de Gunzburg
Myeloma Research Foundation

Finding a Cure for Multiple Myeloma

Successes of the 1st phase – Going for a cure in "Phase II"

September 2019

TABLE OF CONTENTS

A LETTER FROM THE PRESIDENT

DEAR FRIENDS,

Sixteen 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 tens of thousands of people across the globe for more than four thousand years. It is estimated that **200,000 people in the western world and 90,000 Americans are currently affected by multiple myeloma**. While approximately **32 000 Americans are diagnosed every year, myeloma takes the lives of approximately 12 000 people each year**. And **this disease is growing** among us as we get older: **9% of the population 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 though a chronic long term disease. It is up to foundations like the de Gunzburg Myeloma Research Foundation to provide the necessary resources to make sure the vital research work does not stop, is not altered, but continues including academically and in an independent manner.

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. **Finding the cure to myeloma would probably lead to major impacts including enabling finding the cure to many more cancers**.

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 ("MM"), the second most common form of blood cancer**[3].

While approximately 90,000 people currently live with multiple myeloma, 27,000 new cases are diagnosed and 12,000 people die from it every year[4] in the U.S..

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

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 (fight infections), become malignant, and primarily **attack and destroy bones, kidneys and other organs**. This is an immune system defficiency

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.

[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.*

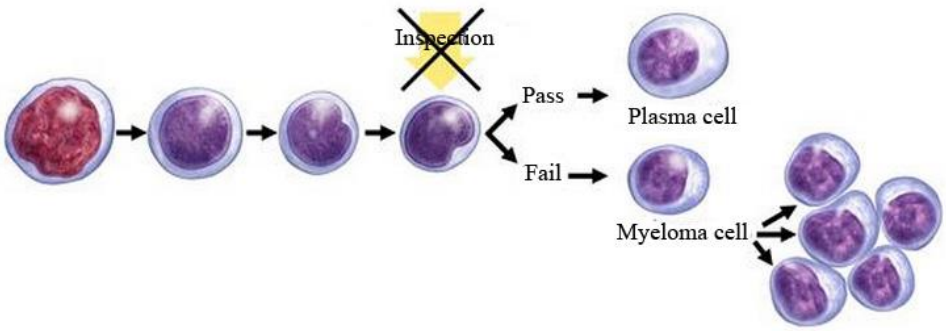
[3] *Source: Dr. Benboubker, CHRU of Tours.*

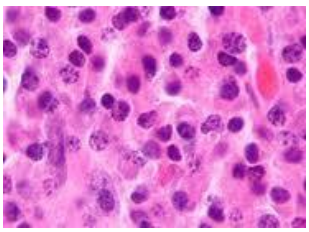
[4] *Source: National Cancer Institute - SEER Stat Fact Sheets 2015: Myeloma.*

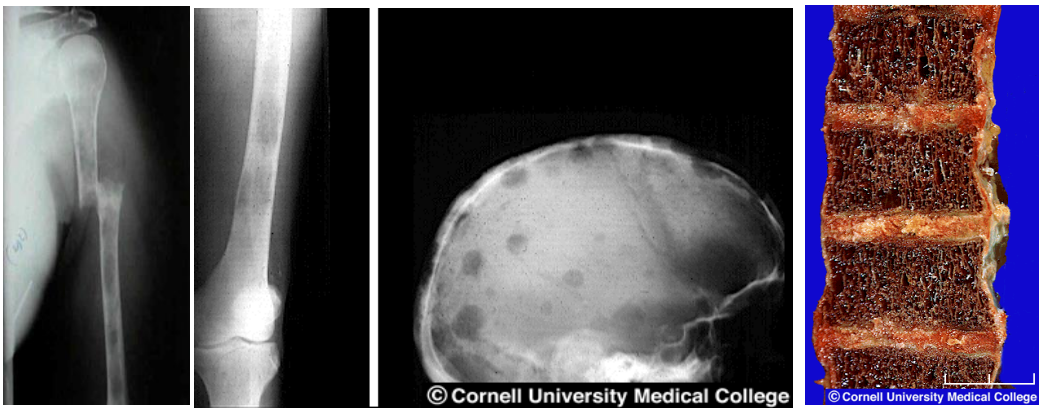
[5] *Source: National Institute of Health - An orphan disease is a disease affecting less than 200,000 people in the U.S.*

UNDERSTANDING MYELOMA

- Myeloma alters the function of plasma cells which mutate into plasmacytes, and leaves them unable to fight infection.
- These plasmacytes build-up in excessive numbers of abnormal cells (myeloma cells by then), accumulate and “colonize” in bones and the bone marrow. By aggregating they create tumor(s), (often by nature in multiple locations throughout the body) especially in the bone marrow. Some doctors call myeloma the disease once it has formed multiple lesions.
- In the bone marrow they interfere with the production of normal blood cells making it harder for the bone marrow to produce 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), ultimately affecting major organs, such as bones, kidney and heart.





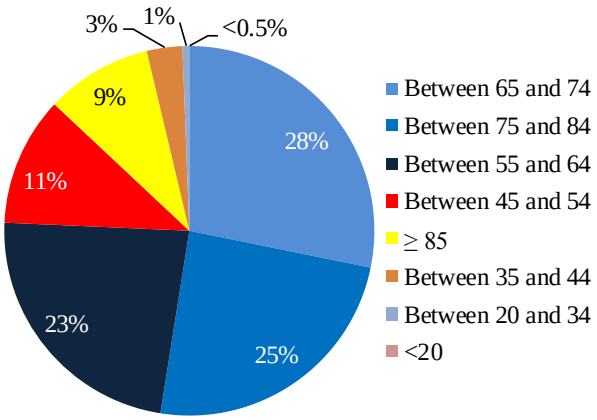


- Because myeloma cells may circulate in low numbers in blood, they sometimes cannot be identified and destroyed by a functioning or altered immune system:
  - → Myeloma cells may populate the bone marrow in various parts of the body, even far from where they originated. **That is why the disease is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

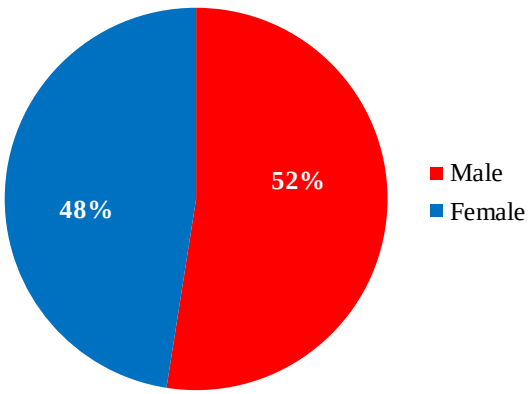
MULTIPLE MYELOMA:

- Is the second most common hematological malignancy in the U.S. (15%) 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 8-9 years**[2] despite progress in research and treatment.

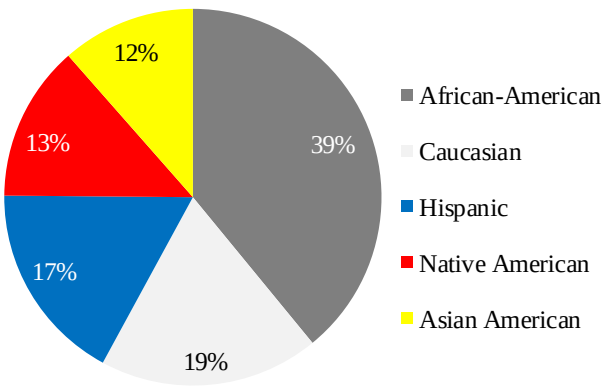
Incidence by Age



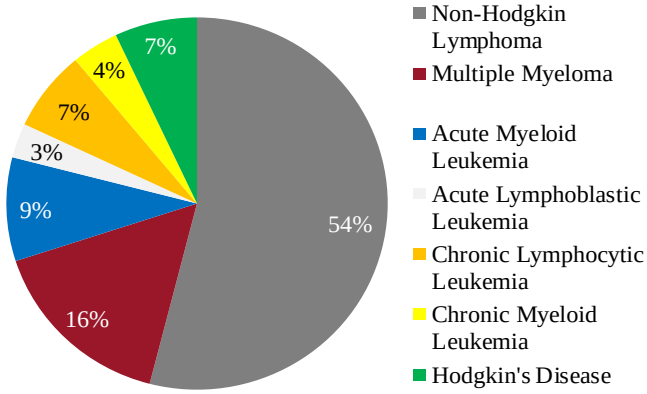
Incidence by Gender



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.*

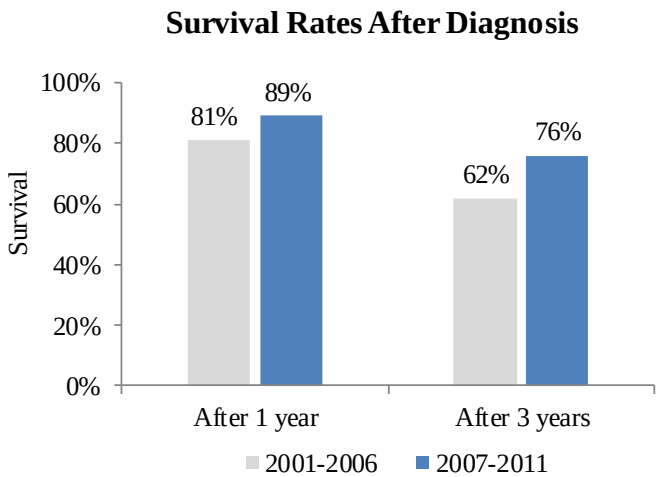
[3] *Source: World Cancer Research Fund International – Myeloma Worldwide Data from 2012.*

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 **9% of people above 85 years old**.

