WORKING
PAPER

Description of Dr. Miriam and Sheldon G. Adelson Medical Research Foundation Collaborative Research Model

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HEALTH

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SUMMARY

BACKGROUND

In the second half of 2007, the Dr. Miriam and Sheldon G. Adelson Medical Research Foundation (AMRF) asked RAND to examine the collaborative model that the Foundation is using to fund medical research. The intent was to: (1) describe the AMRF model and how it works; (2) examine how the AMRF seeks to achieve quality; (3) investigate the AMRF's plans for scale-up; and (4) consider how to measure the AMRF's progress and success.

The AMRF wished to make explicit its model for generating knowledge and provide both insight into the more subtle aspects of the model and clarify how it differs from other sources of research funding and other more conventional strategies for promoting translational medical research. To this end, we have intentionally chosen to write for two readerships: (1) other organizations and foundations that may wish to replicate the model; and (2) scientists who may eventually participate in one of the AMRF's programs.

This document should not be considered an evaluation nor an endorsement of the AMRF model. Rather, RAND's primary task was to make explicit how the AMRF model is designed to work and how the AMRF sees itself as being unique from other mechanisms of research funding. To what degree the AMRF model is more effective at generating new knowledge is an open question that remains to be answered through a more systematic analysis.

METHODS

We used a multi-stakeholder, multi-method case study design to describe the AMRF model of collaborative research. We relied on: (a) semi-structured phone interviews with 25 selected collaborating scientists; (b) multiple face-to-face interviews with all the senior AMRF staff; (c) observations and informal discussions with participants during the AMRF conference held in Las Vegas from March 24th – 29th, 2008; and (d) reviews of multiple AMRF documents (e.g., reports, presentations, glossary, etc.). After analyzing the multiple sources of data, we presented our preliminary synthesis to members of the AMRF administrators and staff. The feedback we obtained has been incorporated into this final report.

THE AMRF MODEL

Since its formation in 2006, the AMRF has rapidly evolved and expanded in terms of its organizational structures, development of its collaborative model for research, its breadth of research interests, and the number of participants. Although the model is likely to undergo further adaptations, its primary features are well established and make it distinct from other models for funding medical research.

The AMRF model was motivated by perceived flaws in the current research system.

The impetus for the AMRF model came in part from a simple question asked by the founders: Why – with all our medical knowledge, well trained researchers, technological advances, and public and private funding resources – does it take us so long to discover medical solutions for common medical problems? On closer inspection, the AMRF founders identified what they considered to be key shortcoming in the current mechanisms for fostering medical research. First, they felt that many public and private funding agencies and foundations focused on short-term discoveries rather than on the long-term goal of developing medical therapies and treatments. Second, they sensed that there was a strong tendency among funding agencies and foundations to compartmentalize their efforts along disease-specific lines thus making it more difficult to fund research related to systemic biological pathways and mechanism that are similar across diseases. Third, the AMRF founders felt that many agencies and foundations were more likely to fund theoretically well-supported but low-risk proposals than they were to fund more exploratory and high-risk proposals. Fourth, the AMRF founders were struck by how little collaboration they found among researchers and laboratories. By not collaborating, they felt that researchers lost the opportunity to draw on a much wider range of expertise that might enhance and accelerate the discovery process. And finally, the founders felt that most funding agencies – particularly public ones like the National Institutes of Health (NIH) – were overly bureaucratic and slow and made it difficult for researchers to quickly pursue new promising avenues of work once they made important breakthroughs. It was in response to these multiple challenges that the idea for the AMRF model was born.

The production processes matters.

What separates the AMRF model from other models seeking to generate medical knowledge is the recognition that the production process matters. The AMRF has incorporated into its model the belief that *how research is organized* affects *what* is produced, *how much* is produced and *at what rate*.

Collaboration is at the core of the AMRF model.

At its core, the AMRF believes that the only efficient way to make significant strategic advances in knowledge is through fostering and supporting open, scientific collaborations. The AMRF model is based on the conviction that collaborative research will generate *more* medical knowledge and therapies, *more robust* scientific breakthroughs, and *at a faster rate* than traditional research models carried out by single individuals or laboratories. Furthermore, the AMRF argues that such collaborative research will be even more productive if: (a) the research focuses on broad areas rather than single diseases; (b) the collaborations are interdisciplinary and cross-institutional; and (c) the collaborative research is supported with timely, responsive and adequate funding and resources.

Collaboration is more than just getting people to work together.

For the AMRF, collaboration is a process that includes three or more entities (e.g., scientists, laboratories, clinics, etc.) working together (e.g., engaged in a set of activities) toward shared purposes/goals within a particular environment. The AMRF believes that the strength of the model comes from not only helping researchers to work together, but getting them to work together for a shared purpose and to reach a real set of tangible goals. For the AMRF, these goals are to: (a) find common denominators across diseases in their genes, cells, molecules and pathways; and (b) ultimately develop therapies and interventions that will improve the human condition. The AMRF tries to leverage the capacity of existing laboratories, tools, and especially intellectual power with additional incentives to create much more than the sum of these parts.

The AMRF model seeks to enhance all aspects of collaborations.

The AMRF model is intentionally designed to foster all aspects of collaborations and their development. This includes, but is not limited to:

1. Establishing initial collaborations in key programmatic areas by:
    - Identifying potential collaborators
    - Providing opportunities for collaborators to initially interact

- Offering incentives (and removing barriers) for collaboration
- Guiding (without dictating) collaborative objectives
- Increasing the potential for success through peer-driven reviews

2. Strengthening and expanding existing collaborations by:
   - Facilitating more frequent and intense interactions among collaborators
   - Assisting in expanding and modifying the pool of potential collaborators
   - Reevaluating each collaboration's objectives and work plans annually
   - Expanding collaborative agendas quickly based on new findings
3. Maximizing the impacts of successful collaborations by:
   - Supporting the dissemination of collaborative products
   - Assisting with issues of intellectual property

The AMRF model consists of a series of ordered steps.

These include:

1. ***Establish research programs*:** Initiated by the trustees or the AMRF staff, programs provide a general set of research objectives for researchers to target (i.e., the regeneration of nerve cells).
2. ***Recruit a cadre of multi-disciplinary scientists*:** The AMRF staff members recruit a Program Director and then work with the Program Director to identify and recruit a diverse team of highly productive researchers.
3. ***Bring the group together to:***
   a. ***Develop a programmatic research agenda*:** With general but regular guidance from the Foundation's Scientific Officer, researchers and program director set a research agenda designed to reach short and long-term program goals.
   b. ***Facilitate the generation of collaborations*:** The Foundation provides opportunities and incentives for researchers to meet each other, share ideas, and form collaborations.
4. ***Evaluate and prioritize proposed collaborations*:** The Foundation has a short application procedure and a relatively quick, multi-level review process for evaluating and prioritizing collaborative proposals.
5. ***Support ongoing research activities*:** The Foundation provides additional research support through research platforms and shared services, and facilitates the interaction of researchers through face-to-face meetings and web-based seminars.
6. ***Promote the dissemination of findings within and outside the program*:**

7. *Help make the program responsive to new knowledge and needs*:

The AMRF both incubates and insulates collaborative research.

As a foundation, the AMRF tries to play two fundamental roles in fostering collaborative research. First, the AMRF acts as an incubator of research. In this role, the Foundation selects programs, recruits collaborating scientists, creates an environment that fosters interaction and open exchanges of ideas, facilitates the development of research agendas and proposals, supports research activities through funding and technical assistance, and aids in disseminating new ideas inside and outside the AMRF community. Second, the AMRF acts as an insulator to reduce the burden on researchers. In this role, the Foundation facilitates and simplifies non-research tasks so that investigators can dedicate more of their time and energy toward the discovery process. For example, the AMRF has established master agreements by which AMRF can more easily negotiate contract and intellectual property rights with each researcher's university or institute. The AMRF also provides researchers with services such as video-conferencing and bioinformatics, and has made internal review processes less burdensome.

The AMRF model tries to address the uncertainty of discovery by structuring it.

The chasm between current research-derived knowledge and therapies and evidence-based medical interventions is wrought with uncertainty on two levels: (1) What kinds of things do we think we need to know to reach our goal?; and (2) What kinds of research do we need to do to learn these things? To address these uncertainties, the AMRF model insists that each of its 6 current research programs (e.g., Neural Repair and Rehabilitation, Cancer Research, Immunological Diseases, Inflammatory Bowel Diseases, Neurodegenerative Disease and Drug Abuse) propose a series of research milestones that will result in the desired outcomes and then develops clear research agendas to reach each milestone. When taken together, milestones represent a kind of scientific roadmap for how one might logically progress from current knowledge to the long-term, desired outcomes. One of the core functions of the collaborating scientists in each program is to work together to propose an intellectual course through this unknown territory. Once the group has established such set of pathways, then its next task is to develop a general research strategy for reaching each of the proposed milestones in as efficient a manner as possible.

The AMRF model is designed to increase the speed of knowledge discovery

The AMRF believes that the speed of discovery, in part, depends on how quickly researchers can: (a) make choices about where to explore next; (b) secure appropriate funding; (c) perform the required research tasks; and (d) disseminate their findings. The AMRF has tried to strategically to establish mechanisms on all four fronts that should theoretically increase the speed of discovery.

First, the AMRF has intentionally switched its expectations of success from "the discovery of new knowledge" to "the progression toward a solution to real problems". The goal is not to make small, carefully planned, incremental steps toward knowledge generation, but rather to make bold, strategic moves toward reaching a set of explicit objectives and milestones. Second, the AMRF model attempts to reduce the amount of time it takes to submit a proposal, have it peer-reviewed, and receive the funding to start research, to approximately 3 to 4 months (in contrast with the typical 2 years at the NIH). Third, the AMRF has worked to reduce the time it takes researchers to complete defined stages in their research, primarily though supporting strategic divisions of labor via collaborations and shared services. Finally, the AMRF has invested to facilitate the distribution of its findings within and between its research programs. The AMRF believes that making results readily available to other researchers fuels the generation of new ideas and speeds up the decision-making process of what to explore next.

The AMRF model is specifically designed to be nimble and flexible.

When working in such an uncertain discovery environment, the ARMF believes that it is critical that a program has the ability to synthesize new information quickly, reassess its current milestones and research strategies and redirect its efforts as quickly and effectively as possible. To promote these capacities, the AMRF has invested a great deal of resources into ensuring that collaborating scientists are continually interacting with each other within and across programs. Information is exchanged on a continuous basis through unstructured (e.g., phone and email) and structured exchanges (e.g., *webinars* and semi-annual face-to-face meetings). At the semi-annual meetings, collaborating scientists associated with each of the research programs discuss their current progress and what kinds of new directions they need to pursue. In addition, participants have the opportunity to hear about finding from other relevant programs and to learn more about new methodologies and techniques from the shared platforms. These ideas are subsequently incorporated in the next round of proposals. Further, the AMRF insists that each project and collaboration be reevaluated on an annual basis to

ensure that: (a) new knowledge has been incorporated into the research agenda; and (b) research remains focused on reaching appropriate agreed-on milestones.

STRIVING TO ACHIEVE QUALITY

The AMRF has established a variety of mechanisms to help improve quality throughout the entire discovery process. In the early stages of a program's development, AMRF strives to identify, vet and recruit the most dynamic, highly qualified and collaborative scientists it can find. The AMRF then relies on a multidisciplinary team of researchers to identify robust and reasonable pathways toward long-term medical therapies, including: (1) establishing a set of realistic short-term milestones; and (2) developing research agendas for reaching each. The AMRF fully recognizes that discovery is not a linear process and expects each research program to continually adjust its direction and emphasis as new knowledge becomes available.

The AMRF relies on three mechanisms to help improve the quality of the research proposals it receives. First, AMRF provides multiple opportunities for researchers from diverse backgrounds to meet, share ideas, and generate new and interesting research proposals. Second, the AMRF model insists that all proposals be collaborative and involve researchers from multiple institutions. Third, the AMRF provides researchers with ready access to a wide array of technical expertise through its platforms and shared services.

