DANA-FARBER CANCER INSTITUTE

de Gunzburg Myeloma Research Foundation

Towards the Goal of a Cure for Multiple Myeloma

The Partnership of the DGMRF and DFCI

Successes of the First Phase and Driving Towards a Cure in the Second Phase

Paul Richardson, MD
Corman Professor of Medicine

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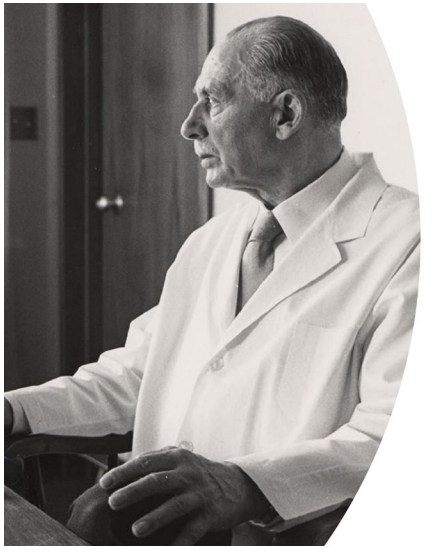
Assistant Professor of Medicine

Harvard Medical School
Boston, MA

NY, New York USA 2019

DANA-FARBER CANCER INSTITUTE
LEADING A REVOLUTION



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

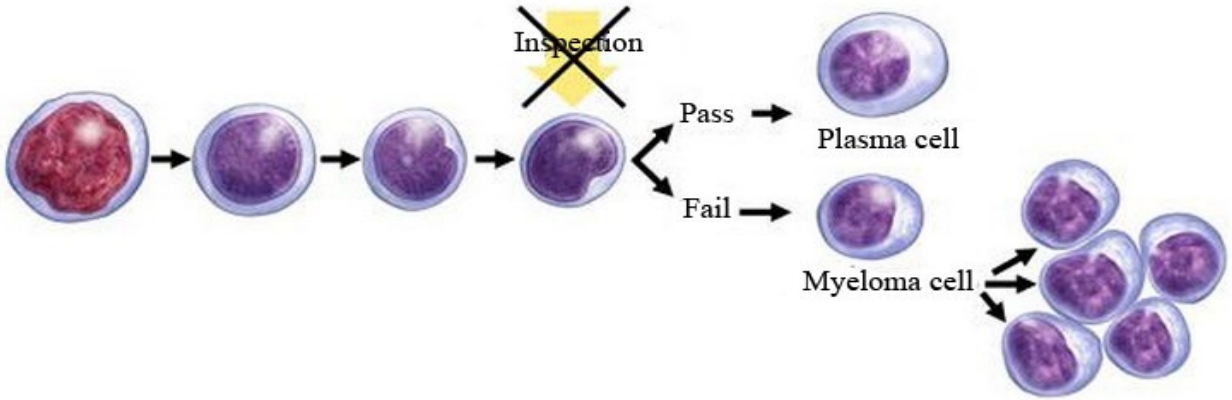
WORLD-RENOWNED
faculty driven by a mission, inspired by opportunity

HARVARD MEDICAL SCHOOL
teaching affiliate

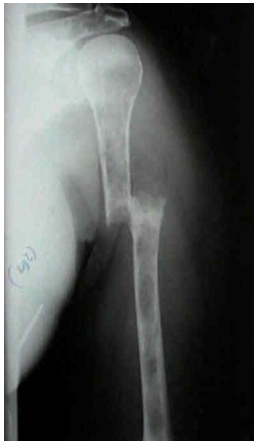
Multiple Myeloma (MM): An Incurable Hematologic Malignancy