DEATHS

- Out of 32,000 estimated new cases diagnosed in the U.S. - and the existing 90,000 – 100,000 people affected by myeloma - approximately 12 000 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. **A global challenge for 1.8 – 2 million 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 median survival rate was: 3-5 years; 2008: 5-7 years; 2012: 7-8 years.

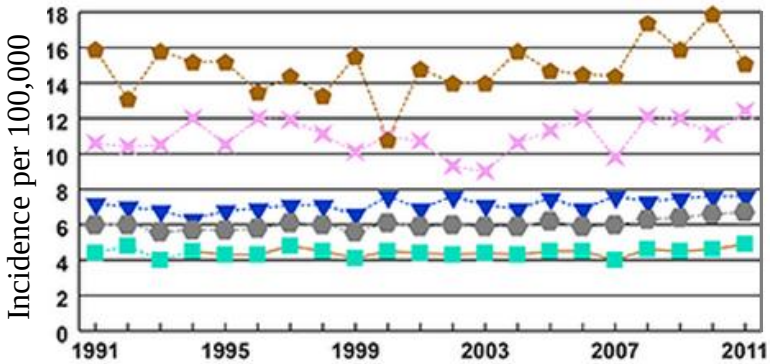


Source: American Cancer Society Facts and Figures 2011-2012, Fact 2012 study & Leukemia and Lymphoma Society.

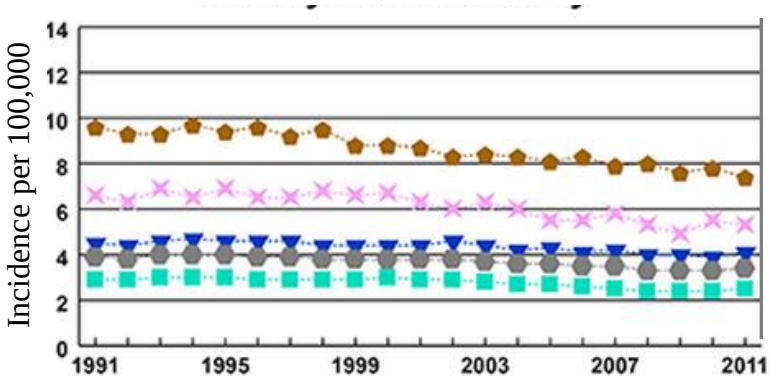
FACTS & FIGURES

- 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

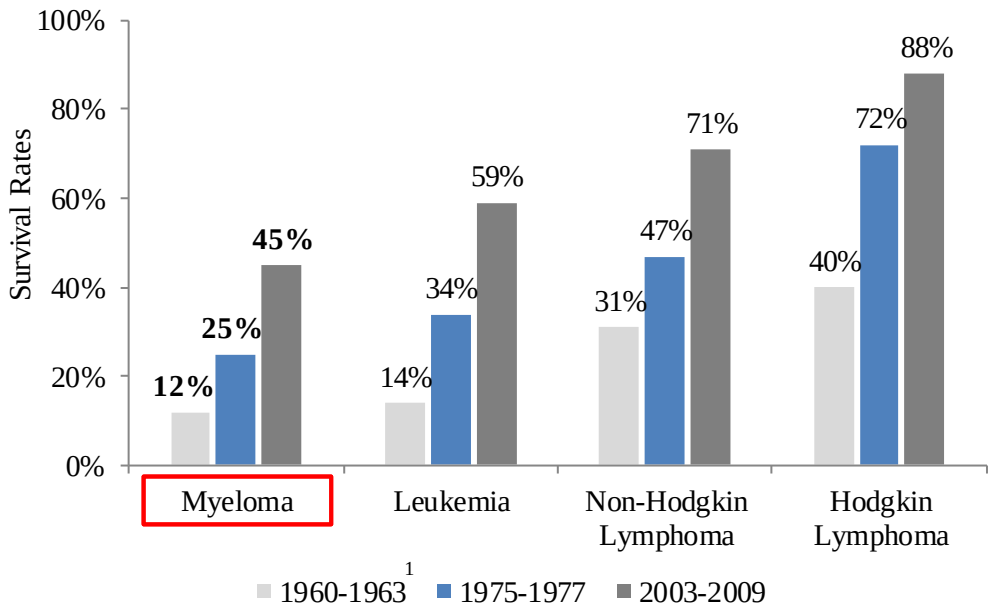


Source: National Cancer Institute, A Snapshot of Myeloma – November 2014.

SURVIVAL RATE

- With currently less than half of the total number of people diagnosed dying every year, the average survival rate could be understood as 4 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 approximately 5 years. With advanced treatments, median survival rate may be extended to approximately 9 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).

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

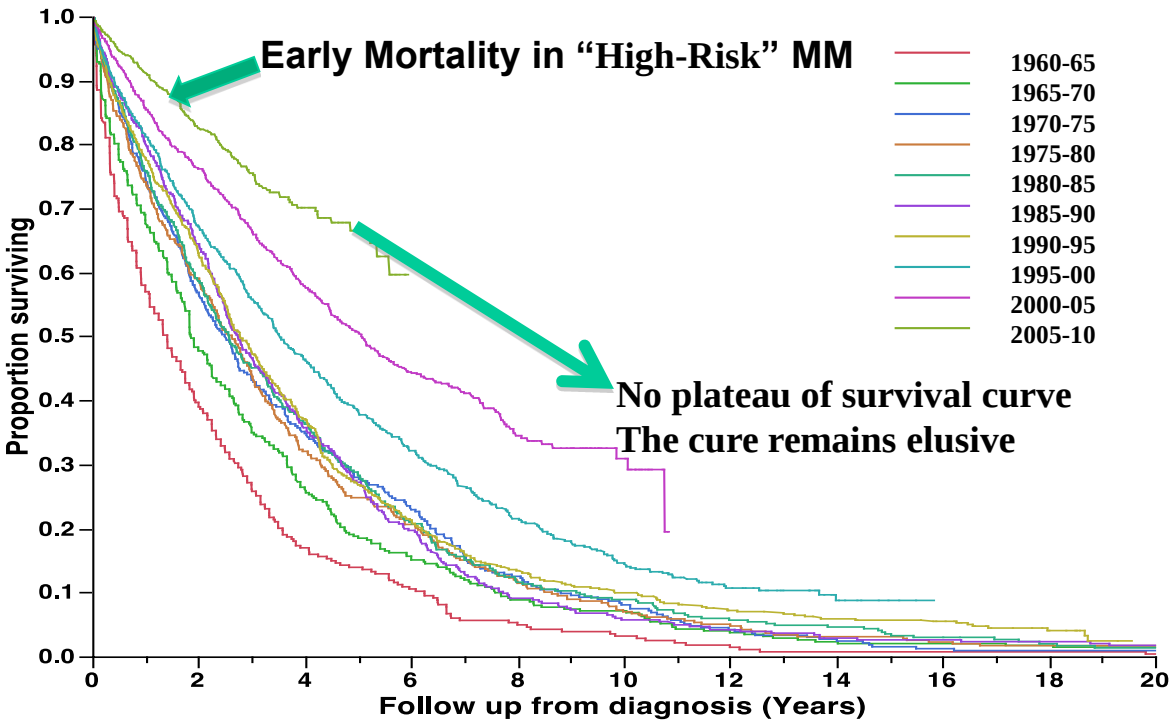


[1] Survival rates among Caucasians.

