myeloma Institute

FORGING THE PATH TO CURE THROUGH EXPLORATION AND DISCOVERY
Multiple myeloma, a cancer of plasma cells in bone marrow, is a biologically complex cancer. As recently as twenty years ago, effective treatments for myeloma were elusive and outcomes were less than optimal. Thanks to pioneering research at the Myeloma Institute, begun in 1989, treatment has evolved to new heights with greatly improved survivals and cures. Our treatments are used across the U.S. and the world.

The Myeloma Institute, the world leader in novel therapies, is embarking on ever-more advanced research that is breaking barriers to cure through targeted, personalized approaches.

One-size-fits-all no longer applies in today’s world of medicine. Customized care based on each individual’s genetic profile and risk factors is the way of the future. This is the driving force of the Myeloma Institute.

An understanding of myeloma biology can be used to unlock the secrets of curing cancer in general.

Our overriding vision is to push the envelope of understanding and discovery to unravel the biology of myeloma and maximize cure.

This vision encompasses four main research paths:

- Identifying Causes of Myeloma
- Myeloma Stem Cell Biology
- Targeted Treatment Based on Genetics and Epigenetics of Myeloma
- Total Treatment Approaches to Curing Myeloma

The Myeloma Institute’s unique “bench to bedside” approach integrates basic science discovery with clinical applications.

We invite you to read further and learn more about our research directions, and to join us in our mission to cure myeloma.
Bone Marrow in Multiple Myeloma

Most blood cells develop from blood-forming stem cells in the bone marrow. (A stem cell is a cell from which other types of cells develop.) These stem cells mature into different types of blood cells – white blood cells, red blood cells and platelets.

Plasma cells are white blood cells that make antibodies. Antibodies are part of the immune system that helps protect the body from germs and other harmful substances.

Myeloma begins when a plasma cell becomes abnormal. The abnormal cell divides to make copies of itself. Through continued cell division, more abnormal cells are made. These abnormal plasma cells are myeloma cells.

Myeloma is supported by myeloma cancer stem cells (MCSCs). MCSCs have to be eliminated in order to cure patients of the disease.

Myeloma begins when a plasma cell in the bone marrow becomes abnormal. Mature myeloma cells secrete immunoglobulins (antibodies) known as M-proteins, which can be detected in the blood.
defining the causes of myeloma
Vision
We envision a world without myeloma. In order to get there, we need to shift the focus from diagnosis and treatment to early screening and prevention.

You can play a critical role in supporting our research on defining the causes and genetic basis of myeloma.

Background
Myeloma development starts when a normal plasma cell develops features of a myeloma cancer stem cell and continues to acquire abnormalities until it becomes a fully cancerous cell. The early steps in the development process may involve the interaction of the environment with the inherited genetics of the patient.

Studying the cancer development process in myeloma can provide a model for studying other cancers.

A major aim in conquering cancer is to prevent its development. Take, for example, MGUS (monoclonal gammopathy of undetermined significance), a precancerous condition and precursor to myeloma, which is present in 5% of individuals over the age of 60. We need to figure out how to prevent the transition from MGUS to myeloma.

Research Plan
We propose to identify the causal factors and genetic basis of myeloma in order to:

- Understand the underlying causes of myeloma – environmental, genetic and other.
- Design strategies to prevent MGUS and smoldering myeloma from developing into active myeloma.
- Understand how inherited genetic factors interact with cancer cells to affect disease progression, side effects of treatment and outcome.

The ultimate goal is to design prevention studies based on population screening.

Federal and other grants cover less than 40% of our research funding needs.
What have we done and what do we know?

- We have identified seven genes that are directly related to the risk of developing myeloma.
- Through the MAGIC Consortium, we have data and treatment details from thousands of cases.

The Myeloma Genetics International Consortium (MAGIC) includes 16 research groups in Europe, Asia, Australasia, the Middle East and the Americas engaged in studying the genetics of myeloma.

What do our findings mean for patients?

1. Myeloma has a genetic basis which is influenced by a limited number of inherited factors.
2. The genes we have identified increase the susceptibility to the disease process, increasing the likelihood of myeloma development.
3. The genetic variants we have identified are common and do not typically have a huge impact on a given person. However, the variants do point to a significant proportion of risk in the general population.

Next Steps

1. Describe rare variants that increase risk within a family. This will be accomplished by analyzing DNA via next-generation sequencing.*
2. Study how inherited factors impact treatment effectiveness and side effects.
3. Investigate how inherited factors affect the normal biology of the cell so we can design strategies to normalize the biology and prevent disease progression.

*Next-generation sequencing refers to technologies that enable quick and cost-effective sequencing of DNA and RNA for the study of genomics and molecular biology.

