Melanoma Research Alliance

MRA Scientific Strategy
2014-2017

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Executive Summary

The Melanoma Research Alliance (MRA) updated its Scientific Strategy in November 2013. MRA's Scientific Advisory Panel and other experts provided feedback on the treatment arena which combined with its prevention, diagnosis/staging objectives form a revised Strategic Research Plan that will guide the MRA scientific portfolio for the coming 3 years.

2014-2017 MRA Strategic Research Plan

Prevention

1. Further elucidate the genetic basis of risk and apply this information for identification and management of high risk groups
2. Develop new agents for melanoma prevention including topical or oral compounds for high-risk groups

Diagnosis and Staging

3. Develop a more accurate, molecularly-based staging system for melanoma
4. Design new imaging agents for detection and staging of metastatic melanoma, including new PET agents
5. Support a centralized, large-scale effort to extract and map molecular data from melanoma cell lines and tumor samples to clinical outcomes, in order to identify new prognostic and therapeutic targets and to optimize current therapies
6. Identify prognostic biomarkers for patients with Stage I – IIIA melanoma to guide clinical management
7. Develop serologic biomarkers to detect early stage melanoma

Treatment

8. Increase melanoma cures via combination therapy, precision medicine and/or earlier treatment
9. Define logical and optimal combinations and optimal usage of drugs via proper pharmacological studies expected to lead to better outcomes and/or curtail resistance
10. Study 'exceptional cases' to provide new insights and markers of response and resistance
11. Study the microenvironment and immunological makeup of melanoma to support new targets and new treatments
12. Broker innovations that improve trial speed and efficiency e.g.
    a. change the patient and/or medical center culture to support more trials
    b. promote the collection/sharing of biopsies
    c. encourage harmonization of data collection and broker cross-company collaboration
13. Define biomarkers of early response, resistance and risk to facilitate speed of clinical development and patient selection for treatment and trials
14. Improve the outcomes for patients with brain metastases via parallel preclinical/clinical studies leading to effective prevention/treatment
15. Support continued work towards a molecular taxonomy of cutaneous melanoma subtypes as well as already recognized subtypes such as acral, uveal, etc.
16. Identify new targets and treatment modalities for melanomas that are not well-managed by existing or emerging therapies

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Introduction

Purpose of the White Paper

The Melanoma Research Alliance (MRA) updated its Scientific Strategy in November 2013 in light of the rapidly evolving melanoma clinical and research landscape. The purpose of this update was to define areas of focus for the coming three to five years that will advance MRA's mission to eliminate suffering and death due to melanoma. MRA's Scientific Advisory Panel and a select group of additional thought leaders comprising academic and industry experts along with MRA Board and staff leadership provided input to the Scientific Strategy. This White Paper documents the purpose, participants, and process underlying the 2013 update of the MRA Scientific Strategy and the results of the planning.

Background

MRA Overview

The Melanoma Research Alliance (MRA) is a public charity formed in 2007 whose mission is to eliminate suffering and death due to melanoma. MRA research awards fulfill this core mission by providing an important and unique source of funds to advance scientific discoveries into tools and treatments for patients. Since its founding, the organization has committed more than $51 million and leveraged an additional $47 million to fuel the pace of melanoma research. MRA is the largest private funder of melanoma research, catalyzing transformative, strategic, and collaborative investments in scientific discovery and translation. The types of awards funded by MRA are summarized below:

Young Investigator Awards: This program aims to attract early career scientists with novel ideas into melanoma research, thereby recruiting and supporting the next generation of

melanoma researchers.

Pilot Awards: Proposals test potentially transformative ideas that do not have extensive preliminary data but articulate a clear hypothesis and translational goals..

Established Investigator Awards: The Established Investigator Award program supports senior investigators with an established record of scientific productivity and accomplishment and who are past the initial four years of their first academic faculty appointment.

Team Science Awards: The Team Science Award Program is the centerpiece of the MRA research funding portfolio. Multidisciplinary teams consist of Principal Investigators with complementary expertise

Academic-Industry Partnership Awards: Designed to facilitate interactions between the academic and industrial research sectors, these were introduced in 2011 and are co-funded by MRA and an industrial collaborator whose involvement is essential to the project. This program is open to Established Investigators and Research Teams.

A world-class Grant Review Committee evaluates research proposals and recommends to the MRA Board research for funding that has outstanding scientific merit, pursues innovative research using novel approaches, and offers the potential for developments that could lead to high impact, near-term clinical application in areas of melanoma prevention, diagnosis, staging, and treatment.