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

SURVIVAL RATE (Cont'd)

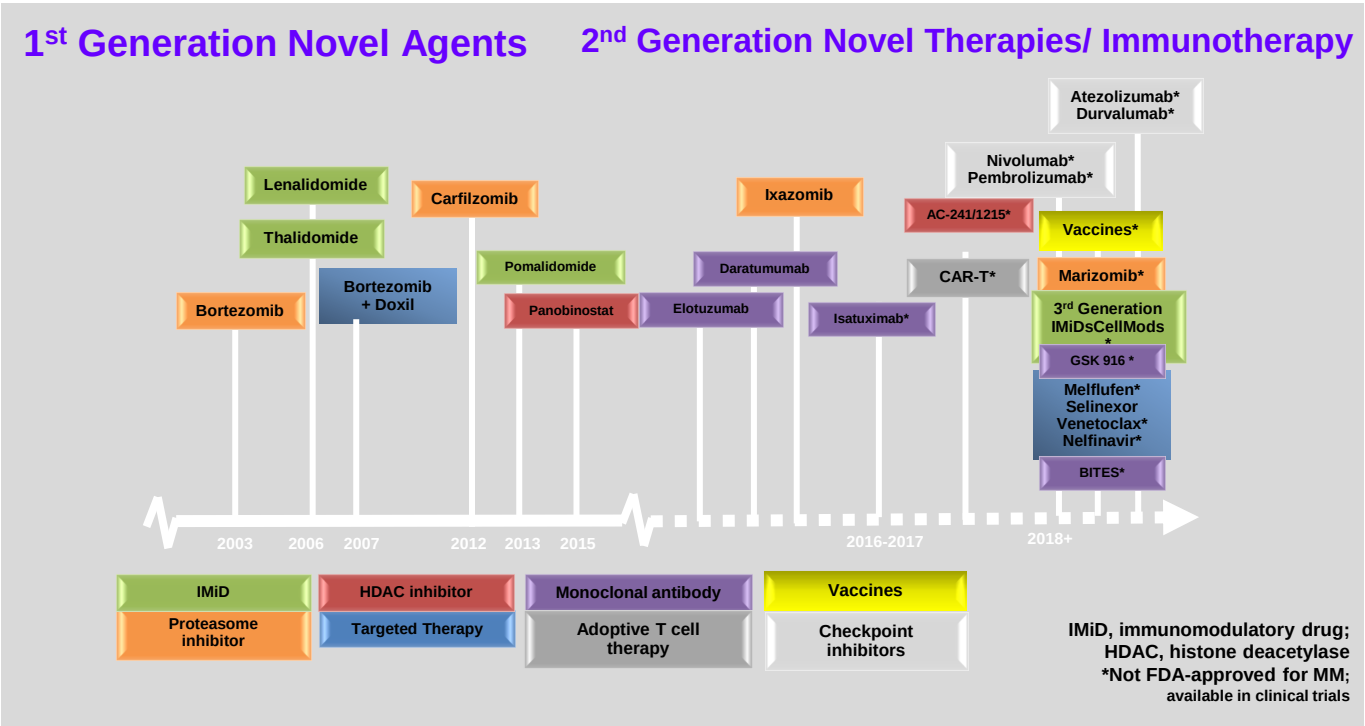
- Thanks to the evolution of drugs, the rate of very good partial response (VGPR) increased from 15% (with Vincristine-Doxorubicin-Dexamethasone or VAD regimen) in the 1990's to 70% using the Velcade-Dexamethasone (VD) regimen. And the addition of a third agent to VD such as Thalidomide (VTD), Doxorubicin (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
- **Still 25% of patients diagnosed with MM are not responsive to any drug/treatment.**



Adapted from Kumar et al *Leukemia* 2014

EVOLUTION OF MULTIPLE MYELOMA TREATMENTS

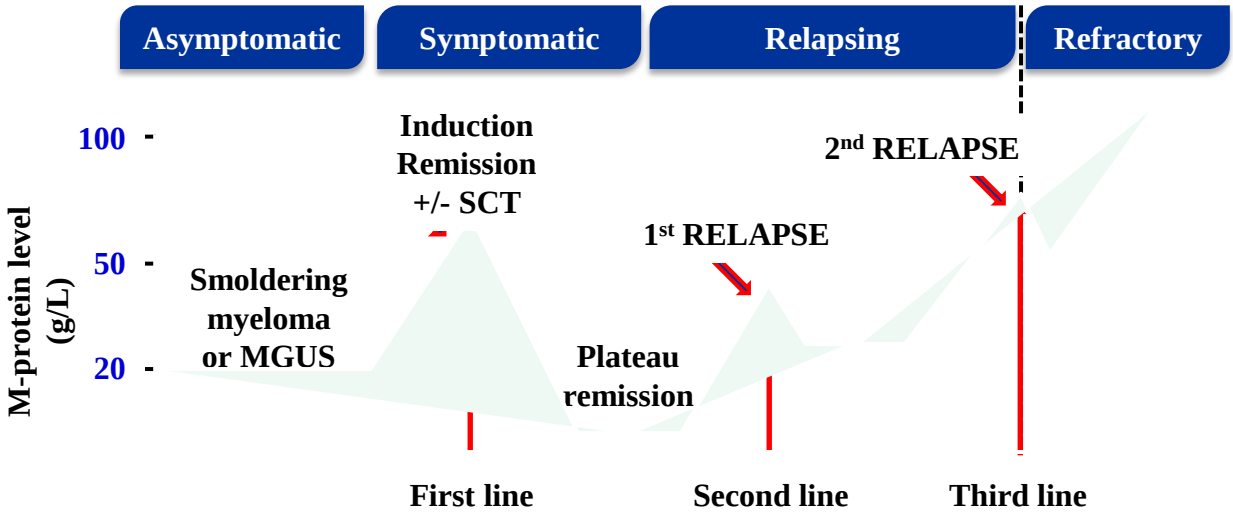
- Myeloma has enjoyed one of the most numerous progressions of new drugs over the last 15 years



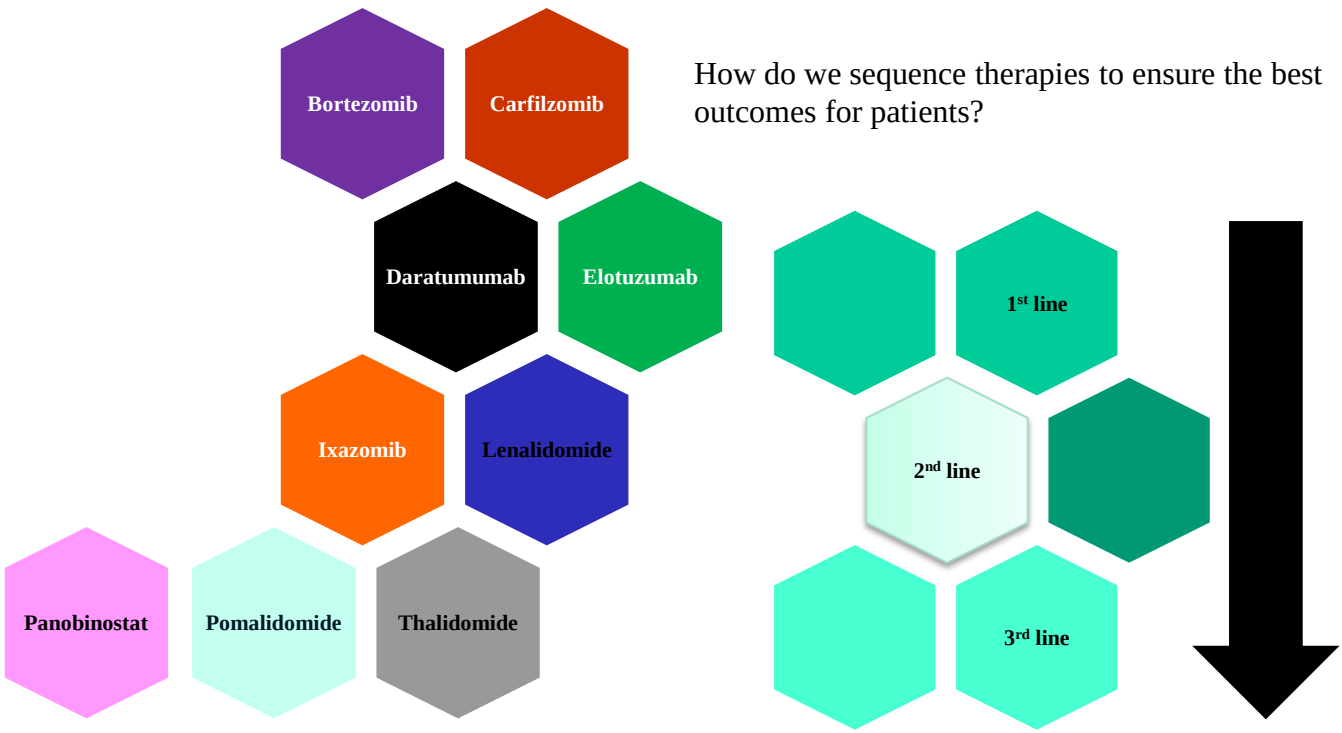
- In addition to the enlarged number of drugs, powerful combination therapies have been a source of treatment to try to achieve remission:
  - Bortezomib, lenalidomide/dex, thalidomide/dex, bortezomib + liposomal doxorubicin, bortezomib + MP, bortezomib/dex, carfilzomib/dex, pomalidomide/dex, panobinostat, elotuzumab, daratumumab, Ixazomib, selinexor/dex, RVD, KRD, PVD, dara and elo-based combos
- Targeting myeloma in the BM microenvironment has also enabled to try to overcome conventional drug resistance
- This has provent effective in relapsed/refractory myeloma
- As well as induction/first-line therapy
- This has led to the emerging role of transplant/maintenance
- Which unfortunately has increased the price of treatment considerably

EVOLUTION OF MULTIPLE MYELOMA TREATMENTS

Treating Multiple Myeloma is a Marathon. It is highly complex, in part due to genomic events and clonal evolution