The quality of research that is ultimately funded is driven by the AMRF's multi-layered evaluation system. The review process is explicitly designed to assess proposals on two fronts: high scientific quality and likelihood to drive the discovery process forward toward short and long-term objectives. The intent is to detect and eliminate poor science – that which is neither rigorous nor innovative – as early as possible in the process. More rigorous and innovative science is then further scrutinized to determine to what degree it is likely to contribute to moving the discovery process forward in significant ways. Those proposals that are unlikely to make significant contributions are eliminated in later stages of the process. Likewise, poor collaborators are soon left out of the process.

Finally, the AMRF model also has embedded a peer-based, quality control mechanism into how research is carried out. Funded researchers share their progress and findings during weekly web-based seminars. These seminars are designed to provide opportunities to receive feedback and suggestions on how the ongoing research

might be modified or improved. The findings and shared ideas are then incorporated into subsequent proposals.

FUTURE PLANS

As the AMRF begins to transition from a phase of building to one that is more operational, its model of collaborative research is likely to face new challenges, particularly in regards to increases in scale, efficiency and monitoring. For example, increases in the number and diversity of programs and participants are likely to require more oversight and resources to ensure that: (1) all new participants have the same understanding of how the model works; (2) on-going and new collaborations remain well integrated within and across programs; (3) research agendas remain directed toward the programs' short- and long-term objectives; and (4) highly collaborative researchers are protected from burnout and over-utilization.

Although the AMRF has spent considerable resources in anticipation of negotiating intellectual property rights and contracts with universities and other institutions, many of the more subtle issues are likely to arise only after negotiations begin and as intellectual products start to become available.

Upon entering this operational phase, it will be critical to establish mechanisms for monitoring the AMRF's performance, and evaluating its accomplishments. Establishing clear and transparent indicators for tracking performance will allow the AMRF to further fine-tune its model over the next several years and will be needed should the AMRF ever wants to show that its model is more effective than other models in promoting scientific discovery.

ACKNOWLEDGMENTS

RAND wants to acknowledge the contribution of all the researchers who are participating in the AMRF–supported programs, who gave us their time and shared with us their experiences to help us understand how the AMRF has helped them shape up their research.

Second, we want to acknowledge the generous collaboration of the AMRF leadership, who walked us step-by-step through the process that they have set up, and provided the supporting documentation to help us put together the big picture.

We would also like to thank our colleagues at the Dr. Miriam and Sheldon G. Adelson Medical Research Foundation for their thoughtful comments and suggestions. We are particularly appreciative of the time and energy that Dr. Bruce Dobkin, Steven Garfinkel, Francis G. Kern, David Beller, and Eric Shipp, and Marissa White contributed in reviewing multiple drafts of the protocol as well as preliminary drafts of our results.

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CHAPTER 1. INTRODUCTION

AIMS AND PURPOSE OF THIS STUDY

In the second half of 2007, the Dr. Miriam and Sheldon G. Adelson Medical Research Foundation (AMRF) asked RAND to conduct a case study of the collaborative model that the Foundation is using to fund medical research. The intent was to:

1. Describe the AMRF model and how it works
2. Examine how the AMRF seeks to achieve quality
3. Investigate the AMRF's plans for scale-up
4. Consider how to measure the AMRF's progress and success

The overall goal was to help the AMRF make explicit its model for generating knowledge and provide both insight into the model that may not be otherwise appreciated and try to articulate how the AMRF differs from other sources of research funding and other more conventional strategies for promoting translational medical research. To this end, we have intentionally chosen to write for two readerships: (1) other organizations and foundations that may wish to replicate the model; and (2) scientists who may eventually participate in one of the AMRF's programs.

This document should not be considered an evaluation nor an endorsement of the AMRF model. Rather, RAND's primary task was to make explicit how the AMRF model is designed to work and how the AMRF sees itself as being unique from other mechanisms of research funding. To what degree the AMRF model is more effective at generating new knowledge is an open question that remains to be answered through a more systematic analysis.

BACKGROUND

The Dr. Miriam and Sheldon G. Adelson Medical Research Foundation (AMRF) and its core programs – the Adelson Program in Neural Repair and Rehabilitation (APNRR), the Adelson Program in Cancer Research (APCR), the Adelson Program in Immunological Diseases (APID), the Adelson Program in Inflammatory Bowel Diseases (APIBD), the Adelson Program in Neurodegenerative Disease (APND), and the Adelson Program in Drug Abuse (APDA) – believe they are taking an innovative approach to the generation of new scientific knowledge. Through highly collaborative

interactions among basic and clinical scientists that aim to solve progress-limiting challenges, the search for common denominators across the biology of diseases, shared resources and data that enrich the activities of each component laboratory of the collaboration, and simplified funding processes, the AMRF aims to more rapidly find treatments for a range of diseases.

Founded in 2006 and still in its early phases of development, the AMRF has rapidly evolved and expanded in terms of its organizational structures, development of its model for research, its breadth of research interests, and the number of participants.

METHODS

We used a multi-stakeholder, multi-method case study design to describe the AMRF model of collaborative research. We relied on: (a) semi-structured phone interviews with 25 selected collaborating scientists; (b) multiple face-to-face interviews with all the senior AMRF staff; (c) observations and informal discussions with participants during the AMRF conference held in Las Vegas from March 24th – 29th, 2008; and (c) reviews of multiple AMRF documents (e.g., reports, presentations, glossary, etc.).

After analyzing the multiple sources of data, we presented our preliminary synthesis of the model to (members of the) AMRF administrators and staff. The feedback we obtained has been incorporated into this report.

LIMITATIONS

This study has several limitations. First, we purposefully chose to speak with a selected group of the AMRF staff and participating researchers whom we knew *a priori* might have different views of the AMRF model. Although we spoke with all the senior staff, not all the researchers who receive support from the AMRF were included in our interview sample, and we recognize that different responses may have been obtained had we expanded on our interviews.

Second, the AMRF is a relatively young foundation, with less than three years since its inception. The model that it has generated and used to fund medical research is an evolving one, and many of its features are being devised or modified over time as new programs are being initiated, and as new researchers are being included in the already on-going ones. Therefore, it is likely that a description like the one that we provide will change in the course of a few years as the Foundation continues to expand in terms of its organizational structures, its breadth of research interests and the number

of participants, and as results from the different programs that it supports reach the stages of publication and drug development.

ORGANIZATION OF THIS REPORT

The remainder of the report is organized as follows. In Chapter 2, we present the general framework that we adopted for assessing the AMRF model. Chapter 3 provides a description of the methodology that we applied, including the research design, sampling strategy, qualitative interview protocol, and analysis techniques. Chapter 4 provides a description of the AMRF model. In Chapter 5, we briefly examine how the AMRF model seeks to achieve quality. Chapter 6 describes the AMRF's plans for scale-up. Finally in Chapter 7, we consider how to measure the AMRF's progress and success in the future.

CHAPTER 2. A GENERAL FRAMEWORKS FOR DESCRIBING THE AMRF MODEL

RAND relied on a systems analysis framework to guide its investigation of Dr. Miriam and Sheldon G. Adelson Medical Research Foundation (AMRF) Collaborative Model. The framework is comprised of two key dimensions:

(a) fundamental components of well-organized systems; and

(b) core activities in the AMRF's collaborative model.

When combined, the two dimensions produce the grid shown in Table 2.1.

Table 2.1. General framework used for examining the AMRF collaborative model

Core AMRF Activities	**Components of Well Organized Systems**				
	Set Expectations	***Establish Roles***	***Create Incentives***	***Monitor & Evaluate Performance***	***Build Capacity***
Select Programs					
Recruit Participants					
Develop Research Agendas					
Generate Proposals					
Prioritize & Fund Proposals					
Support Research Activities					
Disseminate Research Findings					

The columns in Table 2.1 (i.e., the fundamental components of well organized systems) are derived from a variety of experiences we have had at RAND designing and implementing health and education-related reforms. Each represents activities that systems must achieve and align with each other to be successful. We summarize each below.

1. *Set expectations* including establishing where the organization wants to go in the short- and long-term (goals) and how it plans to get there (strategies).
2. *Establish roles* about who is doing what for what purpose. The responsibilities of the AMRF personnel as well as that of participating scientists should be included and should be clearly linked to goals and strategies.
3. *Create incentives* to motivate researchers and staff to comply with expectations. The more aligned the incentives are with expectations and responsibilities, the better.
4. *Monitor and evaluate the performance* of researchers and staff to ensure that they fulfill their responsibilities and further organizational expectations. Sophisticated systems go to great lengths to be transparent and fair and typically rely on multiple sources of information, and allow those being evaluated to not only participate in the process but to challenge the results.
5. *Build capacity* so researchers and staff can efficiently meet their responsibilities. For example, creating a supportive environment so researchers can more readily learn how to collaborate efficiently is particularly important in systems where different kinds of experts are needed to work together and the expectation is that they will continue to collaborate over time..

The rows in Table 2.1 represent the core activities that the AMRF and its participating scientists engage in to promote the generation of innovative scientific knowledge. A short description follows:

1. *Select programs* includes how particular programs (e.g., neural repair, inflammatory bowel disease, melanomas, etc.) are vetted and approved.
2. *Recruit participants* includes how participating scientists are identified, selected, vetted, and retained.
3. *Develop research agendas* includes how to select short and long-term research targets and strategies for obtaining them.
4. *Generate research proposals* includes how scientists form collaborations, formulate questions and develop research strategies that result in formal research proposals and how the Foundation fosters this process.
5. *Prioritize and fund proposals* includes the mechanisms for reviewing, evaluating, selecting and ultimately funding research.
6. *Support research activities* includes how the AMRF fosters research activities and collaborations once projects have been funded.

7. *Disseminate research findings* includes how the AMRF facilitates the dissemination of new ideas and discoveries and how finding are incorporated back into the programs' research agendas.

The framework outlined in Table 2.1 served multiple purposes in our inquiry into how the AMRF model functioned. First, it guided all our interviews with both the AMRF staff as well as with participating scientists, ensuring that we covered the full range of issues. Second, the framework helped us standardize our interviews so we were better able to compare and contrast the perspectives of the many different kinds of actors involved in the AMRF experience.

CHAPTER 3. METHODS

INTRODUCTION

To describe the AMRF's collaborative model of research, we used a multi-stakeholder, multi-method case study design. We conducted semi-structured phone and formal face-to-face interviews with the AMRF leaders and collaborating scientists; we attended the semi-annual AMRF conference held in Las Vegas from March 24th – 29th, 2008 where we observed participant presentations and interactions and conducted informal interviews; and we reviewed multiple AMRF documents and exchanges.

After assessing the multiple sources of data, we presented our preliminary synthesis to members of the AMRF administrators and staff. The feedback we obtained from this briefing has been incorporated into this final report.

DATA COLLECTION

We relied on three sources of data: semi-structured interviews; observations; and document reviews.

Semi-structured phone and face-to-face interviews

In total, we conducted 25 formal telephone interviews with collaborating scientists (15 before the March AMRF meeting and 10 afterwards). Scientists were purposefully selected from among the approximately 50 working in the Adelson Program in Neural Repair and Rehabilitation (APNeRR) and the Adelson Program in Cancer Research (APCaR) – two of the AMRF's longest running programs. We intentionally chose these programs because they had the most history and we expected researchers working in these programs would have the widest range of experiences with the AMRF. Within each program, we intentionally selected scientists with a range of disciplinary and methodological perspectives including basic scientists, clinicians and those providing more technical services such as genomics and proteomics. We also conducted multiple face-to-face interviews with all the senior AMRF staff. Interviews with staff were done one-on-one and in group format.

We used the framework described in Chapter 2 to guide all our interviews. The framework ensured that we covered the full range of topics and allowed us to make comparisons across interviewees. Within each topic area, open-ended questions were asked before close-ended questions so as not to bias an interviewee's answers. The

initial open-ended questions allowed researchers and respondents the opportunity to explore new leads and related topics, and these generated short personal narratives. Answers to such questions indicate the areas that are most important to respondents, which may, or may not, conform to our expectations. We also used standard nonspecific questions (e.g., "Anything else you can think of?", "Can you tell me more?") as well as specific probes such as verification and compare and contrast questions.

