Connecticut Biomedical Research Program: Analysis of Key Accomplishments

July 2014

A Report By

The Connecticut Academy of Science and Engineering

For

The Connecticut Department of Public Health

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This study was initiated at the request of the Connecticut Department of Public Health on March 12, 2014. The project was conducted by an Academy Study Committee with the support of CASE staff. The content of this report lies within the province of the Academy's Biomedical Research Technical Board. Martha Sherman, the Academy's Managing Editor, edited the report. The report is hereby released with the approval of the Academy Council.

Richard H. Strauss
Executive Director

MEMBERS OF THE STUDY COMMITTEE ON CONNECTICUT BIOMEDICAL RESEARCH PROGRAM: ANALYSIS OF KEY ACCOMPLISHMENTS

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Research and Knowledge Translation
Canadian Institutes of Health Research

Justin Brown, PhD
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Department of Biomedical Engineering
Penn State University

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Consultant, Nuclear Power

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Pluripotent Stem Cell and Molecular Biology Lab
PDM-NCE Primary Pharmacology Group
Pfizer, Inc.

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CURE

Stephen Hellman, MS
Executive Director, Portfolio Strategy (ret.)
Novartis OTC

Matthew Kohn, PhD
NYSTEM Scientific Officer
New York State Department of Health
Wadsworth Center

ACADEMY PROJECT STAFF

Richard H. Strauss, Executive Director
Terri Clark, Associate Director
Ann G. Bertini, Assistant Director for Programs

TABLE OF CONTENTS

EXECUTIVE SUMMARY

In 1998, 46 states entered into an agreement with the four largest tobacco companies to settle lawsuits related to Medicaid reimbursement and tobacco-related healthcare costs. As part of the settlement, the states made a commitment to use funds from the settlement to address tobacco-related health issues and to support tobacco prevention and cessation programs.

The original settlement provided Connecticut with an initial upfront settlement payment of $45 million and average annual payments in perpetuity of $141 million. Connecticut established the Connecticut Tobacco Settlement Fund to receive settlement payments.

The Connecticut Tobacco Settlement Fund provides funding for the Connecticut Biomedical Research Grant-in-Aid Program ("Connecticut Biomedical Research Program") through the Biomedical Research Trust Fund. The program is administered by the Connecticut Department of Public Health (DPH).

On behalf of DPH, the Connecticut Academy of Science and Engineering (CASE) was asked to conduct this study for the purpose of determining accomplishments achieved as a result of the research funded through the Connecticut Biomedical Research Program. This study is intended to provide information and recommendations to help decision makers understand the results and products of the program and guide its future activities. For this study, CASE assembled a committee of experts in biomedical research, the healthcare industry, and an academy member to oversee project research, develop conclusions based on the research findings and review the draft study report.

CONNECTICUT BIOMEDICAL RESEARCH PROGRAM

The Commissioner of Public Health was authorized to make grants-in-aid from the fund to eligible institutions as of 2001 with the first awards being made in 2005. A Request for Proposals (RFP) process is used to select grant recipients. Fields of research eligible for funding initially included heart disease, cancer and other tobacco-related diseases. Subsequent legislation was enacted that added Alzheimer's disease and diabetes (2010) and stroke (2013) to fields of research eligible for funding.

A total of 186 of the 270 proposals submitted for consideration during the nine RFP processes conducted from 2005 to 2014 were found to be in compliance with the terms and conditions of the RFP and were reviewed for funding. Fifty-five proposals (29.6%) from 48 principal investigators (PIs) were funded, with the total amount awarded being $16.7M. At the time of this report, 33 of the 55 grants (60%) were completed. Over this period, the average number of proposals found to be in compliance annually for review was 20.7, with a range of 11 to 39; the average number of proposals funded per RFP was 6.1, with a range of 2 to 9 proposals being funded. Additionally, the average amount awarded annually over this period was $1.9M, with a range of $850K to $3.0M. In accordance with the program's enabling legislation, the amount of funding available annually varies based on dollars available at the time of approval of the grants awarded. In practice, this amount is set upon issuance of the annual RFP. Actual amount

expended annually as compared to the amount awarded is provided for 2005 – 2009, with information for the years 2010 – 2014 not available as most of these projects were not completed at the time of this study.

The number of grants and dollars awarded for the years 2005 – 2014 is summarized as follows, according to

- the three major disease focus areas:
    - Cancer Research: 60% of the grants and dollars awarded
    - Heart Disease Research: 18% of the grants and 16% of the dollars awarded
    - Other Tobacco-Related Research: 18% of the grants and 18% of the dollars awarded
- the four major institutions:
    - UConn Health Center: 42% of the grants awarded and 43% of the dollars awarded
    - Yale University: 42% of the grants awarded and 40% of the dollars awarded
    - UConn-Storrs: 10% of the grants awarded and 9% of the dollars awarded
    - Wesleyan University: two grants awarded and 3% of the dollars awarded

REVIEW OF ACCOMPLISHMENTS

Since accomplishments and outcomes of project research generally are reported following completion of a project, it is important to note that this study's research effort focused on the grants awarded from the beginning of the program in 2005 through 2011. These grant awards represent 35 of the 55 (63.6%) total grant awards funded through the 2014 calendar year.

The research methodology included surveying the 32 PIs that received the 35 grant awards from 2005 through 2011 and reviewing interim and final progress reports for these projects. The survey response return rate was 100%. Survey objectives included measuring the accomplishments that resulted from grant-funded research projects, as follows (see Appendix D: Principal Investigator Survey and Appendix E: Principal Investigator Survey Responses):

- key findings that resulted from the research
- additional funding received by the PIs for biomedical research from other sources
- creation of new instrumentation and methodologies within biomedical fields
- patents, published research, licenses, or new research methods
- increased staffing
- creation of companies or collaborations with industry and other institutions

In summary, accomplishments of the Connecticut Biomedical Research Program include:

- For the 35 grants awarded, 30 PIs (86%) reported conducting translational research in the biomedical field, four in clinical research, and one in basic research.
- Of the 54 proposals submitted by 31 PIs to other sources for funding consideration, 25 were funded to 17 PIs, representing 46% of the proposals submitted.
- PIs reporting on 33 of the 35 grants awarded (94%) selected at least one type of outcome from a list of outcomes identified in the survey (see Figure 8), with many reporting multiple types of outcomes:
    - PIs for 29 of the 35 grants awarded (83%) indicated that they had published a peer reviewed research paper/journal article based on their research
    - PIs for 28 of the 35 grants awarded (80%) reported research findings/knowledge creation
    - PIs for 20 of the 35 (57%) reported new research methods and new theories
    - Specific contributions and outcomes noted included formation of new companies (Precision Staging, Inc.; and Mira Dx)
- Total grant-funded staff by year for grants awarded increased steadily from 2005 (13) through 2011 (52) and then declined from 2012 – 2014 as these projects were completed and since grants funded after 2011 were not included in the PI survey. PIs represented 29% of the positions reported, followed by PhD students (18%) and Postdoctoral Fellows (16%)
- PIs cited collaborations with others in their department and with other departments at their hospital or institution. Although less significant in number, it is important to note that nine PIs reported collaborations with other institutions and hospitals in Connecticut, as well as with institutions and hospitals in the United States.

RECOMMENDATIONS

Based on the findings from the research conducted, the following recommendations are offered for consideration regarding identifying and reporting on the accomplishments and performance of the Connecticut Biomedical Research Program to assure accountability of the state's public investment in biomedical research. The recommendations encompass the following: Program Review, Program Administration, and Funding.

1. **Program Review:** DPH should conduct a periodic review of the Connecticut Biomedical Research Program in consultation with institutions and principal investigators that have applied for funding to assess program operations, including: administrative operations, proposal peer review and the selection award process, and progress of grantees awarded funding for in-process and completed projects. The purpose of the periodic review process would be to
    - review RFP requirements to improve/streamline the proposal application process;

- consider ways to reduce administrative requirements for grant recipients, while maintaining accountability. Review a recent National Science Foundation-National Science Board report, "*Reducing Investigators' Administrative Workload for Federally Funded Research*"[1] to achieve this goal while retaining project accountability;
- adapt award criteria to position the program based on lessons learned, past achievements, and scientific developments;
- adjust funding levels and provide grant term flexibility for grant awards based on type of research (basic, translational and clinical research) and project requirements;
- benchmark the program with similar programs in other areas of the country to support decisions including those related to the investment and management of public funds used for scientific research;
- identify best practices for management and investment of public funds in support of biomedical research.

The requirements of the grantee progress and final reports should be modified to include annual review process metrics and data, to be determined, for grantees. This requirement should be included in the annual RFP and in grantee assistance agreements.

It is suggested that the reporting metrics and data be developed in consultation with the biomedical research leadership of the institutions/companies that receive program funding, as well as those that apply for funding. Additionally, best practices of other programs should be considered. Based on initial lessons learned from this review, suggestions for future metrics for reporting on accomplishments and outcomes include the following:

- Staffing and Job Creation: Suggested data to be reported include: project staffing and jobs created reported on a full-time-equivalent basis; wages paid, which would be useful for conducting an economic impact analysis of the program in the future; and new staff relocating to Connecticut as a result of project funding.
- Accomplishments and Outcomes: Many research accomplishments and outcomes occur after the completion of a project and after a final project report is submitted by the PI. Consider including short-term, mid-term and long-term metrics, with some short-and mid-term metrics being proxies for the longer-term impacts that are desired or anticipated. Therefore, consideration should be given to requiring not only progress and final reports, but also annual reporting by PIs for grants that have been completed for a period of time as determined, with this requirement being a condition of grantee assistance agreements. Additionally, based on a review of the PI Survey conducted for this study, the following are suggestions for future surveys:
  - Type of Research Conducted: revise question to gain information on trends in types of research being conducted and planned for the future.
  - Funding from Other Sources: revise the question regarding the amount of funding received from other sources to request the specific amount for grants awarded.

1 National Science Board report: *Reducing Investigators' Administrative Workload for Federally Funded Research (March 10, 2014);* http://www.nsf.gov/pubs/2014/nsb1418/nsb1418.pdf

- Types of Outcomes Reported by PIs: restructure to identify outcomes by type of research being conducted (basic, translational, clinical), including non-commercial outcomes; and for items cited:
  - ◊ Formation of New Companies, Licenses and Patents Issued: request additional details for these outcomes to further show their significance
  - ◊ New Practices: expand question to identify whether the new practices are in use and if they are cost effective
  - ◊ Other: request PI to describe outcomes reported as "Other"
- Research Funding Opportunities: restructure and clarify question to gain more specific information regarding how this grant has impacted the PI's research following completion of their Connecticut Biomedical Research Program grant
- Collaborations: revise question to gain more detailed information on the type of collaboration.

2. **Program Administration:** DPH staff designated to manage and oversee the Connecticut Biomedical Research Program should continually seek to improve the administration of the program and bring consistency to grant funding procedures and annual reporting processes.

   Staff would

   - manage program operations, including an annual review of RFP requirements and consideration of ways to reduce the administrative burden on grant recipients, as noted under Program Review;
   - conduct an annual RFP bidders conference to exchange information between DPH and potential proposers;
   - identify key high-level metrics for the periodic review of program accomplishments and administrative performance in consultation with the program's leadership, including the Peer Review Committee;
   - manage the periodic review process, including reporting to state agencies, the Connecticut General Assembly, research institutions, and others as appropriate;
   - establish relationships between states and/or institutions based on a mutual need for the sharing and reporting of common metrics in collaboration with biomedical researchers and institutional leaders; and
   - research best practices regarding scientific research grant funding, economic development, and institutional practices and processes in collaboration with biomedical researchers and institutional leaders.

3. **Funding:** Based on current operational requirements as set forth in the program's enabling legislation, as amended, the amount of funding available each year can vary significantly. Consideration should be given to stabilizing the annual funding allocation for the program as an indication of the state's commitment to fund tobacco-related research from the Tobacco Settlement Fund.

CONCLUDING REMARKS

Based on this study's findings and recommendations, DPH should consider implementing a process for periodic review of the Connecticut Biomedical Research Grant Program to provide accountability for the state's public investment in biomedical research. Additionally, the recent National Science Board report, "*Reducing Investigators' Administrative Workload for Federally Funded Research,*" will be useful in reducing the administrative requirements for grant recipients while assuring overall program accountability.

1.0 INTRODUCTION

In 1998, 46 states entered into an agreement with the four largest tobacco companies to settle lawsuits related to Medicaid reimbursement and tobacco-related healthcare costs. The settlement required tobacco companies to make annual payments to the states in perpetuity for the purpose of recovering tobacco-related healthcare costs. Total payment to the states over the first 25 years of the settlement is estimated at $246 billion[2]. As part of the settlement the states made a commitment to use funds from the settlement for the purpose of addressing tobacco-related health issues and to support tobacco prevention and cessation programs.

The original settlement provided Connecticut with an initial upfront settlement payment of $45 million and average annual payments in perpetuity of $141 million. Connecticut established the Connecticut Tobacco Settlement Fund to receive settlement payments. The total value of payments to Connecticut over the first 25 years of the settlement is projected to be $5.7 billion. In 2013, Connecticut and 21 other states reached a partial settlement agreement with the tobacco companies over a dispute on payments made to the states[3].

The Connecticut Tobacco Settlement Fund provides funding for the Connecticut Biomedical Research Grant-in-Aid Program ("Connecticut Biomedical Research Program") through the Biomedical Research Trust Fund. For the period of 2005 – 2014 a total of $16.7M was awarded to grant recipients. Key aspects of the public acts that were enacted regarding the establishment of, and changes to, the research program are as follows, and as further described in Appendix A:

- The Biomedical Research Trust Fund was established in 2000.
- The Commissioner of Public Health was authorized to make grants-in-aid from the fund to eligible institutions as of 2001, with the first awards being made in 2005.
- Eligible institutions are defined as non-profit, tax-exempt academic institutions of higher education or hospitals that conduct biomedical research. Legislation was enacted in 2013 that required an eligible institution to have its principal place of business located in Connecticut.
- The total amount of grants-in-aid in any fiscal year cannot exceed 50% of the total amount held in the Biomedical Research Trust Fund as of the date such grants-in-aid are approved.
- Fields of research eligible for funding initially included heart disease, cancer and other tobacco-related diseases. Subsequent legislation was enacted that added Alzheimer's disease and diabetes (2010), and stroke (2013) to fields of research eligible for funding. Appendix B provides a summary of areas of research that were included in the Request for Proposals (RFP) issued by the Connecticut Department of Public Health (DPH) from 2005 – 2014.

2 Broken Promises to Our Children: The 1998 State Tobacco Settlement 15 Years Later; Campaign for Tobacco Free Kids, 12/9/2013

3 Attorney General: Connecticut Joins 21 States in Partial Settlement with Tobacco Companies; News Release: George Jepsen, Office of the Attorney General, 05 /29//13

DPH administers the program and has the following responsibilities:

- Conducts an annual RFP process that includes developing and issuing the RFP and reviewing grant applications for compliance with terms and conditions of the RFP.
- Serves as the fiduciary agent for the program, a role that includes preparing and executing assistance agreements, assuring grantee compliance with the terms and conditions of the agreements, considering amendments to agreements, and processing payments to grantees.
- Works with the Office of Policy and Management to determine the amount of funding available for the program annually.
- Tracks progress on all grants, including receiving and reviewing progress and final reports as well as financial reports in accordance with the terms and conditions of each grant's assistance agreement.
- Additionally, the proposal review process was conducted by DPH staff from 2005 – 2008 and by the Connecticut Academy of Science and Engineering (CASE) from 2009 – 2014 for all proposals as determined by DPH to be in compliance with the terms and conditions of the annual RFP. CASE is responsible for selecting the members of the peer review committee. Currently, the peer review process involves having two reviewers score each proposal using the National Institutes of Health (NIH) scoring system, a proposal score reconciliation process for proposals that receive a score with greater than a one point difference between reviewer scores, and a study section meeting where the peer review committee conducts a final review of the proposals and ranks the proposals by technical merit and the evaluation criteria specified in each RFP for funding action by DPH.

On behalf of DPH, CASE was asked to conduct this study for the purpose of determining accomplishments achieved as a result of the research funded through Connecticut's Biomedical Research Program. This study is intended to provide information and recommendations to help decision makers understand the results and products of the program and guide its future activities. For this study, CASE assembled a committee of experts in biomedical research, the healthcare industry, and an academy member, to oversee project research, develop conclusions based on the research findings and review the draft study report.

2.0 THE CONNECTICUT BIOMEDICAL RESEARCH PROGRAM

For each of the nine RFP processes conducted from 2005 – 2014, Table 1 shows

- dollar range for grant awards;
- grant contract term;
- available program funding;
- amount of grant awards;
- number of grants awarded and completed;
- number of proposals reviewed for funding.

A total of 186 of 270 proposals that were submitted for consideration were found to be in compliance with the terms and conditions of the RFP and were reviewed for funding. Fifty-five proposals (29.6%) from 48 principal investigators (PIs) were funded, with the total amount awarded being $16.7M. At the time of this report, 33 of the 55 grants (60%) were completed. Over this period, the average number of proposals found to be in compliance annually for review was 20.7 proposals, with a range of 11 to 39 proposals; the average number of proposals funded per RFP was 6.1, with a range of 2 to 9 proposals being funded. Additionally, the average amount awarded annually over this period was $1.9M, with a range of $850K to $3.0M. As previously noted, the amount of funding available annually varies based on dollars available at the time of approval of the grants awarded. In practice, this amount is set upon issuance of the annual RFP. Actual amount expended annually as compared to the amount awarded is provided for 2005 – 2009. Information for the years 2010 – 2014 is not available as most of these projects were not completed at the time of this study.

TABLE 1: CONNECTICUT BIOMEDICAL RESEARCH PROGRAM: FUNDING OVERVIEW

Year	RFP Requirements		Amount Available	Amount Awarded	Actual Expended	# of Grants Awarded/ Completed	# of Proposals Reviewed for Funding
	Grant $$$ Range	Grant Contract Term					
2005	$250K - $1M	1 Year	$ 2,000,000	$ 850,000	$ 675,424	2/2	20
2006	$250K - $1M	1 Year	$ 1,650,000	$ 1,359,095	$1,353,759	5/5	11
2007	$250K - $1M	1 Year	$ 1,637,500	$ 1,718,860	$1,591,215	6/6	16
2008	$250K - $1M	1 Year	$ 2,000,000	$ 1,998,868	$1,962,452	7/7	39
2009	$250K - $1M	1 Year	$ 2,178,864	$ 2,228,324	$1,856,238(1)	7/6	29
2010	$250K - $1M	2 Years	$ 2,371,900	$ 2,327,305	*	8/7	17
2012	$250K - $500K	2 Years	$ 968,000	$ 943,003	*	3/0	14
2013	$300K - $1M	2 Years	$ 3,040,990	$ 3,003,364	*	9/0	23
2014	$300K - $1M	2 Years	$ 2,696,665	$ 2,301,391(2)	*	8/0	17
Totals			**$18,543,919**	**$16,730,210**		**55/33**	**186**
Annual Average			**$ 2,060,435**	**$ 1,858,912**		**6.1**	**20.7**

(1) 2010: Grant #2010-0084 was cancelled prior to completion. Grant award was $421,128; amount expended was $82,560.

(2) 2014: One grant that was awarded for $297,446 was not accepted by the proposer due to receipt of funding from NIH that overlapped with the proposed project. Amount shown does not include this award.

* Actual expenditure on grants awarded in 2010 – 2014 was not available as most of these grants were not completed as of the date of publication of this report.

Appendix C: Grants Awarded 2005 – 2014 provides a summary of the grants awarded for the nine RFP processes. This information includes the following:

- RFP Year
- DPH Contract Number that includes a web link to the final reports for those projects that have been completed
- Award Amount
- Disease Field
- Project Title
- Institution of the Principal Investigator
- Principal Investigator of Record

Table 2 provides an overview by disease focus, based on data provided by DPH, of the number of proposals that were reviewed and awarded for each of the nine RFP processes that were conducted from 2005 – 2014. The charts that follow show a graphical representation of the data presented in Table 2 that identify three major disease areas for proposals reviewed and grants awarded:

- Cancer Research represents 46% of proposals reviewed and 60% of grants awarded.
- Heart Disease Research represents 19% of proposals reviewed and 18% of grants awarded.
- Other Tobacco-Related Research represents 24% of proposals reviewed and 18% of grants awarded.

TABLE 2: CONNECTICUT BIOMEDICAL RESEARCH PROGRAM: PROPOSALS REVIEWED/AWARDED BY DISEASE FOCUS (2005 – 2014)

Click for full-size view of Table 2.

Year	Proposals Reviewed	Grants Awarded	Heart Disease		Cancer		Other Tobacco Related		Diabetes (Began in 2012)		Alzheimer's (Began in 2012)		Stroke (Began in 2014)		Multiple Classifications	
			Proposals Reviewed	Grants Awarded	Proposals Reviewed	Grants Awarded	Proposals Reviewed	Grants Awarded	Proposals Reviewed	Grants Awarded	Proposals Reviewed	Grants Awarded	Proposals Reviewed	Grants Awarded	Proposals Reviewed	Grants Awarded
2005	20	2	3	0	5	1	12	1								
2006	11	5	1	0	5	3	5	2								
2007	16	6	4	0	7	5	3	1							1	0
2008	39	7	3	1	27	5	7	1							2	0
2009	29	7	7	3	15	4	7	0								
2010	17	8	4	3	10	4	3	1								
2012	14	3	4	0	2	1	2	1	4	1	1	0			1	0
2013	23	9	7	2	7	5	5	2	3	0	1	0				
2014	17	8	2	1	8	5	1	1	0	0	0	0	3	0	3	1
Totals	**186**	**55**	**35**	**10**	**86**	**33**	**45**	**10**	**7**	**1**	**2**	**0**	**3**	**0**	**7**	**1**

* 2007: One proposal (not funded) had a double classification: Heart Disease/ Other Tobacco Related
* 2008: Two proposals (not funded) had a double classification: Heart Disease/Cancer and Cancer/Other Tobacco Related
* 2012: One proposal (not funded) had a double classification: Cancer/Diabetes
* 2014: Three proposals had multiple classifications. One proposal (funded) was Alzheimer's/Diabetes. Two proposals (not funded) had multiple classifications: Diabetes/Stroke/Alzheimer's; Diabetes/Heart Disease/Stroke/Cancer.

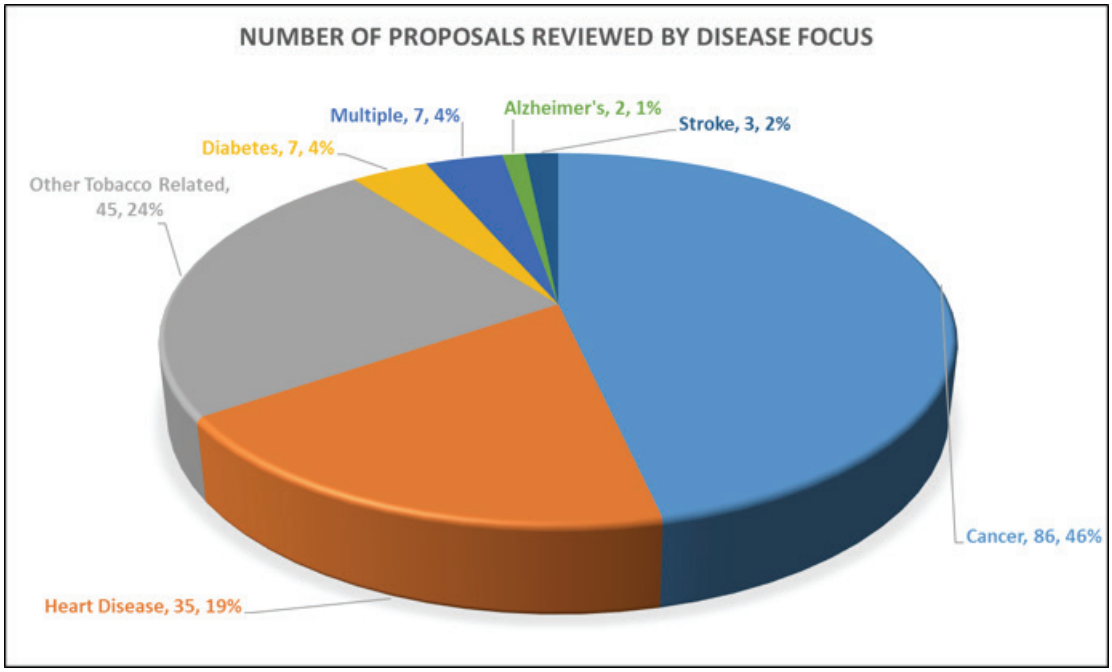


FIGURE 1: NUMBER OF PROPOSALS REVIEWED BY DISEASE FOCUS, 2005 - 2014

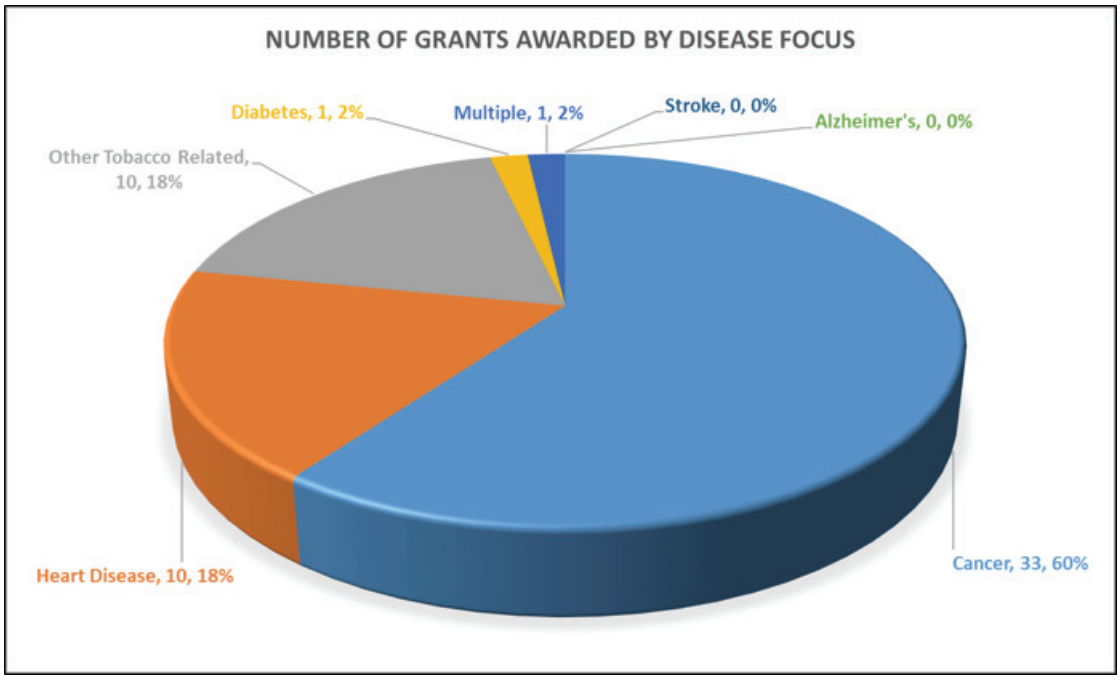


FIGURE 2: NUMBER OF GRANTS AWARDED BY DISEASE FOCUS, 2005 - 2014

Table 3 provides a summary of dollars awarded by disease focus for grants awarded, annually and cumulatively, for the period 2005 - 2014. The chart that follows shows a graphical representation of the data presented in Table 3 that includes dollars awarded for the three major disease focus areas:

- Cancer Research represents 60% of the dollars awarded for funded grants.
- Heart Disease Research represents 16% of the dollars awarded for funded grants.
- Other Tobacco-Related Research represents 21% of the dollars awarded for funded grants. Examples of research funded in this area include projects related to pregnancy, lung disease, infant/child health, the brain, Chronic Obstructive Pulmonary Disease, and the pancreas.

For titles of all projects funded, see Appendix C: Grants Awarded: 2005-2014.

