de Gunzburg
Myeloma Research Foundation

PRESENTATION

Finding a Cure for Multiple Myeloma

December 2015

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A LETTER FROM THE PRESIDENT

DEAR FRIENDS,

Twelve years ago, I was diagnosed with multiple myeloma, a rare and incurable form of blood cancer most common in those above 70. I was only 29 years old.

This disease is one of the oldest forms of cancers. It has been quietly killing thousands of people across the globe for more than four thousand years. It is estimated that 200,000 people worldwide and 90,000 Americans are currently affected by multiple myeloma. While 26,850 Americans are diagnosed every year, myeloma takes the lives of approximately 11,240 people each year. And this disease is growing among us as we get older: 9% of people above 85 years old are likely to be diagnosed with myeloma. Yet despite these troubling figures, not enough attention is being given to this fatal disease.

In March 2012, I established the de Gunzburg Myeloma Research Foundation ("DGMRF") to support research and create greater awareness about the illness. Because it is imperative that 100% of every dollar raised go towards research, I have committed the funds necessary to pay all administrative and non-research related expenses. Therefore, all funds raised are committed exclusively to the research we vitally need to save lives, and will be deployed within the same year to ensure we move faster than the disease.

There are currently no drugs being developed in any pipeline of any laboratory of any organization throughout the world that could offer a cure for multiple myeloma. At the DGMRF we work toward one sole mission: **to find a cure**.

We do this by selecting the world's best research teams and hospitals in the field of myeloma. And within research, wherever money is most scarce, wherever the funding is most needed, that is where we come into play. Hence, we exclusively finance early stage fundamental research. We avoid venture philanthropy and do not expect any economic returns from our projects. We also ensure objective and effective allocation to the best third parties we can find by not having internal drug development or research teams.

A LETTER FROM THE PRESIDENT

During these difficult economic times, funding for medical research is being sharply reduced, and government budgets are dwindling. Pharmaceutical companies are prioritizing other research ahead of multiple myeloma, a currently relatively small market with limited commercial and profit potential. It is up to foundations like the de Gunzburg Myeloma Research Foundation to provide the necessary resources to make sure the vital research work continues.

Without the wonderful contributions from extraordinary donors, our mission might not be possible. These real philanthropists understand the need to focus on the greater good by funding long-term research. They are also visionaries as they understand that with a rapidly aging population, multiple myeloma will become a more common disease and will kill many more.

Through your generous donations, we can increase visibility regarding multiple myeloma while most importantly prolonging, and ultimately, saving lives across the globe. As an American 501(c)3 foundation, every donation is tax deductible. And we value every dollar, which counts for both the Foundation and you.

Myeloma being one of the last forms of cancer still totally incurable today, donors have the opportunity to add substantial value and enable real breakthrough in medical research by tackling one of the most overlooked and challenging disease for the exclusive benefit of saving lives.

At the de Gunzburg Myeloma Research Foundation, we will not stop until breakthrough drugs are found to cure multiple myeloma.

Thank you so much for supporting our cause and offering hope to all of us who are battling this terrible disease.

With utmost gratitude,

Vivien de Gunzburg
President
de Gunzburg Myeloma Research Foundation

INTRODUCTION TO MYELOMA

In the United States, nearly **43% of all men** and **over 38% of all women** will develop cancer in their lifetime[1].

1 person is diagnosed every 4 minutes with blood cancer. And **every 10 minutes someone dies from a hematologic or so-called blood cancer**.

That's more than 6 people every hour[2] or 145 people each day. Among these diseases is **multiple myeloma, the second most common form of blood cancer**[3].

While approximately 90,000 people currently live with multiple myeloma, 26,850 new cases are diagnosed and 11,240 people die from it every year[4] in the U.S..

Myeloma is thus categorized and registered as a **rare** and **orphan disease**[5].

[1] *Source: American Cancer Society, September 2014 - Lifetime Risk of Developing or Dying From Cancer.*

[2] *Source: DFCI, June 2012 - based on a defined set of data points.*

[3] *Source: Dr. Benboubker, CHRU of Tours.*

[4] *Source: National Cancer Institute - SEER Stat Fact Sheets 2015: Myeloma.*

[5] *Source: National Institute of Health - An orphan disease is a disease affecting less than 200,000 people in the U.S.*

UNDERSTANDING MYELOMA

- Multiple myeloma (from Greek myelo -bone marrow-), is a form of cancer where plasma cells, a type of white blood cell normally responsible for the production of antibodies, become malignant, and primarily **attack and destroy bones**.

- These of abnormal cells accumulate in bones and the bone marrow, where they also interfere with the production of normal blood cells. The abnormal growth makes it harder for the bone marrow to make healthy white blood cells, red cells, and platelets. The result is a weakened immune system (creating side effects such as bleeding, fatigue, shortness of breath), and ultimately affecting major organs, such as the kidney and heart.

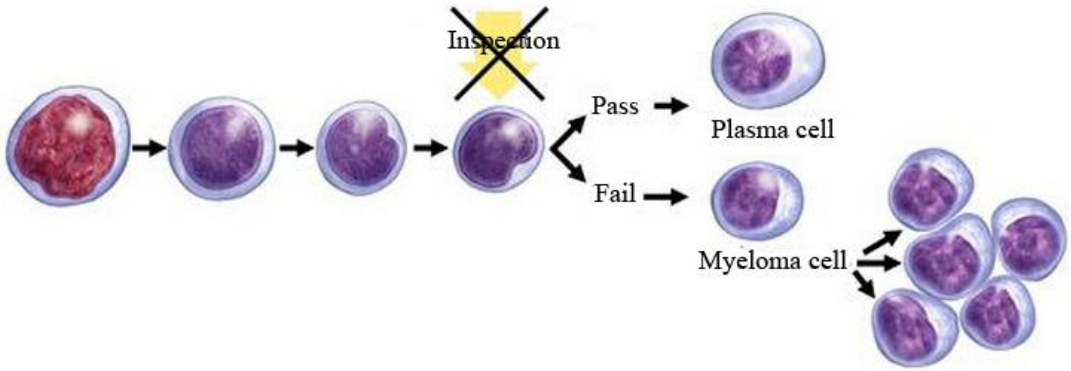
- The causes of multiple myeloma are uncertain. And because it is a rare disease, not much information is available nor is it always precise.

- There is currently no known cure. There are treatments which enable to fight back the disease, and sometimes achieve temporary complete remission. With novel treatments developed over the last ten years, the disease can be better managed including by increasing survival duration.

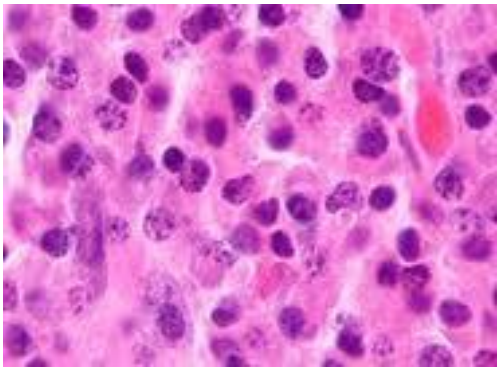
- **Though outcomes are constantly improving, major progress is needed to bring us closer to a real CURE.**

HOW MULTIPLE MYELOMA FORMS

- Myeloma alters the function of plasma cells, and leaves them unable to fight infection. Indeed, they mutate into plasmacytes, build-up in excessive numbers of abnormal cells (myeloma cells by then -though some doctors call myeloma the disease once it has formed multiple lesions-), and aggregate to create tumor(s), especially in the bone marrow (often by nature in multiple locations throughout the body).



- These tumors begin to overcrowd the bone marrow, “colonizing” their environment.