Scientific research is a dynamic process. The ability to direct research dollars where they are needed most, based on continual discoveries and new findings, is key to making efficient progress. Your philanthropic support makes this possible.
Myeloma, as all cancers, is characterized by uncontrolled cell growth. Cancer begins when a single cell mutates, resulting in a breakdown of the normal regulatory controls that keep cell division in check. These mutations can be caused by environmental, genetic and other factors.

Acquiring multiple mutations leads to myeloma.

### Multi-Step Model to Myeloma

<table>
<thead>
<tr>
<th>Initiation</th>
<th>Progression</th>
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</thead>
<tbody>
<tr>
<td>Germinal center → Bone marrow</td>
<td>Peripheral blood</td>
</tr>
<tr>
<td>Post-GC B cell → MGUS</td>
<td>Smoldering myeloma → Myeloma</td>
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<tr>
<td>Inherited variants</td>
<td>Plasma cell leukemia</td>
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<tr>
<td>Primary genetic events</td>
<td>Secondary genetic events</td>
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<tr>
<td>• IGH translocations</td>
<td>• Copy number abnormalities</td>
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<tr>
<td>• Hyperdiploidy</td>
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<tr>
<td>Clonal advantage</td>
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<tr>
<td>Competition selection for bone marrow niche</td>
<td>Migration and founder effect</td>
</tr>
<tr>
<td>Tumor cell diversity</td>
<td>Genetic lesions</td>
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</tbody>
</table>

*Understanding how myeloma develops will help us design strategies to prevent disease progression.*
myeloma
stem cell
biology
Background and Challenge
In order to cure myeloma, we must be able to eradicate the original myeloma cancer stem cell that gives rise to all the myeloma cells.

We need to understand how a normal plasma cell, which produces antibodies that protect the body from infection, changes into a cell with the characteristics of a myeloma cancer stem cell, which eventually morphs over time to high risk myeloma that is resistant to treatment.

Understanding this stem cell biology will enable us to design new treatment regimens based on altering the cell’s behavior to prevent disease progression, resistance to therapy and disease relapse. We will be able to fashion treatments that kill the myeloma cancer stem cells while sparing other cells in the body, resulting in cure with minimal side effects.

Modulating stem cell behavior could stabilize the stem cell in such a way that it becomes more sensitive to treatments, resulting in improved outcomes. Modulation could also prevent the progression of disease from MGUS (monoclonal gammopathy of undetermined significance, a precursor to myeloma) and smoldering myeloma to active myeloma. In this way, cells could be stabilized in a benign phase, changing the landscape from curing patients with myeloma to preventing myeloma from developing in the first place.

Next Steps
We need to develop models for investigating the unique biology of the myeloma stem cell that can be validated in the laboratory and in patients. These models will include:

1. Single cell studies*
2. In vitro systems**
3. Animal model systems

*Many biological experiments are performed on groups of cells under the assumption that all cells of a particular type are identical. However, individual cells within the same population may differ dramatically, and these differences can have important consequences for the health and function of the entire population. Experimental approaches that only examine population-level characteristics can obscure these crucial differences. Single cell analyses are needed to uncover fundamental biological principles of myeloma.

http://commonfund.nih.gov/Singlecell/snapshot

**In vitro refers to studies of biological properties that are done in a test tube rather than in a human or animal. In vitro studies allow scientists to isolate and study specific cells.

With your help, we can change the landscape from curing patients with myeloma to preventing myeloma from developing in the first place.

You can play a critical role in supporting our research on unraveling the biology of myeloma.
**Goals:**

- Better understand how myeloma develops, specifically how MGUS and smoldering myeloma transform into myeloma.
- Gain insight into the biology of high-risk myeloma and treatment resistance.
- Design new treatments aimed at the biology of the myeloma stem cell.
- Cure more patients with less toxic treatments.

Research often progresses unpredictably. The need to modify a path, based on discoveries along the way, requires research dollars that can be reallocated as needed. Your philanthropic support helps speed the process of discovery and enables faster translation to clinical advances.

With federal and other grant funding on the decline, philanthropic support is more important than ever.
Numerous genetic alterations, or mutations, affect myeloma cells, making them complex and difficult to eradicate. A primary mutation, as depicted on the tree trunk, can evolve into many mutations over time, as depicted on the tree branches. All of these mutations are then present in the myeloma cell, as depicted in gray.

It is important to target each alteration with specific inhibitors in order to fully destroy the myeloma cell. Advanced understanding of myeloma genetics and precision medicine enable identification of each genetic alteration and development of targeted therapies.

Targeting treatment to the myeloma cancer stem cell can lead to cure.
Background and Challenge

We need to understand the genetic basis of myeloma and use this information to design targeted treatment strategies aimed at switching off the genetic signals that lead to its development.