TABLE 3: CONNECTICUT BIOMEDICAL RESEARCH PROGRAM: DOLLARS AWARDED BY DISEASE FOCUS (2005 – 2014)

Click for full-size view of Table 3

Year	Grants Awarded	Dollars Awarded	Heart Disease		Cancer		Other Tobacco Related		Diabetes		Alzheimer's		Stroke		Multiple Classifications	
			Grants Awarded	Dollars Awarded	Grants Awarded	Dollars Awarded	Grants Awarded	Dollars Awarded	Grants Awarded	Dollars Awarded	Grants Awarded	Dollars Awarded	Grants Awarded	Dollars Awarded	Grants Awarded	Dollars Awarded
2005	2	$ 850,000	0	$ -	1	$ 350,000	1	$ 500,000								
2006	5	$ 1,359,095	0	$ -	3	$ 709,479	2	$ 649,616								
2007	6	$ 1,718,860	0	$ -	4	$ 1,180,255	2	$ 538,605								
2008	7	$ 1,998,868	1	$ 278,472	5	$ 1,480,458	1	$ 239,938								
2009	7	$ 2,228,324	3	$ 763,092	4	$ 1,465,232	0	$ -								
***2010**	8	$ 2,327,305	3	$ 883,130	4	$ 1,197,885	1	$ 246,290								
2012	3	$ 943,003	0	$ -	1	$ 356,250	1	$ 417,076	1	$ 169,677	0	$ -				
2013	9	$ 3,003,364	2	$ 641,572	5	$ 1,728,398	2	$ 633,394	0	$ -	0	$ -				
2014	8	$ 2,301,391	1	$ 207,440	5	$ 1,520,806	1	$ 268,800	0	$ -	0	$ -	0	$ -	1	$ 304,345
TOTALS	**55**	**$ 16,730,210**	**10**	**$ 2,773,706**	**32**	**$ 9,988,763**	**11**	**$ 3,493,719**	**1**	**$ 169,677**	**0**	**$ -**	**0**	**$ -**	**1**	**$ 304,345**

*2010: One of the cancer grants was canceled due to an overlapping federal grant ($338,568 repaid; actual expenditure $82,560). This table shows the 2010 total with the original award.

FIGURE 3: DOLLARS AWARDED BY DISEASE FOCUS

Table 4 provides a summary of the number of grants and dollars awarded by institution, annually and cumulatively, for the period 2005 - 2014. The charts that follow show a graphical presentation of the data presented in Table 4 identifying the number of grants and dollars awarded to each institution that has received grant funding:

- UConn Health Center: 42% of the grants awarded and 43% of the dollars awarded for funded grants
- Yale University: 42% of the grants awarded and 40% of the dollars awarded for funded grants
- UConn- Storrs: 10% of the grants awarded and 9% of the dollars awarded for funded grants
- Wesleyan University: two grants awarded and 3% of the dollars awarded for funded grants
- Hartford Hospital: one grant awarded and 1.6% of the dollars awarded for funded grants
- Western Connecticut Health Network and Danbury Hospital: one grant awarded and 1.6% of the dollars awarded for funded grants

TABLE 4: CONNECTICUT BIOMEDICAL RESEARCH PROGRAM: NUMBER OF GRANTS AND DOLLARS AWARDED BY INSTITUTION (2005 – 2014)

Click for full-size view of Table 4

Year	Grants Awarded	Dollars Awarded	Hartford Hospital		UConn (Storrs)		UConn Health Center		Wesleyan		Western CT Health Network & Danbury Hospital		Yale	
			Grants Awarded	Dollars Awarded	Grants Awarded	Dollars Awarded	Grants Awarded	Dollars Awarded	Grants Awarded	Dollars Awarded	Grants Awarded	Dollars Awarded	Grants Awarded	Dollars Awarded
2005	2	$ 850,000					1	$ 500,000					1	$ 350,000
2006	5	$ 1,359,095					1	$ 276,629					4	$ 1,082,466
2007	6	$ 1,718,860			1	$ 315,563	4	$ 1,226,074					1	$ 177,223
2008	7	$ 1,998,868					4	$ 1,198,048					3	$ 800,820
2009	7	$ 2,228,324	1	$ 267,186	1	$ 290,304	5	$ 1,670,834						
2010	8	$ 2,327,305			2	$ 612,815	4	$ 1,215,352	1	$ 165,083			1	$ 334,055
2012	3	$ 943,003			1	$ 417,076	1	$ 356,250					1	$ 169,677
2013	9	$ 3,003,364					2	$ 641,572					7	$ 2,361,792
2014	8	$ 2,301,391					1	$ 207,440	1	$ 324,127	1	$ 272,044	5	$ 1,497,780
TOTALS	**55**	**$ 16,730,210**	**1**	**$ 267,186**	**5**	**$ 1,635,758**	**23**	**$ 7,292,199**	**2**	**$ 489,210**	**1**	**$ 272,044**	**23**	**$ 6,773,813**

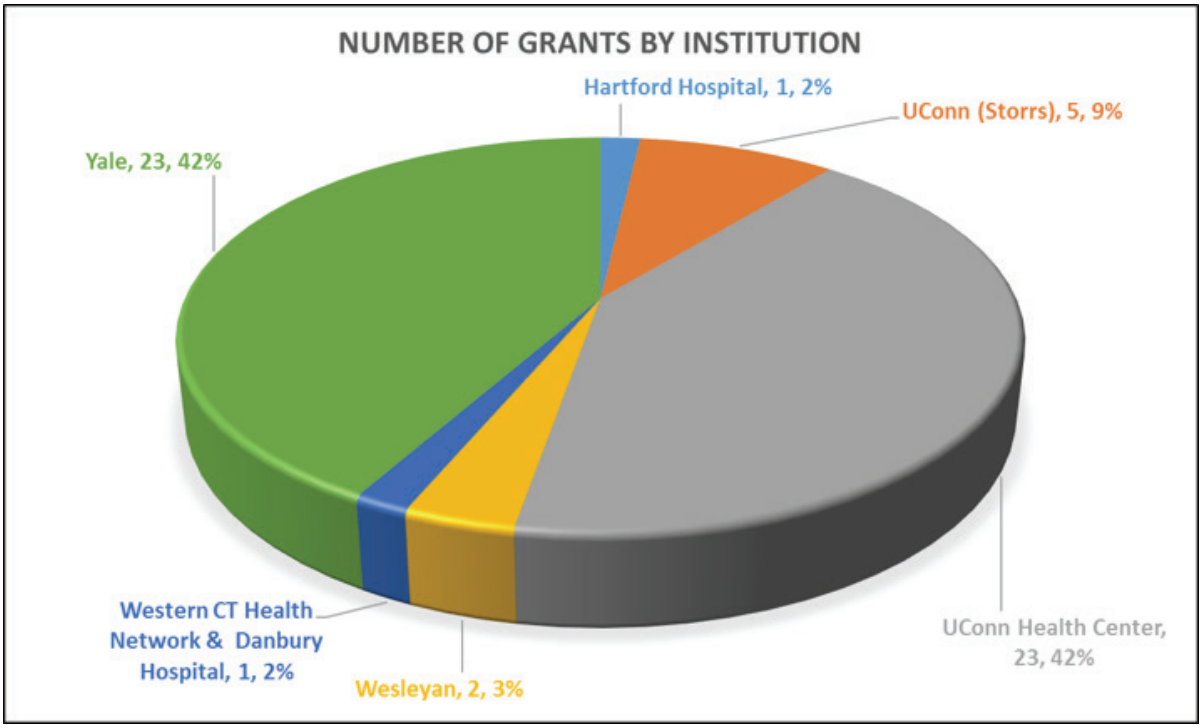


FIGURE 4: NUMBER OF GRANTS AWARDED BY INSTITUTION

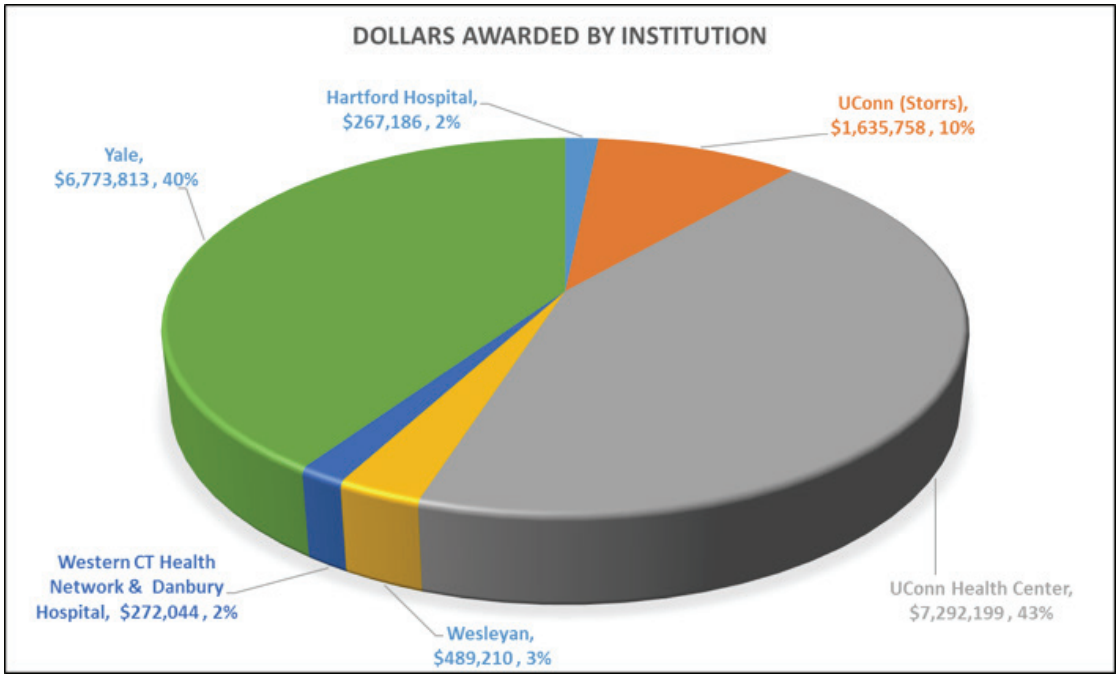


FIGURE 5: DOLLARS AWARDED BY INSTITUTION

3.0 FINDINGS

This study, conducted by CASE on behalf of DPH, is for the purpose of determining accomplishments achieved as a result of the research funded through the Connecticut Biomedical Research Program. Additionally, since accomplishments and outcomes of project research generally are reported following completion of a project, it is important to note that this study's research effort focused on the grants awarded from the beginning of the program in 2005 through 2011. These grant awards represent 35 (63.6%) of the 55 total grant awards funded through the 2014 calendar year.

The goals of the accomplishment review process are to

- identify the accomplishments of the Connecticut Biomedical Research Program, and
- report findings and recommendations to DPH.

The research methodology included surveying the 32 PIs that received the 35 grant awards from 2005 through 2011 and reviewing interim and final progress reports for these projects.

3.1 ANALYSIS OF PRINCIPAL INVESTIGATOR (PI) SURVEY

The PIs of the 35 grants awarded from 2005 through 2011 were administered an electronic survey, with a survey response return rate of 100%. Four PIs were awarded two grants during this period, with each completing a separate survey for each of their grants. Survey objectives included measuring the accomplishments that resulted from grant-funded research projects, as follows (See Appendix D: Principal Investigator Survey and Appendix E: Principal Investigator Survey Responses):

- key findings that resulted from the research
- additional funding received by the PIs for biomedical research from other sources
- vreation of new instrumentation and methodologies within biomedical fields;
- patents, published research, licenses, or new research methods;
- increased staffing; and
- creation of companies or collaborations with industry and other institutions

To this aim, the PI survey captured both the objectives and outcomes as indicated above.

3.1.1 Research Type Conducted

The PIs were asked to select the type of research they were doing by choosing from either Translational or Clinical. The survey did not include an option to choose Basic due to the disease-related focus of the Connecticut Biomedical Research Program. However, one PI commented that her research should be considered Basic.

Definitions for all three research types are as follows:

- **BASIC**: Research directed at understanding the fundamental mechanisms of biologic processes without regard for direct application to the understanding or treatment of human diseases.
- **TRANSLATIONAL** (*definition from Institute of Translational Health Sciences*[4]): Translational research includes:
    - o the process of making discoveries in the research laboratory or in preclinical studies that will have an impact on human health and may lead to the development of studies in humans,
    - o the process of applying discoveries generated during research in the laboratory, and in preclinical studies, to the development of trials and studies in humans, and
    - o research aimed at enhancing the adoption of best practices in the community. Cost-effectiveness of prevention and treatment strategies is also an important part of translational science.
- **CLINICAL** (*definition from NIH – Office of Extramural Research*[5]): Research with human subjects that is:
    1. Patient oriented. Research conducted with human subjects (or on material of human origin such as tissues, specimens, and cognitive phenomena) for which an investigator (or colleague) directly interacts with human subjects. Excluded from this definition are in vitro studies that utilize human tissues that cannot be linked to a living individual. It includes: mechanisms of human disease; therapeutic interventions; clinical trials; and development of new technologies.
    2. Epidemiological and behavioral studies.
    3. Outcomes research and health services research.

For the 35 grants awarded, thirty PIs (86%) reported conducting translational research in the biomedical field, four in clinical research, and one in basic research (See Question 6 in Appendix E).

3.1.2 Impact on Funding Opportunities

Figure 6 provides an overview of PI responses to questions regarding the state of a PI's research and requests for additional funding, if any, as related to the research undertaken through the Connecticut Biomedical Research Program funded projects.

4 https://www.iths.org/funding/definitions
5 http://grants.nih.gov/grants/policy/hs/glossary.htm?print=yes

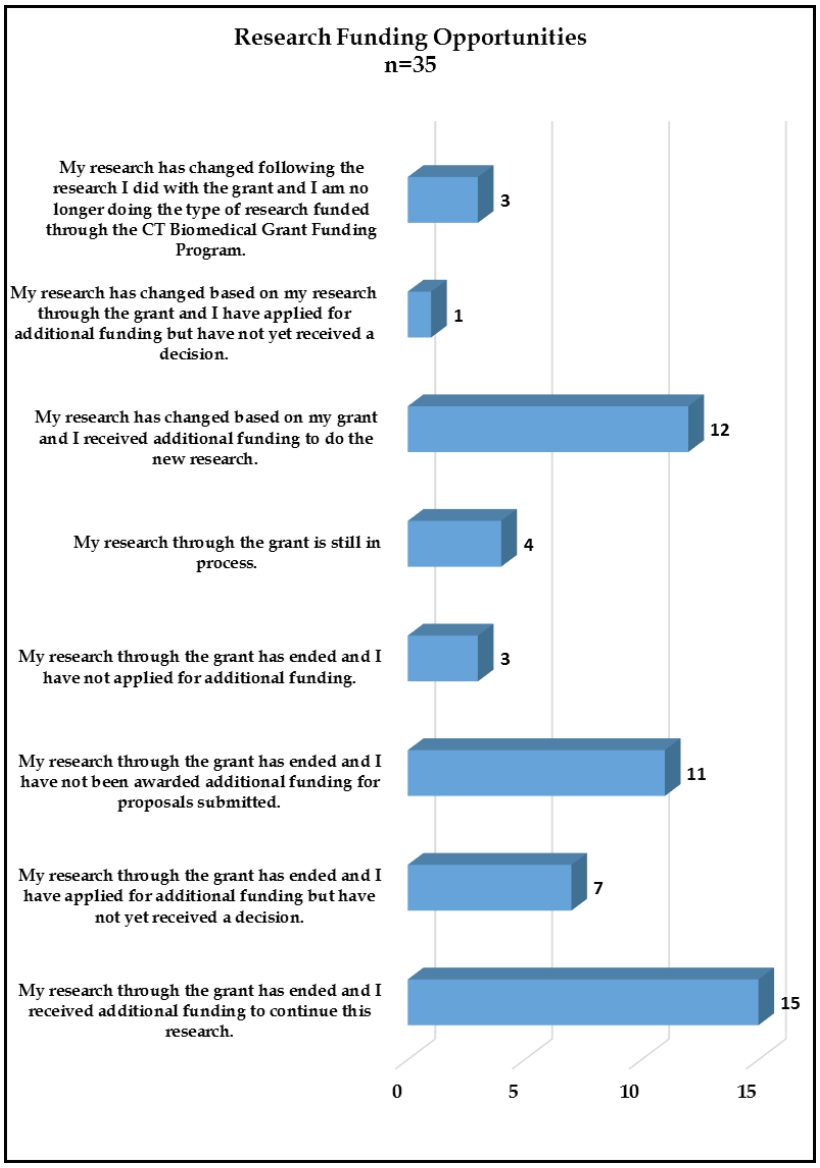


FIGURE 6: PRINCIPAL INVESTIGATORS: BIOMEDICAL RESEARCH FUNDING STATEMENTS

A number of important accomplishments for the Connecticut Biomedical Research Program were reported, including the following:

- Leveraging funding received from the Connecticut Biomedical Research Program to pursue/obtain additional funding for research from other sources.
- Contributions and research outcomes in the form of published papers, new methodologies, etc., and direct achievements including patents, new technology, etc.
- Increase in jobs in the state of Connecticut to support biomedical research.
- Development of collaborations.

3.1.3 Leveraging Funding

Many of the PIs reported that as a result of the funding they received, they were able to pursue and/or obtain additional funding to either continue their research or expand their research. One PI reported an active National Cancer Institute research grant based on the Connecticut Biomedical Research Program grant they received, and another PI reported that Connecticut's funding allowed for obtaining preliminary data for applications to NIH and other federal sources.

PIs were asked about other sources of funding that they have applied to for support of their research. Figure 7 provides a summary of additional funding sources applied to by the PIs.

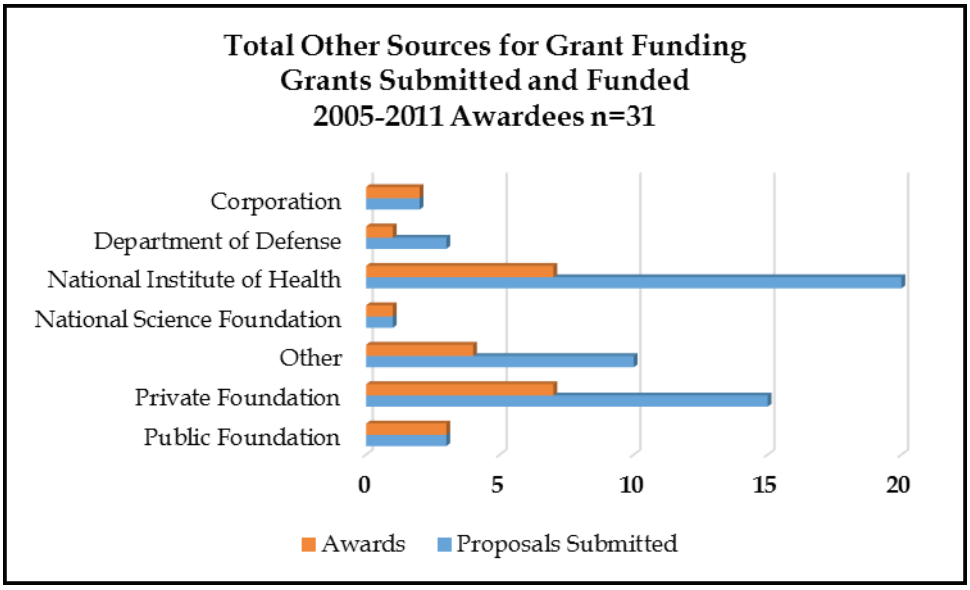


FIGURE 7: OTHER SOURCES APPLIED TO BY PIS FOR GRANT FUNDING
(GRANTS SUBMITTED AND FUNDED 2005 – 2011 AWARDEES)

- Of the 54 proposals submitted by 31 PIs to other sources for funding consideration, 25 were funded to 17 PIs, representing 46% of the proposals submitted. Grant award sources include NIH (7), private foundations (7), public foundations (3), corporations (2), Department of Defense (1), National Science Foundation (1), and other sources (4).
- Nine awards were funded and completed. Grant funding sources included NIH (2), corporations (2), and private foundations (5).
- 16 grants are currently being funded with research in-process. Grant award sources include NIH (5), private foundations (2), public foundations (3), Department of Defense (1), National Science Foundation (1), and other sources (4).
- Seven proposals are awaiting a funding decision, as of April 2014. Possible grant sources include NIH (3), private foundations (1), and other sources (3).

Table 5 shows the range for the level of funding either awarded or requested from other sources.

TABLE 5: RANGE OF FUNDING REQUESTS FROM OTHER SOURCES

Proposal/Award Ranges	Funded Projects: Completed	Funded Projects: Research In-Process	Proposals Awaiting Funding Decision	Proposals Denied Funding	Proposal/ Award Ranges: Subtotal
0–$200,000	4	5	2	5	**16**
$200,001–$400,000	2	0	3	2	**7**
$400,001–$800,000	1	6	0	4	**11**
$800,001–$1,000,000	1	0	1	3	**5**
$1,000,001–$1,500,000	1	2	0	3	**6**
$1,500,001–$2,000,000	0	2	1	2	**5**
$2,000,001–$3,000,000	0	0	0	2	**2**
$3,000,001-$4,000,000	0	1	0	0	**1**
$5,000,001 or more	0	0	0	1	**1**
TOTAL	**9**	**16**	**7**	**22**	**54**

3.1.4 Contributions/Research Outcomes

PIs were asked to report the type of research outcomes they had from a list provided (Figure 8), followed by a request to identify specific scientific contributions and outcomes of their research. PIs reporting on 33 of the 35 grants awarded (94%) selected at least one type of outcome from the list, with many reporting multiple types of outcomes:

- PIs reporting on 29 of the 35 grants awarded (83%) indicated that they had published at least one peer reviewed research paper/journal article based on their research.
- PIs reporting on 20 of the 35 grants awarded (57%) reported new research methods and new theories.
- PIs reporting on 3 of the 35 grants awarded (9%) reported having had a patent issued.

Specific contributions and outcomes noted included formation of new companies (Precision Staging, Inc., and Mira Dx), articles published in peer-reviewed journals, and others. It is noted that some grant recipients reported multiple outcomes for a single type of outcome (i.e., multiple peer-reviewed research papers and journal articles).

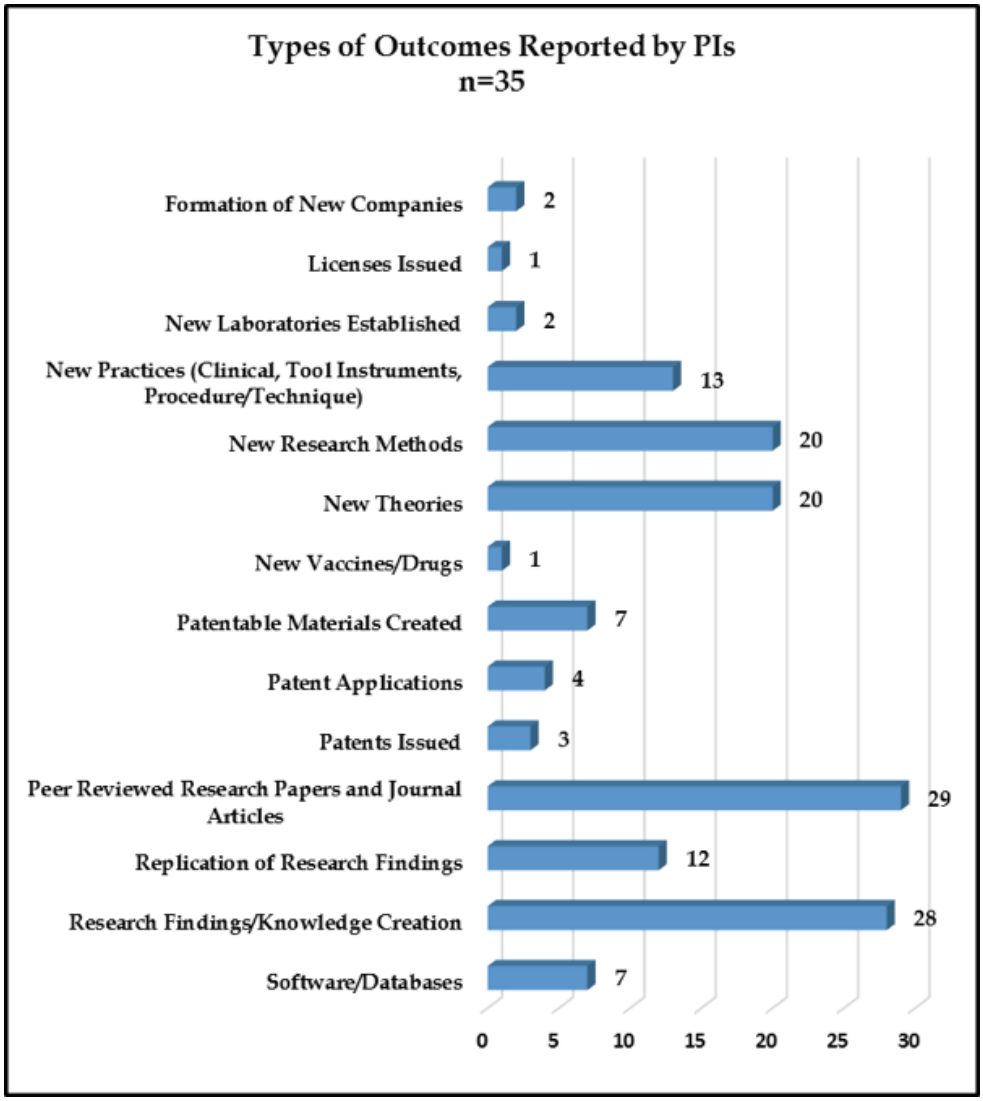


FIGURE 8: TYPES OF RESEARCH OUTCOMES

Selected Key Findings reported by PIs are as follows. A full list of the Key Findings is reported in Appendix E (Principal Investigator Survey Responses; Question 15).

- Smoking cessation is effective in restoring vascular health, but the benefits are greater when smoking cessation is accompanied by dietary γ-T supplementation, which better reduces pro-inflammatory responses that are known to impair vascular homeostasis.
- The cigarette additive menthol may reduce the acute sensory irritancy of tobacco smoke, allowing more rapid and deeper inhalation. This effect may reduce the aversive threshold to smoking in beginning smokers, accelerate establishment of nicotine addiction, and promote a more rapid onset of smoking-induced airway and cardiovascular disease.
- Results provide important preclinical data, which can guide future studies on the early changes associated with smoking-related cancers. By understanding the molecular

mechanism by which these smoking-associated cancers arise, we will be able to improve early-stage cancer detection and prevention for the citizens of Connecticut.

- Our work did lead to a novel and exciting finding that scaffolds insulate kinases from inhibition by certain drugs. This finding will impact our use of these drugs for the treatment of heart disease because it will significantly reduce the efficacy of the drugs. By changing our current theory and practices of drug use, this finding will significantly impact the citizens of Connecticut.
- Development of computational techniques that can predict device deployment pre-operatively. This capability allows cardiologists at a hospital to virtually visualize the device deployment process in a computer. Thus, clinical adverse events can be avoided pre-operatively for high-risk patients. Currently, we have applied these techniques at a Connecticut local hospital. We have prospectively predicted several clinical cases with success. The project is ongoing and is supported by NIH. We are leading this effort in using computational methods to predict, and thus avoid, clinical adverse events in this procedure.
- We greatly advanced the technology of laser capture micro dissection (LCM) coupled to downstream global transcriptional profiling. This has led to the ability to evaluate in situ gene expression of the full transcriptome in small of groups of cells -- or even at the singular cell level. This is a significant leap for the ability to conduct "personalized medicine," as it can potentially enable "cancer profiles" to be evaluated in small biopsy samples, and to more accurately determine the therapeutic efficacy of drugs at the molecular level. This has garnered the attention of pharmaceutical and biotech companies in the state, and is expected to lead to significant funding streams.
- Demonstration that a new protein that we discovered can inhibit tumor growth and metastasis in two tumor animal models. We also demonstrated that increased immune functions are involved in the effect of the protein. Therefore, the protein has the potential to be used in the treatment of cancer patients in the future.
- This award provided resources for us to test the dye in animal tumor models and to develop second- and third-generation hypoxia dyes with superior in vivo tumor targeting capability.
- We found that small molecule Wnt inhibitors suppressed tumor formation in a mouse colorectal tumor model. The significance and potential benefits of our work are clearly evident as colorectal cancer is one of the major killers in the world.
- We completed the most comprehensive screening analyses of colons on 185 Connecticut residents of the State of Connecticut. These data have been invaluable in understanding the very earliest changes that occur within the human colon in subjects at varying risk of cancer.
- Inasmuch as Connecticut has one of the highest rates of breast cancer [in the United States], our research provides great benefit to the citizens and government of the State of Connecticut by uncovering a novel therapeutic strategy for treating this disease.

3.1.5 Biomedical Research Related Staffing and Job Creation

PIs were asked to report on their project staffing that occurred as a result of Connecticut Biomedical Research Program funding. Figure 9 shows total grant-funded staff by year for the 2005–2011 awards, Figure 10 depicts the percent of type of staff positions based on total staff reported for the same award period, and Figure 11 provides the average percent Full Time Equivalent (FTE) positions by type of position reported by the PIs. PI data are calculated from an analysis of the projects in-process each year for the period of 2005–2014. Figure 9 indicates that jobs/staffing steadily increased from 2005 through 2011 and then declined from 2012–2014 as these projects were completed and since grants funded after 2011 were not included in the PI survey.