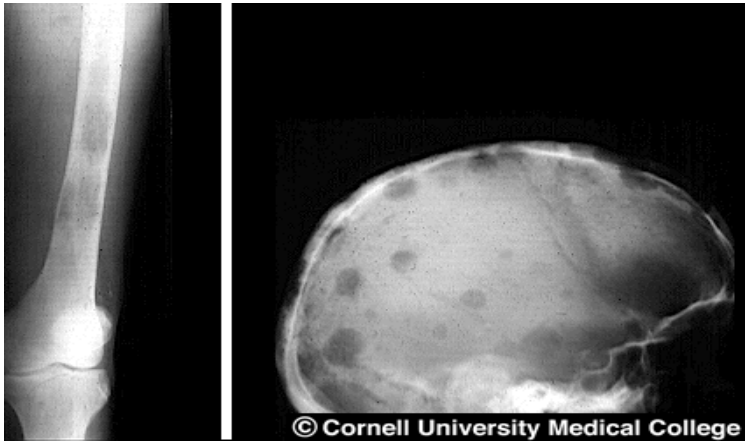
MM is a cancer of plasma cells (PCs).

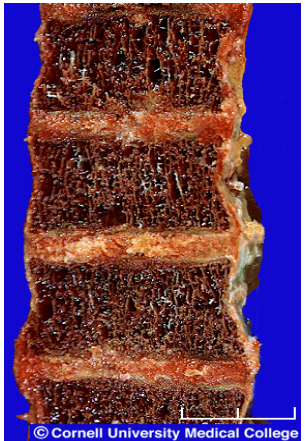
Normal plasma cells produce antibodies that fight infection with long term memory and are key components of immunity.



MM cells are malignant plasma cells. They do not protect from infection and cause immune-paresis with widespread damage to bone, bone marrow function, kidneys and other organs.







Multiple Myeloma Epidemiology

Multiple myeloma (MM) represents 10-15% of all hematologic malignancies[1]

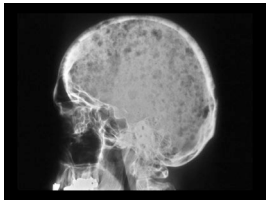
- **Incidence in US:**
  Estimated 32,000 new cases in 2018 [2]
- **Median age at diagnosis is 69 years. More common in men. When compared to people of Caucasian descent, MM is twice as common in African-Americans and twice less frequent in Asian-Americans.**
- **Additional research has found that people of Ashkenazi Jewish heritage are more likely to develop MM.**
- **MGUS (Monoclonal Gammopathy of Uncertain Significance, a precursor for MM) might affects over 10% of people of 85 years old.**
- **Prevalence in US:**
  90,000-100,000 people living with MM in 2018
- **Mortality in US:**

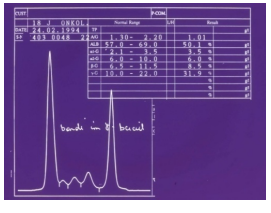
  ~ 12, 000 deaths per annum (2018)
- **A Global Challenge ~ 1.8- 2 million people affected world – wide**

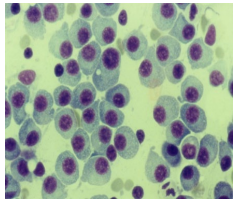
1. Raab MS, et al. *Lancet*. 2009;374:324-39; 2. SEER Cancer Statistics Factsheets: Myeloma. National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/statfacts/html/mulmy.html.

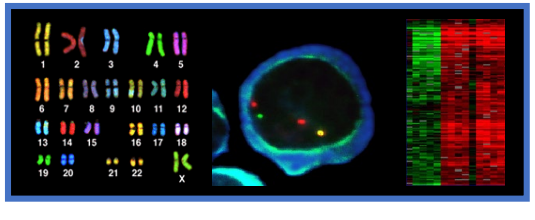
Multiple Myeloma Pathophysiology and Molecular Biology