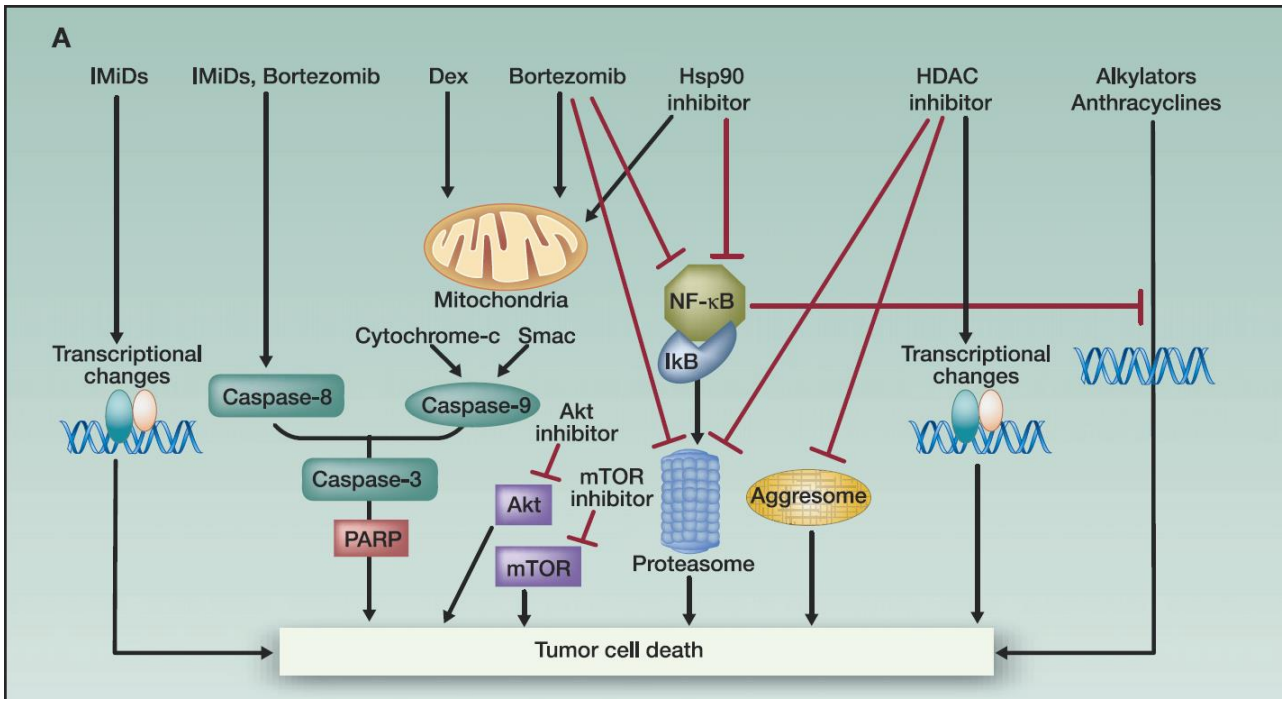


MULTIPLE OPTIONS ARE NOW AVAILABLE TO TREAT IN ND NN AND RR MM…

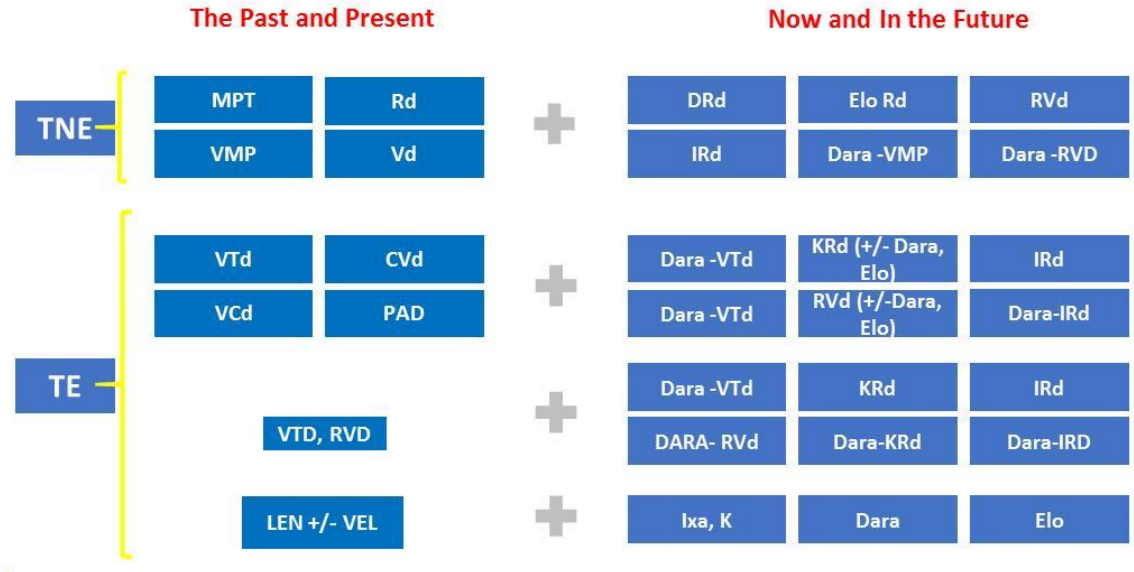


Source: Adapted from Borrello I. Leuk Res. 2012;36 Suppl. 1:S3–12 & Laubach JP et al, Leukemia 2016

RATIONAL COMBINATION STRATEGIES IN RELAPSED REFRACTORY MM



TREATMENT LANDSCAPE IN FRONT-LINE THERAPY OF NDMM IS EVOLVING

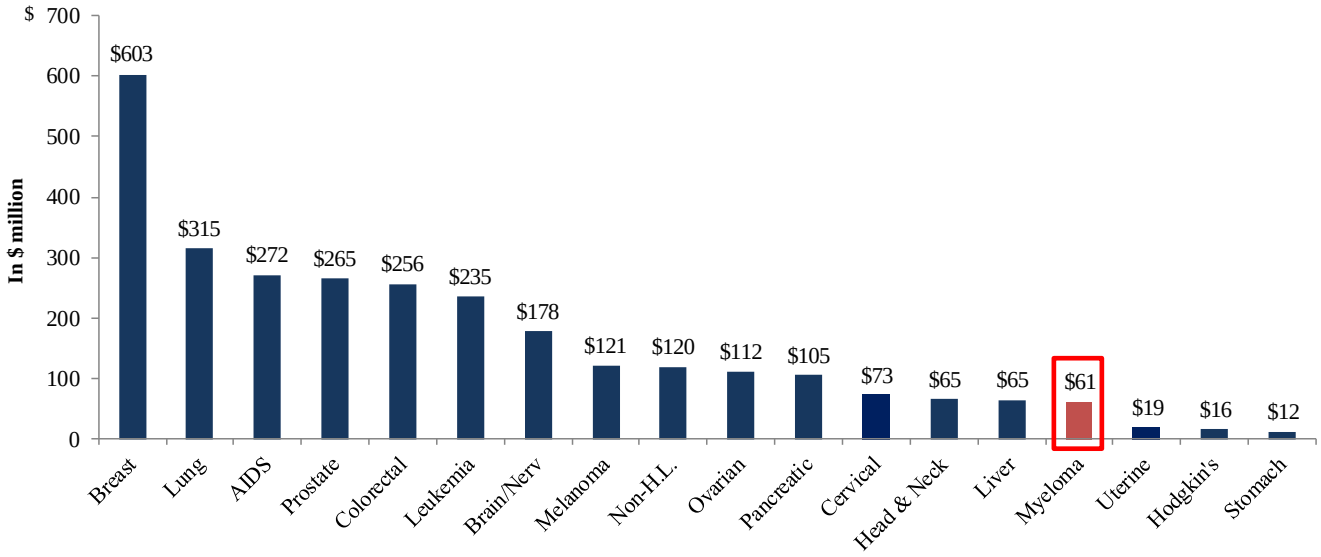


Source: *Lonial S, Mitsiades CS, Richardson PG. Clin Cancer Res 2011;17:1264-77.*

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 elsewhere as well as (ii) private individuals/foundations, (iii) hospitals and (iv) Pharmaceutical/Biotech organizations have placed myeloma **low on their priority list**.
- Only dedicated biotech/pharmaceutical companies have been targeting this disease (Amgen, Celgene, etc.).

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

"**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

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 U.S. 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.

- Progress
  - Better understanding of disease biology
  - Substantial improvements in outcome due to availability of new and effective therapies - potential for myeloma to become a chronic disease
  - Management of adverse events, comorbidities, optimal handling of novel agents much improved

- Challenges
  - Myeloma remains incurable & poor outcome in high risk disease
  - Increasing symptom burden due to disease, cumulative effects of treatments, with need to manage balance of disease control and quality of life
  - Critical need to identify new targets and derive next generation therapeutics
  - Continued clinical research and study participation essential

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.