All phone interviews were audio-recorded and transcribed verbatim. Although we (Ryan and Martínez) did not audio tape the face-to-face interviews with staff, we took extensive notes and compared them afterwards.

Observations and informal interviews

We spent 5 days observing the AMRF conference in March of 2008. Over the course of a week, all of the AMRF research programs held their semi-annual 2 to 3-day overlapping meetings to share their results, discuss future program directions, and to begin to formulate the next round of collaborative research proposals. We attended the plenary sessions and split up to cover the breakout sessions. Our primary objective was to observe how scientists presented themselves and interacted with their peers to develop or pursue specific ideas. During breaks, cocktail hours and meals we engaged in impromptu conversations with a wide range of participants (both the AMRF staff and researchers). We were particularly interested in researcher's experiences with the AMRF and how these experiences had evolved over time. Since we were able to observe meetings of the various AMRF research programs, we were able to get an even wider flavor of how collaborations evolved and the role that different personalities played in guiding the process. During our observations, we took extensive notes and later audio-taped our debriefing sessions.

We also sat in on various conference calls that occurred before and after the conference, where smaller groups discussed their collaborations and participated as silent observers in several weekly video seminars. The purpose of these weekly video seminars was for researchers from each of the AMRF programs to share their most recent work with each other.

Document review

The AMRF staff provided us with a variety of internal documents, including internal reports, presentations, draft copies of glossary and policies and procedures. We were also included in email exchanges where researchers and staff discussed

collaborations as well as issues related to selecting new members and evaluating research proposals and program objectives.

DATA SYNTHESIS

To make sense of the overwhelming amount of interview, notes and documents, we entered the data into text management software (i.e., *Atlas/ti*) and then identified portions of text that were associated with particular topics from our framework. We then pulled the quotes from across our interviews and notes and used these to assess the range of responses and comments we had collected on each topical area. We then synthesized these into key points to describe how the AMRF model works and how collaborating scientists experience it.

To ensure that we had not misinterpreted our data, we presented our preliminary findings to the AMRF staff and solicited feedback from them. This feedback has been incorporated into this final report.

CHAPTER 4. DESCRIPTION OF THE AMRF MODEL

INTRODUCTION

Describing a complex model like that being implemented by the Dr. Miriam and Sheldon G. Adelson Medical Research Foundation (AMRF) presents multiple challenges. First, the model itself consists of a wide range of intents, policies and procedures, and individual and group behaviors. Second, the model is still in the process of development and continues to evolve and expand. Third, the model can be described from multiple (and sometimes contrasting) perspectives, including those of the Trustees, the Foundation staff and the participating scientists. And, finally, the model can be described at various levels of detail, ranging from the general to the specific.

To provide the description that follows, we have made some key and explicit decisions. First, we have intentionally chosen to write for two readerships: (1) other organizations and foundations that may wish to replicate the model; and (2) scientists who may eventually participate in one of the AMRF's research programs. Second, we have divided our description into three sections: (1) What was the model's impetus and what was it designed to improve? (2) What are the key components of the model and how do they work together in their "ideal" form? and (3) How does the model work in practice and how is it viewed by the participating researchers? We describe each below.

MOTIVATIONS FOR DEVELOPING THE AMRF MODEL

The impetus for the AMRF model came in part from a simple question asked by the founders: Why – with all our medical knowledge, well trained researchers, technological advances, and public and private funding resources – does it take us so long to discover medical solutions for common medical problems? On closer inspection, the AMRF founders identified what they considered to be key shortcoming in the current mechanisms for fostering medical research.

First, the founders felt that many public and private funding agencies and foundations were unable to keep their research portfolios focused on the long-term goal of developing medical therapies and treatments. Instead, the founders felt that agencies often emphasized the short-term goal of generating new medical knowledge without a clear strategy concerning how such incremental knowledge might lead to developing or improving medical treatments.

Second, they sensed that there was a strong tendency among funding agencies and foundations to compartmentalize their efforts along disease-specific lines. They heard from the researchers they spoke with that such divisions made it difficult to fund research on the more systemic biological pathways and mechanism that are similar across diseases.

Third, the AMRF founders felt that many agencies and foundations were overly narrow and conservative in the kinds of research proposals they funded. They observed that well-supported but low-risk proposals were more likely to be funded than were more exploratory and high-risk proposals. To the founders who were primarily interested in generating major scientific breakthroughs as quickly as possible, this approach seemed overly slow and plodding.

Fourth, the founders were struck by how little collaboration they observed among researchers and laboratories. Most researchers they spoke with saw themselves in competition with their colleagues and felt uneasy about sharing idea and data before (and sometimes even after) their findings were published. The founders felt that by not collaborating, researchers were unable to drawn on a much wider range of expertise that might enhance and accelerate the discovery process.

And finally, the founders felt that most funding agencies – particularly public ones like the National Institutes of Health (NIH) – were overly bureaucratic and slow. Researchers they spoke with complained of having to spend upwards of two years submitting multiple proposals to move their research agendas forward or often found it difficult to acquire funding quickly to pursue promising new avenues of work.

It was in response to these multiple perceived challenges that the idea for the AMRF model was born.

FUNDAMENTALS COMPONENTS OF THE AMRF MODEL

The AMRF is structured around its collaborative model of research. The AMRF provides a concise description of its philosophy and vision on its webpage:

> *The AMRF is a private foundation committed to a model of open and highly integrated collaboration among outstanding investigators who participate in goal-directed basic and clinical research to prevent, reduce or eliminate disabling and life-threatening illness (http://www.adelsonfoundation.org/AMRF/home.php).*

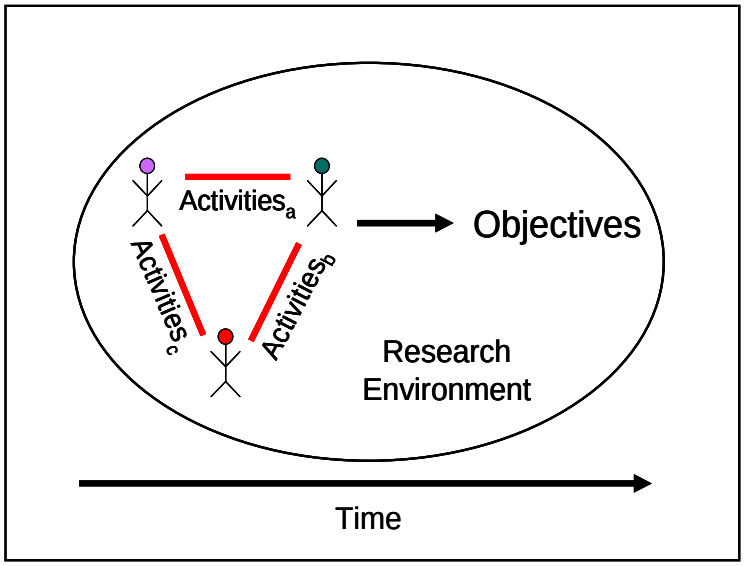
The Foundation's goals are to: (a) find common denominators across diseases in their genes, cells, molecules and pathways; and (b) ultimately develop therapies and

interventions that will improve the human condition. The AMRF explicitly states that it is not interested in focusing on disease-specific problems.

Collaboration is at the core of the AMRF model.

At its core, the AMRF believes that the only efficient way to make significant strategic advances in knowledge is through fostering and supporting open, scientific collaborations. By collaboration we mean a process whereby two or more entities work together (e.g., engage in a set of activities) toward shared purposes/goals within a particular environment (Figure 4.1). The AMRF model is based on the conviction that collaborative research will generate *more* medical knowledge and therapies, *more robust* scientific breakthroughs, and *at a faster rate* than traditional research models carried out by single individuals or laboratories. Furthermore, the AMRF argues that such collaborative research will be even more productive if: (a) the research focuses on broad, interrelated biological mechanisms of disease within and across its research programs rather than single diseases; (b) the collaborations are interdisciplinary and cross-institutional; and (c) the collaborative research is supported with timely, responsive and adequate funding and resources.

Figure 4.1. Key components of collaborations.



Program selection provides focus and direction for collaborations.

Within the AMRF, "programs" refer to working groups whose aims are to develop basic and clinical diagnostic and therapeutic approaches for biologically connected diseases through interactive meetings, presentations and papers and by providing a forum for the development of collaborations. Ideas for programs typically are initiated by the Foundation trustees or staff familiar with the Foundation's overall vision. Programs focus on common denominators across related diseases (e.g., gene expression in response to different brain pathologies or types of cancers), as well as on the development of therapies and interventions that will improve the human condition

(e.g., nerve cell regeneration). A fundamental criteria for establishing an AMRF programs is that the program must be amenable to a multi-disciplinary approach. The specific program objectives are determined by the group of participating scientists.

Currently, AMRF programs include: the Adelson Program in Cancer Research (APCR), that presently examines melanoma, ovarian, lymphoma and lung cancer tissue to find individualized targets for cures; the Adelson Program in Immunologic Diseases (APID) that has initially targeted Inflammatory Bowel Diseases (APIBD); the Adelson Program in Neural Repair and Rehabilitation (APNRR) that aims to regenerate cells and their connections in stroke, brain and spinal cord injury, multiple sclerosis, peripheral neuropathies, etc. and maximize training-induced gains via means that enhance learning and plasticity; and the Adelson Program in Neurodegenerative Diseases (APND) that examines mechanisms relevant to Parkinson's, Alzheimer's, frontotemporal dementias, amyotrophic lateral sclerosis, etc. The most recent program to be initiated is the Adelson Program in Drug Addiction (APDA).

Programs are composed of a group of synergetic collaborations.

Biomedical research is becoming more complex every year through the rapid increase in data that arises from new technologies and discoveries. The AMRF believes that one way to address this issue is to foster dynamic interactions among basic scientists at all levels including: genetic, molecular, pathway modulation, cellular, organ, pathological, physiological, imaging, behavioral, data management, and clinical trial design. In addition, the ARMF also believes that clinical scientists should provide feedback to basic scientists on the relevance of preclinical models of disease and potential therapeutic targets to better develop clinically relevant opportunities. The goal of the AMRF model is to help scientists merge ideas and experimental designs to maximize the ability to apply the results to patients whose impairments and disabilities are mimicked in experimental systems.

The AMRF model has established a formal set of mechanisms for fostering such multi-disciplinary collaborations. Once a program has been approved, the Foundation brings together 8 to 20 carefully recruited "collaborating scientists" from different institutions to identify and conduct a synergetic group of "collaborations" that, when taken together, address some of the core issues framed by the program. Thus, within each program there are multiple, but coordinated, collaborations. Each collaboration consists of at least 3 collaborating scientists from different institutions who have decided to work together. Each collaborating scientist is responsible for his or her own "component project" within the larger collaboration. Component projects may involve

multiple personnel associated with the collaborating scientist's laboratory or clinic. Each component project consists of a set of tasks and activities for which the collaborating scientist is responsible. Each program, collaboration, and project task has its own objectives and goals. The collaborating scientists determine the sequence, timing, scope and direction of the component projects, and the AMRF provides infrastructure and financial support to foster the collaborations and to protect and commercialize resulting biomedical innovation.

The AMRF believes that shared resources are a critical for fostering innovation.

The AMRF model believes that one of the most efficient ways to foster multi-disciplinary and innovative research is to reduce the cost and burden for researchers to engage in such activities. In talking to researchers, the AMRF found that one of the dilemmas faced by most laboratories is that in order to generate knowledge a lab needs to specialize, but in order to be innovative a lab needs to be able to access a wide array of expertise. The AMRF felt that one way of addressing this dilemma is to make specialized expertise readily available to all researchers in the form of shared platforms or core facilities.

In the AMRF model, methodological platforms and the scientists that run them provide a set of methods common to different programs. A platform is defined as a specialized kind of innovation tool that involves a methodology, biomedical skill or process, laboratory or other specialized medical service provided by one or more collaborating scientists, research team members or third-parties and funded by the Foundation to provide expertise to collaborations (e.g., electron microscopy, genomic array analysis, high throughput screens). In specific cases, researchers could propose to explore how to customize an existing platform to provide new applications for one or more programs.