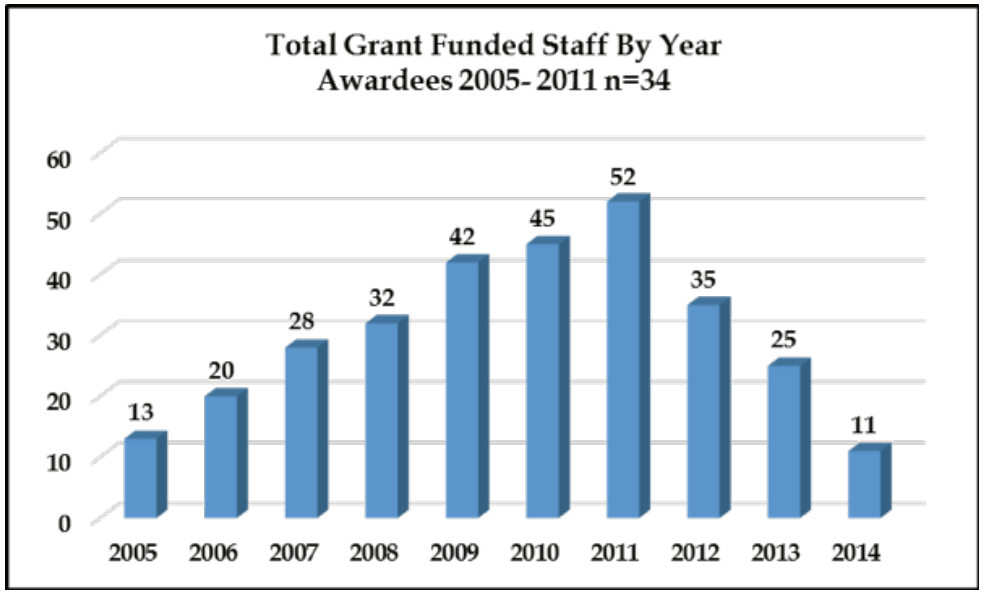


FIGURE 9: TOTAL GRANT-FUNDED STAFF (AWARDEES 2005–2011)

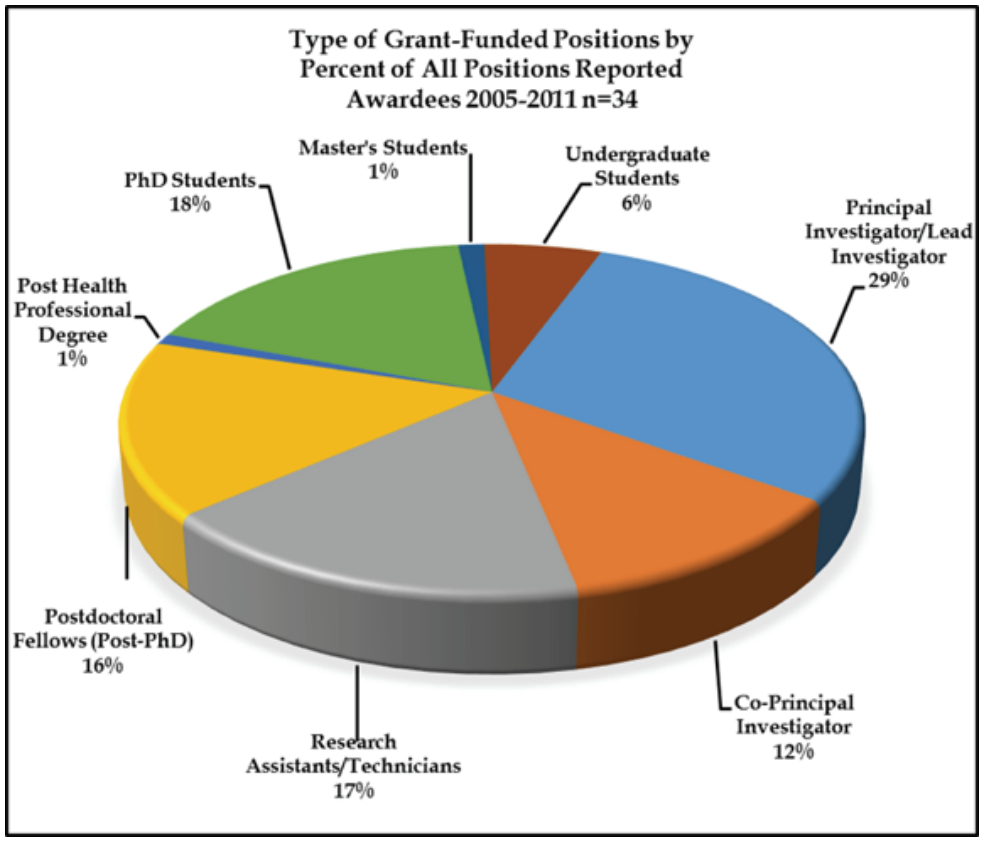


FIGURE 10: TYPE OF POSITIONS BY PERCENT OF ALL POSITIONS REPORTED (AWARDEES 2005–2011)

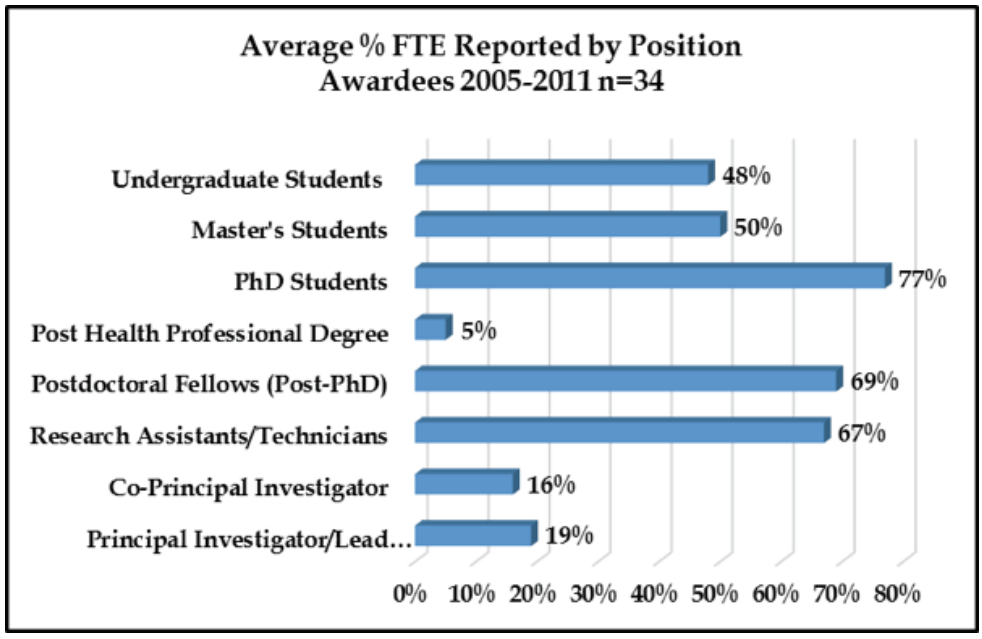


FIGURE 11: AVERAGE % FTE REPORTED BY TYPE OF POSITION (AWARDEES 2005–2011)

3.1.6 Collaborations

Collaborations made possible by Connecticut Biomedical Research Program funding were noted by the PIs, with 22 reporting collaborations with others in their department and 23 with other departments at their hospital or institution. Although less significant in number, it is important to note that nine PIs reported collaborations with other institutions and hospitals in Connecticut and 10 with institutions and hospitals in the United States. When asked about the importance of collaboration to the success of their research, the average weighted response by the PIs was 4.5 on a scale of 1 (Not Important At All) to 5 (Very Important). All PIs (n=35) answered the question, and none selected "Not Important At All" or "Not Important."

Additionally, when asked to what extent their research altered the amount of collaboration they engaged in, the average weighted PI response was 3.5 on a scale of 1 (No Increase in Collaboration), 2 (Minimal Increase in Collaboration), 3 (Moderate Increase in Collaboration), and 4 (Significant Increase in Collaboration). All 35 PIs responded, with five PIs selecting "Minimal Increase in Collaboration" or "No Increase in Collaboration."

4.0 RECOMMENDATIONS

Based on the findings from the research conducted, the following recommendations are offered for consideration regarding identifying and reporting on the accomplishments and performance of the Connecticut Biomedical Research Program to assure accountability of the state's public investment in the program. The recommendations encompass the following: Program Review, Program Administration, and Funding.

1. **Program Review:** DPH should conduct a periodic review of the Connecticut Biomedical Research Program in consultation with institutions and principal investigators that have applied for funding to assess program operations, including: administrative operations, proposal peer review and the selection award process, and progress of grantees awarded funding for in-process and completed projects. The purpose of the periodic review process would be to

   - review RFP requirements to improve/streamline the proposal application process;
   - review RFP requirements to improve/streamline the proposal application process;
   - consider actions to reduce administrative requirements for grant recipients, while maintaining accountability. Review a recent National Science Foundation - National Science Board report, "*Reducing Investigators' Administrative Workload for Federally Funded Research*"[6] to achieve this goal, while retaining project accountability. This report's Executive Summary includes a section on "Focus on the Science" that states:

     > *Investigators' administrative workload could be reduced significantly if requirements that are not critical to a proposal[']s merit review were postponed until the proposal has been positively reviewed and is being considered for funding. Administrative work could be reduced further if progress reports were streamlined and focused solely on performance outcomes. The Board strongly encourages the National Science Foundation (NSF) Director and other Federal agencies funding scientific research to focus the peer-review process and post-award oversight on merit and achievement.*

   - adapt award criteria to position the program based on lessons learned, past achievements, and scientific developments;
   - adjust funding levels and provide grant term flexibility for grant awards based on type of research (basic, translational and clinical research) and project requirements;
   - benchmark the program with similar programs in other areas of the country to support decisions, including those related to the investment and management of public funds used for scientific research; and
   - identify best practices for management and investment of public funds in support of biomedical research.

   The requirements of the grantee progress and final reports should be modified to include annual review process metrics and data, to be determined, for grantees. This requirement should be included in the annual Request for Proposals and in grantee assistance agreements.

6 National Science Board report: *Reducing Investigators' Administrative Workload for Federally Funded Research (March 10, 2014);* http://www.nsf.gov/pubs/2014/nsb1418/nsb1418.pdf

It is suggested that the reporting metrics and data be developed in consultation with the biomedical research leadership of the institutions/companies that receive program funding, as well as those that apply for funding. Additionally, best practices of other programs should be considered. Based on initial lessons learned from this review, suggestions for future metrics for reporting on accomplishments and outcomes include the following:

- Staffing and Job Creation: Suggested data to be reported include project staffing and jobs created reported on a full-time-equivalent basis; wages paid, which would be useful for conducting an economic impact analysis of the program in the future; and new staff relocating to Connecticut as a result of project funding.
- Accomplishments and Outcomes: Many research accomplishments and outcomes occur after the completion of a project and after a final project report is submitted by the PI. Consider including short-term, mid-term and long-term metrics, with some short- and mid-term metrics being proxies for the longer-term impacts that are desired or anticipated. Therefore, consideration should be given to not only requiring progress and final reports, but also annual reporting by PIs for grants that have been completed for a period of time as determined, with this requirement being a condition of grantee assistance agreements. Additionally, based on a review of the PI Survey conducted for this study, the following are suggestions for future surveys:
    - Type of Research Conducted: revise question to gain information on trends in types of research being conducted and planned for the future
    - Funding from Other Sources: revise the question regarding the amount of funding received from other sources to request the specific amount for grants awarded
    - Types of Outcomes Reported by PIs: restructure to identify outcomes by type of research being conducted (basic, translational, clinical), including non-commercial outcomes; and for items cited:
        - Formation of New Companies, Licenses and Patents Issued: request additional details for these outcomes to further show their significance
        - New Practices: expand question to identify whether the new practices are in use and if they are cost effective
        - Other: request PI to describe outcomes reported as "Other"
    - Research Funding Opportunities: restructure and clarify question to gain more specific information regarding how this grant has impacted the PI's research following completion of their Connecticut Biomedical Research Program grant
    - Collaborations: revise question to gain more detailed information on the type of collaboration engaged in

2. **Program Administration:** DPH staff designated to manage and oversee the Connecticut Biomedical Research Program should continually seek to improve the administration of the program and bring consistency to grant funding procedures and annual reporting processes.

Staff would

- manage program operations, including an annual review of RFP requirements and consideration of ways to reduce the administrative burden on grant recipients, as noted under Program Review;
- conduct an annual RFP bidders conference to exchange information between DPH and potential proposers;
- identify key high-level metrics for the periodic review of program accomplishments and administrative performance, in consultation with the program's leadership, including the Peer Review Committee;
- manage the periodic review process, including reporting to state agencies, the Connecticut General Assembly, research institutions, and others as appropriate;
- establish relationships between states and/or institutions based on a mutual need for the sharing and reporting of common metrics in collaboration with biomedical researchers and institutional leaders; and
- research best practices regarding scientific research grant funding, economic development, and institutional practices and processes in collaboration with biomedical researchers and institutional leaders.

3. **Funding:** Based on current operational requirements as set forth in the program's enabling legislation, as amended, the amount of funding available each year can vary significantly. Consideration should be given to stabilizing the annual funding allocation for the program as an indication of the state's commitment to fund tobacco-related research from the Tobacco Settlement Fund.

CONCLUDING REMARKS

Based on this study's findings and recommendations, DPH should consider implementing a process for periodic review of the Connecticut Biomedical Research Grant Program to provide accountability for the state's public investment in biomedical research. Additionally, the recent National Science Board report, "*Reducing Investigators' Administrative Workload for Federally Funded Research,*" will be useful in reducing the administrative requirements for grant recipients while assuring overall program accountability.

APPENDIX A
HISTORY OF LEGISLATION FOR THE CONNECTICUT BIOMEDICAL RESEARCH PROGRAM

Public Act	Enabling Legislation and Major Changes to the Statute
PA 99-2; Sec. 26	**AN ACT CONCERNING PUBLIC HEALTH EXPENDITURES** This legislation established the Tobacco Settlement Fund – a separate non-lapsing fund. Funds received by the state from the Master Settlement Agreement of November 23, 1998, were designated for deposit into the fund. See General Statutes Sec. 4-28e.
Connecticut General Statutes Sec. 19a-32c incorporates the provisions of the following public acts that were adopted from 2000 – 2013 regarding the Connecticut Biomedical Research Program:	
PA 00-216; Sec. 17	**AN ACT CONCERNING EXPENDITURES FOR THE PROGRAMS AND SERVICES OF THE DEPARTMENT OF PUBLIC HEALTH** This legislation created the Biomedical Research Trust Fund – a separate non-lapsing fund that could accept transfers from the Tobacco Settlement Fund. Additionally the legislation provided for the Biomedical Research Trust Fund to apply for and accept gifts, grants or donations from public or private sources to carry out the fund's objectives. This legislation also established that on and after July 1, 2001, the Commissioner of Public Health could make grants-in-aid from the trust fund to eligible institutions to fund biomedical research in the **fields of heart disease, cancer and other tobacco-related disease**s. It was required that the total amount of grants-in-aid made during the fiscal year ending June 30, 2002, should not exceed two million dollars. For each fiscal year thereafter, the total amount of such grants-in-aid made during the fiscal year would not exceed 50% of the total amount held in the trust fund as of the date such grants-in-aid are approved. This legislation required that the Commissioner of Public Health develop an application for grants-in-aid by April 2, 2001 enabling applications from eligible institutions for such grants-in-aid on and after that date. "Eligible institution" meant (1) a non-profit, tax-exempt academic institution of higher education, or (2) a hospital that conducts biomedical research.
PA 10-136	**AN ACT CONCERNING BIOMEDICAL RESEARCH TRUST FUND RESEARCH GRANTS** This legislation permitted grants from trust fund to be used for **Alzheimer's disease and diabetes research, in addition to heart disease, cancer and other tobacco-related diseases**. The legislation was effective July 1, 2010, and was included in RFP solicitations for proposals beginning in 2012.

Public Act	Enabling Legislation and Major Changes to the Statute
PA 13-18	**AN ACT CONCERNING GRANTS FROM THE BIOMEDICAL RESEARCH TRUST FUND FOR STROKE RESEARCH** **Stroke was added** as a research area eligible for grants-in-aid, effective July 1, 2013, and was included in RFP solicitations for proposals beginning in 2014.
PA 13-208	**AN ACT CONCERNING VARIOUS REVISIONS TO THE PUBLIC HEALTH STATUTES** This legislation made technical changes as follows: • Removed reference to "On or after July 1, 2001" • Removed reference to amount of grants-in-aid provided for fiscal year ending 6/30/02 • Removed reference to fiscal year ending June 30, 2003 • Removed reference to "Not later than April 2, 2001" This legislation also provided for 2% of the total available amount held in the trust fund to be made available to the Department of Public Health for administration expenses relating to the trust fund and making the grants-in-aid. In addition, "eligible institution" was further defined as an entity that has its principal place of business located in the state.

APPENDIX B
CONNECTICUT BIOMEDICAL RESEARCH PROGRAM
RFP EXCERPTS SHOWING RESEARCH CHANGES

RFP # BCH-2005 – 920
The Connecticut Department of Public Health (DPH) is pleased to announce the availability of funds for biomedical research projects in the fields of **heart disease** and **cancer** as well as **other tobacco-related diseases.**

RFP # 2006 – 0913
The Connecticut Department of Public Health (DPH) is pleased to announce the availability of funds for biomedical research projects in the fields of **heart disease** and **cancer** as well as **other tobacco-related diseases.**

RFP # 2007 – 0919
The Connecticut Department of Public Health (DPH) is pleased to announce the availability of funds for biomedical research projects in the fields of **heart disease** and **cancer** as well as **other tobacco-related diseases.**

RFP # 2008 – 0911
The Connecticut Department of Public Health (DPH) is pleased to announce the availability of funds for biomedical research projects in the fields of **heart disease** and **cancer** as well as **other tobacco-related diseases.**

RFP # 2009 – 0914
The Connecticut Department of Public Health (DPH) is pleased to announce the availability of funds for biomedical research projects in the fields of **heart disease** and **cancer** as well as **other tobacco-related diseases.**

RFP # 2010 – 0913
The State of Connecticut, Department of Public Health, is seeking proposals for biomedical research projects in the fields of **heart disease** and **cancer** as well as **other tobacco-related diseases.**

RFP # 2012 – 0913
The State of Connecticut, Department of Public Health, is seeking proposals for biomedical research projects in the fields of **heart disease**, **cancer** and **other tobacco-related diseases**, **diabetes** and **Alzheimer's disease.**

RFP # 2013 – 0903
The Connecticut Department of Public Health is seeking proposals for biomedical research projects in the fields of **heart disease**, **cancer** and **other tobacco-related diseases**, **diabetes** and **Alzheimer's disease**.

RFP# 2014 – 0908
The Connecticut Department of Public Health is seeking proposals for biomedical research projects in the fields of **heart disease**, **cancer** and **other tobacco-related diseases**, **Alzheimer's disease**, **stroke** and **diabetes**.

APPENDIX C
GRANTS AWARDED: 2005–2014

Projects not yet completed or without a final report on file as of June 30, 2014 are highlighted in green.
Click on the Contract # (hyperlink) to access the final report for each completed project.

RFP YEAR	CONTRACT #	AWARD	DISEASE FIELD	PROJECT TITLE	INSTITUTION	PI OF RECORD
2005	2005-2500	$350,000	cancer	Phase I Toxicity/Feasibility Study: Combined Modality Treatment with Trans immunization and Radiation for Non-small Cell Lung Cancer	Yale University	Wilson, Lynn
2005	2005-2501	$500,000	other tobacco-related	Effects of maternal Smoking in Infant/Child Health	UConn Health Center	Oncken, Cheryl
2006	2007-0160	$276,629	cancer	Role of VPS4B in Development of Trastuzumab-Resistant Breast Cancer	UConn Health Center	Hansen, Marc
2006	2007-0161-1	$299,723	other tobacco-related	Sensory Irritant Receptors in the Pathogenesis of Smoking-Induced Lung Disease	Yale University	Jordt, Sven-Eric
2006	2007-0162-1	$349,893	other tobacco-related	Genetics and Smoking in Pregnancy	Yale University	Triche, Elizabeth
2006	2007-0163-1	$265,050	cancer	Analysis of miRNA mutations in lung cancer	Yale University	Weidhaas, Joanne
2006	2007-0164	$167,800	cancer	Role of aberrant canonical Wnt signaling in colon cancer formation	Yale University	Wu, Dianqing
2007	2008-0121-1	$315,563	cancer	Hybrid scintigraphy/OCT intraoperative probe for ovarian cancer detection and surgical intervention	UConn	Zhu, Quing
2007	2008-0122	$299,044	cancer	Mitotic Spindle Positioning in Intestinal Cancer	UConn Health Center	Tirnauer, Jennifer
2007	2008-0123-1	$281,016	cancer	PGRMC1 siRNA as an adjunct therapy with cisplatin to kill human ovarian cancer cells in vitro and in vivo	UConn Health Center	Peluso, John
2007	2008-0124	$177,223	cancer	Development of a novel tumor-specific siRNA delivery system for cancer gene therapy	Yale University	Huang, Yingqun
2007	2008-0125	$107,409	cancer	Accuracy/Adequacy of Tobacco Use Data in Cancer Research	UConn Health Center	Gregorio, David
2007	2008-0126	$538,605	other tobacco-related	The effects of tobacco on brain structure and function are amplified by genotype	UConn Health Center	Bauer, Lance
2008	2009-0095	$239,938	other tobacco-related	PKR mediated effects on alveolar progenitor biology in COPD	Yale University	Herzog, Erica

RFP YEAR	CONTRACT #	AWARD	DISEASE FIELD	PROJECT TITLE	INSTITUTION	PI OF RECORD
2008	2009-0096	$374,240	cancer	Targeting Tumor Blood Vessels for Immunotherapy and Photodynamic Therapy of Human Lung Cancer	Yale University	Hu, Zhiwei
2008	2009-0097	$186,642	cancer	Development of a protein-based test to determine which patients with early stage non-small cell lung cancer are cured by surgery alone	Yale University	Rimm, David
2008	2009-0098	$301,188	cancer	Antitumor activity included by a novel hybrid cytokine	UConn Health Center	Lai, Laijun
2008	2009-0099	$278,473	heart disease	Mg^{2+}-permeable channel kinases in Heart Disease	UConn Health Center	Yue, Lixia
2008	2009-0100	$324,375	cancer	Functional Molecular Classification of BRCA Gene Mutations	UConn Health Center	Everson, Richard
2008	2009-0101	$294,013	cancer	Resistance to chemotherapeutic approaches based on targeting the erbB2 pathway as acquired through homozygous inactivating mutations in VPS4A or VPS4B	UConn Health Center	Hansen, Marc
2009	2010-0083	$205,602	heart disease	Circulating Caspase-3 p17 peptide and acute STEMI	UConn Health Center	Liang, Bruce
2009	2010-0084	$421,128 *Canceled. Largely repaid due to over-lapping grant.*	cancer	Testing the feasibility and usefulness of a new molecular test, SH2 profiling (molecular diagnostic assay)	UConn Health Center	Mayer, Bruce
2009	2010-0085-2	$290,304	heart disease	Studying the biomechanics of minimally invasive aortic valve replacement to elucidate the underlying device failure mechanism	UConn	Sun, Wei
2009	2010-0086-1	$457,890	cancer	Inhibition of Breast Cancer Metastasis by Activation of cAMP Signaling	UConn Health Center	Epstein, Paul
2009	2010-0087-1	$366,589	cancer	Identifying Clinical and Molecular Markers of Colon Cancer Risk in Smokers	UConn Health Center	Rosenberg, Daniel
2009	2010-0088-2	$219,625	cancer	A novel animal model to study smoking-associated damage in stem cells	UConn Health Center	Heinen, Christopher
2009	2010-0089	$267,186	heart disease	Does Smoking Cessation Restore Vascular Function in Chronic Smokers?	Hartford Hospital	Taylor (Parker), Beth

RFP YEAR	CONTRACT #	AWARD	DISEASE FIELD	PROJECT TITLE	INSTITUTION	PI OF RECORD
2010	2011-0138-2	$165,083	cancer	Role of DNA Mismatch Repair in Tobacco Smoke-mediated Carcinogenesis	Wesleyan University	Hingorani, Manju
2010	2011-0139	$334,055	heart disease	Magnetic Resonance Imaging (MRI) Assessment of Peripheral Artery Disease at 3 Tesla	Yale University	Sinusas, Albert
2010	2011-0140-2	$303,190	heart disease	Cardioprotective Synergy of Smoking Cessation and gamma-Tocopherol in Restoring Vascular Endothelial Function	UConn	Bruno, Richard
2010	2011-0141-1	$309,625	cancer	Targeted Probes for Breast Tumor Hypoxia Imaging	UConn	Zhu, Quing
2010	2011-0142-1	$245,885	heart disease	A novel signaling complex for the treatment of heart failure	UConn Health Center	Dodge-Kafka, Kimberly
2010	2011-0143-1	$246,290	other tobacco-related	Effects of cigarette smoke on angiogenesis in the aging brain	UConn Health Center	Pachter, Joel
2010	2011-0144-3	$283,934	cancer	Refining and Streamlining Comprehensive Genomic Analysis of Clinical Specimens by Massively Parallel Sequencing of Formalin-Fixed, Paraffin-Embedded Tissues	UConn Health Center	Everson, Richard/ Srivastava, Ranjan
2010	2011-0145-3	$439,243	cancer	Immunotherapy of melanoma and colon cancer by a recombinant IL-7/HGFβ protein	UConn Health Center	Lai, Laijun / LeFrançois, Leo
2012	2012-0222-1	$169,677	diabetes	Measurement of beta cell death in diabetes	Yale University	Herold, Kevan
2012	2012-0223-1	$417,076	other tobacco-related	The effect of chokeberry polyphenols on biomarkers of cardiovascular disease and antioxidant defenses in former smokers	UConn	Bolling, Bradley
2012	2012-0224	$356,250	cancer	Identifying Clinical and Molecular Markers of Colon Cancer Risk in Smokers	UConn Health Center	Rosenberg, Daniel
2013	2013-0194	$284,739	other tobacco-related	Discovering the underlying basis of chronic obstructive pulmonary disease to reveal new potential therapeutic routes	Yale University	Regan, Lynne
2013	2013-0195	$216,043	cancer	Protective and toxic effects of HER2 epitope spreading during trastuzumab treatment	Yale University	Mamula, Mark
2013	2013-0196	$355,902	other tobacco-related	NLRX1 and mitochondrial reactive oxygen species in chronic obstructive pulmonary disease (COPD)	Yale University	Kang, Insoo (PI changed from Elias, Jack)
2013	2013-0197	$300,000	heart disease	NPP4 in Thrombosis and Hemostasis	Yale University	Braddock, Demetrios

RFP YEAR	CONTRACT #	AWARD	DISEASE FIELD	PROJECT TITLE	INSTITUTION	PI OF RECORD
2013	2013-0200	$424,466	cancer	Combinatorial high throughput screening of targeted agents for genotype-selective impact on lung carcinoma	Yale University	Stern, David
2013	2013-0201	$420,488	cancer	Roles of Histone Demethylase RBP2 in Breast Cancer Metastasis	Yale University	Yan, Qin
2013	2013-0202	$367,401	cancer	Regulation of the balance between fatty liver, growth, and liver cancer by InsP3R isoforms	Yale University	Nathansan, Michael
2013	2013-0203	$300,000	cancer	Usp7 - a potential drug target for treatment of cancer	Yale University	Bezsonova, Irina
2013	2013-0204	$341,572	heart disease	Therapeutic Targeting of Vascular Permeability in Cardiovascular Ischemic Disease	UConn Health Center	Claffey, Kevin
2014	2014-0130	$247,824	cancer	Preventative therapies for chemotherapy-induced peripheral neuropathy	Yale University	Kaftan, Edward
2014	2014-0132	$272,044	cancer	Targeting chemoresistance of lung cancer using functional proteomics	Western CT Health Network/ Danbury Hospital	Ferlini, Cristiano
2014	2014-0133	$207,440	heart disease	Therapeutic targeting of a novel signaling complex for the treatment of cardiac disease	UConn Health Center	Dodge-Kafka, Kimberly
2014	2014-0135	$400,362	cancer	Disease Relapse in AML: Clonal evolution in patients and humanized mice	Yale University	Halene, Stephanie
2014	2014-0136	$324,127	cancer	A new biosensor device for cancer diagnostics	Wesleyan University	Hingorani, Manju
2014	2014-0137	$276,449	cancer	A safe and effective therapeutic vaccine to prevent liver cancer	Yale University	Robek, Michael
2014	2014-0138	$268,800	other tobacco-related	Cellular mechanisms of smoking-related pancreatitis	Yale University	Thrower, Edwin
2014	2014-0139	$304,345	Alzheimer's & diabetes	Restoring insulin sensitivity by O-GIcNAc signaling through FoxO1	Yale University	Yang, Xiaoyong

APPENDIX D
PRINCIPAL INVESTIGATOR SURVEY

Connecticut Biomedical Research Grant Program - Accomplishments

Introduction

The Connecticut Academy of Science and Engineering (CASE) is conducting a review of the Connecticut Biomedical Research Program to report on the program's accomplishments on behalf of the Connecticut Department of Public Health.

Principal Investigators of Connecticut Biomedical Research Grants awarded from 2005 to 2011 are requested to respond to the following survey. The survey results will be used to identify accomplishments of the state's investment in biomedical research and as guidance for determining the future of the program.

Survey results will be aggregated and comments provided will NOT BE identified by individual.