We are about:

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

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

OUR GOALS

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

"It is always impossible until it gets done."

— NELSON MANDELA

HOW WE SELECT THE PROJECTS TO SUPPORT

We have supported the research of a team which has already demonstrated its ability to conduct groundbreaking fundamental research in the field of myeloma and translate this innovative research into major clinical benefit for patients.

We thought outside the box and supported this team that offers:

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

We 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 team and institution to support. The experience, dedication, professionalism and infrastructure of this team and hospital facilitated our selection process.

Phase I:

We started with a first pledge of **$1,000,000 over 5 years** to this team of the Dana-Farber Cancer Institute.

This gift provided essential seed monies to develop new therapies specifically designed to overcome resistance in MM 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.

Thanks to Dr Richardson and Dr Mitsiades, DGMRF was directly involved in the development of Daratumumab and Panobinostat, 2 out of 4 drugs that got FDA approval and became available in 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 in 2015**, and generally all the major new drugs and therapies that have came to the market.

Furthermore, the DGMRF-supported work of the Mitsiades Lab (DGMRF 1st Phase) has been making major progress in identifying why MM cells escape from each of these therapies.

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.

DANA-FARBER CANCER INSTITUTE

A REVOLUTION BEGINS

FOUNDED
in 1947 by Sidney Farber, M.D.—visionary in the possibilities of cancer research and care, father of modern chemotherapy

DECADES
of breakthroughs set Dana-Farber as a leader in cancer medicine

HARVARD MEDICAL SCHOOL
teaching affiliate

WORLD-RENOWNED
faculty driven by a mission, inspired by opportunity

de Gunzburg Myeloma Research Foundation

DANA-FARBER CANCER INSTITUTE

Dana Farber Cancer Institute is one of the best cancer centers in the world, a class of its own:

- 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.
- In all cancers, Dana-Farber researchers have significantly **contributed to the development of 35 of the last 76 cancer drugs approved by the FDA**.
- Dana Farber is the only hospital ranked in the **top five nationally** *U.S. News & World Report "Best Hospitals" guide* in both adult and pediatric cancer care. Dana-Farber/Brigham and Women's Cancer Center is ranked the **top cancer center** in New England.
- DFCI is among the top academic recipient of grant funding from the National Cancer Institute (NCI), and
- On average, Dana-Farber has over **1,100 open clinical trials** for adult and pediatric patients.

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 20 (i.e. 77%) of the 26 FDA approved therapies and indications for treating MM over a span of 15 years**, an unprecedented accomplishment in the field that has significantly prolonged the lives of many patients and improved the prognosis of this disease. **The myeloma team represents 57% of drugs and therapies from Dana Farber and more than 26% of all drugs and therapies regarding cancer).**
- 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 colleagues and as part of their larger/highly collaborative group.

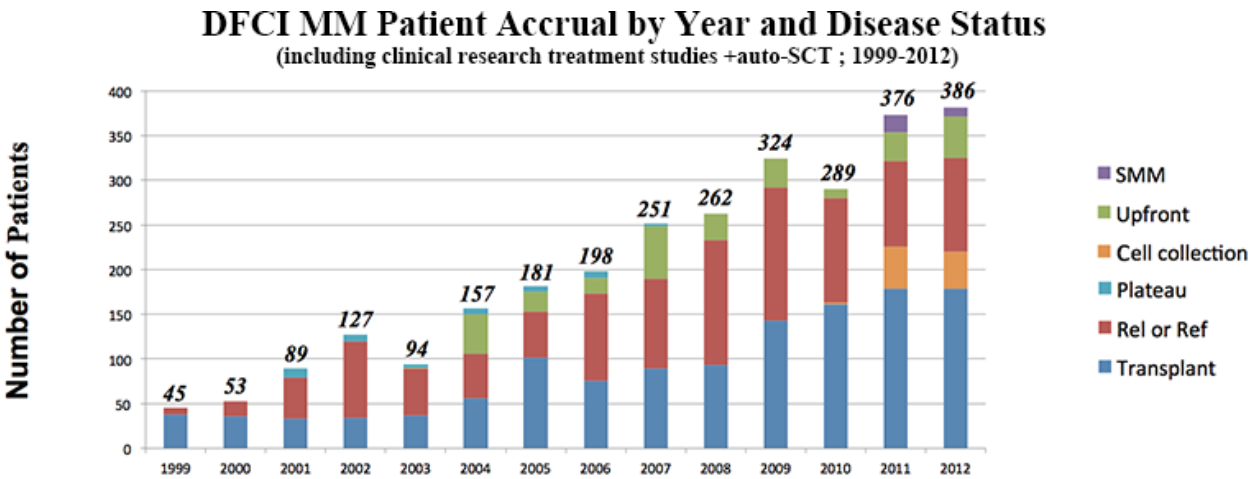
Clockwise from far left: **Paul Richardson, MD**, clinical director of the Jerome Lipper Center for Multiple Myeloma and RJ Corman Professor of Medicine at Harvard Medical School, **Constantine Mitsiades, MD, PhD, Dharminder Chauhan, JD, PhD, Kenneth C. Anderson, MD**, director of the Jerome Lipper Center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

- Global referral center for myeloma, with over **3,000 individual patients each year (10% of the U.S. diagnosed population)**, providing tremendous opportunities for clinical research
- Independently leads **15-20 clinical trials at any given time**. **Currently 18 trials open** and enrolling.
- Additionally:
  - 6 trials pending activation
  - 12 trials in development
  - 50+ completed trials (Data analysis and regulatory activity ongoing)

THE MULTIPLE MYELOMA PROGRAM

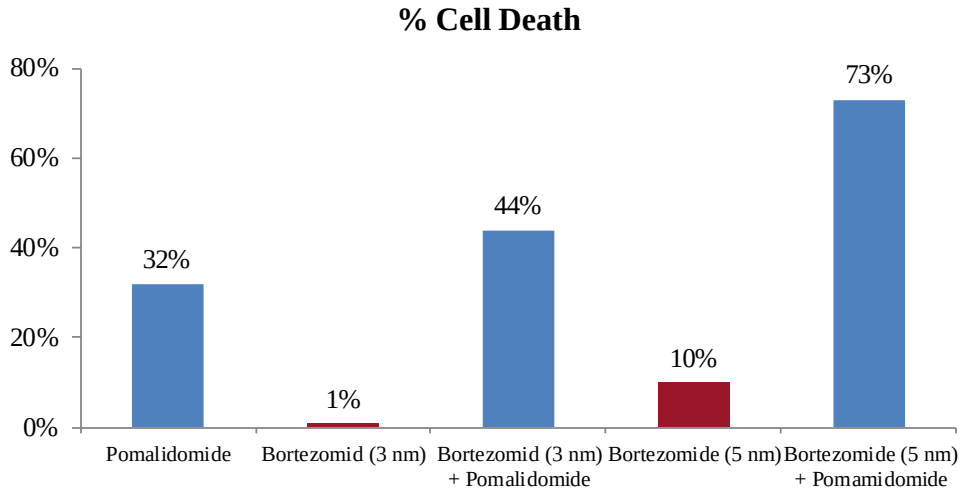
The de Gunzburg Myeloma Research Foundation chose to finance the Dana-Farber Cancer Institute, specifically Dr. Richardson (on the clinical side) and Dr. Mitsiades (on the laboratory side) because:

- **Dr. Richardson and Dr. Mitsiades** and their teams, as well as the colleagues they work with within and outside of DFCI, **are the best in the field**. They positioned Dana Farber Cancer Institute as 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; and
- F.F.R.M.G., the French Foundation also dedicated to Fundamental Research on Myeloma is one of the partners of the MM team at DFCI including with exchange programs.



Hospitals as academic centers are increasingly becoming vital centers of research (vs. biotech/pharmaceutical companies and independent laboratories alone). DGMRF thought it needed to secure that form of research vs. letting biotech/pharmaceutical companies trust the research fields which may lead to a potential shorter tem and less objective research.

