and a full array of specialists, including radiologists and pathologists.

Jethava earned his medical degree from B.J. Medical College, Pune, India, and completed a residency in internal medicine at Lokmanya Tilak Medical College, Mumbai University, Mumbai, India. He subsequently completed subspecialty training in clinical hematology at the University of London. Jethava has more than five years of experience in stem cell transplantation and management of patients with myeloma, myelodysplastic syndromes and acute leukemias, and has been actively involved in clinical research. He is a member of the Royal College of Physicians, UK, and the Royal College of Pathologists, UK.
UAMS-Led Study Earns FDA Approval for First Castleman’s Disease Drug

The first-ever drug for Castleman’s disease was approved earlier this year by the U.S. Food and Drug Administration (FDA) following an international study led by the UAMS Myeloma Institute’s Frits van Rhee, M.D., Ph.D.

The drug is designed for Multicentric Castleman’s disease (MCD), a rare lymph node disorder driven by excess secretion of interleukin 6 (IL6), causing symptoms such as night sweats and fevers. In severe cases patients can develop vascular leak syndrome, organ failure and even death. Treatment has been based on case reports and has included prednisone, rituximab and combination chemotherapy.

Historically, the five-year overall survival rate is only 65 percent, underlining the disease’s potential severity.

The Myeloma Institute was the first to report on the use of a monoclonal antibody to neutralize IL6 in MCD in 1994. Van Rhee, the nation’s foremost expert on Castleman’s disease, was principal investigator on the recent trial of the novel monoclonal anti-IL6 antibody, siltuximab. The clinical trial was the first randomized, placebo-controlled clinical trial in MCD and involved researchers and study participants in 19 countries.

Patients treated with siltuximab fared significantly better than patients treated with placebo in terms of lymph node and symptoms response, improvement in laboratory parameters and prolongation of time to next therapy.

"On the basis of this study, siltuximab is the first approved therapy for MCD by the FDA and the European Medicine Agency and is an important addition to the armamentarium for the management of MCD,” said van Rhee, who has one of the largest volumes of Castleman’s disease patients in the world and directs a laboratory and clinical research program dedicated to the disease.


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MEDICAL CASE STUDY
LATE-STAGE MULTIPLE MYELOMA PATIENT SAVED BY GENETIC SEQUENCING, PIONEERING USE OF DRUG

By Christoph Heuck, M.D.

Prior to presenting to the UAMS Myeloma Institute in 2006, the 53-year-old male patient was treated near his home in Connecticut with standard multiple myeloma therapy, including a stem cell transplant, that failed to stop progression of the disease.

Following a complete work-up at the Myeloma Institute to confirm his multiple myeloma, the patient received tandem transplants, consisting of high-dose chemotherapy combined with autologous stem cell rescue. Due to the extended treatment regimen, the patient temporarily relocated to Little Rock while his wife remained in Connecticut.

**MIXED RESULTS**
The patient initially experienced a complete response post-tandem transplant but relapsed in 2007. He then underwent a series of treatments, including the use of new drugs in clinical trials, and more chemotherapy. The treatments, conducted over several years, stabilized the disease only briefly. With each relapse, the disease became more complex and evolved to a higher risk status.

Eventually the patient developed extramedullary disease, a sign of late-stage cancer. The multiple myeloma exited the bone marrow and began to invade the patient’s soft tissue organs, primarily the liver. Since the extramedullary component of this patient’s myeloma proved to be particularly resistant to therapy, we performed transarterial chemoembolization, directing a catheter to the vessel supplying the tumor, administering chemotherapy directly to the tumor and blocking the tumor’s blood supply. This was effective locally, but new lesions continued to appear on the liver.

**“HOT-SPOT” MUTATIONS**
By mid-2013, the patient was receiving his 15th line of therapy, including intensive chemotherapy. At the time, the Myeloma Institute was initiating targeted sequencing of tumor associated genes, zeroing in on a panel of genes known to be associated with a range of cancers. More importantly, some of these “hot-spot” mutations had recently been found to respond favorably to new drugs in other cancers.

In this case, we took a bone marrow specimen and extracted the myeloma cells and the DNA. Those samples were sent for analysis of a panel of 410 genes. This test can reveal mutations in key signaling pathways that can be targeted by known or novel agents.

Analysis of the patient’s genes revealed a KRAS mutation, which has been associated with many cancers, especially lung and colon cancer. This mutation causes the KRAS enzyme to be continuously switched on, resulting in a permanent activation of a signaling pathway that drives the proliferation and survival of cancer cells.

Several drugs have been identified that will attack various stations along the pathway. We selected Trametinib, a drug approved by the Food and Drug Administration (FDA) for melanoma, which could be prescribed off-label. An oral medication, Trametinib cuts off the disregulated signaling downstream from the KRAS mutation by inhibiting a protein known as MEK.

**OUTCOME**
The patient was able to return home after taking Trametinib for two months, and he continued to take the drug at home. After taking Trametinib for four months, PET and MRI scans showed that his liver lesions had resolved. More recent scans and laboratory tests showed no evidence of multiple myeloma and he was allowed to discontinue the drug after 11 months. At least initially, the patient will return to UAMS every three months for follow-up tests.

We believe this is the first case in which Trametinib has been used as a multiple myeloma therapeutic. Since then, more than 60 patients have received the drug at the Myeloma Institute, and a Phase II multiple myeloma clinical trial is planned.

Other hot-spot mutations associated with myeloma include BRAF and NRAS. Both can be treated with new small molecule drugs to inhibit their signaling. As a result of the sequencing approaches described here, we are beginning to conceptualize multiple myeloma differently. Rather than defining the disease as it relates to its tissue of origin, we are defining it by its molecular makeup. We have shown, for example, that one myeloma may have more in common with melanoma on a molecular basis than another myeloma. By understanding these molecular changes and mutations, we will continue applying that knowledge to most effectively target our treatments.
PET scan of the liver before starting therapy with Trametinib (top) and two months after starting therapy with Trametinib, showing a complete resolution of the liver lesion.

A) A Normal MAPK kinase pathway includes physiological signaling through the MAPK pathway after binding of a ligand to a receptor tyrosine kinase.
B) MAPK pathway activation is due to an activating mutation of a RAS gene in the absence of ligand binding.
C) The drug Trametinib can inhibit abnormally activated MAPK pathway.

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San Antonio Patient ‘Did Homework,’ Chose UAMS Myeloma Institute

I was diagnosed with multiple myeloma on Dec. 24, 2010, after my buddy gave me a bear hug that dropped me to my knees in severe pain. I was 49 years old, and at that moment my priorities went into sharp focus. I became obsessively determined to beat myeloma so I could be there for my wife, children and grandchildren.

I did my homework and sought treatment with Dr. Bart Barlogie (Myeloma Institute founder). Once I had the facts, it was an easy decision for me. The Myeloma Institute treats more myeloma patients than anywhere else; they run more clinical trials, and they have access to more cutting-edge drugs and therapies than any other institution.

I finished my treatments in Little Rock in 2011 and have moved on to maintenance therapy administered in my home town of San Antonio under the direction of Dr. Barlogie and with periodic check-ups back at the Myeloma Institute.

I am living a full and active life with my family without limitations. And, I stay connected with my myeloma buddies from around the world who went through treatment the same time I did at the Myeloma Institute.

Life is good, and with the Myeloma Institute as my partner, I look forward to a long life ahead.

Ken Halliday, San Antonio