The AMRF has invested (and continues to invest) in platforms related to: pre-clinical models, behavioral measures, gene arrays, proteomics, stem cells, bioinformatics, nanotherapy, imaging: structure and function, outcome measures, biomarkers, and clinical trial design. To this end, the scientists who oversee platforms have solved problems for those collaborating scientists who are in relatively small institutes where they do not have access to all the expertise they might need (nor can they afford to develop the expertise in their own labs). Even in large institutions, the ability to get access to experts within core facilities limits investigators.

The AMRF model calls for using such shared platforms or core facilities in a distinctly different way than most universities. The AMRF argues that universities typically only support core facilities in areas of high demand such as biostatistics and grants and contracts. The university strategy is to pay only for those shared platforms that maximally increase investigators' competitiveness (by lowering research costs and improving quality) at the lowest cost to the University. In contrast, the AMRF strategy is to provide exposure and access to such platforms, not only because researchers are demanding them, but also to encourage researchers to think more broadly about how they might use such expertise to expand their collaborative research agendas.

The AMRF model relies on multi-level decision-making processes.

The AMRF has embedded a quasi-consensual decision-making process within a more hierarchical structure. The AMRF (through its Trustees, Executive Director, Scientific Officers and Managers) makes decisions about what programs to initiate and establishes general goals for research programs. The Program Director and the Scientific Officer are primarily responsible for recruiting the initial cadre of collaborating scientists with input from the Executive Director and Scientific Managers. The specific research objectives and milestones are left for the collaborating scientists and the program director to work out through consensus, but the Foundation staff members are involved in the discussions and its Trustees retain the right to approve or disapprove these directions.

The AMRF model seeks to enhance all aspects of collaborations.

The AMRF model is intentionally designed to foster all aspects of collaborations and their development. This includes, but is not limited to:

1. Establishing initial collaborations in programmatic areas by:
   - Identifying potential collaborators
   - Providing opportunities for collaborators to initially interact
   - Offering incentives (and removing barriers) for collaboration
   - Guiding (without dictating) collaborative objectives
   - Increasing the potential for success through frequent and multiple levels of reviews

2. Strengthening and expanding existing collaborations by:
   - Facilitating more frequent and intense interactions among collaborators

- Assisting in modifying the number and composition of collaborators as programs evolve
- Encouraging the reevaluation of the collaborations' objectives and work plans by peers and Foundation staff
- Providing resources for expanding collaborative agendas based on new findings

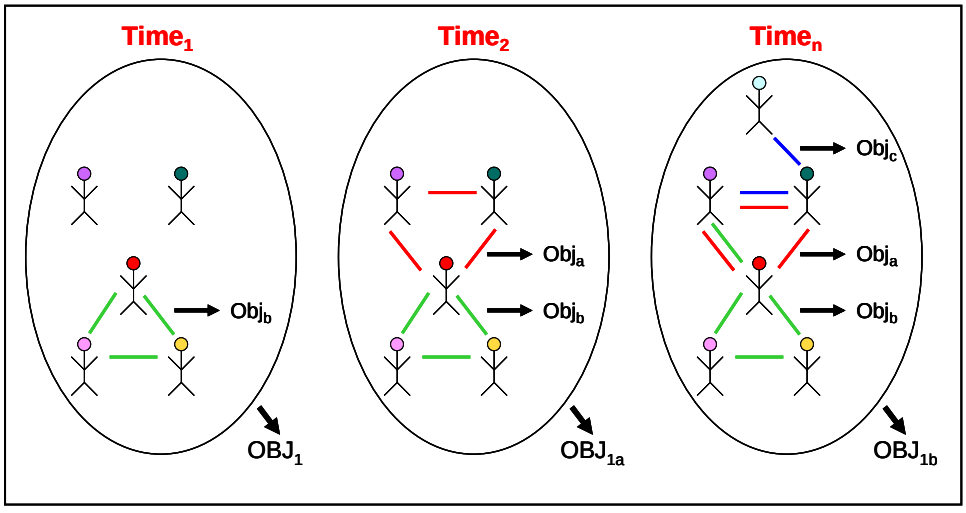
3. Maximizing the impacts of successful collaborations by:
   - Supporting the dissemination of collaborative products
   - Assisting with issues of intellectual property

The AMRF believes that collaborations must evolve and need support at all stages.

As shown in Figure 4.2, the AMRF model assumes that productive collaborations will evolve on a number of key dimensions including:

1. The number and expertise of the participating collaborators
2. The specific goals/objectives of the collaboration
3. The number and kinds of interactions between collaborators, where interactions might include the sharing of:
   - Intellectual ideas and insights
   - Empirical data
   - Methodological tools and techniques
   - Resources such as animal models, reagents, equipment, etc.
   - Labor through specialization

Figure 4.2. Evolution of collaborations over time.



Once collaborations have been initiated, the AMRF model has established formal and informal mechanisms through which it can respond and support the on-going needs of the various

collaborations. For example, the AMRF encourages existing collaborations to continuously reassess their short and long-term goals and objectives through its annual proposal renewal process. It also has established mechanisms so that a program's size and composition can be modified as required to address any new objectives. Finally, the Foundation has intentionally set out to be flexible in the kinds of collaborative activities it is prepared to fund, the amounts it will cover, and how quickly it can provide funding.

The ARMF believes that success occurs when research agendas are aligned with goals and objectives.

The AMRF recognizes that getting researchers to work together does not guarantee successful outcomes. Instead, they believe that success is more likely to be realized when goals/objectives are thoroughly aligned with research agendas. Table 4.1 describes: (a) who is responsible for establishing goals/objectives and research agendas at the program and collaboration levels; and (b) what mechanisms are in place to ensure that they are properly aligned. Success comes when: (a) goals/objectives are aligned with research agendas (left to right alignment); and (b) goals/objectives and research agendas of collaborations are aligned with goals/objectives and research agendas (bottom to top alignment).

Table 4.1. Alignment of goals and objectives with research agendas

Level	Goals & Objectives	Research Agenda
Programs	• Broad goals established by the AMRF on inception • Specific, short-term goals set by program participants and approved by the AMRF leadership	• Determined by program participants and approved by the AMRF leadership
"Collaborations" **(Must involve 3 or more labs)**	• Specific, short-term goals set by collaboration participants • Reviewed by peers, Executive Committee, Scientific Officers and Executive Director, and approved by Trustees	• Determined by collaboration participants • Reviewed by peers, Executive Committee, Scientific Officers and Executive Director, and approved by Trustees

The AMRF both incubates and insulates collaborative research.

As a foundation, the AMRF plays two fundamental roles in fostering collaborative research. First, the AMRF acts as an incubator of research. In this role, the Foundation selects programs, recruits collaborating scientists, creates an environment that fosters interaction and open exchanges of ideas, facilitates the development of research agendas and proposals, supports research activities through funding and technical assistance, and aids in disseminating new ideas inside and outside the AMRF community (described below). We refer to these kinds of activities as the Collaborative Research Role.

Second, the AMRF acts as an insulator to reduce the burden on researchers. In this role, the Foundation facilitates and simplifies non-research tasks so that investigators can dedicate more of their time and energy toward the discovery process. One of the key intentions has been to establish a Master Collaborative Research Agreement (MCRA) and a Discovery Management Agreement (DMA) by which AMRF can more easily negotiate contract and intellectual property rights with each collaborating scientist's university or institute. The AMRF believes that without such agreements, multi-site collaborations like those funded by the Foundation are likely to be slowed considerably. The Foundation also acts on behalf of its members by contracting for services as needed. For example, the AMRF has arranged to make web-based video conferencing accessible 24 hours a day so researchers can readily communicate and share information. It is developing computerized data acquisition and bioinformatics systems that every research program can use to manage complex sets of research data. To further reduce the burden on researchers, the Foundation has streamlined its grant application and review process and has simplified its funding and reimbursement mechanisms. We refer to these kinds of activities as the Foundation Support Role.

The AMRF believes that organizational commitment and staff involvement are critical to success.

The ARMF believes that for a model like this to be successful, the donors must have a strong commitment to and deep understanding of the unique processes of research discovery and translation. While the AMRF model strives to offer greater efficiency in the pursuit of more robust therapies than the usual incremental lab bench to clinic pathways that often take 15 years or more, the AMRF recognizes that biomedical research is still complex and filled with unforeseeable unknowns. The pace to therapies – even with the best minds that work together with the best new tools – is

not linear and may run into scientific barriers that take time to circumvent. For the AMRF or similar models to show tangible results will require trustees and donors funding such research to be patient.

In addition, the model also mandates that its scientific staff be highly involved in every aspect of the work of its funded scientists. The AMRF model of collaborative research is not one that can let investigators run and juggle balls without informed referees. The ARMF staff members play a nurturing role at every stage of program development and evolution to help focus the work on key milestones set by each collaboration and its respective research program, and always in the direction of opportunities for a therapeutic intervention.

THE AMRF MODEL IN PRACTICE

The AMRF performs seven key tasks to foster collaboration.

One way to describe the AMRF collaborative research model is to describe it as a series of core activities – all of which involve multiple layers of decision-making. These include:

1. Establishing research programs
2. Recruiting collaborating scientists
3. Assisting with the development of programmatic research agendas
4. Facilitating the generation of collaborations
5. Participating in the evaluation and prioritization of project proposals
6. Supporting research activities through technical assistance and centralized resources
7. Promoting the dissemination of collaborative products

We describe each in more detail below.

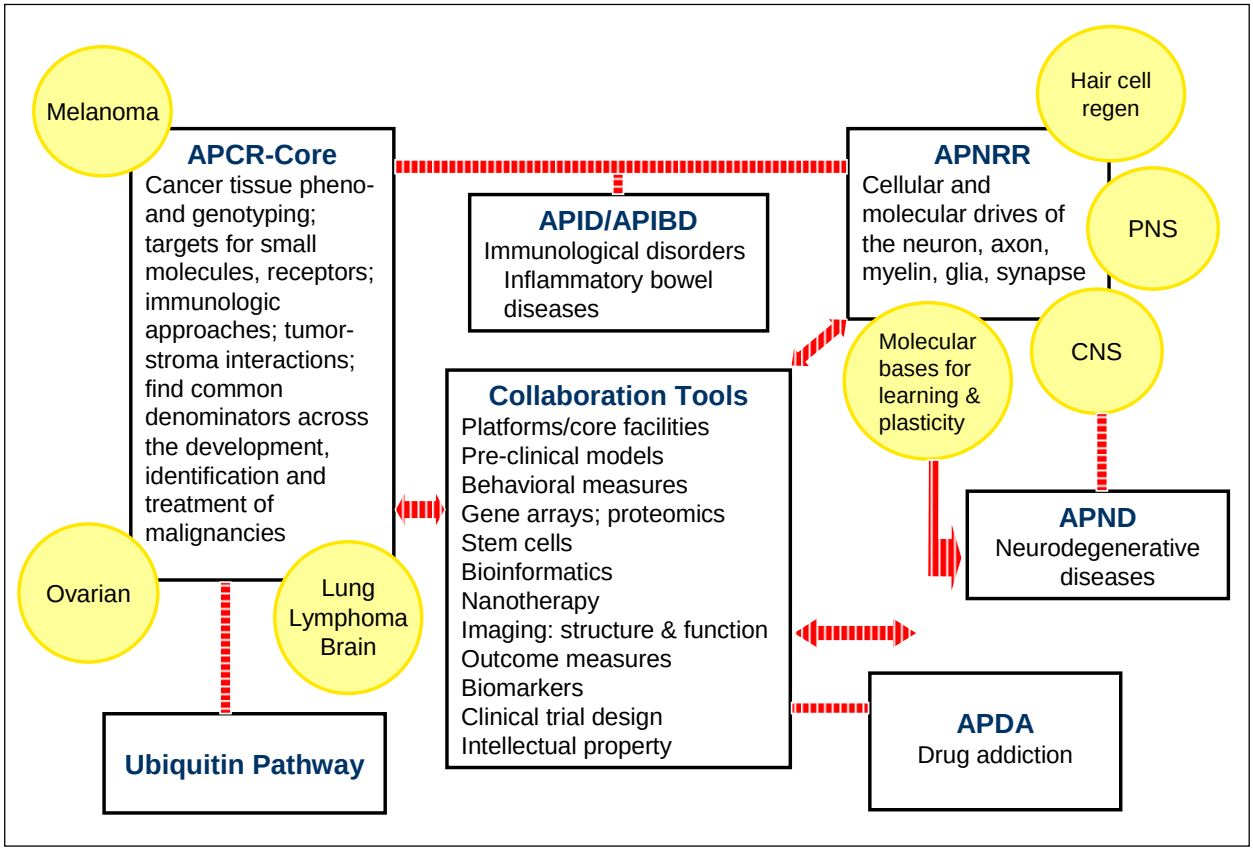
Program selection provides direction for subsequent collaborations.