A CENTRAL COMPONENT OF THE PROGRESS IN MYELOMA



FDA approvals for multiple myeloma therapy:

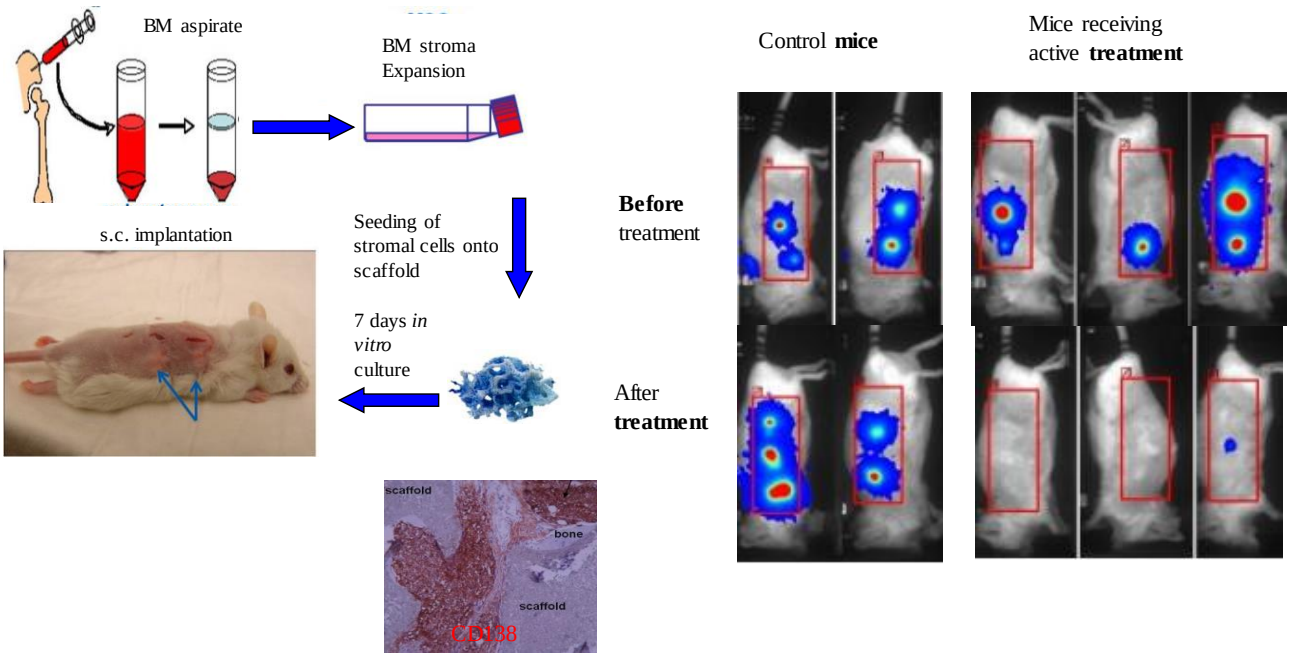
- → 2003: Bortezomib/Velcade (Bort)
- → 2006: Thalidomide + Dex
- → 2006: Lenalidomide (Len) + Dex
- → 2007: Bort + Liposomal Doxorubicin
- → 2010: Bort + Melphalan-Prednisone
- → 2012: Carfilzomib
- → 2013: Pomalidomide
- → 2015: Elotuzumab (Empliciti) + Daratumumab (Darzalex) + Ixazomib (Ninlaro) + Panobinostat (Farydak)
- → 2016: Daratumumab (Darzalex) + Lenalidomide (Len) & Daratumumab (Darzalex) + Bort
- → 2017: Carfilzomib + Lenalidomide (Len) + Dex & Lenalidomide (Len) maintenance
- → 2018: Daratumumab (Darzalex) + Pomalidomide & Daratumumab (Darzalex) + VMP
- → 2019: Daratumumab (Darzalex) + Lenalidomide (Len) & Selinexor

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

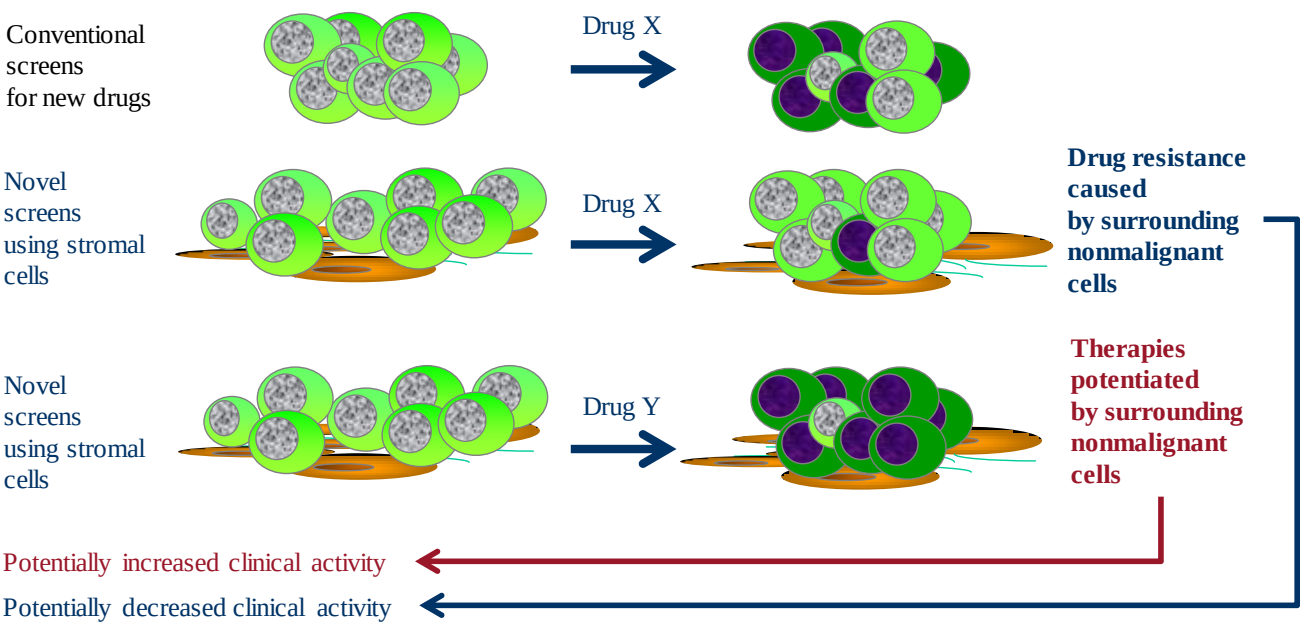
2012: Development of Pomalidomide-Bortezomib-Dex (PVD)

DFCI' MM team was involved in 20 of the 26 FDA approved drugs/combinations over the last 15 years.

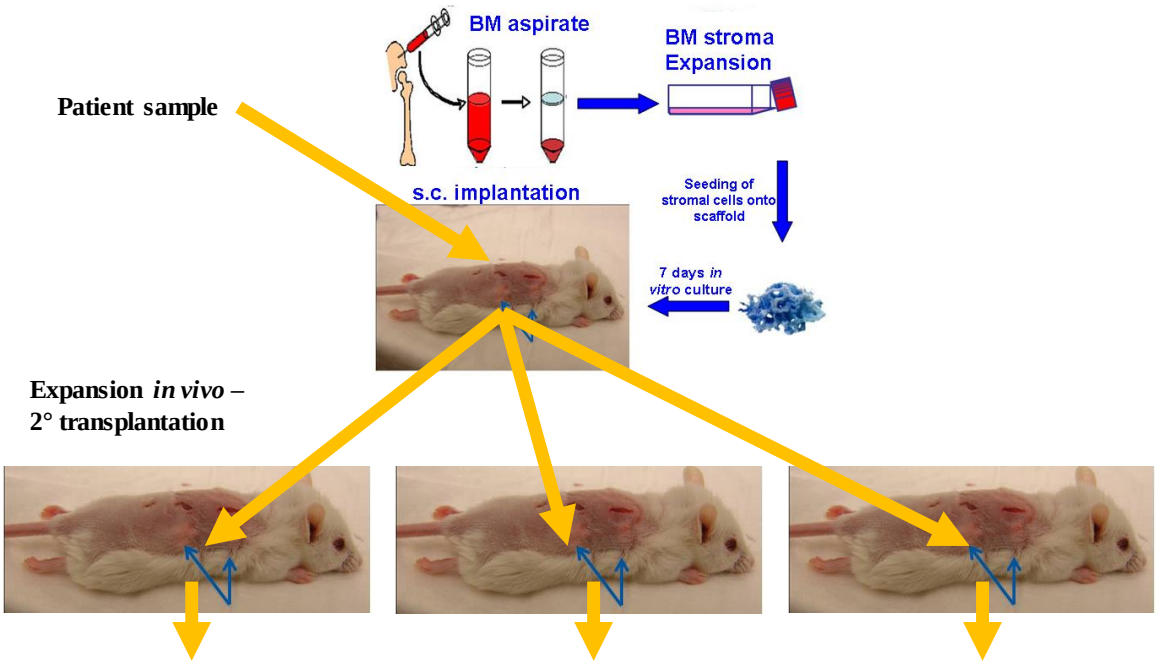
NEW MODELS TO STUDY MYELOMA CELLS FROM PATIENTS



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

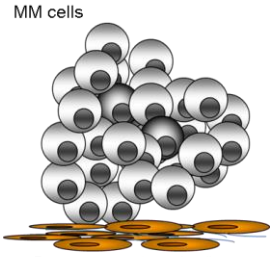
DFCI'S DGRMF Phase I

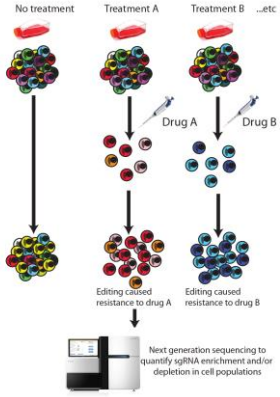
New systems to simulate in the lab the human bone marrow and a deep understanding of MM cells at molecular level and behave in individual patients