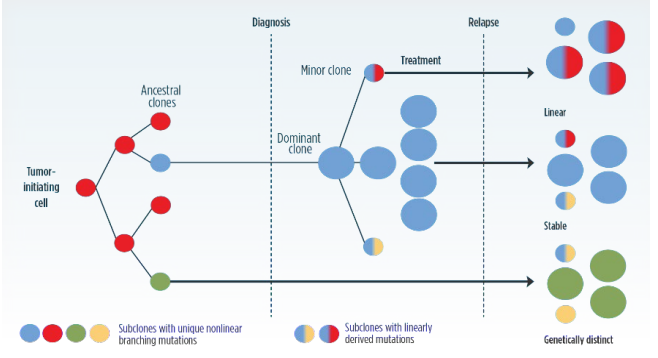
MM is highly complex at diagnosis and relapse due to genomic events and clonal evolution

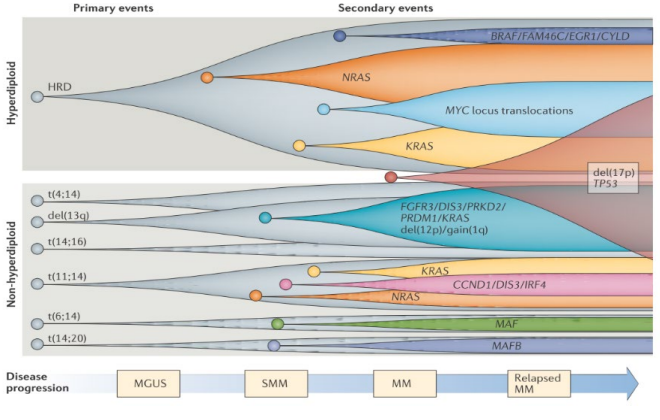


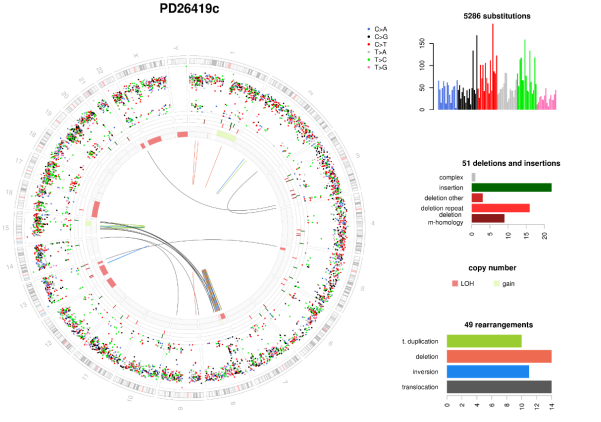


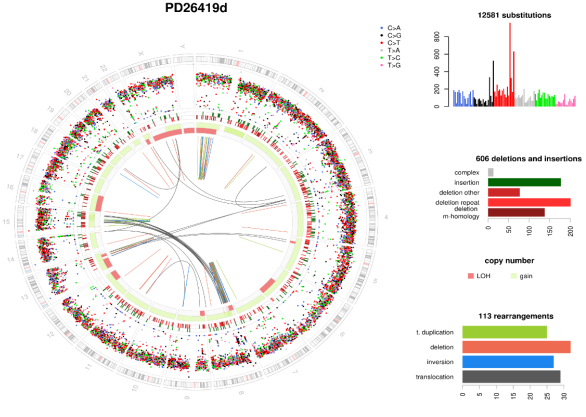










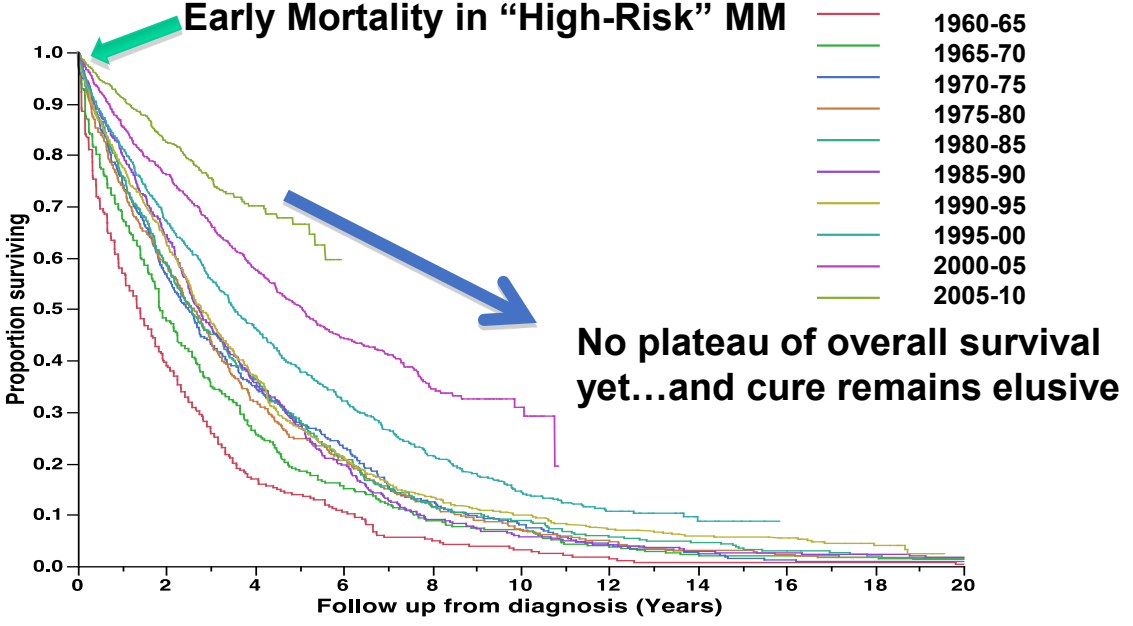


Drach J, ASH 2012; Morgan GJ, et al. *Nat Rev Cancer* 2012;12:335–348; Manier S, et al. *Nat Rev Clin Oncol* 2017;14:100–113.

Courtesy of Nikhil Munshi MD, DFCI, personal communication: 2016.

Multiple Myeloma Remains Incurable

- Over the last 20 years, MM patients survive longer, due to the impact of novel therapies and a continuum of progress
- The majority of these therapies both alone and in combination were introduced and approved through the pivotal work of Drs. Richardson, Mitsiades and their colleagues at DFCI
- Despite these advances, all patients eventually relapse, and MM remains incurable
- Next generation therapies with improved efficacy and the ability to overcome resistance to current therapies are urgently needed