The survey should take approximately 45-60 minutes. If you need to exit the survey before completing it, return to the survey by clicking on the survey link in the email notification.

SURVEY RESPONSE DEADLINE: We respectfully request your prompt response. PLEASE COMPLETE THE SURVEY NO LATER THAN MONDAY, April 28, 2014, AT 5:00 EDT.

NOTE:
If you have served as the Principal Investigator on more than one CT Biomedical Research Grant, you should have been contacted by CASE staff via email and asked to respond to ONE SURVEY PER GRANT FUNDED.

If you have questions or received this in error, contact Terri Clark, Associate Director, CASE at 860-571-7143 or by email at tclark@ctcase.org.

Thank you for your time.

General Information

1. Provide the following information:

Name:

Institution:

2. Indicate the field that was/is the focus of your grant.

- ◯ Heart disease
- ◯ Cancer
- ◯ Tobacco-related diseases other than cancer or heart disease

Page 1

Connecticut Biomedical Research Grant Program - Accomplishments

3. Were you able to complete the research funded through your CT Biomedical Research Grant within your Assistance Agreement timeline? For any drop-down menus that do not apply, select "Not Applicable."

	Completed Within Assistance Agreement Timeline	Required An Extension	Additional Months Required
Grant Funding Assistance Agreement Timeline (select Not Applicable)			

Comment:

4. Select your response to the following questions from the "# of Years" drop-down menu.

	# of Years
How long have you served as a lead scientist/Principal Investigator?	
How long have you had your own laboratory? If you do not have your own laboratory, indicate by selecting 0 years.	

Comment:

5. To what extent do you agree or disagree with each of the following statements.

The CT Biomedical Research Grant Funding

	Strongly Agree	Agree	Neither Agree Nor Disagree	Disagree	Strongly Disagree	N/A
made this particular project possible and it would not have been without the funding.	○	○	○	○	○	○
made it possible to obtain funds from other sources to continue my research.	○	○	○	○	○	○
made it possible to increase staff size to support my research.	○	○	○	○	○	○
made it possible to increase my lab's technology/equipment.	○	○	○	○	○	○

Comment

Basic, Translational and Clinical Research

This section of the survey includes two questions about the type of research you are doing with your CT Biomedical Research Grant Funding. For the purposes of this survey, use the following definitions for Basic, Translational and

Page 2

Connecticut Biomedical Research Grant Program - Accomplishments

Clinical Research.

BASIC:
Research directed at understanding the funadamental mechanisms of biologic processes without regard for direct application to the understanding or treatment of human diseases.

TRANSLATIONAL (from NIH - Institute of Translational Health Services):
• the process of making discoveries in the research laboratory or in preclinical studies that will have an impact on human health and may lead to the development of studies in humans,
• the process of applying discoveries generated during research in the laboratory, and in preclinical studies, to the development of trials and studies in humans.

CLINICAL (from NIH – Office of Extramural Research):
Research with human subjects that is:
1. Patient-oriented research. Research conducted with human subjects (or on material of human origin such as tissues, specimens, and cognitive phenomena) for which an investigator (or colleague) directly interacts with human subjects. Excluded from this definition are in vitro studies that utilize human tissues that cannot be linked to a living individual. It includes:
- mechanisms of human disease
- therapeutic interventions
- clinical trials
- development of new technologies
2. Epidemiological and behavioral studies.
3. Outcomes research and health services research.

6. Indicate the primary type of research you conducted with your CT Biomedical Research Grant Funding.

◯ Translational ◯ Clinical

Comment:

7. Select from the drop-down menu a % estimate for your primary type of research for each of the following:

	% Basic	% Translational	% Clinical
Prior to my CT Biomedical Research Grant Funding			
Concurrent with my CT Biomedical Resarch Grant Funding			
In five years			

Comment:

Funding

Page 3

Connecticut Biomedical Research Grant Program - Accomplishments

8. Are you continuing to do similar research to what your CT Biomedical Research Grant Funding enabled you to do? Check all that apply.

My research

- ☐ through the grant has ended and I received additional funding to continue this research.
- ☐ through the grant has ended and I have applied for additional funding but have not yet received a decision.
- ☐ through the grant has ended and I have not been awarded additional funding for proposals submitted.
- ☐ through the grant has ended and I have not applied for additional funding.
- ☐ through the grant is still in process.
- ☐ has changed based on my grant and I received additional funding to do the new research.
- ☐ has changed based on my research through the grant and I have applied for additional funding but have not yet received a decision.
- ☐ has changed following the research I did with the grant and I am no longer doing the type of research funded through the CT Biomedical Grant Funding Program.

Comment

9. Indicate the sources you have applied to for continued funding of the research you conducted through your CT Biomedical Research Grant. Do not include any additional CT Biomedical Research grant funding you may have been awarded in your response.

	Source	Amount	Status of Funding
Funder - 1			
Funder - 2			
Funder - 3			
Funder - 4			
Funder - 5			
Funder - 6			
Funder - 7			
Funder - 8			

Comment:

Staffing

Page 4

Connecticut Biomedical Research Grant Program - Accomplishments

10. Complete the information in the following table for each staff member that worked on your CT Biomedical Research Grant Funding, including yourself, for the fiscal years in which you received the funding.

- FTE = Full Time Equivalent
- FY = Fiscal Year

	Role of Staff Member	Est. Average % FTE Per FY	Est. Year Staff Member Started	Est. Year Staff Member Ended	Remained in the Field following the Grant	Remained in Connecticut following the Grant
Staff Member #1						
Staff Member #2						
Staff Member #3						
Staff Member #4						
Staff Member #5						
Staff Member #6						
Staff Member #7						
Staff Member #8						

Collaboration

Page 5

Connecticut Biomedical Research Grant Program - Accomplishments

11. Who have you collaborated with on your CT Biomedical Research Grant? Check all that apply.

- ☐ Others in my department at my institution/hospital
- ☐ Others in other departments at my institution/hospital
- ☐ Businesses and industries in Connecticut
- ☐ Businesses and industries in the United States (except Connecticut)
- ☐ Businesses and industries from other countries
- ☐ Other institutions/hospitals in Connecticut
- ☐ Institutions/hospitals in the US (except Connecticut)
- ☐ Institutions/hospitals from other countries
- ☐ Non-profits in Connecticut
- ☐ Non-profits in the US (except Connecticut)
- ☐ Non-profits from other countries

Comment:

12. Rate the importance of collaboration to the success of your research through the CT Biomedical Research Grant.

	Not Important At All	Not Important	Neither Important Nor Not Important	Important	Very Important	Not Applicable
Importance of Collaboration	○	○	○	○	○	○

13. To what extent did the research from your CT Biomedical Research Grant funding alter the amount of collaboration you engage in?

	Significant Increase in Collaboration	Moderate Increase in Collaboration	Minimal Increase in Collaboration	No Increase in Collaboration
Effect on Amount of Collaboration	○	○	○	○

Research Results

The following questions will provide a summary detailing the results and key accomplishments of your CT Biomedical Research Grant. In providing your response, use language that can be understood by the general public.

Page 6

Connecticut Biomedical Research Grant Program - Accomplishments

14. Provide a summary detailing the goals of your research and whether you achieved your goals. (approximately 250 word maximum)

15. Highlight the key finding(s) from your research and describe the benefits your research provides to the citizens and government of the State of Connecticut. (approximately 250 word maximum)

16. Describe how your research progressed the field of study. (approximately 100 word maximum)

Page 7

Connecticut Biomedical Research Grant Program - Accomplishments

17. Did your research lead to new collaborations that are currently on-going? (approximately 100 word maximum)

18. Which of the following outcomes can you attribute to your research through the CT Biomedical Research Grant?

	Yes	No	Not Applicable
Licenses Issued	◯	◯	◯
New Laboratories Established	◯	◯	◯
New Practices (Clinical, Tool Instruments, Procedure/Technique)	◯	◯	◯
New Research Methods	◯	◯	◯
New Theories	◯	◯	◯
New Vaccines/Drugs	◯	◯	◯
Patentable Materials Created	◯	◯	◯
Patent Applications	◯	◯	◯
Patents Issued	◯	◯	◯
Peer Reviewed Research Papers and Journals	◯	◯	◯
Replication of Research Findings	◯	◯	◯
Research Findings/Knowledge Creation	◯	◯	◯
Software/Databases	◯	◯	◯
Formation of New Companies	◯	◯	◯

Other (please specify)

Page 8

Connecticut Biomedical Research Grant Program - Accomplishments

19. If yes to any of the outcomes listed in Question 18, please briefly comment and indicate the number, if appropriate.

Licenses Issued	
New Laboratories Established	
New Practices (Clinical, Tool Instruments, Procedure/Technique)	
New Research Methods	
New Theories	
New Vaccines/Drugs	
Patentable Materials Created	
Patent Applications	
Patents Issued	
Peer Reviewed Research Papers and Journals	
Replication of Research Findings	
Research Findings/Knowledge Creation	
Software/Databases	
Formation of New Companies	

CT Biomedical Research Program Considerations

20. List three to five benefits unique to conducting Biomedical Research in Connecticut.

21. List three to five challenges unique to conducting Biomedical Research in Connecticut.

Page 9

Connecticut Biomedical Research Grant Program - Accomplishments

22. Currently, the Biomedical Trust Fund provides grants-in-aid for research in the fields of heart disease, cancer and other tobacco-related diseases, as well as Alzheimer's disease, stroke and diabetes. Are there other biomedical research fields of high importance that you recommend the state should consider for inclusion in this program?

23. Identify any current CT Biomedical Research Program policy issues (obstacles/barriers/concerns) that should be considered by the state. (approximately 250 word maximum)

24. How would you suggest the CT Biomedical Research Program be improved? (approximately 250 word maximum)

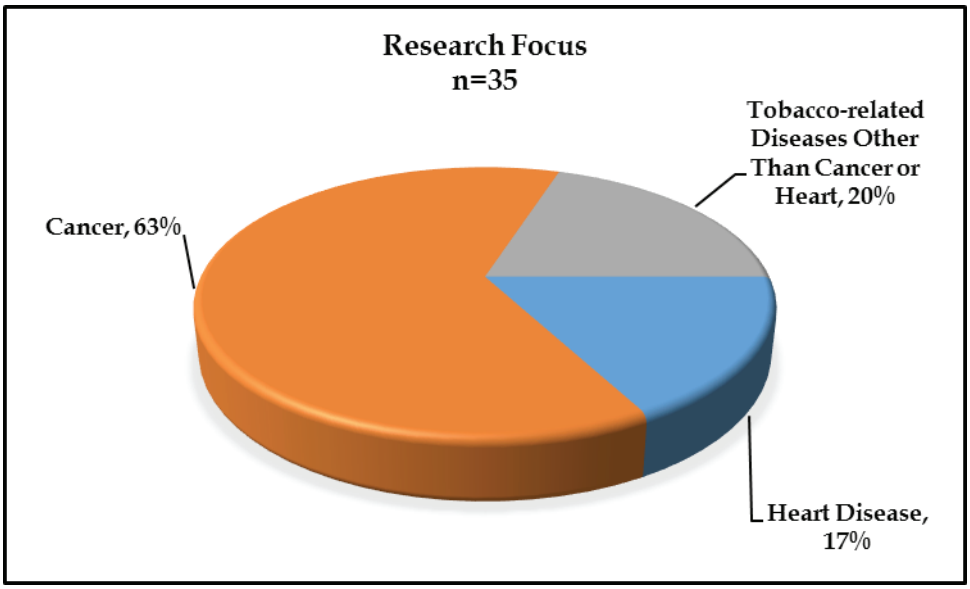
Page 10

APPENDIX E
PRINCIPAL INVESTIGATOR SURVEY RESPONSES

A total of 32 PI representing the 35 grants awarded from 2005 – 2011 responded to the survey. In addition to providing specific responses to the questions asked, the respondents were given the opportunity to provide additional comments. Therefore, the comments listed are those received and each should be considered separately.

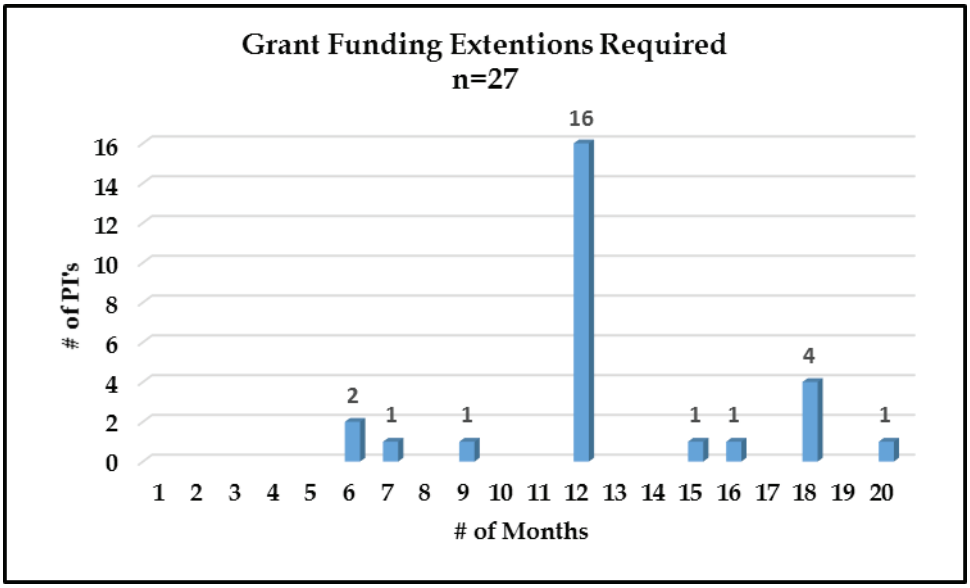
Question 1.
NOTE: Responses to this question confirmed who was responding to the survey and from which institution. These responses are not included in the survey results.

Question 2.
Indicate the field that was/is the focus of your grant.



Question 3.
Were you able to complete the research funded through your Connecticut Biomedical Research Grant within your Assistance Agreement timeline?

All 35 PIs responded, with six (17%) indicating they were able to complete the research within the assistance agreement timeline and 29 (83%) reporting that an extension was required. The following table provides the number of months beyond the assistance agreement timeline that was required, as reported by 27 of the 29 PIs.



Comments:

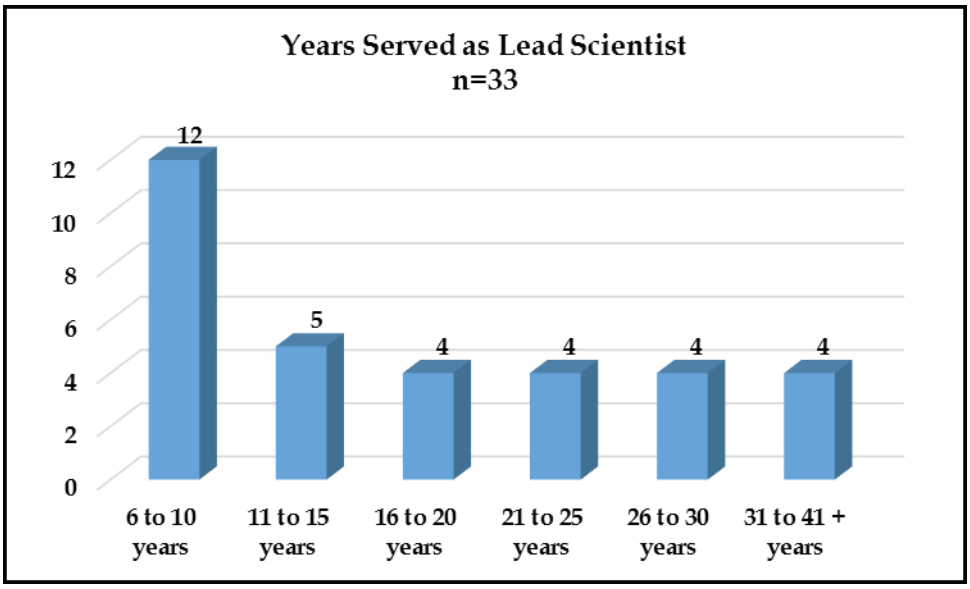
- One year funding time is not enough due to Institution Review Board (IRB) related issues and recruitment of graduate students to work on the project.
- There was a switch of PIs for the project, which required an extension.
- The project focused on improving methods for sequencing clinical samples. Sequencing was being done at the UConn Health Center's (UCHC) DNA Sequencing Core. Midway through the project UCHC closed its Sequencing Core, giving away the instrumentation used for the project and laying off staff collaborating on the project through the core. Lack of staff and instrumentation required developing workarounds and resulted in a prolonged delay in the project.
- Funding was only for one year, but needed an additional year.
- The funding activation date was delayed and that set us back.
- Unanticipated challenges and delays primarily resulted from prolonged negotiations with the IRBs at UCHC, obtaining collaboration at multiple institutions in the region, and the resignation of multiple UConn staff involved with the project.

  Unanticipated benefits were dramatic progress in technology for gene expression analysis by arrays and gene expression and mutation analyses by sequencing. The combination of progress obtaining access to specimens and establishing the registry/ repository for the program will provide future ongoing access to the specimens with dramatic improvements in the technology. This has led to placing our program in a solid competitive position for obtaining additional funding and contributing to rapid developments in our ability to understand the implications of DNA sequence variations.

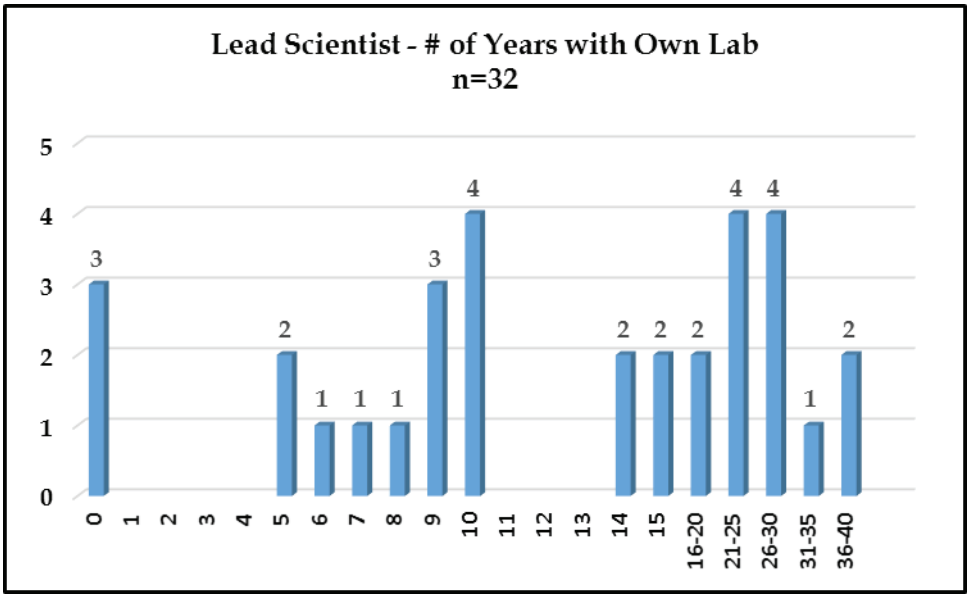
- A delay in initiation of funding resulted in a lost hiring opportunity. The grant extension was necessary, easy to obtain (with justification) and much appreciated, as it enabled hiring of another qualified person for the project in due time.

- Grant was rescinded soon after it began due to scientific overlap with a federal grant awarded just after the DPH start date.
- Regretfully, an extension was needed as several key personnel had to leave the laboratory for one reason or another during the project. Information Technology also took more time than expected to acquire the smoking machine needed, which was custom ordered.
- Establishing a contract between UConn and Ohio State University took nearly one year due to administrative difficulties on the UConn end in fulfilling their duties in managing the grant appropriately.
- The trial was phase I and did not accrue due to FDA approved therapy coming online.

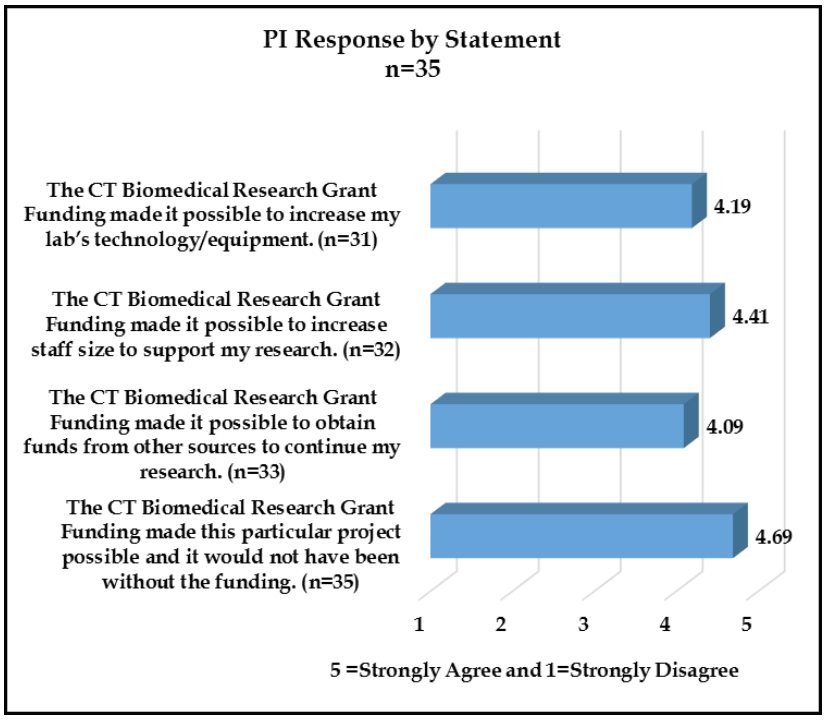
Question 4.
4a. How long have you served as a lead scientist/Principal Investigator? Indicate in number of years.



4b. How long have you had your own laboratory? If you do not have your own laboratory, indicate by selecting 0 years.



Question 5.
To what extent do you agree or disagree with each of the following statements as a recipient of Connecticut Biomedical Research Grant Funding.



Comments:

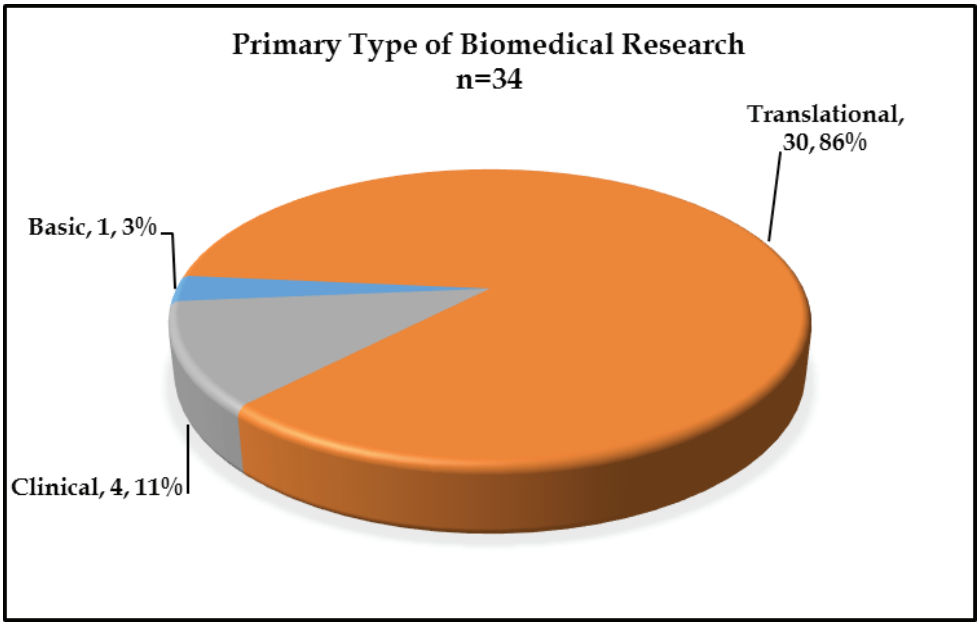
- This funding mechanism was absolutely critical to launching a major human translational project. We have had enormous success as a direct result of this funding, including a major NIH grant from the National Cancer Institute and a series of publications directly related to this project.
- This grant enabled me to maintain but not to increase staff size.
- While the basic research supported by this grant has not been used as foundation for funding from other sources yet, the results did enable a translational project proposal that was competitive for DPH grant funding in 2014.
- This grant supported existing staff levels.
- The grant did not make it possible to increase my staff size, but did make it possible to keep my research assistant.
- The grant made a huge difference.
- The Connecticut Biomedical Research Program funding made it possible for us to pioneer new technology to quantitatively evaluate gene expression in specific cell types in situ. The advantages of this new technology extend beyond this particular research project to playing a key role in the development of personalized medicine. It has led to

collaborations between the UConn Farmington and Storrs campuses, as well as critical interactions with colleagues at Yale and pharmaceutical companies in Connecticut. In short, it has paved the way for "Bioscience CT," and opened several funding streams for UConn and the State.

- This grant gave me the funds to begin a project, and complete the project outlined in the grant. However, I have tried to get funding to continue this project from the National Institute of Health and have not been successful so far. I believe this is due to low levels of funding at the NIH and does not represent the quality of work performed.

Question 6.
Indicate the primary type of research you conducted with your Connecticut Biomedical Research Grant Funding.

NOTE: Basic research was not included as an option for "Type of Research," as all grant funding required a disease focus. One PI commented that their research was Basic, which was added to the Figure.

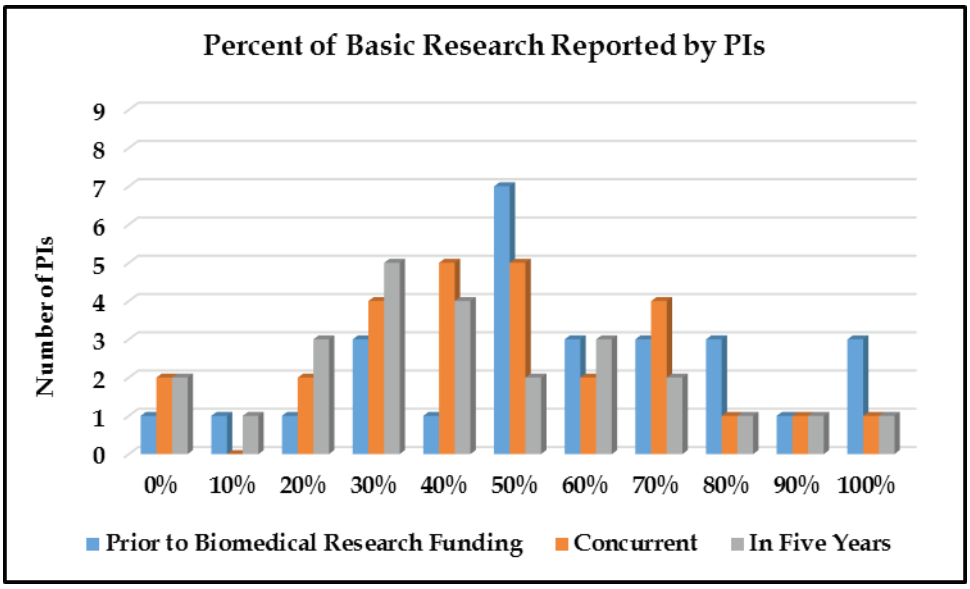


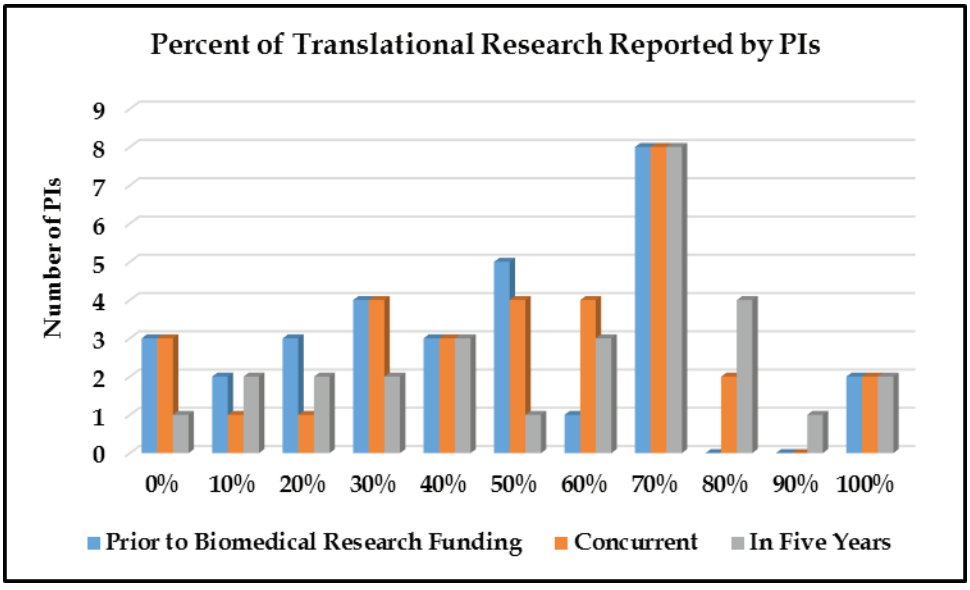
Comments:

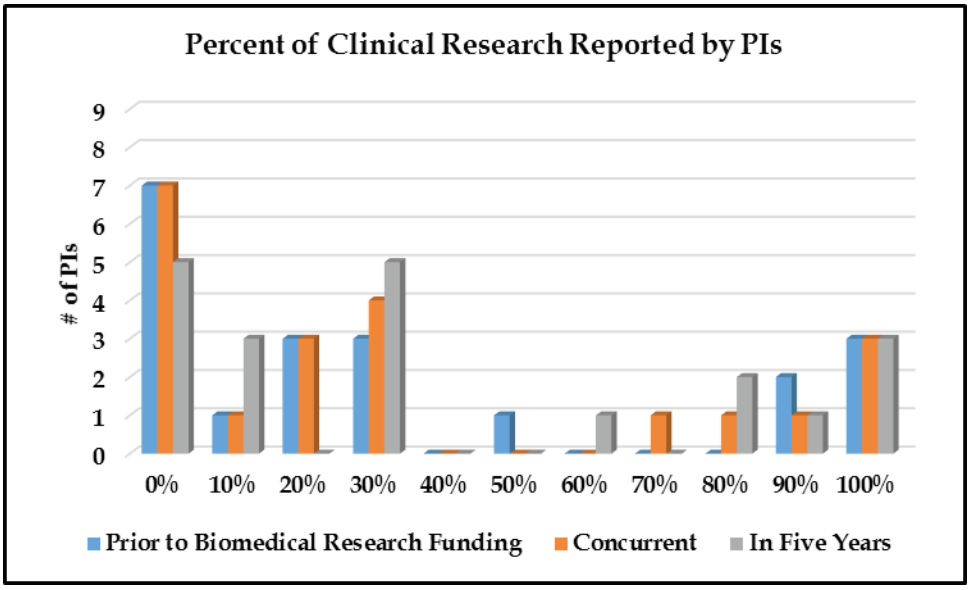
- As part of our DPH-funded project, we accrued and studied 185 subjects from the State of Connecticut. This included a full, high-definition, chromoendoscopic examination of their entire colon with sampling of 12 bio-specimens, blood, demographics, food frequency intake data and other input data.
- Project had components of both translational and clinical research (developed methods/applied them to populations).
- There is no choice button for Basic in this survey setup? In any case, the research in my laboratory was completely basic research on the mechanisms of some proteins implicated in carcinogenesis.