Historically, treatment options for patients with metastatic melanoma have been severely limited, but recent advances have considerably changed the landscape. In 2011, two new drugs were approved by the FDA for metastatic melanoma, ipilimumab and vemurafenib, providing the proof-of-concept for use of immunotherapy as well as targeted therapy in metastatic melanoma in addition to the use of molecular diagnostics to select melanoma patients eligible for BRAF inhibitor therapy. Progress in treatment has continued with the

2013 approval of two additional drugs for patients with BRAF mutations, trametinib and dabrafenib and the combination of these two in 2014.

While these newly approved drugs alone will not cure most patients (although a small subset of patients have experienced longer term durable benefit from them), they establish the foundation for new, more successful approaches. Moreover, genomics studies have revealed a large number of drug targets for melanoma that offer significant opportunity to avert or treat drug resistant disease as well as for personalized medical approaches. As a result, there is unprecedented transformational progress on behalf of patients highlighted by the more than 100 new melanoma drugs in the pipeline, with nearly 300 clinical trials underway.

Through MRA's global research grant portfolio and extensive contacts with academia, industry and government, the organization continues to be the field leader in spurring advances for patients, accelerating progress from bench to clinical trials to bedside.

Purpose and Objectives of the Project

MRA focuses its efforts to create and build on opportunities that accelerate progress in melanoma. A key guiding source for this goal is the MRA Scientific Strategy. In 2007, MRA was established with an initial Call to Action to guide its scientific activities, and 17 key scientific and clinical questions were identified. At that time, no new drug had been approved by FDA for melanoma in nearly a decade.

The MRA Scientific Strategy was updated in 2011 - the same year during which the immunotherapeutic ipilimumab and the BRAF inhibitor vemurafenib garnered FDA approval. i Analysis of MRA's research portfolio showed that the majority of these 17 areas were being robustly addressed through its grants program. This strategy update identified 16 key questions as a focus for MRA and was intended as a five-year plan.

The evolution of the melanoma field continues apace. In 2013, two new drugs were granted approval: the BRAF and MEK inhibitors dabrafenib and trametinib, respectively, and promising clinical results have been reported for new immuotherapeutic anti-PD1 antibodies, nivolumab and MK-3475. Other innovative treatments are under study and cutting-edge research continues. Not only has the melanoma treatment and research landscape evolved dramatically, so too have the capabilities of MRA.

In consideration of this change, the MRA therefore undertook a 2013 evaluation of its Scientific Strategy in the context of the evolution of the environment to maximize the results of its scientific programming for the coming three to five years. This update focused on scientific and clinical aspects of developing new treatments for patients with metastatic melanoma due to the rapidly changing landscape in drug development. Prevention, early diagnosis, and staging are also important areas for MRA's mission and are being addressed in separate activities.

Process / Methodology

Introduction

To assess the current state of melanoma research, challenges and opportunities, a series of interviews were undertaken with thought leaders from academia as well as the for-profit and non-profit sectors. A number of key findings emerged that were discussed in an in-depth face-to-face meeting of the MRA Scientific Advisory Panel along with MRA's Board of Directors Science Planning Committee. Arising from this work, a core set of scientific questions emerged as high priority areas for the future.

Participants

For this update, MRA scientific staff interviewed 20 individuals, mainly PhD and MD researchers, across the spectrum of preclinical and clinical research representing academia as well as the non-profit and for-profit sectors (Table 1). Most of those interviewed are either members of MRA's Scientific Advisory Panel, Grant Review Committee, or Medical Advisory Panel. Additional participants provided input from the vantage of other non-profits in the health research space, pharmaceutical drug development and the field of myeloma which has undergone a transformational change akin to that shaping melanoma care today.

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Table 1.

Interviewees

1. Jeff Allen, Friends of Cancer Research
2. Kenneth Anderson, Dana-Farber Cancer Institute
3. Margaret Anderson, FasterCures
4. Christopher Austin*, National Center for Advancing Translational Sciences
5. Boris Bastian*, University of California, San Francisco
6. Paul Billings*, Life Technologies
7. Gideon Bollag*, Plexxikon
8. Paul Chapman***, Memorial Sloan-Kettering Cancer Center
9. Lynda Chin*, University of Texas, MD Anderson Cancer Center
10. Richard Gaynor*, Eli Lilly
11. Michael Giordano*, Bristol-Myers Squibb
12. Kris Grzegorzewski, Novartis
13. Jeffrey Legos*, GlaxoSmithKline
14. Kim Margolin**, University of Washington
15. Neal Rosen*, Memorial Sloan-Kettering Cancer Center
16. Ellen Sigal*, Friends of Cancer Research
17. Elliott Sigal*, MRA Board of Directors
18. David Solit**, Memorial Sloan-Kettering Cancer Center
19. Steven Stein*, Novartis
20. Michael Weber*, University of Virginia

*MRA Scientific Advisory Panel
**Grant Review Committtee
***Medical Advisory Panel

One-on-One Interviews

Between September and November 2013, telephone interviews were conducted by the MRA Chief Science Officer, Scientific Program Director and Scientific Program Manager with the MRA Scientific Advisory panel and additional experts.