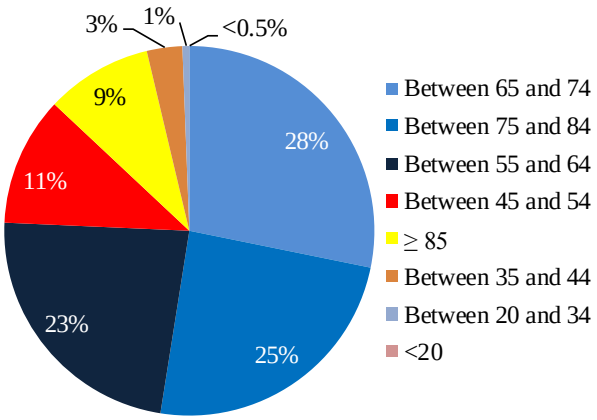


- Because myeloma cells may circulate in low numbers in blood, they sometimes cannot be identified and destroyed by a functioning immune system:
  - → They are not always traceable by the most advanced blood tests, radiography, MRIs or CT PET scans. **That is what we call <u>temporary</u> remission;** and
  - → Myeloma cells may populate the bone marrow in various parts of the body, even far from where they originated. **That is why the disease is called <u>multiple</u> myeloma.**

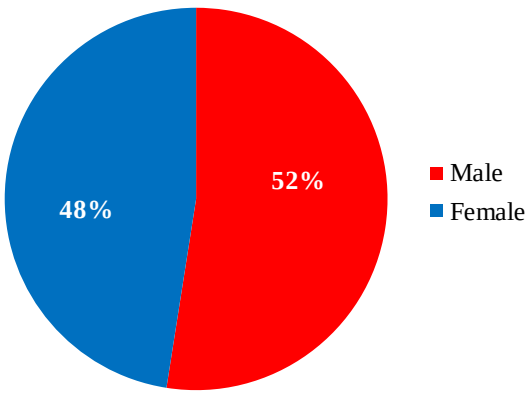
MULTIPLE MYELOMA:

- Is the second most common hematological malignancy in the U.S. (16%) after Non-Hodgkins Lymphoma (54%).
- Constitutes 1.5% (growing from 1% in 2012) of all cancers in terms of number of patients affected/diagnosed/treated, **and 2% of all cancer deaths**[1] (steady relative to all cancers, but decreasing vs. the number of people diagnosed thanks to new treatments).
- Remains a **chronic incurable disease** with a current estimated **median survival rate of 7-8 years**[2] despite progress in research and treatment.
- As a comparison, in France, nearly 12,000 patients are affected by the disease. 4,000 new cases are diagnosed every year (114,000 worldwide[3]), making it the 3rd most common blood cancer after lymphoma and leukemia in France.

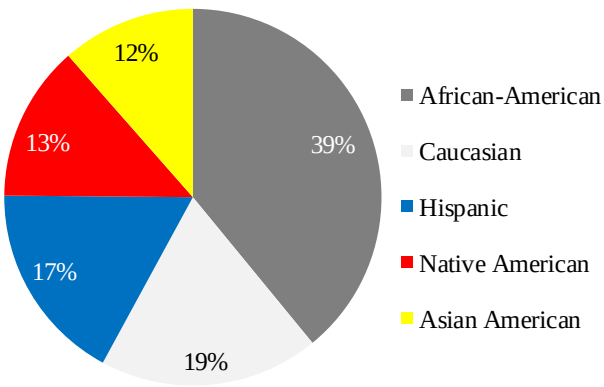
Incidence by Age



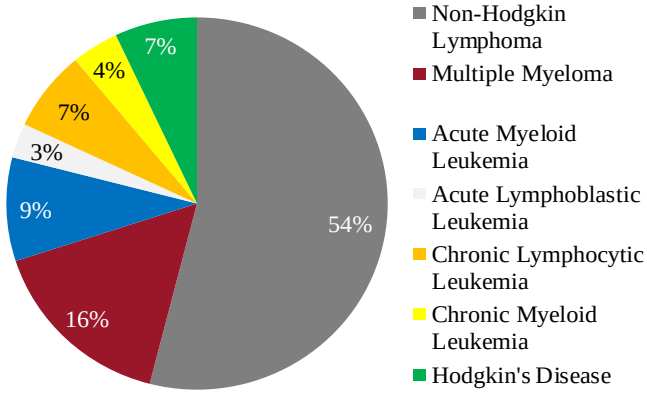
Incidence by Gender



Incidence by Origin



Incidence by Type



[1] *Source: National Cancer Institute - SEER Stat Fact Sheets 2015: Myeloma.*

[2] *Source: Leukemia and Lymphoma Society - Fact 2012 study.*

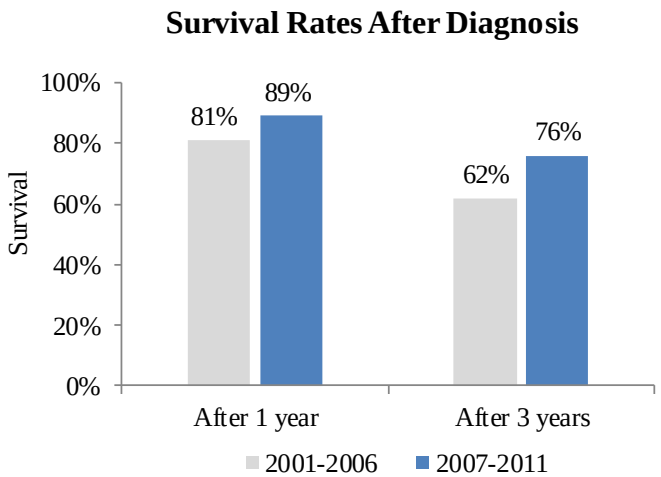
[3] *Source: World Cancer Research Fund International – Myeloma Worldwide Data from 2012.*

WHO IS MOST AFFECTED?

- Predominantly the elderly: 62% of patients are above 65 years of age. Myeloma rarely occurs in people under age 45. The median age at diagnosis is 69 (66 for African-Americans).
- Multiple myeloma is more common in men. When compared to people of Caucasian descent, multiple myeloma is twice as common in African-Americans and twice less frequent in Asian-Americans.
- Additional research has found that people of Jewish Ashkenazi origins are also more likely to develop multiple myeloma.
- It is estimated that MGUS (Monoclonal Gammopathy of Uncertain Significance) might affect as much as 10% of people of 85 years old.

DEATHS

- Out of 26,850 estimated new cases diagnosed in 2015 in the U.S. - and the existing 89,658 people affected by myeloma - approximately 11,240 are expected to succumb to their illness. The U.S. median age for death from myeloma is 75 years; 71 years for African-Americans; 68 years for Hispanic people.
- The American Cancer Society estimates that approximately 3% of all cancer-related deaths among African-Americans are caused by myeloma (vs. 2% in the U.S.).
- From 2004-2008, myeloma was the 7th most common cause of cancer deaths among African-American women and the 12th among Caucasian women. In details, from 2008-2012, the mortality of African-American men and women due to myeloma was nearly double that of Caucasian men and women (7.6 per 100,000 versus 4.0 per 100,000 for men, and 5.3 per 100,000 versus 2.4 per 100,000 for women).
- Advances in research and treatment are helping enhance survival period rate: In 2003 it was: 3-5 years; 2008: 5-7 years; 2012: 7-8 years.

