Bioengineering Research Partnership Program Feasibility Study

Deliverable 5: Final Report

Contract Number GS-00F-0024M
Purchase Order Number 263-FJ-517731

April 26, 2006

Table of Contents

List of Exhibits

Appendices

Appendix A—BRP Logic Model

Appendix B—Evaluation Framework

Appendix C—Online Interview Form

Appendix D—Debriefing Survey

Appendix E—Online Interview Emails

Appendix F—Case Study Format

Acknowledgements

Contract support for this study was provided from the NIH One Percent Program Evaluation Set-Aside Fund. Humanitas, Inc., in collaboration with NIH officials, planned the study methodology, developed the evaluation metrics, prepared the case studies, implemented an online interview questionnaire, and reviewed and analyzed the resulting data.

The study team wishes to thank NHLBI members who provided guidance and oversight for the survey questions, particularly Tim Baldwin, Ph.D., Pankaj Ganguly, Ph.D., Andrea Harabin, Ph.D., Cheryl Howard, M.S., Martha Lundberg, Ph.D. (Chair), Sunil Pandit, Ph.D., and Gail Weinmann, M.D. Additionally, gratitude is expressed to members of the NIH Bioengineering Consortium for important insight and perspective about the Bioengineering Research Partnership (BRP) program, especially Christine Kelly, Ph.D., Jeffery Schloss, Ph.D., Dan Sullivan, M.D., and Fei Wang, Ph.D.

Special appreciation is also extended to the NHLBI Executive Staff who provided guidance for this study: Liana Harvath, Ph.D. (for Charles Peterson, M.D.), James Kiley, Ph.D., Alice Mascette, M.D., Stephen Mockrin, Ph.D., and Carl Roth, Ph.D., LL.M.

Finally, many thanks to the BRP awardees who so willingly participated in the study to describe their experiences and project outcomes.

Executive Summary

The NIH established the Bioengineering consortium (BECON) in 1997 to focus on bioengineering in public health and, a year later, the Bioengineering Research Partnership (BRP) Program to solicit multidisciplinary bioengineering research teams applying an integrative approach to developing knowledge and methods focused on important biological or medical problems. Since 1999, NHLBI has funded 42, or more than 25%, of the 160 BRP grants supported by NIH, with annual total average costs of $785,000. Given this significant amount of support, NHLBI wants to know how best to evaluate the success of the BRP Program and make useful suggestions to NIH on its administration.

NHLBI engaged Humanitas, Inc., to conduct a feasibility study to establish a methodology and metrics of success that could be used to evaluate the NHLBI-funded BRP grants and could further serve to assess the trans-NIH BRP Program. NHLBI's goals for the feasibility study are to:

- Evaluate, through information obtained from a small number of case studies and/or questionnaires of NHLBI awardees, the extent to which there are recognized standards of performance that could be used to assess success.
- Provide recommendations that will be useful to the NIH in administering the program.

Working closely, the NHLBI and Humanitas teams developed a logic model and an evaluation framework to inform the feasibility study. The team met with the NHLBI Division Directors to finalize the evaluation framework and select nine key metrics to address in the feasibility study. To meet time and budget constraints, the overall strategy for the feasibility study was to collect information from existing data sources and in online in-depth interviews. The case studies summarized existing data from BRP award applications and reports to provide an overview of project goals and progress. The online interviews collected information addressing primarily the nine key metrics.

Because of Paperwork Reduction Act regulations limiting data collection to nine or fewer persons in preliminary studies using standardized collection instruments, data were abstracted from existing records for case studies of *nine* BRP awardee projects and collected via online in-depth interviews for another *nine* BRP awardee projects. Criteria used in selecting awardees for the case studies and the online interviews were that (1) a minimum of three years have elapsed since receipt of the BRP award, (2) for case study awardees, relatively complete data records exist, and (3) for online interview awardees, awardees not be also among those selected for case studies.

Estimates of the nine key metrics and additional information culled from the case studies or asked of the online respondents paint a picture of the "typical" NHLBI BRP awardee partnership and its project outcomes—keeping in mind that "typical" is based on the preliminary results

obtained from nine BRP awardee respondents to the online interviews and nine BRP awardee projects summarized in case studies for this feasibility study. A snapshot follows.

- Because of its relatively large scope, cross-disciplinary nature, and design-driven as well as hypothesis-driven research, the typical BRP project was crafted and proposed specifically for a BRP Program award. It is not a project hypothesis or design that was submitted and then rejected by another NIH grant program before it was submitted for BRP funding. All of the awardees believe that the BRP Program funds research that might not otherwise be funded by other NIH programs, and that the project aims and goals could not be accomplished by smaller, independent investigator grants.

- The typical BRP-funded project includes lead investigators from both medical and science fields. Most of the partners have worked together or collaborated previously with the PI. Three of the nine BRP partnerships include a partner that had never partnered previously in an NIH-funded project prior to this award. This new partner is a commercial entity.

- Ideally, awardees believe that the best way to evaluate the success of the BRP Program is to gauge the impact of awardee research on improved healthcare, to measure the degree of achievement of the results promised in the award application, and to assess the quality of the research by peers. Pragmatically, however, the awardees understand that numbers of publications and citations, though far from perfect, are "an index of productivity" and "impact of the work on the scientific community."

- The typical BRP partnership publishes in peer-reviewed journals and yields approximately .6 articles per lead investigator per funded year of research. Five or more years of funding tends to increase this publication rate. More than 50% of the publications are in journals that the awardees deem most esteemed in their fields. Achieving patents, registered products, and clinical trial approvals—other important metrics of success—take time, usually a minimum of four to five years of funded research.

- Though there is no perfectly comparable group to serve as a good comparison set in comparing the successes of BRP awardees with those of other awardees, the BRP awardees believe that the Program Project Grant (PPG) and Specialized Centers of Research (SCOR) awardees may be the best available comparison groups. BRP-supported research is more design-driven than PPG-supported research; therefore, outcomes are not directly comparable but nonetheless provide a basis for a comparison.

The BRP awardees cited three ways NIH could further assist awardees—by providing expedited renewals or bridge monies to cover ongoing research until renewal funds were awarded, by enhancing the training and orientation of reviewers in the criteria appropriate for reviewing design-driven, clinically-oriented research, and by continuing the encouragement of cross-disciplinary research and interactions that bridge the life sciences with the physical/engineering sciences.

Conclusions and recommendations for future evaluations of BRP Program success include information about both 1) the metrics that differentiate best between successful and less successful awardees, and 2) the most efficacious methods for collecting data addressing those metrics. Suggestions for metrics include the following:

- To assess significant contributions made by BRP awardees to improving human health, the first goal of the BRP Program, use metrics that are both respected by the BRP awardees and differentiate among project outcomes:

  - Publications and articles accepted for publication in peer-reviewed journals and in highly esteemed journals
  - Citations of publications in peer-reviewed journals
  - Patents, copyrights, and trademarks
  - Sales and sales of licenses

- Additional metrics not evaluated in this study but present in some case studies and likely indicative of degrees of awardee success in meeting this BRP goal include:

  - Abstracts of conference and other presentations
  - Receipt of additional non-NIH funding or capital
  - FDA approvals for clinical trials and other statuses

- The following metrics about partnership members addressed successfully the second goal of the BRP Program—encouraging collaborations among the allied quantitative and biomedical disciplines:

  - BRP awardees with professionals who have engineering, physical, and computational science degrees
  - BRP awardees that include a research partner that never partnered in an NIH-funded project previously

In addition to information about metrics that differentiate between successful and less successful BRP awardees, this feasibility study showed that much rich evaluation material already exists in awardee data files. Given this state of affairs, the **ideal** way for the BRP Program to collect evaluation data likely occurs before the receipt of award funding, as a condition of that funding, or before renewal of funding—when there is both need and motivation. The following suggestions for collecting evaluation data emerge from the feasibility study:

- If possible, consider minimizing respondent burden by incorporating data collection of evaluation metrics online within BRP award applications, progress reports, and final reports. In the near term, during the transition period as the NIH implements online collection of BRP applications and reports, consider using an online survey to collect evaluation data.

- In the future, use online data collection to both collect and organize data simultaneously. Plan for storing complex information as separate numeric and text variables to make it easy to locate information, summarize data in tables and other displays, and prepare reports.

- Consider programming standard reports summarizing BRP awardee progress to date that can be produced at regular intervals, and using standard metrics and similar procedures to evaluate other NIH award programs, such as Program Project Grant (PPG) and Specialized Centers of Research (SCOR), to provide metrics for comparing BRP awardees with other similar awardees.

1. Introduction and Methodology

The NIH established the Bioengineering consortium (BECON) in 1997 to focus on the increasing importance of bioengineering in public health. A year later, BECON created the Bioengineering Research Partnership (BRP) Program to solicit multidisciplinary bioengineering research teams applying an integrative, systems approach to develop knowledge and methods focusing on important biological or medical problems. The research teams could propose either design-driven or the more typical hypothesis-driven research projects.

Since 1999, the NHLBI has funded 42, or more than 25%, of the 160 BRP grants supported by the NIH. The application priority score and annual total costs of the NHLBI-funded BRP grants have averaged 175 and $785,000, respectively. Given this significant amount of support during the initial five years of the BRP Program, the NHLBI wants to know how to best evaluate the success of the program and make useful suggestions to the NIH for administering the program.

1.1 Background

The NHLBI, in coordination with the NIH BECON, developed the BRP Program Announcement to facilitate research that addresses gaps in the NIH portfolio that result from the structure of the NIH review process. The BRP review criteria provide equal status and ensure a fair evaluation of both design-driven and hypothesis-driven research applications. Two specific BRP goals are to:

- Encourage basic, applied, and translational bioengineering research that could make a significant contribution to improving human health.
- Encourage collaborations and partnerships among the allied quantitative and biomedical disciplines.

Program officials wish to learn the extent to which the goals of the growing NIH-wide BRP Program are being met. In 2004, a subcommittee of BECON informally surveyed the BRP Program officials. This survey collected anecdotal data that provided only a snapshot of the program at that point in time and lacked standardized evaluation criteria.

Thus, the NHLBI engaged Humanitas, Inc., to conduct a five-month feasibility study from November 2005 through March 2006 to establish a methodology and metrics of success that could be used to objectively evaluate the NHLBI-funded BRP grants and could further serve to assess the trans-NIH BRP Program.

The NHLBI's goals for the feasibility study are to:

- Evaluate, through information obtained from a small number of case studies and/or questionnaires of NHLBI awardees, the extent to which there are recognized standards of performance that could be used to assess success.

- Provide recommendations that will be useful to the NIH in administering the program.

The NHLBI and Humanitas teams worked closely to develop a logic model and an evaluation framework to inform the feasibility study. The logic model graphically showed how the BRP Program is intended to operate to achieve the program goals and objectives. The evaluation framework described performance indicators for each of the program objectives. These standards, indices, and measures document Program officials' consensus about the expected performance levels, standards of attainment, and ways to measure performance attainment. (Appendices A and B contain the logic model and evaluation framework.)

The BRP evaluation team met with the NHLBI Division Directors to finalize the evaluation framework and consider methodologies appropriate for collecting data to address the measurement criteria delineated in the framework. Participants agreed that a methodology combining a case-study approach with the collection of objective measures to address *nine key metrics* would meet the needs of the short-term feasibility study. For a long-term evaluation of the BRP Program, benchmarking measures to provide a context for interpreting them was deemed important. It was agreed that the feasibility study would not include comparison benchmarks, but it would attempt to locate appropriate reference measures for use in a long-term evaluation.

The nine key metrics deemed most important for the feasibility study follow. The numbering scheme for these metrics matches that of the evaluation framework (Appendix B).

BRP Awardees with hypothesis-driven research:

- 1A.1.4: Articles published or accepted by peer-reviewed journals on BRP-supported research findings in health-related fields (number and names of journals)
- 1A.1.6: Research and educational tools derived from BRP-supported research that increase health knowledge directly or indirectly by enabling others to do so (number and types)
- 1A.1.7: Published citations of BRP-supported research (number and type)

BRP Awardees with design-driven research:

- 1A.2.3: Articles published or accepted by peer-reviewed journals on new or improved BRP-supported products, processes, usages, services, or clinical research (number and names of journals)
- 1A.2.4: New or improved BRP-supported products, processes, usages, services, or clinical research in health-related fields (number and types)
- 1A.2.6: Patents, copyrights, trademarks, or licenses for new or improved BRP-supported products, processes, or services in health-related fields (number and details)

All BRP Awardees:

- 1B1.2: BRP awardees who submitted BRP project hypothesis or design to another NIH program (specify name) before submission to BRP program and did not receive NIH funding prior to BRP
- 2A.1.1: BRP awardees with staff professionals who have engineering, physical, and computational science degrees
- 2A.3: BRP awardees that include a research partner that had never partnered in an NIH-funded project prior to the date of award

1.2 Methodology

A feasibility study is quicker and less costly than a full-scale evaluation because its goal is to assess the viability of conducting an actual evaluation. The feasibility study assesses the availability of data to address study metrics and the best methodology for collecting those data. It uses the findings to make appropriate recommendations for the full-scale evaluation. Thus, these goals, as well as the need for actual findings to aid in making recommendations useful for NIH, shaped the methodologies selected for data collection.

The overall strategy for the feasibility study was to collect information from existing data sources—primarily grant applications, progress reports, and the NIH databases—and from online in-depth interviews with Principal Investigators (PIs) of nine BRP Projects. It was anticipated that the existing data sources could provide information about the BRP awardees, their planned projects, and interim measures of progress in meeting their project goals and commercializing their products, which could be summarized in case studies. Online in-depth interviews could provide current information addressing the nine key measures of special interest selected from those enumerated in the evaluation framework, as well as rich detail about the road from project inception to success.

Analysis of the data from both case studies and online interviews would yield findings and conclusions about important metrics, assessment of data availability for a long-term evaluation, suggestions for comparison benchmarks, and near-term recommendations useful for NIH in administering the BRP Program.

Selecting the BRP awardees to be the focus of the feasibility study was the first evaluation task. The strategy was to spotlight different BRP awardees in the case studies and the in-depth interviews to learn about as many projects as possible within available resource constraints. Because of Paperwork Reduction Act regulations limiting data collection to nine or fewer persons in preliminary studies using standardized collection instruments, data were abstracted from existing records for just nine case studies and collected in nine online in-depth interviews.

The criteria used in selecting the nine NHLBI-funded BRP awardees as the focus of the case studies were:

- Minimum of three years elapsed since receipt of BRP award

- Even distribution across years elapsed since receipt of BRP award—that is, approximately even numbers of awardees with three, four, and five years elapsed since receipt of award
- Even distribution of project types—that is, approximately even numbers of awardees with design-driven and hypothesis-driven projects
- Relatively accessible and complete existing data—that is, award applications, progress reports, and database information

Because the NIH is in the process of transitioning from paper to electronic data records, and thus some data records are in transit or otherwise not locatable, the last criterion became the determining one after the initial three-year minimum was met.

The criteria used in selecting the NHLBI-funded BRP awardees who were invited to participate in the online in-depth interviews were:

- Minimum of three years elapsed since receipt of BRP award
- Not included as a case study

We selected 21 BRP awardees that met these criteria as candidates for the online interview. The determining criterion for inclusion in the feasibility study was the cooperation of the BRP awardees with the online interview. The online form was closed after nine awardees completed their in-depth interviews. Awardees who finished the in-depth interview were asked to complete a short debriefing survey about the evaluation process. Seven of the nine interview respondents did so. Copies of the online in-depth interview form and the debriefing survey are in Appendices C and D, respectively.

Humanitas sent advance email messages to prospective respondents to the in-depth interview on January 30, 2006. Subsequently, emails containing the link to the interview site and password, reminder messages, and thank you messages were sent beginning on February 6 and continuing through February 22nd, the end of the field period. Appendix E contains copies of the email messages.

Using data supplied by the Project Officer, Humanitas abstracted information for the awardee case studies from the official grant files, primarily BRP Program award applications, progress reports, and the NIH IMPAC II database, and available public information, such as BRP grantee meeting abstracts. Some of the case studies used different subsets of data, depending upon what data were available. Appendix F contains a copy of the format used to organize the case study information.

In the remaining portions of this report, Chapter 2 presents study findings about the nine key metrics of interest and discusses how to best measure the success of the BRP Program, possible benchmarks for a future evaluation, and suggestions for improving the Program. Chapter 3 presents an overview of the typical BRP awardee and gives recommendations about administering and evaluating the BRP. Chapter 4 presents a summary of case study methods and findings, as well as each of the nine case studies.

2. Findings

This section summarizes the findings from the online in-depth interviews and incorporates information from the cases studies where appropriate. Discussion focuses on the nine key metrics deemed most important for this initial feasibility study. Considerations about the usefulness and accuracy of these measures are included to inform future large-scale evaluations. Discussion pertinent to the data sources and their availability, the viability of the online data collection methodology, and suggested comparison benchmarks for use in future evaluations follow.

The findings should be viewed only as rough estimates of the more precise ones that could be obtained in a full-scale evaluation. The data in this feasibility study come from the nine awardee respondents to the online interviews and the nine case studies. Neither group of nine constitutes a random selection. The data from the online interviews were supplied by the respondents in response to specific questions. The data in the case studies were abstracted from files by a Humanitas analyst who was researching specific issues. Thus, the two sets of data come from different sources and are not responses to the same uniformly-worded questions. Additionally, groups of nine are much too small to yield estimates with statistical significance. Nonetheless, the data indicate sources and directions worthy of further exploration, and they suggest findings that a large-scale evaluation could confirm or reject.

2.1 Estimates of Nine Key Metrics

The BRP evaluation team selected nine key metrics in which they were most interested as the focus of the feasibility study. They agreed that evaluating these nine measures, selected from among those in the evaluation framework, would afford a sense of the ease or difficulty of collecting data and provide preliminary information about and estimates of useful measures.

The nine key metrics fall into three groups—those appropriate for BRP awardees with hypothesis-driven research, design-driven research, and both types of research combined. When it made most sense, findings from the three groups were combined for presentation.

Publications. In this section, we discuss two metrics dealing with articles published or accepted for publication in peer-reviewed journals.

- **1A.1.4: Articles published or accepted by peer-reviewed journals on BRP-supported research findings in health-related fields (number and names of journals)—Hypothesis-driven research**

- **1A.2.3: Articles published or accepted by peer-reviewed journals on new or improved BRP-supported products, processes, usages, services, or clinical research (number and names of journals)—Design-driven research**

The online interview asked awardee respondents to "list the top five peer-reviewed journals" that they felt "are most esteemed" in their field of research. The next exhibit lists the journals cited by the online awardees with both hypothesis-driven and design-driven research. The goal of this

question was to evaluate the *quality* of publications—to learn which peer-reviewed journals are most esteemed, differences that exist between the journals cited by hypothesis-driven and design-driven researchers, and the extent to which published awardee articles appear in the most esteemed journals.

Exhibit 1. Most Esteemed Peer-Reviewed Journals Cited by Online BRP Awardees

JOURNAL	TOTAL	HYPOTHESIS-DRIVEN RESEARCH	DESIGN-DRIVEN RESEARCH
American Journal of Physiology	2	1	1
American Journal of Respiratory Cell and Molecular Biology	1	1	
Annals of Biomedical Engineering	1	1	
Annals of Thoracic Surgery	3	1	2
Circulation	4	1	3
Circulation Research	3	1	2
Clinical Pharmacology and Therapeutics	1		1
IEEE Proceedings on Robotics and Automation	1		1
IEEE Transactions in Medical Imaging	1		1
Journal of American Society of Nephrology	1		1
Journal of Artificial Organs	1		1
Journal of Biomechanical Engineering	2	1	1
Journal of Magnetic Resonance	1		1
Journal of Thoracic and Cardiovascular Surgery	3	1	2
Kidney International	1		1
Magnetic Resonance in Medicine	1		1
Medical Physics	1		1
Nature	4	2	2
Nature Materials	1		1
Pharmaceutical Sciences	1	1	
Physical Review Letters	1		1
Proceedings of the National Academy of Sciences	3	1	2
Proceedings on Medical Image Computing and Computer-Assisted Intervention	1		1
Science	4	2	2
Trans American Society of Artificial Internal Organs	1		1
TOTAL	**44**	**14**	**30**

The nine BRP awardees with hypothesis-driven and design-driven research projects listed these journals among their "top five peer-reviewed journals" that they felt "are most esteemed" in their fields of research. The counts show the number of times each journal was mentioned. (One awardee listed only four journals.)

The fields of BRP awardee research clearly influence which journals are deemed most esteemed. However, with just nine respondents, we did not attempt to control for this or to group journals by the fields of research. Peer-reviewed journals most esteemed by all types of researchers (in order of most citations and alphabetical when tied) include:

Circulation	4
Nature	4
Science	4
Annals of Thoracic Surgery	3
Circulation Research	3
Journal of Thoracic and Cardiovascular Surgery	3
Proceedings of the National Academy of Science	3

There is some overlap in journals cited as most esteemed by hypothesis-driven and design-driven researchers. Journals in some fields, however, seem to relate more to design-driven research—those in the fields of robotics and imaging. This finding may be merely an artifact of the small group size and the specific fields of research included within this group.

The *quantity* of articles published or accepted for publication in peer-reviewed journals is an important component of this key metric. The following exhibit shows the numbers of publications for the seven BRP awardee respondents who provided them in the online interviews and the eight BRP awardees who were the subject of the case studies and had data in their files on publications. The numbers of publications are tabulated by the type of research, the source of the data, the years of funding through 2005, and the number of lead investigators. A publication "index" is calculated to show the number of publications per lead investigator per funded year of research.

Exhibit 2. Publications by Years of Funding to Date and Number of Investigators

Research Type	Data Source	Years of Funding to Date	Number of Lead Investigators	Number of Publications	Publication "Index"
Design-Driven Research (N=9)	Case Study (N=4)	4	3	6	.50
		5	3	47	3.13
			4	7	.35
		7	7	13	.27
	Online Interview (N=5)	3	4	1	.08
			5	0	0
			5	1	.07
			10	15	.50
		4	4	8	.50
Hypothesis-Driven Research (N=6)	Case Study (N=4)	4	4	3	.19
			7	10	.36
		5	3	21	1.40
			5	16	.64
	Online Interview (N=2)	4	11	12	.27
		6	6	42	1.17
Totals		**65**	**81**	**202**	
Means		**4.33**			**.63**

For 15 BRP awardees, this table tabulates the number of publications by the type of research, the source of the data, the years of BRP funding to date (through 2005), and the number of lead investigators. A publication "index" is calculated to show the number of publications per lead investigator per funded year of research—the typical lead investigator produces an average of .63 publications per funded year of research.

Collectively, the 81 lead investigators produced 202 publications during an average funding period of 4.3 years. The typical lead investigator produces an average of .63 publications per funded year of research.

Keeping in mind that this "statistic" is based on very limited data from varying sources, one can use this mean publication rate to note publication rates that are markedly above average. There are three such rates—3.13, 1.40, and 1.17. These rates are associated with higher than average years of funding—5, 5, and 6 years, respectively. It is likely that with the passage of time, research progresses and produces definitive results that are appropriate for publication. There was no difference in the publication rate for design-driven and hypothesis-driven researchers.