New approaches to define biomarkers of response vs. resistance to treatments

Next-generation CRISPR systems to determine which groups of genes drive MM

New approaches to make immunotherapy more active against MM

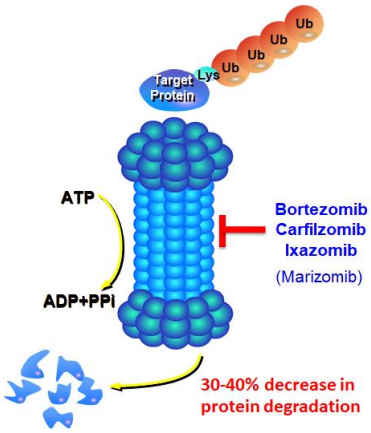




15+ Abstracts at ASH2016-2018
Shirasaki et al . *Cell Reports*

Close Collaboration of the Mitsiades Lab with Paul Richardson

Bench-to-Bedside Translation of novel agents & combination therapies for MM



Delmore et al. Cell. 2011
McMillin D. et al. Nat Med. 2010
de Haart SJ et al. Clin Cancer Res. 2013
McMillin D. et al. Blood. 2012
McMillin D. et al. Nat Rev Drug Discov. 2013
Lu G et al. Science. 2014
Shirasaki et. al Cell Rep 2019

Our preclinical studies have informed transformative successes in clinical treatment of MM, with new MM therapies that are:

- ***FDA approved***
- ***Used as Standard of Care (SOC)***
- ***Promising early clinical results translated into Phase 3 success***

Mitsiades et al. PNAS 2003
Mitsiades et al. Blood. 2002
Mitsiades et al. Blood. 2003
Mitsiades et al. PNAS 2004
Mitsiades et al Cancer Res. 2008
Richardson et al JCO 2009
Richardsin et al. Blood 2010
Richardson et al Blood 2013
Richardson et al Blood 2014
Richardson et al Blood 2016

Examples: combining proteasome inhibitors with:
✓Thalidomide Derivatives (IMIDs) ~ eg RVD
✓Alkylators – eg VCD, VMP
✓HDACs
✓Anthracyclines
✓Bcl-2 inhibitors
✓Aplidin

Transformative Tangible Impact on the Clinical Development of New Therapies in MM:
Most major new combination regimens tested in MM today build on the foundation laid by the bench-to-bedside collaboration of the Mitsiades Lab and others with the MM Clinical Research Program led by Paul Richardson and his team thanks to the help of DGMRF

de Gunzburg Myeloma Research Foundation

PROGRESS REPORT OF DFCI's DGMRF PHASE I

"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 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 DFCI's DGMRF PHASE I (Cont'd)

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.

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.

Mitsiades Lab:
Top row: from left to right:
Ryosuke Shirasaki, MD
Ricardo de Matos Simoes, PhD
Constantine S. Mitsiades, MD, PhD
Ray Wang PhD
Eugen Dhimolea, PhD
Megan Bariteau BSc
Huihui Tang, PhD

Lower row Seated: from left to right
Olga Dashevsky PhD
Sara Gandolfi, MD
Sondra Downey PhD,
Emily Lowry, B.Sc.
Jeff Sorrell, B.Sc.

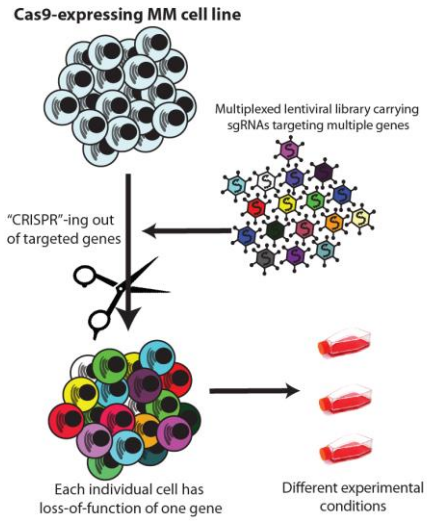
Other team members not represented:
Michal Sheffer, PhD
Brian Glassner, PhD
Dhvanir Kansara, B.Sc.
Isaure Vanmeerbeek, B.Sc.

DFCI'S DGRMF Phase I

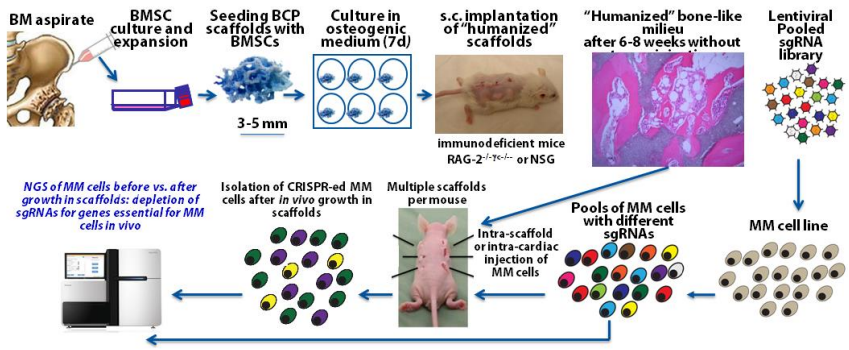
"Phase I" of DGMRF has had MAJOR SUCCESSES with the contribution to 2 FDA approved drugs in the market, including one of the three best drugs Daratumumab
Yet MM is not cured yet
Several years of focused effort and appropriate funding will be needed to create the new therapies needed
"PHASE II" IS REQUIRED TO ACHIEVE A CURE

Building new systems to:
- Better simulate in the lab how MM behaves in <u>individual</u> patients
- Define more precisely the molecular <u>vulnerabilities</u> of MM cells

Defining new therapeutic targets and biomarkers of "exceptional response" through novel CRISPR approaches



"Engineering" in mice systems to simulate human bone marrow Examining which therapies work against MM cells of individual patients



2019: CHALLENGES IN TREATING MM

There is a pressing need to accelerate clinical research to:

- Understand the most effective combinations and minimize side effects of these combinations
- Refine treatment approaches to extend remissions
- Prevent secondary cancers
- Personalize the approach for each patient based on the genetic make up of that individual's disease

Genomic abnormalities

- Target and overcome mutations
- Critical role of combination and continuous (maintenance) therapy
- Evolving position and timing of ASCT (graft/stem cell transplant)

Excess protein production

- Target protein degradation

Immune suppression

- Restore anti-MM immunity, including combination approaches

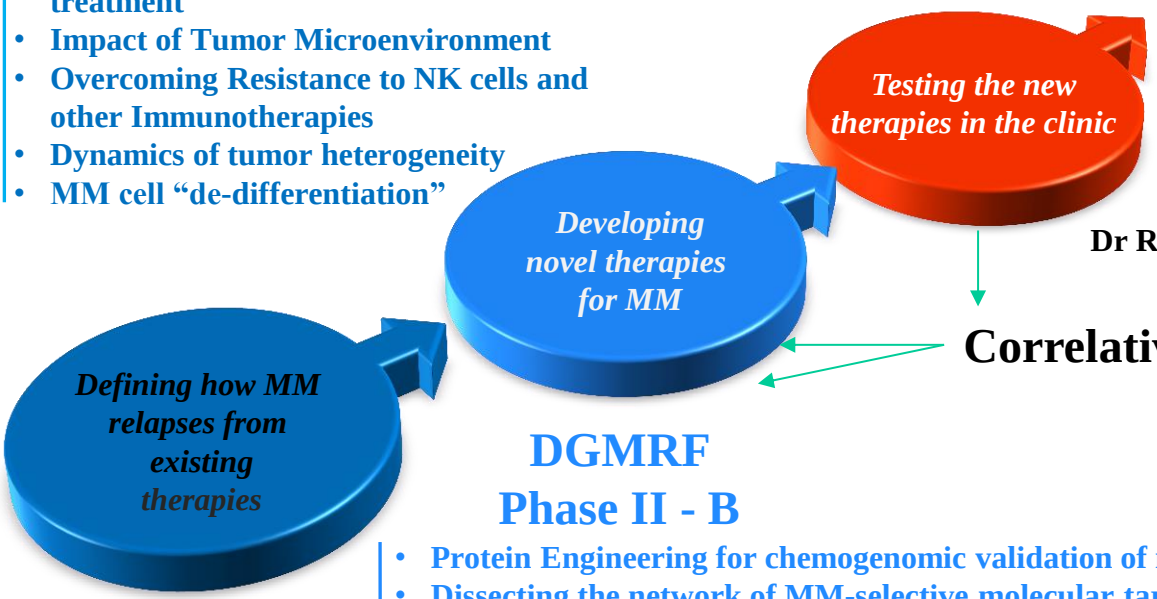
DFCI'S DGRMF Phase II

DGMRF Phase II - A

- Mapping how MM cells escape current therapies
- "Plasticity" of MM cells after treatment
- Impact of Tumor Microenvironment
- Overcoming Resistance to NK cells and other Immunotherapies
- Dynamics of tumor heterogeneity
- MM cell "de-differentiation"