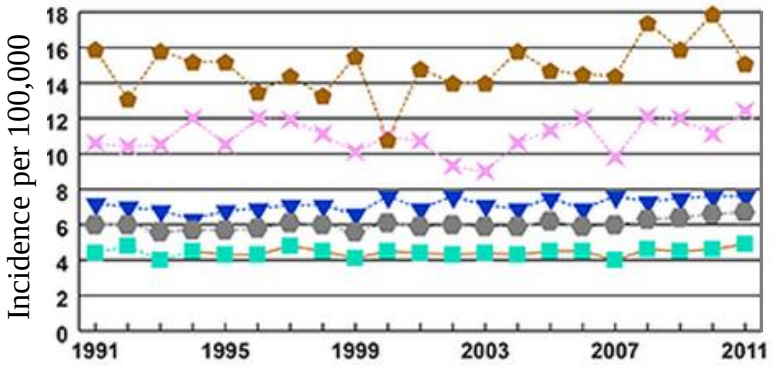


Source: American Cancer Society Facts and Figures 2011-2012, Fact 2012 study & Leukemia and Lymphoma Society.

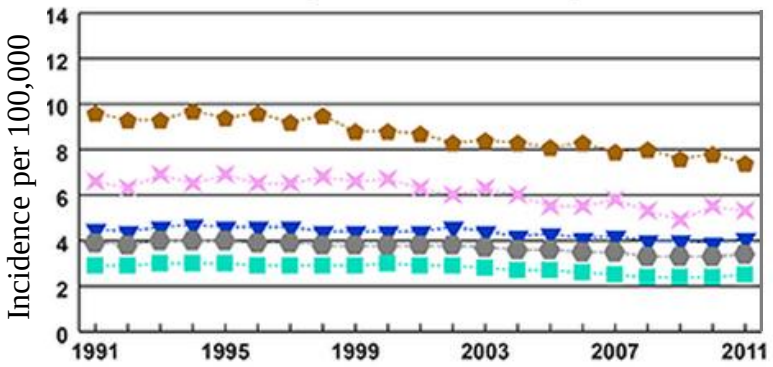
FACTS & FIGURES

- The number of people being diagnosed with multiple myeloma is growing on an absolute basis and as a percentage of the population.
- The number of people affected by multiple myeloma is hence increasing every year, including due to the population growing older.
- Though the aging population creates a larger number of patients, myeloma has also spread to younger people and to women (slowly balancing ages and genders incidence).

U.S. Myeloma Incidence



U.S. Myeloma Mortality

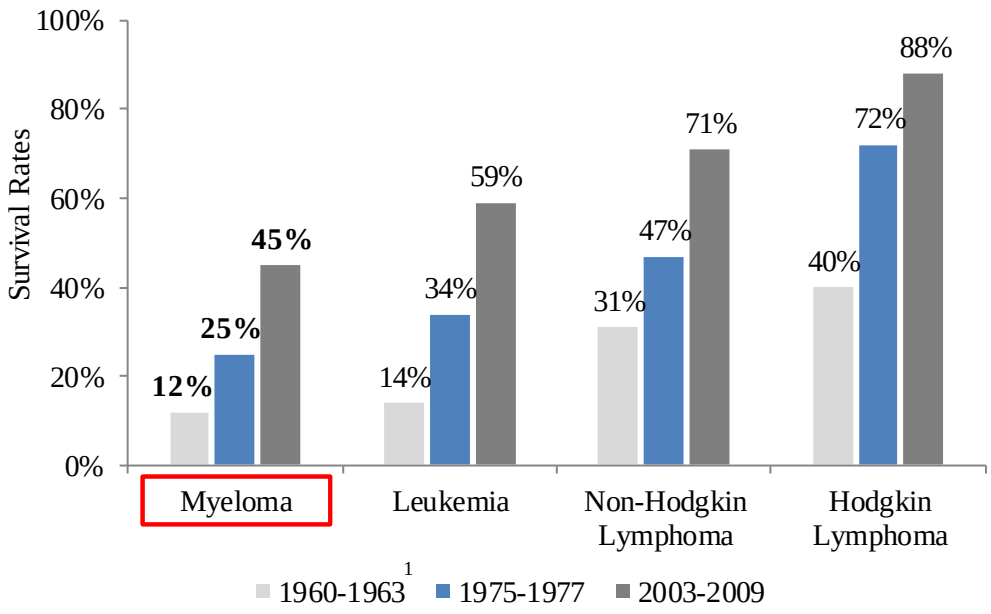


Source: National Cancer Institute, A Snapshot of Myeloma – November 2014.

SURVIVAL

- With currently less than half of the total number of people diagnosed dying every year, the average survival rate could be understood as 3 years.
- The 3-year overall survival rate as of January 1, 2008 was 55.6 %.
- The 5-year overall relative survival rate has improved significantly since the 1960s, and is now approximately under 45%.
- With conventional treatment, median survival is 3-4 years. With advanced treatments, median survival rate may be extended to 7-8 years.
- Differences of survival rate are partly based on stage of disease at discovery, nature of the disease, profile of the patient, how specialized are the doctors, the strategy adopted as well as personal income especially in the U.S. and the U.K. (affordability of latest/most expensive drugs, healthcare coverage).
- Thanks to the evolution of drugs, the rate of very good partial response (VGPR) increased from 15% (with Vincristine-Doxorubicin-Dexamethasone or VAD regimen) in the 1990's to 70% using the Velcade-Dexamethasone (VD) regimen. And the addition of a third agent to VD such as Thalidomide (VTD), Doxorubicin (PAD), Lenalidomide (RVD) or Cyclophosphamide further improved response rates, becoming the standard of care prior ASCT autologous stem cell transplantation/graft (ASCT). "Consolidation" therapy (chemo regimen after ASCT) is aimed at "disease control" while "maintenance" therapy (during a medium/long term period after ASCT) is aimed at prolonging response/remission duration.

Five-Year Relative Survival Rates Are Much Lower for Myeloma than for Other Forms of Blood Cancer



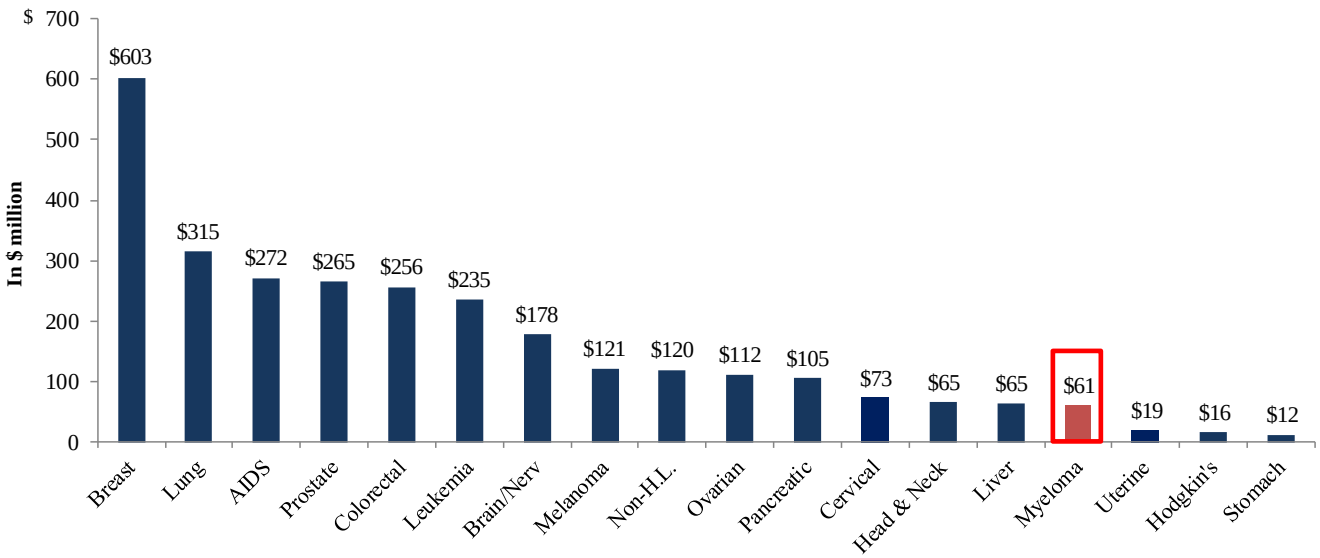
[1] Survival rates among Caucasians.