Interviewees were asked to:

1. Describe the current environment and future (5 to 10-year) outlook for melanoma and cancer, in general, considering additional factors that might influence the environment such as changes in technology, policy, etc.
2. Summarize and prioritize the challenges to success in the elimination of melanoma suffering/death and potential solutions to overcome them.
3. Describe the most important role(s) for MRA now and in the future.

With the permission of the interviewee, the interviews were recorded and transcripts prepared to document the feedback for future reference.

From these interviews, an extensive list of needs and perceived areas of promise was generated.

Key Findings

Initial Analysis

Aggregated results from the interviews fell into two areas.

1. **Clinical and Correlative Science**
   - Improving Trial Speed and Efficiency, in particular, changing the patient and/or clinical center culture to support trials and biopsies
   - Expanding Treatments to Problematic Disease e.g. brain metastasis
   - Advancing Treatments to Earlier Stage Disease
   - Attaining Increasing Numbers of Functional Cures
   - Improving Benefit/Risk of Immunotherapy
   - Biomarkers of Risk, Early Response, Resistance
   - Defining Logical Combos, Sequences and Overcoming Resistance
   - Precision Medicine – Role of PDX models and Genomics
   - Defining Role for other Immunotherapies e.g. Vaccines, Adoptive Cell Therapy
   - Long-term Complications and/or Sequelae of Molecular Target "Cures"
2. **Preclinical and Translational Research**
   - Identifying New Targets and New Biology
   - Elucidating Means to Overcome or Prevent Treatment Resistance
   - Integrating Immuno- and Molecular Target Biology
   - Defining Logical Treatment Combos e.g. via Systems Biology
   - *Process improvements to increase sample collection/sharing/analysis*
   - *Preclinical modeling of difficult disease e.g. brain mets*

(*added in face to face discussion of November 20, 2014*)

There is recognized overlap and interaction between these two categories consistent with the translational emphasis of MRA. For example, biomarker analysis relies upon collecting and

analyzing clinical samples but may also yield new targets via preclinical study. Similarly, clinical approaches to overcome resistance or improved selection of drug combination, dose or schedule may benefit from preclinical studies and modeling. However, for the purpose of this strategy, this separation allowed for preclinical and clinical experts to separately explore the topics in detail. It is worth noting, too, that while MRA remains committed to activities in prevention, diagnosis and staging, these were not addressed in high detail by the Scientific Advisory Panel.

MRA Scientific Strategy Roundtable

On November 20, 2013 the MRA held the Scientific Strategy Meeting in Philadelphia, PA at the American Association for Cancer Research (AACR) offices after the close of the annual Society for Melanoma Research meeting. Attending the Scientific Strategy Meeting were many members of the MRA Scientific Advisory Panel, the chair of the Medical Advisory Panel, as well as one of the two co-chairs of the Grant Review Committee (Table 3). Additional participants included members of the MRA Board of Directors and Science Planning Committee along with MRA staff.

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Table 3

November 20, 2013

MRA Scientific Strategy Meeting Participants

MRA Advisors

1. Christopher Austin, NCATS (via phone)
2. Boris Bastian, University of California, San Francisco
3. Gideon Bollag, Plexxikon
4. Paul Chapman, Memorial Sloan-Kettering Cancer Center, MAP Chair
5. Lynda Chin, University of Texas, MD Anderson Cancer Center (via phone)
6. Michael Giordano, Bristol-Myers Squibb
7. Jeffrey Legos, GlaxoSmithKline
8. Kim Margolin, University of Washington, GRC Co-Chair
9. Neal Rosen, Memorial Sloan-Kettering Cancer Center
10. Mace Rothenberg, Pfizer (via phone)
11. Ellen Sigal, Friends of Cancer Research (via phone)
12. Steven Stein, Novartis
13. Suzanne Topalian, Johns Hopkins Medical School, SAP Chair
14. Michael Weber, University of Virginia

MRA Board of Directors Science Planning Committee

1. Debra Black, Board Chair
2. Ellen Davis
3. Jeffrey Rowbottom
4. Elliott Sigal
5. Jonathan Simons (via phone)

MRA Staff

1. Laura Brockway-Lunardi
2. Alexandra Carney
3. Louise Perkins
4. Wendy Selig, President and CEO

The discussion began with an overview of MRA activities, research funding and results to-date. This was followed by a review of the process of collecting information and a summarization of the key themes prior to the meeting. During this session, the themes identified in the interviews were refined by the addition of the topics in italics in Table 2, above.