In an attempt to assess publications in terms of both quantity *and* quality, a tally was made of the publications cited by the online awardee respondents that were published or accepted for publication in journals designated as most esteemed. Publications cited in the case studies are not included in this tally because these awardees did not have a group of journals designated as most esteemed. Also, it is unlikely that their specific fields of research overlap perfectly with those of the online respondents, and thus the group of esteemed journals cited by online awardees is likely not sufficiently inclusive.

A total of 26 or 58% of the 45 publications listed by online awardees were or will be published in peer-reviewed journals deemed most esteemed by these same awardees. Esteemed journals with the most publications are:

- Journal of Biomechanical Engineering 5
- Proceedings of the National Academy of Sciences 5
- Journal of Thoracic and Cardiovascular Surgery 4
- American Journal of Physiology 3

These attempts at quantifying the quality and quantity of publications should be viewed as preliminary in their approaches and procedures. Considerations for future evaluation include the following.

- ***Esteemed journals likely differ by subject fields and type of research***
  Researchers in different subject fields and conducting hypothesis-driven and design-drive research probably esteem different groups of journals. Obtaining consensus about which journals are most esteemed in the different fields and types of research will be useful in evaluating the quality of publications.

- ***Counting publications is not straightforward***
  The case studies list publications resulting "in whole or part from support" by the BRP award. The online interview asked about articles "published or accepted for publication" by "this BRP research partnership." Some awardees included abstracts among their publications. Some included publications not authored by a lead researcher. Future evaluations should craft precise instructions that define the type of publications to be listed—for example, that their authors include a lead researcher in the BRP partnership, and that the findings reported in the article result from BRP support.

- ***Recognize the limitations of counting publications***
  The concept of using numbers of publications in esteemed peer-reviewed journals as an important metric of the success of the BRP Program may not be valid or easily implemented. Counting publications and computing publication indices assumes that the value of articles in peer-reviewed journals is equivalent, regardless of content. Nonetheless, even with its limitations, the publication metric may be more doable and better than other metrics.

Research and Educational Tools. One key metric addresses whether research and educational tools are interim products for hypothesis-driven researchers:

► **1A.1.6: Research and educational tools derived from BRP-supported research that increase health knowledge directly or indirectly by enabling others to do so (number and types)—Hypothesis-driven research**

The online interview asked the three BRP awardee respondents who classified their research as hypothesis-driven about research or educational tools:

> "To date, have any research or educational tools been derived from the BRP-supported research? (Research and educational tools are any products, processes, or services that increase health knowledge directly or indirectly by enabling others to do so.)"

These three awardee respondents answered affirmatively, but only two specified or described the tools:

- Src reporter to determine the dynamics of Src by fluorescence resonance energy transfer
- Surgical planning tools are being developed

The case studies provided in-depth descriptions of the BRP research—its goals and achievements, thus making it possible to abstract information on research and educational tools. For the four awardees with hypothesis-driven research, these accomplishments appear to qualify as tools derived from the BRP-supported research:

- BRISK (Block Regional Interpolation Scheme for K-Space) magnetic resonance imaging approach to assess valvular dysfunction quantitatively
- Developed a reproducible coarctation-induced hypertension model in the pig; mathematical model for vascular growth and remodeling
- Demonstrated directional arterialization, importance of PDGF-BB and TGF-β from vascular cells in vascular patterning, and constructed the first multi-cell simulation for vessel assembly
- Illuminated the mechanisms of inflammatory responses induced by oscillatory shear exposure of endothelial cells; developed a micro-CT based methodology to determine and correct for distortions caused by acrylic processing

It seems obvious that these sophisticated approaches, models, and methodologies must increase health knowledge. However, it is not clear how to assess methodically if they indeed do so or to quantify the degree to which they do. In many ways, the text supplied by the online respondents or abstracted from awardees' files (BRP applications and progress reports) appears to be much

the same as the accomplishments of the goals of their research. Thus, considerations for using this metric in a future evaluation include:

- ***Defining research and educational tools more precisely is important***
  Our experience in reviewing data about this metric leads us to now believe that research and educational tools may not be distinct from the end-products of hypothesis-driven research. The initial understanding for this project was that research evaluating hypotheses yields information, and that tools produced along the way as part of the learning or discovery process could be viewed as an additional bonus. This issue should be clarified in future evaluations.

- ***Counting research and educational tools may not differentiate between successful and less successful awardees***
  Obtaining a listing of research and educational tools is informative and illustrative of the range and kinds of achievements BRP awards fund. However, it may not differentiate between successful and less successful awardees, even if research and educational tools were defined well enough to distinguish them from the BRP projects' end results or products. It is not apparent how to evaluate and order the quality of research tools and products.

Citations. Another key metric relates to published citations about BRP-supported research:

► **1A.1.7: Published citations of BRP-supported research (number and type)—Hypothesis-driven research**

In order to learn if the awardee authors could provide information on the number of times their articles had been cited by other authors, the online interview asked awardee respondents who classified their research as hypothesis-driven:

> "To the best of your knowledge, have any of these publications been cited by other authors in their published articles?"

If so, the respondents were asked to estimate the number of such citations. Two of the three awardees with hypothesis-driven research responded positively and provided estimates of 650 and 25 citations. The third awardee respondent indicated that he was "not sure; didn't know." The number of publications cited by these three respondents is 42, "many," and 12, respectively.

It is not clear how accurate awardee recall is with regard to numbers of citations. It is likely that the two provided responses are "guesstimates." Resources likely to yield more reliable counts of citations exist. The Science Citation Index (SCI) provides access to current and retrospective bibliographic information, author abstracts, and cited references. An expanded format is available online through Thomson Scientific's Web of Science, "SciSearch." It is likely that consulting firms with expertise in using this and similar databases could provide better counts of citations.

"Google Scholar" is currently in beta test online and freely available for anyone to use. It searches, locates, and displays articles by authors, giving counts of publications and the numbers of citations of each of the publications. The advanced search mode lets the searcher define a time period for the publications, a subject area, explicit words and phrases to look for, and specific journals to search. An initial quick foray into using this

tool resulted in over 350 articles (10+ screen pages of results) for one BRP awardee (the one who cited 42 publications and 650 citations) and an average count of 70 or so citations for each article. Clearly, the problem is one of limiting the search by precisely defining the various parameters that should constrain it.

Considerations for using citation enumeration as a metric of BRP awardee success include these:

- ***Locating and counting citations requires skill and is time consuming***
  Awardees probably do not have accurate knowledge of how many times their publications are cited. Experienced or professional searching of citation databases should yield more precise counts.

- ***Citation searches need to be limited to publications resulting from BRP support***
  The initial foray mentioned above likely located publications based on research supported by the BRP Program and by other entities as well. This is why it located so many articles. Also, it may include publications by authors with similar names (many use just a first initial that, combined with a common last name, may not define a unique author). Defining parameters to limit a citation search to avoid these and similar errors is important.

BRP Outcomes. Two key metrics focus on a variety of results of BRP-supported research:

► **1A.2.4: New or improved BRP-supported products, processes, usages, services, or clinical research in health-related fields (number and types)—Design-driven research**

► **1A.2.6: Patents, copyrights, trademarks, or licenses for new or improved BRP-supported products, processes, or services in health-related fields (number and details)—Design-driven research**

The online interview asked the six NHLBI BRP awardees who define their research as design-driven:

> "Which one of the following most characterizes the product, process, usage, or service that was planned under this BRP partnership?"

The awardee respondents characterized their project output as:

A totally new product, process, usage, or service	2
A combination of products, processes, usages, or services	3
A new use for an existing product, process, usage, or service	1

Clearly, all BRP awardees with design-driven research are planning and working to produce novel or improved products. The interview attempted to learn more about the BRP-supported products, processes, usages, and services by asking:

> "Has this research partnership received any patents, copyrights, trademarks, sales of licenses, or sales related to the BRP-supported product, process, or service?"

None of the six partnerships responding online had received any of these items yet. Data abstracted from the *case studies* of design-driven research yield three partnerships that received

some of these items or other indications of progress towards commercialization of their products, processes, or services:

BRP Award: Magnetic Resonance Guided Electrophysiology Intervention (1999)
- 8 patents
- FDA approval for human testing of a new clinical grade catheter for use with low-power MR scans
- 4 young investigator awards

BRP Award: Bioengineering Design of Artificial Blood (2000)
- MP4 (Hemospan®)
- Completed European clinical trials; approval by Swedish MPA to proceed to Phase Ib/IIa studies; U.S. clinical trials scheduled to begin (as of 2005)

BRP Award: New Approach for the Treatment of Asthma (2001)
- Alair® System

Note that the start dates for their BRP funding (shown in parentheses above) are 1999, 2000, and 2001. This means that these partnerships have had at least six, five, or four years of funding to date (through 2005). The design-driven BRP partnerships that responded online had funding start dates from 2000 through 2003. The funding start dates, years of funding to date, and numbers of partnerships within each category are shown below.

- 2000 5 years 1 partnership
- 2001 4 years 1 partnership
- 2002 3 years 1 partnership
- 2003 2 years 3 partnerships

Clearly, receiving patents, registered trademarks, and clinical trial approvals takes time. Considerations for using 1) enumeration of novel products and 2) achievements such as patents, copyrights, trademarks, and licenses for future evaluations include:

- ***Enumerating new or improved products may not be meaningful***
  A categorization and listing of the products could be informative and descriptive of BRP achievements, but this metric is not likely to differentiate between successful and less successful awardees. The degree of achievement may be the critical element, and that may be measured better by the attainment of concrete metrics such as patents and the like.

- ***Counting interim measures could be useful***
  Achieving patents, register products and clinical trial approvals takes time, so counting interim measures could be useful in monitoring success. Enumerating provisional patents filed at the patent office (public information) and the number (not content because this is private information) of patent disclosures written within the university or company, for example, might serve as additional measures of success during the time period when actual patents are yet to be achieved. Similarly, enumerating interim steps along the road to achieving FDA approvals could serve as additional metrics.

The online interview asked about a related issue that tends to be associated with successful achievement or commercialization of the project's end goals—whether the partnership had received any additional non-NIH funding or capital for the BRP project. Two of the nine online awardee respondents reported that they had received additional non-NIH monies from these sources:

- Department of Veterans Affairs; Dialysis Research Foundation (non-profit); National Kidney Foundation of Utah and Idaho (non-profit)

- Cleveland Clinic Foundation; Foster Miller Technologies, Inc.

Importance of BRP Funding. A key indicator of interest was the importance of funding—whether the BRP Program was funding projects that would not otherwise be funded by another NIH program:

► **1B1.2: BRP awardees who submitted BRP project hypothesis or design to another NIH program (specify name) before submission to BRP program and did not receive NIH funding prior to BRP—All awardees**

The online interview asked the nine BRP awardee respondents:

> "Was your BRP project hypothesis or design rejected by another NIH grant program before it was submitted to the BRP Program?"

All nine answered negatively. Information to answer this question was not contained within the data files used for the case studies.

The purpose of this key metric was to learn if the BRP Program was indeed meeting a need in funding research that would not otherwise be funded. This interview question did not yield any information to address this issue. However, several others did—one in the online interview and two in the online evaluation.

This question was asked of all nine BRP awardees during the online interview:

> "If the BRP Program were not available, would the project funded by the referenced award still have been pursued?"

Two awardee respondents said that it would have been pursued, but seven respondents said that it would not have or they were not sure if it would or would not have been pursued.

The online debriefing survey asked about this issue more specifically in two questions:

> "Do you believe that the BRP Program funds research that might not otherwise be funded by other NIH programs?"

> "Do you think that the aims and goals of your project could be accomplished by smaller, independent investigator grants?"

All seven BRP awardees who participated in the debriefing survey answered "Yes" to the first question and "No" to the second. Clearly, the awardees believe that the BRP Program funds research that might not otherwise be funded, and that without such funding, many of their projects might not have been pursued. It may be that funding for this type of large-scale, multi-discipline, design-driven research was not sought previously by the awardees because they knew that it was not available until the creation

of the BRP Program. Thus, their project hypothesis or design was not submitted to another NIH grant program prior to the BRP submission.

Several of the respondents' verbatim comments convey these beliefs well:

> "Smaller, independent investigator grants would not have the kind of interdisciplinary synergism [that the large ones do] under the BRP. Without the BRP, not only would we lose the synergistic cooperation across disciplines, [but] in fact many of the proposed research [projects] would never have been thought of and pursued."

> "Our project needs a TEAM approach with researchers with different backgrounds. Smaller grants would not allow such a large team as we have (10-12 investigators) to collaborate in a truly interdisciplinary manner."

An important consideration about using this metric enumerating the BRP project hypotheses and designs submitted previously to an NIH grant agency, but not funded, follows.

- ***Hypotheses and designs submitted to BRP differ from other grant requests***
  The research proposals submitted for funding by the BRP Program differ from other grant requests. They more typically involve cooperation across disciplines, large research teams, higher budgets, and design-driven as well as hypothesis-driven research. It is not likely that these types of proposals would have been submitted previously to NIH grant agencies. Thus, this metric may not be a useful one for learning whether the BRP Program is funding research that might not otherwise be funded.

BRP Researchers' Disciplines. A key metric of interest was the scientific field of BRP awardees' professional staff:

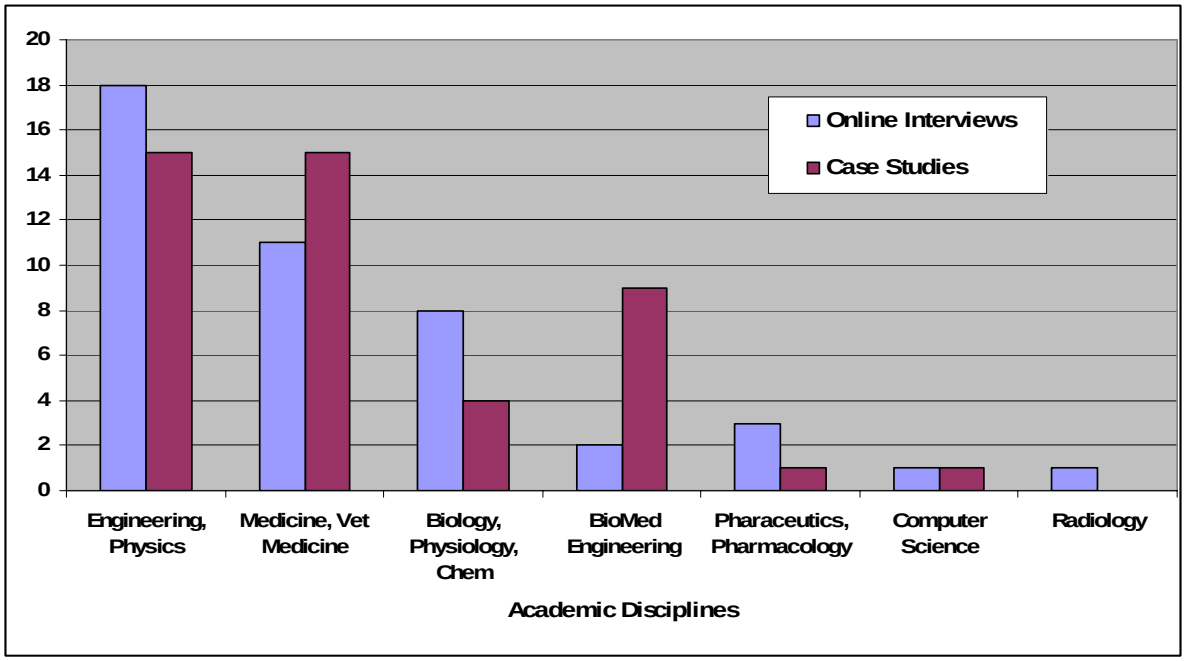
► **2A.1.1: BRP awardees with staff professionals who have engineering, physical, and computational science degrees—All awardees**

The BRP awardee partnerships include researchers from both medical and scientific fields. The two most common academic disciplines are engineering/physics and medicine/veterinary medicine. The following chart shows the disciplines of PIs and lead investigators, as reported in the online interviews and summarized in the case studies.

Nearly all of the 18 BRP partnerships in either the online interviews or the case studies included at least one lead investigator from the discipline Medicine/Veterinary Medicine. Three of the partnerships included in the interviews and one among the case studies did not include either an M.D. or D.V.M.

For this feasibility study, when investigators held either M.D. or D.V.M. and Ph.D. degrees, they were classified under Medicine/Veterinary Medicine. When the academic discipline on the most recent degree differed from the academic field of the current position, the investigator was classified by the discipline on the degree.

Exhibit 3. Academic Disciplines of Lead BRP Awardee Investigators



Engineering/Physics and Medicine/Veterinary Medicine are the two most common academic disciplines reported by respondents in the online interviews and summarized in the case studies.

A consideration for future evaluation of academic disciplines represented within the BRP partnerships follows.

- ***Classifying Investigators' Academic Disciplines is Difficult***
  Many investigators hold multiple degrees, such as a Ph.D. and an M.D., that can be classified within different disciplines. University appointments are not necessarily in the same field of research as the investigator's most recent academic degree. Additionally, some researchers hold joint appointments within universities and medical schools, medical schools and hospitals, universities and private companies, and other combinations of institutions that involve research in multiple disciplines. Asking the PI and lead investigators to define or select from among a list their key fields of research within the partnership for this BRP award may yield more useful information.

Research Partners' Experience at NIH. Another key metric of interest is whether the BRP Program is increasing collaborations:

► **2A.3: BRP awardees that include a research partner that had never partnered in an NIH-funded project prior to the date of award—All awardees**

The online interview asked the BRP awardee respondents:

"How many institutions are partnering together on this BRP award?"

"Please list all of the institutions that are partnering together on this BRP award. Put an asterisk (*) before any of the institutions that, to the best of your knowledge, have never partnered in an NIH-funded project prior to the receipt of this award."

The nine online awardees reported the following numbers of partners on their BRP projects. Five of the BRP awardee partnerships—more than half—contained four partners:

- 2 BRP awardee partnerships contained 1 partner
- 2 BRP awardee partnerships contained 3 partners
- 5 BRP awardee partnerships contained 4 partners

Three of the nine online awardees—that is, three of the four-partner partnerships—indicated that they included an institution that, to the best of their knowledge, had never partnered in an NIH-funded project before. The three new institutions appear to be commercial entities (not universities or hospitals).

The case studies abstracted data from the BRP award files to answer two questions: Was the PI new to NIH funded research? Were the award partners new to NIH-funded research? All nine of the PIs whose awards are profiled in the case studies had received NIH funding prior to the BRP award. Two of the partnerships included one partner who had never partnered in an NIH-funded project before. (For four of the case study BRP partnerships, the data files did not contain sufficient information to answer the second question about partners new to NIH funding.)

The online debriefing survey asked about a related issue:

> "Do you feel that the BRP Program increases collaborations between the engineering, physical, and computational sciences and the biomedical and/or clinical sciences?"

All seven of the respondents believed that the BRP Program did—six felt that it definitely does increase collaborations, and one that it sometimes does increase collaborations.

A consideration for using this metric about partners new to NIH funding in a future evaluation:

- ***Ask for this information directly***
  The question about whether any of the partners were new to NIH-funding appears to be easily answered by the PI. It is more difficult to locate this information in the awardee data files. Thus, it makes sense to ask specifically for this information.

2.2 Measuring Success of the BRP Program

Measuring the success of the BRP Program is a challenge for many reasons. This section discusses findings from the feasibility study that address what constitute ideal measures, which measures are pragmatic, the validity of a distinction between hypothesis-driven and design-driven research, and sources of data that might yield good measures.

Best Measures of Success. The first and probably most important of the two specific goals of the BRP Program is to "encourage basic, applied, and translational bioengineering research that could make a significant contribution to improving human health." Simply put, what NHLBI wants to know, as a staunch and ardent funder and promoter of this research is, "How successful is the BRP Program? Are the recipients of BRP awards making significant contributions to improving human health?" When you address their issues directly, as the online interview did,

all the BRP awardees believe strongly that they are making significant contributions to improving human health. Several awardee respondents state this eloquently:

> "The goal of this Partnership is to develop techniques and procedures to correct heart defects without the use of conventional open heart techniques such as cardiopulmonary bypass and heart arrest, [which] cut off the blood supply to the heart temporarily. Bypass and heart arrest techniques account for much of the morbidity and mortality of open heart surgery. Therefore, avoiding their use will have a significant impact on survival and complications of cardiac surgery."

> "We have obtained the world's first human images of pulmonary gas exchange with this BRP. In addition, we have already demonstrated that some of the long accepted mechanisms of pulmonary physiology are actually not correct. Therefore, my colleagues and I all are extremely excited about our research and believe it will have enormous potential both in assisting diagnosis of pulmonary disease [and] enhancing our basic understanding of lung physiology, and providing a tool for the pharmaceutical industry that will speed up aerosol drug development and thereby reduce the development cost of these drugs, which will reduce the cost to the consumer."

Nonetheless, these statements of goals and achievements describing major contributions to the improvement of human health are not quantifiable. Also, alas, some may remain merely goals and never achieve realization. So, we are left grappling with the question of how to best measure success, granted that we have only imperfect yardsticks and procedures that in no way can presume to quantify the quality and quantity of significant contributions to improving human health.

The online debriefing survey asked BRP awardees directly how to measure success:

> "How should NIH measure the successes achieved by BRP awardees? What metrics or measures are most important?"

The awardee respondents know what should be measured, yet understand the inherent difficulties:

> "The impact on improved healthcare"

> "The metric is achievement of results promised in the grant [application]."

> "Evaluation of the work by peers is the only true measure of importance."

> "Perhaps by surveying the opinions of peers in the field, which is rather difficult. Short of that, number of citation seems to be the only option, though it is not ideal."

> "The number of publications is an index of productivity and the number of citations evaluates the impact of the work on the scientific community. Number of citations, unfortunately, takes time to build up, even on work that turns out to be very important to a given field. Truly objective metrics are difficult."

When the awardee respondents were asked how important an indicator of success is the number of citations of articles published by BRP awardees, six of the seven respondents to the debriefing survey responded "Important" and one said "Unimportant." No one answered "Very important"

or "Very unimportant." It seems that citations may not be the best measure of success, but it was not apparent what metrics were both better and yet practical.

Design-Driven Versus Hypothesis-Driven Research. The evaluation framework, which drafted and organized the metrics for assessing the success of the BRP Program, took its clues from the statements of missions and goals that BECON promulgated. They make a distinction between hypothesis-driven research, which is typical of the research funded by more traditional NIH grants, and design-driven research, which can "focus on technology development rather than on proving or disproving scientific hypotheses" (BECON Symposia recommendation). Thus, this feasibility study used somewhat different metrics for these two types of research in assessing project success.

The online debriefing survey asked respondents about the validity of this division:

> "This evaluation makes a distinction between hypothesis-driven or discovery-driven research and design-driven or developmental driven research. Do you think that this is a valid or important distinction in assessing the outcomes of BRP awards?"

All of the seven respondents answered "Yes." They provided various reasons why.

> "[This distinction is] critical, because the issues and objectives of performing these kinds of research are very different. My attempt to renew my grant has been badly handicapped by reviewers who don't see enough new innovations in my development-oriented project. Making things work doesn't impress them."