Source: Surveillance Epidemiology and End Results – Cancer Statistics Review 1975-2008. National Cancer Institute, 2011.

FUNDING

- Overall cancer funding focusing on myeloma was increasing until 2010. Nevertheless, the growth of funding is lagging as compared to overall cancer, with an estimated allocation of less than 1% of all money raised for cancer.
- The lack of awareness, lobbying and the low number of affected people does not motivate commercially driven entities to dedicate energy/resources/funds to research in the field.
- Money coming from (i) government in the U.S. and France as well as (ii) private individuals/foundations, (iii) hospitals and (iv) Pharmaceutical/Biotech organizations have placed myeloma **low on their priority list**.

2012 NCI[1] Cancer Funding by Type



[1] *National Cancer Institute.*

Source: NCI 2012 Fact Book.

THE MANY FACES OF MYELOMA

TESTIMONIALS

"**AS AN ATHLETE**, I've always tackled adventurous terrains. I've raced cars and motorbikes in the middle of the desert. Three years ago when I was diagnosed with multiple myeloma, I suddenly felt lost for the first time in my life. With an incurable rare disease with no set treatment, you tend to feel very lonely. And the options offered to you are even more frightening. A friend of mine mentioned that Vivien had myeloma as well, and put us in touch. Vivien immediately helped me by recommending the best specialist in Paris. He also explained the risk/rewards of each potential treatment, and to avoid making quick decisions but rather think strategically. I owe him a lot, and since then, not only have we become partners in facing this horrible disease, we've become good friends."

– HUBERT AURIOL

3-time champion - Paris-Dakar Rally
10 years General Manager - Paris-Dakar Rally organization

TESTIMONIALS

"**VIVIEN** de Gunzburg is a longtime friend. I have witnessed his various discreet battles against myeloma, a chronic incurable disease, and his drive to do something about this awful disease while he still can. The de Gunzburg Myeloma Research Foundation is a unique foundation as it focuses solely on this rare and overlooked disease. Its founder dedicates enormous energy to finding the best teams to perform cutting edge early stage research, structuring grants, and allocating funds where research money is scarce and most needed with the goal of ultimately finding a cure for this orphan disease. The quest to fight multiple myeloma is that of David against Goliath: myeloma is a disease that has been around for millennia, and where so many have failed to find a cure. Although Vivien will probably never benefit from his foundation's work, it is his dream that many lives might ultimately be saved thanks to the work of the de Gunzburg Myeloma Research Foundation. As a member of the board of a number of charities (including Charity Navigator a not-for-profit rating other charities) and as a friend, I admire and am humbled by Vivien's dedication and the work of the de Gunzburg Myeloma Research Foundation"

— WILLIAM VON MUEFFLING

Board Member - Charity Navigator
Founder - Cantillon Capital Management

LIVING WITH MULTIPLE MYELOMA

"**MULTIPLE MYELOMA** is a very challenging disease. It's all about strategy and how you treat it. I'm lucky enough to be young and currently in remission again and good shape. It gives me time to do something about it, to dedicate the energy and resources towards this cause. Not everybody has this chance especially with most patients being older and having a limited survival rate, and probably less resources. It saddens me that very few people are paying attention to multiple myeloma, nor trying to prevent what is foreseeable as an even greater issue in years to come."

– VIVIEN DE GUNZBURG

President - de Gunzburg Myeloma Research Foundation
Founder - Findercod

OUR MISSION

Established in 2012, the de Gunzburg Myeloma Research Foundation is dedicated to improving the quality of life of myeloma patients while working towards a cure. We work with leading groups within hospitals and laboratories from leading institutions comprised of researchers and scientists specializing in myeloma. Through our scientific network, we strive to identify the myeloma research/treatment projects with the greatest impact, and provide critical funding to accelerate the path for next-generation treatments.

Myeloma being one of the last forms of cancer still totally incurable today, the foundation has the opportunity to add substantial value and enable real breakthrough in medical research by tackling one of the most disregarded and challenging disease for the exclusive benefit of saving lives.

Thanks to Mr. de Gunzburg's involvement in the 13th International Myeloma Workshop in Paris in May 2011, and his board membership in the U.K. (Myeloma UK) and France's (FFRMG) leading and unique myeloma foundations, we uncovered state-of-the-art teams specializing in myeloma research.

We are about:

→ **Obsessive innovation**
→ **Radical changes**
→ **Contagious leadership**

OUR GOALS

- **Develop treatments and find a cure to extend survival rates and save people's lives**
- **Fund the formation/education of young scientists (including exchange programs)**
- **Bring awareness to the disease**

We also work on a "Global Myeloma Initiative" with other non-profit organizations to help bring awareness to myeloma.

"It is always impossible until it gets done."

– NELSON MANDELA

WHAT WE SUPPORT

Teams that come with a potential groundbreaking fundamental research project in the field of myeloma.

We think outside the box with teams that offer:

- → **Innovative ideas;**
- → **Breaking technologies;** and
- → **A high risk/high reward approach to research.**

We have identified the team of Dr. Paul Richardson and Dr. Constantine Mitsiades within the Dana-Farber Cancer Institute (Harvard) and its dedicated Jerome Lipper Center for Multiple Myeloma in Boston as one of the best teams and institutions to support. The experience, dedication and professionalism of this team facilitated our selection process.

A pledge of **$1,000,000 over 5 years** to this team of the Dana-Farber Cancer Institute will provide essential seed monies to develop new therapies specifically designed to overcome resistance in patients with the following goals:

- → **To define** in detail the molecular lesions that allow multiple myeloma cells to become clinically aggressive and resistant to existing therapies;
- → **To serially test** the response of primary myeloma cells isolated from patients to extended panels of investigational agents and combinations with conventional agents;
- → **To develop** a comprehensive system of bioinformatics and computational support that will facilitate the analysis of the volumes of data that result; and
- → **To devote** a clinical research team to design and conduct trials of the most promising therapies being pre-clinically tested to develop new drugs also designed to overcome resistance.

DANA-FARBER CANCER INSTITUTE

- The **Dana-Farber Cancer Institute**'s ("DFCI" or "Dana Farber") mission is to provide expert, compassionate care to children and adults with cancer while advancing the understanding, diagnosis, treatment, cure, and prevention of cancer and related diseases.
- The institute is internationally renowned for its blending of research and clinical excellence, bringing novel therapies that prove beneficial and safe in the laboratory setting into clinical use as rapidly as possible to benefit patients.
- Dana-Farber/Brigham and Women's Cancer Center is ranked the **top cancer center** in New England and fifth overall in the United States by *U.S. News & World Report 2013-2014 "Best Hospitals" guide.*