To facilitate discussion, separate pre-clinical and clinical Working Groups were convened and were asked to:

1. Review challenges and prioritize the most pressing ones facing melanoma in the near and longer term.
2. Describe two to three actionable programs for MRA that overcome critical challenges.
3. Report findings to group for overall discussion and prioritization.

Board members remained with the Clinical and Correlative Science working groups. When the participants reconvened, the Working Group chairs (Michael Weber, Preclinical and Jeffrey Legos, Clinical) delivered a presentation summarizing the group's output that was followed by vigorous discussion by all attendees.

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Prioritization of Projects

Overview

Arising from the Scientific Strategy meeting and subsequent discussion, the strategic priorities are summarized here at a high level:

- Fund a portfolio of research with intent to cure ever greater numbers of patients and a focus on early treatments for high-risk melanoma
- Improve trial efficiency and accessibility to clinical samples for study: engage with patients and aim for a culture in which most melanoma patients participate in clinical research.
- Fuel the development of new discoveries via sharing and utilization of cross-institutional data and samples from multiple companies, research centers and/or from completed clinical trials
- Ensure the availability of cohorts of melanoma patients, samples and data across stages of disease to identify contextual drivers that act with primary drivers in the era of modern therapy
- Maintain urgency within pharma for, and a regulatory and research environment that encourages, approval of new melanoma treatments in an era of ever more approvals
- Increase melanoma cures via combination therapy, precision medicine and/or earlier treatment
- Define logical and optimal combinations and optimal usage of drugs via proper pharmacological studies expected to lead to better outcomes and/or curtail resistance
- Study ‘exceptional cases’ to provide new insights and markers of response and resistance
- Study the microenvironment and immunological makeup of melanoma to support new targets and new treatments
- Broker innovations that improve trial speed and efficiency e.g.
    - change the patient and/or medical center culture to support more trials
    - promote the collection/sharing of biopsies

  - encourage harmonization of data collection
  - broker cross-company collaboration

- Define biomarkers of early response, resistance and risk to facilitate speed of clinical development and patient selection for treatment and trials

- Improve the outcomes for patients with brain metastases via parallel preclinical/clinical studies leading to effective prevention/treatment

- Support continued work towards a molecular taxonomy of cutaneous melanoma subtypes as well as already recognized subtypes such as acral, uveal, etc.

The approaches described above are expected to lead to marked improvements in the outcomes for patients.

Unfortunately, not all of the objectives defined in this Scientific Strategy planning may be pursued simultaneously given MRA's resources and limitations of technology and funding within the research community. Thus, prioritization remains important. Meanwhile, a first step towards this has been undertaken with the integration of these objectives into this MRA Strategic Research Plan (Appendix) that encompasses not only the treatment arena explored fully above as well as prevention and diagnosis/staging. This updated MRA Strategic Research Plan provides key objectives to be addressed in the 2014-2017 MRA Strategic Plan.

Integration with MRA Strategic Plan

The output from the Scientific Strategy was refined through internal discussions and communications with the MRA Staff and Board of Directors. Based upon the input of the advisors at the Scientific Strategy meeting, a series of priority areas were drafted by the MRA scientific staff for implementation in the 2014 – 2017 MRA Strategic Plan.

Conclusion

This current update to the MRA Strategic Research Plan (Appendix) provides a robust guide to assist MRA for the coming three to five years. However, it must be noted that the major changes in treatment that are taking place in melanoma and the concomitant evolution of the entire field will continue to shape the MRA's research efforts in the coming years. This is an exciting and dynamic time in melanoma research, and MRA expects the need to adapt and fund the scientific programming necessary to continue to drive advancements as we move steadily towards eliminating melanoma.

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Appendix
2014-2017 MRA Strategic Research Plan

Prevention

1. Further elucidate the genetic basis of risk and apply this information for identification and management of high risk groups
2. Develop new agents for melanoma prevention including topical or oral compounds for high-risk groups

Diagnosis and Staging

3. Develop a more accurate, molecularly-based staging system for melanoma
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25. Identify new targets and treatment modalities for melanomas that are not well-managed by existing or emerging therapies