> "Because the way research is conducted, and hence the criteria of review, is different between these two."

> "I answered yes, but it is a soft yes. All design-technology driven proposals are fundamentally based on the need to advance a technology to address a specific problem, and that component is hypothesis driven. It merely provides a venue to support research to develop new, USEFUL tools that must be justified in terms of a hypothesis-driven project."

Best Sources of Data. The feasibility study collected data from two sources—BRP awardee data files (award applications and progress reports that were summarized in the case studies) and in-depth online interviews (followed by a short debriefing survey). Both of these data sources provided good information, yet each has limitations. This section discusses these two sources of data and offers suggestions for future evaluations.

Awardee Data Files. Much rich data already exist in the BRP awardee data files. In theory, these data have the advantage of not needing collection, just abstraction. Because the majority of the information to assess the BRP Program is factual—enumeration of specific concrete achievements—and not opinion that is best collected by surveys, using existing data is efficient and economical. No additional burden is imposed on busy awardees, who have already supplied much of the desired information, and no extra costs need be incurred.

As NIH implements electronic receipt and storage of award applications and progress reports, the online data will become more readily accessible. Currently, however, perhaps as an artifact of paper record keeping, the data are not organized as well as they could be—both physically and

logically. BRP award folders are not always complete. Some information exists in hard copy and others as electronic reports. Often, there is no cross-referencing in the folders that indicates there are additional data records online or on paper. Additionally, what information is stored online appears to be saved primarily as page images, not in databases. Thus, it is more difficult to locate specific facts, tally numbers, and produce summary tables and reports.

With online collection of award applications and project reports moving full steam ahead in the NIH, some data responses—particularly quantifiable data—could be categorized for easier access. Other textual data could be stored as discrete responses to specific questions. The goal should be to store information so that the facts about particular issues and the answers to specific questions are easily retrieved. It should be possible to easily learn how many publications a partnership has authored, without counting them. That total number could be stored as a separate value. It should also be possible to view all the authors, the dates of publication, the names of the journals, and the titles of the articles as separate variables, and not just as pages of words. This would make listing and evaluating the journals, for example, in terms of the esteem in which they are held, relatively straightforward. One could just view or print the database field containing "Journal Titles." One could code each journal in terms of its rank in peer esteem. In addition, online collection would enable tracking of publication status over time, as manuscripts move through the publication process. Separate fields could be used to identify status, such as "in preparation," "submitted," "in press," or published.

Also, at the time that BRP awardees are strongly motivated to provide information—for example, when they are applying for funding or citing their progress in a required report—questions useful in evaluating success could be included among the application and report requirements. For example, if one wants to learn how many patents a partnership has, there should be a specific question asking that. The number of patents should be stored, as well as the listing of patents—and that listing should be stored with the information broken out into separate variables, such as patent number, patent name, date of patent, and so on. This would make computing the total or mean numbers of patents or tabulating numbers of patents by years of funding trivial. It would make reviewing the titles of patents straightforward and easy.

In summary, much useful information for evaluating the success of the BRP Program exists, will exist, or could exist in award application and progress report data files. Better organization and storage as categorical data and discrete numeric and text variables would make the data easy to access, quantify, and tabulate. Asking for and including the precise information desired for measuring success will ensure that metrics for evaluation are available and obtainable.

Online Interviews. Online data collection is an efficient and relatively quick way to gather new or different information. As typically happens in most online surveys, the in-depth interview and debriefing survey confirmed this. Additionally, because the data are supplied as categorical or text responses to specific questions, it is relatively straightforward and easy to locate specific information, summarize categorical and quantitative responses, and search text. If the move within the NIH from paper to electronic data collection will take time and result in some disorganization during the transition period, and if near-term BRP evaluation needs require immediate information, then an online survey is an alternative approach.

The online in-depth interview and short debriefing questionnaire were not a survey but can be considered to represent an initial, informal pretest of an actual, full-scale survey. Fielding an actual survey would require strict adherence to accepted survey procedures, schedules, and follow-up techniques that were not employed for this feasibility study. This would enhance the likelihood of obtaining a high response from the awardee population. Such an approach would probably require one or two focus groups and pilot testing to finalize the metrics, precise wording of the survey items, and most efficacious procedures, prior to implementing a full-scale survey.

For example, the collection method for some responses to the in-depth interview could be improved to maximize retrieving, sorting, listing, and tabulating data. Using procedures similar to those described for online collection of application and report data, the lists of partner institutions could be stored with their names, address information, and status in terms of previous partnering in NIH-funded projects as separate variables. This would make it simple to sort and list partner institutions by various parameters such as type of institution (university, hospital, or commercial) or geographical location.

The feasibility study conducted an online in-depth interview with just nine participants; it did not pretest a survey. Thus, calculating response rates is not meaningful. Nonetheless, eliciting participation with the online interviews highlighted the issues associated with respondent burdens. Care should be taken to ensure that electronic messages can reach intended recipients. Awardee respondents have to take time to answer questions and list information, and they are busy people. Sometimes, they have already have supplied the required data in award applications, progress reports, and final reports. Awardees need motivation to participate. Responding needs to serve a positive purpose and meet an awardee need before awardees feel inclined enough to overcome the perceived burdens of responding and participate in an interview or survey.

In summary, the ideal online data collection is likely one that occurs before the receipt of award funding, as a condition of that funding, or before renewal of funding—when there is both need and motivation. To minimize respondent burden and make use of this motivation, the best long-term approach is to include evaluation metrics within the award application, progress report, and final report data collections that already take place. Conducting these collections online and storing much of the data as discrete variables would make it easily available for analysis in future evaluations. Depending upon BRP evaluation needs, the best near-term approach might be conducting an online survey soon and planning to meet future evaluation needs using ongoing existing data collections.

2.3 Possible Comparison Benchmarks for Future Evaluations

The online in-depth interview asked respondents which group of researchers would be a good comparison group for BRP awardees:

> "NIH seeks to compare the successes achieved by BRP Program awardees with those achieved by other comparable groups. Which group of comparable researchers do you think would make a good comparison group for BRP awardees?"

The awardee respondents appeared to have some difficulty specifying an ideal comparison group, but eight of the nine did give one or more suggestions. The most commonly recommended comparison group is Program Project Grant (PPG) awardees (six mentions). The next most common is Specialized Centers of Research (SCOR) awardees (two mentions).

> "There is no comparable group. Perhaps the closest would be NSF, or certain NIH Program Project Grants."

> "Program Project Grants are the closest similar funding program. However, in contrast to PPGs, the BRP program deals with somewhat smaller projects that involve two to four groups, with smaller budgets and a tighter focus on the individual components compared to PPGs. In this respect, it is fair to say that the BRP program is unique, in that it expects investigators from different fields to merge and join their efforts to a common goal. PPGs tend to deal with the same topic but the approaches to solving the problem can be similar and there is no expectation that the projects have to be combined for its ultimate success."

> "Specialized Centers of Research (SCOR) Grants"

> "Program Projects and SCORS"

> "Program Project Grants based around technology development, or the recently announced NIBIB P20 Quantum Exploratory Grants"

2.4 Improving the BRP Program

With a view towards making suggestions to NIH on the administration of the BRP Program, the online interview asked awardee respondents about obstacles or difficulties that the partnership had encountered and how NIH could further assist awardees:

> "What is the greatest obstacle or difficulty that this partnership has encountered so far in its progress toward achieving the goals set out in the partnership's application for the BRP award?"

> "What could NIH do to further assist BRP Program awardees—in applying for a BRP award, in producing progress reports, in achieving success reaching stated goals, or in any other areas?"

There appear to be two general areas of obstacles or difficulties—one concerns funding and the other project organization. In the area of funding, awardees cited the relatively short duration of the funding period, needing enough money to include all the people necessary to do all the project tasks, and delays related to not funding applications with scores near the "pay line" initially that were subsequently funded. In the areas of difficulty relating to project organization, awardees mentioned organizing the project infrastructure, re-orienting PI priorities toward completing the proposed experiments, and interactions with all of the institutional intellectual property offices.

When asked how NIH could further assist BRP awardees, three awardees included strong praise for the BRP Program along with their suggestions:

> "Overall NIH has done an outstanding job with the management of the BRPs."

"Well designed outstanding program"

"In general, I think the concept of the BRP is excellent."

The suggestions on how NIH could assist BRP awardees organize themselves into three main areas—funding, reviewers, and cross-discipline research. With regard to funding, awardees asked for monies to cover continuing research. They wanted the provision of bridge funding at the end of the first five years until renewal funding could be obtained, a program where BRP projects that produce exceptional results could be considered for additional funding with faster turnaround than normal, and the expansion of the BRP Program with more grants (not more funds per grant) to fund subsequent related studies.

With regard to reviewers of BRP award applications, the awardees had a consensus that the reviewers did not always have the correct orientation when reviewing design-driven research:

"Train reviewers better. I have troubles with people who approach my design-oriented work with a basic science orientation….. [Reviewers need to] understand that not all grants are the old fashioned RO1 type of project."

"Recruit more clinically-oriented reviewers in review process."

"Although the BRP is aimed at hypothesis-driven research, it often relies [on] and proposes the development of a new method or technique, which is critical to advance a field. The development of a new method then becomes the apparent driving force of the BRP, and study sections penalize the applicants severely if the proposal not only addresses all concerns regarding the new technology but also provides in detail the subsequent studies that will apply the technology to test a specific hypothesis."

Awardees appreciated the fostering of cross-discipline research that is the basis of BRP Program awards and offered suggestions that this be continued:

"By encouraging more cross-disciplinary interactions between biomedical engineers and clinicians."

"Continue to foster bridging of the life sciences with physical/engineering sciences."

"The yearly PI meetings especially provide an opportunity to interact with other investigators and facilitate cross-fertilization. There needs to be more of this type of activity."

One awardee valued the basic premise of the BRP Program because:

"Senior leadership within my school neither values nor relates to research that bridges life sciences with physical/engineering sciences."

3. Conclusions and Recommendations

This section of the report summarizes conclusions based on the findings presented previously and makes recommendations. The first part describes a typical BRP award and project by summarizing their predominant characteristics. The next part gives recommendations for administering and evaluating the BRP Program.

The conclusions and recommendations are based on preliminary findings from this feasibility study. Because they are based on data from just nine respondents to the online interview and nine case studies, the findings have to be viewed only as rough estimates of the more precise ones that could be obtained in a full-scale evaluation. Thus, the conclusions and recommendations are also preliminary and merely suggestive of the more definitive ones that would derive from a large respondent base.

3.1 Typical BRP Award and Project Characteristics

This feasibility study was able to identify some BRP award and project characteristics that may be typical. The summary of these characteristics afford an overview the BRP Program.

Because of its relatively large scope, cross-disciplinary nature, and design-driven as well as hypothesis-driven research, the typical BRP project was crafted and proposed specifically for a BRP Program award. It is not a project hypothesis or design that was rejected by another NIH grant program before it was submitted for BRP funding. All of the awardees believe that the distinction between hypothesis-driven and design-driven research is critical. They think that the BRP Program funds research that might not otherwise be funded by other NIH programs, and that the project aims and goals could not be accomplished by smaller, independent investigator grants. Most of the BRP awardees believe that the project funded by the BRP Program might not have been pursued if BRP funding was not available.

The typical BRP-funded project includes researchers from both medical and science fields. All of the partnerships include investigators in engineering, physical, or computational sciences, and nearly all include at least one lead investigator in medicine or veterinary medicine. Most of the partners have worked together or collaborated previously with the PI. Three of the nine BRP partnerships include a partner that had never previously partnered in an NIH-funded project prior to this award. This new partner is a commercial entity. All of the awardees believe that the BRP Program increases collaborations between the engineering, physical, and computational sciences and the biomedical and/or clinical sciences.

Ideally, awardees believe that the best way to evaluate the success of the BRP Program is to gauge the impact of awardee research on improved healthcare, to measure the degree of achievement of the results promised in the award application, and to assess the quality of the research by peers. Pragmatically, however, the awardees understand that numbers of publications and citations, though far from perfect, are “an index of productivity” and “impact of the work on the scientific community.”

The typical BRP partnership publishes in peer-reviewed journals and yields approximately .6 articles per investigator per funded year of research. Five or more years of funding tends to increase this publication rate. More than 50% of the publications are in journals that the awardees deem most esteemed in their fields. Estimates of the number of citations of publications provided by the awardees were variable and could not be validated in this feasibility study. Projects with a minimum of four to five years of funded research may report achieving patents, registered products, and clinical trial approvals.

There is probably no perfectly comparable group to serve as a good comparison set in comparing the successes of BRP awardees with those of other awardees. The BRP awardees believe that the Program Project Grant (PPG) and Specialized Centers of Research (SCOR) awardees may be the best available comparison groups.

3.2 Near-Term Recommendations for Administering the BRP Program

The BRP awardee respondents offered suggestions that could enhance the BRP Program:

- Continue training and orienting reviewers so that they understand the basic premise underlying BRP Program awards and evaluate award applications appropriately.
- Speed up renewals of funding to avoid delaying important research.
- Enhance cross-disciplinary research by promulgating government health needs and desires and organizing conferences to foster learning and new relationships.

Findings about the availability and accessibility of awardee records suggest the need for Program officials to take steps to ensure that complete files are available for all awardees in either paper or electronic form. During the transition from paper to electronic recordkeeping, consider using a system to cross-reference records that are stored in multiple files.

3.3 Best Options for Future Evaluations of Program Success

Future evaluation of BRP Program success should build on the lessons learned in this feasibility study about what data are likely to be most useful in gauging degree of performance attainment. As a first step for future assessment of the success of the BRP Program, Program officials should review the evaluation framework developed during this project. They may wish to trim the list of metrics to include those identified as the most useful and pragmatic indicators of success. As a second step, Program officials will need to evaluate the urgency of their assessment needs and consider the relative burdens and costs of conducting a full-scale online survey or incorporating performance metrics into regular reporting requirements.

Evaluation Metrics. The metrics evaluated in this feasibility study that appear to be both respected by the awardees and to differentiate among BRP project outcomes in terms of the first BRP Program goal—to make a significant contribution to improving human health—include:

- Publications and articles accepted for publication in peer-reviewed journals and in highly esteemed journals

- Citations of publications in peer-reviewed journals
- Patents, copyrights, and trademarks
- Sales and sales of licenses

Additional metrics not evaluated in this study but present in some case studies and likely indicative of degrees of awardee success in meeting this BRP goal include:

- Abstracts of conference and other presentations
- Receipt of additional non-NIH funding or capital
- FDA approvals for clinical trials and other statuses

Other metrics that did not appear to differentiate among BRP awardees in terms of relative success include the following. These metrics did, however, provide richness of detail about the kinds of research undertaken by the partnerships and important types of project outcomes:

- Research and educational tools that increase health knowledge directly or indirectly
- New or improved products, processes, usages, services, and clinical research

The following metrics about partnership members did address the second goal of the BRP Program—encouraging collaborations among the allied quantitative and biomedical disciplines:

- BRP awardees with professionals who have engineering, physical, and computational science degrees
- BRP awardees that include a research partner that never partnered in an NIH-funded project previously

Evaluation Procedures. In deciding whether and how to evaluate the BRP Program in the future, Program officials will need to assess the relative benefits and costs of such an undertaking. Depending on the urgency of learning evaluation results, two options that might be considered are 1) conducting a full-scale evaluation using an online survey and 2) incorporating performance monitoring into routine reporting practices. Minimizing respondent burden is a factor that must be considered in making this decision.

If Program officials require evaluation data in the near term, fielding a survey may be indicated. Some of the evaluation metrics are now developed and tested; others would likely benefit from further evaluation in a focus group and pilot test. Designing a survey instrument to collect data about performance indicators could be a relatively quick process, but it would be judicious to plan for a long enough lead time to obtain internal consensus and OMB clearance. The earliest feasible time to field such a survey is likely in the spring of 2007. Results could be reported by summer. This could be the first step of a long-term performance monitoring approach that meshes with routine electronic performance reporting at a later time.

If Program officials prefer to immediately begin to incorporate performance monitoring into extant data collection practices, they will need to coordinate the evaluation effort with one to define data collection methods, templates, systems, and outputs for incorporation into an NIH electronic framework. Ideally, data collection that can be incorporated within existing awardee requirements could minimize respondent burden to some degree. Currently, BRP awardees submit applications, progress reports, and final reports to apply for and meet the requirements of

their awards. If these required documents incorporated requests for the data needed for subsequent evaluations, the burden of data collection would be reduced. Additionally, awardees would be relatively highly motivated to provide this information. As NIH moves toward online collection of award applications and reports, evaluation items could be included in these online collections.

Online data collection could both collect and organize data simultaneously. Complex information could be stored as separate numeric and text variables. For example, publication information could be organized and stored so that the journal name, article author, article title, and publication date were separate fields. This would make it easy to locate information, summarize data in tables and other displays, and prepare reports. For example, a list containing counts of all journals could easily be displayed or printed. Counting citations, however, would be a separate project.

Additional suggestions for future evaluation of the BRP Program include 1) programming standard reports summarizing BRP awardee progress to date that can be produced at regular intervals and 2) using standard metrics and similar procedures to evaluate other NIH award programs, such as PPGs and SCORs, to facilitate comparisons among BRP and these awardees. BRP-supported research is more design-driven than PPG-supported research; therefore, outcomes of BRP and PPG programs are not directly comparable but nonetheless provide a basis for a comparison.

4. Case Studies

This chapter presents nine case studies of projects from these lead institutions:

- Allegheny-Singer Research Institute
- Cleveland Clinic/Volcano
- Emory University
- Johns Hopkins University (two different projects)
- Texas A&M
- University of California San Diego
- University of Michigan
- University of Virginia

The case studies reviewed nine different NHLBI BRP grants that have been funded for at least three full years. Case study information is organized using a standard template for all nine projects. As shown by the sample format in Appendix F, the template contains these sections:

- Grant Number
- Project Title
- Awardee Institution
- Project Period
- Principal Investigator (PI)
- PI New to NIH Funded Research (Y/N)
- BRP Partner Affiliate Institution
- Contact at BRP Partner Institution
- Partner Discipline(s)
- Partner New to NIH-Funded Research (Y/N)
- Partner Previously Collaborated with PI
- Project Type
- Project Objectives
- Challenges and Setbacks Encountered
- Project Performance
- Sources of Additional Information

4.1 Summary

This section presents summary highlights from the nine case studies. Of the nine projects, one has been funded since FY 99, one since FY 00, three since FY 01, and four since FY 02. Five were deemed hypothesis-driven and the other four were deemed design driven, although the distinction was fine in some cases.

The nine awardees reflect the bioengineering focus of the BRP Program:

- Six were medical or public health schools
- Two were engineering schools
- One was a small business

The partners reflect the bioengineering focus of the BRP Program as well:

- All but one BRP project included a partner from a medical or public health school and one from an engineering school.

- Six projects involved partners that were businesses, not academic or nonprofit.

- Other partner types represented included veterinary schools, pharmacology schools, and non-profit engineering laboratories.

- None of the PIs were new to NIH-funded research.

- Most, but not all, partners had previously collaborated with the PI. For about half the partners, it could not be determined from the existing files whether or not the partner investigators had previously participated in the NIH-funded research.

Partner discipline was an issue of interest to program sponsors.

- For these case studies, discipline is defined as the formal degree/training listed on the CV in the grant application (e.g., subject in which terminal degree was awarded, usually a PhD or MD). If no information was in the file, then we listed the current position. This means the discipline of someone with a PhD in electrical engineering would be identified as "engineering," even if they are currently a Professor of Biomedical Engineering.

- Some BRPs had lengthy lists of personnel and multiple subprojects. Disciplines are listed for the PI and for senior members of each partner or subproject who are identified as "co-investigators," "co-PI," "subcontractor," "project manager," and the like.

- Bioengineering faculty and departments were found at either medical or engineering schools and faculty had backgrounds in both medicine and engineering fields.

Project performance information from grantee progress reports and NHLBI staff notes indicated that awardees typically reported steady progress towards their research aims, including multiple publications. Some PIs reported abstracts and conference presentations, while others did not.

4.2 Case Studies

4.2.1 Allegheny-Singer Research Institute

Grant Number: HL072317
Project Title: Rapid Flow Evaluation by Magnetic Resonance Imaging
Awardee Institution: Allegheny-Singer Research Institute

Award Amount:

FY 2002	FY 2003	FY 2004	FY2005	FY 2006	Total Award to Date
296,138	283,862	282,321	280,734	278,705	1,421,760

Project Period: 3/01/2002 – 2/28/2007

Principal Investigator:
Mark Doyle, Ph.D.
Associate Professor of Medicine
Allegheny-Singer Research Institute
Allegheny General Hospital
320 East North Avenue
Pittsburgh, PA 15212-4774
412-359-4243
mdoyle@wpahs.org

PI New to NIH-funded Research: No

BRP Partner/Affiliate Institution(s):
Bioengineering, University of Alabama at Birmingham, Birmingham, AL
Computer Science, University of New Orleans, New Orleans, LA

Contact at BRP Partner Institution:

Andreas Anayiotos, Ph.D.
Associate Professor
Bioengineering Department Hoen 370
University of Alabama at Birmingham
1075 13th Street South
Birmingham, AL 35294-4440
205-934-8465
aanayiot@eng.uab.edu

Eduardo Kortright, Ph.D.
Assistant Professor
Department of Computer Science
University of New Orleans
Math 312-D
New Orleans, LA 70148
504-280-6626
eduardo@cs.uno.edu

(2005 progress report notes that Dr. Kortright has moved, to a Grove City College, PA, and will continue on the project, but does not offer new contact information)

Partner Discipline(s):

At Allegheny: PI: Physics
Investigator: Biederman: Medicine

At UAB: Investigator: Anayiotos: Engineering (Fluid Dynamics)

At UNO: Investigator: Kortright: Computer Science

Partners New to NIH-funded Research: Insufficient information in file to determine

Partners Previously Collaborated with PI: Yes

Project Type: Hypothesis

Project Objectives: This BRP seeks to validate the following hypothesis: The Block Regional Interpolation Scheme for K-Space (BRISK) MR approach can be applied in vivo within the duration of a breath-hold to generate VEC images that permit quantitative assessment of aortic valve performance. The specific aims are to:

1. To implement an optimized version of BRISK VEC imaging on a cardiovascular-specific scanner to acquire cine images within a breath-hold's time and with velocities measured in three orthogonal directions.

2. To validate BRISK VEC flow field imaging in phantoms by measuring the distribution of velocity and flow rates by independent experimental and numerical techniques including conventional MRI VEC imaging, Laser Doppler Velocimetry (LDV), and Computational Fluid Dynamics (CFD).

3. To develop clinical protocols employing BRISK VEC imaging to quantify flow through incompetent valves and apply it to patients exhibiting 1) valvular stenosis, and 2) valvular insufficiency.

Project Synopsis: This BRP seeks to implement a magnetic resonance imaging approach on a cardiovascular-specific scanner and to demonstrate its clinical utility in assessing valvular dysfunction in a quantitative manner. The PI changed institutions after funding approval, but before the award was actually made by NIH, so the project was transferred from UAB to Allegheny before it began. One research partner was retained from the old institution (UAB), and a new clinical investigator (Biederman) from the new institution was substituted for one originally proposed at the old institution. The other partner remained unchanged (UNO).