JEROME LIPPER CENTER FOR MULTIPLE MYELOMA & LEBOW INSTITUTE FOR MYELOMA THERAPEUTICS

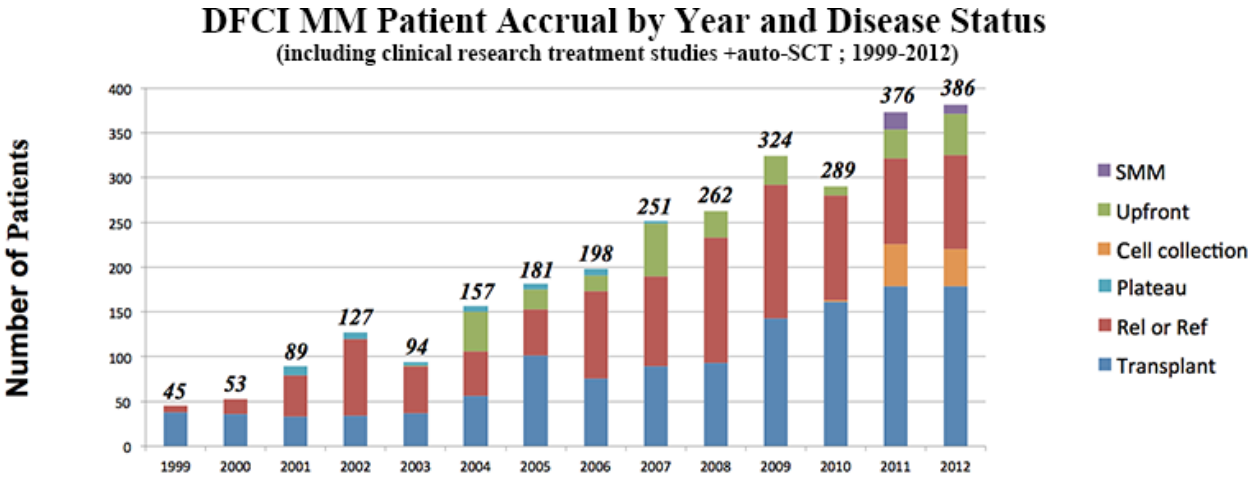
- Jerome Lipper Center for Multiple Myeloma and LeBow Institute for Myeloma Therapeutics are world-renowned for their cutting-edge fundamental and clinical research, comprehensive state-of-the-art care, and the effective and fast delivery of new therapies to patients with myeloma through innovative clinical trials.
- Led by **Kenneth Anderson, MD** and **Paul Richardson, MD**, fortified by their large team, Dana-Farber pre-clinical and/or clinical studies have led to or been part of the regulatory approval of **sixteen new multiple myeloma therapies over a span of ten years**, an unprecedented accomplishment in the field that has significantly prolonged the lives of many patients and improved the prognosis of this disease.
- Central to this success is the ability to pursue innovative translational research in multiple myeloma, and this is exemplified by Drs. Richardson and Mitsiades, working closely together with their respective colleagues and as part of their larger and highly collaborative group.

Clockwise from far left: **Paul Richardson, MD**, clinical director of the Jerome Lipper Center for Multiple Myeloma and RJ Corman Professor of Medicine at Harvard Medical School, **Constantine Mitsiades, MD, PhD, Dharminder Chauhan, JD, PhD, Kenneth C. Anderson, MD**, director of the Jerome Lipper Center and LeBow Institute for Myeloma Therapeutics and the Kraft Family Professor of Medicine at Harvard Medical School, and **Teru Hideshima, MD, PhD.**

THE MULTIPLE MYELOMA PROGRAM

The de Gunzburg Myeloma Research Foundation chose to finance the Dana-Farber Cancer Institute, particularly Dr. Richardson and Dr. Mitsiades because:

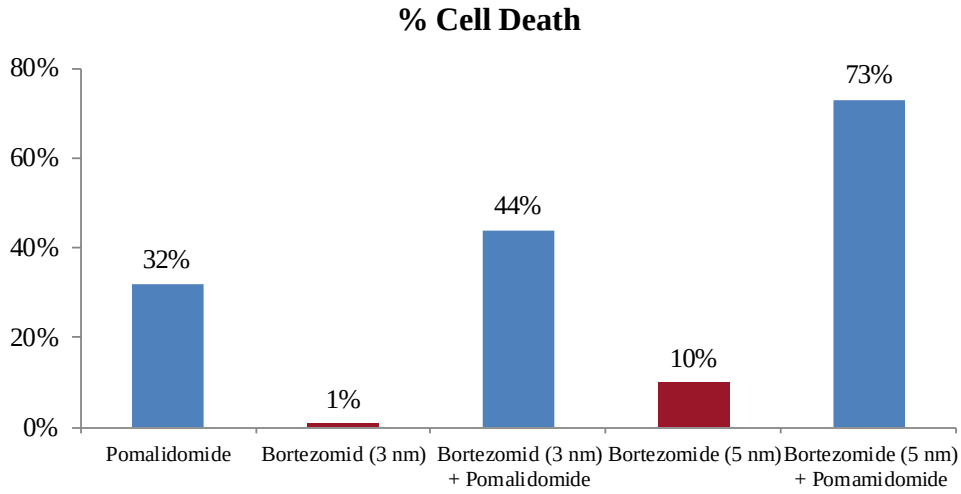
- They and their teams, as well as the colleagues they work with outside of DFCI, are the best in the field and they are based at one of the top hospitals specializing in myeloma treatment in the world;
- They are already involved in essential research and have a proven track record in drug development, making their group leveraged to potentially develop a cure;
- They are located in the U.S., which has the necessary means to analyze a critical mass of patients in this rare disease and best integrate both laboratory and clinical research globally;
- They have established critical partnerships both nationally and internationally, as exemplified by other leaders in their group, such as Dr. Nikhil Munshi who has a correlative science program in collaboration with the Intergroup Francophone du Myélome (IFM) in France.



In addition, hospitals as academic centers are increasingly becoming vital centers of research (vs. biotech/pharmaceutical companies and independent laboratories alone).

DFCI'S LAST RESEARCHES AT A GLANCE

A CENTRAL COMPONENT OF THE PROGRESS IN MYELOMA



FDA approvals for multiple myeloma therapy:

- → 2003: Bortezomib/Velcade (Bort)
- → 2006: Thalidomide + Dex
- → 2006: Lenalidomide (Len) + Dex
- → 2007: Bort + Liposomal Doxorubicin
- → 2010: Bort + Melphalan-Prednisone
- → 2012: Carfilzomib
- → 2013: Pomalidomide
- → 2015: Elotuzumab (Empliciti) + Daratumumab (Darzalex) + Ixazomib (Ninlaro) + Panobinostat (Farydak)

2006: Introduction of Lenalidomide-Bortezomib-Dex (RVD)

2012: Development of Pomalidomide-Bortezomib-Dex (PVD)

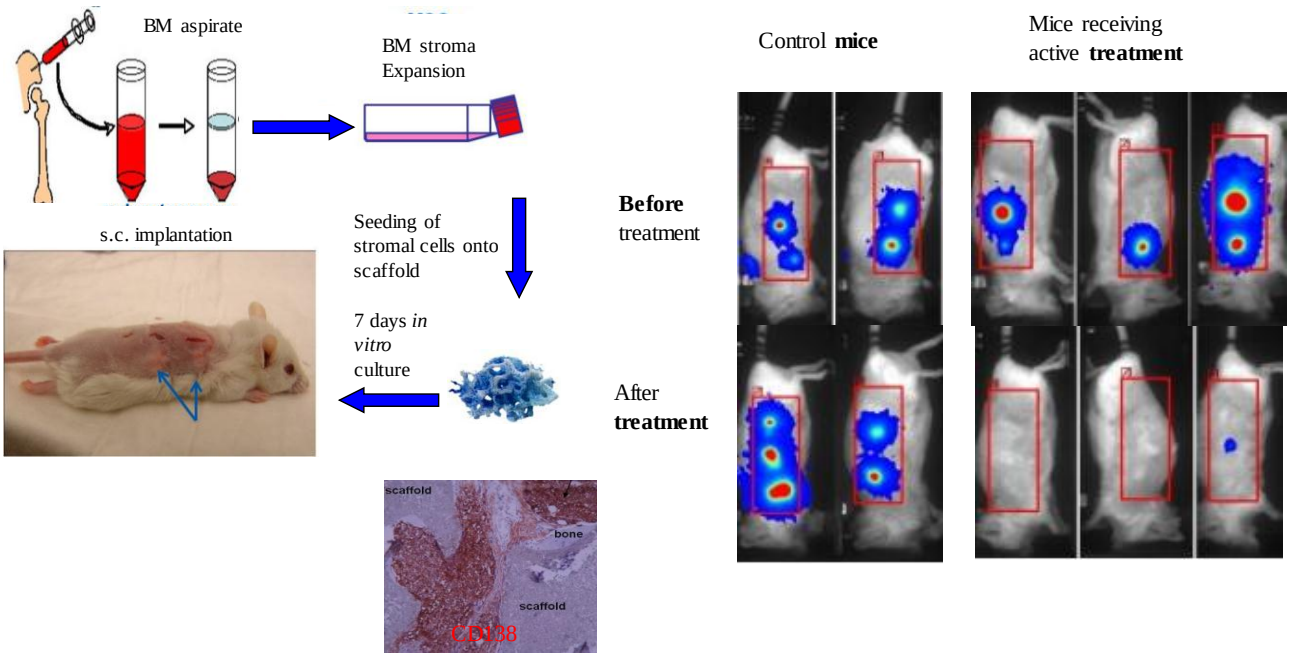
DGMRF was directly involved in the development of Daratumumab and Panobinostat, or 2 out of 4 drugs that made it to the market in 2015.