- Our work is clearly at the "translational" intersection. Though focused on basic pathogenic mechanisms, the technology developed in this study has broad applications in the clinical arena.
- The proposal was to determine if targeting a signaling complex in the heart would attenuate the progression of heart disease.

Question 7.
Indicate a % estimate for your primary type of research for each of the following categories whether basic, translational and/or clinical. **NOTE: Response Rate on for the following three tables ranged from n=27 to n=20, with an average response for Basic n=26.3, for Translational n=30.7 and Clinical n=20.3**





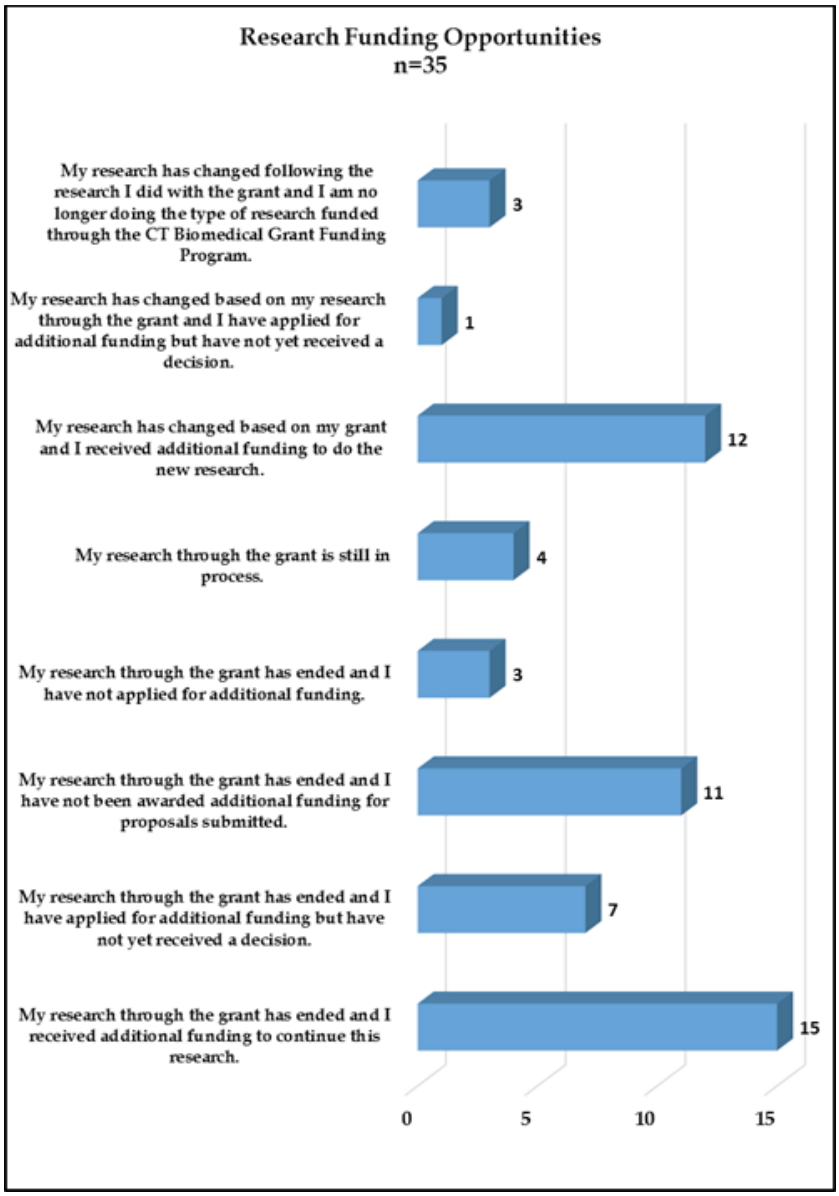


Comments:

- This DPH funding was instrumental in enabling my laboratory to make a serious entry into translational research.
- While my research is rooted in basic science, the clinical applications are constantly expanding.
- All of my funding, both from the National Institute of Health and the American Heart Association, was to investigate mechanisms of heart disease and therefore, translational. *(Note: In PI's survey response, 100% translational research was selected for research conducted prior to, concurrent with, and planned in the future.)*

Question 8.
Are you continuing to do similar research to what your Connecticut Biomedical Research Grant Funding enabled you to do? Check all that apply.

All 35 PIs responded to the question, with several selecting multiple statements for a total of 56 responses.

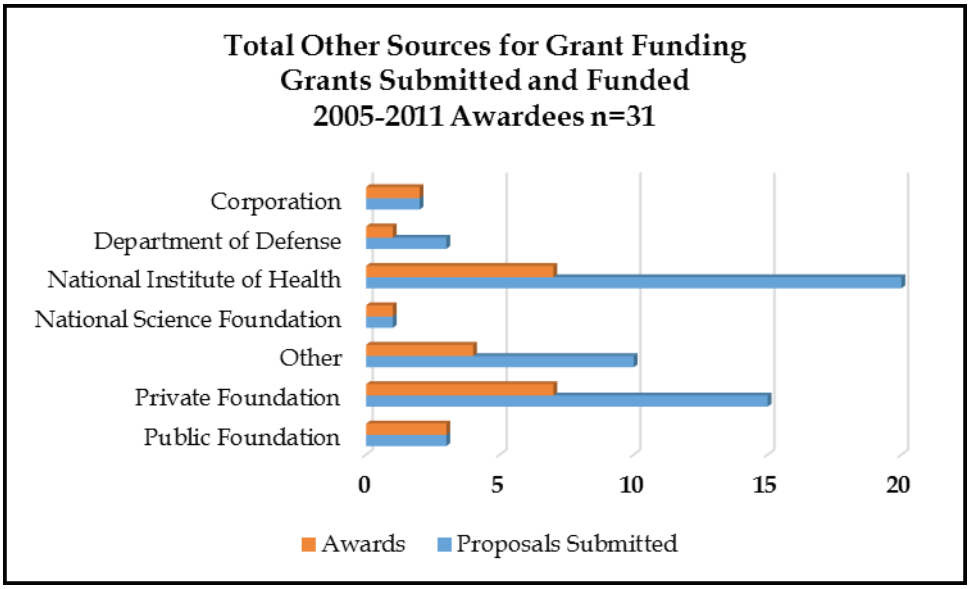


Comments:

- I had received further funding in the topic area of the DPH grant, but now am doing slightly different things.
- I have an active National Cancer Institute Research Project Grant (R01) based on the Connecticut Biomedical Research Program grant and I have applied for additional National Institutes of Health support based on this ongoing study started from the DPH grant. I received a score of 40 percentile on a Provocative question grant and we intend to resubmit later this year (2014). The focus is on obesity as a risk factor for Colon and Rectal Cancer.
- This grant stimulated new avenues of research that are currently still underway, as well as the original direction of research.

- I left research several years after the grant ended to take a more clinical job, in part due to a declining funding environment.
- The grant is currently in a no-cost extension, and we expect to compete for federal funding in the near future.
- The results of the analyses were mostly non-significant. Therefore, there was no point in continuing that line of research.

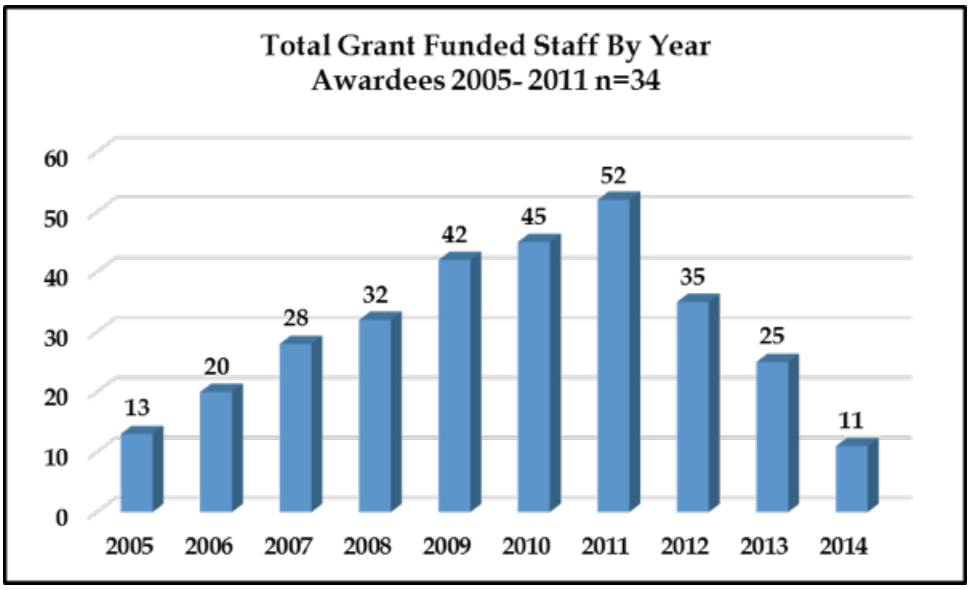
Question 9.
Indicate the sources you have applied to for continued funding of the research you conducted through your Connecticut Biomedical Research Grant. Do not include any additional Connecticut Biomedical Research Program grant funding you may have been awarded in your response.

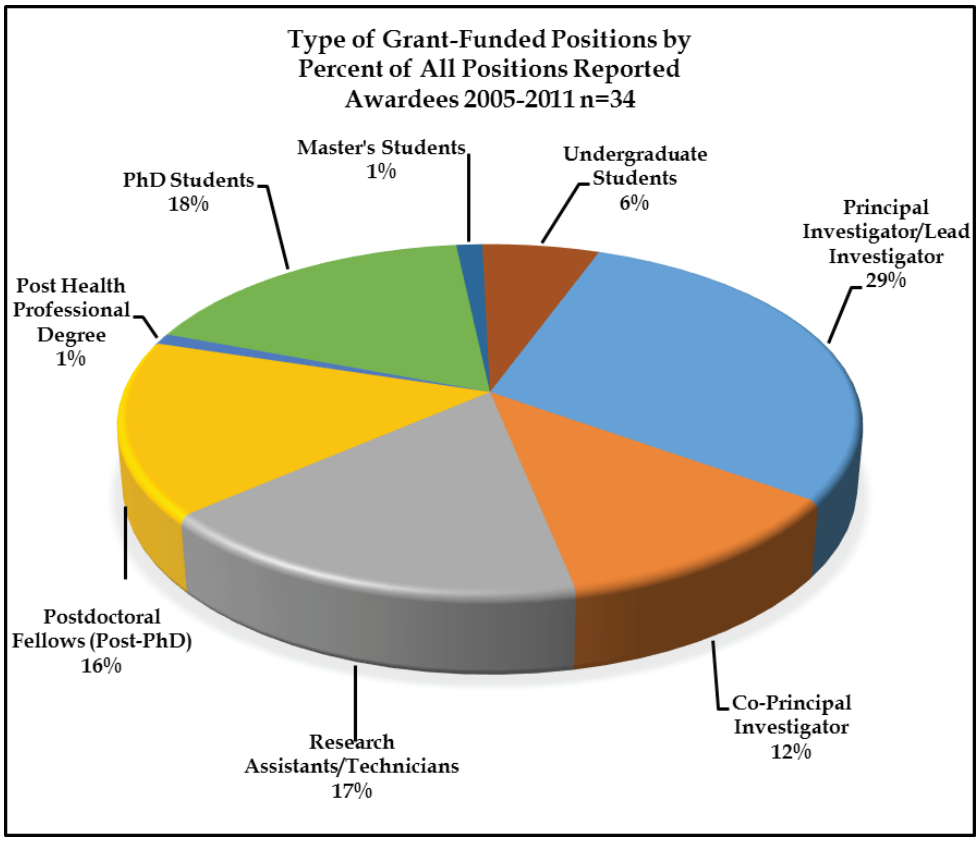


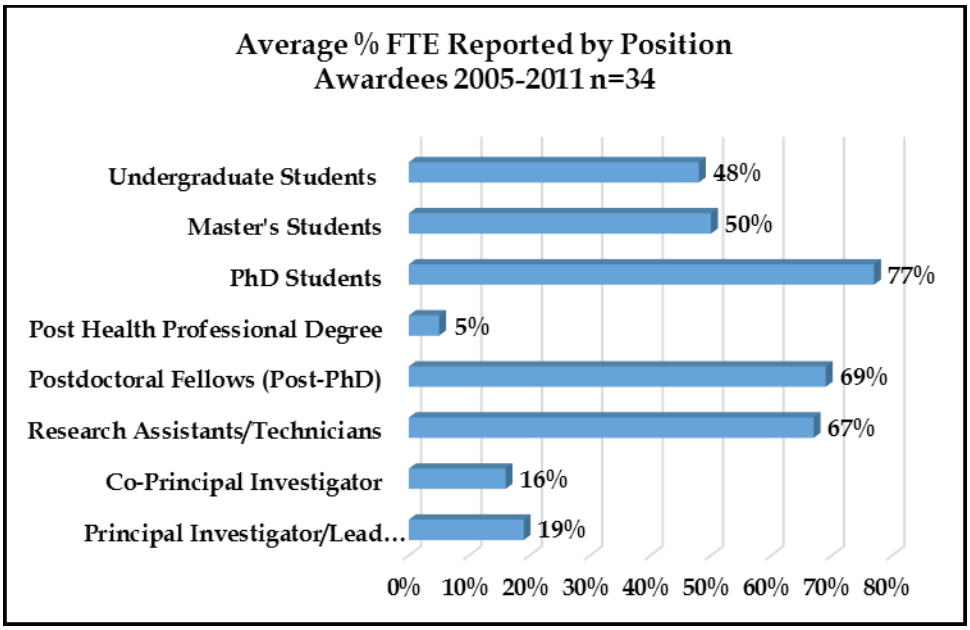
Question 10.
Complete the information in the following table for each staff member that worked on your Connecticut Biomedical Research Program Grant Funding, including yourself, for the fiscal years in which you received the funding.

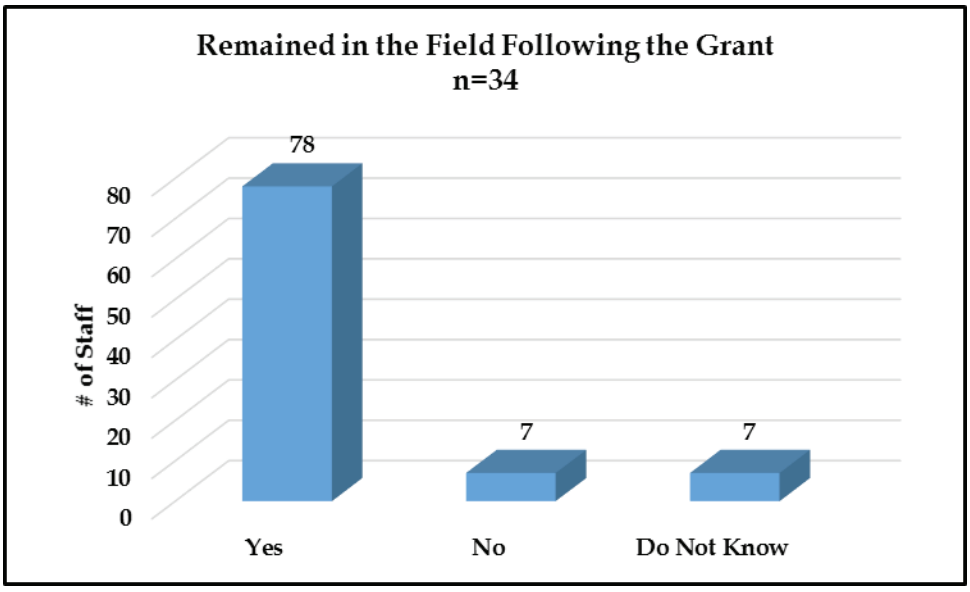
- *FTE: Full Time Equivalent*
- *FY: Fiscal Year*

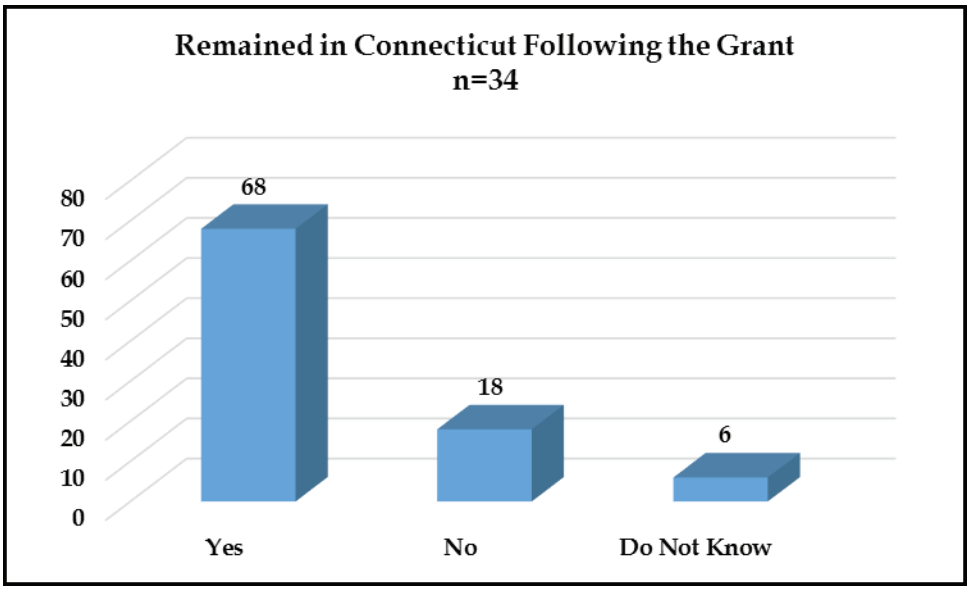
The following five figures identify total grant-funded staff by year, percent of grant-funded staff by total staff reported for each year, # of staff by staff type during all years reported, average FTE by type of staff, and staff remaining in the field and in Connecticut after completion of the grant award.


Total Grant Funded Staff By Year
Awardees 2005- 2011 n=34
60
50
40
30
20
10
0
13
20
28
32
42
45
52
35
25
11
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014


Type of Grant-Funded Positions by
Percent of All Positions Reported
Awardees 2005-2011 n=34
Master's Students
1%
Undergraduate
Students
6%
PhD Students
18%
Principal
Investigator/Lead
Investigator
29%
Post Health
Professional
Degree
1%
Postdoctoral
Fellows (Post-PhD)
16%
Co-Principal
Investigator
12%
Research
Assistants/Technicians
17%

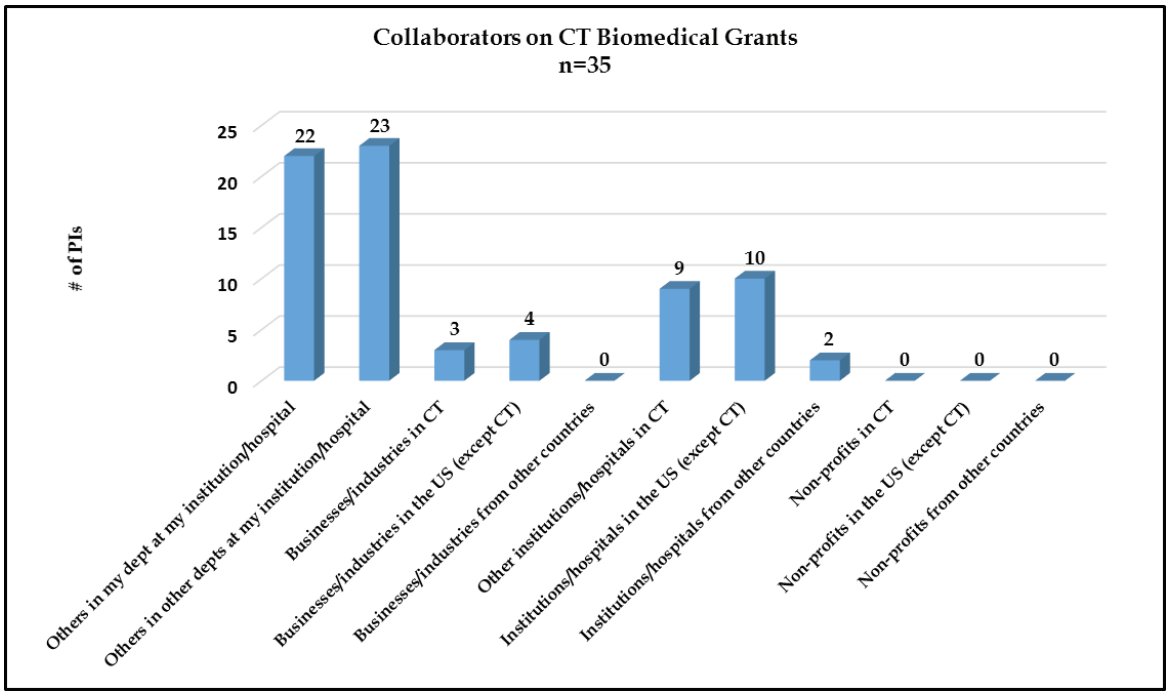

Average % FTE Reported by Position
Awardees 2005-2011 n=34
Undergraduate Students
Master's Students
PhD Students
Post Health Professional Degree
Postdoctoral Fellows (Post-PhD)
Research Assistants/Technicians
Co-Principal Investigator
Principal Investigator/Lead...
48%
50%
77%
5%
69%
67%
16%
19%
0% 10% 20% 30% 40% 50% 60% 70% 80%


Remained in the Field Following the Grant
n=34
# of Staff
0
10
20
30
40
50
60
70
80
78
7
7
Yes
No
Do Not Know



Question 11.
Who have you collaborated with on your Connecticut Biomedical Research Grant? Check all that apply.

All 35 PIs responded to the question, with several selecting multiple collaborations for a total of 73 responses.



Comments:

- Lost key collaborators when the core was closed, which was a key resource for the project.

- I have collaborated with investigators in Community Medicine and Gastroenterology and Connecticut Institute for Clinical and Translational Science at UConn Health Center and with Molecular Cell Biology and Nutrition at UConn, Storrs Campus. Additionally, I have collaborated with investigators at the City of Hope (Duarte, CA) related directly to this project.
- We are working with colleagues at UConn, Storrs Campus and Yale, as well as with Life Technologies/Thermo-Fisher.

Question 12
Rate the importance of collaboration to the success of your research through the Connecticut Biomedical Research Grant.

The average weighted PI response to the importance of collaboration was 4.5 on a scale of 1 (Not Important At All) to 5 (Very Important). All 35 PIs responded, with no PI selecting a rating of "Not Important At All" or "Not Important."

Question 13
To what extent did the research from your Connecticut Biomedical Research Program Grant funding alter the amount of collaboration you engage in?

The average weighted PI response to the extent of collaboration they engage in was 3.5 on a scale of 1 (No Increase in Collaboration), 2 (Minimal Increase in Collaboration), 3 (Moderate Increase in Collaboration), and 4 (Significant Increase in Collaboration). All 35 PIs responded, with five PIs selecting "Minimal Increase in Collaboration" or "No Increase in Collaboration."

Questions 14-17 Responses to the four questions were collated by PI, with the results provided below for 34 projects.

Question 14 -- *Provide a summary detailing the goals of your research and whether you achieved your goals (approximately 250 word maximum).*

Question 15 -- *Highlight the key findings and benefits that the research provides to the citizens and government of the State of Connecticut (approximately 250 word maximum).*

Question 16 -- *Describe of how your research progressed the field of study (approximately 100 word maximum).*

Question 17 *-- Did your research lead to new collaborations that are currently ongoing (approximately 100 word maximum)?*

RFP YEAR: 2005

PI: Cheryl Oncken, Project Title: Effects of Maternal Smoking in Infant/Child Health

Goals

The overall goals of this project were to examine the impact of maternal smoking on maternal and child health. Specifically, we sought to examine mechanisms by which maternal smoking contributes to an increased risk of low birth weight, premature delivery and other adverse infant outcomes. We conducted an analysis of DNA methylation, microarray analyses, and HuR expression on cord blood and/or tissue obtained at delivery of mothers who smoked compared to mothers who did not smoke. Another goal was to examine the impact of maternal smoking on auditory processing (a surrogate measurement later correlated with language skills) in newborn infants born to smoking compared to nonsmoking mothers. We also sought to examine potential mechanisms by which smoking could impact auditory processing. Further we correlated specific gene expression of specific nicotinic receptors and inflammatory biomarkers in cord blood and tissue to auditory processing findings in newborns.

Key Findings

Our research showed that maternal smoking can alter gene expression in placenta (Morris, B, 2008) and the offspring. Specifically, in one published article we found that smoking up regulates genes important for fetal growth and down regulates genes important for immune function (Hussain et al., 2008). The results of this study (microarray analyses) have provided the basis for further studies examining mechanisms of tobacco's effect in early development (Liswecki et al 2012). We also found that maternal smoking influences auditory processing in newborns (Praveen et al, 2008), although the exact mechanism is poorly understood.

The following presentations/publications have been made regarding our study

1. Shama Praveen, Naveed Hussain, Cheryl Oncken, Denise Ortiz, Vijayakumar Praveen, Anna Dongari Bagtzoglou, Jonathan Covault, Henry Kranzler, Stephen Walsh. Impact of Maternal Smoking on Auditory Behavior in Infants. ***Pediatric Research. E-PAS2007:617934.7.*** (Published in proceedings of the meeting as an abstract – available for download from meeting website. This was also a poster presentation at the ***Pediatric Academic Society's Meeting*** in Toronto, Canada in 2007)

2. Morris B, Moschenross D, Furneaux H, Stepnowski R, Greene J, Sanders M, and Oncken C. Effect of Maternal smoking on the expression of the mRNA binding of the term placenta. Presented at the ***Society for Maternal Fetal Medicine,*** Dallas Tx, Feb 2008.

3. Hussain, N., Krueger, W., Covault, J., Walsh, S., Kranzler, H., Oncken C. Effects of Prenatal Tobacco Exposure on Gene Expression Profiling in Umbilical Cord Tissue. ***Pediatric Research*** 2008 Aug;64(2):147-53.

4. Liszewski W, Ritner C, Aurigui J, Wong SS, Hussain N, Krueger W, Oncken C, Bernstein HS. Developmental effects of tobacco smoke exposure during human embryonic stem cell differentiation are mediated through the transforming growth factor-β superfamily member, Nodal. ***Differentiation.*** 2012; 83(4):169-78.

How Research Progressed the Field
Our results help contribute the knowledge on how smoking may affect the offspring. Our results provide data for others to better understand the molecular mechanisms. Results also provide a basis for further studies aimed at education and treatment.

New Collaborations
Yes, I was able to work with a number of other scientists in basic science departments within my and at other institutions.