Awardee reports steady progress towards achieving project goals, including the following advancements:

- Successfully implemented the basic BRISK acquisition that allows VEC data to be acquired in as little as 20% of the conventional scan time for segmented k-space approaches

- Conducted computational fluid dynamic (CFD) investigations into the complex flow patterns in curved tubes and showed that BRISK and variations on BRISK can accurately represent major flow characteristics quantitatively, and that temporal MRI flow data is the dominant factor affecting accuracy when studying pulsatile flow

- Investigated issues associated with slice thickness and orientation for the calculation of control volumes for convergent flow patterns associated with restrictive cardiac values, and showed that for MRI data with adequate temporal resolution, accurate representation of flow is dominated by slice orientation, which should be arranged such that the slice thickness dimension is oriented along the direction with the lowest flow gradient

- Developed a variant termed FRISK (Fragmented Regional Interpolation Scheme for K-Space) in which the sections of k-space that are sampled are not treaded as discrete blocks but are explicitly treated as temporally distributed data, resulting in data sets that have lower artifact than conventional BRISK

- Investigated the direct visualization of jet flow and showed by simulation and direct acquisition that accurate representation of jet flow is possible using the processes developed as part of this BRP.

PI states that "each investigative arm enhances understanding in the other disciplines involved. This has led to a greater depth to the research." As an example, he suggests that the cross-disciplinary nature of the partnership enabled appreciation for features other than scan speed that affect accuracy, noting that, in the literature, slice orientation relative to flow is usually discussed in terms of scan efficiency. But the BRP group showed that this approach is insufficient for accuracy and efficiency.

Challenges and Setbacks Encountered: None reported.

Project Performance

List of publications:

1) Kortright E, Xia R, Anayiotos AS, and Doyle M. Alternative Control Volume Geometries for Measuring Regurgitant Flow Through a Valve. Technology and Health Care. 2004; 9:1-14.
2) Hershey BL, Doyle M, Kortright E, More R, Rayarao G, Anayiotos AS. Extension of Rapid Phase-Contrast Magnetic Resonance Imaging Using BRISK in Multidirectional Flow. Annals of Biomedical Engineering. [no other citation information provided]
3) Doyle, M, Kortright, E and Anayiotos, A. Conventional and Fast Blood Flow Imaging by MRI (Wiley Web encyclopedia). [no other citation information provided]

List of products, processes, usages, or services developed -- None reported

List of academic or professional lectures, presentations, or abstracts

1) Hershey BL, Doyle M, Kortright E, More R, Rayarao G, Anayiotos A*S.* Fast MRI Imaging by Sparse Sampling and Segmentation [abstract]. International Mechanical Engineering Congress and Exposition Bioengineering Division*,* Anaheim CA, Nov 2004.
2) Rathi VK, Doyle M, Ymrozik J, Williams RB, Truman C, Vido D, Bress V, Caruppannan K, Biederman RW. Cardiovascular 3D MRI Assessment of Diastolic Dysfunction: A Comparison with Echocardiography #2962 [abstract]. Oral presentation at the Scientific Sessions of the American Heart Association, New Orleans, November 7-10, 2004.
3) Doyle M, Rayarao G, Kortright E, Anayiotos A, Longchuan Ll, Capemanum, K, Rathi, VK, Biederman, RW. Correction of Temporal Misregistration Artifacts for Jet Flow [abstract]. Society of Cardiovascular Magnetic Resonance, Annual Meeting, Miami, FL, Feb 20 - 22, 2006.

List of milestones to commercialization achieved -- None reported

List of awards or other recognition -- None reported

Sources of Additional Information: None reported.

4.2.2 Cleveland Clinic/Volcano

Grant Number: HL069094
Project Title: High Frequency Nonlinear Acoustic Intravascular Imaging
Awardee Institution: VOLCANO Corporation

Award Amount:

FY 2002	FY 2003	FY 2004	FY2005	FY 2006	Total Award to Date
625,771	614,650	627,574	627,188	628,230	3,123,413

Project Period: 1/01/2002 – 12/31/2006

Principal Investigator:
D. Geoffrey Vince, Ph.D.
Director of Research
VOLCANO Corporation
Advanced Technology Laboratory/ND20
9500 Euclid Avenue
Cleveland, OH 44195
216-444-1211
gvince@volcanocorp.com

PI New to NIH-funded Research: No

BRP Partner/Affiliate Institution(s):

- Case Western Reserve University (Department of Biomedical Engineering, and Department of Electrical Engineering and Computer Sciences)
- University of Missouri-Kansas City (Department of Biomedical Engineering) – added in mid-project when subcontractor Katz changed institutions

Contact at BRP Partner Institution:

Cheri X. Deng, Ph.D.
Assistant Professor
Department of Biomedical Engineering
Case Western Reserve University
10900 Euclid Avenue
Cleveland, OH 44106-7207
216-368-0659
cxd54@case.edu

J. Lawrence Katz, Ph.D.
University of Missouri-Kansas City
5100 Rockhill Road
Kansas City, MO 64110

Partner Discipline(s):

At Cleveland Clinic: PI: Biomedical engineering
Co-investigators: Fleischman, Roy, Kharin: Engineering
Tuzcu, Thomas: Medicine (Cardiology)

Originally at Case Western; then moved to University of Missouri-Kansas City:
PI on Subcontract: Katz: Physics

At Case Western: Hazony, Deng: Engineering

Partners New to NIH-funded Research: Insufficient information in file to determine

Partners Previously Collaborated with PI: Some individuals already worked with PI -- others unknown; Original institutions (Cleveland Clinic Foundation and Case Western Reserve U.) have history of strong collaboration

Project Type: Design

Project Objectives: This BRP was designed to test two primary hypotheses**:** (1) high-frequency nonlinear tissue-generated ultrasound can be implemented to dramatically improve the quality of IVUS images; and (2) IVUS backscattered signal analysis of nonlinear acoustical data provides accurate information regarding the composition of atherosclerotic plaques in human coronary arteries. To this end, the project contains 3 specific aims:

1. Develop a model for the predication and simulation of acoustic nonlinearly distorted diffractive fields of high frequency ultrasound transducers for intravascular imaging which account for absorption and energy exchange between fundamental and second harmonic modes.

2. Design and develop broadband transducers that permit harmonic imaging.

3. Develop automated algorithms to determine plaque composition.

Project Synopsis: This BRP is intended to improve the intravascular ultrasound methods available to assess and delineate atherosclerotic plaque, with the ultimate aim of improving therapeutic intervention. The original BRP consisted of the PI and colleagues from the Cleveland Clinic Foundation with partners from the Case Western Reserve University Department of Biomedical Engineering. In 2004, the PI changed institutions and the award was transferred from the Cleveland Clinic Foundation to Volcano Corporation, a privately-held medical device company that opened a Cleveland office at that time. The PI maintains an adjunct staff position at the Cleveland Clinic Foundation. Some other project personnel have also shifted institutions.

The PI reported specific scientific developments in the progress reports covering 2002, 2003, and 2005 (the report covering 2004 was not provided for review). However, the PI did not include a list of publications, if any, in the available progress reports. The 2003 report mentions that one manuscript was submitted to *Ultrasound in Medicine and Biology* and 2 more were in preparation.

Based on the PI's reports, the model for Specific Aim 1 was completed and tested, and the awardee is seeking further improvement of a novel imaging technique, a Born-approximation deconvolved inverse scattering technique, which provides significant improvement of resolution without sacrificing penetration depth. The bulk of the research is devoted to Specific Aim 2, development of broadband transducers that permit harmonic imaging, with the team testing multiple designs and alternative materials. For Specific Aim 3, the awardee was working on a theory of impedance analysis and spectral analysis of harmonic

data. The awardee was also preparing to test a custom-built bi-frequency piezoceramic annular array transducer for the separation of transmit and receive modes and second harmonic super-resolution inverse scattering harmonic imaging.

Challenges and Setbacks Encountered: In the second year, the awardee encountered difficulty in locating a commercially available 100MHz bandwidth needle hydrophone for characterizing transducers. In addition, the awardee's efforts to develop polymeric broadband transducers that permit harmonic imaging were challenged by a poor signal-to-noise ratio due to parasitic capacitance, requiring the awardee to redesign the transducers using different substrates and polymers.

Project Performance

- *List of publications* -- None reported
- *List of products, processes, usages, or services developed* -- None reported
- *List of academic or professional lectures, presentations, or abstracts* -- None reported
- *List of milestones to commercialization achieved* -- None reported
- *List of awards or other recognition* -- None reported

Sources of Additional Information: www.volcanocorp.com.

4.2.3 Emory University

Grant Number: HL070531
Project Title: Biology, Biomechanics and Atherosclerosis
Awardee Institution: Emory University

Award Amount:

FY 2002	FY 2003	FY 2004	FY 2005	FY 2006	Total Award for 5 Years
1,313,708	1,286,201	1,323,198	1,362,895	1,403,783	6,689,785

Total Project Period: 6/01/2002 – 5/31/2007

Principal Investigator:
W. Robert Taylor, MD, PhD
Associate Professor of Medicine/Cardiology
Emory University School of Medicine
1639 Pierce Drive, WMB 319
Atlanta, GA 30322
404-727-8921
WTAYLOR@EMORY.EDU

PI New to NIH-funded Research: No (Previous NIH RO1s, and NIH research fellowship support)

BRP Partner/Affiliate Institution(s):
Georgia Institute of Technology
Guidant Corporation

Contact at BRP Partner Institution:

Don P. Giddens, PhD
Dean, College of Engineering
Georgia Institute of Technology
Administration Building
225 North Avenue NW
Atlanta, GA 30332-0360
404-894-3350

Deborah Kilpatrick, PhD
Guidant Corporation
3200 Lakeside Drive
Santa Clara, CA 95054
408-845-3000

Partner Discipline(s):

At Emory School of Medicine:	PI: Physiology and Medicine Co-Investigator (Jo): Physiology Co-Investigator (Wilcox): Neuroscience Co-Investigator (Vega): Medicine
At GA Tech:	Co-Investigator (Giddens): Engineering (Aerothermodynamics) Co-Investigator (Vito): Engineering/Theoretical and Applied Mechanics
At Guidant:	Subcontractor (Kilpatrick): Mechanical Engineering

Partners New to NIH-funded Research: Insufficient information in file to determine.

Partners Previously Collaborated with PI: Insufficient information in file to determine - The project features a joint Department of Biomedical Engineering with faculty from both Emory U. and Ga. Tech, which had just been established at the time of the proposal.

Project Type: Hypothesis

Project Objectives: The goal of this BRP is to obtain a greater understanding of the biology and engineering of atherosclerosis. The specific aims of the project are to:

I. Determine the distribution of stress and strain in atherosclerotic plaques in relation to markers of inflammation and apoptosis

II. Evaluate the inflammatory response characteristics of vascular smooth muscle cells to defined levels of mechanical strain

III. To determine the detailed hemodynamic environment of atherosclerotic lesions in coronary arteries of explanted human hearts

IV. Examine the responses of the endothelium to the flow dynamics found in the micro-environment of the atherosclerotic plaque

V. Determine the effects of the coronary artery stent placement in explanted coronary arteries on the local flow field and the distribution of stress and strain in the atherosclerotic plaque and the arterial wall.

The proposal also described 16 sub-aims under these five aims.

Project Synopsis: This BRP is focused on improving understanding of the role of mechanical forces in the pathogenesis of atherosclerosis. Of particular note, it includes plans to use explanted human hearts from transplant patients as a model system to study living human arteries with established atherosclerosis. The project is an early collaboration of a new trans-institutional Department of Biomedical Engineering, comprised of faculty from both Emory and GA Tech.

From the first three years of the project, the awardee reported key findings in the following sub-areas:

- Endothelial Gene Expression and Atherosclerosis – progress in illuminating the mechanisms of inflammatory responses induced by oscillatory shear exposure of endothelial cells; showed clear focal expression of VCAM-1 at the branch point that is co-localized with macrophages.

- Atomic Force Microscopy (AFM) Studies – demonstrated a first step towards quantitative analysis of the force-energy curves to determine cell elasticity.

- Mechanics of the Atherosclerotic Plaque – development of a micro-CT based methodology to determine and correct for distortions caused by acrylic processing, an improvement over prior models.

- CFD Studies – see Challenges section below

By the end of Year 3, the awardee reported ten publications and 12 abstracts or presentations. The Year 3 (2005) progress report notes that the BRP group has been expanded to include interactions with other BRP groups at Emory and GA Tech, but offers no further details. The original proposal describes a novel concept of offering two $10,000 seed grants to expand and diversify faculty involvement in the BRP, awarded via a mini-NIH RO1 process to interested applicants from Emory or GA Tech. However, by Year 3, no mention is made of the status of this concept.

Challenges and Setbacks Encountered: The original proposal called for MRI scans on patients on the heart transplant list to determine aortic and coronary geometry, as well as MR velocity mapping studies to determine the aortic and coronary flow. However, all subjects then on the transplant list had non-MR-compatible devices implanted. Therefore, the PI revised the research plan to substitute multi-detector ECG gated contrast-enhanced CT coronary angiography to obtain coronary and aortic geometry on the subjects. Otherwise, the only noted challenges appeared to be routine personnel changes associated with promotions, new jobs, etc.

Project Performance

Publications

1) Boo YC, Sorescu G, Boyd N, Shiojima I, Walsh K, Du J, and Jo H. Shear stress stimulates phosphorylation of eNOS at Ser1179 by Akt- independent mechanisms - Role of Protein Kinase A. J Biol Chem 2002; 277:3388-3396.
2) Boo YC, Hwang J, Sykes M, Mitchell J, Kemp BE, and Jo H. Shear stress stimulates phosphorylation of eNOS at Ser^{635} residue by a protein kinase A-dependent mechanism. Am.J Physiol Heart Circ. Physiol . 2002; 283:H1819-H1837.
3) Bauer PM, Fulton D, Boo YC, Sorescu GP, Kemp BE, Jo H, Sessa WC. Compensatory phosphorylation and protein-protein interactions revealed by loss of function and gain of function mutants of multiple serine phosphorylation sites in endothelial nitric oxide synthase. J Biol Chem. 2003 in press.
4) Guldberg RE, Ballock RT, Boyan BD, Duvall CL, Lin AS, Nagaraja S, Oest M, Phillips J, Porter BD, Robertson G, Taylor WR. Analyzing bone, blood vessels, and biomaterials with microcomputed tomography. IEEE Eng Med Biol Mag. 2003; 22(5):77-83.
5) Hwang J, Saha A, Boo YC, Sorescu GP, McNally JS, Holland SM, Dikalov S, Giddens DP, Griendling KK, Harrison DG, Jo I-I. Oscillatory shear stress stimulates endothelial production of 02- from p47phox-dependent NAD(P)H oxidases, leading to monocyte adhesion. JBC 2003; 278(47):47291-8.
6) Sorescu GP, Sykes M, Weiss D, Platt MO, Saha A, Hwang J, Boyd N, Boo YC, Vega JD, Taylor WR, Jo H. Bone morphogenic protein 4 produced in endothelial cells by oscillatory shear stress stimulates an inflammatory response. JBC 2003; 278(33):31128-35.
7) Suo J, Oshinski J and Giddens D.P., "Effects of Wall Motion and Compliance on Flow in the Ascending Aorta." Journal of Biomechanical Engineering, 2003; 125:347-354.
8) Duvall CL, Taylor WR, Weiss D, Guldberg RE. Quantitative microcomputed tomography analysis of collateral vessel development following ischemic injury. Am J Physiol Heart Circ Physiol. 2004 March 11.

9) Johnson KR, Patel SJ, Whigham A, Hakim A, Pettigrew RI, Oshinski JN. Three dimensional, time-resolved motion of the coronary arteries. J Cardiovasc Magn Reson. 2004;6(3):663-73.
10) Sorescu GP, Song H, Tressel SL, Hwang J, Dikalov S, Smith DA, Boyd NL, Platt MO, Lassegue B, Griendling KK, Jo H. Bone morphogenic protein 4 produced in endothelial cells by oscillatory shear stress induces monocyte adhesion by stimulating reactive oxygen species production from a nox1-based NADPH oxidase. Circ Res 2004; 95:773-9.

List of products, processes, usages, or services developed – None reported

List of academic or professional lectures, presentations, or abstracts – **Abstracts**

1) Giddens, D.P., "Hemodynamics and Atherosclerosis: Arteries to Cells, and Back Again." IV World Congress of Biomechanics, Calgary, August 2002 (Plenary Talk).
2) Oshinski, JN, Suo, J, and Giddens DP, "Wall Movement and Compliance are Required to Produce Helical Flow in the Ascending Aorta". Presented at the 2003 ISMRM meeting, Toronto Canada, May 2003.
3) Suo, J., Oshinski, J. and Giddens, D.P., "Entrance Flow Patterns in the Coronary Arteries: A Computational Study." Presented at the ASME Summer Bioengineering Conference, Key Biscayne, FL, June 2003.
4) Suo, J., Oshinski, J. and Giddens, D.P., "Numerical Simulation of Flow Patterns in the I'-ntrance Regions of the Left and Right Coronary Arteries." Presented at 2$^{\circ d}$ Joint Conference of the IEEE Engineering in Medicine and Biology Society and the Biomedical Engineering Society, October 2003.
5) Giddens, DP, Suo, J and Oshinski, JN, "Observed Asymmetric Atherosclerotic Plaque Localization in the Coronary Arteries May Relate to Flow Patterns in the Human Ascending Aorta." Presented at a Workshop on Biofluid Dynamics, California Institute of Technology, Pasadena, CA, December 2003.
6) Agahtehrani A, Onaran AG, Degertekin FL, and Taylor, WR. The Effect of cGMP on the Mechanical Properties of Vascular Smooth Muscle Cells, ET-2004, 8th Annual Hilton Head Workshop on Cardiovascular Tissue Engineering: From Basic Biology to Cell-Based Therapies, 2004.
7) Johnson K, Oshinski JN. "Three-Dimensional, Time-Resolved Motion of the Coronary Arteries." North American Society of Cardiac Imaging (NASCI), Jacksonville, FL, 2004.
8) Penn B, Hudgins P, Oshinski JN. "Compatability of Microcoils with a 3.0 Tesla MRI System." Annual Biomedical Research Conference for Minority Students (ABRCMS) 2004, Dallas, TX.
9) Sun B, Giddens DP, Long RL, Taylor WR, Weiss D, Oshinski JN. "Ex vivo multi-contrast MRI of the coronary artery wall at simulated in vivo condition". International Society of Cardiac Imaging (ISMRM), 2004, Miami FL.
10) Sun B, Giddens DP, Oshinski JN. "A Penalized Fuzzy K-means Algorithm for Multi-contrast MRI of Atherosclerotic Plaque Constituent Classification". International Society of Cardiac Imaging (ISMRM), Miami FL. 2005.
11) Agahtehrani A, Whalin M, Boo YC, Jo H, Griendling KK, and Taylor WR. "Modulation of strain-mediated PAI-1 gene expression in vascular smooth muscle cells by cGMP-elevating agents: Role of protein kinase A". [*Ed note*: No other information provided.]

List of milestones to commercialization achieved -- None reported

List of awards or other recognition -- None reported

Sources of Additional Information: -- None reported

4.2.4 Johns Hopkins University—Mitzner

Grant Number: HL066020
Project Title: New Approach for the Treatment of Asthma
Awardee Institution: Johns Hopkins University

Award Amount:

FY 2001	FY 2002	FY 2003	FY2004	FY 2005	Total Award for 5 Years
857,480	763,051	783,436	804,434	817,885	4,026,286

Total Project Period: *9/30/2001 – 8/31/2006*

Principal Investigator:
Wayne A. Mitzner, Ph.D.
Professor of Environmental Health Sciences
Bloomburg School of Hygiene and Public Health
Johns Hopkins University
615 N. Wolfe Street
Baltimore, MD 21205
410-614-5446
wmitzner@jhsph.edu

PI New to NIH-funded Research*:* No (Previous NIH RO1s; NIH Training support)

BRP Partner/Affiliate Institution(s)*:*

Broncus Technologies – in 12/2003, became Asthmatx, Inc. (company split into two separate organizations)

Contact at BRP Partner Institution:

Bryan Loomas
Vice President, Product Development
Broncus Technologies
1400 N. Shoreline Blvd.
Buliding A, Suite 8
Mountain View, CA 94043

Company later became:
Asthmatx, Inc.
1340 Space Park Way
Mountain View, CA 94043
650-810-1100

***Partner Discipline(s)**:*

At Johns Hopkins: PI: Biomedical Engineering
Co-Investigator (Brown): Medicine
Co-Investigator (Foster): Physiology

At Broncus Technologies (later Asthmatx): Senior Manager (Loomas): Mechanical Engineering

***Partners New to NIH-funded Research**:* Insufficient information in file to determine

Partners Previously Collaborated with PI: Insufficient information in file to determine

***Project Type**:* Design

Project Objectives: The goal of this BRP is to develop and evaluate a potential clinical treatment for asthma. Specifically, it is a biomedical device system (Alair® System) that uses radio frequency (RF) heat transfer to the airway wall in order to disrupt the ability of the airway smooth muscle to narrow the airways. The specific aims of the project are to:

1. To use results from the functional studies in an iterative manner to alter design parameters to maximize the long term attenuation of smooth muscle contractility, while minimizing any undesirable secondary side effects.

2. To evaluate the effect of treatment on the distribution of airway responses in large and small airways along the airway tree.

3. To evaluate the effect of treatment on mucociliary clearance.

4. To evaluate the effect of treatment on the intrinsic responsivity of airway muscle assessed in excised bronchi.

5. To evaluate the effect of treatment on the inflammatory response of airways.

6. To evaluate the effect of treatment on vascular supply to the airways.

Project Synopsis: This BRP is focused on developing and evaluating a device that is effective in treating asthma, independent of the source of the trigger (e.g., allergic, cold air, stress, neural). It is not a pharmaceutical, but a bioengineering approach to managing the biomechanical element of asthma. Broncus Technologies, Inc., a small biomedical engineering company in CA, developed a device called the Alair® System that seeks to use precise distribution of RF energy to the smooth muscle airway wall to minimize the obstruction caused by smooth muscle contraction. However, Broncus lacked the biological and physiological resources to carry out the function testing needed to advance development of the treatment device. Therefore, researchers at the Johns Hopkins University School of Public Health partnered with Broncus to conduct the research and testing. In mid-project, Broncus was split into two companies focused on different diseases, and the BRP partnership continued uninterrupted with the same personnel at the successor company focused on asthma treatment, Asthmatx.

The awardee reported steady progress toward its stated goals, including demonstrations of the safety and efficacy of the device in an animal model and the safety in human patients, as well as in "very preliminary clinical trials not associated with this grant." Work on the first 2 specific aims has led to improvements in the design and modification of the existing thermal probe, aided by the computational fluid dynamic modeling work. This model has shown that the differences in electrical and thermal conductivity between the airway wall and the parenchyma significantly affect the resulting transient temperature distribution in

the airway wall and the parenchyma. Ongoing work will include modeling the effects of anatomical heterogeneities, determination of tissue properties, and in vivo confirmatory experiments. Experimental work at Johns Hopkins showed that bronchial thermoplasty treatment significantly alters the ability of airways to dilate with lung inflation and reduces the ability of airways to completely close.