In addition, the DFCI clinical team led by Dr. Paul Richardson that DGMRF supports was involved in all 4 drugs that came to the market.

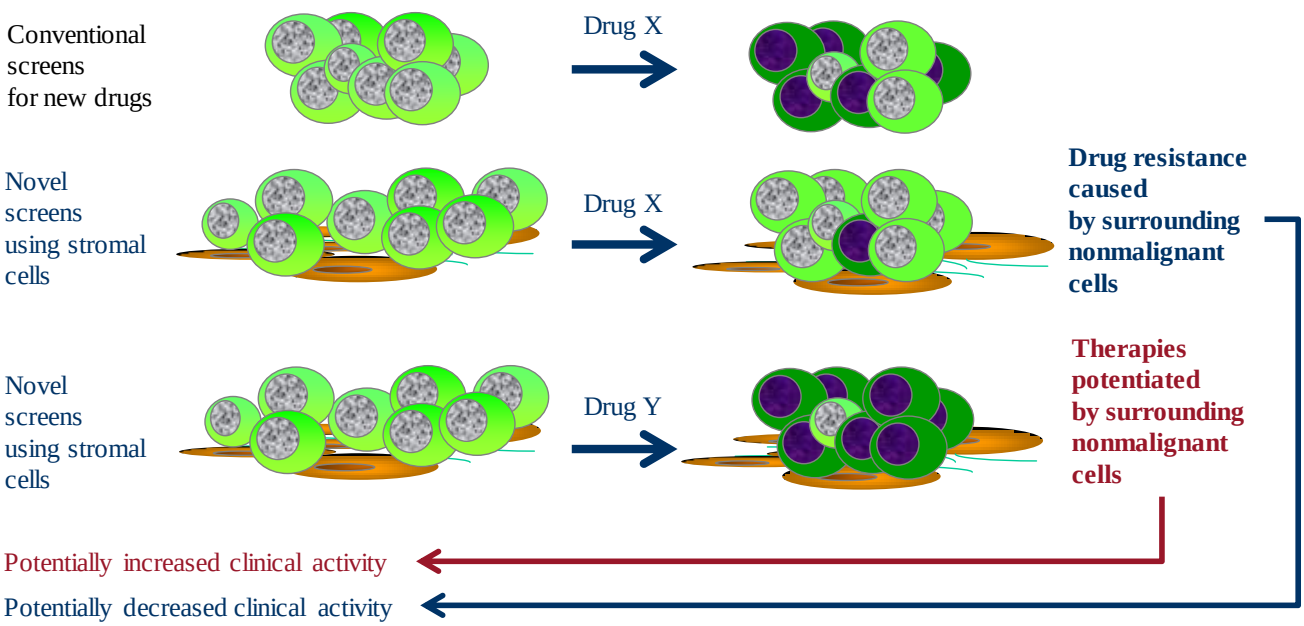
This highlights that with a relatively new and small foundation, DGMRF contributed to making real changes in the field of myeloma thanks to the team it selected to fully support.

The DFCI team is involved in the development of 16 drugs over a span of 10 years.

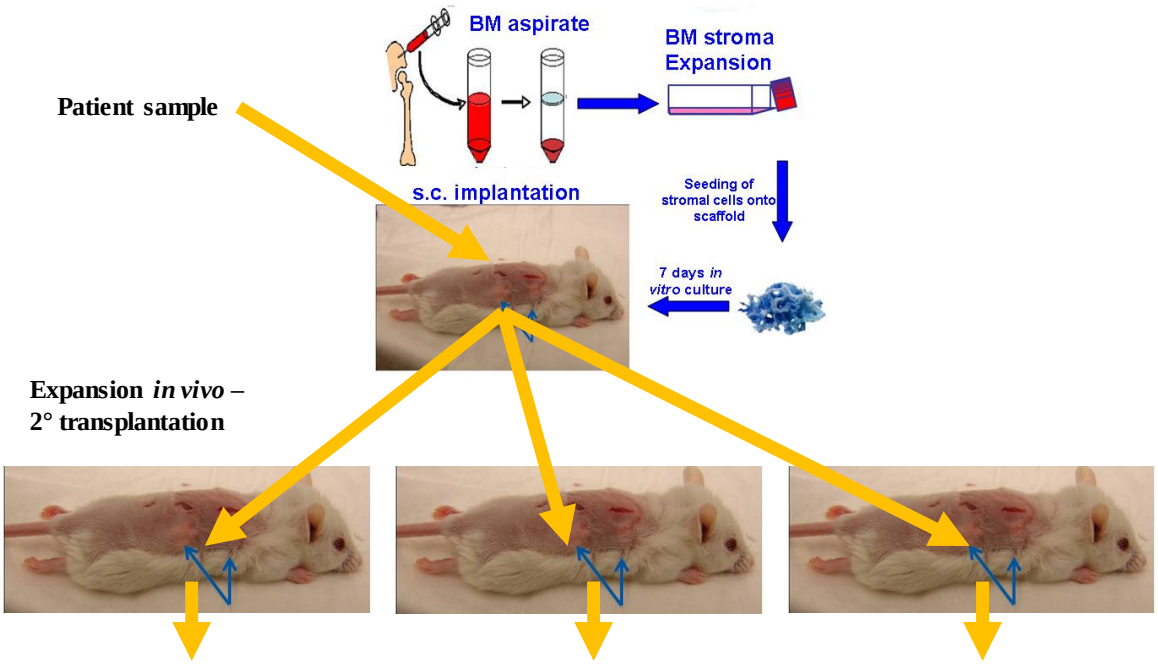
NEW MODELS TO STUDY MYELOMA CELLS FROM PATIENTS



Targeting tumor cells and protection they receive by surrounding nonmalignant cells



UPCOMING WORK SUPPORTED BY DGMRF



Isolation of primary patient-derived multiple myeloma cells for:

1. Molecular profiling studies (Aim 1)
2. In vitro drug sensitivity testing (Aim 2)
3. In vivo validation of activity of promising candidate therapeutics

KEY INNOVATIVE ASPECTS

Emphasis on primary tumor cells from patients

- Enabling individualized treatments in the future
- Advantages for implementation
  - e.g. cryopreserved MSO-frozen patient samples

Ability to test how the local microenvironment influences response to therapies

- Major issue that confounds interpretation of classical preclinical testing of anticancer therapeutics
- May explain why many promising new treatments for cancer do not reach FDA approval

Translation into clinical trials in multiple myeloma

Addressing in our myeloma models critical barriers for treatment of many other malignancies

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Dr. Richardson, is an internationally recognized expert in multiple myeloma, and in particular for his pioneering development of novel therapies for the treatment of this disease, including highly effective combination approaches, such as lenalidomide, bortezomib, and dexamethasone (so called RVD). His primary research interest over the last decade has been the rapid translation of bench discovery to bedside therapeutics, and he has been a leader in the clinical development of bortezomib, lenalidomide and pomalidomide leading to FDA approvals with all three agents. Currently, he is leading multiple efforts studying the use of combination therapies in relapsed and refractory myeloma, an area of primary interest to him. As mentioned above he developed with his colleagues RVD which is now one of the most widely used combinations nationwide in the USA for the upfront treatment of myeloma , and as an approach of exploring synergy between agents, this platform has been validated by several promising other combinations since. He is also serving as a principal investigator for several clinical trials relating to other areas of myeloma treatment, including the use of combination therapies in earlier disease designed to target resistance and reduce toxicity.