MM Clinical Research Program

- Innovative clinical trial designs
- Faster initiation and completion of clinical trials
- Correlative Science
- Rapid translation to clinical benefit and FDA approval



Dr Richardson

Correlative Science

Dr Mitsiades

DGMRF Phase II - B

- Protein Engineering for chemogenomic validation of novel targets
- Dissecting the network of MM-selective molecular targets for treatment
- How are MM-selective targets regulated
- Identifying small molecules binding to currently "undruggable" MM-selective targets
- Immune therapy including NK cell platforms
- Optimizing the properties of candidate drugs against MM-selective targets
- Preclinical testing of novel agents against MM-selective targets
- Developing more potent, efficient and safe cell-based immunotherapies
- Optimizing combinations of immunotherapies and anti-MM drugs

Fundamental Research: Dr Mitsiades Lab

Bench to Bedside and Back…

Clinical Research: Dr Richardson

de Gunzburg Myeloma Research Foundation

DFCI'S DGRMF Phase II

DGMRF Phase II- A:
"Defining how MM relapses from existing therapies"

Why is Phase II-A needed?
- *The major barrier to curing MM is that it eventually become resistant to all currently available therapies or their combinations*

What will Phase II-A accomplish ?
- *We will define which new specific molecular targets in MM cells we need to develop therapies for in order to prevent MM resistance*
- *These new molecular targets will be the focus of development of new therapies in Phase II-B*

How did the progress of Phase I prepare us to be ready for Phase II-A?
- *We established the advanced systems, infrastructure, talented personnel, know-how and track record to be ready for Phase II-A*
- *One element studied was the Natural Killer Cells ("NK") which will be one of the areas of interest to further study in Phase II-A*

DGMRF Phase II- B:
"Developing novel therapies for MM"

Why is Phase II-B needed?
- *Many therapeutic targets we already identified in Phase I are very specific to MM. Limited application to other forms of cancer is reducing the interest of the private sector. Further research to develop therapeutics for these targets can only be led by the academic sector and financed by philanthropy*
- *The Mitsiades lab and its colleagues at DFCI will tackle this goal, to accelerate the early stages of development of these new therapies*

Why are we optimistic about phase II-B?
- *Because of our long-standing experience in all the steps of developing new therapies from the lab to the clinic, especially in developing combination therapies to safely target maximize anti-tumor activity*
- *Comforted by the close collaboration of Drs Mitsiades and Dr Richardson which will ensure that the therapies being developed in the lab will optimally match the needs of patients in the clinic*

SPECIFICS ON OUR DANA-FARBER DOCTORS

PAUL G. RICHARDSON, MD

RJ Corman Professor of Medicine, Harvard Medical School
Clinical Director, Jerome Lipper Center for Multiple Myeloma Dana-Farber Cancer Institute
Boston, Massachusetts

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. He has been a leader in the clinical development of bortezomib, lenalidomide and pomalidomide, panobinostat, elotuzumab, daratumumab and selinexor, leading to FDA approvals with all these 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 at Harvard Medical School for his role in the development of bortezomib. Dr Richardson received the Ernest Butler award in December 2015 from the American Society of Hematology and the Robert Kyle Lifetime Achivement Award in 2017 from the International Myeloma Foundation. He has published approximately 380 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.

CONSTANTINE MITSIADES, MD, PHD

Assistant Professor of Medicine, Harvard Medical School Department of Medical Oncology
Dana-Farber Cancer Institute, Boston, Massachusetts

Constantine Mitsiades MD, PhD, is an Assistant Professor at Dana-Farber Cancer Institute (DFCI), Harvard Medical School, Boston, MA, an Associate member of the Broad Institute, Cambridge, MA, and holds the "Shawna Ashlee Corman" Investigatorship in Multiple Myeloma at DFCI. He received his MD, PhD and a Master's degree in Basic and Clinical Medical Sciences from the University of Athens, School of Medicine, in Greece. He also received a Master's degree in Medical Sciences from Harvard Medical School.

His research focuses on developing novel therapies which neutralize the ability of tumor cells to develop resistance to currently available pharmacological and immune therapies. Towards this goal, he and his lab have been developing preclinical models to simulate more faithfully the biology of multiple myeloma (MM) in patients and the clinical impact of interactions between MM cells and their local microenvironment. With these models and CRISPR-based functional genomic studies, Dr Mitsiades and his lab have been defining the mechanisms through which MM develops resistance to established/investigational drugs or immunotherapies, determining the molecular "drivers" of MM cells, particularly those with treatment resistance. and designing rational combinations of established or novel anti-MM therapies to overcome, delay or prevent treatment resistance.

Dr Mitsiades' studies documented that nonmalignant "accessory" cells of the tumor microenvironment, e.g. bone marrow stromal cells, can decrease the sensitivity of MM cells to many drug classes and immune effector cells. The research of Dr Mitsiades informed the design of several regimens (e.g. combinations of proteasome inhibitors with thalidomide derivatives [e.g. RVD], alkylators, anthracyclines, histone deacetylase inhibitors or Bcl-2 inhibitors) which are now FDA-approved, represent a standard-of-care for MM treatment or demonstrated promising activity in clinical trials. Several of these regimens contributed to the increased overall survival of MM patients in the last decade and are a "backbone" for combination with other novel agents, such as monoclonal antibodies.

Dr Mitsiades' studies established that inhibition of BET bromodomain proteins (e.g. BRD4) suppresses the function and expression of the oncoprotein c-Myc, leading to major interest for BET bromodomain inhibition in MM and other cancers. He has published more than 250 articles in peer-reviewed scientific journals (including Cell, Nature Medicine, Cancer Cell, et.c.) and his research has been supported by the National Cancer Institute, Multiple Myeloma Research Foundation, Leukemia and Lymphoma Society, International Myeloma Foundation, the De Gunzburg Myeloma Research Foundation, Stand Up to Cancer and other foundations.

He is Senior Editor of the journal Clinical Cancer Research and Vice-Chair for Translational Science in the Myeloma Committee of the Alliance for Clinical Trials in Oncology.

Dr Mitsiades was selected to receive the 2019 Award for Basic and Translational Research in MM by the International Myeloma Society.

FUNDING FOR CLINICAL RESEARCH

- The influx of new FDA approved therapies and possible combinations has resulted in a bottleneck; **new trials cannot open due to funding constraints** :
  - **Of the $144M DFCI received in federal grants from the NIH in 2017, only $5.8M or 4% funded clinical research**
  - Clinical **trials that are not fully industry sponsored cannot move forward**, *despite scientific merit*, without outside support

THE ROLE OF PHILANTHROPY

- To rapidly deliver new drugs to patients and their families, the clinical research team needs additional bandwidth to open new trials that are:
  - Patient driven
  - Safe
  - Effective
- Philanthropic investment in human capital is critical to the pace of progress and discovery
- Philanthropy makes it possible to design more successful clinical trials, ensuring trials are organized in the most impactful manner at the outset
- Flexible dollars support strategic research investments, including:
  - People -- Clinical research nurses, clinical research coordinators, pathologists, and biostatisticians who oversee and ensure the successful implementation of clinical trials
  - Patient Samples -- Collection and processing of patient samples to study the biological effects of the treatment and assess not only whether a protocol works but how it works
  - Analysis to inform future studies -- Analyzing patient samples informs which patients are most likely to benefit from which therapies and why
- **Your support represents an opportunity to change the trajectory of MM and dramatically improve outcomes for patients and families** *in the near term*
- Your generosity makes a major difference for patients in the near and long term. **Any new therapy enables to prolong the lives of tens of thousands of people**.

CURRENTLY AT AN INFLEXION POINT, MULTIPLE MYELOMA OFFERS THE MOST IMPORTANT IMMEDIATE SIGNIFICANT IMPACT IN THE MEDICAL FIELD, TO MYELOMA BUT ALSO TO MANY OTHER BLOOD AND CANCERS GENERALLY

DGMRF

It is thanks to the extraordinary contribution of donors 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.

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.

The de Gunzburg Myeloma Research Foundation (the "DGMRF") is a non-profit private foundation established in March 2012 under the meaning of section 509(a) of the Code. DGMRF applied for tax-exempt status in May 2012 under section 501(c)(3) of the Internal Revenue Code, and received its formal tax exempt status from Federal income tax in August 2012. Tax-exempt status having been granted, donations from US, Canadian and Israeli donors are deductible under section 170 of the code for income tax purposes to the extent permitted by the law. DGMRF is also qualified to receive tax deductible bequests, devises transfers or gifts under section 2055, 2106 or 2522 of the Code. The de Gunzburg Myeloma Research Foundation will exclusively select and finance research programs within hospitals and laboratories in the US only, which have experienced teams and which entities also benefit of the 501(c)(3) non-profit tax deductible status. The de Gunzburg Myeloma Research Foundation hereby also confirms that no goods or services will be provided in consideration for your gift. Upon donation, a formal thank you letter will be sent to the donors to serve as a tax deductible receipt.

CONTACTS & DONATIONS

de Gunzburg Myeloma Research Foundation

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Website: www.Gunzburg-Myeloma.org

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