Adapted from Kumar et al *Leukemia* 2014

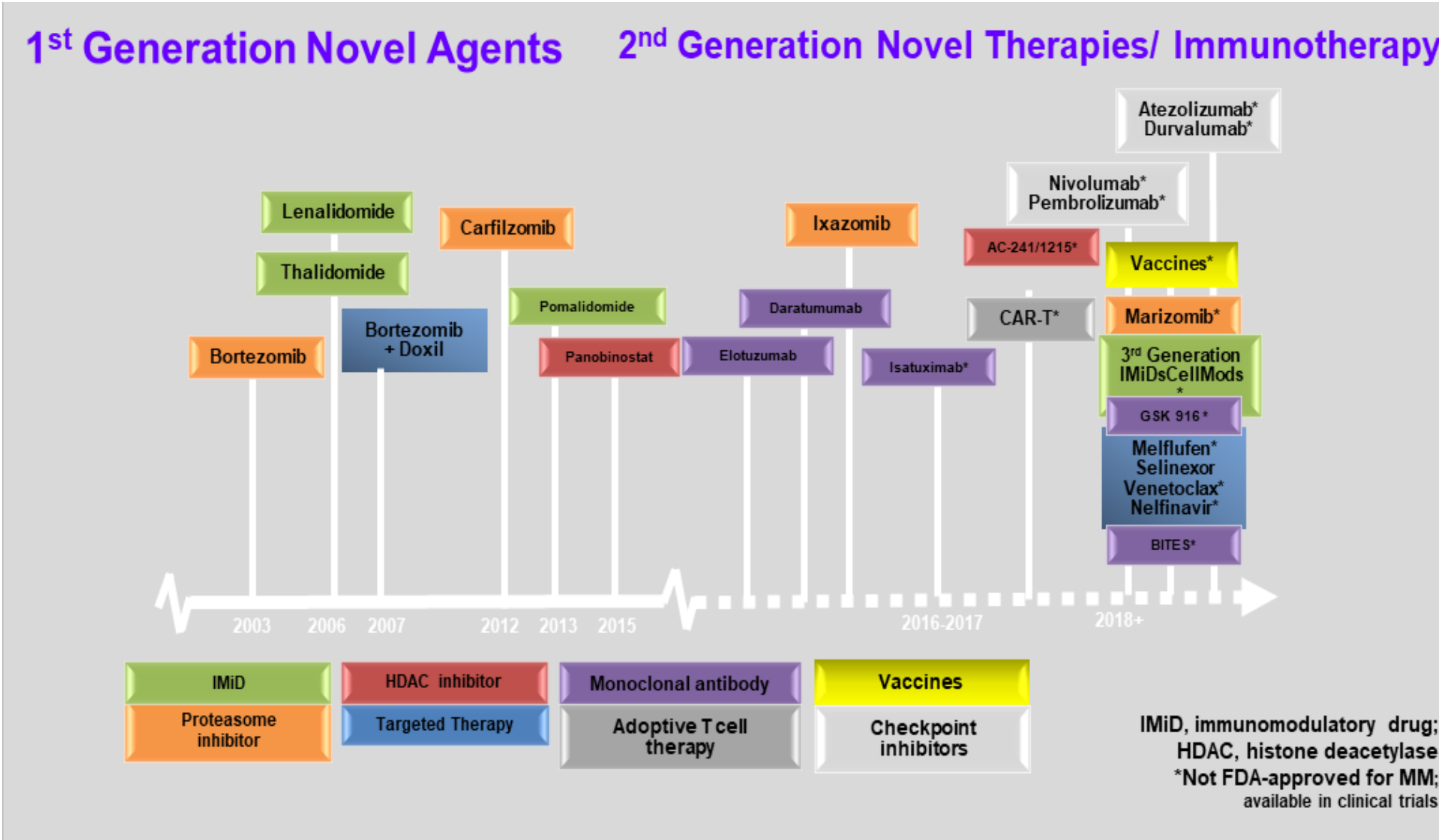
Changing the Treatment Landscape

- **Powerful combination therapies**
  - **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 to overcome conventional drug resistance *in vitro, in vivo***
- **Effective in relapsed/refractory myeloma**
- **Effective as induction/first-line therapy**
- **Emerging role of transplant/maintenance**

Richardson et al, IMWG 2019

Evolution of Multiple Myeloma Treatment

Selected New Classes of Therapies and Molecular Targets 2018-2019 almost all of which involved/led by DFCI



Jerome Lipper Multiple Myeloma Center and the Clinical Research Program at Dana-Farber Cancer Institute

Global referral center for myeloma, with over 3,000 individual patients each year, 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**
- **Over 50 completed trials (Data analysis and Regulatory Activity ongoing)**

Visionary and Supportive Leadership

LAURIE H. GLIMCHER, MD
PRESIDENT AND CEO

Laurie H. Glimcher, MD, is the President and CEO of the Dana-Farber Cancer Institute, Director of the Dana-Farber/ Harvard Cancer Center and the Richard and Susan Smith Professor of Medicine at Harvard Medical School. Previously, she was the Stephen and Suzanne Weiss Dean and Professor of Medicine of Weill Cornell Medicine and Provost for Medical Affairs of Cornell University. Dr. Glimcher is a distinguished immunologist, widely renowned for her work in one of the most promising areas of cancer research.

She is a Member of the National Academy of Sciences, Fellow of the American Academy of Arts and Sciences, a Member of the National Academy of Medicine and the former President of the American Association of Immunologists. She is a member of the Cancer Research Institute, Prix Galien, Parker Institute for Cancer Immunotherapy, Repare Therapeutics, Abpro Therapeutics and Kaleido BioSciences, Inc. Scientific Advisory Boards, the Lasker Award Jury, the American Association for Cancer Research, Association of American Cancer Institutes, and the American Society of Clinical Oncology. She is the co-founder of Quentis Therapeutics. She previously served on the Board of Directors of Bristol-Myers Squibb Pharmaceutical Corporation and is currently on the Corporate Board of Directors of GlaxoSmithKline Pharmaceutical Corporation and the Waters Corporation.