Recommendations for programs typically are initiated by trustees or the AMRF staff familiar with the Foundation's overall vision. Programs typically focus on either: (a) common denominators across diseases (e.g., gene expression in cancer pathologies that are likely to share common master switches); or (b) the development of therapies and interventions that will improve the human condition (e.g., the regeneration of hair cells in the inner ear). To function within the AMRF model, new programs must be

amenable to a multi-disciplinary approach and increasingly must be able to be linked to existing programs.

Figure 4.3 shows some of the current set of the AMRF programs and key subgroups and their interfaces. For example, APCR (the Adelson Program in Cancer Research) and the Ubiquitin Pathway program share clear biological affinities with each other, as do APNRR (the Adelson Program in Neural Repair and Rehabilitation) and APND (the Adelson Program in Neural Degeneration). In addition, the genes and proteins that affect cancer cell growth (interventions aim to interfere with these pathways) often overlap with the developmental genes that APNRR investigators aim to upregulate to enable regeneration. Subgroups (represented by circles) can be primarily affiliated with a single program or can interface between multiple programs, like the Plasticitiy group across the APNRR and APND. At the heart of this network lie the Collaborative Tools which include platforms and core facitilites as well as methodological techniques. Individuals and labs that specialize in methodological techniques play a pivotal role in sharing information and ideas across substantive areas.

Figure 4.3. The AMRF programs and subgroups and their interactions.[1]



[1,] From AMRF presentation in Los Vegas, March 2008.

The topical focus of the program provides the general objectives for programs. Specific program objectives, however, are ultimately be determined by the collaborating scientists who are recruited into the program.

Programs typically begin with the recruitment of a Program Director.

The responsible Scientific Officers and Executive Director identify and recruit a Program Director for the new program. The primary considerations are that the Program Director has: (a) a broad and extensive knowledge and expertise in clinical and basic science in the program's area; and (b) the ability to work collaboratively and collegially with his or her peers. Ideally, both of these characteristics would be equally strong.

The primary role of the Program Director is twofold. The most immediate task is to work with the Scientific Officer to define in preliminary fashion the strategic focus of the new program, then identify and recruit initial collaborating scientists to the group. Once the group is established, the Program Director role (again in collaboration with the Scientific Officer) is to work with the collaborating scientists to develop the program's short and long-term research and clinically-oriented opportunities and objectives, as well as to make explicit the research strategies that the group will use to reach these objectives. The leadership roles taken by the Program Director and the Scientific Officer vary across programs and evolve over time. Indeed, the Program Director is not meant to be a permanent position. Another person from the program may assume this responsibility and commitment of time as the research agenda evolves.

A multi-disciplinary cadre of experts is recruited.

After selecting a Program Director, the next step is to assemble a cadre of collaborating scientists that bring a diverse portfolio of expertise and skill sets. Anywhere from 8 to 20 collaborating scientists are typically recruited in this initial stage. Members are identified primarily based on their knowledge and expertise in the program area but are also vetted (as best possible) for their ability to work collaboratively and congenially with peers and their willingness to work in areas in which they are less familiar. Developing a well-rounded team is a challenging task. Too much duplication in experience and skill sets is discouraged, but some overlap is useful to facilitate discussions. Once the collaborating scientists have been selected, their role is to work together to articulate short and long-term program objectives and design and carry out the research agendas required to meet these objectives

Leadership plays a critical role in the early phases of collaborative ventures.

Our observations and conversations with researchers and AMRF staff suggest that in unstructured environments, personality and style of formal and informal leaders often shape the dynamics and direction of the group. Formal leaders include Trustees, the Executive Director, Scientific Officers, Program Managers, and Program Directors. Each has a role to play in shaping a research program's general aims, as well as in selecting the cadre of collaborating scientists who will eventually participate. As the program evolves, however, informal intellectual or charismatic leaders are likely to arise from among the recruited collaborating scientists. Informal leaders play a key role in determining what kinds of research questions the program will pursue and how these questions will be addressed. Ultimately it is the combination of formal and informal leadership that guides a program forward.

Scientists weigh the risks and benefits when invited to join an AMRF program.

When first contacted by the Foundation, potential collaborating scientists typically reported they were both intrigued and skeptical. They reported being excited about new funding opportunities to support high risk or innovative research and review mechanisms that appeared less arduous and conservative than those utilized by the National Institutes of Health (NIH). Collaborating scientists readily identified clear distinctions between the way the NIH approached knowledge generation and the way the AMRF approached the issue. For example, one scientist remarked,

> *"Everybody knows that the most high-payoff research is high-risk research, but when times get tough financially, with the NIH funding the way it is now, you almost can't get that sort of work funded."*

Another scientist was even more expansive:

> *"We write grants to the NIH in a way that is completely artificial, and we have a very clear hypothesis which we're going to test. We design experiments to test it and if the hypothesis turns out to be wrong, we then make corrections and etc. But, in fact, that's not how science works. Science is much more like an amoeba. It's a mental probing. So, you have a little probe here and that turns out to be technically not feasible or, frankly wrong, and so you then put your efforts somewhere else. And so it's all this ongoing little bits of probing and then suddenly you find, wow, this direction is the one that at this particular moment with this technology and our knowledge, provides the very rapid movement."*

However, although some scientists were clearly interested in the potential for developing collaborations, many were uncertain that such an endeavor could work especially among peers they saw as competitors. As one research put it, "*My initial expectations were, basically, very low.*" Some were even quite distrustful and nervous about the prospects of sharing ideas and data. Another researcher noted, "*Usually by the time you're willing to present a story to your colleagues, you're well along the way, so you can feel relaxed that no one's going to try to reproduce it or start competing with you or use it in some way.*"

Scientists also reported being uncertain about the stability of the support the AMRF offered for long-term funding. Some were apprehensive that they would have to apply for funding on an annual basis, raising uncertainty in how they could run a lab that depended on supporting personnel over longer periods of time. A few others were uncertain how long a relatively new foundation like the AMRF, with a short track record, would continue to support medical research, and if the funding would quickly disappear. As researchers noted, a one-year funding cycle is quite short relative to usual 5-years worth of funding provided from by the NIH.

Overall, however, the benefits seemed to outweigh the risks and most researchers told us they were willing to at least come to a meeting to see what this new model was all about.

Initial program workshop is designed to foster early collaborations.

Before the initial program meeting, the Program Director and the Scientific Officer spend a great deal of time communicating with 8 to 20 invited scientists about what to expect. They hold smaller face-to-face or conference calls to prepare for the upcoming meeting including deciding who will be key speakers and how to organize the multiple breakout sessions.

Regardless of the time spent in preparation, however, the initial program meeting is an intense interactive event. The meeting is specifically organized to give scientists a chance to get to know each other, and to foster initial collaborations. Participants typically spend 2-3 days together, usually from 7 AM to 10 PM including breakfast, lunch and dinner. The AMRF staff members provide a brief overview of the Adelson Foundation and its vision, describe what is expected in terms of collaborative proposals and cover how the application process works. The Program Director also provides a preliminary outline of broad and long-range program objectives. Finally, each collaborating scientists briefly describe their own and their laboratory's or clinic's research.

The environments that such interdisciplinary workshops create are extremely stimulating for researchers. As one researcher noted,

> *This is fantastic. It brings me together with experts in the field that I wouldn't normally have an opportunity to interact with. So I view this as a fantastic mechanism to meet and talk with other investigators who can complement my work and hopefully whose work I can, in turn, complement.*

As a group, the collaborating scientists are responsible for two tasks. First, they need to work with the Program Director to articulate a program-specific research agenda, including answering key questions such as: Where do we want to go as a group? What are the most promising research paths to get there? What kind of time frame will be needed? What are reasonable milestones in the next 12 to 18 months?

Second, each of the collaborating scientists are expected to begin exploring the opportunities to collaborate with their peers. In some cases, collaborations are solidified during the meeting itself. In other cases, early tentative discussions are followed up via phone calls and e-mail after the meeting.

For collaborations to occur, issues of mistrust and uncertainty must be overcome. Most scientists reported some kind of initial concerns related to mistrust. They were leery of sharing novel unpublished insights with others and are unsure of what prevents others from stealing or scooping their stock in trade – "ideas." They were particularly sensitive in regards to sharing data. They were willing, however, to take risks. As one researcher described,

> *We sent them data that we had so they could analyze it. And suddenly [XX] mounted this on their common web page. And when we arrived at this meeting, he gave a little speech and he used us as an example and put our data out there in the public domain [LAUGHS]… for our entire field to see! Normally, we would have been more secretive about that, until we got it published because that's what … you know. But we figured, "What the hell. This is, you know, this is part of this crazy process that we're involved in. Well, let's see how it goes."*

Mistrust diminishes as sharing increases.

Our observations and conversations with scientists suggested that collaborating scientists distrust often dissipate quickly as collaborating scientists begin to share with each other. We were surprised at how quickly researchers were willing to put aside their initial concerns to begin to work together. Nearly every person we interviewed

offered at least one example of how others in the group provided important ideas, information or data that had been helpful for their own research. Examples ranged from small to large. One researcher recalled having a conversation about a particular technique he was thinking about using and another researcher volunteered that a post-doctorate fellow in his lab had that particular technique and found that it really didn't work but had never published on it. Instead the other researcher suggested an alternative strategy that might be tried. Another researcher recalled that,

> *We had one person who came to the meeting last fall … , and he presented some data and had some reagents that I thought would be really useful for my work, and I called him up immediately afterwards and he sent those to me, and then I called him and said, 'You know, we've got this result with it', and he spent an-hour-and-a-half discussing the results, looking a the data on slides that I'd sent him, and then opened up his freezer to me... 'I've got these reagents that I haven't published yet. You're welcome to them. Let me know what you get with them.' … That's fairly rare; exceptionally rare, and everything he gave us has answered questions."*

The AMRF model uses multiple incentives to promote collaborative relationships.

The AMRF offers researchers a number of incentives to participate in collaborative relationships. First, it provides access to research funding in addition to what is typically available through the NIH, universities, the pharmaceutical industry and other philanthropic foundations. Second, the AMRF offers researchers the chance to fund high-risk research proposals, namely those pursing exploratory ideas and hypothesis generation that offer the potential for major scientific breakthroughs. Third, it offers investigators the opportunity to interact with a collaborative network of multidisciplinary scientists. As members of such a "club", investigators have access to other well-recognized scientists with complementary skills and expertise and have access to shared resources (such as reagent and animal models) as well as data from other collaborative efforts. Fourth, the funding mechanism is flexible and timely, allowing investigators to request and receive needed resources quickly so as not to slow the research process. Fifth, the application process is relatively simple compared to more onerous and competitive processes required by the NIH and other funding mechanisms. And, finally, the AMRF model offers scientists the opportunity to share with their colleagues in the discovery process. As one researcher emphatically noted, "*the AMRF has made science fun again*."

One researcher summed up the general sentiment we heard repeatedly from participants:

"It is more than just the money. I mean, the money's great, don't get me wrong, because it means that we can do high-risk experiments that we could never do otherwise. So that's huge. Then, the second big thing is the collaborative aspect of it. You know, things are so specialized now in science that no one lab has ability in all possible techniques and so that has been a fantastic aspect of Adelson, that there's labs that have expertise in proteomic and labs that have expertise in genomics and there's labs that have expertise in how to make transgenic mice and they are core facilities and so forth. So people are sharing their knowledge and their expertise. This sort of interdisciplinary sharing is very synergistic, so that's been a huge aspect of it."