By the time the renewal application was submitted in the fourth quarter of Year 4, the awardee reported 7 publications and 4 abstracts. The awardee notes in the progress report/competing renewal application "that the first year of the grant was involved with device development, so without a research device, it was not possible to carry out publishable experiments till the 2nd year."

Challenges and Setbacks Encountered: In the second year of the grant, the awardee carried forward about 40% of the annual funding for administrative reasons related to the partner's subcontract (the file contains two different explanations for this: uncertainty re: F&A rate and partner cutting back on spending). At the end of the third year, funds were again carried forward due to difficulties in hiring an experienced technician.

Project Performance

List of Publications

1) Cox PG, Miller J, Mitzner W, and Leff AR. Radiofrequency ablation of airway smooth muscle for sustained treatment of asthma: preliminary investigations. Eur Respir J 2004; 24: 659-663.
2) Danek CJ, Lombard CM, Dungworth DL, Cox PG, Miller JD, Biggs MJ, Keast TM, Loomas BE, Wizeman WJ, Hogg JC, and Leff AR. Reduction in airway hyperresponsiveness to methacholine by the application of RF energy in dogs. J Appl Physiol 2004; 97:1946-1953.
3) Mitzner W. Airway smooth muscle: The appendix of the lung. Am J Respir Crit Care Med 2004; 169: 1-4.
4) Miller JD, Cox G, Vincic L, Lombard CM, Loomas BE, and Danek CJ. A prospective feasibility study of bronchial thermoplasty in the human airway. Chest 2005; 127: 1999-2006.
5) Brown RH, Wizeman W, Danek C, and Mitzner W. In vivo evaluation of the effectiveness of bronchial thermoplasty with computed tomography. J Appl Physiol 2005; 98: 1603-1606.
6) Brown RH, Wizeman W, Danek C, and Mitzner. W. Effect of bronchial thermoplasty on airway distensibility. Eur Respir J 2005; 26: 277-282.
7) Mitzner W, C Danek, W Wizeman, RH Brown. Effect of bronchial thermoplasty on airway closure. (submitted 2005). [No other citation information provided.]

List of products, processes, usages, or services developed -- None reported

List of academic or professional lectures, presentations, or abstracts – ***Abstracts***

1) Danek DJ, Cox G, Miller JD, Mitzner W, Brown RH, Biggs M, Keast T, Loomas BE, Leff AR, Thermal bronchoplasty reduces canine airway responsiveness to local methacholine challenge. Am J Respir Crit Care Med. 2002; 165:A716.
2) Leff AR, Cox G, Miller JD, Lombard CM, Danek CJ, Hogg JC. Thermal bronchoplasty alters airway smooth muscle and reduces responsiveness in dogs: a possible procedure for the treatment of asthma. Am J Respir Crit Care Med. 2002; 165:A216.
3) Mitzner, W, Danek C, Wizeman B, and Brown RH. Effects of Bronchial thermoplasty on airway responsiveness evaluated with computed tomography. Am J Resp Crit Care Med. 2003; 167: A883.
4) Wizeman WJ, C Danek, R Brown, W Witzner. A computer model of therman treatment of airways by radiofrequency (RF) energy delivery. Am J Resp Crit Care Med. 2004; 169:A314.

List of milestones to commercialization achieved -- None reported

List of awards or other recognition -- None reported

Sources of Additional Information: www.asthmatx.com

4.2.5 Johns Hopkins University—Halperin

Grant Number: HL064795
Project Title: Magnetic Resonance Guided Electrophysiology Intervention
Awardee Institution: Johns Hopkins University

Award Amount:

FY 1999	FY 2000	FY 2001	FY2002	FY 2003	Total Award for 5 Years
727,055	713,552	689,211	705,597	722,495	3,557,910

Project successfully re-competed for second five year period:

FY 2004	FY 2005	FY 2006	FY2007	FY 2008	Total Award for 5 Years
907,363	851,006	871,454	892,517*	914,213*	4,436,553

*Funds scheduled for future fiscal years

Total Project Period: 9/30/1999 – 5/31/2009

Project Period Covered in this Case Study: 9/30/1999 – 8/31/2004

Principal Investigator:
Henry R. Halperin, MD
Professor of Medicine and Biomedical Engineering
School of Medicine
Johns Hopkins University
600 N. Wolfe Street
Baltimore, MD 21287-6568
410-955-2412
HHALPER@JHMI.EDU

PI New to NIH-funded Research: No (Previous NIH RO1s; NIH Training support)

BRP Partner/Affiliate Institution(s):
Johns Hopkins University Applied Physics Laboratory
Robin Medical, Inc.
Surgi-Vision, Inc. (dropped in Year 4)
Bard Electrophysiology, Inc. (dropped in Year 4)
Micro Helix Incorporated (added in Year 4
Irvine Biomedical (added in Year 4)
NaviCath (added in Year 4)

Contact at BRP Partner Institution:

Guy Clatterbaugh
Johns Hopkins University
Applied Physics Laboratory
Institute for Advanced Science and Technology in Medicine
11100 Johns Hopkins Road
Laurel, MD 20723-6099

Nancy Taylor, J.D.
President and CEO
Surgi-Vision, Inc.
Suite 100
9250 Rumsey Rd
Columbia, MD 21045
410-730-8998

Stephen Sagon
General Manager
Bard Electrophysiology, Inc
C.R. Bard, Inc.
129 Concord Road
Billerica, MA 01821
978-667-1300

Erez Nevo, MD., D.Sc.
Robin Medical, Inc.
3101 Northbrook Rd
Baltimore, MD 21208

Donna Dolinar
Micro Helix Incorporated
16125 SW 72nd Ave.
Portland, OR 97224
503-986-1600

Peter Chen, Ph.D.
Irvine Biomedical
2382 Morse Ave.
Irvine, CA 92614
949-851-3062

NaviCath
Haifa, Israel
No further contact information

Partner Discipline(s):

At Johns Hopkins School of Medicine:	PI: Medicine and Physics Co-Investigator (Berger): Electrical Engineering and Medicine Co-Investigator (Bottomley): Physics Co-Investigator (Lardo): Chemical Engineering & Bioengineering
At Johns Hopkins Applied Physics Lab:	Co-Investigator (Clatterbaugh): Physics Co-Investigator (Lennon): Engineering
At Robin Medical:	Subcontractor (Nevo): Medicine and Engineering

Partners New to NIH-funded Research: Yes – for those from Applied Physics Lab
Insufficient information in file to determine -- for other partners

Partners Previously Collaborated with PI: Yes (ongoing partnership already in place)

Project Type: Design

Project Objectives: The goal of this BRP is to develop and test new technologies for using magnetic resonance imaging (MRI) to provide accurate navigation of catheters without radiation, provide the ability to visualize ablated lesions, and to accurately correlate anatomical and electrical information. The specific aims of the project are to:

1. To further develop the technology for guidance of electrophysiologic studies and catheter ablation with magnetic resonance imaging
    - To further develop MRI-compatible electrode catheters.
    - To further develop catheter interfaces, for optimization of noise reduction in the ECG signal from the MR scanner and in the MR image from the RF ablation.
    - To further develop transesophageal and intracardiac MR receivers.
    - To develop an MRI-compatible catheter for combined measurement, pacing, ablation, and imaging.
    - To further develop real-time catheter guidance, including image optimization with enhanced ECG gating, MRI-fluoroscopy, dynamic image plane manipulation, and catheter-tip tracking.
    - To further develop software to allow real-time or near-real time display of cardiac structures in 3 dimensions during interventions, with superimposed catheter-tip-localization and electrical maps.
    - To develop needles and receiver-antennas for high-resolution MRI-guided transseptal needle puncture.
2. To investigate MR guidance for electrophysiologic studies and catheter ablation in an animal model.
3. To study the use of MRI for guiding electrophysiologic studies and catheter ablation in patients.

Project Synopsis: This BRP is focused on improving clinical tools used in the diagnosis and treatment of cardiac problems, especially atrial fibrillation. The awardee is working to develop, refine, and test new technologies for using MRI to improve electrophysiologic testing and radiofrequency (RF) catheter

ablation. This project is part of an ongoing collaboration between partners. Within the School of Medicine, which is the lead institution of the partnership, the project features collaboration between the Departments of Medicine (Cardiology), Radiation, and Biomedical Engineering. One major partner is another division of the Johns Hopkins University -- the Applied Physics Laboratory. Robin Medical, Inc. is a subcontractor responsible for developing the catheter-tip tracking technology. Surgi-Vision, Inc. committed to developing clinical-grade miniature MRI receivers, and Bard Electrophysiology committed to developing non-magnetic electrode catheters for use in the MRI scanner, but these two partners were dropped in mid-project (see Challenges section below). In Year 4, Micro Helix Incorporated was added as an additional partner with the principal task of developing miniature coils for incorporation into the catheter electrodes; Irvine Biomedical was added as a source for standard MRI-compatible catheters that can be used with low-power MRI scans (a mid-project development); and, Navicath was added to modify a remote control catheter manipulation system to make it MRI-compatible.

Throughout the project, the awardee reported steady progress towards its stated goals. Technology development has been marked by a number of patents and product refinements, as well as FDA approval (IDE #G010093) in 2004 for human testing of a new clinical grade catheter for use with low-power MR scans. The awardee also conducted animal (Aim 2) and human (Aim 3) studies of magnetic resonance guided electrophysiology intervention. Of note, by the end of Year 4, the findings from this BRP had established MRI as the standard of care for assessing pulmonary veins prior to ablation in the clinical EP laboratory at Johns Hopkins. Other key developments include:

- Design and/or modification of various technologies and components, such as catheter tip location sensors, 3-D volume and surface rendering software, esophageal MRI receiving coil
- Evidence of real-time positioning of catheters using MR guidance alone and increasing ability to visualize and treat lesions
- Development of a clinical-grade catheter system for performing electrophysiologic procedures in patients
- Evidence that patients with current generation pacemakers and implantable defibrillators can undergo MRI without complications
- Sufficient progress on initial aims to permit awardee was able to shift emphasis of imaging studies to patients with ventricular tachycardia

By the time the renewal application was submitted in the fourth quarter of Year 4, the awardee reported 13 publications and 11 abstracts attributed to this grant. In addition, the awardee reported 8 patents and 4 young investigator awards.

Challenges and Setbacks Encountered:

During Year 1, the rate of enrollment of women and minorities in the study fell below expectation. During Year 2 (March 2001), the awardee applied to FDA for an Investigational Device Exemption (IDE) for a clinical-grade non-magnetic catheter to be developed by Bard, but the partnership ended when the partner (Bard) was unwilling to do additional studies required by FDA. Instead, the awardee partnered with Irvine Biomedical, who was able to modify an existing catheter to meet FDA standards without triggering additional testing. A second IDE was submitted and ultimately received FDA approval.

Project Performance

Publications

1) Freid N, Lardo AC, Berger RD, Calkins H, Halperin H: Linear lesions in myocardium created by laser using diffusing optical fibers: in vitro and in vivo results. Lasers in Surgery and Med. 2000; 27:295-304.
2) Lardo A, McVeigh E, Yeung C, Jumrussirikul P, Atalar E, Berger R, Calkins H, Halperin H: Magnetic resonance guided radiofrequency ablation: Visualization and temporal characterization of thermal lesions. Circulation. 2000; 102(6): 698-705.
3) Fried N, Tsitlik A, Berger RD, Lardo AC, Calkins H, Halperin H: Laser ablation of the pulmonary veins using a fiberoptic balloon catheter: implications for treatment of paroxysmal atria) fibrillation. [Images Selected for Cover]. Lasers in Surgery and Med. 2001: 28(3):197-203
4) Susil R, Yeung C, Lardo A, Halperin H, Atalar E: Multifunctional interventional devices for MRI: A combined electrophysiologic/ MR imaging catheter. Magnetic Resonance in Med. 2002; 47(3):584-600.
5) Leclercq C, Faris 0, Tunin R, Halperin H, Evans F, Spinelli J, McVeigh E, Kass D: Systolic improvement and mechanical resynchronization does not require electrical synchrony in the dilated failing heart with LBBB. [Images selected for Cover] Circulation. 2002 Oct 1;106(14):1760-3.
6) Lickfett L, Kato R, Berger R, Halperin H, Calkins H: Magnetic resonance angiography and virtual endoscopic view of a common pulmonary vein trunk. Journal of Cardiovascular Electrophysiology. 2002 Sep;13(9):955.
7) Kato R, Lickfett L, Meininger G, Dickfeld T, Wu R, Juang G, Angkeow P, LaCorte J, Bluemke D, Berger R, Halperin HR, Calkins H: Pulmonary vein anatomy in patients undergoing catheter ablation of atrial fibrillation: lessons learned by use of magnetic resonance imaging. Circulation. 2003 Apr 22; 107(15):2004-10
8) Roguin A, Zviman M, Meininger G, Rodrigues R, Dickfeld T, Bluemke D, Berger R, Calkins H, Lardo A, Halperin H: Modern Pacemaker and Implantable Cardioverter-Defibrillator Systems can be MRI safe: In vitro and in vivo assessment of safety and function at 1.5 Tesla. Circulation. 2004 Aug 3;110(5):475-82. Epub 2004 Jul 26.
9) Dickfeld T, Solomon S, Zvieman M, Lickfett L, Meininger G, Berger R, Halperin H, Calkins H: Anatomic stereotactic guidance of radiofrequency ablation on three dimensional MR images in real-time. Circulation (In Press)
10) Kato R, Hiraki T, Rioux-Leclercq N, Lardo A, Berger R, Calkins H, Halperin H: Magnetic resonance imaging identifies the maximum gap in linear ablative lesions associated with conduction block. (Submitted)
11) Dickfeld T, Kato R, Rodriguez R, Lickfett L, Meininger G, Berger R, Calkins H, Halperin H: Energy and time dependency of magnetic resonance imaging of acute radiofrequency ablation lesions. (Submitted)
12) Dickfeld T, Calkins H, Zvieman M, Meininger G, Lickfett L, Roguin A, Berger R, Halperin H, Solomon S: Stereotactic magnetic resonance guidance for anatomically targeted ablations of the foramen ovate and the left atrium. (Submitted)
13) Meininger G, Kato R, Susil R, Zviman M, Dickfeld T, Berger R, Calkins H, Halperin H: Real time cardiac magnetic resonance imaging system for the performance of an electrophysiology study. (Submitted)

List of products, processes, usages, or services developed

(not reported per se, but research clearly goes to products and new useages)

List of academic or professional lectures, presentations, or abstracts – **Abstracts**

1) Lardo A, McVeigh E, Berger R, Calkins H, Freid N, Leng C, Halperin H: Transesophageal magnetic resonance imaging can quantify gaps in discontinuous atrial radiofrequency lesions. Circulation 1999; 100(18): 1-201
2) Fried N, Lardo A, Berger R, Calkins H, Halperin H: Circumferential lesions in pulmonary veins produced using an Nd:Yag laser and fiberoptic balloon catheter. PACE 2000;23:567
3) Fried N, Lardo A, Berger R, Calkins H, Halperin H: Linear epicardial lesions created using a Nd:Yag laser and fiberoptic catheter. PACE 2000;23:69
4) Fried N, Tsitlik A, Berger R, Lardo A, Calkins H, Halperin H: Laser ablation of the left atrial appendage using a fiber optic balloon catheter: a model for electrical isolation of the pulmonary veins during treatment of paroxysmal atrial fibrillation. Circulation 2000;102(18):II-526.
5) Lardo A, McVeigh E, Freid N, Berger R, Calkins H, Halperin H: Magnetic resonance imaging of sub-eustacian isthmus anatomy and radiofrequency lesions in patients undergoing catheter ablation for atrial flutter. PACE 2000;23:553
6) Lardo A, McVeigh E, Fried N, Berger R, Calkins H, Halperin H: Quantification of pulmonary vein sleeves using high resolution endoesophageal magnetic resonance imaging: Implications for focal atrial fibrillation ablation. PACE 2000;23:574
7) Lardo A, Berger R, Calkins H, Halperin H: High resolution endoesophageal and intracardiac magnetic resonance imaging of pulmonary vein radiofrequency ablation lesions. Circulation 2000; 102(18):11-598.
8) Lardo A, Yang X, Serfaty JM, Halperin H, Atalar E: Branch pulmonary artery balloon angioplasty and stent deployment guided by real-time magnetic resonance imaging. Circulation 2000; 102(18):11-424.
9) Kato R, Hiraki T, Rioux-Leclercq N, Lardo A, Berger R, Calkins H, Halperin H: Magnetic resonance imaging identifies the maximum gap in linear ablative lesions associated with conduction block. Circulation. 2001; 104(17):11-2185.
10) Susil R, Yeung C, Halperin, H, Lardo A, Atalar E: A trackable electrophysiology catheter for use under MRI. Circulation. 2001;104(17): II-1947.
11) Dickfeld T, Kato R, Rodriguez R, Lickfett L, Meininger G, Berger R, Calkins H, Halperin H: Energy and time dependency of magnetic resonance imaging of acute radiofrequency ablation lesions. PACE 2002; 24:523.
12) Dickfeld T, Solomon S, Kato R, Meininger G, Berger R, Halperin H, Calkins H: Real-time catheter navigation on three-dimensional CT and MRI images. PACE 2002; 24:523.
13) Faris 0, Leclercq C, Kato R, Evans F, Spinelli J, Halperin H, McVeigh E: Systolic improvement and mechanical resynchronization do not require electrical synchrony in the dilated failing heart with LBBB. Circulation 2002; 106(19):11-382
14) Kato R, Lickfett L, Meininger G, Dickfeld T, Berger R, Calkins H, Halperin H: Noncircular orifice of pulmonary veins in patients with paroxysmal atrial fibrillation evaluated by magnetic resonance imaging. PACE 2002; 24:590.
15) Lickfett L, Kato R, Dickfeld T, Kamel I, Nasir K, Halperin H, Meininger G, Solomon S, Berger R, Calkins H: How do pulmonary vein and left atrial morphology correlate with pulmonary vein potentials in patients with focal atrial fibrillation? A study using magnetic resonance angiography and circumferential decapolar mapping catheters. PACE 2002; 24:590.
16) Meininger G, Kato R, Susil R, Zviman M, Dickfeld T, Berger R, Calkins H, Halperin H: Real time cardiac magnetic resonance imaging system for the performance of an electrophysiology study. PACE 2002; 24:588.
17) Meininger G, Zviman M, Dickfeld T, Kato R, Susil R, Calkins H, Berger R, Halperin H: Standardized views for the performance of interventional electrophysiologic procedures using magnetic resonance imaging. Circulation 2002; 106(19): 11-86
18) Dickfeld T, Calkins H, Zvieman M, Meininger G, Lickfett L, Roguin A, Berger R, Halperin H, Solomon S: Stereotactic magnetic resonance guidance for anatomically targeted ablations of the foramen ovale and the left atrium. PACE 2003; 26:1053.

19) Jayam V, Lickfett L, Kato R, Dickfeld T, Bradley D, Eldadah Z, Tamdri H, Bluemke D, Halperin H, Berger R, Calkins H: Left atrial remodeling after pulmonary vein isolation evaluated by magnetic resonance imaging. PACE 2003; 26:1033.
20) Lickfett L, Kato R, Dickfeld T, Tamdri H, Meininger G, Jayam V, Berger R, Halperin H, Calkins H: Variant pulmonary vein ascending from the roof of the left atrium: Incidence, characteristics, and importance for RF ablation. PACE 2003; 26:1005
21) Meininger G, Kato R, Zviman M, Susil R, Roguin A, Dickfeld T, Rent K, Calkins H, Berger R, Halperin H: Electrophysiology testing guided by real time MRI. PACE 2003; 26:1003.
22) Roguin A, Zviman M, Meininger G, Dickfeld T, Berger R, Calkins H, Halperin H: Effects of MRI on Pacemaker and ICD systems. PACE 2003; 26: 959

List of milestones to commercialization achieved – **Patents**

1) Atalar E, Bottomley P, Zerhouni E, Halperin H, McVeigh E, Lardo A: Method for in-vivo magnetic resonance imaging. #6,549,800
2) Nevo E: Method and apparatus to estimate location and orientation of an object during magnetic resonance imaging. #6,516,213
3) Nevo E: Method and apparatus for generating torques on objects particularly objects inside a living body. #6,594,517
4) Lardo A, McVeigh E, Halperin H: Magnetic resonance imaging transseptal needle antenna. # 6,606,513.
5) Halperin H, Berger R, McVeigh E, Atalar E, Lima J, Lardo A, Calkins H: System and method for magnetic resonance guided electrophyiologic testing and catheter ablation. Application # 09/428,990
6) Susil R, Atalar E, Lardo A, Halperin H, Berger R, Calkins H, Bottmley P: Systems and methods for magneticresonance-guided interventional procedures Application # 20030050557
7) Fried, N, Halperin H, Berger R, Lardo A, Tsitlik A: Circumferential pulmonary vein ablation using a laser and fiberoptic balloon catheter. Application # 20020052621
8) Tulley S, Lardo A, Karmarkar P, McVeigh E, Halperin H, McNamara C, Bottomley P, Atalar E, Yang X: Magnetic resonance imaging probe. Application # 20030028095

List of awards or other recognition -- **Young Investigator Awards**

1) Lardo A, Mc Veigh E, Fried N; Berger R, Calkins H, Leng C, Halperin H: Transesophageal magnetic resonance imaging can quantify gaps in discontinuous atria) radiofrequency ablation lesions; (Melvin Judkins Young Investigator Award Winner, American Heart Association Scientific Sessions, 1999).
2) Lardo A, McVeigh E, Yeung C, Jumrussirikul P, Atalar E, Berger R, Calkins H, Halperin H: Magnetic resonance guided radiofrequency ablation: Visualization and temporal characterization of thermal lesions. (Young Investigator Award Finalist, NASPE Scientific Sessions, 1999).
3) Dickfeld T, Solomon S, Zvieman M, Lickfett L, Meininger G, Berger R, Halperin H, Calkins H: Anatomic stereotactic guidance of radiofrequency ablation on three dimensional MR images in real-time. (Melvin Judkins Young Investigator Award Winner, American Heart Association Scientific Sessions, 2002).
4) Roguin A, Zviman M, Meininger G, Rodrigues R, Dickfeld T, Bluemke D, Berger R, Calkins H, Lardo A, Halperin H: Modern Pacemaker and Implantable Cardioverter-Defibrillator Systems can be MRI safe: In vitro and in vivo assessment of safety and function at 1.5 Tesla. (Melvin Judkins Young Investigator Award Finalist, American Heart Association Scientific Sessions, 2003)

Sources of Additional Information: www.robinmedical.com
www.ibiep.com
www.navicath.com
www.microhelix.com

4.2.6 Texas A&M

Grant Number: HL064372
Project Title: Histo-Mechanics & Biology of Remodeling In Hypertension
Awardee Institution: Texas A & M Engineering Experiment Station