Dr. Richardson holds leadership positions in several professional bodies and serves on the Editorial Board of multiple distinguished hematologic journals.

He is the prior Chairman of the Multiple Myeloma Research Consortium Clinical Trials Core. He now chairs the newly formed Multiple Myeloma Committee for the Alliance for Clinical Trials in Oncology (the former CALGB). His honors include numerous teaching awards and achievements for clinical research and patient care, including being a co-recipient of the prestigious Warren Alpert Prize for his role in the development of bortezomib. Dr Richardson received the Butler award in December 2015. He has published approximately 250 original articles, and more than 150 reviews, chapters, and editorials in peer-reviewed journals.

Dr. Paul Richardson received his medical degree from the Medical College of St. Bartholomew's Hospital in London, UK and he is also an honorary Fellow of the Royal College of Physicians (FRCP). He completed fellowships in hematology/oncology and medical oncology at Tufts University School of Medicine, Baystate Medical Center, and Harvard Medical School, Dana-Farber Cancer Institute before coming on staff at DFCI in 1994. He is board certified in Hematology, Medical Oncology, and Internal Medicine.

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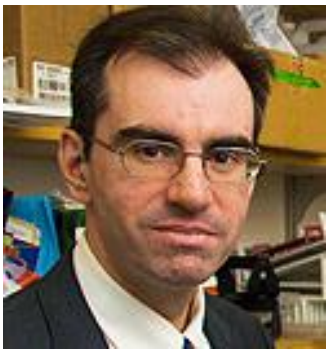


Constantine S. Mitsiades is an Assistant Professor of Medicine and Principal Investigator at the Dana-Farber Cancer Institute (Department of Medical Oncology), and the Department of Medicine, Brigham and Women's Hospital, Harvard Medical School. He received his M.D., PhD, and Master's in Basic and Clinical Medical Sciences from the University of Athens, School of Medicine in Greece; as well as Master's in Medical Sciences from Harvard Medical School in Boston. He has been a faculty member at Dana-Farber since 2003 and his work has focused on the development of novel biologically-based therapies for multiple myeloma and other neoplasias. His research studies guided the clinical development of a series of combination regimens currently used for the treatment of multiple myeloma, including the FDA approved combinations of proteasome inhibitors with alkylating agents or anthracyclines; the combination of proteasome inhibitors with immunomodulatory thalidomide derivatives.

In the field of myeloma research, Dr. Mitsiades was the first to introduce a series of novel classes of investigational therapeutics, including BET bromodomain inhibitors, IGF1R inhibitors, HDAC inhibitors and heat shock protein inhibitors. A particular emphasis of the Mitsiades lab is to delineate how nonmalignant cells present in the local microenvironment at the tumor sites can in many cases suppress the activity of anticancer therapeutics, and how the treatment of patients can be individualized to overcome the protective effects on the tumor by its surrounding nonmalignant tissues.

Dr. Mitsiades has published over 200 scientific papers and is a member of the editorial board of the scientific journals "Clinical Cancer Research", "Haematologica" and "Cancers". He also serves on the Myeloma Committee (member and Vice Chair for Correlative Studies) and in the Executive Committee of the Translational Research Program (member) of Alliance in Clinical Trials in Oncology.

PROGRESS REPORT OF OUR DFCI PROGRAM

"All of us at Dana-Farber, and especially Dr. Richardson and Dr. Mitsiades, would like to express our heartfelt appreciation to the de Gunzburg Myeloma Research Foundation for the kind and generous support of our research studies, both preclinically and clinically over the last year.

Thanks to the Foundation's significant support and the joint efforts of Dana-Farber's clinical and laboratory research program we have achieved significant progress towards our goal of targeting critical barriers that have prevented the cure of myeloma, and developing new therapies specifically designed to overcome resistance in patients. We place particular emphasis on studying myeloma cells which harbor complex molecular features that are not targeted directly, and specifically by pharmacological therapies available for myeloma patients.

With support from the de Gunzburg Myeloma Research Foundation, we have advanced the cause by defining which molecular lesions allow multiple myeloma cells to become clinically aggressive and resistant to existing therapies. For instance, in our innovative models of myeloma, we achieved engraftment and expansion of patient-derived tumor cells from far-advanced cases of myeloma (including plasma cell leukemia or pleural effusions). We then proceeded to evaluate the molecular lesions present in these multiple myeloma cells, before and after their proliferation in mice. The comprehensive analyses of these samples are ongoing.

We have already identified, though, candidate molecular lesions, which could serve to function as critical "progression events" that contribute to transition of myeloma from its earlier stages to its more advanced ones. To further complement this effort, we also initiated in our mouse models treatment of myeloma cells with established anti-myeloma therapy (e.g. proteasome inhibitors, thalidomide derivatives, alkylating agents), in order to identify molecular lesions which are selectively enriched for in myeloma cells once they develop in vivo resistance to these treatments. We anticipate that the first results from these comparative analyses will allow us to initiate in 2014 specific targeting of individual candidate lesions, with the intent to reverse resistance to existing anti-myeloma therapeutics.

We have established molecular tools necessary for customized engineering of myeloma cells with molecular lesions present in patients with myeloma resistant to currently available treatments. Some of these lesions are individually present in myeloma cell lines that our labs and others have previously worked with. However, up until now, there has been so far very few, if any, efforts in the myeloma field to stringently compare the behavior of myeloma cells which harbor one of these "progression" lesions compared to cells that do not harbor such "progression lesions" but are otherwise genetically identical.

The molecular tools that we have been developing represent a major step forward and a critical investment towards the ultimate success of this research program and we are greatly appreciative of the support of the de Gunzburg Myeloma Research Foundation in this regard.

PROGRESS REPORT OF OUR DFCI PROGRAM

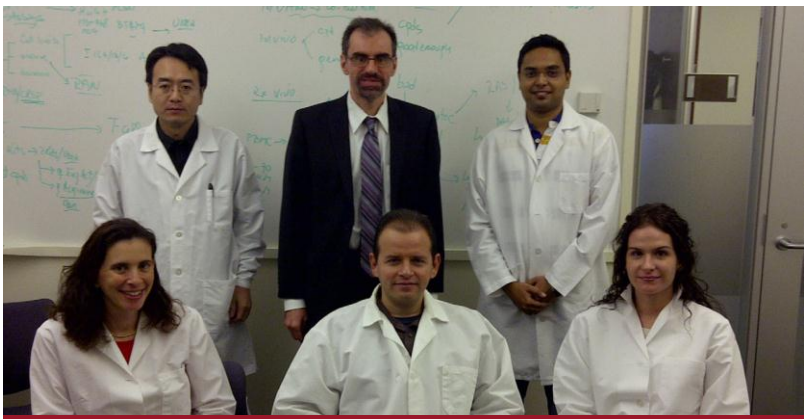
Building on the extensive experience of our laboratory with high-throughput scalable testing of candidate therapeutics for their antitumor activity, we have further improved our ability to perform these studies with small numbers of cells under each experimental condition. This progress, combined with the previously mentioned progress in expanding patient-derived tumor cells in our mouse models, will allow us to test patient-derived myeloma with extended panels of investigational agents and their combinations with established therapeutics.