The AMRF model incentivizes collaboration primarily through its funding criteria.

The AMRF only funds collaborations. The Foundation insists that all collaborations consist of a minimum of 3 interactive project components (i.e., goals and tasks performed by collaborating scientists and their associated laboratories or clinics) and assumes that productive (and therefore fundable) collaborations will draw on multi-disciplinary and complementary methods and techniques. Further, the Foundation insists that all funded collaboration be explicitly linked to reaching the program's long-term objectives and milestones.

The requirements to work across typical research boundaries and to explicitly link each research collaboration with larger objectives are critical if the Foundation's vision is to be met – namely to find common denominators across diseases in their genes, cells, molecules and pathways and ultimately to develop therapies and interventions that will improve the human condition. The advantages of this collaborative approach are apparent to most participating scientists. As one notes,

What often happens is that basic scientists work on something that looks very promising, either in vitro or at some level, but they don't necessarily pursue that to the next level in going up the translational research ladder or towards, let's say, a rodent model or a larger mammalian model, or maybe to human clinical trials, because they don't know how to do it, and they don't have the resources. But within our group, we have people at every step of this process that know those bits and pieces.

Collaborations and project components are screened via an internal review process.

Each collaborating scientist submits a short, 5-page proposal via the Web describing the project component that he or she will oversee. The proposal covers the project component's aims, methods, expected outcomes and milestones, and budget. In

addition, the collaboration coordinator (for which the project component is a part) submits a short overview of how the collaboration will work and outlines the role that each project component will play.

All members of the program (with the exception of those directly involved with the collaboration) review each project component abstract and evaluate its appropriateness relative to the overall program and collaboration objectives. A selection of peers from the program then reviews in more detail each project component's aims, methods and budgets and confidentially scores each. An Executive Committee (EC) then reviews the aggregated scores, makes comments, and recommends funding levels. The Executive Director and appropriate Scientific Officer review EC findings and present recommendations to the Trustees. The Trustees in turn review the EC recommendations and make final decisions.

Unlike other review processes, like those at the NIH that typically rely on an outside panel of experts to evaluate each proposal's methodological rigor, this review process uses internal reviewers who place a stronger emphasis on determining the degree to which the research will help make significant advances toward the program's short and long-term objectives. Although each proposal's research methods are explicitly reviewed, reviewers typically make the assumption those proposing the work are highly competent and will make the appropriate methodological decisions as needed. Most unsuccessful component projects or collaborations are unfunded because their research is seen by peers as not being innovative or collaborative enough to lead to significant knowledge generation. Here, the role of the shared goals and vision is critical. The AMRF model assumes that close peers will be motivated to weed out less-good proposals because they will be of less value to the group as a whole.

One of the other advantages the AMRF sees in its internal review process is that all members of the program are able to see what each of their colleagues is doing. In many instances, this leads to further collaborations in subsequent funding cycles.

Once initial awards are made, the real collaborative work begins.

The AMRF believes that bringing diverse scientists together to write an innovative proposal is just the first step in collaboration development. In AMRF experience, collaborations typically begin to mature after projects are funded. Knowledge is generated through facilitating interactions and sharing information across the collaborative network. In the AMRF model, this is done primarily via regular weekly video conferences (*Webinars*), constant e-mail and telephone interactions, face-to-face semi-annual meetings and workshops, and occasional exchanges of research personnel.

Researchers report that the amount of communication that occurs between not only the collaborating scientists but among the other researchers in their labs and clinics is substantial. As one researcher on the West Coast stated, "*I wake up and I turn on my computer, and I'm three hours behind because the East Coast has been working already and there is such expansive communication between the labs. We call each other. We e-mail each other. We are sharing data back and forth."*

This intense communication appears to be driven by multiple factors. First, the AMRF has invested substantially in providing opportunities for collaborating scientists (and the research personnel in their labs and clinics) to interact. They hold semi-annual meetings so members of the programs can meet face-to-face. (The AMRF expects all collaborating scientists to attend these meetings as part of their inclusion in the program.) The AMRF also regularly funds smaller face-to-face meetings for subgroups to meet as needed. Researchers clearly recognize the importance of such interactions. One observed that it *"lets you see people face-to-face, and develop what you might call 'human ties', that make collaboration possible."* And another remarked, "*Although we can do a lot via the internet, there's nothing like personal communication, which occurs during the [semi-annual] meetings."*

Second, the AMRF has established a web-based seminar series and invested in the infrastructure so that all collaborative scientists and their research staff can participate. Not only does this help members keep track of what their colleagues are doing, it often generates new ideas. For example, one scientists recalled that, "*When I presented my seminar on the internet, I got several e-mails from people who attended and said, 'Hey, here, I have something which might be very interesting to check', and so it creates a lot of new ideas, every seminar.*"

Third, members of an active collaborative network have ready access to each other. "*The accessibility to all these people in this consortium is incredible. I mean, just picking up the phone – normally you would have to e-mail someone and try to set up an appointment and all these things, and it can take a long time. But it's just calling a direct line, and it's just so direct and everyone is really bending over backwards to help each other.*"

Fourth, regular interaction allows the conversations to be less formal and more spontaneous and innovative. "*So, somebody calls you up, and says, 'I've got this problem. What do you think?' And you think about it for a minute, and all of a sudden you go, 'Ok, I see what's going on!' And you say, 'This is what I think is going on. From the previous five things that I've done with other labs, why don't you try this.*"

In the AMRF model, negative findings play a critical role in deciding next steps.

The AMRF staff members and researchers report that one unexpected result of the collaborations has been the sharing of negative findings. Negative findings are rarely published and are rarely shared outside of individual laboratories. In collaborative research where the primary objective is to move the research agenda forward, negative findings play a significant role in making strategic decisions about next steps. Knowing what does not work may be as important as knowing what does work. Awareness of negative findings reduces the likelihood of proceeding down known blind alleys, thus saving valuable time and resources. By sharing negative findings broadly and quickly, members of the program believe they can make more informed choices about where to turn next.

One researcher described the issue this way: "*You can actually share negative results much easier than you would ever be able to share them in publications. So, if I had to decide which way to go – left or right – a lot of your left and right is decided in labs by negative results, not positive results*." Another researcher points out that negative findings are particularly important in translational research where the decisions to move from one level to another are filled with uncertainty.

> *Those are very important things when you're dealing with new treatments and translational science, because you need to kind of pick a winner. Of all the candidates at the in vitro level – what should go to an animal model? And from a rodent model to a larger mammal model? And then ultimately to the human? And, of course, there are a lot of negative data along the way that need to be taken into consideration. And those pieces of data are very important and one of the frustrations in journal publications has been that it's very hard to publish negative data, even if it's important to the field.*

The AMRF believes that shared resources and platforms contribute to innovation.

Some scientists reported that the shared services and platforms have taken on an innovative life of their own. The scientists overseeing platforms help design the experiments of colleagues to best utilize their mutual capabilities. Instead of simply acting as service providers responding to the demands of collaborating researchers, however, platform personnel often suggest new approaches and research strategies. For example, "*we just developed this [technique] for this lab, but we have it up and running now, so if you want to run your things here, you can too*." In addition, the platforms are making their own methodological advances. They report not only are they being constantly challenged by collaborating researchers

to solve increasing more complex and difficult problems, the economies of scale make it more feasible to attempt to develop new solutions. "*We can bring in the bigger bang for the buck, because if we develop something for one or two labs, if it's of broader interest, we should apply it more broadly*."

In some cases, it is hard to tell whether the substantive fields are pushing the methodology forward or the new methodologies are pushing the substantive fields forward. For example, one researcher working with the electron microscopy platform described the following experience:

> *"We are now also looking into taking electron microscopy from two dimensions to three dimensions. For the next year, one of our goals is to take the two-dimensional images and using computer programs and a special technique that's called electron tomography, to get three-dimensional images of very tiny structures. And that could be structures that are involved, let's say, the growth of nerve endings or plasticity of synapses and so forth. And those are concepts, as far as nerve axon growth or plasticity of synapses, that occur across multiple diseases. And that is something that, as an individual researcher, if I wanted to come up with that project, it would be impossible… I couldn't do it, it's absolutely impossible, because here it's the interplay of multiple labs, [and] each lab is, in its own right, a world leader in what the lab is doing."*

Finally, the platforms – in the full spirit of collaboration – have also taken on the role of helping to build capacity in other laboratories. *"In the platform we have had people from other labs coming to my lab to learn things. And then they take some aspects of that with them back home, so that they can provide better quality material for us to process and so forth. Some labs would actually like to pick up some skills along the way and be more involved in some of the platform aspects."*

The number and composition of participants are modified as programs evolve.

The AMRF explicitly recognizes that the effectiveness of the overall program is strongly influenced by the size and composition of its members. The AMRF has begun to establish semi-formal mechanisms to make decisions about how to best modify the group, including adding and removing members.

Collaborating scientists may be replaced for a number of reasons. They may not conform to the collaborative model either by refusing to develop relationships with other researchers or by failing to broaden their own lines of research into other areas. In such cases, their proposed project components are not funded and after several cycles in

which their proposals remain unfunded, hey are not invited back to the semi-annual meetings.

A number of informal mechanisms are also used to "try out" potential new participants. Staff and program leaders observe the interactions of new individuals, including the degree to which researchers share ideas in the group, are constructive in their comments and are unthreatened by alternative ways of looking at phenomena. Individuals who exhibit non-collaborative behaviors are often taken aside and spoken with. In the rare instance where such behaviors are disruptive to the group dynamic, someone may not be invited back.

Typically, however, movement out of the group is based on a dynamic social process. The forming of collaborations within a program is similar to a internal labor market. Collaborations appear to be driven by shared interests and complementary expertise or resources. Since participants can work with whomever they choose, individuals who develop reputations for being good team players are invited to participate on more collaborations, while individuals who develop reputations for being poor team players find themselves on fewer collaborations.

Adding members poses another set of challenges. The AMRF staff members recognize that the success of their model will come in part from the intense, interactive group dynamics that comes from having a relatively small number of members. We heard concerns expressed by both the staff and collaborating scientists that making the group too big will change its collaborative structure and might weaken its overall effectiveness. There were differences of opinion among staff and collaborating scientists, however, about what constitutes getting "too big."

The pressure to avoid over-expanding makes leaders more sensitive to adding new members to already existing research programs. The ideal is to involve participants who are already members of one of the existing groups. However, a specific research project may identify a need for a specific tool or expertise not already present in those collaborating with the program. In such cases, the project may ask a non-collaborating scientist to join their team when the annual request for funding is submitted. Also, as the AMRF becomes more widely known, other scientists may request to be involved. This interest often is the result of conversations with current collaborating scientists. The AMRF has established a policy that for a new member to attend one of the bi-annual meetings or to join an on-going collaboration, the Foundation must first extend a formal invitation. The invitation is extended only after careful consideration is given to the potential role of the proposed scientist in the AMRF Program. This includes weighing what strategic, methodological or intellectual insights the potential scientist

might bring to the research program, how the scientist's proposed work and perspective differs from that already represented in the program, and how the individual's participation might further advance the AMRF Program's objectives.

Fostering cross-program and cross-group interactions and collaborations is critical.

As the programs expand, efforts are made to ensure that programs interact with each other and offer overlapping synergy (see Figure 4.3 on page 22). What is important is not who belongs in which group, but rather that individuals are affiliated with multiple groups. For example, collaborating scientists from the Hair Cell Regeneration group of the APNRR may attend the meetings of the Central Nervous System group and exchange insights, models or techniques.

Mechanisms differ for disseminating findings inside and outside the AMRF community.

As discussed earlier, the dissemination of ideas and positive and negative findings within the AMRF community are enhanced formally through the weekly web-based seminars, semi-annual meetings, and *ad hoc* face-to-face meetings, teleconferences and web-pages supported by the Foundation. Information is also disseminated within and between programs via informal contacts between collaborating scientists and their staff. Typically these are done through e-mail and phone.