Award Amount:

FY 2001	FY 2002	FY 2003	FY2004	FY 2005	Total Award to Date
552,337	563,572	636,520	639,178	653,288	3,044,895

Project Period: 9/24/2001 – 8/31/2006

Principal Investigator:
Jay D. Humphrey, Ph.D.
Professor
Biomedical Engineering Program
Texas A&M University
233 Zachry Engineering Center; 3120 TAMU
College Station, TX 77843-3120
409-845-5558
JHUMPHREY@TAMU.EDU

PI New to NIH-funded Research: No (Previous NIH RO1s; NIH Training support)

BRP Partner/Affiliate Institution(s):

Texas A&M College of Veterinary Medicine, Small and Large Animal Clinics
Texas A & M College of Medicine, Cardiovascular Research Institute and Medical Pathology Laboratory
College of Engineering, Washington University (St. Louis, MO), Department of Biomedical Engineering,
University of Illinois at Urbana-Champaign, College of Veterinary Medicine, Dept. of Veterinary Pathobiology

Contact at BRP Partner Institution:

Theresa Fossum, DVM, Ph.D.
Associate Professor and Chief of Surgery
Department of Small Animal Medicine and Surgery
College of Veterinary Medicine
Texas A&M University
No further contact information provided

Lih Kuo, Ph.D.
Associate Professor
Department of Medical Physiology
Texas A&M University Health Sciences Center
College Station, TX
No further contact information provided

Larry Taber, Ph.D.
Professor
Department of Biomedical Engineering
Washington University in St. Louis
Campus Box 1097
One Brooklings Drive
St. Louis, MO 63130-4899
314-935-6164

Philip Solter, D.V.M, Ph.D.
Assistant Professor
University of Illinois at Urbana-Champaign,
College of Veterinary Medicine, Dept. of Veterinary Pathobiology
2001 South Lincoln Avenue
Urbana, IL 61802
217-333-2449
No email provided

Partner Discipline(s): PI: Bioengineering
Co-PIs: Clinical veterinary medicine
Co-PI and Co-Investigator: Medicine
Co-Investigator: Mechanical engineer

Partners New to NIH-funded Research: Mechanical engineer: yes; Others: no
Partners Previously Collaborated with PI: Some are new collaborators
Project Type: Hypothesis

Project Objectives: The awardee envisioned a ten-year project with long-term goals and objectives that are described in the project application. This BRP focuses on the time-course, extent, and reversal of hypertension-induced changes in cerebral and coronary arteries and arterioles. The specific aims for this 5-year BRP are to test the following hypotheses:

- That the basic function of the coronary and cerebral microvasculature is changed by the altered axial and circumferential stresses that accompany hypertension
- That vascular nitric oxide and angiotensin are involved in the functional impairment of coronary and cerebral microvessels that results from hypertension
- That the adenosine receptor subtypes and potassium ATP channels that are responsible for vasodilation in response to adenosine are downregulated during chronic hypertension
- That the vascular extracellular matrix experiences an increase in Arg-Gly-Asp (RGD) integrin-binding sites, which serves as important signals for increasing cellular activity regionally within the vascular wall as the hypertension develops from the sub-acute to the chronic phase
- That hypertension-induced changes in large arteries are multiaxial, with transmural remodeling and growth seeking to restore the circumferential response but altering the axial response as well
- That the effectiveness of ACE-inhibitors in reversing vascular remodeling depends on the phase of development of hypertension during which they are first administered, and
  That multiaxial biomechanical responses of vessels can be described by constitutive relations that are based on a rule-of-mixtures approach with changing mass fractions of the constituents described by first order kinetics at altered natural configurations.

Project Synopsis: This BRP is focused on testing hypotheses related to the local regulatory activities of the vascular wall by using a novel, controllable, renovascular micro-pig model of hypertension developed by the awardee. By quantifying the time-course of structural and functional changes in coronary and cerebral arteries and arterioles during both the development and reversal of hypertension, the awardee aims to identify preferred times to initiate and continue particular anti-hypertensive therapies.

Throughout the project period, awardee reports steady progress towards its stated goals. Significant accomplishments include the following:

- Development of a reproducible coarctation-induced hypertension model in the pig.
- Development of a general mathematical model for vascular growth and remodeling, which permits the exploitation of data on the individual rates of turnover of cells and structurally important matrix proteins, and a more natural correlation between the mechanics and the biology.
- Findings suggesting that general growth and remodeling theory for arteries may be applicable to vascular biomechanics and pathophysiology; and, that the growth and remodeling of large vessel occurs very quickly in response to hypertension while resistance vessel changes more slowly.

By the end of Year 4, the awardee had 14 publications. Two more had been submitted and one was under review.

Challenges and Setbacks Encountered: Twice during the first four years, over 25% of annual funds were carried over to the following year for various reasons, including personnel changes, delays in animal availability, and revised scheduling of laboratory and data analyses to improve efficiency.

Research findings led the awardee to reverse the originally states goals for Years 4 and 5, opting to study the effects of mechanically reversing the hypertension before the effects of pharmacologically doing so.

Project Performance

List of Publications

1) Humphrey JD. On mechanical modeling of dynamic changes in structure and properties in adherent cells. Math Mech Solids 2002;7: 521-539.
2) Humphrey JD, KR Rajagopal and E Wilson. Biomechanics and the ubiquitous role of growth and remodeling in the vasculature. Appl Mech Reviews. 2002 (invited, submitted).
3) Aguirre-Sanceledonio M, Fossum TW, Miller MW, Humphrey JD, Berridge BR, and Herraez P. Collateral circulation in experimental coarctation of the aorta in minipigs: A possible association with hypertrophied vasa vasorum. J Compar Pathol 2003;128: 165-171.
4) Fossum TW, WI Baltzer, MW Miller, M Aquirre, D Whitlock, P Solter, LA Makarski, MM McDonald, M-Y An, and JD Humphrey. A novel aortic coarctation model for studying hypertension in the pig. J Invest Surq 2003;16: 35-44.
5) Humphrey JD. Continuum biomechanics of soft biological tissues. Proc R Soc Lond A. 2003;459: 3-46.
6) Humphrey JD and Wilson E. A potential role of smooth muscle tone in early hypertension: A theoretical study. J Biomech 2003;36: 1595-1601.
7) Humphrey JD and Rajagopal KR. A constrained mixture model for arterial adaptations to a sustained step-change in blood flow. Biomech and Model Mechanobiol 2003;2: 109-126.
8) Rao IJ, Humphrey JD, and Rajagopal, KR. Biological growth and remodeling: A uniaxial example with possible application to tendons and ligaments. Comp Mod Engr Sci 2003;4: 439-455.
9) Gleason RL, Hu JJ, and Humphrey JD. Building a functional artery: Issues from the perspective of Mechanics. Frontiers in Bioscience 2004;9: 2045-2055.
10) Gleason RL and Humphrey JD. A mixture model of arterial growth and remodeling in hypertension: Altered muscle tone and tissue turnover J Vas Res 2004;41:352-363.
11) Gleason RL, Taber LA, and Humphrey JD. A mathematical model of flow-induced changes in the geometry, structure and properties of arteries. ASME J Biomech Engr 2004;126:371-381.
12) Na S, Sun Z, Meininger GA, and Humphrey, JD. On atomic force microscopy and the constitutive behavior of cells. Biomech Model Mechanobiol 2004;3: 75-84.
13) Zhang C, Hein TW, Wang W, Miller MW, Fossum TW, Mertens MM, Humphrey JD, Kuo L. Upregulation of vascular arginase in hypertension decreases nitric oxide-mediated dilation of coronary arterioles. Hvperten 2004;44:1-9.
14) Gleason RL and Humphrey JD. Effects of a sustained extension on arterial growth and remodeling: A theoretical study. J Biomech 2005;38: 1255-1261.
15) Gleason RL, Humphrey JD. A 2-D constrained mixture model for arterial adaptations to large changes in mechanical loading. Math Model Medicine 2005 (accepted).
16) Baek S, Rajagopal KR, Humphrey JD. Competition between radial expansion and thickening in the enlargement of an intracranial saccular aneurysm. J Elast 2005 (accepted).

List of products, processes, usages, or services developed -- None reported

List of academic or professional lectures, presentations, or abstracts -- None reported

List of milestones to commercialization achieved -- None reported

List of awards or other recognition -- None reported

Sources of Additional Information: -- None reported

4.2.7 University of California San Diego

Grant Number: HL064395
Project Title: Bioengineering Design of Artificial Blood
Awardee Institution: University of California at San Diego

Award Amount:

FY 2000	FY 2001	FY 2002	FY2003	FY 2004	Total Award to Date
1,112,548	963,528	960,256	984,323	1,009,112	5,029,767

Project Period: 5/05/2000 – 4/30/2005
(Competing continuation pending)

Principal Investigator:
Marcos Intaglietta, Ph.D.
Professor of Bioengineering
University of California, San Diego
9500 Gilman Drive, Dept. 0412
San Diego, CA 92093-0412
858-534-4275
mintaglietta@ucsd.edu

PI New to NIH-funded Research: No (Previous NIH RO1s)

BRP Partner/Affiliate Institution(s):

Northeastern University Department of Pharmacological Sciences
Sangart, Inc.

Contact at BRP Partner Institution:

Vladimir Torchilin, Ph.D., D.Sc.
Professor and Chair,
Dept. of Pharmacological Sciences
Northeastern University
Boston, MA

Robert W. Winslow, MD
President
Sangart, Inc.
11199 Sorrento Valley Road, Suite L
San Diego, CA 92121

Partner Discipline(s): At UCSD: PI: Engineering (Applied Mechanics)
At Northeastern: Co-Investigator (Torchilin): Bioorganic Chemistry
At Sangart: Co-Investigator (Winslow): Medicine

Partners New to NIH-funded Research: No

Partners Previously Collaborated with PI: Yes

Project Type: Design

Project Objectives: This BRP's goal is to produce source human hemoglobin, the raw material, and design, develop, and produce an economic O_2-carrying plasma expander (OCPE) engineered to embody physical properties that insure the maintenance of microvascular function, leading to improved survival and tissue oxygenation relative to blood. The project is organized into three subprojects in the areas of synthesis, production and testing, and microcirculation and modeling, with specific aims identified for each subproject.

Abbreviated descriptions of the specific aims for this 5-year BRP are:

Project 1– Long-Circulating Poly (Ethylene Glycol)-Modified Hemoglobin and Dextran as Blood Substitutes (Synthesis)

- Specific Aim 1: To prepare optimized PEG-modified hemoglobin. To select an optimum preparation and develop its scaled up production.
- Specific Aim 2: To synthesize biocompatible and biodegradable polymer with solutions properties required for blood substitutes. To select an optimum preparation and to develop its scaled up production.

Project 2– Streamlined Production of Hyperviscous Hemoglobin Solutions for Low-Volume Resuscitation Therapy (Production and testing)

- Specific Aim 1: Develop a self-contained, automated device to produce raw hemoglobin material from red blood cells using a commercially-available red blood cell separator.
- Specific Aim 2: Implement production of PEG-modified hemoglobins.
- Specific Aim 3: Evaluate the extent of hemoglobin pegylation on physiochemical properties of hemoglobin solutions.
- Specific Aim 4: Measure diffusion of O_2 in an artificial capillary.
- Specific Aim 5: In Year 2, initiate pre-clinical evaluation of PEG-hemoglobin solutions produced and characterized under Aims 1 – 4 in a hemorrhage shock/resuscitation model.

Project 3 – Bioengineering and Microcirculatory Methods for the Development of Artificial Blood (Microcirculation and modeling)

- Specific Aim 1: Determine the role of arterioles in tissue oxygenation under normal and in the presence of free Hb solutions of different molecular weight.
- Specific Aim 2: Determine the role of FCD in tissue oxygenation and survival.

- Specific Aim 3: Role of shear stress generated NO production in the control of tissue oxygen consumption.

- Specific Aim 4: Distribution of blood pO_2, viscosity, and shear stress in the microcirculation.

- Specific Aim 5: To test efficacy and microvascular function of concentrated, small volume Hb solutions for resuscitation in hemorrhage.

The awardee envisioned a ten-year project with long-term goals that include optimization of the product.

Project Synopsis: This BRP is focused on the development of an economic blood substitute that is both medically effective and practicable. Throughout the project period, awardee reported steady progress towards its stated goals and reported achieving its central goal – development of MP4 (Hemospan®), an O_2-carrying blood substitute that restores/maintains microvascular function. Interestingly, the properties of MP4 are counterintuitive to the conventional perception of a "blood substitute" since MP4 has a high O_2 affinity and is effective at low Hb concentrations.

Awardee reports that design targets were reached: the product achieved microvascular efficacy: better than blood in resuscitation, and reduced incidence of adverse cardiovascular events when compared with conventional transfusion regimes. MP4 has completed Phase II clinical trials in Europe (Karolinska, Stockholm) and is starting Phase II clinical trials in the US (as of 2005). (In December 2002, an IND was submitted to the US FDA in preparation for the US Phase II clinical trials to be carried out at Johns Hopkins and the Cleveland Clinic.) By September 2005, when the renewal application was submitted, the awardee provided an enumerated list of 47 publications. However, the narrative reported a total of 64 publications, including 56 that were peer-reviewed. Two are invited reviews, 3 are conference proceedings, and 3 are book articles. A pending competing renewal proposes to further explore how MP4 works and its applications.

One cautionary note about these results is that the partners bring additional resources to this research and it is difficult to tease out the separate results of each funding stream. For example, in FY 04, Sangart, Inc. conducted studies of the modified hemoglobin (MP4) and albumin in hamsters, rats, pigs, and humans, but only the rat and hamster studies were funded by this BRP. Similarly, the clinical trials conducted in Sweden were funded by Sangart not by this BRP, but the purpose was to test the product developed under this BRP.

Challenges and Setbacks Encountered: None reported, beyond routine personnel changes.

Project Performance

List of Publications:

1) Bishop JJ, Nance PR, Popel AS, Intaglietta M, and Johnson PC. Erythrocyte margination and sedimentation in skeletal muscle venules. Am J Physiol Heart Circ Physiol 281: H951-958, 2001.
2) Bishop JJ, Popel AS, Intaglietta M, and Johnson PC. Effects of erythrocyte aggregation and venous network geometry on red blood cell axial migration. Am J Physiol Heart Circ Physiol 281: H939-950, 2001.
3) Bishop JJ, Popel AS, Intaglietta M, and Johnson PC. Rheological effects of red blood cell aggregation in the venous network: a review of recent studies. Biorheology 38: 263-274, 2001.
4) Kerger H, Groth G, Kalenka A, Washke KF, and Intaglietta M. Oxygen transport from systemic arteries to capillaries - Studies using phosphorescence quenching technique. Anasthesiol & Intensivmedizin 42: 569-576, 2001.
5) Tsai AG. Influence of cell-free hemoglobin on local tissue perfusion and oxygenation after acute anemia after isovolemic hemodilution. Transfusion 41: 1290-1298, 2001.

6) Tsai AG and Intaglietta M. Hemodilution and increased plasma viscosity for the design of new plasma expanders. Transfuion Alternatives Transfusion Med 3: 17-23, 2001.
7) Tsai AG and Intaglietta M. High viscosity plasma expanders: Volume restitution fluids for lowering the transfusion trigger. Biorheol 38: 229-237, 2001.
8) Haidekker MA, Tsai AG, Brady T, Stevens HY, Frangos JA, Theodorakis E, and Intaglietta M. A novel approach to blood plasma viscosity measurement using fluorescent molecular rotors. Am J Physiol Heart Circ Physiol 282: H 1609-1614, 2002.
9) Lukyanov A, Kare S, Tsai AG, Intaglietta M, and Torchilin V. Hemoglobin modified with polyethylene glycol via p-nitrophenylcarbonyl groups: Preparation and properties. Proceedings, 29th Annual Meeting of the Controlled Release Society & Korean Society for Biomaterials 1: 666-667, 2002.
10) Tsai AG and Intaglietta M. The unusual properties of effective blood substitutes. Keio J Med 51: 17-20, 2002.
11) Sakai H, Takeoka S, Wettstein R, Tsai AG, Intaglietta M, and Tsuchida E. Systemic and microvascular responses to hemorrhage shock and resuscitation with Hb vesicles. Am J Physiol Heart Circ Physiol 283: H 1191-H 1199, 2002.
12) Bishop JJ, Popel AS, Intaglietta M, and Johnson PC. Effect of aggregation and shear rate on the dispersion of red blood cells flowing in venules. Am J Physiol Heart Circ Physiol 283: H1985-1996, 2002.
13) Cabrales P, Acero C, Intaglietta M, and Tsai AG. Measurement of the cardiac output in small animals by thermodilution. Microvasc Res 66: 77-82, 2003.
14) Kerger H, Groth G, Kalenka A, Vajkoczy P, Tsai AG, and Intaglietta M. p02 measurements by phosphorescence quenching: characteristics and applications of an automated system. Microvasc Res 65: 32-38, 2003.
15) Manjula BN, Tsai AG, Upadhya R, Perumalsamy K, Smith PK, Malavalli A, Vandegriff K, Winslow RM, Intaglietta M, Prabhakaran M, Friedman JM, and Acharya AS. Site-specific PEGylation of hemoglobin at Cys-93(beta): correlation between the colligative properties of the PEGylated protein and the length of the conjugated PEG chain. Bioconj Chem 14: 464-472, 2003.
16) Saltzman DJ, Toth A, Tsai AG, Intaglietta M, and Johnson PC. Oxygen tension distribution in postcapillary venules in resting skeletal muscle. Am J Physiol Heart Circ Physiol 285: H1980-1985, 2003.
17) Saldivar E, Cabrales P, Tsai AG, and Intaglietta M. Microcirculatory changes during chronic adaptation to hypoxia. Am J Physiol Heart Circ Physiol 285: H2O64-2071, 2003.
18) Tsai AG, Cabrales P, Winslow RM, and Intaglietta M. Microvascular oxygen distribution in awake hamster window chamber model during hyperoxia. Am J Physiol Heart Circ Physiol 285: H1537-H1545, 2003.
19) Tsai AG, Johnson PC, and Intaglietta M. Oxygen gradients in the microcirculation. Physiol Rev 83: 933-963, 2003.
20) Tsai AG, Vandegriff KID, Intaglietta M, and Winslow RM. Targeted 02 delivery by low-P50 hemoglobin: a new basis for 02 therapeutics. Am J Physiol Heart Circ Physiol 285: H1411-H1419, 2003.
21) Wettstein R, Tsai AG, Erni D, Winslow RM, and Intaglietta M. Resuscitation with MaIPEG-Hemoglobin improves microcirculatory blood flow and tissue oxygenation after hemorrhagic shock in awake hamsters. Crit Care Med 31: 1824-1830, 2003.
22) Bishop JJ, Nance PR, Popel AS, Intaglietta M, and Johnson PC. Relationship between erythrocyte aggregate size and flow rate in skeletal muscle venules. Am J Physiol Heart Circ Physiol 286: H113120, 2004.
23) Briceno JC, Cabrales P, Tsai AG, and Intaglietta M. Radial displacement of red blood cells during hemodilution and the effect on arteriolar oxygen profile. Am J Physiol Heart Circ Physiol 286: H12231228, 2004.
24) Cabrales P, Tsai AG, Frangos JA, Briceno JC, and Intaglietta M. Oxygen delivery and consumption in the microcirculation after extreme hemodilution with perfluorocarbons. Am J Physiol Heart Circ Physiol 287: H320-330, 2004.

25) Cabrales P, Kanika ND, Manjula BN, Tsai AG, Acharya SA, and Intaglietta M. Microvascular p02 during extreme hemodilution with hemoglobin site specifically pegylated at cys-93(beta) in hamster window chamber. Am J Physiol Heart Circ Physiol, 2004.
26) Cabrales P, Tsai AG, and Intaglietta M. Hype rosmotic-hyperoncotic vs. hype rosmotic-hyperviscous small volume resuscitation in hemorrhagic shock. Shock, 2004.
27) Cabrales P, Tsai AG, and Intaglietta M. Increased tissue p02 and decreased 02 delivery and consumption after 80% exchange transfusion with polymerized hemoglobin. Am J Physiol Heart Circ Physiol, 2004.
28) Cabrales P, Tsai AG, and Intaglietta M. Microvascular pressure and functional capillary density in extreme hemodilution with low and high plasma viscosity expanders. Am J Physiol Heart Circ Physiol 287: H363-H373, 2004.
29) Drobin D, Kjellstrom BT, Maim E, Malavalli A, Lohman L, Vandegriff KID, Young MA, and Winslow RM. Hemodynamic response and oxygen transport in pigs resuscitated with maleimide-polyethylene glycolmodified hemoglobin (MP4). J Appl Physiol 96: 1843-1853, 2004.
30) Frangos JA, White CR, and Intaglietta M. Shear stress effects on endothelial cells. In: Microcirculatory effects of hemoglobin solutions, edited by Messmer K, Burhop KE and Hutter J. Basel: Karger, 2004, p. 1-7.
31) Friesenecker B, Tsai AG, Dunser MW, Mayr AJ, Martini J, Knotzer H, Hasibeder W, and Intaglietta M. Oxygen distribution in microcirculation after arginine vasopressin-induced arteriolar vasoconstriction. Am J Physiol Heart Circ Physiol287: H1792-1800, 2004.
32) Hangai-Hoger N, Cabrales P, Briceno JC, Tsai AG, and Intaglietta M. Microlymphatic and tissue oxygen tension in the rat mesentery. Am J Physiol Heart Circ Physiol 286: H878-H883, 2004.
33) Intaglietta M. Microvascular transport factors in the design of effective blood substitutes. In: Microcirculatory effects of hemoglobin solutions, edited by Messmer K, Burhop KE and Hutter J. Basel: Karger, 2004, p. 8-15.
34) Lukyanov AN, Sawant RM, Hartner WC, and Torchilin VP. PEGylated dextran as long-circulating pharmaceutical carrier. J Biomater Sci Polym Ed 15: 621-630, 2004.
35) Tsai AG, Cabrales P, Hangai-Hoger N, and Intaglietta M. Oxygen distribution and respiration by the microcirculation. Antioxidants & Redox Signaling 6: 1011-1018, 2004.
36) Tsai AG, Cabrales P, and Intaglietta M. Microvascular perfusion upon exchange transfusion with stored RBCs in normovolemic anemic conditions. Transfusion, 2004.
37) Tsai AG, Cabrales P, and Intaglietta M. Oxygen-carrying blood substitutes: a microvascular perspective. Expert Opin Biol Ther 4: 1147-1157, 2004.
38) Tsai AG, Sakai H, Wettstein R, Kerger H, and Intaglietta M. An effective blood replacement fluid that targets oxygen delivery, increases plasma viscosity and has high oxygen affinity. TA TM 5: 507-514, 2004.
39) Wettstein R, Cabrales P, Erni D, Tsai AG, Winslow RM, and Intaglietta M. Resuscitation from hemorrhagic shock with MalPEG-albumin: Comparison with MalPEG-hemoglobin. Shock 22: 351-357, 2004.
40) Wettstein R, Tsai AG, Erni D, Lukyanov AN, Torchilin VP, and Intaglietta M. Improving microcirculation is more effective than substitution of red blood cells to correct metabolic disorder in experimental hemorrhagic shock. Shock 21: 235-240, 2004.
41) Winslow RM. MP4, a new nonvasoactive polyethylene glycol-hemoglobin conjugate. Artif Organs 28: 800-806, 2004.
42) Winslow RM. Oxygen transport agents: a new approach to red blood cell alternatives. TATM 5: 498-504, 2004.
43) Winslow RM, Lohman J, Malavalli A, and Vandegriff KID. Comparison of PEG-modified albumin and hemoglobin in extreme hemodilution in the rat. J Appl Physiol 97: 1527-1534, 2004.
44) Cabrales P, Sakai H, Tsai AG, Takeoka S, Tsuchida E, and Intaglietta M. Oxygen transport by low and normal oxygen affinity hemoglobin vesicles in extreme hemodilution. Am J Physiol Heart Circ Physiol 288: H 1885-1892, 2005.
45) Cabrales P, Tsai AG, and Intaglietta M. Alginate plasma expander maintains perfusion and plasma viscosity during extreme hemodilution. Am J Physiol Heart Circ Physiol 288: H1708-1716, 2005.