RFP YEAR: 2006

PI: Marc Hansen, Project Title: Role of VPS4B in Development of Trastuzumab-Resistant Breast Cancer

Goals
The goals of the research were to study the mechanism of resistance to chemotherapy through the loss of expression of the VPS4B gene, a component of the endosomal protein degradation pathway. The endosomes are a complex cellular apparatus that is involved in protein degradation. The endosomal protein degradation pathway is the major mechanism for regulating and recycling activated growth factor receptors. When this pathway is disrupted, these activated growth factor receptors continue to stimulate the cell to proliferate and are a factor in tumorigenic stimulation and resistance. We were able to show that breast cancer cells that had lost VPS4B had become resistant to Geldanamycin, and that the mechanism of resistance was due to entrapment of activated growth factor receptors in the endosomal compartment of the cell. We had initially planned to also study resistance to Trastuzumab (Herceptin) to our study but were not able to obtain the compound from the manufacturer.

Key Findings
The major discovery of our research was that loss of expression of VPS4B correlated with loss of function of the endosomal protein degradation pathway. This pathway is critical for a number of functions in the cell including degradation and recycling of activated growth factor receptors and also important in viral infections such as HIV. Loss of function of the endosomal pathway can act in two ways. It stimulates cancer by preventing inactivation of activated growth factor receptors. It also inhibits viral transmission by inhibiting the mechanism by which viruses such as HIV release viral particles from the cell. It also blocks release of extracellular particles known as exosomes, which are an important part of metastasis. The benefit of this research to the citizens of Connecticut is that it is provides a new target for attacking cancers and may be a possible means of attack for preventing viral transmission.

How Research Progressed the Field
We were able to show that loss of VPS4B blocked endosome-mediated protein degradation and increased resistance of the cancer cells to chemotherapeutic targets such as Geldanamycin.

New Collaborations
Yes. We have continued to study a number of discoveries from this work including how VPS4B regulates endosomal function and now exosome signaling, which is an important part of metastasis.

PI: Sven-Eric Jordt, Project Title: Sensory Irritant Receptors in the Pathogenesis of Smoking-Induced Lung Disease

Goals
The goal of our funded research was to examine the role of chemosensory nerve endings in the irritation and inflammation induced by volatile toxicants in tobacco smoke. These irritant chemicals include unsaturated aldehydes such as acrolein (2-propenal) that are highly enriched in tobacco smoke. In humans, sensory neural activation by acrolein in tobacco smoke has been implicated in the pathogenesis of acute lung injury, chronic pulmonary obstructive disease (COPD) and asthma. Smoking-related COPD is the fourth leading cause of death in Connecticut and nationwide. Despite its important role in human tobacco health effects, the molecular targets of acrolein and other unsaturated aldehydes in tobacco smoke were unknown. We hypothesized that acrolein and other unsaturated aldehydes activate sensory neurons in the lung by stimulating Ca2+ influx through the ion channel TRPA1. TRPA1 is exclusively expressed sensory C-fibers known to mediate irritant effects and inflammatory pain. In addition, we found that dissociated sensory neurons from mice deficient in TRPA1 receptors are insensitive to acrolein. Our specific aims were to 1) compare sensory neural responses to acrolein and tobacco smoke in wild-type and TRPA1-deficient mice 2) to elucidate the mechanism of block of TRPA1 3) examine the effects of other noxious irritants on sensory neural activity and sensory neural receptors. These studies were performed in cell culture and in mouse models. We completed research on all specific aims and published data in peer-reviewed journals since 2008.

Key Findings
Smoking-related lung disease is a major cause of morbidity in Connecticut, the United States and worldwide. In recent years, smoking-induced Chronic Obstructive Pulmonary Disease (COPD) was the fourth leading cause of death in women in Connecticut with similar rates in men. The disease process leading to chronic bronchitis and emphysema in COPD is largely unknown. Our funded studies aimed to elucidate the role of the sensory neuronal ion channel, TPRA1, in the etiology of smoking-induced airway disease. We hypothesized that TRPA1 is a major neuronal target for toxic aldehydes in tobacco smoke, initiating cough, airway irritation and inflammation, contributing to chronic remodeling of airway tissue. This hypothesis was based on the discovery of TRPA1 being activated by acrolein, the major reactive unsaturated aldehyde in tobacco smoke, in vitro. Our experiments revealed that: 1. TRPA1-deficient mice show decreased levels of smoking-induced proteases, cytokines and chemokines in the airways and airway-lining fluid 2. TRPA1 is the target for all major smoke aldehydes in dorsal root ganglia neurons. 3. Aldehyde-induced activation of TRPA1 is blocked by the cigarette additive, menthol. 4. TRPA1 protein is expressed in sensory nerve endings lining the airways. Taken together, these findings confirm our initial hypothesis and point to a major role of TRPA1 as a mediator of tobacco smoke-induced irritation, inflammation and, potentially, airway tissue remodeling. Inhibition of TPRA1 by the cigarette additive, menthol, may reduce the acute sensory irritancy of tobacco smoke,

allowing more rapid and deeper inhalation. This effect may reduce the aversive threshold to smoking in beginning smokers, accelerate establishment of nicotine addiction, and promote a more rapid onset of smoking-induced airway and cardiovascular disease.

How Research Progressed the Field
Our research identified a molecular target (TRPA1) for smoke irritants that induces the sensation of irritation and promotes inflammation in the respiratory system. Previously, smoke irritation was considered a non-specific response, with no particular molecular target involved. Small molecules inhibiting this target were subsequently tested and anti-inflammatory action confirmed in animal models.

New Collaborations
Yes, we are currently collaborating with Dr. John Morris in the School of Pharmacy at UConn Storrs on tobacco health effects research. This has been funded by NIH since 2011 through a joint R01 grant and a supplement funded by FDA. Dr. Jordt recently relocated his lab from Yale to Duke University, with the collaboration with Dr. Morris still ongoing through a subcontract from Duke to UConn.

PI: Elizabeth Triche, Project Title: Genetics and Smoking in Pregnancy

Goals
The goal of the research was to examine specific genetic and psychosocial factors associated with biochemically-confirmed smoking cessation among pregnant women who are strongly motivated to quit smoking for the health of their babies. We had initially planned to recruit 450 subjects but were only able to recruit 151 women even with the additional 1-year extension.

Key Findings
Using novel biostatistical methods, we found that none of the psychosocial factors examined were strongly associated with smoking cessation. We have begun to examine the genetic factors, but may be limited by the sample size and the limited number of variants we genotyped.

How Research Progressed the Field
I believe we have shown that differences in smoking cessation cannot be explained based on psychosocial factors, suggesting that genetic factors play a role.

New Collaborations
I had begun some new collaborations at the time of the grant, but those collaborations have not gone forward because I haven't been funded again to look at smoking cessation. As I am analyzing the data, I have developed a collaboration with a biostatistics colleague, Dr. Andres Houseman, who was at Brown but is now at Oregon State. This is an ongoing collaboration.

PI: Joanne Weidhaas, Project Title: Analysis of miRNA Mutations in Lung Cancer

Goals
We discovered, and validated, a new type of mutation in KRAS. Our finding led to the

launch of a new field in science, start a non-profit and a for-profit company.

Key Findings
The KRAS-variant.

How Research Progressed the Field
It is the first example of this type of mutation.

New Collaborations
On manuscripts, new collaborators from Clinical Science Institute, National University of Ireland and Maastricht University Medical Center, the Netherlands.

PI: Dianqing Wu, Project Title: Role of Aberrant Canonical Wnt Signaling in Colon Cancer Formation

Goals
Colorectal cancer is one of the leading causes of morbidity and mortality in the world and the state, and smoking is a major factor that influences its occurrence. Previous studies have shown that aberrant Wnt signaling activity plays a key role in the formation of this cancer. In this research proposal, we plan to test small Wnt antagonistic compounds that we have previously identified for their ability to block the tumor formation. Our proposed work will provide not only new insights into the pathogenic basis for the formation of this cancer, but also potential therapeutic targets and agents for treating this disease.

Key Findings
In this study we tested and found that small molecule Wnt inhibitors suppressed tumor formation in a mouse colorectal tumor model. The significance and potential benefits of our work are clearly evident as colorectal cancer is one of the major killers in the world, and there is no exception for the people of this state. Colorectal cancers rank the third highest incident rates for both males and females in Connecticut based on the data up to 1996. Our proposed work will not only provide new insights into the pathogenic mechanisms for this cancer, but also potential therapeutic targets and agents.

How Research Progressed the Field
Our work has demonstrated that Wnt inhibitors are potential therapeutics for treating colon cancers and thus broke a new ground for our understanding of colon cancer formation and is also of important translational potential.

New Collaborations
Ya Ha, Department of Pharmacology, Yale University |
Titus Bogon, Department of Pharmacology, Yale University
Zihai Li, UConn Health Center (now at Medical University of South Carolina)

RFP YEAR: 2007

PI: Lance Bauer, Project Title: The Effects of Tobacco on Brain Structure and Function are Amplified by Genotype

Goals
The general goal of our project was to provide information about functional brain abnormalities in middle-aged adults at increased risk for cerebrovascular disease. We recruited 68 adults varying in environmental risk as defined by the presence versus absence of a history of heavy tobacco use. Each of these groups was further stratified by genetic risk, i.e., ApoE-ε4, Factor XIII Val34Leu, and Paraoxonase-1 Gln192Arg genotypes. We recorded evoked electroencephalographic responses, magnetic resonance images, and performance

on tests of cognitive function. The analyses primarily examined the interactive effects of smoking and genotype. The general hypothesis stated that smoking alone is insufficient to cause detectable or significant neurophysiological impairment. Instead, smoking and a genetic risk factor for impairment is necessary. The hypothesis was supported by some of the results. We achieved our goal—the study was completed.

Key Findings
The results were disappointing because the major hypothesis about smoking was not supported. It is possible that the patients were simply too variable in other characteristics. We attempted to control for this background variability but the sample size might not have been adequate. Eventually, we were able to derive a publishable result from an analysis of a secondary question. Those results were reported in the following article: Patel, K.T., Stevens, M.C., Pearlson, G.D., Winkler, A., Hawkins, K., Skudlarski, P., Bauer, L.O. (2013). Default mode network and white matter integrity in healthy middle aged ApoE4 carriers. Brain Imaging and Behavior 7:60-67.

How Research Progressed the Field
Sometimes the best and most interesting hypotheses are not confirmed by the results. In our sample, the hypothesized adverse effects of smoking, and its possible interactions with genetic risk, did not appear.

New Collaborations
Yes. We have been meeting with researchers at another Connecticut hospital around the planning of a different project.

PI: David Gregorio, Project Title: Accuracy/Adequacy of Tobacco Use Data in Cancer Research

Goals
Our understanding of therapeutic effectiveness, quality of life, health service utilization, and disease prognosis of persons with cancer may be compromised by a reluctance among oncologists and, in particular, clinical trialists to systematically monitor tobacco's effect(s) on patients undergoing adjuvant treatment. A cross-sectional study of interventional trials cited on ClinicalTrials.gov was undertaken to determine whether Connecticut-based studies of breast, prostate, or colorectal cancer chemotherapy (N = 68) measured tobacco use by trial participants. Information pertaining to 46 trials (68%) was collected and report in Gregorio DI* Hollenbeck M, Samociuk, Who's assessing tobacco use in cancer clinical trials? Nicotine and Tobacco Research, 2009;11 (11):1354-8.

Key Findings
Only 3 trials (7%) reported routine collection of tobacco use information at baseline and no trial reported monitoring tobacco use during treatment follow-up. None of the 3 trials collecting tobacco data reported using exposure information in analysis of treatment effects. Survey respondents suggested that uncertainty about the relevance of tobacco exposure to therapeutic efficacy, ambivalence about how to incorporate such data into analyses, insufficient resources for collecting such information, and uncertainty about the validity of assessment methods might be reasons why tobacco use is not routinely assessed.

How Research Progressed the Field
Our analysis was the first empirical investigation of attention within clinical trial protocols to the measurement of tobacco use among patients enrolled in treatment studies. To the extent that cancer patients who smoke are unstudied participants in interventional research, therapeutic effectiveness and treatment-related morbidities remain insufficiently understood, possibly hindering the care of smokers and nonsmokers alike. Overlooking tobacco's effects on cardiovascular, renal, pulmonary, and other system functioning, or the diminished quality of life of smokers, may lead clinical trialists to overstate adverse consequences of treatment and/or fail to report measurable treatment benefits within subgroups not exposed to tobacco.

New Collaborations
No.

PI: Yingqun Huang, Project Title: Development of a Novel Tumor-Specific siRNA Delivery System for Cancer Gene Therapy

Goals
My laboratory has developed a strategy to tether small interfering RNAs (siRNAs) to ligand-conjugated oligodeoxynucleotides. This complex is up taken by cells upon direct application and the siRNA cargo is available for targeted gene silencing. The goal of the research was to test whether the strategy could be used to treat cancer. As a proof of principle, we used the folate receptor that is highly expressed in diverse human tumor cells for delivery of siRNAs. We demonstrated that this strategy was effective on cancer cells derived from both human breast and larynx tumors. The findings have led to a publication in a high-profile journal (Zhang K et al, Receptor-mediated delivery of siRNAs by tethered nucleic acid base-paired interactions. *RNA*, 2008, 14:577-583). Importantly, the studies severed as a foundation for our serendipitous discovery showing that two stem cell factors, Lin28 and Oct4, play important roles in cancer stem cells (Peng S et al, Pluripotency factors Lin28 and Oct4 identify a subpopulation of stem cell-like cells in ovarian cancer. *Oncogene,* 2010, 29:2153-2159).

Key Findings
We found that the folate-tethered siRNAs could be specifically targeted to cancer cells that express high levels of folator receptors on their surface. The delivered siRNAs could enter the cell and silence the expression of genes targeted by the designed siRNAs. We also found that two stem cell factors, Lin28 and Oct4, were expressed in a subset of human ovarian cancer stem cells. Together, our findings provide the foundation for developing novel strategies for diagnosing and treating human ovarian cancer, which would be beneficial to the citizens and government of the State of Connecticut.

How Research Progressed the Field
Our findings, especially those described in our 2010 *Oncogene* paper, have generated great impact on the field of cancer stem cell research. This is evident that the paper has been cited by at least 112 articles so far.

New Collaborations
Our research described above has led to multiple collaborative projects involving research teams from both Yale and institutions outside. A current ongoing-project concerns the molecular mechanism of a long noncoding RNA in the pathogenesis of human ovarian and endometrial cancers.

PI: John Peluso, Project Title: PGRMC1 siRNA as an Adjunct Therapy with Cisplatin to Kill Human Ovarian Cancer Cells in Vitro and In Vivo

Goals
The overall goal was to assess the role of the protein, progesterone receptor membrane component 1 (PGRMC1), on the ability of ovarian human cancer cells to form tumors in nude mice. This work was completed and revealed that PGRMC1 was an important factor in determining the formation and growth of tumors in mice. Specifically, human ovarian cancer cells that are deplete in PGRMC1 had a significant decrease in:

- the number of mice that formed tumors
- the number of tumors that formed in those mice which did form tumors
- the size of the tumors which formed.

Key Findings
Given that PGRMC1 plays an important role in the formation of tumors, it is likely that PGRMC1 could be targeted for therapeutic agents, which could be used to treat ovarian cancers. Subsequent work has identified sites within PGRMC1 that attenuate its action.

How Research Progressed the Field
Our work was the initial study on PGRMC1 and cancer. Subsequent studies by our group as well as other labs have shown findings in uterine, breast and lung cancer, further demonstrating the importance of PGRMC1 in various cancers.

New Collaborations
Yes, we are presently collaborating with our pathology department and Dr. Jim Pru of Washington State University on PGRMC1's actions in uterine and breast cancer.

PI: Jennifer Tirnauer, Project Title: Mitotic Spindle Positioning in Intestinal Cancer

Goals
The goal of the research was to understand how cells divide abnormally in colon cancer. This understanding helps us to figure out how the tumors grow, and what parts of the cell could be targeted for therapy. We achieved our goals and learned some important information about how the cells lose their alignment when they divide.

Key Findings
We found that colon cancer cells divide out of alignment, and the major gene responsible for colon cancer is defective in the cells that divide abnormally. We also got suggestions of other genes that do the same thing.

How Research Progressed the Field
This helped scientists understand which genes determine the alignment of cells as they divided.

New Collaborations
From the UConn Health Center: Dr. Wu from Pathology; Dr. Rosenberg from Center for Molecular Medicine; and from UConn/Storrs, Dr. O'Neill.

PI: Quing Zhu, Project Title: Hybrid Scintigraphy/OCT Intraoperative Probe for Ovarian Cancer Detection and Surgical Intervention

Goals
Ovarian cancer has the highest mortality of all the gynecologic cancers and the overall survival is poor due to the late stage of diagnosis, the development of resistance to chemotherapy and the apparent persistence of an adult stem cell population that can stay quiescent for a variable period of time. This proposal addresses the stage of diagnosis and proposes development of a novel combination of imaging technology to accomplish earlier detection of ovarian cancer that would have the potential for improving survival from this highly fatal cancer. Optical coherence tomography (OCT) is an imaging technique that can provide subsurface high-resolution images on the order of 2 to 10 microns. At present, OCT provides structural information and is not capable of screening cancers at early stages with cellular-level metabolism changes. Nuclear intraoperative imaging has the significant advantage of detecting localized lesions labeled by highly specific radioactive tracers. Radiotracer uptake is associated with the functional activity of pre-cancers and early-stage cancers and the positron signal can be detected by a beta probe. Combining these technologies in one intraoperative probe, however, could leverage the advantages of both technologies to provide a powerful tool for identifying and characterizing both the structure and function of pre-invasive and early-stage cancers which would offer optimal survival for those women destined to develop ovarian cancer. We have proposed a novel hybrid endoscope-based device, which integrates high-resolution OCT imaging and high-contrast radioactive tracer detection. The developed probe can be used intra-operatively at the time of prophylactic oophorectomy or surgery for suspected ovarian cancer and fitted for use in a 5 mm laparoscopy port. We have achieved our goals and the device has validated ex vivo with ovaries from 10 patients.

Key Findings
A novel hybrid intraoperative probe has been developed and evaluated for its potential role in detecting and characterizing ovarian tissue. The hybrid intraoperative dual-modality device consists of multiple scintillating fibers and an optical coherence tomography imaging probe for simultaneously mapping the local activities of 18F-FDG uptake and imaging of local morphological changes of the ovary. Ten patients were recruited to the study and a total of 18 normal, abnormal and malignant ovaries were evaluated ex-vivo using this

device. Positron count rates of 7.5/8.8-fold higher were found between malignant and abnormal/normal ovaries. OCT imaging of malignant and abnormal ovaries revealed many detailed morphologic features that could be potentially valuable for evaluating local regions with high metabolic activities and detecting early malignant changes in the ovary. These initial results have demonstrated that our novel hybrid imager has great potential for ovarian cancer detection and characterization during minimally invasive endoscopic procedures.

How Research Progressed the Field
This device is the first hybrid probe that is capable of measuring tumor morphology and tumor glucose metabolism simultaneously.
New Collaborations
Yes. This work has resulted in an ongoing collaboration with a surgeon at UCHC.

RFP YEAR: 2008

PI: Richard Everson, Project Title: Functional Molecular Classification of BRCA Gene Mutations

Goals
The goal of the project is to develop a method for predicting the clinical significance of BRCA1 and BRCA2 gene sequence variants of uncertain significance by gene expression analysis of existing formalin-fixed, paraffin-embedded (FFPE) breast cancer specimens from known affected carriers of BRCA1 and BRCA2 mutations. The project is designed to be a model for interpreting the biological impact of DNA sequence changes by high-throughput functional assays for gene expression, which could be applied in many clinical settings to understand the functional significance of variations in DNA sequence. Specific objectives were to use a recently developed, highly-multiplexed genomic assay (called DASL) to test tumors (clinical specimens) from women with VUBS (sequence Variant of Unknown Biological Significance) to determine whether their BRCA1/BRCA2 alterations are deleterious or non-functional. The assay could be developed into commercial procedures for supplementing sequencing in the evaluation of women with BRCA1/ BRCA2 VUBS. The classification scheme will be applied to tumors from women with germ line BRCA1/2 VUBS, classifying them according to whether they do not have gene expression profiles characteristic for deleterious BRCA1 or BRCA2. Genes that are important for these classifications may be developed into gene panels that could be analyzed by other procedures such as rt-PCR, and may be developed into commercial procedures for supplementing sequencing in the evaluation of women with BRCA1/2 VUBS.

Key Findings
The ability to use FFPE tissues will also make it possible to dramatically enhance the research programs available in the Connecticut Tumor Registry (CTR), by coupling its vast archive of clinical and follow-up data with comprehensive molecular analysis of FFPE tissues from hospitals within the state. We believe that the sequence data alone are not sufficient to understand the biological significance of germ line variation and its role as a determinant of somatic impact, but that progress will be made by coupling the functional data from gene expression assay with sequence data including additional mutations in DNA. The recent extraordinarily rapid progress in technology for analyzing FFPE

tissues coupled the CTR's vast information resources will provide a new paradigm for understanding and controlling cancer risk and neoplastic progression.

How Research Progressed the Field
The support provided by this grant enabled our research program to develop a pipeline of clinical data, specimens, and rapidly developing state-of-the-art analysis. Developing these procedures at UConn, which did not have a history of similar research, proved arduous but has made our program competitive at a national level.
New Collaborations
New yes; not currently ongoing but hopefully will set the groundwork for future work.

PI: Marc Hansen, Project Title: Resistance to Chemotherapeutic Approaches Based on Targeting the erbB2 Pathway as Acquired through Homozygous Inactivating Mutations in VPS4A or VPS4B

Goals
The initial goal was to understand the role of VPS4B in regulating the endosomal protein degradation pathway and its role in developing chemoresistance in cancer. The project developed into a study of how VPS4B regulates extracellular vesicles (exosomes) which are critical in signaling between cancer cells and the cells in the microenvironment during tumorigenesis and metastasis. We have made important strides in both the chemoresistance and the extracellular signaling aspects of this research.

Key Findings
We were able to demonstrate that regulation of endosomes is an important component of the mechanism of chemoresistance. We were also able to demonstrate that alterations in VPS4B affected the ability of the cell to release exosomes, which are small nanoparticles which contain proteins and RNAs, which are taken up by cells in the surrounding environment as cause those cells to alter expression to make the environment more favorable to the cancer cells. This is an important component of metastasis.

How Research Progressed the Field
We have shown that exosome signaling, regulated by VPS4B, can alter the microenvironment of the cancer cell to make the normal cells change to be a more favorable environment for the cancer cells.

New Collaborations
Yes, we have developed collaborations with people at UConn Storrs as well as outside Connecticut.

PI: Erica Herzog, Project Title: PKR Mediated Effects on Alveolar Progenitor Biology in COPD

Goals
Goals of this proposal included determining the contribution of anti viral innate immune signaling pathways to injury and repair processes in a mouse model of COPD.

Key Findings

We have found that injury and repair are regulated via different facets of the antiviral innate immune response. This finding has led to further investigation in how we can develop lung protective strategies for patients with COPD who develop viral infections.

How Research Progressed the Field
Our studies revealed an unexpected role for certain antiviral pathways in the regulation of lung progenitor cell function.

New Collaborations
Yes *[no specific collaborations noted]*

PI: Zhiwei Hu, Project Title: Targeting Tumor Blood Vessels for Immunotherapy and Photodynamic Therapy of Human Lung Cancer

Goals
The major goals of this project were to test the effect and safety of novel tumor blood vessel-targeting ICON molecules for immunotherapy and photodynamic therapy of human lung cancer, as a model example of tobacco-related cancers, in vitro in tissue culture and in vivo in preclinical mouse models. We achieved the goals after successful completion of the proposed research.

Key Findings
The key findings from our research are that ICON immunotherapy and fVII-targeted photodynamic therapy are effective and safe in the treatment of lung cancer in preclinical studies.

The benefits our research provides to the citizens and government of the State of Connecticut would be that cancer patients with lung cancer in the State of Connecticut could eventually benefit from the novel therapeutics, which were tested in the studies supported by DPH Contract 2009-0096, in future clinical trials at the Yale Cancer Center and Yale Smilow Cancer Hospital.

How Research Progressed the Field
ICON immunotherapy and fVII-targeted photodynamic therapy are novel therapeutics with an ability to target and eradicate tumor cells and tumor neovasculature, the two major tumor compartments, thus we expect that they could achieve better therapeutic effect and outcome for cancer therapy than the current therapeutic agents, which are designed for targeting either tumor cells or tumor neovasculature alone.

New Collaborations
Yes. Although I left Yale in November 2012 and joined the faculty of The Ohio State University, I am still closely and actively collaborating with my colleagues in the Yale Department of Obstetrics, Gynecology and Reproductive Sciences and the Yale Cancer Center on translational research projects for the treatment of malignant cancer and non-malignant gynecological diseases.

PI: Laijun Lai, Project Title: Antitumor Activity Included by a Novel Hybrid Cytokine

Goals
The project was designed to examine the anti-cancer activity on a variety of cancer cells of a reagent that we developed and to study the mechanisms by which the reagent inhibits the growth of leukemic cells. We have achieved our goals.

Key Findings
We found that the reagent could inhibit some cancer cells in vitro, and understood some of the mechanisms by which the reagent inhibits the growth of leukemic cells. These studies provided the basis for the potential applications of the reagent in patients.
How Research Progressed the Field
Our studies led to new sight into the signal molecules that regulate the growth of cancer cells, which have potential to be used in designing new protocols to inhibit cancer cells.

New Collaborations
No

PI: David Rimm, Project Title: Development of a Protein-based Test to Determine which Patients with Early Stage Non-small Cell Lung Cancer are Cured by Surgery Alone

Goals
We proposed the construction of a predictive model to determine which patients with low stage lung cancer will progress and which are cured by surgery. We were successful in the first population, but need more validation.

Key Findings
The predictive model has not yet been commercialized, although we are working toward that goal. If and when it is commercialized, it could benefit patients with lung cancer in Connecticut.

How Research Progressed the Field
A prognostic model was developed, but not yet commercialized.

New Collaborations
Yes, we collaborated with investigators in Greece and at MD Anderson for validation sets. We are also starting a new collaboration with a corporate entity that could commercialize the test if it validates

PI: Lixia Yue, Project Title: Mg^{2+}-Permeable Channel Kinases in Heart Disease

Goals
The major goal of this project is to identify potential therapeutic targets for heart diseases. Heart disease is the number one cause of death in the United States and in Connecticut, and the number one cause of heart disease is smoking. Smoking is also a high risk factor for magnesium deficiency. We have recently demonstrated that TRPM6 and TRPM7 are Mg2+- and Ca2+-permeable channel kinases. Dysfunction of TRPM6 causes magnesium deficiency, a high risk factor for heart disease. TRPM7 has also been shown to play a role in Mg2+ homeostasis. In this research proposal, we will investigate whether TRPM6 and TRPM7 may

serve as novel therapeutic targets for magnesium deficiency associated heart disease.

Key Findings
Found that nicotine differentially regulates TRPM6 and TRPM7. It inhibits TRPM6 but enhances TRPM7. Since TRPM6 mutation causes Magnesium deficiency, which is associated with a variety of diseases including heart disease, our finding suggest that TRPM^ can be a potential therapeutic target.

How Research Progressed the Field
Our findings are novel in the research field.

New Collaborations
N/A

RFP YEAR: 2009

PI: Paul Epstein, Project Title: Inhibition of Breast Cancer Metastasis by Activation of cAMP Signaling

Goals
This aim of this proposal was to test the concept that cyclic nucleotide phosphodiesterases (PDEs) are potential therapeutic targets for treatment of non-estrogen dependent tumors, by inhibiting distal metastatic disease. The application involved three specific aims: 1) To analyze the expression of different forms of PDE in breast cancer cells, 2) To examine the effects of selective inhibition of these expressed forms of PDE on breast cancer cell proliferation, migration and invasion, and 3) To evaluate the effective PDE inhibitors on tumorigenesis, angiogenesis and metastasis in vivo. The goals of the proposal were achieved in that we 1) analyzed the full expression profiles of all 21 PDE genes in breast cancer cells, 2) showed that inhibition of the expressed PDEs inhibited breast cancer cell migration and 3) developed assays for testing these inhibitors in vivo for effects on breast cancer metastasis.

Key Findings
We investigated cyclic nucleotide phosphodiesterases (PDEs) in breast cancer cells as potential targets for inhibiting breast cancer motility and migration. PDEs regulate the levels in cells of the signaling molecule, cyclic AMP (cAMP) which, among other things, regulates cell movement. PDEs are encoded by 21 different genes, many of which are selectively expressed in different tissues and subcellular compartments. We analyzed the full expression profile of all 21 PDE genes at both the mRNA and protein levels in 5 different estrogen receptor-positive and estrogen receptor-negative breast cancer cell lines and in 8 patients' breast cancer tissues. We then tested inhibitors of the PDE forms expressed in these tissues for their ability to inhibit breast cancer cell migration using two different assays, a transwell assay and a wound healing assay. Inhibition of PDEs inhibited cell migration as measured by both of these assays. Finally, we set up in vivo models of breast cancer cell migration in mice in order to study the effects of these inhibitors on metastasis to the lungs. The results of our study indicate that PDEs may be valuable therapeutic targets for inhibition of breast cancer metastasis. Inasmuch as Connecticut has one of the highest rates of breast cancer [in the United States], this research provides great benefit to the citizens and government of the state of Connecticut by uncovering a novel therapeutic strategy for

treating this disease.