A gene mutation is a permanent alteration in the DNA sequence that makes up a gene, such that the sequence differs from what is found in most people. Since the mutation is permanent, treatment must be aimed at reversing the biological impact of the alteration.

Philanthropy comprises more than 60% of our research funding. Federal and other grant funding simply cannot meet the full need.

Epigenetics refers to the biological mechanisms that switch genes on and off in a stem cell, causing different types of tissue.

You can play a critical role in supporting our research on targeted treatment based on genetics and epigenetics.

Epigenetics-based treatments are based on programming cells in order to modify the on-off mechanisms.
What have we accomplished so far?

- Identified specific cancer mutations and demonstrated that targeting these mutations can result in disease response.

- Characterized mutations in the DNA coding sequence and incorporated these into prognostic testing.

- Studied epigenetic patterns typical of genetic subtypes of myeloma and have begun development of subtype-specific targeted agents.

- Studied mutations at relapse, how they are impacted by treatment and how treatment resistance develops.

Next Steps

While we have characterized mutations in the coding sequence of DNA, it is now important to turn our attention to understanding the changes in the non-coding sequences of what was previously considered “junk DNA.” It is likely that changes in the non-coding sequences and subsequent subtle changes in gene expression could initiate cancerous activity in cells.

Our goal is to identify these mutations and design a strategy to help us understand what the mutations mean in terms of cellular behavior, treatment design and patient outcome.

What was once known as junk DNA turns out to hold hidden treasures.
Epigenetics refers to the way DNA is packed and wound into chromosomes.

Epigenetics describes modifications to the genome that can be passed on to future cells. These changes do not alter the nucleotide sequence of the DNA that make up our genes. Rather, they modify the “backbone” that supports the DNA sequence. These modifications influence when and how often a gene is active.

Deciphering when and how genes are turned on and off enables researchers to study gene pathways that influence myeloma progression.
Total Treatment Approaches to curing myeloma
Vision
We believe there are treatment agents that can revolutionize the outcome for myeloma.

We want to take giant leaps forward in identifying agents that can have a major impact on cure, rather than focusing on the nuances of drugs already in use.

We will do this by employing novel clinical trial designs and developing endpoints that yield early, reliable results. This will be done within an excellent clinical trial and data analysis infrastructure.

This approach can greatly improve the speed with which we screen new agents and utilize those agents that are effective and benefit patients in the shortest possible time.

Background
The Myeloma Institute was the first center to achieve truly curative outcomes through its novel Total Therapy treatment approach. Total Therapy incorporates proven effective agents up front for an “all-out attack” on myeloma. The idea is to knock out the myeloma cells at the outset, even the tough, resistant cells, and not give them an opportunity to survive.

Curing myeloma at last; defining criteria and providing the evidence. Blood. 2014; 124:3043-51. PMID: 25293776

Variations of the Total Therapy regimen have been designed to target specific molecular subtypes of myeloma.

The Myeloma Institute was the first to identify molecular subtypes and mutation patterns of myeloma and alter treatment accordingly. It was also the first to describe achievable cure.


With advanced knowledge, improved diagnostics and new therapeutic agents, it is now time to take Total Therapy to the next level.

Using molecular diagnostic tests and functional imaging studies, we can determine if the treatment is effective. If it is not working as desired, it can be adapted to include different agents. Through a targeted approach we can achieve more and deeper responses which in turn lead to cure for more patients.

Philanthropy holds the power to advance research effectively and efficiently and bring promise to patients.
How are we improving Total Therapy protocols to cure the most patients?

- Harnessing the immune system.
- Targeting treatment to the molecular lesions that cause myeloma.
- Reducing treatment toxicity.
- Modifying and personalizing regimens for frailer patient populations.

Harnessing the Immune System
The immune system can be tapped to overcome resistance to treatment. The immunomodulatory drugs (IMiDs) Revlimid and Pomalyx have worked successfully in this manner. We plan to develop antibody-based strategies which can enhance the activity of IMiDs by further activating an immune response to the cancer cells and then integrating them into the Total Therapy approach.

Targeting Treatment to the Molecular Lesions that Cause Myeloma
Genetic analysis conducted on DNA from myeloma cells reveals mutations in the signaling pathways that regulate the growth of cancer cells. Signaling pathways that are continuously switched “on” due to a mutation drive the proliferation and survival of cancer cells and can be switched off with new drugs.

Reducing Toxicity
The Total Therapy regimen has transformed myeloma from a fatal disease to a curable disease. But, with high-dose chemotherapy that can cause a host of toxicities, the regimen can be an ordeal for patients.

While we will continue to employ Total Therapy, given its high cure rates, we will concurrently develop immunotherapy-based mechanisms that can ultimately replace the toxic chemotherapies.