46) Hangai-Hoger N, Tsai AG, Friesenecker B, Cabrales P, and Intaglietta M. Microvascular oxygen delivery and consumption following treatment with verapamil. Am J Physiol Heart Circ Physiol 288: H295-H300, 2005.
47) Tsai AG, Friesenecker B, and Intaglietta M. Oxygen partition between microvessel and tissue: significance for the design of blood substitutes. In: Artificial Oxygen Carrier: Its Frontline, edited by Kobayahi K, Tsuchida E and Horinouchi H. Tokyo: Springer-Verlag, 2005, p. 38-52.

List of products, processes, usages, or services developed -- MP4 (Hemospan®)

List of academic or professional lectures, presentations, or abstracts -- None reported

List of milestones to commercialization achieved

1) European clinical trials completed and approval by Swedish MPA to proceed to Phase Ib/IIa studies.
2) US clinical trials scheduled to begin (as of 2005).

List of awards or other recognition -- None reported.

Sources of Additional Information: www.Sangart.com

4.2.8 University of Michigan

Grant Number: HL069420
Project Title: Development of a Total Artificial Lung
Awardee Institution: University of Michigan
Award Amount:

FY 2002	FY 2003	FY 2004	FY2005	FY 2006	Total Award to Date
884,809	910,781	978,673	1,113,508	1,251,436	5,139,207

Project Period: 12/01/2001 – 11/30/2006

Principal Investigator:
Robert H. Bartlett, M.D.
Professor of General and Thoracic Surgery, and
Director of Surgical Intensive Care
University of Michigan School of Medicine
2920 Taubman Center
Ann Arbor, MI 48109-0331
734-936-5822
ROBBAR@UMICH.EDU

PI New to NIH-funded Research: No (Previous NIH RO1s; NIH Training support)

BRP Partner/Affiliate Institution(s):

University of Michigan College of Engineering
Michigan Critical Care Consultants, Inc. (MC3) -- a medical device research and development company

Contact at BRP Partner Institution:

Co-Investigator:
James B. Grotberg , Ph.D., M.D.
Professor, Biomedical Engineering
Professor, Surgery
Director, NASA Bioscience and Engineering Institute
2125 Carl A. Gerstacker Building
2200 Bonisteel Boulevard
Ann Arbor, MI 48109-2099
phone: (734)936-3834
grotberg@umich.edu

Subcontractor:
Scott I. Merz, Ph.D.
President
Michigan Critical Care Consultants, Inc. (MC3)
3550 West Liberty
Suite 3
Ann Arbor, MI 48103
734-995-9089
No email provided

Partner Discipline(s): PI: Medicine (Surgery)
Co-Investigators: Biomedical engineering and/or Medicine (Surgery)
Subcontractor company: Biomedical engineering

Partners New to NIH-funded Research: No
Partners Previously Collaborated with PI: Yes
Project Type: Design

Project Objectives: This objective of this BRP is to model, construct prototypes, and test in-vitro and in-vivo a Total Artificial Lung (TAL). The specific aims are to:

1. Redesign the TAL to eliminate fiber leak, optimize the fluid dynamic characteristics, maximize blood flow and gas exchange, and to reconfigure the shape and size to allow implantation.

2. Develop servoregulation mechanisms for controlling device ventilation to achieve desired systemic blood CO_2 levels.

3. Characterize, model, and recreate the requirements for pulmonary vascular replacement in terms of device impedance.

4. To evaluate the redesigned clinical prototype for function and durability in animal studies.

Project Synopsis: This BRP is focused on developing and refining a TAL so that it can be implanted successfully as a total lung replacement. It complements research underway in another BRP project (HL64373 - Total Liquid Ventilation: A Bioengineering Partnership) with overlapping project personnel. This project is a collaboration between partners who had previously worked together from different components (engineering school and medical school) of the same institution. A third partner is a small medical device research, development, and testing business (MC3) that was co-founded by the PI (Bartlett) with initial funding from the University of Michigan. MC3 will own the patents on the artificial lung, and the PI would collect royalties on the lung.

After a slow start due to administrative issues, the awardee reported steady progress toward its stated goals. Specifically, the TAL was redesigned for reduced fiber leak, improved fluid dynamics, and optimized configuration for implantation. A gas flow controller to achieve desired systemic blood CO2 levels was developed and tested, completing project aim 2 during Year 3. Multiple computerized, bench, and animal studies were carried out to characterize the compliance and impedance of the TAL, including testing under the conditions of chronic pulmonary hypertension. Short-term animal studies were carried out, encountering some initial practical problems, but eventually generating results showing that 7-day TAL use is feasible without deterioration of artificial lung or major organ function. During the fourth year of the project, the awardee conducted 7–day testing of prototype artificial lungs in sheep and had begun 30-day pre-clinical studies using the final prototype configuration. Continuing device development will occur following GLP guidelines with a eye toward qualifying for later FDA submission. By the end of Year 4, the awardee had four publications, plus one in press and another submitted, along with 15 abstracts.

Challenges and Setbacks Encountered: At end of first year, awardee carried forward 55% of funds due to protracted subcontracting and intra-University liaison processes, delays in hiring of personnel, and logistics associated with establishing chronic animal studies, including delayed availability of research staff. During Year 3, in vitro testing of its then-current TAL compliance chamber achieved some goals (i.e., maximizing cardiac output), but would not minimize the total work of the right ventricle, therefore the awardee needed to work on an improved compliance chamber. Fiber leak has also been a challenge, requiring the awardee to test multiple alternatives.

Project Performance

List of Publications Resulting in Whole or Part from Support from this Grant:

1) Haft JW, Griffith BP, Hirschl RB, Bartlett RH: Results of an artificial-lung survey to lung transplant program directors. J Heart Lung Transplant 2002; 21:467-473.
2) Lynch WR, Bartlett RH: "Rationale for an Implantable Artificial Lung", IN: The Artificial Lung, SN Vaslef, et al, (eds.), Eurekah.com/Landes Bioscience, Georgetown, TX, 2002.
3) Funakubo A, Taga I, McGillicuddy JW, Fukui Y, Hirschl RB, Bartlett RH. Flow Vectorial Analysis in an Artificial Implantable Lung. ASAIO Journal. 2003; 49(4):383-387.
4) Haft JW, Bull JL, Rose R, Katsra J, Grotberg JB, Bartlett RH, Hirschl RB. Design of an artificial lung compliance chamber for pulmonary replacement. ASAIO Journal. 2003 Jan.- Feb.; 49(I):35-40.
5) McGillicuddy JW, Chambers SD, Galligan DT, Hirschl RB, Bartlett RH, Cooke KE. In vitro, fluid mechanical effects of thoracic artificial lung compliance. ASAIO Journal, in press.
6) Sato H, McGillicuddy JW, Griffith GW, Cosnowski AM, Chambers SD, Hirschl RB, Bartlett RH, Cooke KE. Effects of artificial lung compliance on in vivo pulmonary system hemodynamics. ASAIO Journal, submitted.

Abstracts associated with national presentations

1) McGillicuddy JW, Cook KE, Lambert MB, Griffith GW, Chambers SD, Hirschl RB, Bartlett RH. In-parallel artificial lung returns pulmonary resistance to normal in chronic lung disease model. ASAIO Abstracts 49: 170, 2003.
2) McGillicuddy JW, Cook KE, Chambers SD, Hirschl RB, Bartlett RH. Determination of compliance requirements in artificial lung design. ASAIO Abstracts 49: 214, 2003.
3) Sato H, McGillicuddy JW, Cook KE, Griffith GW, Dusset CM, Li P, Chambers SD, Hirschl RB, Bartlett RH. Design of an artificial lung compliance chamber for right ventricular function. ASAIO Abstracts 50: 154, 2004.
4) Sato H, McGillicuddy JW, Griffith GW, Dusset CM, Hirschl RB, Cook KE. Embolic, chronic pulmonary hypertension model in sheep. ASAIO Abstracts 50: 157, 2004.
5) McGillicuddy JW, Chambers SD, Hirschl RB, Bartlett RE, Cook KE. Determination of ideal thoracic artificial lung compliance at various right ventricular outputs. ASAIO Abstracts 50: 171, 2004.
6) Lin Y.C. and Bull J.L. An experimental model of flow in an artificial lung. ASAIO Conference, 2004 (Y.C. Lin received an ASAIO Biomedical Engineering Student Fellowship Travel Award based on this work).
7) Calderon A.J. and Bull J.L. An experimental investigation of bubble splitting. Bulletin of the American Physical Society 48(10): 226, East Rutherford, NJ, November 2003.
8) Zierenberg J.R., Fujioka H., Suresh V., and Grotberg J.B. Pulsatile flow over a cylinder. BMES Annual Conference, Philadelphia, PA, October, 2004.
9) Chan K.Y., Fujioka H., and Grotberg J.B. Pulsatile flow over arrays of cylinders. BMES Annual Conference, Philadelphia, PA, October, 2004.
10) Chan K.Y., Fujioka H., and Grotberg J.B. Pulsatile flow and gas transfer over arrays of cylinders. Bulletin of the American Physical Society 49(9):134135, Seattle, WA, November 2004.
11) Lin Y.C. and Bull J.L. Pulsatile flow around a single cylinder-an experimental model of flow inside an artificial lung. Bulletin of the American Physical Society 49(9):134-135, Seattle, WA, November 2004.
12) Sato H, Griffith GW, Dusset CM, Chambers SD, Toomasian JM, Hirschl RB, Bartlett RH, Cook KE. 7-day, in parallel artificial lung testing in sheep. ASAIO Journal 51: 50A, 2005.
13) Sato H, Odeleye ME, Chambers SD, Hirschl RB, Bartlett RH, Cook KE. Thoracic artificial lung (TAL) development: determining the most suitable fiber for TAL. ASAIO Journal 51: 50A, 2005.

14) Griffith GW, Sato H, Kim J, Odeleye ME, Hirschl RB, Chambers SD, Cook KE. Hemodynamic effects of in-parallel artificial lung attachment in healthy and hypertensive sheep. ASAIO Journal 51: 50A, 2005.
15) Cook KE. Right Ventricular Function During Thoracic Artificial Lung Attachment. BMES Annual Conference Proceedings, 2005.

List of products, processes, usages, or services developed -- None reported

List of academic or professional lectures, presentations, or abstracts

1) June 2002 – Drs. Bartlett and Hirschl chaired workshop on implantable artificial lungs at the American Society of Artificial Organs
2) Narrative describes annual ASAIO conference presentation/participation without specific dates provided

List of milestones to commercialization achieved -- None reported

List of awards or other recognition -- None reported

Sources of Additional Information: Michigan Critical Care Consultants, Inc. (MC3) company website -- www.mc3corp.com

4.2.9 University of Virginia

Grant Number: HL065958
Project Title: Integrated Control of Vascular Pattern Formation
Awardee Institution: University of Virginia
Award Amount:

FY 2001	FY 2002	FY 2003	FY2004	FY 2005	Total Award to Date
656,880	705,026	715,626	725,019	724,046	3,526,597

Project Period: 9/01/2001 – 8/31/2006
(Competing continuation through 2011 pending)

Principal Investigator:
Thomas C. Skalak, Ph.D.
Professor and Chair
Department of Biomedical Engineering
School of Engineering and Applied Science
University of Virginia
415 Lane Road; P.O. Box 800759
Charlottesville, VA 22908-0759
434-924-0270
TCS4Z@VIRGINIA.EDU

PI New to NIH-funded Research: No (Previous NIH RO1s; NIH Research Career Development Award)

BRP Partner/Affiliate Institution(s): University of Virginia School of Medicine

Contact at BRP Partner Institution:
Gary K. Owens, Ph.D.
Professor
Department of Molecular Physiology and Biological Physics
University of Virginia School of Medicine
PO Box 800736
Charlottesville, VA 22908-0736
Office: 434-924-2652
Lab: 434-924-5993
gko@virginia.edu

Partner Discipline(s): PI and Co-PI: Biomedical Engineering
Co-PI: Molecular physiology

Partners New to NIH-funded Research: No
Partners Previously Collaborated with PI: Yes
Project Type: Hypothesis

Project Objectives:

1) To determine the role of PDGF and TGF-β in arteriolar assembly and pattern formation during embryonic development.

2) To determine the cell types involved, role of PDGF and TGF-β signaling, and spatial and temporal expression patterns of arteriolar assembly in adults.

3) To develop and use a new cell-based computer simulation to perform integrative spatio-temporal analysis of the arterialization process in the embryo and adult, including multi-signal control of fibroblast and smooth muscle cell proliferation, migration, and differentiation.

Project Synopsis: This BRP on the integrative control of vascular pattern formation has used an integrative systems approach to measure the dynamics of arteriolar pattern formation in vivo across time scales from the embryo to the adult, and spanning spatial scales from genes to cells to whole networks, and to create a new computational approaches to understand the complex interplay of multiple interacting cells and signal molecules. The project is a collaboration between partners who had previously worked together from different components (engineering school and medical school) of the same institution. The BRP proposal was not funded on its initial submission, but after it was revised and resubmitted. However, it has proven to be a productive partnership.

By the end of the first four years, the awardee has 21 publications attributed in whole or in part to this grant and reports having accomplished its stated goals for the project period, including demonstration of directional arterialization, importance of PDGF-BB and TGFβ_1 from vascular cells in vascular patterning, and construction of the first multicell simulation for vessel assembly, as proposed. In addition, the researchers reported several new discoveries and advances: the first directional arterialization guidance studies; a first and unique transgenic model allowing real-time visualization of GFP under control of SMC myosin heavy chain gene expression; a new pericyte marker (NG2) of angiogenic adaptation; related hemodynamics in the network to in vivo adaptations via the model; and reported on bone marrow-derived cell dynamics in the networks. A pending competing renewal for years 6-10 proposes to focus on: “role of BMCs in adult vascular patterning, cell-scale spatial signaling and outcomes, the vessel-scale "positional address system", novel transgenic models in mice, new cell-scale interventions with exogenous sources of signaling molecules, and a new multidimensional computer simulation capable of 2D and 3D prediction of BMC regulation of vascular pattern.”

Challenges and Setbacks Encountered: None reported.

Project Performance

List of Publications Resulting in Whole or Part from Support from this Grant:

1) Hirschi KK, Skalak TC, Peirce SM, and Little CD. Vascular assembly in natural and enginered tissues. Ann NY Acad Sci 2002; 961: 223-242.
2) Price RJ, Less JR, VanGieson EJ, and Skalak TC. Hemodynamic Stresses and Structural Remodeling of Anastomosing Arteriolar Networks: Design Principles of Collateral Arterioles. Microcirculation. 2002*; 9:* 111-124.
3) Skalak TC. In vivo and in silico approaches for analysis and design of multisignal, multicomponent assembly processes in vascular systems. Ann NY Acad Sci 2002; 961: 243-245.
4) Ponce AM, and Price RJ. Angiogenic Stimulus Determines the Positioning of Pericytes Within Capillary Sprouts In Vivo. Microvasc. Res. 2003*;* 65: 45-48.
5) Peirce SM, Skalak TC. Microvascular remodeling: a complex continuum spanning angiogenesis to arteriogenesis. Microcirculation. 2003; 10: 99-111.
6) Van Gieson EJ, Murfee WL, Skalak TC, and Price RJ. Enhanced Spatial Smooth Muscle Cell Coverage of Microvessels Exposed to Increased Hemodynamic Stresses In Vivo. Circ. Res. 2003; 92*:* 929-936.
7) Anderson CR, Ponce AM, and Price RJ. Absence of OX-43 Antigen Expression In Invasive Capillary Sprouts: Identification of a Capillary Sprout-Specific Endothelial Phenotype. Am. J. Physiol. Heart Circ. Physiol. 2004*;* 285: H346-H353.
8) Anderson CR, Ponce AM, and Price RJ. Immunohistochemical Identification of an Extracellular Matrix Scaffold that Microguides Capillary Sprouting During Angiogenesis. J Histochem Cytochem. 2004; 52: 1063-1072.

9) Dandre F, Owens GK. Platelet-derived growth factor-BB and Ets-1 transcription factor negatively regulate transcription of multiple smooth muscle differentiation genes. Am. J. Physiol. 2004; 286: H2042-2051.
10) Hoofnagle MH, Wamhoff BR, Owens GK. Lost in Transdifferentiation. J. Clin. Invest. 2004; 113(9): 12491251.
11) Murfee WL, Van Gieson EJ, Price RJ, and Skalak TC. Cell Proliferation in Mesenteric Microvascular Networks Remodeling in Response to Elevated Hemodynamic Stress. Ann. Biomed. Eng. 2004; 32:1662-1666.
12) Owens GK, Kumar MS, Wamhoff BR. Molecular regulation of vascular smooth muscle cell differentiation in development and disease. Physiol. Review 2004; 84:767-801.
13) Peirce SM, Price RJ, and Skalak TC. Spatial and Temporal Control of Angiogenesis and Arterialization Using Focal Applications of $VEGF_{164}$ and Ang-1. Am. J. Physiol. Heart Circ. Physiol. 2004; 286: 918-925.
14) Peirce SM, Van Gieson EJ, Skalak TC. Multicellular simulation predicts microvascular patterning and in silico tissue assembly. FASEB J. 2004b; 18: 731-733.
15) Sinha S, Hoofnagle MH, McCanna ME, Kingston P, Owens GK. Transforming Growth Factor-R1 Signaling Contributes to Development of Contractile Smooth Muscle Cells from Embryonic Stem Cells. Am. J. Physiol. 2004; 287: C1560-1568.
16) Wamhoff BR, Bowles DK, Sinha S, McDonald OG, Somlyo AP, Somylo AV, Owens GK. L-type voltage-gated Ca2+ Channels Regulate Smooth Muscle Differentiation Marker Gene Expression by Rho Kinase Circ. Res. 2004; 95: 406-414.
17) Yoshida T, Kawai-Kowase K, Owens GK. Forced expression of myocardin is not sufficient for induction of smooth muscle differentiation in multipotential embryonic cells. Atherioscierosis Thrombosis and Vascular Bioloqy 2004; 24:1-7.
18) Murfee WL, Peirce, SM, Skalak TC. Differential arterial/venous expression of NG2 proteoglycan in perivascular cells along microvessels: Identifying a venule-specific phenotype. Microcirculation 2005; 12: 151-160.
19) Skalak TC. Angiogenesis and microvascular remodeling: a brief history and future roadmap. Microcirculation 2005; 12: 47-58.
20) O'Neill TJ, Wamhoff BR, Owens GK, and Skalak TC. Mobilization of Bone Marrow Derived Cells Enhances the Angiogenic Response to Hypoxia, Without Transdifferentiation into Endothelial Cells. Circ. Res. 2005 (in press).
21) Yoshida T and Owens GK. Molecular Determinants of Vascular Smooth Muscle Cell Diversity.Circ Res 2005; 96:280-291.

Listed in progress report but not in renewal application; publication status unclear

1) Peirce SM, Price RJ, and Skalak TC. Spatial and temporal guidance of angiogenesis and arterialization: L Focal application of VEGF. Circ. Res. 2003 (in review).
2) Peirce SM, Price RJ, and Skalak TC. Spatial and temporal guidance of angiogenesis and arterialization: II. Focal application of VEGF and Ang-1 in combination. Circ. Res. 2003 (in review).
3) Wamhoff BR, Kumar MS, and Owens GK. Role of alterations in the differentiated state of smooth muscle cells in atherothrombogenesis. In: Atherosclerosis and Coronary Artery Disease. Lippocott-Raven. Editors: V. Fuster, B. Nabel, and E.J. Topol. Circ Res 2004 (in press).

- *List of products, processes, usages, or services developed* -- None reported
- *List of academic or professional lectures, presentations, or abstracts* -- None reported
- *List of milestones to commercialization achieved* -- None reported

- *List of awards or other recognition* -- None reported

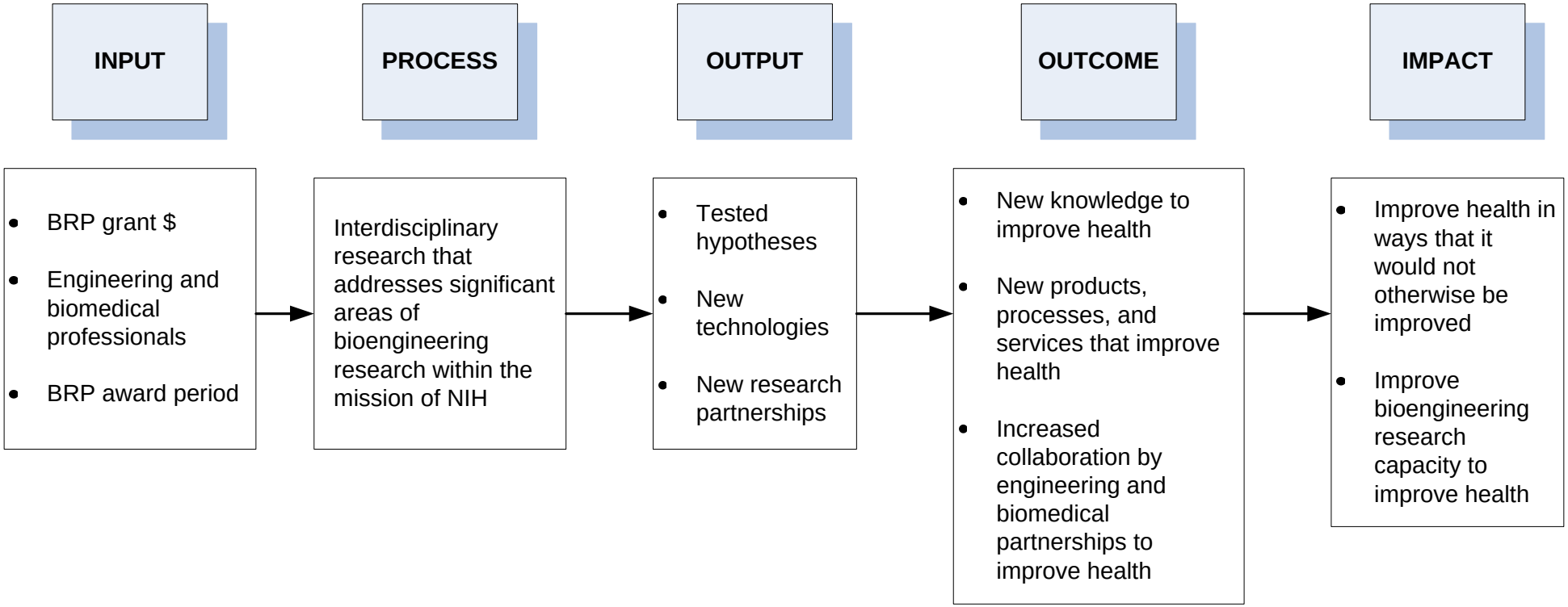
Sources of Additional Information: None reported.