Dissemination to the larger scientific community is currently investigator-driven, and occurs primarily through peer-reviewed publications, scientific meetings and eventually through patent applications. It is clear that collaborating scientists have a vested interest in distributing their results as widely as possible. One of the dangers of having a strong internal dissemination process, however, is that information does not need to be shared with outside audiences before decisions can be made about where to explore next and new funding can be received to move forward. Several collaborating scientists admitted that they really needed to take time to write up their results that have accumulated over the past 12 to 18 months, but they just didn't have time because they were proceeding forward as fast as they could.

The AMRF model is designed to increase the speed of knowledge discovery.

The speed of discovery, in part, depends on: (a) how fast researchers can make choices about where to explore next; (b) how fast they can secure appropriate funding; (c) how quickly they can perform the required research tasks; and (d) how quickly and broadly they can disseminate their findings. The AMRF has worked strategically on all

four fronts, establishing mechanisms that should theoretically increase the speed of discovery.

First, one of the places where the model posits a speedier process is to increase the rate at which investigators make decisions about what to do next through a number of mechanisms. Its programs have intentionally switched the expectations of success from "the discovery of new knowledge" to "the progression toward a solution to real problems". Although somewhat subtle, to AMRF believes this represents a significant change in how most research is done. Researchers are rewarded (through funding) for making bold, strategic moves toward reaching a set of explicit objectives and milestones rather than small, carefully planned, incremental steps toward knowledge generation. In addition, the AMRF also has helped increase the frequency and rate at which laboratories communicate with each other, and are therefore able to share both positive and negative findings, both of which are critical for making better and timely decisions about next steps.

Second, the AMRF has reduced the amount of time it takes to submit a proposal, have it peer-reviewed, and receive the funding to start research, to approximately 3 to 4 months. A typical proposal submitted through the NIH investigator-initiated process will take a minimum of one year before funds are received, and more typically 2 years depending on how many resubmissions are required.

Third, the AMRF has tried to reduce the time it takes researchers to complete defined stages in their research, primarily though supporting strategic divisions of labor via collaborations and shared services. Researchers no longer need to rely on their own labs to do everything (including purchasing and installing new equipment and training personnel on new techniques). Instead, researchers can rely on collaborators to handle specific tasks. Such collaborators (especially those working in the shared platforms) typically have more expertise and are likely to be more efficient at producing high quality results.

Finally, the AMRF has invested to facilitate the distribution of its findings within and between its research programs. The AMRF believe that making results readily available to other AMRF researchers fuels the generation of new ideas and speeds up the decision-making process concerning what to explore next by identifying the most promising paths and eliminating less productive ones. Although the AMRF programs are just beginning to produce publishable results, they are already considering mechanisms to improve the speed and scope of dissemination of their findings to the larger outside world.

CHAPTER 5. HOW THE AMRF STRIVES TO ACHIEVE QUALITY

INTRODUCTION

Like all well-run organizations, the Dr. Miriam and Sheldon G. Adelson Medical Research Foundation (AMRF) strives to promote and achieve quality in its activities and ultimately in its products. Unlike organizations that generate clearly defined products or services (e.g., cars, toothpaste, training, financial services, etc.), however, the AMRF's products are qualitatively different: discovery of _____. The AMRF must struggle with a simple, but challenging, question: How to define quality if the end product is discovery? Put another way, if you had to build an assembly process to produce new scientific knowledge that would eventually lead to real-world medical solutions, how would you design the process and how would you know if what you were producing along the way is of high quality?

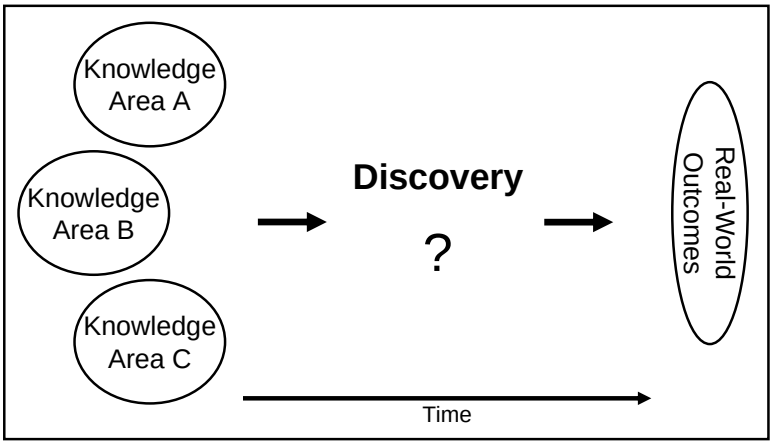
ACHIEVING QUALITY IN THE PROCESS OF DISCOVERY

The AMRF model focuses on a directed and strategic discovery process.

The AMRF model is based on the assumption that the primary goal of all medical research is to discover new knowledge. At its core, discovery results in the expansion of our knowledge in a particular topical area. Discoveries can be small and incremental or they can be large and comprehensive, opening up new ways of understanding phenomena.

The AMRF model has intentionally chosen to focus its energies on a discovery process that is far more directed and strategic than most. In the AMRF model, "discovery" refers to what needs to be learned to move from what is already known (shown on the left of Figure 5.1) to solutions of real-world outcomes (shown on the

Figure 5.1. The discovery chasm lies between what is currently known and the real-world outcomes that are desired.

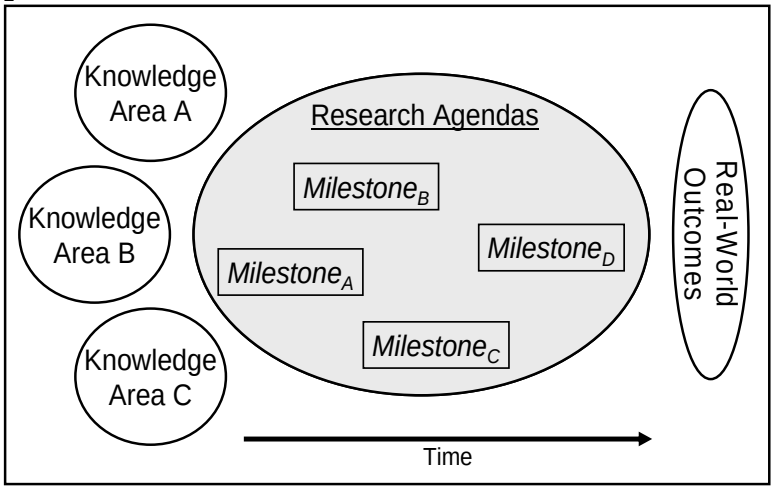


right). The AMRF is clearly not interested in funding projects just to generate new knowledge, and it is only interested in funding small, incremental discovery projects if they are likely to lead to important next steps on the way towards clinical therapies.

The AMRF model addresses the uncertainty of discovery by explicitly structuring it.

The chasm between what is currently known and real-world outcomes, shown in Figure 5.1, is wrought with uncertainty on two levels: (1) What kinds of things do we think we need to know to reach our goal?; and (2) What kinds of research do we need to do to know these things? To address these uncertainties, the AMRF model insists that each program propose a series of research milestones that will result in the desired outcomes and then developing clear research agendas to reach each milestone (see Figure 5.2).

Figure 5.2. Establishing milestones and research agendas help reduce uncertainty in the discovery process.



Milestones represent more than just intermediate outcomes. When taken together, milestones represent a kind of scientific roadmap for how one might logically progress from current knowledge to the long-term, desired outcomes. The AMRF argues that it is this larger scientific roadmap that is often missing from most funding mechanisms such as the investigator-initiated grants awarded by the NIH. One of the core functions of the collaborating scientists in each program is to work together to propose an intellectual course through this unknown territory. Once the group has established such a set of pathways, then its next task is to develop a general research strategy for reaching each of the proposed milestones in as efficient a manner as possible. The AMRF model, explicitly recognizes that the discovery process is not linear. As the research evolves and new discoveries are made, the group continually reassesses and adjusts its milestones and research strategies as needed.

Maintaining quality in discovery means assessing both process and outcomes.

Ideally, the AMRF would like to assess the quality of its activities based on whether its programs contribute to the long-term goal of improving the human

condition. This is not feasible, however, given the potentially long time frame and the many unknowns in the discovery process that have yet to be realized. Consequently, most quality assessments related to the AMRF model are based on more intermediate process-oriented factors. To this end, the AMRF has put in place a variety of mechanisms to improve the quality throughout the entire discovery process, particularly in regards to: (1) recruitment; (2) setting program milestones and research agendas; (3) improving the quality and innovativeness of research; (4) evaluating collaborations and project components; and (5) reassessing and redirecting program directions as new knowledge is generated. We briefly review each below.

Recruiting of participants. In the AMRF model, ensuring quality in the discovery process begins with identifying, vetting, and recruiting a team of highly qualified and collaborative scientists. The AMRF spends considerable time and energy to build a diverse, dynamic and energetic cadre. It vets individuals on their substantive and methodological knowledge as well as their ability to think beyond their own immediate research and their capacity to work well with others. It also continuously monitors the group to identify areas that need further strengthening and areas of weakness that may need to be reinforced. The AMRF believe that the composition and dynamics of the group are critical, as they affect all other quality assurance mechanisms.

Establishing program milestones and research agendas. Working together with the Program Manager, group members are responsible for guiding the discovery process forward in terms of establishing milestones and the program's research agenda. The AMRF model recognizes that no single individual is capable of understanding the full array of issues that it would take to develop an effective plan for reaching a program's long-term objectives. As a group, however, members can draw on each other's diverse expertise and act as checks and balances on each other to identify the more robust and reasonable pathways forward. As a further check, program milestones and research agendas are reviewed and commented on by the Scientific Officer and Executive Director. These milestones are then approved by the Trustees. The multiple layers of review ensure that the long-term objectives do not get lost in the details of the research.

Improving the quality and innovativeness of research. The core of the AMRF model is based on generating high quality and innovative research through collaborations. The recipe is quite simple: take individuals who are highly competent in a diverse (but related) set of substantive and methodological areas and insist that they work collaboratively. In addition to spending a great deal of effort building and maintaining teams with diverse expertise (discussed above), the AMRF has also invested heavily into developing shared platforms and services. Specialized methodological and

technological expertise provided through shared services make it less expensive to access new and innovative technology and expertise than most collaborating scientists would have access to in their own labs or institutions.

The AMRF model has invested in shared platforms and services and other collaborative efforts. The AMRF believe that the shared platforms and services have improved the quality of the research on five fronts. First, they have improved the level of rigor of studies in terms of research designs, statistical analysis, and more appropriate use of measurement techniques and procedures. Second, researchers are able to tackle larger and more complex problems through the judicious division of labor. What no lab could have done alone can be realistically accomplished by working together. Third, access to new innovative technology has changed the kinds of questions that collaborating investigators now examine. Fourth, by posing new questions, collaborating scientists have challenged platforms to also become more innovative. And fifth, by working together and pooling data, researchers have created datasets that can be used to answer questions that previously could not be addressed or even conceptualized.

Evaluating collaborations and project components. Unlike other review systems that tend to focus primarily on the methodological and technical rigor of research proposals, the AMRF model places an equal (if not greater) emphasis on ensuring that the research is likely to generate significant new knowledge and, most importantly, will provide the information needed to make subsequent research decisions that will lead to the discovery of medical therapies. To this end, each project component (and the collaboration with which it is associated) is reviewed at multiple levels as part of an internal review process.

As described in Chapter 4, the process begins with collaborating scientists independently assessing each proposal on several important dimensions: (1) to what degree does the work proposed fit in with the larger program research agenda and contribute in reaching the program milestones set out by the group; (2) to what degree does the proposed project component make explicit its own micro-objectives and mini-milestones and align with macro-objectives and general milestones proposed by the rest of the collaboration; and (3) to what degree are the research methods and techniques proposed reasonable and appropriate given the stated aims. Next, an Executive Committee reviews the aggregated scores, makes comments, and recommends funding levels. These are then reviewed by the Executive Director and responsible Scientific Officer, who summarize and make recommendations to the Trustees, who make the final decisions.

The multiple layers in the evaluation system are designed specifically to drive the discovery process toward reaching short and long-term objectives. The intent is to detect and eliminate poor science – that which is neither rigorous nor innovative – as early as possible in the process. More rigorous and innovative science is then further scrutinized to determine to what degree it is likely to contribute to moving the discovery process forward in significant ways. Those proposals that are unlikely to make significant contributions are eliminated in later stages of the process.