Each patient is a unique individual with unique disease characteristics. Your support can help us further define and target the disease process for each patient.

We will explore how we can enhance this epigenetic approach by building combinations of agents that work together to overcome complex and diverse signaling activity.
Modifying Regimens for Frailer Patient Populations
Elderly, frail patients cannot usually tolerate the Total Therapy regimen. We plan to introduce adaptations to treatment intensity and utilize immunotherapy as a less strenuous approach for this patient population.

Developing Targeted Therapies to Complement Total Therapy
We will employ a number of approaches to develop effective targeted therapies.

- Use antibodies for previously untreated patients before they undergo chemotherapy. This innovative strategy will enable us to identify markers of the best responders and target treatment to specific groups.

You can play a critical role in supporting our research on a total treatment approach that employs the most effective regimens for each individual patient.

- Create umbrella studies for high-risk myeloma. Through innovative trial design, we will investigate how immunotherapy and targeted therapy can impact responses and indicators of cure. The study design will enable us to get answers quickly so that effective interventions can be readily integrated into the Total Therapy program.

“Umbrella” trials are employed to improve the efficiency of clinical trials. Umbrella studies are designed to test the impact of different drugs on different mutations in a single type of cancer.

- Initiate cellular therapy, using expanded natural killer cells. Natural killer cells are white blood cells and are part of the immune system.

- Employ virotherapy to destroy myeloma with a virus that infects and kills the myeloma cells but spares normal cells.

- Develop novel imaging studies that can yield response information in a quick time frame so that treatment can be immediately adjusted.

- Collect and record biological samples and clinical data to establish an effective revolving “bedside to laboratory back to beside” conduit. This real-time information will allow us to readily determine which patients respond optimally and how we can improve therapy.
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The goal of the Total Therapy approach is to get patients into remission and to hold the remission by using the power of the immune system.
Our Big Challenges for Enhancing Total Therapy Approaches to Curing Myeloma

Tackling High-Risk Disease
While we have demonstrated that we can cure low-risk myeloma, which affects 85% of myeloma patients, we have yet to make great strides for the 15% of patients with high-risk myeloma. We need to examine why this group has failed to respond, understand the biology of high-risk disease and design treatment regimens accordingly.

It is important to run the diagnostic tests that reveal high-risk status when patients first present to the Myeloma Institute so they can be assigned at the outset to the most appropriate treatment regimen that will increase the likelihood of good outcomes.

Preventing Progression from Precursor States to Active Myeloma
In general, early treatment for cancer imparts improved outcomes. We have every reason to believe this approach is also effective for myeloma. We have developed a test that indicates which patients with MGUS or smoldering myeloma have a likelihood to develop full-fledged myeloma. It makes sense to explore the option of treating them up front with low-toxicity agents to prevent progression to active disease.

With your support, comprehensive strategies for treatment can be fine-tuned and customized on a patient-by-patient basis.
Our Mission:
The Myeloma Institute is committed to accelerating curative therapies for multiple myeloma and related diseases through an integrated program of innovative research and outstanding patient care.

Ensuring a Firm Path to Accomplish our Mission
The Myeloma Institute invites you to play a critical role in supporting the research that offers the promise of cure.

Advances in cancer treatment depend on advances in cancer research. We have made major strides in myeloma research and continue to lead the way, with the goal of curing myeloma for as many patients as possible across the globe.

The Myeloma Institute is unraveling the biology of myeloma and maximizing cure through personalized treatment approaches. Your support ensures that our ground-breaking research will continue at a steady pace.

Research often progresses unpredictably. The need to modify a path, based on discoveries along the way, requires funding that is nimble and flexible. Your philanthropic support helps speed the process of discovery and enables faster translation to clinical advances for improved patient outcomes.

Help us reduce the reach of myeloma and related diseases and improve the health of patients worldwide.

Naming Opportunities are available. Gifts can be in the form of cash, securities, property or bequests.
Philanthropy for Research
Two-Pronged Approach

Endowment for Research
A solid endowment ensures a steady stream of usable funds to support our research over the long-term.

Goal: $65 million by 2020

Spendable Funds for Research
Spendable funds fill the gap that federal and other grant funds cannot meet.

These funds are applied immediately to active research.

Goal: $3 million per year

Philotropy for Research supports all facets of our comprehensive research enterprise, including state-of-the-art laboratory equipment, high-caliber, specialized materials and the brightest minds in the field.

Philanthropy supports more than 60% of our ground-breaking research.

“I have complete confidence that the Myeloma Institute clinicians and scientists, armed with unparalleled knowledge, ingenuity and perseverance, can deliver the goods.”
Carol Ammon, Myeloma Institute Advisory Board Chairman