How Research Progressed the Field
Our research provided the first full expression analysis of PDEs in breast cancer and provided data indicating their importance as potential therapeutic targets for this disease.

New Collaborations
Yes, I began collaborating with other breast cancer researchers at my institution and have continued these collaborations ever since.

PI: Christopher Heinen, Project Title: A Novel Animal Model to Study Smoking-Associated Damage in Stem Cells

Goals
The immediate goal of this application was to further our understanding of the relationship between tobacco smoke and mismatch repair (MMR)-defective colon cancer. A fundamental question was how does loss of MMR function in stem cells promote tumorigenesis and how does smoking impinge on this process? We hypothesized that a stem cell with defective MMR will lose a protective DNA damage response and gain a growth and/or survival advantage over neighboring stem cells when challenged with mutagens such as found in cigarette smoke. We used planaria as a model organism and sought to determine whether we could eliminate MMR function in planaria and whether this provided a survival advantage to adult stem cells, termed neoblasts, in these animals when treated with a DNA damaging agent. We successfully showed that we could use RNA-interference to significantly knockdown the levels of the MMR gene products and that this loss of MMR resulted in increased survival when animals were injected with the DNA damaging agent MNNG. Furthermore, we demonstrated that this was associated with an increased survival of adult stem cells in the MMR-defective animals. Overall, we accomplished all the goals of the proposal.

Key Findings
The main emphasis of the proposal is to examine the effects of loss of MMR in animals treated with a DNA damaging agent that produces lesions similar to those caused by tobacco smoke. The successful experiments as summarized above provide insight into the role of the MMR pathway in protecting adult stem cells from mutagens. These results may help explain why smokers are at an increased risk of developing MMR-defective colorectal cancer. Our results provide important preclinical data that can guide future studies on the early changes associated with smoking-related cancers. By understanding the molecular mechanism by which these smoking-associated cancers arise, we will be able to improve early-stage cancer detection and prevention for the citizens of Connecticut.

How Research Progressed the Field
Our research helped move the field of MMR and cancer forward by establishing an important role for the MMR pathway in the elimination of damaged adult stem cells, an important protective response against tumor genesis.

New Collaborations
The collaboration that existed during the studies covered by the grant is no longer ongoing as we have moved our research into new model systems. However, new collaborations have

resulted.

PI: Bruce Liang, Project Title: Circulating Caspase-3 p17 Peptide and Acute STEMI

Goals
The goals of the research were to develop an ELISA assay that can quantify the serum levels of an apoptotic marker, named caspase-3. Caspase-3 is an end-effector of cell death by apoptosis. When caspase-3 is activated, it is cleaved into a smaller fragment called p17 peptide. Once the assay is adapted to measure p17 in blood of patients with heart failure, the goal is then to measure it in patients with acutely decompensated heart failure and during recovery. Both goals were achieved in that we were able to quantify the serum level of p17 in humans, first tested in healthy volunteers and then in patients with heart failure. The preliminary data suggest that patients with acute heart failure had a higher level of p17 than when they are in a stable condition.

Key Findings
The key findings are as follows. First, we validated the detection of p17 peptide in the human HeLa cells that were induced to undergo apoptosis. The degree of apoptosis was directly reflected in the amount of p17 released from the damaged cells to the media bathing the HeLa cells. The HeLa cell study provided a proof of concept that the smaller cleaved p17 peptide is released into the extracellular space, suggesting that p17 can be detected in blood from apoptotic tissue. Second, the assay quantified the amount of p17 in serum of healthy human volunteers. Third, the assay was successfully applied to quantify p17 levels in serum of patients with heart failure. Finally, preliminary data suggest that patients with acute decompensated heart failure have a higher level of p17 than during stable condition. Although not originally proposed in the grant, we were able to show that p17 levels rose and fell during acute myocardial infarction in patients that received reperfusion therapy. The peak level of p17 correlated with that of traditional biomarker troponin I and CK-MB.

How Research Progressed the Field
The research showed for the first time that apoptosis occurs in humans who suffered from acute myocardial infarction. The ELISA assay to quantify apoptosis opens up the possibility of detecting tissue apoptosis by measuring p17 levels in the blood, paving the way for a simple blood test in humans.

New Collaborations
Yes, the research led to new collaboration with investigators at UMass and the US Army research. The new collaboration is testing the ability of p17 level as a marker of tissue injury arising from skeletal muscle.

PI: Bruce Mayer, Project Title: Testing the Feasibility and Usefulness of a New Molecular Test, SH2 Profiling (Molecular Diagnostic Assay)

Goals
The goal was to test a new method of classifying lung cancers based on a particular chemical modification, tyrosine phosphorylation. The project is ongoing but continues to look promising. [Note: The PI terminated the DPH grant shortly after it started to accept a

overlapping federal grant.]

Key Findings
The new classification method holds promise and is being further developed. In the long run such tests will help physicians choose the most effective therapy for the individual tumor based on its individual properties.

How Research Progressed the Field
New methods to classify tumors and predict clinical outcomes such as response to specific drugs are becoming increasingly important for cancer treatment. This study provided pilot data for a novel method not being explored elsewhere.

New Collaborations
No, but it allowed ongoing collaborations to continue and set the stage for new collaborations that have since been initiated.

PI: Daniel Rosenberg, Project Title: Identifying Clinical and Molecular Markers of Colon Cancer Risk in Smokers

Goals
We set out to determine whether smoking cigarettes may influence risk of colon cancer. Our research has been instrumental in making a very important and novel finding regarding smoking status, NSAID intake and risk of early neoplasia (adenomas). The work that details this latest finding is under review at the Journal of the National Cancer Institute (JNCI). In addition, based on instrumentation obtained from funding support from my previous DPH tobacco grant, we published a paper in 2013 in the journal Proteomics detailing the post translation modifications that occur within a very important signaling pathway in the colons of normal subjects, the ERK pathway. This paper has been highly cited. We also recently published a paper in Molecular Cancer Research, again using samples from the DPH study population that describes the set of cancer related mutations that occur in very early hyperplastic colon lesions in subjects at varying risk of cancer, including APC, KRAS, BRAF and EGFR. This work appeared in press within the past two weeks. A much larger study that will provide details on molecular epidemiology of this study population is under preparation and we expect to submit this manuscript by the middle of the summer. We also presented several abstracts at the annual AACR meeting that was held in San Diego, CA. David Drew's abstract detailing the mutational analyses was selected for an award at the meeting (outstanding translational science award).

Key Findings
Please see above; we have completed the most comprehensive screening analyses of colon on 185 residents of the State of Connecticut. This data has been invaluable in understanding the very earliest changes that occur within the human colon in subjects at varying risk of cancer. We have removed many early lesions from normal subjects that we believe may harbor significant genetic changes that would have placed their colons at increased risk of cancer down the road. The food intake data, blood cytokine analysis etc., are not even completed yet and once we have developed this additional large set of data, we will be able to assign cancer risk across large populations of people.
How Research Progressed the Field

We have developed highly novel new methodologies for working with extremely small colon biopsy specimens. We can now perform virtual western blots on laser or UV/IR captured colonocytes (as few as 100 cells), as well as detailed proteomic analysis of these specimens, allowing the analysis of post translational modifications (ERK signaling) (Proteomics, 2013). We also can now laser capture ACF samples and perform genome-wide Sequenom analysis on up to 124 somatic mutation targets (initial results just published in Molecular Cancer Research, 2014). Our studies suggest that small, hyper plastic ACF that form in the proximal colon of normal subjects may harbor a complex set of molecular defects that may provide new insights into early cancer pathogenesis and the contribution of risk factors to a field defect in the colon. Our newest unpublished findings in collaboration with Dr. Gerd Pfeifer at City of Hope have uncovered a large set of epigenetic changes that we believe may contribute to driving early neoplasia. This work has just begun and the first set of epigenetic data suggests very interested alterations to dozens of early developmental genes. Now we can begin to assess whether diet and environmental factors (e.g., smoking, obesity) may play a role in the epigenetic changes.

New Collaborations
Yes, this is absolutely 100% correct! My work with Dr. Gerd Pfeifer at the City of Hope has uncovered novel new epigenetic changes within very early preneoplasia in the human colon that we believe may provide new insights into how cancer risk may be modified. This first set of 20 human samples was recently completed and we are now engaged in bioinformatics analysis of the genome-wide data. Additionally, this project has enabled us to begin a study with Dr. Craig Nelson (Storrs) to develop methods to perform single cell, genome-wide transcriptome analysis on human biopsies. An NIH grant was recently submitted.

PI: Beth (Parker) Taylor, Project Title: Does Smoking Cessation Restore Vascular Function in Chronic Smokers?

Goals
The proposal aimed to assess brachial artery endothelial and smooth muscle function in approximately 75 chronic smokers (> 10 years of continuous smoking). A small sample of healthy subjects (n=10) was studied to provide a control comparison at baseline. Following baseline measurements, smokers entered a structured ten-week smoking cessation program conducted at Hartford Hospital. The goal was to then repeat measurements in approximately 35-40 smokers who ceased smoking (determined by weekly self-reports and verified with carbon monoxide measurements as well as pre/post study serum cotinine measurements). At the conclusion of the study, 96 subjects were screened and enrolled in the Smoking Cessation study. 25 subjects were either disqualified or dropped out of the study due to inability to meet the smoking cessation commitment associated with the study or changes in personal circumstances that preclude participation in the study. Accordingly, 71 subjects successfully completed "pre-testing" requirements. Of the 71 subjects, we successfully post tested and completed 31 smokers and 15 controls. We closed recruitment and testing in May 2011 because we had met the goals of the study.

Key Findings
We are still analyzing final endothelial function data from the study as each study takes approximately a day to analyze. At baseline, smokers exhibited blunted endothelial function as measured by flow-mediated dilation and higher oxidative stress. In addition, preliminary

data analysis indicates that quitting smoking did not evoke large changes in any measure of cardiovascular or vascular health in the smoking population. This suggests that the changes on vascular function in smokers are not just due to oxidative damage and thus are not as easily reversed. Instead they may reflect structural changes in vascular parameters that may necessitate additional health interventions to restore function, such as physical activity and diet modification. Therefore, our results to date indicate that successful smoking cessation interventions may also include lifestyle counseling, education and diet/physical activity modification so that smokers who successfully quit also improve parameters of cardiovascular and vascular health.

How Research Progressed the Field
By studying various markers of vascular function—endothelial function, smooth muscle dilation, arterial stiffness, and oxidative stress—as well as general cardiovascular risk factors in smokers vs health controls before and after smoking cessation, we have been able to investigate whether smoking cessation restores these parameters of vascular health or whether alternative interventions should be paired with smoking cessation programs to optimize health and reduce cardiovascular disease risk.

New Collaborations
Yes, due to my research I partnered with Dr. Ellen Dornelas (a behavioral psychologist at Hartford Hospital) to run the smoking cessation intervention. Dr. Dornelas now works in the Cancer Center and I have started a new line of inquiry with her looking at vascular function after chemotherapy in cancer survivors. In addition, I consulted with Dr. Rich Bruno on his DPH biomedical grant on a similar line of research and since have collaborated with him on the resultant publication.

PI: Wei Sun, Project Title: Studying the Biomechanics of Minimally Invasive Aortic Valve Replacement to Elucidate the Underlying Device Failure Mechanism

Goals
Our goal was to study the biomechanical interaction between calcified aortic valve and transcatheter aortic valve replacement device. Such transcatheter valves were not approved in the United States at the time of funding; we were the first group that used clinical patient CT scans to reconstruct patient-specific aortic root and simulated such biomechanical interactions. We successfully completed the project and generated a substantial amount of preliminary data, which allowed us to secure additional funding from NIH to continue this research.

Key Findings
We have developed the computational techniques that can predict the device deployment pre-operatively. This capability allows the cardiologists at hospitals to virtually visualize the device deployment process in computer. By that, clinical adverse events can be avoided pre-operatively for high-risk patients. Currently, we have applied this technique at a local hospital at Connecticut. We have prospectively predicted several clinical cases with success. The project is ongoing and is supported by NIH.

How Research Progressed the Field

With more and more valve patients being treated with the transcatheter valves, our research results will be applied to more patients. We are leading this effort in the United States in using computational methods to predict and thus, avoid clinical adverse events in this procedure.

New Collaborations
Yes, we have collaborations now with Columbia University Medical School, Emory Hospital and Yale School of Medicine.

RFP YEAR: 2010

PI: Richard Bruno, Project Title: Cardioprotective Synergy of Smoking Cessation and gamma-Tocopherol in Restoring Vascular Endothelial Function

Goals
The central goal of this application is to conduct an intervention study that aims to reduce cardiovascular disease risk by defining the mechanisms by which smoking cessation and gamma-tocopherol (γ-T) restore vascular function. We successfully demonstrated that vitamin E supplementation (provided as γ-T) concurrently with smoking cessation (by "cold turkey") additively improved the restoration of vascular function compared to smoking cessation alone. Separate studies examining γ-T in combination with nicotine-replacement therapy (NRT) as the mode of smoking cessation showed that NRT with γ-T, but not NRT alone, increased vascular function.

Key Findings
The key finding from our study is that smoking cessation is effective in restoring vascular health, but the benefits are greater when smoking cessation is accompanied by dietary γ-T supplementation, which better reduces pro-inflammatory responses that are known to impair vascular homeostasis.

How Research Progressed the Field
Our study provides proof-of-concept that γ-T is an important mediator of vascular health. These findings will therefore serve as the basis for more detailed mechanistic studies in rodent models that will better our understanding of the vasoprotective effects of γ-T.

New Collaborations
New collaborations were established at the University of Utah, University of Connecticut, and Linus Pauling Institute at Oregon State University.

PI: Kimberly Dodge-Kafka, Project Title: A Novel Signaling Complex for the Treatment of Heart Failure

Goals
Previous work has shown that the sustained activity of the protein kinase PKC in the cardiac myocyte results in the increased phosphorylation of targets found at the sarcoplasmic reticulum, altered calcium dynamics, and a change in cardiac contractility. In our grant, we proposed to isolate the scaffolding protein that localizes PKC to the sarcoplasmic reticulum and develop compounds to disrupt targeting, thereby potentially alleviating the PKC-

mediated disease phenotype. We determined the scaffold that localized the kinase was a protein named AKAP7. We determined which isoforms of the kinase bound to AKAP7 and the resulting affect on PKC activity induced by binding to the AKAP. This work was published in 2012. We tried to map the PKC binding domain by several proven methods, but were unable to develop reagents to disrupt association. However, while undertaking these experiments, we discovered a novel component of PKC binding to the AKAP that had not previously been appreciated. Important, binding of the kinase to AKAP7 insulated the kinase from inhibition from pharmacological inhibition. This finding would greatly impact the use of these common drugs for the treatment of heart disease, as their efficacies would be significantly reduced when PKC is bound to the scaffold. These observations influenced us to develop a computational model of kinase signaling and a collaboration with a well-respected bioengineer at The University of Virginia. Our work was published in 2014.

Key Findings
Completion of this work provided two key findings. First, we identified the scaffolding protein that bridged PKC to its place of action, the sarcoplasmic reticulum. However, because we were unable to make reagents to disrupt this association, we were not able to develop novel tools to alleviate the effect of the kinase at the sarcoplasmic reticulum and alleviate the progress of the disease. However, our work did lead to a novel and exciting finding that scaffolds insulate kinases from inhibition by certain drugs. This finding will impact our use of these drugs for the treatment of heart disease because it will significantly reduce the efficacy of the drugs. By changing our current theory and practices of drug use, this finding will significantly impact the citizens of Connecticut.

How Research Progressed the Field
We have identified a novel and previously unappreciated component of kinase signaling. Importantly, when kinases are bound to a scaffold, they are protected from pharmacological inhibition. This new finding will impact all work on the use of drug therapy to target these kinases in disease.

New Collaborations
Yes, our findings that AKAP7 insulated PKC from drugs that inhibit its activity stimulated us to begin a collaboration with Dr. Jeff Saucerman, a bioengineer at The University of Virginia. We developed a computational model of how scaffold proteins protect kinases from pharmacological inhibition. While our original results were published in 2014, we are still working together to further test how this finding impacts drugs used to treat heart disease.

PI: Richard Everson, Project Title: Refining and Streamlining Comprehensive Genomic Analysis of Clinical Specimens by Massively Parallel Sequencing of Formalin-Fixed, Paraffin-Embedded Tissues

Goals
The purpose of the project is to demonstrate the extent that comprehensive genomic analyses of clinical specimens, such as the formalin-fixed, paraffin-embedded (FFPE) tissues that would be available through a statewide biobank, can be conducted successfully and can provide molecular data similar to that provided by cryopreserved tissues. More specific goals were to show that deep sequencing will characterize gene expression and microRNA

levels as well as mutations, translocations, and copy number changes in FFPE specimens with maintenance of critical information compared with cryopreserved specimens, and that results were consistent whether obtained by gene expression arrays, deep sequencing, or traditional analyses. We were able to successfully conduct the analyses using FFPE clinical specimens.

Key Findings
Tissue-based translational research requires three resources: clinical data characterizing available tissue samples and annotating the tissue, access to tissue specimens, and methods for laboratory analyses of the specimens. Coupling data resources of the Connecticut Tumor Registry with the statewide biorepository and analytic methods from this project will both accelerate scientific progress toward understanding the molecular nature of cancer and provide our state with a powerful data/specimen/laboratory infrastructure for studying cancer, a resource that should dramatically improve the competitive position of our state as a place for conducting cancer research.

How Research Progressed the Field
Specimen processing by FFPE is the worldwide standard procedure used to process tissue specimen for pathologic analysis. Vast quantities of FFPE specimens are available from pathology archives, including the pathology specimens resulting from clinical care for the 20,000 cancer cases diagnosed annually in Connecticut. For the preponderance of clinical situations where cryopreserved specimens are not available, use of the FFPE specimens would dramatically improve access to specimens and accelerate scientific progress toward understanding of the molecular characteristics of cancer and development of effective treatments.

New Collaborations
No.

PI: Manju Hingorani, Project Title: Role of DNA Mismatch Repair in Tobacco Smoke-mediated Carcinogenesis

Goals
The goals of the research project were to characterize the biochemical properties of proteins that recognize damage lesions in DNA (such as that caused by chemicals in tobacco smoke), and initiate DNA repair or cell death. The knowledge gained from this work was expected to improve our understanding of why and how mutations that render these proteins defective promote cancer. The goals of the project were largely met.

Key Findings
The key findings from this basic research project include: (1) comprehensive biochemical characterization of two mutants of the DNA repair protein found in the hereditary colon cancer database, and (2) confirming that the protein studied in this project uses the same core mechanism to initiate DNA repair or cell death in response to DNA damage.

How Research Progressed the Field
Our laboratory specializes in detailed kinetic analysis of proteins that work on DNA. Because of the techniques involved, this is a somewhat niche approach, therefore many of

our published findings are utilized (in small and large ways) in refining model mechanisms of DNA repair. Overall, this effort contributes toward better understanding of the complex mechanisms that protect our genome from wear and tear.

New Collaborations
The basic research funded by the current DPH grant was critical for development of a translational idea and initiation of a new collaboration with a bioengineer at another educational institute in Connecticut. This idea (essentially a proof-of-principle project for a diagnostic device) was developed into a proposal that was selected for funding in the 2014 round of Connecticut biomedical research grant awards.

PI: Laijun Lai, Project Title: Immunotherapy of Melanoma and Colon Cancer by a Recombinant IL-7/HGFβ Protein

Goals
The goal of my project is to determine the antitumor activities of a new protein, and to study the mechanisms of its effects. We have achieved our goals.

Key Findings
We have demonstrated that a new protein that we discovered can inhibit tumor growth and metastasis in two tumor animal models. We have also demonstrated that increased immune functions are involved in the effect of the protein. Therefore, the protein has the potential to be used in the treatment of cancer patients in the future.

How Research Progressed the Field
Our research further confirmed the notion that enhanced immune function is an efficient approach to prevent or to treat cancers. We have found a new way to enhance immune functions.

New Collaborations
Yes, our research led to a new collaborations with an investigator at UConn.

PI: Joel Pachter, Project Title: Effects of Cigarette Smoke on Angiogenesis in the Aging Brain

Goals
The major goal of our research was to determine if both normal aging and smoking impacted the ability of the brain's small blood vessels to grow and repair themselves. We have been able to establish that the normal aging process does significantly impair the expression of "angiogenic" genes, those genes that encode proteins responsible for blood vessel growth. It is our hypothesis that this contributes to the reduced ability of the aging brain to repair its blood vessel supply following vascular insult, as well as a heightened susceptibility to stroke and its consequences. We anticipate soon extending these studies to smoking, specifically to see if smoking worsens the impact of aging on angiogenesis. Since it is typically older smokers that are at risk for stroke, we feel that the paradigm under study will provide unique insight into why this is the case, and highlight molecular targets for therapeutic intervention.
Key Findings

Our major observation so far is that normal aging alters the profile of expression of angiogenesis-related genes - referred to the as the "angiogome." By both altering "pro-angiogenic" and "anti-angiogenic" genes, aging affects the overall "angiogenic potential" of the brain. We further found that exercise can counteract some of the negative impact of normal aging on angiogenic potential—especially in an area of the brain that exerts significant control over memory. This underscores the prospect that behavioral modification —as opposed to drug or surgical intervention—can be highly therapeutic and without adverse effects in promoting overall brain health. Through this funding mechanism we have also greatly advanced the technology of laser capture microdissection (LCM) coupled to downstream global transcriptional profiling. This has led to the ability to evaluate in situ gene expression of the full transcriptome in small of groups of cells—or even at the singular cell level. This is a significant leap for the ability to conduct "personalized medicine," as it can potentially enable "cancer profiles" to be evaluated in small biopsy samples, and to more accurately determine the therapeutic efficacy of drugs at the molecular level. This has garnered the attention of pharmaceutical and biotech companies in the state, and is expected to lead to significant funding streams.

How Research Progressed the Field
The pioneering efforts in LCM/transcriptional profiling has led to the capacity to evaluate the entire transcriptome in a single cell in situ. In turn, this has greatly expanded the ability to study cell lineages in animals and better understand the actions of stem cells. This technology will further help elucidate the transition and progression of cancer cells, as well as more accurately assist in evaluating the effects of chemotherapy.

New Collaborations
Extensively! We have ongoing collaborations with Drs. Don Kreutzer and David Rowe at UCHC, which directly stemmed from this funded work, and have led to the acquisition of new federal funding by these investigators. We also have developed collaborations with the Statistics Department at Storrs, as well as collaborations with colleagues at Yale. This work has also led to industrial collaborations, particularly with Life Technologies/Servo Fisher, which have enabled us to recently establish a LCM Core facility at UCHC. It is expected this Core Facility will be patronized worldwide, as this laboratory has become an international leader in this technology (in significant part because of this Connecticut funding).

PI: Albert Sinusas, Project Title: Magnetic Resonance Imaging (MRI) Assessment of Peripheral Artery Disease at 3 Tesla

Goals
The primary aims were: 1) To relate acute changes in wall shear stress, as computed from 3D phase contrast velocity magnetic resonance imaging, with compensatory structural enlargement of collateral vessels, 2) To relate acute changes in regional blood oxygen levels, as quantified by MR imaging, with microvascular proliferation and perfusion, 3) To study early and late hyperemic response of the collateral vessels, as computed by flow mediated compliance, and the capillary network, as computed by regional tissue perfusion. The proposed MR imaging approaches were validated in animal models of peripheral artery disease, and translated to normal volunteers. Most of the stated goals were achieved except for establishment of the direct relationship of vascular flow velocity to vascular structural

remodeling. The data related to this goal are still being analyzed.

Key Findings
The key accomplishments relate to the validation of several novel non-invasive MR imaging approaches for the evaluation of lower extremity perfusion and oxygenation. These imaging approaches were then translated to normal volunteers. These imaging approaches are now being used to understand the effects of exercise on lower extremity perfusion and oxygenation and are also being applied to patients with peripheral artery disease a major complication of smoking.

How Research Progressed the Field
The non-invasive imaging approaches developed and validated in this project are now being applied to patients in the state of Connecticut, and can be used to better understand the pathophysiology of collateral development in patients with peripheral artery disease. These approaches are also being applied in young student athletes undergoing intensive exercise and weight training.

New Collaborations
This project led to a new collaboration with investigators at the University of Virginia evaluating gene therapy for the treatment of peripheral vascular disease, which is funded by the NIH.

PI: Quing Zhu, Project Title: Targeted Probes for Breast Tumor Hypoxia Imaging

Goals
In this application, we proposed to evaluate and test the sensitivity of the novel ICG-2-nitroimidazole conjugate targeted to tumor hypoxia using pre-clinical breast tumor models in mice. We have developed a real-time fluorescence system and demonstrated its potential for imaging tumor hypoxia. We have performed correlation of in vivo tumor targeting and imaging to biological and molecular markers of hypoxia to validate the hypoxia probe. To further improve the sensitivity of the ICG-2-nitroimidazole conjugate, we have designed and synthesized hypoxia-targeting dye-conjugates with improved fluorescent output. As results, four peer reviewed journal papers have been published and the fifth manuscript reporting the third generation ICG-2-nitroimidazole hypoxia dye with three times higher quantum yield than the first two generation hypoxia dyes is in the process of submission.

Key Findings
The tumor microenvironment is recognized as a critical factor that influences not only the response to conventional anti-cancer therapies, but also helps define the potential for malignant progression and metastasis. In particular, tumor hypoxia is now considered a fundamentally important characteristic of the tumor microenvironment. This proposed work was motivated by the significance and importance of assessing the hypoxic status of advanced breast cancers and monitoring patient treatment responses under different hypoxia conditions. Prior to this award, we have synthesized first generation tumor hypoxia dye. This award provided resources for us to test the dye in animal tumor models and to develop second and third generation hypoxia dyes with superior in vivo tumor targeting capability. We have achieved our goals and have submitted a grant to DOD breast cancer program to continue this work. Unfortunately, we did not receive an award. Currently, we

are preparing a manuscript to report the results of the third generation hypoxia dye and will use these data to apply for an NIH grant in the future.

How Research Progressed the Field

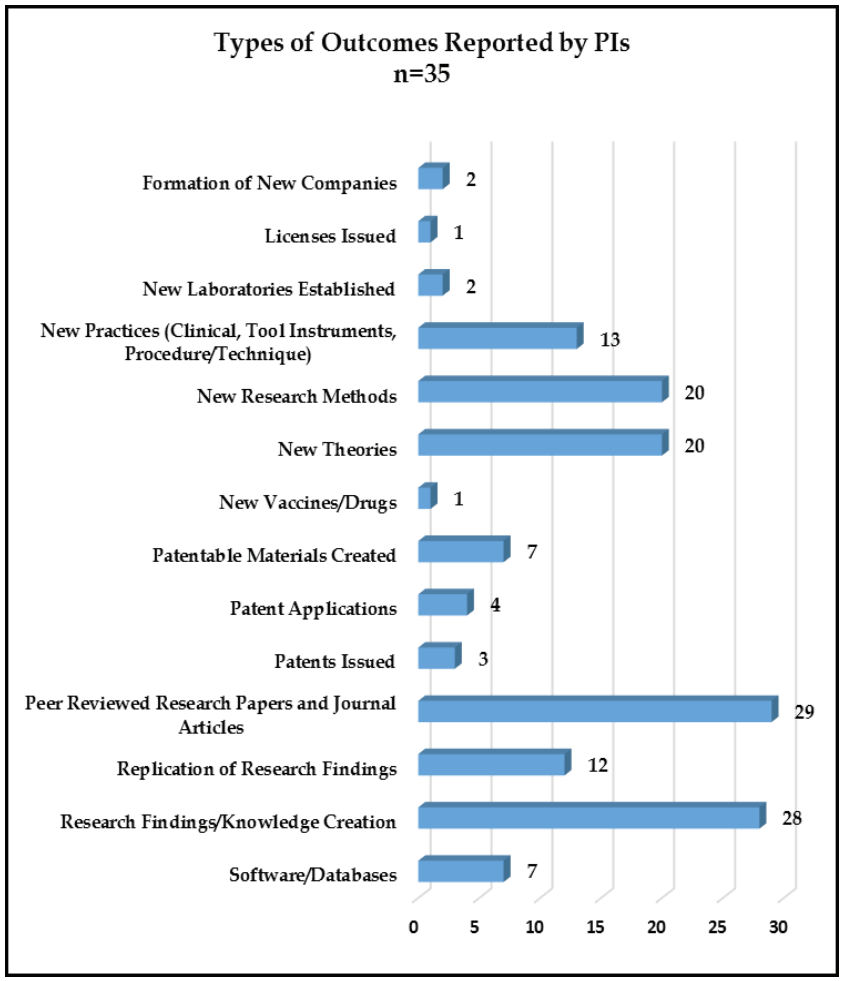
The lack of any hypoxia imaging probes in the near infrared spectrum prompted our synthesis of novel dye-conjugates that link a hypoxia marker 2-nitroimidazole moiety to an indocyanine green (ICG) derivative. Our hypoxia dyes have advanced the field of molecular imaging on tumor hypoxia targeting.