A trailblazer in cancer research, Dr. Glimcher is celebrated for her research discoveries in immunology, critical for both the development of protective immunity and for the patho-physiologic immune responses underlying autoimmune, infectious and malignant diseases. Dr. Glimcher speaks nationally and internationally on cancer, immunology, and translational medicine and has contributed more than 350 scholarly articles and papers to the medical literature.

Aside from her research efforts, Dr. Glimcher has been a staunch proponent of improved access to care, health policy, and medical education, while simultaneously serving as a pioneering mentor and role model for cancer research trainees and for all women in science. Notably, she was the first female to be appointed as dean of Weill Cornell Medicine in New York and is the first female President and Chief Executive Officer of Dana-Farber Cancer Institute in Boston.

DFCI/DGRMF Partnership
Focus on Excellence - Track Record of Success

Paul G. Richardson, MD
Clinical Program Leader and Director of Clinical Research for the Jerome Lipper Multiple Myeloma Center, Dana-Farber Cancer Institute;
RJ Corman Professor of Medicine,
Harvard Medical School

- **Led the development of several first-generation novel drugs including bortezomib and lenalidomide and then second generation novel drugs including ixazomib and pomalidomide.**
- **Subsequent studies have focused on next generation novel drugs including histone deacetylase inhibitors such as panobinostat and other small molecule combinations such as RVD with the goal of further improving patient outcome.**
- **More recently, his clinical innovations have been in the development of the breakthrough monoclonal antibodies including Daratumumab and Elotuzumab for the treatment of both untreated and relapsed myeloma, as well as other immunotherapeutic strategies.**
- **Leading the development of melflufen, a targeted cytotoxic and most recently the approval of another first-in-class small molecule inhibitor selinexor in MM , which inhibits XPO-1, a key nuclear export protein.**
- **Other important contributions include the management of treatment-emergent neuropathy in myeloma and other toxicities associated with treatment.**
- **Published extensively, having authored or co-authored over 380 original articles and an additional 300 reviews, chapters, and editorials in peer-reviewed journals.**
- **Prior Chairman of the Multiple Myeloma Research Consortium (MMRC), Clinical Trials Core and current Chair of the Alliance Myeloma Committee from 2011 to the present. He also serves as a Senior Editor for several leading journals in Hematology, including the British Journal of Hematology**
- **Awarded the prestigious Warren Alpert Prize at Harvard Medical School in 2012, the Ernest Beutler Prize in Hematology by the American Society of Hematology in 2015 and the COMY Award for the global impact of his MM research in 2016, as well as most recently the prestigious IMF Robert A. Kyle Lifetime Achievement Award in 2017.**

DFCI/DGRMF Partnership
Focus on Excellence - Track Record of Success

Constantine Mitsiades, MD, PhD
Assistant Professor in Medicine, Medical Oncology,
Dana-Farber Cancer Institute;
Assistant Professor of Medicine,
Harvard Medical School

- **Research focuses on developing novel therapies which neutralize the ability of tumor cells to develop resistance to currently available pharmacological and immune therapies.**
- **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.**
- **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.**
- **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 has published more than 250 articles in peer-reviewed scientific journals 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.**
- **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.**
- **Most recently, he was selected to receive the prestigious 2019 Award for Basic and Translational Research in MM by the International Myeloma Society**

Key Targets in Multiple Myeloma in 2019

Genomic abnormalities:

Target and overcome mutations
Critical Role of Combination Therapy
Evolving Position and Timing of Therapy

Excess Protein Production:

Target Protein Degradation

Immune Suppression:

Restore anti-MM immunity, including combination approaches

DFCI/DGRMF Partnership
Focus on Excellence - Track Record of Success Phase 1

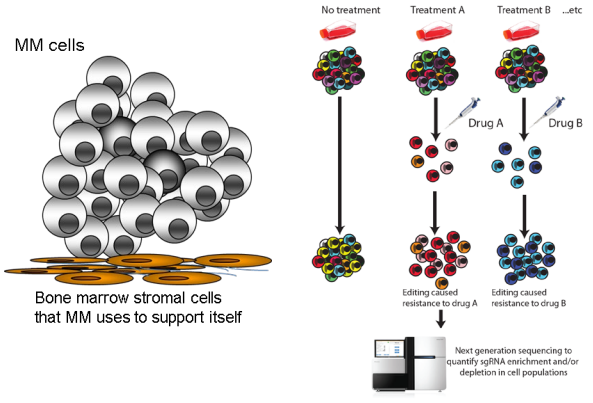
The close collaboration and partnership between the Mitsiades Lab, Dr. Paul Richardson and the MM Clinical Research Program at Dana-Farber Cancer Institute "*Inspired by Vivien's vision to convert myeloma into a curable disease*"

New systems to simulate in the lab the human bone marrow and how MM cells behave in individual patients

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

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

New approaches to make immunotherapy more active against MM



de Gunzburg Myeloma Research Foundation

$1M of "Phase I" support

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
Richardson 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
- ✓Histone Deacetylase inhibitors
- ✓Anthracyclines
- ✓Bcl-2 inhibitors
- ✓Aplidin

Tangible impact on the clinical development of multiple new therapies for MM

Transformative Impact :
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

Key Targets in Multiple Myeloma in 2019

Genomic abnormalities:

Target and overcome mutations
Critical Role of Combination Therapy
Evolving Position and Timing of Therapy

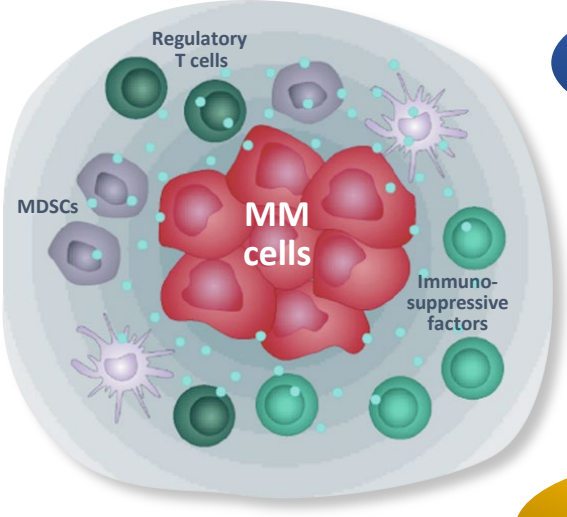
Excess Protein Production:

Target Protein Degradation

Immune Suppression:

Restore anti-MM immunity, including combination approaches

Reversing Immune Suppression
Overcoming the Tumor Immune- Microenvironment



- IMiDs/CEL-MoDs
- MoAbs (SLAM F7, CD38)
- Engineered T cells
- Vaccines
- Checkpoint inhibitors
- NK Cell Activation