APPENDIX A

BRP LOGIC MODEL

APPENDIX A

BRP Logic Model



APPENDIX B

EVALUATION FRAMEWORK

Appendix B

Evaluation Framework

NHLBI BRP Program Goal	BRP Program Objective	Standard	Index	Measure
The NIH BRP Program goal is to catalyze and support basic, applied, translational, behavioral, or clinical research in bioengineering conducted by interdisciplinary teams using integrative systems approaches to improve human health.	1. Stimulate interdisciplinary research to advance fundamental concepts, test hypotheses, or develop technology to improve human health that might not otherwise be NIH-funded.	1A. Within 3 years of BRP award, all BRP awardees demonstrate progress towards: making novel contributions to bioengineering knowledge; or, developing innovative or improved products, processes, usages, services, or clinical research.	1A.1 Within 3 years of funding, 100% of those BRP awardees funded to conduct hypothesis-driven bioengineering research generate at least one scientific deliverable reporting findings from their BRP-supported research on new knowledge about using engineering principles to improve human health.	Within 3 years of funding, 100% of those BRP awardees funded to conduct hypothesis-driven bioengineering research achieve one or more of the following measures: 1.A.1.1 Lectures, such as grand rounds, and other dissemination efforts within RFP partner institutions or within academic settings (#, titles, and institution name) 1.A.1.2 Presentations at national health conferences or engineering symposia on BRP-supported research in bioengineering-related fields (#, titles, and venues) 1.A.1.3 Abstracts or poster sessions on BRP-supported research accepted by peer-reviewed panels for publication or presentation (# and name of sponsoring organization) 1.A.1.4 Articles published or accepted by peer-reviewed journals on BRP-supported research findings in health-related fields (# and name s of journals) 1.A.1.5 Awards for or other recognition of BRP-supported research findings in health-related fields (# and types) 1.A. 1.6 Research and educational tools derived from BRP-supported research that increase health knowledge directly or indirectly by enabling others to do so (# and types) 1.A.1.7 Published citations of BRP-supported research (# and type)
			1A.2 Within 3 years of funding, 100% of those BRP awardees funded to conduct design-driven research achieve at least one scientific or commercial milestone showing progress towards development of new products, processes, and services that use engineering principles to improve human health.	Within 3 years of funding, 100% of those BRP awardees funded to conduct design-driven research achieve one or more of the following measures: 1A.2.1. Presentations at national health conferences or engineering symposia on new or improved BRP-supported products, processes, usages, services, or clinical research in health-related fields (#, titles, and venues) 1.A.2.2 Abstracts or poster sessions on new or improved BRP-supported products, processes, usages, services, or clinical research accepted by peer-reviewed panels for publication or presentation (# and name of sponsoring organization) 1.A.2.3 Articles published or accepted by peer-reviewed journals on new or improved BRP-supported products, processes, usages, services, or clinical research (# and name s of journals) 1.A.2.4.. New or improved BRP-supported products, processes, usages, services, or clinical research in health-related fields (# and types)

NHLBI BRP Program Goal	BRP Program Objective	Standard	Index	Measure
				1A.2.5 BRP-supported clinical studies or trials that are approved, underway, or completed (# and type) 1A.2.6 # and % of patents, copyrights, trademarks, or licenses for new or improved BRP-supported products, processes, or services in health-related fields 1A.2.7 # and % of BRP-supported drugs or medical devices that are undergoing FDA review or have received FDA approval 1A.2.8 # and % of BRP-supported products, processes, and services that yield sales 1A.2.9 # and % of other evidence of commercialization of BRP--supported innovations
		1B Many BRP awardees pursue hypotheses or designs that might not be funded by other NIH programs.	1.B.1 75% of BRP awardees pursue hypotheses or designs that might not be funded by other NIH programs.	1.B.1.1 # and % of BRP awardees who submitted BRP project hypothesis or design to another NIH program before submission to BRP program 1.B1.2 # and % of BRP awardees who submitted BRP project hypothesis or design to another NIH program before submission to BRP program and did not receive NIH funding prior to BRP 1.B1.2 # and % of BRP awardees who submitted BRP project hypothesis or design to another NIH program before submission to BRP program and were referred to the BRP program
		1C Many successful BRP awardees share common characteristics or engage in best practices that help them achieve success	1C.1 75% of BRP awardees share identifiable common characteristics or engage in identifiable best practices that help them achieve success	1C1.1 Rank-ordered list of characteristics and best practices correlated with achievement of many measures of success (such as years since award, scientific fields of research, age/experience of researchers, grant dollar amount, need for FDA approval, nature of research (hypothesis or design-driven), priority score on grant application, number of collaborators in BRP partnership, type of partnership organization, etc. 1C1.2 # and % of BRP awardees sharing each identified characteristic or best practice

: **NHLBI BRP Program Goal**	**BRP Program Objective**	**Standard**	**Index**	**Measure**
The NIH BRP Program goal is to catalyze and support basic, applied, translational, behavioral, or clinical research in bioengineering conducted by interdisciplinary teams using integrative systems approaches to improve human health.	2. The NIH BRP Program increases collaborations between the engineering, physical, and computational sciences and the biomedical and/or clinical sciences to build interdisciplinary bioengineering research capacity in support of the NIH mission.	2.A. All BRP projects feature collaboration between the engineering, physical, and computational sciences and the biomedical and/or clinical sciences	2.A.1 100% of BRP projects include partners from engineering, physical, and computational science partners	2.A.1.1 # and % of BRP awardees with staff professionals who have engineering, physical, and computational science degrees 2.A.1.2 # and %of BRP awardees with staff professionals who have engineering, physical, and computational science fields of study
			2.A.2 100% of BRP projects include partners from biomedical and/or clinical sciences	2.A.2.1 # and % of BRP awardees with staff professionals who have biomedical and/or clinical sciences degrees 2.A.2.2 # and %of BRP awardees with staff professionals who have biomedical and/or clinical science fields of study
			2.A.3. 50% of BRP awardees include first-time NIH research partners	2.A.3. # and % of BRP awardees that include a research partner that had never partnered in an NIH-funded project at the date of award
		2.B. Some BRP awardees develop effective interdisciplinary research partnerships	2.B.1 50% of BRP awardees develop effective inter-disciplinary research partnerships	2.B.1.1 # and % of BRP-supported articles or abstracts with named authors from multiple partner institutions from date of award to the time of measurement 2.B.1.2 # and % of BRP awardee partnerships that receive additional funding for BRP-supported projects or innovations from sources other than the BRP program from date of award to the time of measurement 2.B.1.3 # and total dollars awarded to BRP awardee partnerships by non NIH sources for BRP-supported projects or innovations from the date of award to the time of measurement 2.B.1.4 # and titles of disseminations of BRP-supported research in engineering or business venues 2.B.1.5 Number of new researchers in BRP-supported topics at organizations with NIH BRP awards

: NHLBI BRP Program Goal	BRP Program Objective	Standard	Index	Measure
				2.B.1.6 # and % of spin-off companies resulting from BRP-supported innovations at time of measurement 2.B.1.7 # and % of awardees experiencing high levels of satisfaction with the NIH BRP program from date of award to time of measurement

APPENDIX C

ON-LINE INTERVIEW

Online In-Depth Interview Form

The following award was identified through the National Institutes of Health (NIH) databases as a Bioengineering Research Partner (BRP) Program award. Please keep this particular award in mind when responding to the questions in this in-depth interview.

Lead Institution:	Principal Investigator:
Award Number:	Institute Contact:
Project Period:	NIH Sponsoring Institute: NHLBI
Project Title:	

SECTION A

The following questions ask for information about the award and the awardee identified above that received the referenced BRP award.

1. How many institutions are partnering together on this BRP award?

_____

2. Please list all of the institutions that are partnering together on this BRP award.

Put an asterisk (*) before any of the institutions that, to the best of your knowledge, have <u>never partnered in an NIH-funded project prior to the receipt of this award</u>.

3. Was your BRP project hypothesis or design rejected by another NIH grant program before it was submitted to the BRP program?

☐ Yes → Which NIH program? _____

☐ No

4. **How many lead professionals—PIs and other key researchers—are working on this BRP award? Please include lead professionals from all of the partner institutions.**

_____

5. **Please list the educational degrees of all of the lead professionals—PIs and key other researchers—working on this project and give their fields. (For example: Ph.D., Physics)**

6. **Has this partnership received any additional non-NIH funding or capital for this project?**

☐ No or none yet

☐ Yes → Please explain the source or sources of this additional funding or capital.

7. **Which one of the following best characterizes the anticipated main outcome of this BRP-supported project?**

☐ Tested hypothesis or discovery

☐ Research, information, or increased knowledge

☐ Material, device, design, or other product

☐ Process, procedure, or usage

☐ Service

☐ Other (please specify): _____

8. **Overall, how would you classify the research supported by the referenced BRP award?**

☐ Hypothesis-driven or discovery-driven → CONTINUE WITH Q.9

☐ Design-driven or developmental → GO TO Q.13

SECTION B: Hypothesis-Driven Research

The following questions ask about the journals in your field of research and products resulting from the research conducted under the referenced award.

9. Please list the top five peer-reviewed journals that you feel are most esteemed in your field of research.

10. Has this BRP research partnership had any articles published or accepted for publication in peer-reviewed journals?

☐ None yet

☐ Yes → Please give complete references for all articles published or accepted for publication.

11. To the best of your knowledge, have any of these publications been cited by other authors in their published articles?

☐ Yes → Please estimate the number of citations:

☐ No

☐ Not sure; don't know

12. To date, have any research or educational tools been derived from the BRP-supported research? (Research and educational tools are any products, processes, or services that increase health knowledge directly or indirectly by enabling others to do so.)

☐ No or none yet

☐ Yes → Please specify how many and describe the tools.

ALL → GO TO Q.17

SECTION B: Design-Driven Research

The following questions ask about your research goal, the journals in your field of research, and products resulting from the referenced award.

13. Which one of the following most characterizes the product, process, usage, or service that was planned under this BRP partnership?

- ☐ A totally new product, process, usage, or service
- ☐ An improvement to an existing product, process, usage, or service
- ☐ A combination of products, processes, usages, or services
- ☐ A new use for an existing product, process, usage, or service
- ☐ Other (please specify): _____

14. Please list the top five peer-reviewed journals that you feel are most esteemed in your field of research.

15. Has this BRP research partnership had any articles published or accepted for publication in peer-reviewed journals on new or improved products, processes, usages, services, or clinical research?

- ☐ None yet
- ☐ Yes → Please give complete references for all articles published or accepted for publication.

16. Has this research partnership received any patents, copyrights, trademarks, sales of licenses, or sales related to the BRP-supported product, process, or service?

☐ None yet

☐ Yes → Please give complete details about all patents, copyrights, trademarks, sales of licenses, or sales related to this product, process, or service

SECTION C

The final questions ask about the BRP Program and how it might be improved.

17. If the BRP Program were <u>not</u> available, would the project funded by the referenced award still have been pursued?

☐ Yes

☐ No

☐ Not sure; don't know

18. One main objective of the BRP Program is to <u>improve human health</u>. In what ways do you believe this BRP project makes or will make a significant contribution to improving human health?

19. **What is the greatest obstacle or difficulty that this partnership has encountered so far in its progress toward achieving the goals set out in the partnership's application for the BRP award?**

20. **NIH seeks to compare the successes achieved by BRP Program awardees with those achieved by other comparable groups. Which group of comparable researchers do you think would make a good comparison group for BRP awardees?**

21. **What could NIH do to further assist BRP Program awardees—in applying for a BRP award, in producing progress reports, in achieving success reaching stated goals, or in any other areas?**

Thank you very much for your input and assistance with this pilot evaluation of the BRP Program.

APPENDIX D

ONLINE DEBRIEFING SURVEY

Online Evaluation Form

NIH greatly appreciates your participating in this pilot evaluation of the BRP Program.

Please help by taking a few additional minutes to provide NIH with feedback and suggestions for improving the evaluation process.

1. This evaluation makes a distinction between hypothesis-driven or discovery-driven research and design-driven or developmental driven research. Do you think that this is a valid or important distinction in assessing the outcomes of BRP awards?

☐ Yes

☐ No

Why?

2. How important an indicator of success is the number of citations of articles published by BRP awardees?

☐ Very important

☐ Important

☐ Neither important nor unimportant

☐ Unimportant

☐ Very unimportant

☐ Not sure; don't know

3. How should NIH measure the successes achieved by BRP awardees? What metrics or measures are most important?

4. **Do you believe that the BRP Program funds research that <u>might not otherwise be funded</u> by other NIH programs?**

☐ Yes

☐ No

Why do you believe that?

5. **Do you feel that the BRP Program increases collaborations between the engineering, physical, and computational sciences <u>and</u> the biomedical and/or clinical sciences?**

☐ Definitely does increase collaborations

☐ Sometimes does increase collaborations

☐ Does not particularly increase collaborations

☐ Not sure; don't know

6. **Do you think that the aims and goals of your project could be accomplished by <u>smaller, independent investigator grants</u>?**

☐ Yes

☐ No

Why do you think that?

Thank you very much for your input and assistance with this pilot evaluation of the BRP Program.

APPENDIX E

ONLINE INTERVIEW EMAILS

E-1—Advance Email
E-2—First Email
E-3—Second Email
E-4—Extension Email
E-5—Thank You Email

Appendix E-1

Advance Email

Evaluation of the NHLBI Bioengineering Research Partnership (BRP) Program

From: **Martha S. Lundberg, Ph.D., NHLBI BRP Coordinator [BRP@Humanitas.com]**
Sent: **January 30, 2006**
To: **Dr. [Name] [Email Address]**
Subject: **ALERT - Online Interview about the BRP Program**
Importance: **High**

Dear Dr. [Name],

The National Heart, Lung, and Blood Institute (NHLBI) is seeking your help to evaluate its Bioengineering Research Partnership (BRP) Program. As one of the initial awardees of BRP funding, you are uniquely qualified to provide NHLBI with feedback about the utility and value of this mechanism for funding multidisciplinary bioengineering research teams.

NHLBI, in conjunction with the NIH Bioengineering Consortium (BECON), developed the BRP program to address research gaps in the NIH portfolio that result from the structure of the NIH review process. The BRP review criteria provide equal status and ensure a fair evaluation of both design- and hypothesis-driven research applications. In FY 2005, NHLBI invested approximately $30M in the BRP Program. Now NHLBI wants to learn:

- How to best foster multidisciplinary bioengineering research in the future, and
- How the BRP program is improving human health and encouraging collaborations among quantitative and biomedical disciplines

I am writing in advance because I want to emphasize the importance of this assessment. Within the next week, you will receive an e-mail message from Humanitas, Inc., the contractor that is managing the analysis for NHLBI. The message will ask you to participate in an interview that will be conducted online. This interview should take only about 15 to 20 minutes to complete. Your participation is extremely important, and the information provided by you and your peers may influence the administration of the BRP Program in the coming years.

I encourage you to complete the online interview, and I thank you in advance for your participation. We would like to confirm that we have the correct contact information for you:

[Telephone Number] [Email Address]

If either of these is not correct, please call the toll-free number or email the BRP Assessment Coordinator at Humanitas, Inc:

Ms. April Smith 877-608-3290, x228 April.Smith@Humanitas.com

Should you have any questions about the analysis, please contact me at: lundberm@nhlbi.nih.gov.
Please do not reply to this message.

Thank you for your time and cooperation.

Sincerely,

Martha S. Lundberg, Ph.D.
NHLBI BRP Coordinator
National Institutes of Health

Appendix E-2

First Email

Evaluation of the NHLBI Bioengineering Research Partnership (BRP) Program

From: **Martha S. Lundberg, Ph.D., NHLBI BRP Coordinator [BRP@Humanitas.com]**
Sent: **February 6, 2006**
To: **Dr. [Name] [Email Address]**
Subject: **ACTION REQUESTED - Link to Online Interview Form**
Importance: **High**

Dear Dr. [Name],

Recently, I sent you an email asking for your help in evaluating NHLBI's BRP Program. This evaluation will allow NHLBI to assess the need for funding that specifically targets multidisciplinary bioengineering research, and the degree to which the BRP program is improving human health and encouraging collaborations among quantitative and biomedical disciplines.

As one of the initial awardees of NHLBI funding for a BRP grant, you are uniquely qualified to provide NHLBI with feedback about the utility and value of the BRP Program for funding multidisciplinary bioengineering research teams. I encourage you to take a few moments to complete the online interview and thank you in advance for your participation. **Please note that the online site closes at the end of the day, Tuesday, February 14th.**

The location of the online interview form is: https://www.Humanitas3.com/BRPInterview

>>> Please click on this link to access the form, or copy and paste the location into your Internet browser window. Once you have accessed the introductory screen, you will be asked to enter your user name and unique personal password:

UserName: **<UserName>**
Password: **<Password>**

The form is implemented using SSL (Secure Socket Layer) encryption technology. After you access the form, you will see a "lock" in the lower right-hand corner indicating that you have a secure connection. If you have trouble accessing the online form, please call the toll-free number or email the BRP Assessment Coordinator at Humanitas, Inc:

Ms. April Smith 877-608-3290, x228 April.Smith@Humanitas.com

All responses will be kept completely confidential and will be provided to NHLBI only as summaries in which no individual's answers can be identified. Should you have any questions about the analysis, please contact me at : lundberm@nhlbi.nih.gov. Do not reply to this message.

Thank you for your time and cooperation.

Appendix E-3

Second Email

Evaluation of the NHLBI Bioengineering Research Partnership (BRP) Program

From: **Martha S. Lundberg, Ph.D., NHLBI BRP Coordinator [BRP@Humanitas.com]**
Sent: **February 13, 2006**
To: **Dr. [Name] [Email Address]**
Subject: **FINAL CALL - Completing the Online Interview**
Importance: **High**

Dear Dr. [Name],

We need your help. We have extended the response period so that the online interview site will remain open until the end of the day, Thursday, February 16th.

NHLBI is in the process of evaluating the BRP Program to guide future research policy decisions. We want to learn:

- If there is continuing need for funding specifically targeting multidisciplinary bioengineering research, and
- If BRP awardees are achieving the Program goals of improving human health and encouraging collaborations among quantitative and biomedical disciplines

We are especially appreciative of your help. It is only by the efforts of individuals such as you that NHLBI can gauge the success of the BRP Program and plan constructively for its continuance.

Thank you again for your time and cooperation.

If you have misplaced the earlier email, the location of the online interview form is:

https://www.Humanitas3.com/BRPInterview

>>> Please click on this link to access the form, or copy and paste the location into your Internet browser window. Once you have accessed the introductory screen, you will be asked to enter your user name and unique personal password:

UserName: **<UserName>**
Password: **<Password>**

The form is implemented using SSL (Secure Socket Layer) encryption technology. After you access the form, you will see a "lock" in the lower right-hand corner indicating that you have a secure connection. If you have trouble accessing the online form, please call the toll-free number or email the BRP Assessment Coordinator at Humanitas, Inc:

Ms. April Smith 877-608-3290, x228 April.Smith@Humanitas.com

We look forward to your participation.

Appendix E-4

Extension Email

Evaluation of the NHLBI Bioengineering Research Partnership (BRP) Program

---

From: **Martha S. Lundberg, Ph.D., NHLBI BRP Coordinator [BRP@Humanitas.com]**
Sent: **February 16, 2006**
To: **Dr. [Name] [Email Address]**
Subject: **NEWS - Online Interview Site Open Until Feb. 22**
Importance: **High**

Dear Dr. [Name],

We will be keeping the online interview site open until close of day, Wednesday, February 22, to accommodate respondents with busy schedules who nonetheless have expressed interest in participating in this interview.

It is important that NHLBI BRP awardees affirm:

- If there is continuing need for funding specifically targeting multidisciplinary bioengineering research, and

- If BRP awardees are achieving the Program goals of improving human health and encouraging collaborations among quantitative and biomedical disciplines

We are very appreciative of your help and thank you for your time and cooperation.

If you have misplaced the earlier email, the location of the online interview form is:

https://www.Humanitas3.com/BRPInterview

>>> Please click on this link to access the interview, or copy and paste the location into your Internet browser window. Once you have accessed the introductory screen, please enter your user name and personal password:

UserName: **<UserName>**
Password: **<Password>**

If you have trouble accessing the online form, please call the toll-free number or email the BRP Assessment Coordinator at Humanitas, Inc:

Ms. April Smith 877-608-3290, x228 April.Smith@Humanitas.com

We look forward to your participation.

Appendix E-5

Thank You Email

Evaluation of the NHLBI Bioengineering Research Partnership (BRP) Program

---

From: **Martha S. Lundberg, Ph.D., NHLBI BRP Coordinator [BRP@Humanitas.com]**
Sent: **February 27, 2006**
To: **Dr. [Name] [Email Address]**
Subject: **Thank You**
Importance: **Normal**

Dear Dr. [Name],

Thank you for your time and cooperation to complete the online interview, and provide NHLBI feedback about the BRP Program. Your efforts will help NHLBI better meet the needs of the research community.

I look forward to our continued interactions.

APPENDIX F

CASE STUDY FORMAT

Appendix F

Case Study Format

FORMAT FOR NHLBI BRP EVALUATION CASE STUDIES

Grant Number:
Project Title:
Awardee Institution:
Award Amount:
Project Period:
Principal Investigator: [Contact information for PI]
PI New to NIH-funded Research: (Y/N?)

BRP Partner/Affiliate Institution(s):
BRP Partners: [Contact Information]
Partner Discipline(s): [Disciplines represented in BRP.]
Partners New to NIH-funded Research: (Y/N?)
Partners Previously Collaborated with PI? *(Y/N)*

Project Type: [Hypothesis or design-driven?]
Project Objectives: [List of research aims.]

Project Synopsis: [Brief narrative telling the "story" of an individual BRP. It will describe the rationale for this project and key developments to date, including scientific insights and other factors that have influenced the course of the project. The goal is to convey the character and unique aspects of this BRP.]

Challenges and Setbacks Encountered: [List of difficulties encountered in meeting stated project goals.]

Project Performance

- *List of publications*
- *List of products, processes, usages, or services developed*
- *List of academic or professional lectures, presentations, or abstracts*
- *List of milestones to commercialization achieved*
- *List of awards or other recognition*

Sources of Additional Information:
[If appropriate, information for websites or other sources will be provided. For example, an awardee that is a small business may have a website featuring BRP-supported work.]