New Collaborations

We have continued our collaboration with a professor at UConn chemistry on dye synthesis and in vivo animal model testing. This award is invaluable to foster collaboration.

Question 18

Which of the following outcomes can you attribute to your research through the Connecticut Biomedical Research Program Grant?



Comments:

- The databases that we are assembling from our research are just beginning to yield what we expect to be many translational and molecular epidemiological papers and grant applications as an offshoot of the data.
- We are in the process of finishing several manuscripts on the research that will be submitted to peer-reviewed journals. This work may create patentable material, as well as new vaccines/drugs.
- This work has largely been responsible for the recent establishment of the Laser Capture Microdissection Core at UCHC, which will be critical to the success of Bioscience CT.
- One year of support for a research effort is not likely to yield an important outcome. With the delays accompanying the hiring of new staff, human subjects/animal care protocol approvals, and technical issues in research, it is not enough time.

Question 19
If yes to any of the outcomes listed in Question 18, please briefly comment and indicate the number, if appropriate.

Formation of New Companies

- Precision Staging, Inc.
- Mira Dx

Licenses Issued

- License was for the intellectual property for Mira Dx

New Laboratories Established

- For the two new laboratories established as noted in response to Question 18, no additional comments were made by the PIs

New Practices (Clinical, Tool Instruments, Procedure/Technique)

- One new practice on oxidative stress as a biomarker for vascular function was established
- Developed a new catheter probe suitable for pre-clinical studies
- Several new clinical diagnostic tools
- Showed that clinical specimens can be successfully analyzed and presented at national meetings
- Developed methods for examining endosome function and exosome expression.
- New model created

New Research Methods

- Developed new synthesize methods to produce hypoxia dyes
- New methods to evaluate perfusion and oxygenation of extremities
- Showed that clinical specimens can be successfully analyzed by adapting methods previously used only for basic research
- Developed methods for examining endosome function and exosome expression
- Fluorescence-based assays for kinetic analysis of DNA repair proteins
- Development of in vivo mouse models of breast cancer metastasis
- Develop a new method to assay for apoptosis marker in human circulation (19)
- Methods to look at cell division in whole pieces of tissue that had not previously been done
- LCM coupled TLDA and RNA sequence
- Our new findings should change the way we use drugs to inhibit kinases that result in disease

New Theories

- A new theory on additional interventions necessary to optimize vascular health in smokers was established
- Smoking up regulates genes important for growth, and down regulates genes important for immune function
- The theory of how VPS4B-mediated endosomal signaling is important in exosome-mediated signaling between normal and cancer cells
- The theory of how endosomal signaling is important in chemotherapeutic resistance
- That PDEs may be excellent therapeutic targets for treating breast cancer
- Theories about how cell division goes wrong in cancer
- Impact of exercise on brain vascular effects of normal aging
- A novel and previously unappreciated finding that kinases are protected from drugs
- First study to examine co-treatment of antioxidants with smoking cessation

New Vaccines/Drugs

- Specific inhibitors of the expressed PDEs may be developed as new clinical drugs

Patentable Materials Created

- Filed discloser of this novel device to UConn. However, UConn did not pursue patent application
- Potential patentable discovery

- A provisional patent based on this research was filed by the UConn Health Center
- Patentable method

Patent Applications

- A provisional patent based on this research was filed by the UConn Health Center
- Invention disclosed

Patents Issued

- For the three patents awarded as noted in response to Question 18, no additional comments were made by the PIs

Peer Reviewed Research Papers and Journals

- Two papers in process and one abstract published
- More than 20 papers have been published on this field since the research
- Two peer-reviewed journal papers have been published
- Four peer-reviewed journal papers and one more in the process of submission
- Several peer-reviewed publications
- At this point papers were presented at a series of national meetings. Despite ending the work, journal articles are in progress.
- Hussain N, Krueger W, Covault J, Walsh S, Kranzler HR, Oncken C*. Effects of prenatal tobacco exposure on gene expression profiling in umbilical cord tissue. Pediatric Research. 2008 Aug; 64(2):147-53.
- Results presented at a series of national scientific meetings
- At least one paper and several now in preparation. Also presentations at national meetings.
- The findings from this project are included (in part) in two peer-reviewed research articles thus far.
- Two papers stemming from this work have been published and several more are in process of being written.
- Several publications in important biomedical research journals
- Paper in the Journal of Clinical Endocrinology and Metabolism
- Three publications and more submitted
- Two manuscripts were published from the work performed in this grant
- Hollenbach et al., 2011, PLoS ONE, 6(7): e21808
- 3 Papers

- Published one study and a second research paper is currently under review for publication
- Patel, K.T., Stevens, M.C., Pearlson, G.D., Winkler, A., Hawkins, K., Skudlarski, P., Bauer, L.O. (2013). Default mode network and white matter integrity in healthy middle aged ApoE4 carriers. Brain Imaging and Behavior 7:60:67.

Replication of Research Findings

- Verified some existing data
- Replication of some related findings about the most important colon cancer gene
- Throughout the literature. Published by national and international research groups
- Confirmed earlier findings about smoking cessation and provided novel evidence that antioxidants better restore vascular function than smoking cessation alone

Research Findings/Knowledge Creation

- New publications will be added to the field
- Research led to many papers published on this field
- Defined temporal pattern of collateral development in PAD
- Smoking up regulates genes important for growth, and down regulates genes important for immune function
- The theory of how VPS4B-mediated endosomal signaling is important in exosome-mediated signaling between normal and cancer cells
- Demonstrated ability to use vast repositories of existing clinical specimens for genomics research
- The theory of how endosomal signaling is important in chemotherapeutic resistance and exosome signaling
- This represents the first full analysis of PDEs in breast cancer and shows their importance as targets
- New knowledge about cell division in cancer and normal intestines
- PGRMC1 action in cancer cells
- ICON immunotherapy and fVII-targeted phototherapy are effective in the treatment of human lung cancer in preclinical studies
- New areas of work were developed from completion of this grant
- Provided novel evidence that antioxidant better restore vascular function than smoking cessation alone

Software/Databases

- Developed a database of such patients
- Developed imaging software
- New software was created to analyze MR images

Question 20
List three to five benefits unique to conducting Biomedical Research in Connecticut.

Comments:

- There is a rich research community with multiple opportunities to collaborate; Funding for preliminary studies and pilot investigations is available; Several large clinical institutions make it easier to recruit clinical populations; There is a diverse population in the greater Hartford area.
- Close collaboration with hospitals
- Many funding opportunities, for example DPH and Bioscience Fund
- Many opportunities, such as DPH Biomedical Research Fund, Connecticut Bioscience Fund, etc.
- Established research networks; Unmatched resources for research; Available personnel with technical expertise
- The overall high quality of medical care and records provides information for research, and the Connecticut Tumor Registry, which for cancer, makes these clinical resources accessible at a population level
- Work with a number of qualified investigators in Connecticut; Funding with some preliminary data; Explore new areas of research
- The relatively intimate relationships among a small number of research programs around the state
- Collaborated with individuals within and outside of my department at Yale, as well as individuals in hospitals in the state.
- The collaborative environment in Connecticut is very strong between investigators and between institutions; The strong support by the state for translational research is very unique in the United States; The new Connecticut Bioscience initiative, which will strengthen the biomedical research environment and attract new investigators to the state, as well as provide a foundation for new external grant funding; The pool of educated technicians and postdoctoral fellows attracted to the state.
- A major potential benefit was the high standard of care and especially pathology at regional hospitals and, for cancer, the data resources provided by the Connecticut Tumor Registry.

- The collaborative environment in Connecticut for both basic and translational research; The institutional support for translational research at the UConn Health Center; The strong support for research by the state (e.g., these grants are almost unique in the United States); The strong support for translational research by the state government which has brought in institutions like the Jackson Lab; The new ties of collaboration between UConn and UConn Health Center, which bring together different disciplines to the same problems.
- High density of researchers and services in a variety of educational institutions within easy driving distance; Easy access to premier institutions in Boston and NYC, facilitating out-of-state collaborations; Access to a talented and well-educated student pool, both at the undergraduate and graduate level
- That the state is willing to at least make some funds available for research; That there are generally adequate facilities available at its medical schools; That there are a number of large pharmaceutical firms in the state with which to collaborate
- This funding was very key for us and reasonable to get. There also were not many restrictions. Building a commercial laboratory was also fairly easy.
- Willingness to take risk on the research; Fair assessment of merits
- Excellent state support of research; Excellent research environment; Top scientists at several institutions
- Easy state to live and work in; Great place to settle down and have a family; Opportunities to teach, research, and patient care, which is RARE; Support of stem cell research
- More translational; Good environment for commercialization
- The major benefit is that these funds can be used to test a hypothesis. If successful, then additional funding for NIH, etc., is possible.
- Interactions with the many colleges/universities in the state; Interactions with the many pharmaceutical and biotech companies in the state; Numerous funding opportunities provided by the state
- Connecticut Biomedical Research Program funding is unique; Yale University has very strong collaborative and core facilities; The State of Connecticut government is committed to supporting cancer and stem cell research
- Reduced competition for funding, as compared to national grants; Work must impact important fields such as heart disease; Work should impact Connecticut citizens
- Strong support of the state for basic and translational biomedical research
- Highly educated specialist workforce; Entrepreneurial base (is small, but highly productive and innovative); High quality of university graduates (but many move out of state).
- Made it possible to continue my research on cancer treatment; Increased my staff size and created jobs; Increased my lab's technology; Obtained more preliminary data for the NIH grant applications

- Providing funding to do translational research that has potential to be used in the diagnosis and/or treatment of patients; Providing funding to allow for obtaining more preliminary data for the applications of federal funding, such as NIH; Creating jobs
- It facilitates research on priorities important to Connecticut residents; It provides employment opportunities; It potentially can be used to establish new recommendations and policies important to Connecticut residents
- There is nothing unique about Connecticut
- Excellent resources for research material, expertise and collaborators
- Outstanding universities; Willing patient populations; Collaborative spirit
- To get funding support from DPH

Question 21
List three to five challenges unique to conducting Biomedical Research in Connecticut.

Comments:

- It can be difficult to recruit certain minority patient populations; Often times researchers work in "silos" and do not communicate as effectively and collaboratively as they should; Clinical institutions such as Hartford Hospital and UConn do not collaborate as effectively as they should
- Investment on translational cardiovascular research is not enough
- Yale and UConn collaborations need to be strengthened; Locations of hospitals and UConn (Storrs Campus) are too far apart
- The hospitals and UConn (Storrs Campus) are in different locations with at least a 45- minute drive. This is a significant challenge in conducting translational studies in Connecticut
- Intense regulatory issues for translational and clinical research
- Less state support than available elsewhere; Lack of stable infrastructure/research cores in UConn Health Center; No effective exchange between UConn-Storrs and UConn Health Center staff or students; Unionization of research assistants limit access to appropriate research personnel: Union policies at the health center result in technical staff being assigned based on seniority rather than having the background needed for the project; and the union also precludes the use of volunteers for research (a volunteer could not perform functions that could be performed by union staff). I know of faculty who have not hired a technician in twenty years because of the impact of these policies. In other state institutions the use of volunteers and interns was promoted. They both allowed expansion of effort on projects and provided the volunteer with important training opportunities that developed their careers and the state's workforce.
- Working with people of other disciplines; Frequent reporting to DPH; Time pressure of grant

- Because there is so much research going on, patients tend to be heavily recruited. We end up competing with each other for patients to enroll.
- Delay in receiving funding by many months, held up by the bureaucracy; Also, and most importantly, we decided to submit a new (or continuing) application to the Connecticut Biomedical Research Program's RFA in December. I worked extremely hard on this proposal that involved clinicians, basic scientists (UCHC and Storrs), and several outside investigators. A truly multi-disciplinary and multi-institutional application to keep our amazing translational study going forward. We were still way under our enrollment goals for active cigarette smokers (~20) and wanted to accrue up to 100 current smokers, as well as up to 200 more never smokers and former smokers from Connecticut. We also wanted to be able to expand the data collection, continue the food intake questionnaires, develop a new and related food intake survey (from Dr. Duffy in Storrs) and increase our databases with more molecular and epidemiological analysis. We also would be able to use the additional funding to continue to publish papers related to our findings and to expand upon the recently developed human adenoma database that was begun with Dr. Thomas Devers. Unfortunately, although the application was submitted in December, I found out in late March that I had forgotten to check off a form saying that I would submit progress reports (which I have always done in the past) and was informed that the grant WOULD NOT BE REVIEWED because of this missing statement! This despite our incredible amount of scientific progress, the tremendous direct benefit to residents of Connecticut, the great progress (publications, awards, NIH funding) and interdisciplinary interactions that were fostered between so many programs and individuals in Storrs and Farmington. Not to mention the large number of undergraduate students that were trained in the labs during the funding period. This rejection based on purely non-substantive reasons is unconscionable and extremely disheartening to this highly motivated research team that is now threatened with closure.
- Recruitment of new junior faculty at the UConn Health Center is a serious challenge to research by preventing new ideas to enter into the collaborative field. Overshadowing of the state by the Boston research community—makes it difficult to recruit and obtain funding.
- I will focus comments on the situation at UCHC. For at least a decade senior management of UCHC has shown little understanding of the unusual circumstances of the Health Center resulting from its small size. University hospitals in many parts of the country are typically large institutions that command an important market share of care in their communities. In contrast, UCHC is among 10 or so of the smallest of the 150 urban teaching hospitals in the United States, a situation that will not change with its new facilities. In urban settings nationwide, a sizeable portion of hospitals the size of UCHC are closing, as did 2 or 3 of the 10 smallest urban teaching hospitals. In addition hospitals are rapidly combining to develop large regional consortia. An isolated hospital of UCHC's size is an anachronism. Instead of responding to these realities by focusing on developing collaborations aimed at improving care at all facilities in the region, the Health Center insists on trying to compete with the much larger, high-quality community hospitals. It has made little meaningful attempt at developing collaborations; witness the progressively declining competitiveness of its CTSA grant. A consequence of these policies is that the many areas and stages of translational research, which require access to larger numbers of patients or specimens,

are not feasible. Until management is replaced with leadership that understands the unsustainability of an isolated, competitive approach, biomedical research will not be able to develop broad components of programs in translational science or promote economic development in the state.

- Difficulty of recruiting new faculty at UConn, which affects the ability to develop new collaborations and new avenues of exploration
- There should be more funding available from the state; The fringe benefit rate for lab assistants is way too high and should be reduced; There should be more tissue bank repositories set up and a place for data to be stored for sharing among different research groups
- It was impossible to find good business staff to work in New Haven, Connecticut
- Inadequate amount of funding
- Same as the rest of the country—funding is drying up; UCHC is too small; Some unhealthy competition between the Hartford area hospitals; UCHC does not allow volunteers due to union issues
- Smaller cities create personnel challenges
- The major problem is that the state contract process is not typical of other grant applications. It would be great if the format could become more like NIH.
- Competition from surrounding areas/institutions; An unfortunate bureaucracy; Intra-university competition
- Will the Connecticut Biomedical Research Program continue to support Connecticut cancer research projects? Will the funding levels maintain or increase in next 5-10 years?
- The biggest challenge is the time constraints. Determining the amount of work that can be performed in the time allowed by the grant can be challenging. It has to be something that is already up and going and not in new areas. This limits that impact of the work.
- Aging and unreliable infrastructure (frequent power outages in winter, during hurricanes; Metro North system failures and accidents, Amtrak delays & failures, I-95); Crime and violence in New Haven discourages workforce and makes it difficult to hire from out of state; Competition with New York and Boston area; Retention of successful mid-career scientists is poor; Political and educational efforts against justified and necessary animal research threatens long-term investments
- Funding is still very limited
- Limited funding available
- Awards are administratively complicated to manage
- Execution of contracts is not timely following favorable review
- Communications with DPH tend to be difficult because all correspondences must be made in writing, often with an original signature

- For clinical research in Connecticut newspapers and radio are in decline as outlets for study advertising
- Duration of support is too brief
- No challenge compared to other states. In fact, advantages.
- Very competitive

Question 22
Currently, the Biomedical Trust Fund provides grants-in-aid for research in the fields of heart disease, cancer and other tobacco-related diseases, as well as Alzheimer's disease, stroke and diabetes. Are there other biomedical research fields of high importance that you recommend the state should consider for inclusion in this program?

Thirty of the 35 PIs responded to the question, with 11 indicating the research areas should not change. The remainder of the responses are grouped by additional or existing research fields.

Additional Biomedical Research Fields Recommended

- Autoimmune disease
- Genetics and personalized medicine
- HIV and HIV-associated sarcoma
- Inflammation and autoimmunity
- Lung disease
- Musculoskeletal research such as osteoarthritis and rheumatoid arthritis as well as fracture should be supported by the Biomedical Trust Fund. These are important unaddressed problems in our state.
- Musculoskeletal research such as osteoarthritis and rheumatoid arthritis. This is a major health problem in Connecticut yet it is not supported by Connecticut Biomedical Research Program grants.
- Obesity
- Obesity, Adult-onset disabilities
- Reproductive and pregnancy outcomes
- Stem cell or regenerative therapy
- Support of research on asthma and other respiratory and allergic conditions would complement the current efforts. Pain research is also an underfunded area with significant expertise present in Connecticut.
- The areas that are at the interface of engineering and clinical research
- These are all top priorities. We also could use aging research, musculoskeletal research; nutrition research.

Comments Based on Existing Areas of Funding

- Cancer is the most critical need
- Do not think expansion is necessary. Would consider it if it opened up other sources of funding for the program.
- Should only focus on tobacco-related diseases. Otherwise it is misuse of tobacco funds.
- The current scope has the potential advantage of helping the fund obtain funds from the Tobacco Trust Settlements. If expanding the fund detracted from its competitiveness for these funds, it could be a detriment to the program. If expanding the scope provided access to additional funds, it would be a benefit.
- These are important and useful areas of focus. I would urge a (continued) strong emphasis on basic research, especially since we are losing young sharp minds at the graduate, post-graduate and faculty level from the shrinkage in federal funding, including the NIH's overly strong emphasis on translational research; and unless there are other sources of state funding for this research already, it would be useful to fund research on infectious disease mechanisms and drug targets, especially those diseases projected to be emergent in Connecticut with climate change.

Question 23
Identify any current Connecticut Biomedical Research Program policy issues (obstacles/barriers/ concerns) that should be considered by the state (approximately 250 word maximum).

Twenty-eight of the 35 PIs responded to the question, with nine indicating they had no policy issues to identify. The remaining responses are grouped by improving the grant award process or additional policy issues.

Improving the Grant Award Process:

- Perhaps have two RFP periods (fall and spring) to facilitate more researchers utilizing the program
- A one-year grant funding period is too short, a no-cost extension is almost unavoidable.
- Average funding size could be about $150K, instead of $300K to allow more PIs to receive the program support
- Configuration of budgets do not match structure used by other national funding agencies; Grant application form also does not match that typically used by other funding agencies
- The rejection of our most recent submission to continue an enormously important and productive program based 100% on a non-substantive and extremely minor (and obviously accidentally overlooked) technical omission is absolutely demoralizing to all of us that have worked so hard to bring new knowledge and treatment approaches to the people of Connecticut that deserve the best.
- The guidelines and procedures for grant applications are a bit, shall we say, byzantine?

- Short-term grants for large amounts of money are a very inefficient use of funds. It would be much more efficient to have long-term grants for lower amounts per year. Most labs cannot hire personnel specifically for a project, then get rid of them a year later. The current budget constraints cause a waste of money through overinflated budgets and inefficient use of awarded funds.
- Paper submissions are obsolete; should be electronic
- The application form is very difficult to complete given that is not typical for grant applications.
- The application form can be a bit unworkable, and part is redundant
- The most challenging thing about this program is writing the actual grant. This grant format is unlike any other used in any other funding agency. As a researcher, we need to not only write a strong research proposal, but also know about cost allocation plans, and many other administrative aspects that we are completely unfamiliar with.
-
- Another challenge is the flexibility of the grant. Personal changes are difficult to make and many employees are constantly changing, such as students and post-docs.
- While the current Connecticut Biomedical Research Program Tobacco-related grants are an extremely important source of research funding for investigators and the total budget amount is appropriate, the necessity to limit initial budgets to a one-year time frame is not practical, especially when considering hiring new personnel to perform the research. A two- to three-year budget period is a minimum in order to be able to hire new personnel.
- Grants should be awarded for 2-3 years, not just 1 year.

Additional Policy Issues Identified:

- Need more state support for start-up funds, pilot grants, etc.
- State should have its own Small Business Innovation Research program to fund start-up companies
- DPH has less staff with backgrounds in science and biomedical research to manage the program without greater use of outside help
- This funding should be used to also treat smokers
- A major problem is the progressive decline of scientific and medical science expertise with DPH, the component of government that administers the Program. While components of the department's program remain strong, the decline in more traditional biomedical science has reached a critical level both for oversight of this program and protection of public health.
- The need for more funding
- For clinical research in Connecticut newspapers and radio are in decline as outlets for study advertising.

Question 24

How would you suggest the Connecticut Biomedical Research Program be improved (approximately 250 word maximum)?

- Should be an emphasis on younger/new investigators or new investigations/lines of research or new collaborations so as to promote growing the biomedical field in Connecticut.
- One-year grant funding period is too short, a no-cost extension is almost unavoidable; Average funding size could be about $150K, instead of $300K to allow more PIs to receive the program support; The funding review process should be more transparent
- More funding opportunities; more transparent grant evaluation, for example provide reviews for both funded/non-funded proposals; More Small Business Innovation Research type of grants.
- Provide reviews of the grants that were not recommended for funding; Once a year grantee workshop to foster more collaborations
- Standardize application process to match other agencies
- The application forms/process has many complexities and requirements that add to the applicant's burden. Simplification, pilot testing of application materials (in some years it appeared the budget had to be entered in multiple places on the forms), and bringing procedures more in line with those used by NIH and other institutions would improve the process.
- Should focus only on tobacco
- The grant applications should be in line with National Institutes of Health formats. The formats that we need to prepare are extremely difficult and seem to change every year, which just makes things ever more difficult. Why do we need to spend so much time focused on forms that are better suited for state contractors and not on the science that we want to undertake? And to return a grant three months later because of a single, minor omission cannot be tolerated by a state that wants to place biomedical research as the highest of priorities!!
- Reduce the amount of funds per grant to allow more grants to be funded. In the current national funding environment, it is critical to support as many investigators as possible.
- It could be useful to expand the scope to helping the development of small businesses and non-profit corporations. While there are other state programs for corporate development, they tend to be most appropriate for relatively late stages of product development. In comparison with other states. Connecticut's efforts pale in support of the biomedical sciences needed for the continuum of basic to applied product research required for competitiveness in the biomedical sciences.
- Potentially limit the amount of money per grant to allow more grants to be awarded.
- It seems that the application process should be simplified (guidelines should be clarified) and the review process made more transparent. From my experience with applying for two grants in the past four years, significant advances have been made in this direction already and these need to continue; perhaps offer an informational

workshop, especially for junior faculty early enough to improve the quality of applications.

- Provide more funding. Provide funding for more than one year.
- Better feed into state venture capitalist funding. This process was political and impossible to navigate.
- Short-term grants for large amounts of money are a very inefficient use of funds. It would be much more efficient to have long-term grants for lower amounts per year. Most labs cannot hire personnel specifically for a project then get rid of them a year later. The current budget constraints cause waste of money through overinflated budgets and inefficient use of awarded funds; also, the application form is incredibly cumbersome—it is totally unlike any other biomedical research grant application, and much time and effort is wasted trying to figure out the forms, what is requested, and formatting everything in a new/unfamiliar way. It is almost impossible to get help/advice from the state on what information is needed and in what format.
- Just keep funding it; opportunities to get additional funding for further projects; Bridge funding for investigators who are struggling to get funding.
- More $$$!
- The key is to change that application.
- The application form can be a bit unworkable, and parts are redundant.
- If possible, please increase the total amount of grant money and provide a longer period for funding in support of cancer research.
- More flexibility and help with the paperwork.
- While the current Connecticut Biomedical Research Program Tobacco-related grants are an extremely important source of research funding for investigators and the total budget amount is appropriate, the necessity to limit initial budgets to a one-year time frame is not practical, especially when considering hiring new personnel to perform the research. A two- to three-year budget period is a minimum in order to be able to hire new personnel.
- The administrative workload for grantees and their organizations for this program is substantially bigger than for comparable federal programs. Policies should be streamlined and clearly spelled out; reporting should be facilitated as much as possible so that researchers can focus on research
- Because of the nature of biomedical research, funding period should be increased to three years for each project.
- Funding period should be increased from current 1.5-2 years to three years for each project
- Be more flexible and timely with fiscal management. It is very difficult to administratively manage these awards, particularly when the need arises to remove/add personnel to a project.
- Excellent already.
- Hope the research fund can provide support for a longer time period.

MAJOR STUDIES OF THE ACADEMY

2014

- Peer Review of a CL&P/UConn Report Concerning Emergency Preparedness and Response at Selective Critical Facilities
- Connecticut Disparity Study: Phase 2

2013

- Analyzing the Economic Impact of Transportation Projects
- Health Impact Assessments Study
- Connecticut Disparity Study: Phase I
- Connecticut Stem Cell Research Program Accomplishments

2012

- Strategies for Evaluating the Effectiveness of Programs and Resources for Assuring Connecticut's Skilled Workforce Meets the Needs of Business and Industry Today and in the Future
- Benchmarking Connecticut's Transportation Infrastructure Capital Program with Other States
- Alternative Methods for Safety Analysis and Intervention for Contracting Commercial Vehicles and Drivers in Connecticut

2011

- Advances in Nuclear Power Technology
- Guidelines for the Development of a Strategic Plan for Accessibility to and Adoption of Broadband Services in Connecticut

2010

- Environmental Mitigation Alternatives for Transportation Projects in Conecticut
- The Design-Build Contracting Methodology for Transportation Projects: A Review of Practice and Evaluation for Connecticut Applications
- Peer Review of an Evaluation of the Health and Environmental Impacts Associated with Synthetic Turf Playing Fields

2009

- A Study of the Feasibility of Utilizing Waste Heat from Central Electric Power Generating Stations and Potential Applications
- Independent Monitor Report: Implementation of the UCHC Study Recommendations

2008

- Preparing for Connecticut's Energy Future
- Applying Transportation Asset Management in Connecticut
- A Study of Weigh and Inspection Station Technologies
- A Needs-Based Analysis of the University of Connecticut Health Center Facilities Plan

2007

- A Study of the Feasibility of Utilizing Fuel Cells to Generate Power for the New Haven Rail Line
- Guidelines for Developing a Strategic Plan for Connecticut's Stem Cell Research Program

2006

- Energy Alternatives and Conservation
- Evaluating the Impact of Supplementary Science, Technology, Engineering and Mathematics Educational Programs
- Advanced Communications Technologies
- Preparing for the Hydrogen Economy: Transportation
- Improving Winter Highway Maintenance: Case Studies for Connecticut's Consideration
- Information Technology Systems for Use in Incident Management and Work Zones
- An Evaluation of the Geotechnical Engineering and Limited Environmental Assessment of the Beverly Hills Development, New Haven, Connecticut

Connecticut Academy of Science and Engineering
805 Brook Street, Building 4-CERC, Rocky Hill, CT 06067-3405
Phone: 860-571-7143 • e-mail: acad@ctcase.org
web: www.ctcase.org

Connecticut Academy of Science and Engineering

The Connecticut Academy is a non-profit institution patterned after the National Academy of Sciences to identify and study issues and technological advancements that are or should be of concern to the state of Connecticut. It was founded in 1976 by Special Act of the Connecticut General Assembly.

Vision

The Connecticut Academy will foster an environment in Connecticut where scientific and technological creativity can thrive and contribute to Connecticut becoming a leading place in the country to live, work and produce for all its citizens, who will continue to enjoy economic well- being and a high quality of life.

Mission Statement

The Connecticut Academy will provide expert guidance on science and technology to the people and to the State of Connecticut, and promote its application to human welfare and economic well-being.

Goals

- Provide information and advice on science and technology to the government, industry and people of Connecticut.
- Initiate activities that foster science and engineering education of the highest quality, and promote interest in science and engineering on the part of the public, especially young people.
- Provide opportunities for both specialized and interdisciplinary discourse among its own members, members of the broader technical community, and the community at large.

Connecticut Academy of Science and Engineering
805 Brook Street, Building 4-CERC, Rocky Hill, CT 06067-3405
Phone: 860-571-7143 • e-mail: acad@ctcase.org
web: www.ctcase.org