Recruitment of immunosuppressive cells

Ineffective presentation of tumor antigens to the immune system

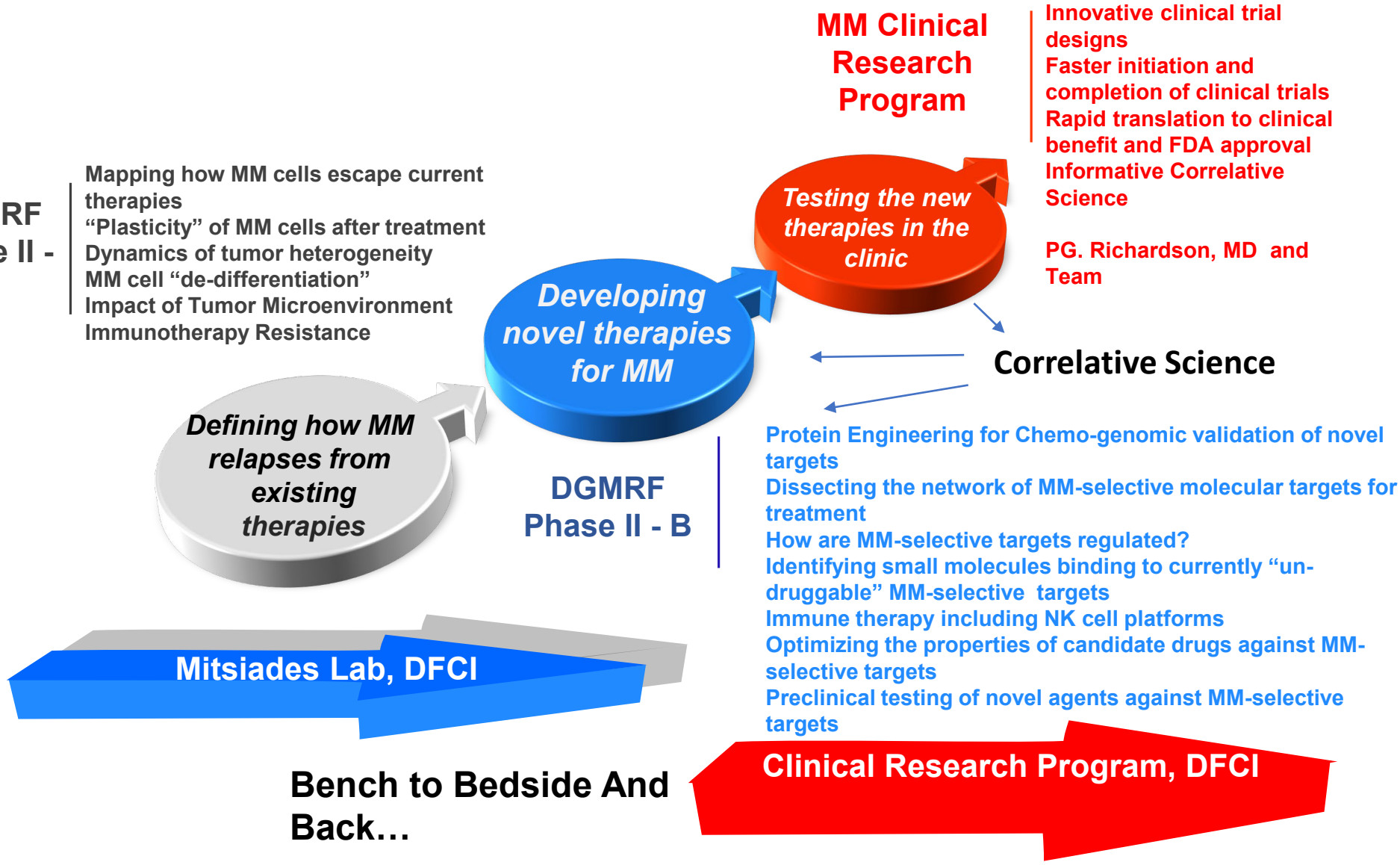
Release of immunosuppressive factors

T-cell checkpoint dysregulation

Adapted from Davies M. *Cancer Manag Res*. 2014;6:63
Richardson PG, ASH 2018.

The Vision for Phase II

The Mitsiades Lab and the MM Clinical Research Program at Dana-Farber Cancer Institute; the critical role of continuous collaboration:



Summary and Next Steps….

>> Continued Progress against MM and Improvements in Survival….
but no Cure in a highly Important Disease with Global Impact

>> Extraordinary Translational Success to date, poised for the Next Step

>> The most Innovative and Informative Laboratory Platform to guide Clinical Research towards further Improvements in Outcome

>> A Clinical Research Program Unsurpassed in Consistency and Quality for Translating Bench Discovery to Bedside Success, partnered with Outstanding and deeply Personal, Effective Philanthropy