The goal of these experiments will be to identify candidate therapeutics with selective activity against myeloma cells which harbor specific combinations of molecular lesions associated with more advanced and extramedullary disease.

During 2014, we hope to advance, with the help of the de Gunzburg Myeloma Research Foundation, the goal of developing a comprehensive system of bioinformatics and computational support for the laboratory. These systems would facilitate the analysis of the higher volumes of data that we expect to get from the molecular analyses of samples evaluated from our in vitro and in vivo studies.

The support kindly provided by the de Gunzburg Myeloma Research Foundation has allowed us to achieve significant progress towards the goals that we initially set out to reach. In turn, we anticipate these advances rapidly translating into important early phase clinical trials over the next 2 years.

Reflective of this ongoing process, several current clinical studies underway at our center illustrate the rapid translation of bench discovery to bedside therapy for patients with second generation novel agents. The robust accrual from our clinical trials program shown below demonstrates our ability to complete early phase studies quickly and so provide essential results from which to go forward. Overall, therefore, major progress has been achieved of our studies in the laboratory and in animal models as well as in the clinic. We are thus highly optimistic that this progress will result in an exponential acceleration of our team and the group's overall productivity over the next several years towards the goal of yet further improving patient outcome.”



Top row: from left to right: Yiguo Hu, PhD; Constantine S. Mitsiades, MD, PhD; Subhashis Sarkar, PhD
Seated: from left to right: Michal Sheffer, PhD; Eugen Dhimolea, PhD; Megan Bariteau B.Sc., ALAT.
(other team members not on this photograph: Richard Groen, PhD; Julio Cesar Marin, MD; Jeffrey Sorrell, B.Sc)

MULTIPLE MYELOMA Q&A

Q: What is multiple myeloma?

A: Multiple myeloma is a cancer formed by malignant plasma cells. Normal plasma cells are found in the bone marrow and are an important part of the immune system.

Q: What is the immune system and how does this impact multiple myeloma?

A: The immune system is composed of several types of cells that work together to fight infections and other diseases. Lymphocytes (lymph cells) are the main cell type of the immune system. There are 2 major types of lymphocytes: T cells and B cells. When B cells respond to an infection, they mature and change into plasma cells, which make the antibodies that help the body attack and kill germs. When plasma cells become cancerous and grow out of control, they can produce a tumor. When more than one plasma cell tumor exists, it is called multiple myeloma.

Q: What are the complications of multiple myeloma?

A: In multiple myeloma, the overgrowth of plasma cells in the bone marrow can crowd out normal blood-forming cells, leading to low blood counts. This can cause anemia, which is a shortage of red blood cells. People with anemia become pale, weak, and fatigued. Multiple myeloma can also cause the level of platelets in the blood to become low, which can lead to increased bleeding and bruising. Another condition that can develop is leukopenia, which is a shortage of normal white blood cells and can lead to problems fighting infections. Because myeloma produces excessive amounts of antibody, or so-called “M protein”, normal antibodies are suppressed, further increasing the risks of infection. In addition, these abnormal proteins can thicken the blood and damage the kidney, leading to renal failure. Myeloma cells also interfere with cells that help keep the bones strong. Bones are constantly being remade to keep them strong. Two major kinds of bone cells normally work together to keep bones healthy and strong: the cells that lay down new bone are called osteoblasts. The cells that break down old bone are called osteoclasts. Myeloma cells make a substance that tells the osteoclasts to speed up dissolving the bone. Since the osteoblasts do not get a signal to put down new bone, old bone is broken down without new bone to replace it. This makes the bones weak and they break easily. Fractured bones are a major problem in people with myeloma as is the effect of chemicals released from excessive bone breakdown, such as calcium.

MULTIPLE MYELOMA Q&A

Q: Do we know what causes multiple myeloma?

A: Scientists still do not know exactly what causes most cases of multiple myeloma. However, they have made progress in understanding how certain changes in DNA can cause plasma cells to become cancerous. DNA is the chemical that carries the instructions for nearly everything our cells do. Some genes (parts of our DNA) contain instructions for controlling when our cells grow and divide. Certain genes that promote cell division are called oncogenes. Others that slow down cell division or cause cells to die at the appropriate time are called tumor suppressor genes. Cancers can be caused by mistakes, or defects, in the DNA called mutations that turn on oncogenes or turn off tumor suppressor genes.

Q: Can multiple myeloma be prevented?

A: With multiple myeloma, few cases are linked to risk factors that you can avoid. For those people with monoclonal gammopathy of undetermined significance or solitary plasmacytomas there is no known way to prevent multiple myeloma from developing.

Q: Can multiple myeloma be found early?

A: It is difficult to diagnose multiple myeloma early. Often, multiple myeloma causes no symptoms until it reaches an advanced stage. Sometimes, it might cause vague symptoms that at first seem to be caused by other diseases. Sometimes, multiple myeloma is found early when a routine blood test shows an abnormally high amount of protein in the blood.

Q: What are the signs & symptoms of myeloma?

A: These can include bone pain and weakening, low blood counts, problems with the nervous system, infections, high levels of calcium in the blood, and kidney problems.

Q: How is myeloma treated?

A: The treatment for multiple myeloma may include chemotherapy and other drugs, bisphosphonates, radiation, surgery, other forms of biologic therapy (such as vaccines), stem cell transplant and plasmapheresis, which helps reduce the protein load in the blood stream.

MULTIPLE MYELOMA Q&A

Q: Who is at risk for developing myeloma?

A: People over the age of 65 are most at risk, as are those of African-American descent. Men are more likely to develop the disease than women. There is also a link to obesity, certain chemicals, such as pesticides and herbicides, and radiation exposure as well as other plasma cell diseases.

Q: Is there a cure?

A: Currently, there is no cure for multiple myeloma. However, there are now numerous treatments that exist and some in particular appear to extend life expectancy.

Q: What is the expected survival rate?

A: The estimated median survival rate is up to 7-8 years but varies widely. Out of 26,850 cases in the U.S. diagnosed each year, 11,240 are sadly expected to lose their battle with myeloma during this year alone.

Q: Is there a common response and treatment for people diagnosed with myeloma?

A: Every treatment is adapted the particular stage of the disease as well as the profile of the patient since myeloma is a chronic, incurable disease. Various approaches to treatment are recommended by different doctors.

Q: Is myeloma hereditary?

A: There is only a weak familial tendency to develop myeloma. Approximately 3-5% of patients with myeloma report a history of myeloma or a related blood/bone marrow condition within the extended family. So far, no specific gene has been linked to this myeloma tendency.

DGMRF

It is thanks to the extraordinary contribution of donors like **William and Clémence von Mueffling** and **Thomas and Ximena Sandell** to the DGMRF foundation that people suffering from this rare incurable blood cancer can have the hope for a better future.

Even though new drugs have been developed to extend survival rates over the last ten years, a cure is yet to be found. Non-profit early stage research is vital to help laboratories and expert clinical teams create a brand new future pipeline of therapeutics with the goal of ultimately finding new molecules to reach for a cure.

This is especially true in this current difficult economic and social environment which affects innovative research and start-up ideas in particular. Research is increasingly dependent on the kindness, generosity, philanthropic vision and selflessness of donors like William and Clémence von Mueffling, Thomas and Ximena Sandell, and yourselves.

Mr. de Gunzburg committed to financing all expenses (direct and indirect) required by the Foundation to operate, so that any donation received goes entirely to early-stage research to find innovative novel therapeutics and most importantly **a cure**.

We will also try to match any donation you make directly or any money you may raise indirectly.

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