Reassessing and redirecting research directions. The AMRF believes that when working in such an uncertain discovery environment, it is critical that a program has the ability to synthesize new information quickly, reassess its current milestones and research strategies and redirect its efforts as quickly and effectively as possible. To address these issues, the AMRF has invested a great deal of resources into ensuring that collaborating scientists are continually interacting with each other within and across programs. Information is exchanged on a continuous basis through unstructured (e.g., phone and email) and structured exchanges (e.g., *webinars* and semi-annual face-to-face meetings). At the semi-annual meetings, program members discuss their current progress and what kinds of new directions they need to pursue. In addition, participants have the opportunity to hear about finding from other relevant programs and to learn more about new methodologies and techniques from the shared platforms. These ideas are subsequently incorporated in the next round of proposals.

CHAPTER 6. FUTURE ADAPTATION OF THE AMRF MODEL

INTRODUCTION

Over the last two years, the Dr. Miriam and Sheldon G. Adelson Medical Research Foundation (AMRF) has grown rapidly in terms of the number and kinds of programs and participants it supports as well as the types and amounts of shared services it provides. At the same time, AMRF has also evolved and matured as an organization. The Foundation has expanded its staff and expertise and has developed from scratch the formal organizational structures needed to run its enterprise. Not surprisingly, the AMRF model has gone from a general notion of how collaboration should work and what was needed to support it, to a more well-defined process including explicit policies and procedures that help codify how the AMRF model functions. Given where the AMRF started just a few years ago and the great amount of flux it has experienced in the interim, the AMRF has had to adapt to many challenges.

Although much of the basic groundwork has been laid, we expect the AMRF and its model of collaborative research will continue to adapt as it encounters new challenges in the future. While some of these challenges can be anticipated, others are harder to forecast. Below we briefly examine some of the key issues the AMRF is likely to confront.

ADAPTING TO INCREASES IN SCALE

One of the greatest pressures facing any growing organization is how to respond to increases in scale. For the AMRF, the growing number and diversity of programs, participants, shared services and staff are likely to pose significant organizational and logistic challenges.

In collaborative models, increases in scale have geometric consequences.

Adding a single new AMRF program has the immediate effect of adding 8 to 20 new collaborating scientists in the first year and upwards of 30 to 40 scientists in subsequent years. For a collaborative model, a larger group size presents more opportunities for possible collaboration. For example, among a group of 10 researchers there are 45 possible dyadic (i.e., one-to-one) interactions and 120 possible triadic (i.e., 3-person) interactions. Among a group of 20 researchers, there are 190 possible dyadic

relationships and 1140 triadic relationships. Not surprisingly, the more opportunities there are for interaction, the easier it is for researchers to form collaborations.

At the same time, the increase in opportunities to collaborate does not necessarily lead to more diverse or productive collaborations. Instead, as a program grows in size, more sub-groups or cliques are likely to be formed in which the same researchers find themselves working together over time and projects. On one hand, such sub-groups are useful because they allow a smaller group of researchers to concentrate their efforts on a narrow set of topics, usually in a more efficient way, as they come to know each other better. On the other hand, such subgroups risk isolation; they require careful monitoring so they stay well integrated with the rest of the group.

Finally, integrating a new program with the rest of the AMRF community are likely to require that: (1) additional resources be made available to support inter-program collaboration efforts; and (2) at least some collaborating scientists dedicate their time to their current and the new programs. Depending on how distinct the new program is from existing programs, additional shared platforms and services may need to be developed.

In sum, increasing the number and diversity of programs and participants is useful for increasing *opportunities* for collaboration. But for such opportunities to be realized and productive, more oversight and resources will be needed to ensure that the collaborations remain well integrated and directed toward the programs' short- and long-term objectives.

At some point, adding more researchers may be detrimental to collaborative efforts.

One challenge that is unlikely to go away is how to best maintain and modify an existing program's size and composition as the direction and needs of the research agenda change. Although the AMRF has created explicit policies for inviting new members to existing programs, it is extremely difficult to know *a priori* what the ideal group size should be. Most researchers we talked to who had been affiliated with one of the older programs were concerned that their program was becoming too big. (In some cases, the number of participants has more than doubled since they first began.) They were primarily worried that everyone would not be in sync and they would not know each others' work well enough to move forward effectively. The AMRF leadership is clearly aware of such issues, but it will take more time and experience to know when a program has become too big, and under what circumstances it would be important to continue to grow but to manage that growth by creating sub-groups.

The more people involved, the more difficult it is to faithfully replicate the model.

Organizations that grow rapidly are often in danger of losing sight of what works. The more new people who join the AMRF as either staff or collaborating scientists, the more difficult it will be to ensure that everyone has the same understanding of how the model works. In more bureaucratic organizations, this kind of problem is often addressed by formulating explicit policies and procedures and making sure participants comply with the rules. The downside to this approach is that such policies and procedures can easily become overly rigid, and reduce an organization's ability to adapt to new challenges. In the case of the ARMF, the trick will be: (1) to make the model explicit and easily understandable to everyone; (2) to establish policies and procedures that are transparent, but flexible; and (3) to create positive incentives so that individuals want to follow the model rather than feel they have to.

Creating an inter-organizational collaborative model poses a new set of challenges. The AMRF has begun talks with the NIH and other foundations to enter into an international genomic collaboration that would fund existing investigators and the use of very new tools to search for therapeutic targets. The collaboration would begin by focusing on malignant melanoma. Inter-organizational collaborations pose different challenges to a collaborative model. Some of the key questions to ask are: (1) Who is responsible for fostering the collaborations between researchers?; (2) How will researchers be incentivized to collaborate?; (3) What role will each of the organizations play in setting the short- and long-term milestones and establishing the research agenda to meet them?; (4) How will specific collaborations be vetted and approved?; and (5) How are previous questions linked to who pays for what? Currently, the AMRF model works well because the Foundation simultaneously acts as both an incubator and an insulator of the collaborative research. It will be important to determine who will be responsible for these activities in a multi-organizational setting and how they will be coordinated and aligned.

MAXIMIZING EFFECTIVENESS

The AMRF is still in the process of honing its collaborative research model and is likely to continue to do so over the coming years as its programs mature. Part of this process involves taking lessons learned and making them more explicit parts of the model.

Maximizing the effectiveness of inter- and intra-program collaborations is critical.

Unlike AMRF programs that have formal leadership roles and mechanisms for setting milestones and research agendas, inter-program collaborations appear less structured and somewhat more *ad hoc*. Currently, a combination of collaborating scientists and AMRF staff play key roles in identifying, establishing, championing, incentivizing and monitoring the progress of such joint research endeavors and disseminating the results. Although these current mechanisms are well suited for the existing environment and are responding to emerging needs in a flexible manner, as the number of programs and inter-program collaborations grow, they are likely to become less efficient; more formal and transparent mechanisms may need to be established.

Similar kinds of issues arise in coordinating the relationships between programs and their associated subgroups. As long as there are only a few subgroups, coordination between the larger program and a subgroup is best done on an informal basis. As the number of sub-groups or the size of the sub-group expands, collaboration is likely to become more difficult and will require more formal mechanisms to guide the process.

Balancing intra- and inter-program collaborations could be tricky.

One of the greatest threats to the success of a particular AMRF program is to lose focus on the program's short and long-term objectives. Clearly, sharing knowledge and collaborating across programs is in the long-term interest of the Foundation. Program leaders, however, will need to determine carefully how to weave inter-program collaborations into their research agenda without overburdening the collaborating scientists or expanding the scope of the program to the point of slowing progress toward its explicit milestones.

Highly collaborative individuals may be at risk of burnout and over-utilization.

In the AMRF model, some individuals are involved in more collaborations than others. More collaborative individuals play a key role in a program where they often act as informal leaders and distributors of new knowledge to the rest of the group. There are downsides, however, to being too collaborative. Individuals who work on a wide range of collaborations can easily be pulled in too many directions and become overcommitted. In addition to being susceptible to burnout, such individuals may be unable to effectively respond to the needs of all the collaborating partners and unintentionally slow the discovery process for the group.

In addition, individuals who are sought after for a particular expertise may become over-utilized. This appeared to be particularly true of researchers associated

with shared platforms. Increased demand for such services can be met either by increasing the capacity of the key person's laboratory or by adding additional laboratories. There are advantages and disadvantages to both options. The single laboratory model more readily centralizes and helps standardize the methodological approach across studies but makes the whole system somewhat vulnerable if something were to happen to the key collaborating scientist or laboratory. The multiple laboratory model introduces new challenges for ensuring standardized quality and procedures, but may increase the chances of discovering new methodological techniques.

Publications and intellectual property issues are likely to arise in the future.

Although the AMRF has spent considerable resources in anticipation of negotiating intellectual property rights and contracts with universities and institutions, many of the more subtle issues are likely to arise only after the negotiations begin. The same is likely to occur with how credit is given on publications. Conflicts are likely to arise over who can and cannot be an author on a particular publication and about the order of authorship. It is not clear to what degree the AMRF will be drawn into these discussions as an arbitrator or to what degree it may need to establish guidelines for such joint publications.

MONITORING PERFORMANCE

Now that most of the key components of the AMRF model have been established, the Foundation is beginning to transition from a phase of building to one that is more operational. During this early operational phase, it will be critical to establish mechanisms for monitoring the AMRF's performance. Establishing transparent indicators for tracking performance is important for two reasons. First, these tools can be used as part of a continuous quality improvement process (CQI) and will allow the AMRF to further fine-tune its model over the next several years. Second, the information that the tools generate will be needed if the AMRF ever hopes to make an evidence-based case that its model is more effective than other models in promoting scientific discovery.

Performance tracking must consider outcomes, progress and processes.

Tracking the performance of an organization dedicated to scientific discovery is extremely challenging. The AMRF is clear that it is not interested in simply generating more scientific knowledge, but instead it is interested in: (a) finding common denominators across diseases in their genes, cells, molecules and pathways; and (b)

ultimately developing therapies and interventions that will improve the human condition.

One way to monitor the Foundation's performance is to ask whether common denominators were found or therapies and interventions developed and if so how quickly. Although such *outcome measurements* are clearly an important aspect of monitoring the Foundation's success, they are relatively limiting. First, given the interconnectedness of science, it will always be difficult to determine to what degree research funded by the AMRF model (in the context of other sources of funding of participating scientists) contributed to such discoveries. Second, these outcomes will typically take years to be reached, and therefore cannot provide much information regarding the Foundation's interim performance.

A second way to monitor the Foundation's performance is to track progress toward its goals. To do this, one could measure progress from what is currently known toward the goals that are desired. One of the challenges in using *progress measurements* to track discovery is that we typically do not know how wide the chasm is between these two points nor what kinds of barriers we are likely to encounter along the way. It is like trying to determine how far one has progressed across an ocean without knowing how big the ocean is or what obstacles lay ahead. The AMRF, however, has already developed some creative solutions to this problem, by requiring all programs and collaborations to make explicit their milestones and research agendas (see Chapter 5 for more details). Progress, for example, could be measured by tracking how often and how quickly milestones are reached and what discoveries are made along the way (e.g., as evidenced by publications or by the setting of new milestones in different directions).

A third method for tracking the performance of the AMRF model is to actually measure changes in the collaboration process and to link such changes to the products of discovery – namely the generation of new knowledge (either positive or negative). The AMRF staff members have already begun to compile such basic *process measurements* by creating network graphs of who collaborates with whom and comparing them over time. By treating all AMRF participants as overlapping networks of actors, it is possible to monitor changes in collaborations over time by network size (i.e., number of collaborators and collaborations); network composition (i.e. characteristics of collaborators, strength of relationship, and what is being exchanged); and network structures (i.e., patterns of interactions including density, centrality, etc.). If indeed, the AMRF is correct in assuming that collaborations matter, then it will be possible to not only show that this is true, but also to identify what particular aspects of collaborations are most important for maximizing the discovery process. Well thought

out process measures are likely to be quite beneficial for continually improving the AMRF model.